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RARE DISEASES EPIDEMIOLOGY

Edited by
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Rare Diseases Epidemiology

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On a personal note it is essential to recognize and thank our family members who have enabled us to make the personal commitments to the necessary programs leading to interventions and a better quality of life for patients with rare diseases.

To my wife, Jan Groft, I remain forever grateful to permit this quest to continue for over twenty-eight years.

To my wife, Mercedes and our children, whose love and support, gives me the strength I need to work for a better world and for a more generous dedication to others.

Preface

In our etiologic research, we epidemiologists need to leave behind the concepts of 'cohort' study and 'case–control' study and adopt that of the etiologic study as the singular substitute for these.

With this sentence, the famous epidemiologist Professor Olli S. Miettinen began his personal reflection on the future of the epidemiology [1]. He sought to highlight the fact that the role of the epidemiologist should be mainly focused on aetiological research. Nevertheless, the widespread idea still exists that epidemiology is limited to purely providing figures and descriptive data on the frequency and distribution of disease. Indeed, it is more than likely that the precise aim of those first classic epidemiological steps, i.e., methods essentially based on describing the distribution of a given disease, is still not all that well understood by many scientists, let alone the general public. Such descriptions seek to generate hypotheses and afford explanations for key factors (be these risk factors or the presumable causes themselves), which might justify differences in terms of persons, time or place and, in turn, ultimately serve to develop preventive measures and/or gain quality-adjusted life years. To restrict the goals of epidemiology to activities exclusively concerned with reporting figures or even complex statistical results is a great mistake, one that renders it difficult to take full advantage of the epidemiologist's true role, which is "to study disease determinants and to assess the actual impact of factors involved in their development, distribution and dissemination".

Only once these tasks have been completed, can prevention and population health improvement activities follow, namely, the reasonable steps that public health experts are in charge of developing.

"Rare diseases" is a new term that groups diseases by reason of their low prevalence and, to some extent, their severity and chronically debilitating clinical course. It is surprising how, in the field of rare diseases, the role of epidemiology is always mentioned but is somehow solely associated with lack of knowledge of some estimates – generally prevalence – or linked to information systems. Needless to say, epidemiology does have an important role to play in this field but one that is not simplistically and exclusively associated with websites featuring decorative graphs and tables. On the one hand, it must provide a benchmark for drawing up public

health policies affecting rare diseases, and on the other, it must assume its rightful crucial role in the design and development of aetiological research into such diseases.

Many disciplines and subspecialisations associated with epidemiology have been developed over the past 30 years. Yet, this is controversial and many epidemiologists are of the opinion that most of these so-called "disciplines" are not really disciplines at all, but merely epidemiology applied to some specific population, e.g., clinical epidemiology, molecular epidemiology, genetic epidemiology, pharmacoepidemiology, occupational epidemiology, etc. [2]. In much the same way, there are those that think that epidemiology, rather than being targeted at furnishing methods or sophisticated statistical technological support, should, by correctly using appropriate methods and tools for assessing exposures and health outcomes, show instead how better in-depth knowledge of disease origins can be acquired.

Aside from the above differences however, the current situation can by no means be regarded as negative. Many epidemiologists are working in specific units and furnishing new knowledge of undoubted interest for rare diseases. Some questions where epidemiology is called upon to play a role in aspects such as study design, selection of study subjects and variables to be measured, and selection and development of statistical analysis, among others, include the following: how do traditional socio-economic factors intervene in the origin and prognosis of some rare diseases?; is a particular screening programme cost-effective?; is a specific preventable measure really effective?; is a given drug effective in terms of reducing the mortality of the target disease?; is some specific gene the true cause of a given disease?; and, does a specific molecular marker predict endophenotypes with better or worse prognosis?.

Rare diseases are complex because their causes are often not very well understood, their mechanisms are mostly on the very frontiers of current scientific knowledge, and they call for approaches from and viewpoints of different specialised areas. Epidemiology is one of the medical specialisations that provide tools, methods, and ways of thinking and extensive experiences in working in collaboration with other scientists, clinicians and basic researchers.

It is for this reason that this book sets forth new knowledge and insights drawn, not only from epidemiologists, but also from economists, sociologists, psychologists, pharmacologists, clinicians, biochemists and biologists. This was a genuinely co-operative effort aimed at expanding the relevance of epidemiology as a science essentially devoted to aetiological research yet involving the collaboration of many other experts and specialists.

It is clear that, at this point in time, relatively little epidemiological data on rare diseases is available. Nevertheless, as editors, we firmly believe that in the wake of this book, a number of experts will look at epidemiology with fresh interest, funding agencies and charities will provide funds for development within a rare-disease research framework, and some epidemiologists will also be roused to take note of this new era, in which rare diseases are becoming a new group of diseases with

different aetiologies, different prognoses and different clinical features, yet with similar social and medical problems affecting patients, their families and society alike.

Manuel Posada de la Paz
Stephen C. Groft

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Part I
Rare Diseases

Chapter 1
Rare Diseases – Avoiding Misperceptions and Establishing Realities: The Need for Reliable Epidemiological Data

Stephen C. Groft and Manuel Posada de la Paz

Abstract The rare disease community suffers from the absence of reliable epidemiological data on the prevalence and incidence of rare diseases in the national and global populations. The rare diseases community includes all of the stakeholders involved in the research and development and dissemination of products and information for the diagnosis, prevention or treatment of rare diseases or conditions. To replace many of the perceived myths with realities, several global efforts are required if we are going to sustain and increase the reported progress with the thousands of rare diseases. One is the identification and expansion of worldwide partnerships and collaborations of Patient Advocacy Groups for individual rare diseases. Another requirement is to develop a global research infrastructure of qualified investigators to stimulate and coordinate research efforts by seeking ways to provide access to clinical trials at multi-national research sites with common protocols and multi-disciplinary research teams. Providing ready access to the information about rare diseases, patient advocacy groups, research studies and products in research protocols will continue to improve the lives of patients and their families. Many scientists, public and private sector organizations, patient advocacy groups, foundations, and the pharmaceutical, biotechnology, and medical devices industries are committed to translating research discoveries that will be useful in the care of patients with rare diseases over their lifespan. Evidence from well constructed epidemiological studies will provide the evidence that point to the value of additional clinical studies to increase the understanding of rare diseases.

Keywords Rare diseases · Clinical research networks · Epidemiology · Information systems · Training · Patient organizations

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1.1 Introduction

The rare disease community suffers from the absence of reliable epidemiological data on the prevalence and incidence of rare diseases in the national and global populations. The rare diseases community includes all of the stakeholders involved in the research and development and dissemination of products and information for the diagnosis, prevention or treatment of rare diseases or conditions.

The majority of rare diseases are inherited conditions but a significant number are acquired through various processes including the effects of environmental factors. Incorrect perceptions exist and continue to provide troubling and often weak responses to the needs of the community. We know there are an ever increasing number of disorders falling under the term rare disease. Estimates approaching or even exceeding 7,000 conditions have been expressed. As sophisticated analytic capabilities continue to improve, more and more diseases will be subcategorized into distinct disorders. Expanded genomic analyses will explain many of the phenotypic differences observed in patients. Frequently, those involved with larger numbers of patients in their practice or in their research protocols recognize the expression of a rare disease may vary from patient to patient. In many instances, it is the active patient advocacy group leader who describes the differences in patients. Appropriate epidemiologic studies are required to confirm the opinions offered by clinicians, patients, and families.

The discussion that follows addresses many of the perceptions that may or may not be realities for patients with rare diseases. The lack of access to appropriate information to aid in the decision making process remains a major barrier to an improved quality of life for patients and their families, caregivers and friends.

The words of William Harvey in a letter responding to an inquiry from Dr. Jan Vlackveld of Haarlem in the Netherlands (24 Apr 1657) resonate in today's society. "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her working apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual laws of nature by careful investigation of cases of rarer forms of diseases. For it has been found in almost all things that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way."

1.2 Very Few People Have the Rare Condition

One of the first perceptions a patient frequently encounters at the time of obtaining a diagnoses is the conclusion presented that very few patients have their disease. The response is usually based on the publication of results in a very narrowly defined population from one study. Unfortunately, most of the results published do not include a sufficiently large population to draw realistic conclusions about the incidence or prevalence of a particular disorder. Only after an individual or a family

becomes aware of the availability of services from a patient advocacy group are they convinced there are many others living with the same disease who could provide vital information about the presentation of the disease and how best to live with their condition. In some respects, this connection eliminates the stigmatization that can occur with visible symptoms or an incapacitating rare disease, whether they are developmental, psychological or physical expressions of the disease. Stigmatization of children with rare diseases remains a major concern. In recent years, we are seeing a reduction of the problem due to the willingness of the families, patients, or parents to address the disease openly and to educate the public about their disease. Between six percent and eight percent of the population may experience a rare disease [7]. In the USA an estimated 25–30 million patients have a rare disease. Estimates from the European Union are even higher of between 27 and 36 million people due to a larger population base. When a multiplier of 3–4 people who are directly affected by rare diseases including a family member or a caregiver, the number of people directly affected by rare diseases begins to approach and may even exceed 100 million people in both the USA and the European Union. It has been stated that each person has the probability of being affected by four to five significant disorders during their lifetime.

Most rare diseases do not recognize geographical, historical or political borders. However, some diseases may occur more frequently in selected populations or in individual countries. The possible occurrence of different inherited conditions points to the need for families to establish and maintain an extensive family history of the health and illnesses of their family members through multiple generations. In the absence of information from longitudinal or natural history of diseases studies, extensive family history studies may be very good predictors of the occurrence of genetic and acquired disorders until the time when large data sets of information from significantly larger cohorts can be mined for more reliable information [3].

1.2.1 International Classification of Diseases

One of the persistent requests from the rare disease community has been the need for appropriate classification of rare diseases in standard diagnostic coding resources available to the health care providers and reimbursement from third-party payers and national governments after establishing medical necessity. Dr. Ségolène Ayme of Orphanet chairs the Rare Diseases Technical Advisory Group for the World Health Organization's efforts to revise the International Classification of Diseases. Obtaining an appropriate ICD classification and coding will assist in determining the prevalence of rare diseases. However, the difficulty of obtaining the correct diagnosis may require several years of visits to practitioners, clinics, and hospitals. In many cases, coding of symptoms of a disease may continue until an agreed upon diagnosis is obtained. At the time of obtaining the correct diagnosis, clinicians need to have a diagnostic code to address the uniqueness of individual patients. The assignment of an appropriate code for rare diseases is also crucial if we are to monitor global health trends by the use of reliable statistical data [9].

1.3 Little or No Information Is Available About the Rare Disease or Condition

This is an accurate statement if made before the arrival of the Internet and World Wide Web or if people do not have ready access to the extensive collection of information now available. Even though there are significant sources of educational materials available to most people in the developed nations, lack of ready access to these resources remains a major need for millions of individuals and families in the developing nations around the world. Identifying methods to convey the increased body of literature available from groups such as the National Institutes of Health, the National Library of Medicine, the Office of Rare Diseases Research, the Genetic Alliance, National Organization for Rare Disorders (NORD), Eurordis, Orphanet, Office of Orphan Products Development (OOPD) at the United States Food and Drug Administration (FDA), European Medicines Agency (EMEA), patient organizations, industry, foundations, health care provider organizations, and other government sources around the world is key to increasing access to the ever-increasing, reliable and useful information developed by numerous sources. Extensive use of data sources is sought by the public. MEDLINE/PubMed, the NLM's database recorded almost a billion searches in FY 2008, with over a million users daily. The NLM indexes 5,319 biomedical journals for the MEDLINE/PubMed database to assist users in identifying articles on specific biomedical topics. A combination of staff, contractors, and cooperating USA and international institutions indexed 671,904 articles in FY 2008, bringing the total number of MEDLINE citations to over 15 million. Considerable information on rare diseases is readily available to those with access to the world wide web [4].

The most recent figures from the Genetic and Rare Disorder Information Center supported by the NIH/ORDR and NHGRI reveal that information has been made available for over 6,800 rare and genetic diseases to requests from 120 countries in their eight year history. Orphanet, located in France's INSERM, continues to provide useful and reliable information to the European Union member states and worldwide from multiple sources for over 5,600 different rare diseases.

New sources of useful information appear regularly from help-lines established by individual countries and organizations to supplement currently available information. Traditional sources of information continue to expand their information base as improved search engines enable the identification and collection of more information from many sources and are presented in a more systematic fashion to potential users. For some rare diseases, it is not a lack of information, but information overload that can be overwhelming to patients and their families. It is important with multiple sources presenting information to the patients or their families to remain aware that not all patients are capable of accepting and absorbing the same amount of information and at the same pace as others. Recognizing variability in perceptions of the disease and desire to learn more about a rare disease occurs at a different rate for everyone. Health care providers, family members, and friends have to be prepared to meet patients where they are or where they want to be intellectually

or psychologically with respect to their disease and not where others believe they should be.

Facilitating or guaranteeing access to useful information is a major step to enable patients to understand their disease better, to live with their disease, and to learn about the various aspects of their disease on their time schedule. When accomplished on their own schedule, it will improve the understanding and acceptance of the disease with or without available treatments.

Types of information generally recognized as significant for patients and health care providers fall into several major categories. These include but are not limited to the following:

(a) Information about the disease, expected cause of the disease, and prognosis,
(b) Inheritance capability,
(c) Available treatments approved by regulatory agencies or products in investigational status,
(d) Ongoing or planned research studies,
(e) Gaining access to knowledgeable health care providers or specialty clinics, and
(f) Availability of patient advocacy groups to prove real life experiences with a rare disease.

Lack of ready access to information frequently leads to other misperceptions.

1.4 Little or No Research Interest

Because there are so many disorders under the rare diseases umbrella, it is frequently felt there is little research interest in a particular disease. In many cases this is a reality. However, we are observing a continued emphasis on research of rare diseases. For example, the ClinicalTrials.gov database, developed and made available by the NIH National Library of Medicine and the US Food and Drug Administration, presents information on approximately 92,000 planned, ongoing and completed studies for rare and common diseases reported from more than 173 countries throughout the world. This database highlights completed, planned and ongoing phase 1, 2, 3, 4, longitudinal and behavioral studies. Starting in September of 2008, results from completed studies receiving support from the USA government and the pharmaceutical industry are required to provide the results in a timely fashion after the completion of the clinical studies [8].

Evidence exists that the research community will investigate special groups of rare diseases if priority is given by funding agencies. Research efforts have been known to follow research funds. As an example, 10 research consortia requiring multiple research sites and investigators received funds from five research NIH institutes when the Rare Diseases Clinical Research Network was first funded in 2003. In 2009, 19 consortia received support from the ORDR and seven of the research institutes of NIH (NINDS, NIAID, NICHD, NIDDK, NIDCR, NIAMS and NHLBI) [5].

The European Union (EU) through their Framework Programs 6 and 7 and through the General Directorate of Health and Consumers (DG SANCO) funded different types of networks such as fundamental research consortia, European Reference Networks (ERN), surveillance networks, and translational networks. On the other hand, Member States of the EU have funded at national level several consortia on rare diseases. It is important to mention the interesting experience of E-Rare, a consortium of national European agencies for funding rare diseases projects. E-Rare has funded in their two previous calls for proposals in 2007 and 2009, 13 and 16 different rare diseases consortia respectively. The significance of the benefit offered by multi-institutional collaborative efforts and an expanded role of the patient advocacy groups has gained acceptance as a model for research of rare diseases. This is a desirable method to gain access to a critical mass of research investigators and patients. Many investigators and organizations are working to direct their efforts to establishing common protocols which ultimately increase the scientific understanding of the disease and the pathophysiology of specific diseases and molecular pathways of many other disorders.

It is anticipated that the future expansion of these consortia and networks will compare favorably to the sophisticated research and treatment networks developed in oncology and infectious diseases, and other more common diseases such as arthritis, diabetes, HIV/AIDS, and hypertension.

NIH has recently redesigned their system for coding and monitoring selected diseases, including several rare diseases and orphan drugs. During this process of establishing the Research, Conditions, and Disease Categorization (RCDC), the coding system known as Computer Retrieval of Information on Scientific Projects (CRISP) has been replaced and results can now be found under RePORTER (http://projectreporter.nih.gov). This system provides ready access to information on basic and clinical research projects receiving support from NIH, FDA, HRSA and CDC. This information is often the starting point for developing a systematic research agenda by identifying ongoing research projects and helps individuals and organizations identify the missing gaps in research. In 2009, NIH is expected to provide nearly $644 million to support research for orphan drugs.

Many patient advocacy organizations have found that a useful mechanism to initiate research interest in their disease is to support research fellows who are seeking funds to support their continued research training. After receiving funding support, sufficient data can be gathered to support a grant application for an expanded research project that requires considerably more funds.

One observation from the experience gained with the focus on rare diseases is the relative lack of information from natural history studies of diseases. Knowledge from these studies is essential for the development or research hypotheses, identification of potential biomarkers, and phenotypic variations in patients. Due to the high costs of initiating and maintaining studies for many years, there has been a reluctance to support these studies. Only in recent years has the value of these studies been accepted by the research community as a generator of new research hypotheses and information for research and treatment for rare diseases.

1.5 Limited Access to Treatments for Rare Diseases

Even with the significant emphasis placed on rare diseases research and orphan products development by national governments, drug, biological and medical devices industries and foundations, adequate treatments for most rare diseases do not exist. This lack of treatment can be traced to numerous causes including high costs of research and development, the high risk of failure of most potential compounds to reach the marketplace, the large number of diseases, small patient populations for many rare diseases, better return on investment with other projects and different regulatory requirements around the world.

1.5.1 Gaining Access to Treatments and Investigational Products for Rare Diseases

With the rare disease community experiencing extreme difficulty in gaining access to the development of new chemical entities, other potential compounds could be identified by a global coordinated and systematic approach to the repurposing or repositioning of products approved for other rare or common conditions that might be useful for different rare diseases and conditions. To expand existing regulatory product approval processes, it would be necessary to develop research and regulatory pathways to identify potential new uses from astute clinical observations and a systematic review of the published literature. These processes would also be assisted by gaining access to chemical libraries and compounds not under development or not of further interest to the pharmaceutical industry. The transfer of compounds between the inventor and a company or between two companies is dependent upon successful completion of negotiations related to intellectual property and liability issues. This approach frequently requires an analysis of the current status of the compound and the completion of the necessary adequate studies that will meet the requirements of the regulatory agencies. Absence of information for regulatory approval will be identified as noticeable gaps of required data. To fill these gaps, collaborative efforts will require utilization of resources from the public and private sectors.

One method to identify potential compounds is the careful observation of clinicians providing care for patients with rare diseases. If improvement is observed in the condition of the patient while taking another compound, additional observation or analysis of data from an observational study of patients receiving similar treatment with the same compound may prove useful to confirm the preliminary clinical conclusion of the potential usefulness of the compound. Clinical trials may follow if clinical improvement is noticed in the patient.

Adopting this approach will require expanded efforts of the traditional pharmaceutical industry research and development activities. This process will also require a much broader approach to identify potential new uses for products other than existing indications for marketed products or products of little commercial interest.

The magnitude of this approach for over 6,500 rare diseases requires a globalization of efforts. It could entail a collaborative pooling of research and development assets with a sharing of research results and possible sharing of benefits to a number of potential commercial sponsors in emerging niche markets for specific rare diseases. In some respect this activity requires a re-visiting to the origins of the USA Orphan Drug Act looking at drugs of limited commercial value for the prevention, diagnosis and treatment of rare diseases and conditions not from a perspective of the 1970s but of the capabilities offered in the twenty-first century. These efforts could be assisted by more robust and powerful tools from information technology advances in searching large datasets over very short time periods.

1.5.2 Gaining Access to Experienced Rare Diseases Clinicians

The appropriate diagnosis of a particular rare disease may result after numerous visits to specialists at multiple locations. The difficulty in obtaining the correct diagnosis can be a frustrating and difficult experience for patients, their families and treating clinicians. For many patients, ending the diagnostic odyssey is an accomplishment and a relief to finally have a name for the constellation of symptoms that frequently leads to a separation and isolation from the traditional medical care systems. In a survey of patients with a rare disease, reported by the USA National Commission on Orphan Diseases (NCOD), fifteen percent of patients indicated it took more than five years to obtain the correct diagnosis. The NCOD patient study results also indicated that gaining access to appropriate care can be very difficult to obtain and adequate information and clinical expertise is often insufficient to meet the unmet needs of patients and their families.

Eurordis reported in 2006, the results of a survey of diagnostic delays for patients with eight diseases in 17 European countries (Crohn's Disease, Cystic Fibrosis, Duchenne Muscular Dystrophy, Ehlers-Danlos Syndrome, Marfan Syndrome, Prader-Willi Syndrome, Tuberous Sclerosis and Fragile X Syndrome). Between 5 and 30 years had elapsed between the appearances of the first symptom to obtaining the correct diagnosis for 25 percent of the patients. Twenty-five percent of the respondents traveled to a location outside of their home region to obtain the confirmatory diagnosis. A review of inquiries completed by the Genetic and Rare Diseases Information Center supported by the USA ORDR and NHGRI at NIH discovered six percent of inquires related to undiagnosed diseases [2].

After a diagnosis is obtained, patients and their families continue to search for specific information about their diseases. The quest for information about the cause, expected outcome, heritability, possible future manifestations, the availability of an investigational or approved treatments, learning how to live, cope and manage the condition over their lifespan is an important goal in the pursuit of information. Information on planned, ongoing, and completed research studies is considered essential. Recommendations from review committees in the USA and Europe have identified the need to identify knowledgeable clinicians and locations of research and treatment centers with expertise in their disease.

With approval by the High Level Group on Health Services and Care, the European Rare Diseases Task Force has defined general criteria. DG SANCO designates reference centers for rare diseases. Identifying these centers should increase public awareness of possible centers of treatment and research excellence. Many research centers have transformed into treatment centers of excellence as information is gained from research and translated into clinical care as a result of having access to relatively large patient populations. Research or treatment centers of excellence frequently are considered regional or even national referral centers. Many centers of excellence provide active genetic counseling services to help educate the patient, their families, and public and health professionals about the rare diseases in their center. These research centers of excellence frequently serve as the optimal training program for the new rare disease research investigator [1, 6].

Resistance to the identification of reference centers of excellence is often heard and may impede providing optimal care for many patients with rare diseases by not making information readily available to the patients in need of specialized treatments. There is recognition that due to current limitations on treatments, cures for most diseases are difficult to obtain. For many disorders, the development of treatments, an improvement in the quality of care of symptoms and in the quality of life remain the goals. The patient advocacy groups have played a major role in improving the care of patients with rare diseases as well as educating health care providers about optimal care of patients. In many cases, the patient advocacy groups, utilizing their experiences with patients and health care providers, are able to identify the most skillful and knowledgeable clinicians who are able to provide the best services for their patient community. Developing and providing this information to the rare diseases community indicates the need for increased collaboration of patient advocacy groups on a global basis. A major deficiency exists in identifying and addressing the needs of the many patients who do not receive benefits from the support of an organized effort for their diseases by active patient advocacy organizations.

1.6 Training of Rare Diseases Research Investigators

To address the needs of training the next generation of research investigators, traditional research and training funding mechanisms from government and industry are used to foster the development of young investigators deciding on career choices or experienced clinicians who are seeking a career change. Continued emphasis on the value of research emphasis on rare diseases needs to be provided to pre-doctoral students, postdoctoral trainees and physician scientists.

Many patient organizations have established a program priority to provide research support to younger investigators to establish a research interest of their disease and to develop results from smaller pilot studies that will prove useful in the competition for larger multiple year grants that provide more stable funding. Generating interest with a particular disease can lead to a very rewarding career as new information is discovered and shared with others.

Consortia in the Rare Diseases Clinical Research Network are supported by the ORDR and research institutes at NIH and require an active clinical research training component for new and usually younger investigators. In several of the research consortia the trainees have completed their research fellowships, moved to a different academic institution, and opened a new research site as part of the consortia.

The individual consortia are expected to offer a unique environment for clinical research in rare diseases for new investigators, post-doctoral or clinical fellows, junior faculty or established scientist investigators to re-direct their research careers to emphasize rare diseases research. Support from the academic institution or other outside organizations is allowed. The consortia are required to have two trainees in these positions at all times during the grant period. It is possible after the training period has been completed, the new rare diseases clinical research investigator assumes a position at a different institution and can join the consortia as a new research site as part of the anticipated expansion of the individual consortia. As mentioned previously, this has occurred and is an expected outcome of the research plan.

1.7 Conclusions

To replace many of the perceived myths with realities, several global efforts are required if we are going to sustain and increase the reported progress with the thousands of rare diseases.

The first is the identification and expansion of worldwide partnerships and collaborations of Patient Advocacy Groups (PAGs) for individual rare diseases and umbrella organizations representing numerous PAGs such as NORD, Eurordis, Genetic Alliance, Eurordis, New Zealand Organization for Rare Disorders, Korean Organization for Rare Diseases, Japan Patients' Association, Taiwan Foundation for Rare Disorders, Canadian Organization for Rare Disorders, the Geiser Foundation and many others. Improving communication among the PAG will also eliminate the feelings of isolation, loneliness or stigmatization that are reported by patients around the world. Knowing there are others with the same condition and connecting these individuals regardless of language barriers is often helpful to learn to live with a rare disease and maximize the quality of the life of the individual and their families and friends.

The next requirement is to develop a global research infrastructure of qualified investigators to stimulate and coordinate research efforts by seeking ways to provide access to clinical trials at multi-national research sites with common protocols and multi-disciplinary research teams. Several rare diseases organizations have discovered the value of encouraging these global interactions such as the Treat-NMD Network, Prader-Willi Syndrome Association and Progeria Research Foundation. Many excellent research teams exist in individual countries. Expansion into global research networks will improve recruitment of patients into studies and increase the number of patients in research studies. The end result is increased access for all patients to clinical trials and the facilitation of the speedy completion of clinical trials.

To provide easy access to useful and reliable information for patients, families, health care providers and the public is the goal of many government and non-government organizations. The development and dissemination of information through information centers, help lines, clearinghouses, government organizations, individual PAG, multi-disease organizations and the industry is a costly, but very helpful, process in terms of time, personnel and financial support. Excellent sources are readily available and provide information on a regular and updated basis, including NIH's National Library of Medicine, the Genetic and Rare Diseases Information Center, Orphanet, NORD, Eurordis, Genetic Alliance, National Center for Rare Diseases in Italy, Information Center for Rare Diseases and Orphan Drugs in Bulgaria (ICRDOD), and many other help lines in numerous countries. To avoid duplication of effort, organizations are encouraged to seek these existing sources of information and determine the usefulness of available information for their constituent members and then identify and fill in the missing gaps of information for their constituents. It is desirable to have the consolidation of information sources to ease the burden of the rare diseases community in their pursuit of information about their diseases.

Gaining access to research investigational protocols frequently leads to an improvement in the quality of care available to patients from knowledge and experiences gained by the clinic staff treating many patients with rare diseases in the study protocol. Improving communication and best practices information available between a referring physician and a rare disease specialist will increase the spread of best-care information to the local treatment facility or practitioner. It will also increase the likelihood of patients gaining access to approved treatments shortly after approval by regulatory agencies.

Providing ready access to the practitioners knowledgeable about a particular rare disease and ongoing or planned research projects will help the patients, their families and practitioners gain a better understanding of their rare disease. By removing the existing misperceptions, patients and their families can adopt a realistic approach to the treatment of a rare disease that is based on the hope that others do care about their disease. Many scientists, government, private sector, and patient organizations, foundations and the pharmaceutical, biotechnology, and medical devise industries are committed to research discoveries that will be useful in the care of patients with rare diseases over their lifespan. Evidence from well constructed epidemiological studies will provide the evidence that point to the value of additional clinical studies to increase the understanding of rare disease.

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Part II
Methods and Approaches

Chapter 2
Rare Diseases Epidemiology Research

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Abstract Rare Diseases Epidemiology is a novel action field still largely unexplored. However, Rare Diseases is a topic of growing interest at world level. The aims of this chapter are to revise useful epidemiological tools and define areas where epidemiology can help improve the rare disease knowledge, and facilitate policy decisions taking into account the real burden of rare diseases in society. This chapter also seeks to describe: the problems of coding and classification of diseases, measuring disease frequency, the study designs and association studies, the causality, the evolution from descriptive to epigenetic epidemiology and the natural history of disease. One of the major challenges facing analytical epidemiology and clinical epidemiological research into rare diseases is that genes can be involved in both aetiology and prognosis. Despite the many similarities between genetic association studies and classic observational epidemiological studies, the former pose several specific limitations, including an unprecedented volume of new data and the likelihood of very small individual effects, as well other limitations. Selecting the appropriate pathway from among all those available, i.e. the one that best relates genes from the various known regions and disease mechanisms, is crucial for the success of this type of studies

Keywords Genetic epidemiology · Analytical epidemiology · Environmental epidemiology · Hypotheses generation · Epidemiological methods · Risk factors · Epigenetic

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2.1 Introduction

Rare Diseases Epidemiology is a novel action field still largely unexplored. However, Rare Diseases is a topic of growing interest at world level and several countries and stakeholders [13, 15, 33] are joining efforts to develop national rare diseases health plans [19], improving the promotion of international and coordinated research projects on rare diseases, facilitating harmonized orphan drugs regulations, and taking into considerations some other important aspects such as social, education and patients empowerment [9]. In addition, the importance of rare diseases *epidemiology* has been highlighted in some European documents [29, 55] but a conceptual framework of its potential to fill important knowledge gaps have not still been fully described. The main topics of this chapter are to revise useful epidemiological tools and define areas where epidemiology can help improve the rare disease knowledge, and facilitate policy decisions taking into account the real burden of rare diseases in society.

Epidemiology is a science usually defined as "the study of the distribution, determinants and control of health related states and events in populations" [39]. The ultimate goal of epidemiological research is to use the inferential method to improve the health status and quality of life of a target population, defined as the population to which the study results are sought to be applied. Nevertheless, to ensure that useful results are applied it is necessary to focus on a specific population, defined as a group of subjects included in a specific study, and it is clear that this study population will be made up of individuals or "study subjects", who will be the ones providing the requisite social, personal, clinical, biological and molecular information. However, the task of epidemiology is to test the validity of hypotheses, with a view to the interests of the population as a whole. To do so, study subjects should have similar characteristics to the target population from which they are drawn, and it is only then that inferences for the same type of person living in whatever other similar place, time period and socio-economic circumstance may be valid. In summary, the epidemiology is interested in the health status of the population as a whole, studying the dynamic of the disease in that particular population and covering, when possible, the determinants of its occurrence and evolution. Individuals and families are also under the scope of the epidemiology because the knowledge gained have to be applied in many situations at the subject level [52].

Epidemiological research relies on simple methods to achieve its aims. It seeks to: (1) describe health status by measuring disease frequency, distribution and trends; (2) to know *who* becomes ill, *what* are the specific characteristics of cases, *where* and *when* these cases occur; (3) explain disease aetiology; and (4) control the spread of specific diseases and their effects, by setting up preventive measures, improving prognosis and/or quality of life, and reducing mortality and any other devastating complications. Most of these goals would appear to be shared by clinicians, and even by basic scientists, yet, while epidemiologists invariably have their sights trained on the target population, clinicians' and basic scientists' focus is on individual health and disease mechanisms respectively [43]. Fortunately,

these ostensible barriers are fast disappearing because any attempt to understand the complex world of rare diseases specifically requires an interdisciplinary approach.

Medical research has been changing its traditional paradigms from a physiopathological interpretation, in which only clearly explained facts about mechanisms can justify the clinical outcomes observed, towards evidence-based medicine, in which final results obtained after unimpeachable methods are accepted as scientific evidence despite the fact that not all the mechanisms might be fully explained (evidence-based medicine also takes into account the importance of physiopathological knowledge based on the concept of biological plausibility. For more details, see chapter 3). Lastly, modern medicine is focusing on the concept of personalised medicine, whereby each patient would be able to receive appropriate individual treatment based on his/her personal genetic and metabolic background. Rare diseases are currently becoming targets for this latest paradigm, owing to the view that individual susceptibility might now be well explained by the subject's genetic background, whether mono- or polygenic, and epigenetic changes. Based on this paradigm, a massive increase in new scientific data, generated mainly by different types of novel high-throughput technologies, is resulting in a great amount of traditional phenotypes being split into different diseases, on the understanding that these would have different risk factors, different risk prognoses or, at the very least, different inherited mechanisms [47].

Predicated on the greatest respect for these new advances and personalised-medicine criteria, epidemiology has to play its role in rare disease research by finding solutions to the lack of descriptive knowledge and proposing methods for analysing risk and prognostic factors, drug efficacy and efficiency, and social modifiers of disease. Without this type of knowledge, prevention would not -apart from some sporadic exceptions- be achievable. As the EC Council Recommendations state, "Because of their low prevalence, their specificity and the high total number of people affected, rare diseases *call for* a global approach based on special and combined efforts to prevent significant morbidity or avoidable premature mortality, and to improve the quality of life and socio-economic potential of affected persons" [11].

2.2 Coding and Classification

One of the main problems facing health care planning in the case of rare diseases is that, due to misclassification and lack of appropriate coding, the burden of most of these diseases remains invisible to the health system [10]. The international reference for classification of diseases and conditions is the International Classification of Diseases (ICD), a system co-ordinated by the World Health Organisation (WHO) [67]. However, not only are the 9th and 10th revisions of the ICD (ICD-9 and ICD-10) being simultaneously used in several countries around the world, but the same ICD version is not always used by all health information systems in a given country.

According to the Orphanet database, fewer than 300 specific rare diseases can be identified with a single ICD-10 code [50]. In our experience, this figure could rise as high as 1000 if rare disease groups are considered. At present, other rare disease classifications as well as catalogs are being used by different medical information systems, such as the Systematized Nomenclature of Medicine (SNOMED) [56], Online Mendelian Inheritance in Man (OMIM) [47], Medical Subject Headings (MESH) [46] and the Orphanet's own internal codes [49], among others. An appropriate classification and coding system that covered all rare diseases and afforded adequate codes and valid traceable mechanisms, among some other advantages, would facilitate proper recognition of such diseases by national healthcare and reimbursement systems, enable implementation of harmonised disease surveillance systems and promote well-conducted epidemiological studies. Such a system is thus urgently needed.

In 2007, the World Health Organisation (WHO) launched the process of revising the ICD-10, in order to adopt the new (11th) version of this classification at the World Health Assembly to be held in 2014 [65]. As Chair of the Topic Advisory Group on Rare Diseases, the WHO has appointed the Chair of the EU Rare Diseases Task Force [50] for the purpose of contributing to this revision process by putting forward proposals for the coding and classification of rare diseases. While this advisory group goes about tackling this extremely complicated process, several experts have already been working on the topic and a number of proposed rare disease lists, based on the WHO's current large group of diseases, are under discussion. It would be advisable for some updated version of the ICD-10 to be released soon to act as a bridge between the current ICD-10 and the future ICD-11 projected for 2014.

2.3 Definition of Prevalence, a Crucial Estimator in Rare Diseases

The European Union (EU) deems diseases to be rare when they affect "not more than 5 in 10,000 persons" (e.g., the EU population should be considered for Europe as a whole) [9]. The same definition was adopted by the European Medicines Agency (EMEA) in its European Orphan Drugs Regulation [20]. Yet in its definition, this regulation considers, not only the rareness, but also the severity and chronically debilitating or life-threatening nature of the disease. Moreover, the definition is not universal since: other countries use different prevalence cut-off points (e.g., 4 per 10,000 in Japan); and the USA, which was the first country to establish policies in favour of such diseases, defines a rare disease as one that affects fewer than 200,000 patients nationwide.

The real origin of this limit – at least in Europe – was the definition of a threshold below which investing in new drug research was not profitable, in terms of cost-benefit, for the industry. Whichever threshold is used, however, the ultimate goal is the same, i.e., to increase investment in rare diseases by public and private organisations, and to enhance the social awareness and visibility of these diseases in an effort

to ameliorate most of the difficulties and constraints affecting the lives of patients and their families.

Nevertheless, for the purposes of this article, the real interest lies in how the concept of prevalence should be used in a definition of a rare disease.

Prevalence is one of most popular epidemiological measures and is defined as the probability that an individual in a population will be a case at time *t* [30, 38, 53]. Generally speaking, the target population for this measure should be the population at risk but, owing to the difficulty of ascertaining the latter, the general population is regularly used as the denominator. Indeed, another more practical definition of prevalence is the proportion of the population that has any given disease at some specific point in time – usually called *point prevalence*. A second prevalence measure is the *period prevalence*, which is the probability that an individual in a population will be a case anytime during a given period of duration (Table 2.1). It is usually used when the exact time of onset for individual cases is not known [38].

Although rare diseases affect all age groups, most cases are identified at birth or at an early age. In such a case, some adaptation of the definition of prevalence is needed because, whereas the official definition only refers to fewer than 5 cases per 10,000 inhabitants in the EU, most prevalence figures currently available in the literature refer to so-called prevalence at birth [2, 32, 42], a term that is not always uniformly applied. At all events, time should always be well defined, since "days after birth", "first year of life" or any other term is bound to yield different results and give rise to different types of bias. There is no real follow-up of these patients, and so to estimate the prevalence of a given disease at some other point in time, the disease case-fatality rate should be taken into account in cases where prevalence at birth is used as the epidemiological measure. The same methodological problems can arise whether one wishes to estimate prevalence of diseases affecting only one gender (generally males, as some inherited diseases are linked to the X chromosome), diseases restricted to certain age strata, diseases affecting some specific ethnic group, or diseases delimited to some specific geographical region. In all such situations, the prevalence measure used should be clearly defined and the population used as denominator, clearly stated [21].

There are few rare disease prevalence studies and those existing are mainly focused on congenital anomalies [16]. The reason is that they are costly and their utility is limited to ascertaining health status at one point in time and in one place, drawing up health plans and/or making disease-burden estimates; and, insofar as research is concerned, their utility is not even as well acknowledged. Nevertheless, ORPHANET, the European database on rare diseases, has published an update report which shows prevalence and incidence figures or simply absolute number of cases/family for several hundred of rare diseases [48]. Though based on a broader review of the literature, this study provides only general descriptions about methods used but it is extremely useful as preliminary information in that it affords an initial idea of several rare disease prevalence figures. Moreover, it is a good source of information for drawing inferences about the absence of reliable data, the low consistency of different data sources, and the poor methodological quality of many of the existing epidemiological studies.

Table 2.1 Main measures of disease frequency[a]

Frequency	Formula	Meaning
Incidence rate or incidence density	I=Number of new cases during the period t_0–t PT= Amount of person-time included in the population under surveillance $\hat{ID}_{(t_0,t)} = {\mathrm{I}}/{\mathrm{PT}}$	The incidence rate is the number of new cases per unit of person-time at risk
Cumulative incidence	I= Number of new cases during the period t_0–t N_0 = Number of disease-free subjects at t_0 R= Risk at t_0 $\hat{R}_{(t_0,t)} = \hat{CI}_{(t_0,t)} = {\mathrm{I}}/{N_0}$	Proportion of people who become diseased during a specified period of time. CI provides an estimate of the probability, or risk, that an individual will develop a disease during a specified period of time
Period prevalence	$C_{(t_0,t)}$ = Number of cases that have the diseases between the period t_0–t N = Population size at the same time period C_0 = Number of cases that have the diseases at time 0 $\hat{PP}_{(t_0,t)} = {C_{(t_0,t)}}/{N} = {(C_0 + I)}/{N}$ I= Number of new cases during the period t_0–t	Quantifies the proportion of individuals in a stable population who have the disease during a specific period of time
Point prevalence	Point prevalence calculation is the same but referred only at time t $\hat{P}_t = {C_t}/{N_t}$	Quantifies the proportion of individuals in a population who have the disease at specific time
Lifetime prevalence	Calculation is the same at point prevalence $\hat{P}_t = {C_t}/{N_t}$	Retrospective measure that account for current cases and also for all cases previously occurred (already cured and in remission)

Table 2.1 (continued)

Frequency	Formula	Meaning
Birth prevalence rate	LB = Livebirth FD = Fetal deaths SB = Stillbirths BPR = No cases (LB+FD) / No births (LB+SB)	The prevalence of a specific disorder in a geographic area, among children of a specific age who were born in that geographic area, within a specified time interval (for more details see the chapter 20)
Mortality rate or mortality density	D_x = Number of new cases death having the diseases × during the period $t_0 - t$ PT= Amount of person-time included in the population under surveillance $\hat{MD}_{(t_0,t)} = D_x/PT$	Mortality rate refers mortality due to disease × in the total of population
Case fatality rate	$\text{CFR} = \frac{\text{number of deaths from a disease}}{\text{number of cases of that disease}} \times 100$	Proportion of the number of deaths caused by a specified disease to the number of diagnosed cases of that disease, during the period of observation

[a] Adapted from Kleinbaum et al. [38].

2.4 Measuring Disease Frequency

Incidence is the most important measure in epidemiology because it takes into account the time when a new disease or a new case of a known disease occurs among members of a population and thus captures the dynamic of the disease in a particular population. Incidence is expressed as the incidence rate, which provides a measure of the occurrence of new disease cases per person-time unit [30, 38, 53]. There is also another incidence measure, namely, the incidence proportion, which gives the proportion of the population that develops the disease during a specific period of time. This second measure is sometimes also known as "cumulative incidence" or risk and is, in some way, reminiscent of prevalence, inasmuch as both measures account for sick persons per unit of time [38]. However, while the former accounts for newly diagnosed cases during a specified period, without any consideration to whether they remain or not alive, prevalence accounts for cases alive at a specific point in time, independently of the moment of diagnosis. With regard to incidence rates, when the person-time unit refers to one year (e.g., for the purpose of estimating the incidence of a specific disease in a given year), the denominator is the number of persons under surveillance multiplied by one (i.e., 1 year), which is ultimately equal to the number of persons under surveillance. If the population is stable, the disease is not frequent and there are not loses or unrelated deaths, the incidence rate per year is equal to cumulative incidence. Generally, the cumulative incidence estimates only the first occurrence of the disease and the populations consists of disease-free subjects at the beginning of the study period. Conversely, when the incidence rate is used in a non-stable population, denominator is estimated at the middle of the study period [38].

In view of the recent debate as to whether a rare disease definition should be based on cumulative incidence or prevalence, it is important to be conversant with the difference between the two. Incidence is informative because it accounts for the real number of cases occurring per person-time unit. In addition, it may prove useful for measuring disease occurrence and differences across time and space. Prevalence, on the other hand, only accounts for cases alive at a defined place and time. What then is the real difference between these two measures? Mathematically, the equation that links these two estimates is as follows:

$$\text{Prevalence proportion} = \text{Incidence rate} \times \text{Duration of the disease}$$

This equation is not always applicable because it requires that the population remain stable, i.e., that population size is not being overly affected by the migration rate and disease-sufferers are not moving elsewhere to receive treatment or for other socio-economic reasons. In addition, estimates of disease duration are always an average of real duration, which in turn depends on a number of other variables, such as individual and socio-economic factors and the quality of health care provided. Similarly, incidence must be stable throughout the study period. Despite the simplicity of the equation, robust methods and initial good-quality data are nevertheless needed to obtain accurate results in cases where these are to be used for epidemiological estimates [14].

Accordingly, what is the true applicability of prevalence as a measure? Prevalence is more informative for health planning and estimating disease burden, yet incidence is a faithful reflection of the occurrence of a disease. Moreover, the case fatality rate (number of deaths divided by total patients per time unit) and survival rate are measures that complement incidence and prevalence (Table 2.1).

If incidence is the preferred choice to study the occurrence of a disease in epidemiology, then why has incidence not been adopted for the purpose of defining rare diseases?. In point of fact, rare cancers *are* measured in terms of incidence rather than prevalence because most of them display high mortality rates and, by extension, low prevalences. A further reason for using incidence in cancer research is that, where an individual is affected by and has been treated for a rare cancer, and is still alive three to five years after therapy, it is not that easy to ascertain whether such a person constitutes a real case for a prevalence estimate or should be regarded as not yet being a patient, i.e., as being already cured or only in a subclinical situation [51]. The same problem arises in certain congenital anomalies which can be corrected by surgery: these are both incident and prevalent cases until such a time as the corrective intervention is performed, i.e., rare congenital hearth defects. If both situations were to occur in the same study period, then this would be an incident case and could not be a prevalent case for that time unit.

The reason of defining rare diseases in terms of their prevalence is related with the fact that policy makers are conscious of the cost of estimate incidence. Prevalence studies are less expensive since, as a rule, prevalence is measured regularly in cross-sectional studies and the ensuing results are used for a long time. Incidence studies, in contrast, require a medium-or long-term follow-up study using the same population, with new cases and new episodes of the same condition being monitored by means of perfect surveillance of the target population. Some exceptions to this general rule are the congenital anomalies that some of them can be clearly detected at born [2, 18]. In addition, though rare diseases have been defined in terms of their low prevalence, most of them also have a low incidence. Moreover, in the case of rare diseases, survival could be largely improved; hence, it is likely that, if the prevalence criterion were still used, some specific rare diseases might lose their "rare" status in the near future.

In the following example, some measures of frequency, or same, such as mortality rates in two European countries and hospital burden for the rare disease group in many countries are shown, in order to demonstrate the way in which existing information can still be useful for epidemiological purposes. This is best way to generate hypotheses as to explain any differences observed (Fig. 2.1, Table 2.2).

2.4.1 Mortality Measures Related to Early Life

Paediatric ages display higher frequencies of rare diseases and thus the main epidemiological estimates must be suitably adjusted to their corresponding estimated time period. Mortality rates at these ages can be divided into the following age strata: stillbirth or foetal death rate (20–28 weeks gestation or more); perinatal mortality

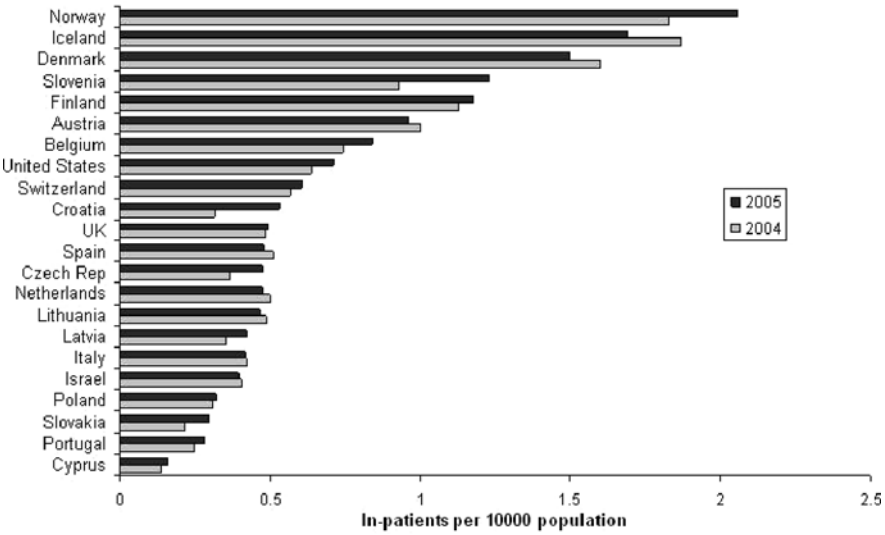


Fig. 2.1 Polyarteritis nodosa and allied conditions admission by countries

rate (foetal and deaths up to 7 days of life); neonatal mortality rate (under 28 days); post-neonatal mortality rate (28 days to 1 year); infantile mortality rate (up to 1 year); and child death rate (ages 1–4 years). Denominators in all these cases are the corresponding risk populations [64]. Rare diseases in general, and some congenital anomalies and severe metabolic diseases in particular, register a range of early mortality. Hence, some of these estimates should be considered if more is to be learnt about the natural history of these diseases, their true disease burden, appropriately adjusted incidence and case-fatality rates.

2.4.2 Other Health Status Measures

Life expectancy is the average number of years that an individual of a given age is expected to live, if current mortality rates remain unchanged. Premature mortality is measured by Years of Potential Life Lost (YPLL), by reference to the number of years between a subject's age of death and his/her corresponding life expectancy. It is a real measure of years of life lost and is also related to mortality incidence rates (Fig. 2.2). In fact, it is a numerical measure that only reports the difference between age at death and the supposed age when death should have been occurred if no competitive cause of death had interfered. However, measures that gauge how years are lived are becoming increasingly popular because years of life can be lived in disability ranging from moderate to severe, and quality, which is a personal choice, can lend greater interest to enjoying quality of life for some years even though the same level of disability is present. It is for this reason that two other measures closely

Table 2.2 Polyarteritis nodosa and allied conditions admission per 10,000 of all in-patients admissions

					Min–max	
Country	ICD version	Period	Min	Max	2003–2006	
Australia[a]	ICD-10	1999–2008	2.28	2.62	2.38	2.45
Austria[b]	ICD-10	2001–2007	3.36	3.73	3.45	3.73
Belgium[b]	ICD-9	2003–2007	4.17	4.86	4.3	4.86
Croatia[b]	ICD-10	2002–2006	2.44	4.09	2.44	4.09
Cyprus[b]	ICD-10	2002–2007	0.59	2.39	0.59	2.39
Czech Republic[b]	ICD-10	2000–2007	1.01	2.75	1.19	2.13
Denmark[b]	ICD-10	2003–2006	8.23	9.21	8.23	9.21
Finland[b]	ICD-10	2002–2007	4.63	6.61	4.63	5.85
Iceland[b]	ICD-10	2000–2006	6.45	15.27	8.2	11.61
Israel[b]	ICD-9	1999–2007	2.2	2.93	2.22	2.62
Italy[b]	ICD-9	2002–2006	2.57	2.91	2.57	2.91
Latvia[b]	ICD-10	2004–2008	1.63	2.55	–	–
Lithuania[b]	ICD-10	2001–2008	1.45	2.37	1.45	2.15
Luxembourg[b]	ICD-10	2007	2.09		–	–
Netherlands[b]	ICD-9	2004–2005	4.57	4.92	–	–
Norway[b]	ICD-10	2002–2007	8.00	9.54	8.00	9.54
Poland[b]	ICD-10	2003–2007	1.66	3.03	1.66	2.68
Portugal[b]	ICD-9	2004–2005	3.00	3.43	–	–
Slovakia[b]	ICD-10	2002–2007	1.05	1.59	1.22	1.59
Slovenia[b]	ICD-10	2004–2007	5.15	8.00	–	–
Spain[b]	ICD-9	2000–2005	5.39	6.22	–	–
Switzerland[b]	ICD-10	2002–2005	3.31	3.73	–	–
United Kingdom[b]	ICD-10	2000–2007	3.52	3.98	3.55	3.75
United States[c]	ICD-9	1996–2006	4.23	5.35	4.23	5.35

[a]National hospital morbidity database (NHMD). Australian Institute of Health and Welfare. http://www.aihw.gov.au/hospitals/nhm_database.cfm

[b]European countries: European Hospital Morbidity Database. World Health Organization Regional Office for Europe. Last updated: AUGUST 2009. http://data.euro.who.int/hmdb/index.php

[c]National Hospital Discharge Survey. CDC. http://www.hcup-us.ahrq.gov/databases.jsp & http://www.cdc.gov/nchs/surveys.htm

(–) Not available data.

associated with YPLL, namely, disability-adjusted life year (DALY) [45], a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health, and quality-adjusted life year (QALY) [59], based on the number of quality years of life that would be added by an intervention, were standardised and are widely used in the literature. The former is associated with estimated disease burden and the latter is a useful additional tool for evaluating new treatments and/or new modern health technologies prior to their inclusion in health care delivery systems (the use of this measure is more fully discussed in chapter 16).

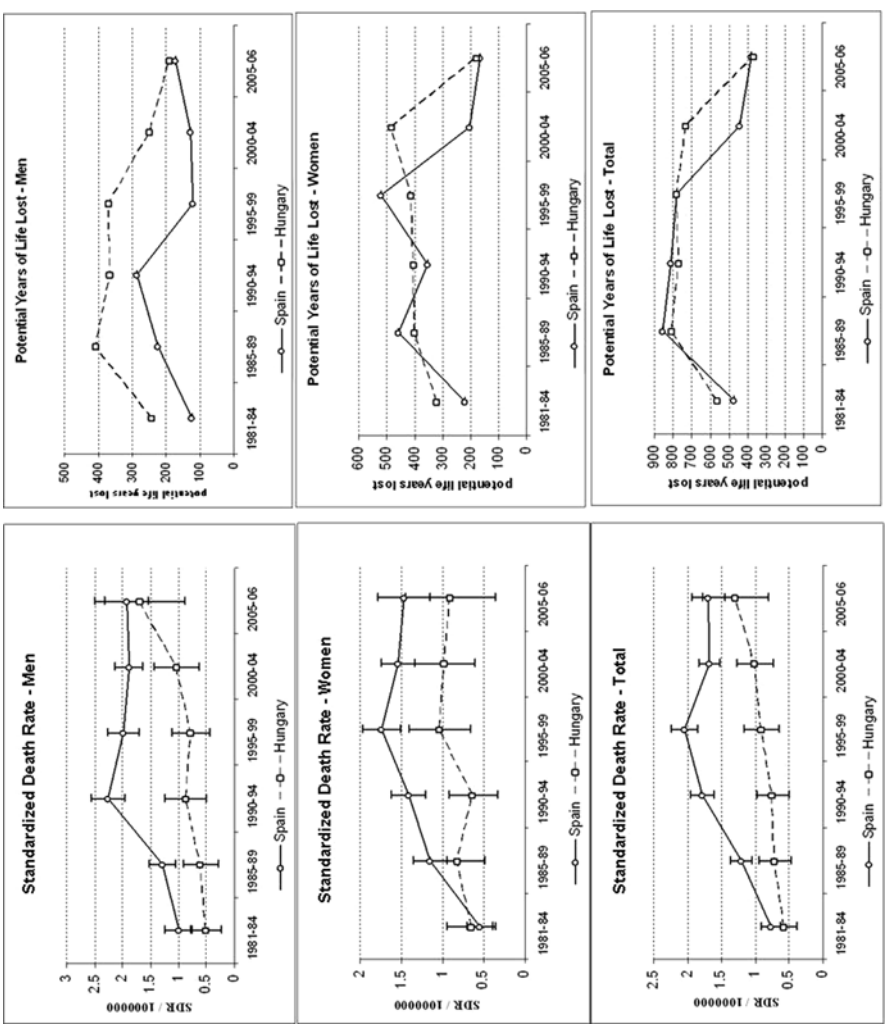


Fig. 2.2 Polyarteritis nodosa and allied conditions: Standardized Death Rate adjusted by the European reference population (*left*) and Potential Years of Life Lost (*right*), in Spain and Hungary

2.5 Study Designs and Association Measures

2.5.1 The CONSORT – STROBE – STREGA Triangle: Epidemiological Quality-Study Reporting Guidelines

The clinical trial has been traditionally considered to be the most challenging type of clinical study because its main goal is to prove the efficacy and detect the undesirable side-effects of a new treatment. Consequently, it was the first study design to be made subject to strict scientific rules and regulations under national and international law. Methods for improving clinical trials have become one of the key issues in clinical epidemiological research, and one of the latest examples of this are the criteria drawn up by the CONnsolidated Standards Of Reporting Trials (CONSORT) Group [3, 7, 44] (clinical trial designs and analyses applied to rare disease research are more fully discussed in chapter 11).

Observational studies have also undergone in-depth methodological analysis, and discussions on their weaknesses and strengths have likewise been debated for years. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) is one of the latest initiatives geared to drawing up recommendations on what should be included in an accurate and complete report of an observational study [58, 60]. It initially restricts the scope of the recommendations to "the three main analytical designs that are used in observational research", namely, cohort, case-control and cross-sectional studies. The STROBE recommendations should not be regarded as regulating style or terminology. Authors are encouraged to use narrative elements, including the description of illustrative cases, to complement the essential information about their study, and to make their articles an interesting read. This guideline was developed by means of an open process, taking into account the experience gained from previous initiatives, CONSORT in particular. These study designs have their respective association and impact measures and they must be appropriately used (Table 2.3).

Like research into high-frequency diseases, rare disease research also uses epidemiological observational studies, and the quality of methods to be applied to rare diseases should be equal to high prevalence diseases in any way. In some circumstances, however, limits become evident when all guideline points are sought to be applied to rare diseases. The problems -among others- of sufficient sample size, an appropriate control group, lack of long-term case follow-up in cohort studies, cluster presentation of cases (generally in familial aggregates) and scarce and biased information are difficulties that must be taken into account and remedied if rare disease research results are to be improved.

One of the major challenges facing analytical epidemiology and clinical epidemiological research into rare diseases is that genes can be involved in both aetiology and prognosis. Despite the many similarities between genetic association studies and classic observational epidemiological studies, the former pose several specific challenges, including an unprecedented volume of new data [4, 12] and the likelihood of very small individual effects (Table 2.4). Genes may operate in complex

Table 2.3 Measures of association and potential impact

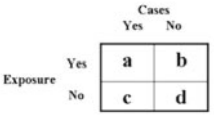
Potential impact	Formula	Meaning
Incidence density ration or rate ratio	I = Number of new cases in population i and population 0 PT= Number of person-time in populations i and population 0 $I\hat{D}R_i = I\hat{D}_i \Big/ I\hat{D}_{t_0} = \dfrac{I_i / PT_i}{I_0 / PT_0}$	Rate Ratio is ratio comparison between two rates from two different populations. In general the numerator is the population exposure and the population 0 is the reference population
Incidence density difference	See above for symbols meaning $I\hat{D}D_i = I\hat{D}_i - I\hat{D}_0 = \left(I_i / PT_i\right) - \left(I_0 / PT_0\right)$	This measure provides information about the aboslute risk size
Risk ratio	See Cumulative Incidence in Table 2.1 $R\hat{R}_i = \hat{R}_i \Big/ \hat{R}_0 = C\hat{I}R_i = \hat{C}I_i \Big/ \hat{C}I_0 = \dfrac{I_i / N_i}{I_0 / N_0}$	Risk Ratio is a ratio comparison between Cumulative incidences from two different populations
Standardized incidence/morbidity ratio	$SIR = \dfrac{\text{observed cases (O)}}{\text{expected cases (E)}}$ x 100%	Ratio of the observed number of cases to the expected number
Odds ratio	 **OR = a*d / b*c**	The odds of exposure group people of being a case with regard the non-exposure group
Prevalence ratio	P_i = Prevalence of cases in the exposure group P_o = Prevalence of cases in the reference group $PR = P_i / P_o$	How often is more probable of being a case among exposure group regarding the non-exposure group in a cross-sectional study
Mortality density ratio	D_x = Number of new cases death having the diseases x during the period $t_0 - t$ in two different populations PT= Amount of person-time inlcuded in the two populations under surveillance	Mortality Density Ratio is ratio comparison between two mortality rates from two different populations. In general the numerator is the
	$M\hat{D}R_i = M\hat{D}_i \Big/ M\hat{D}_{t_0} = \dfrac{D_{xi} / PT_i}{D_{x0} / PT_0}$	population exposure and the population 0 is the reference population

Table 2.3 (continued)

Standardized mortality ratio	$SMR = \frac{\text{observed deaths (O)}}{\text{expected deaths (E)}} \text{ x } 100\%$	Ratio of the observed number of deaths to the expected number
Proportional mortality ratio	$PMR = \frac{\text{observed deaths from specified cause (O)}}{\text{expected deaths from specified cause (E)}} \text{ x } 100$	Proportion of the number of deaths attributed to a specific cause and the total number of deaths, expressed in percentages
Survival rate	$S(t) = 1 - F(t) \quad \lambda(t) = \frac{f(t)}{1 - F(t)}$ λ(t) is the hazard rate or hazard function, f(t) is density and F(t) is the distribution function	Percentage of people in a study or treatment group who are alive for a certain period of time after they were diagnosed with or treated for a disease
Population attributable fraction or attributable risk	P= Exposure prevalence among cases RR= Relative Risk (it can also be replaced by the OR) PAF = P*(1-(1/RR))	Proportion of cases that could been prevented if the exposure was withdrawn

Adapted from Kleinbaum et al. [38].

pathways with gene-environment and gene-gene interactions and also with the epigenetic mechanisms playing some important role. The STrengthening the REporting of Genetic Association studies (STREGA) [40, 61] initiative builds on the STROBE statement and provides additions to items on the STROBE checklist which address genetic epidemiology study design: The additions concern population stratification, genotyping errors, modelling haplotype variation, Hardy-Weinberg equilibrium, replication, selection of participants, rationale for choice of genes and variants, treatment effects in studying quantitative traits, statistical methods, relatedness, reporting of descriptive and outcome data, and the volume of data issues that are important to consider in genetic association studies [35].

2.5.2 Cluster Analysis

A cluster is defined as an aggregation of relatively uncommon events or diseases in space and/or time in amounts that are believed or perceived to be greater than could be expected by chance [8]. The term is usually restricted to describe an aggregation of cases of rare and non-infectious diseases. In general terms, underlying this

Table 2.4 Main study designs in epidemiology

Study designs in general epidemiology	Study designs applied in genetic epidemiology
Descriptive studies	*Descriptive studies*
Case report and case series	Case report and case-only
Cross-sectional	Familial aggregation and segregation analysis
Analytical studies	Cross-sectional
Case-control	*Analytical studies*
Cohort studies	Family based
Retrospective cohorts	Case families (Extended families and relatives)
Prospective cohorts	Case-control families (population based case-control and their relatives)
Nested case-control studies	Twin families
Case cohort studies	Adopted child and parents/relatives
Intervention studies	Case-parent triads
Population-based interventions	Single-marker tests
Randomized controlled clinical trials (several variants)[a]	Multi-SNP markers
Parallel group designs	Population based
Adaptive sampling designs	Case-Case
Sequential designs	Case-control
Crossover clinical trial designs	Cohort
N-of-1 trials	
Factorial designs (several treatments)	

[a]Gerß and Köpcke (For more details, see chapter 11).

concept is the suspicion of an unusual environmental exposure affecting some susceptible part of the target population. This is specifically important in the analysis of rare congenital malformations, and methods for conducting such analysis have been widely described by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) [2, 17, 68]. A comprehensive list of protocols and guidelines is provided on the organisation's website [8, 63]. However, cluster analysis methods are by no means confined to congenital malformation studies: they may be applied to any aetiological study into rare diseases that show a temporal and/or geographical aggregation of cases. Although rare diseases are invariably found in some types of cluster, such as familial aggregations, family relationships are not always clear at the beginning of the study, while familial aggregations do not necessarily indicate a genetic origin. Most rare diseases are widely disseminated around the world and are probably not recognised as clusters because their risk factors are also widely distributed and the size of the susceptible population is small in comparison with the population as a whole. On other occasions, lack of communication among research teams or the belief that some preconceived, specific -though as yet undiscovered- factor is the cause of the cluster being studied prevents a connection being made with similar cases occurring in other places and time frames. Facilitating such communication would yield major benefits for rare disease research. Opening the doors to these possibilities and using cluster analysis methods could be extremely useful for some rare disease research and should therefore be included among the tools used by epidemiologists.

2.6 Causality

If the ultimate goal of epidemiology is aetiological research, the relationship between potential causes and health outcomes will be the main source of inspiration, and methods will be like pieces of a puzzle when it comes to understanding this relationship. Yet, the criteria for defining and, indeed, establishing causation have been discussed in many papers and books for years [26, 27]. A simple theory of causation is to assume that there is a unique cause for each disease. In other words, if this cause is not present, the disease cannot appear; and conversely, if the cause exists, the disease will necessarily also exist. This approach is still to be seen in modern science and is still supported by many researchers when intent on seeking a single, sufficient cause for a specific disease, e.g., a unique mutation in a high penetrating gene. This is particularly important in the field of rare diseases, where a simple Mendelian monogenic model of inheritance could be theoretically applied to thousands of diseases. Unfortunately, reality is harsher, and on many occasions many diseases only occur if a variety of coincident factors are present in the same person. It is well known that a specific phenotype can show great variability depending on age, gender and place, in spite of seemingly having the same genetic background. Yet, very few rare diseases respond to only one deterministic cause, despite the fact that many of them are genetic in origin and are in fact monogenic diseases.

On the other hand, no one study is always enough to define causation because a single study will rarely allow for generalisation -external validity- of results based on its findings alone. The most important aspect of any single study is to ensure internal validity, namely, that the results obtained are true in the context of that particular population. Other valid studies would have to be conducted under different circumstances and report similar results, thereby leading to a general assumption that the findings are sufficiently reliable to be deemed generalisable. These principles are valid even in intervention studies (e.g., providing folic acid to women before they fall pregnant, treating patients with an orphan drug, implementing population prevention for some external or internal exposure by reducing abnormally cumulative substances in cells, etc.). This is why epidemiology uses the concept of risk factors (in the plural), develops measures for risks associated with some level of precision (confidence intervals), takes into account confounding factors (factors linked to both exposure and outcome but not participating in the origin of the disease), and defines study designs for addressing different problems and preventing equivocal conclusions from being drawn. Even so, with the exception of some specific study designs such as clinical trials and population-intervention studies, epidemiology is not an experimental science. It is essentially an observational science in which, rather than being modified or acted upon, reality is observed and modelled in an attempt to discover relationships among variables. Hence, the importance of using good methods, quality data and bias control [54] (some discussion about type of bias is included in the chapter 6).

In brief, causation is not a simple matter. Apart from philosophically interesting theories, causal-network relationships and marvellous modern technologies, the causation criteria described by Bradford Hill [31] some years ago are still useful for

understanding how to reach a degree of consensus in the midst of a world besieged by uncertainty.

2.7 From Descriptive to Epigenetic Epidemiology

As pointed out above, if it is accepted that descriptive epidemiology is essential for generating hypotheses even in the rare disease field, then analytical epidemiology and its different areas of application (clinical epidemiology, molecular epidemiology [34], genetic epidemiology, etc.) are equally important for improving aetiological and empirical knowledge. At the same time, however, new high-throughput screening technologies are yielding very interesting results. In particular, most recent genetic association studies have been covered by single nucleotide polymorphism (SNP) analyses using the genome-wide association study (GWAS) design [37, 57], but replication has proved somewhat difficult due to the need for large samples of patients and controls, the high cost entailed and the fact that lack of a previous hypothesis hampers explanation of some of the observed results. New approaches, such as the candidate gene association study (CGAS) design [36], based on testing an a priori hypothesis and focused on a specific genome region, is a good method for applying to rare diseases in cases where recruiting a large cohort of patients poses problems; and, in addition, it may afford better, direct interpretation of results. Selecting the appropriate pathway from among all those available, i.e., the one that best relates genes from the various known regions and disease mechanisms, is crucial for the success of this type of studies. Notwithstanding the fact that several statistical methods have been developed for both study designs [1], the main aim of identifying the real risk factors should still be to choose the best hypothesis. Like SNPs, copy number variations (CNVs) have also yielded very important findings, not only acting as disease markers but also furnishing interesting information on rare disease mechanisms. The epidemiological methods applicable to analysis of CNVs are similar to those used for GWAS and CGAS.

As yet, however, the epigenetic phenomenon is not well known. The modern definition of epigenetics is the study of "modifications of the DNA or associated proteins, other than DNA sequence variation, that carry information content during cell division" [23, 24]. Currently, rare diseases such as Rett Syndrome, Silver–Russell [6] and even Fragile X syndrome have been linked to epigenetic mechanisms, and it is foreseeable that their involvement in other rare diseases will be elucidated in the near future. The common hypothesis of epigenetic issues is the ability of cells to change their behaviour in response to environmental factors and, indeed, their role in phenotypic plasticity. One of the most famous findings of external influence on the epigenome is the case of the folic acid supplement that was administered to women prior to pregnancy and its effects on methylation [28]. A comprehensive in-depth understanding of the influence of genes or their derived proteins, and epigenetic mechanisms is one of the future challenges facing rare diseases. *Epigenetic epidemiology* has to be developed by learning from the experience gained in genetic epidemiology and, where feasible, by adapting some of its methods [25]. Yet the

most important issue is how analysis of external factors should be integrated in the same causal diagram models as epigenome and genome data. If this could be done, it would truly herald the birth of epigenetic epidemiology.

2.8 Natural History of Diseases

Researchers and physicians recognize the interest of broadening the knowledge about all features occurring in a specific disease along its pre and clinical course and this is particularly important in the rare diseases field because the low number of patients, which do not allow us to concentrate the experience and provide easily this knowledge. A term that summarizes the focus of this interest is the Natural History of Diseases. Epidemiology is an applied science providing methods and tools for getting this knowledge together with other basic and also applied sciences such as sociology and economics [22, 66].

There is no one definition of natural history of diseases. Nevertheless, it can be easily defined for any given disease as, "the natural course of a disease from the time immediately prior to its inception, progressing through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead without external intervention". The interest inherent in this concept has been stressed because, in theory, during this process several factors can be introduced with the aim of intervening and modifying the natural disease course. Preventive measures, such as reducing toxic exposures (e.g., drugs, chemicals) [41], giving supplementary medication (e.g., folic acid) or genetic counselling to descendants, developing screening programmes targeted at preventing side-effects and improving prognosis, treating the mechanisms of diseases, their clinical features and/or complications, improving quality of life through family and social support, among others, are important interventions to be included in the natural history of diseases, with the aim of changing some of the epidemiological estimates by, for instance, reducing incidence and/or prevalence, improving patients' quality of life, reducing disability, increasing life expectancy and diminishing the risk of inherited problems among their children.

Other than diseases having a high mortality rate at early ages, it is highly unlikely that the whole picture can ever be seen by just one physician or researcher. Methods used for the study of the natural history of a disease consist of developing a well-designed cohort [5] or using a population-based registry, where other studies can be nested within the study design [62].

It is vital to develop large population-based registries or, alternatively, well-designed cohorts, if one is seeking to intervene in rare diseases at different phases. Collaborative efforts -in some cases on an international scale- are essential for gaining a real understanding of spatial variability in diseases (including genetic markers, environment and socio-economic variations). The future of our knowledge of rare diseases is proportional to the degree of collaboration among different specialisations and disciplines, including epidemiology, which could prove most useful as a cross-sectional science with a building capacity for improving this knowledge base.

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Chapter 3
Evidence-Based Medicine and Rare Diseases

Simon Day

Abstract This chapter discusses the meaning of evidence-based medicine and where it relates to randomised controlled trials, but also where it does not. The need for good quality evidence is stressed through a discussion of high failure rates in drug development and arguments against access to unlicensed (and largely untested) treatments are set out (despite the good intentions of those who advocate such access to treatments). Good quality, reliable evidence does not always have to come from clinical trials. Other forms of evidence are discussed. Meta-analyses of individual trials may help to resolve the problem that, in rare diseases, it may be very difficult or impossible to do adequately powered clinical trials – but that does not imply those trials have no value at all. The importance of patients' choices is stressed but the difficulties of making choices and the general poor understanding of risk makes patients very vulnerable to making poor decisions. They need to be adequately guided through the evidence to make proper informed decisions.

Keywords Bias · Bradford Hill · Evidence · Meta-analysis · Patient preference · Precision

3.1 Introduction

This chapter covers both the use of, and production of, best evidence about "treatments". Although discussion is in the context of therapeutic treatments, essentially very similar ideas and concepts also apply to diagnostics and patient management/palliative care. The context is within that of rare diseases (however one might chose to define "rare") and, importantly, whilst there is nothing inherently different about evidence-based medicine for rare diseases as opposed to more common diseases, often the rarity brings with it some new and special problems. "Rare" and

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"serious" are, on the face of it, nothing to do with each other. There are many quite rare conditions that are not too serious and there are undoubtedly many serious and life threatening diseases that are frighteningly common: heart disease and lung cancer, for example, but also malaria in some regions of the world (although typically this is still considered a rare disease in many other areas of the world). Rarity and severity do, in many cases, go hand in hand – particularly in cases where infants are born with rare congenital disease. The severity of the disease often results in a limited life span so that the *prevalence* (total number of cases) remains low. This also implies a disproportionate distribution of young patients with rare diseases. The combination of rarity, severity and children makes this a particularly emotive topic.

3.2 What Is Evidence-Based Medicine?

Various definitions of evidence-based medicine exist. It is probably impossible to really identify when evidence-based medicine began but its major development was during the 1980s and 1990s and was epitomised by the work of such people as David Sackett and Gordan Guyatt at McMaster University. Sackett et al. [24] defined evidence-based medicine in this way:

> Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

They also comment that, through increased expertise of the treating physician, there can be "more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care".

Po [22] in his *Dictionary of Evidence Based Medicine*, built on Sacket et al. and described evidence-based medicine in the following way:

> Evidence-based medicine has been defined as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'... [Sackett and colleagues] also states that the practice of evidence-based medicine means integrating individual clinical expertise with the best available external evidence from systematic research. However, the term evidence-based medicine is now used much more generally to mean systematic, explicit and judicious use of best evidence in patient care.

So he narrows the focus a bit and takes out the aspects of patient preference. It is probably true that most people's use of the term "evidence-based medicine" does centre on getting reliable evidence, assuming, perhaps, that treatments shown to be best in good quality research will naturally be the patient's first choice. However, one suspects that is not always the case. Not only do patients (or sometimes their carers) decide on something other that what is apparently the current best option (according to current best evidence), but patients' choices for a treatment, in the *absence* of reliable evidence are important to incorporate into the scope of evidence-based medicine. Otherwise, how else will such patents be managed?

In this chapter we clearly separate the two aspects of *evidence* and *patient choice*. We begin by considering what is good quality evidence (that someone else might

subsequently use) about which treatments to use for treating patients of a certain type who have a particular disease. Interpreting and evaluating what is best evidence and producing that best evidence are, of course, the same problem simply viewed from a different angle. In treating a patient, my clinical colleague will know what types of evidence(s) he would ideally like to see; as a researcher, it is my task to get that evidence, whenever I can. When ideal (or "gold standard") evidence is not available, still the aim of my clinical colleagues will be to use the best evidence that there is (however good or bad that might be) – why would they use anything other than the best? It is a happy luxury that using the best evidence typically is not associated with any more cost or effort than using poor evidence (assuming we are going to some effort to get evidence). Similarly, it is my task also to present the best evidence that I can, even when gold standard evidence may not be obtainable. This, of course, is so often the case when researching treatments for rare diseases when there are simply not enough patients to produce the quantity of evidence that we might generally wish to see. It must be realised though that in contrast to *using* best evidence, *producing* that best evidence may often involve considerable time, effort and expense. So pragmatism in all forms of research (common diseases or rare ones) is always necessary. It is important to understand where pragmatism and compromise still allow reliable evidence to be produced and where the degrees of compromise lead to unreliable and potentially misleading evidence.

We want to strive for the best possible evidence but when patients are a very scarce resource and it is not easy to get much evidence, it is most important to get the very best evidence that we can. These aspects of *quantity* of evidence and *quality* of evidence both contribute to our understanding of the benefits and harms of treatments and we need to proactively work on the quality of evidence (which will mostly including data) as a means to help balance for the inevitable limitations on quantity. Whether the quantity, quality or persuasiveness of that evidence matches what we might expect in (for example) major cardiovascular randomised controlled trials that might recruit tens of thousands of patients is really not relevant. Because we cannot get that *quantity* of evidence should not in any way prevent us trying to get similar *quality* evidence and, indeed, it may sometimes be that the results from small studies can be just as persuasive as those from large studies.

3.3 Evidence-Based Medicine and the Randomised Controlled Trial

"Evidence-based medicine" and "clinical trial" are not synonymous terms. Even setting aside the aspects of clinical experience and judgement and that of patient preference, the pure "evidence" aspect of evidence-based medicine still does not necessarily equate to a randomised controlled clinical trial. Elsewhere in this book, Köpcke and Gerss have written specifically on clinical trials and so in this chapter we will not dwell on aspects of their design, management, analysis and interpretation but rather their context as a research tool.

It is worth commenting here on some of the objections put forward to carrying out randomised controlled trials in rare – and often life threatening – diseases. The most frequent objection put forward is that of "no other treatment option" and a compelling, compassionate argument to give patients any hope that there is of a cure, extension of and/or improved life, relief of symptoms, or some other endpoint. There are, perhaps, three counter arguments to this position.

Firstly (and a somewhat brutal argument) is that most new experimental treatments sadly do not work – or, even if they do work, their overall benefit-risk balance [17] is not positive. Surveys of pharmaceutical industry success rates (or, more specifically, attrition rates of compounds as they move through the development pipeline) bare this out. Pearson [19] showed that of all compounds entering phase I trials in man, 90% of them never make it to market. Why might this be? Di Masi [7] presented evidence on why drugs fail during development (for the periods 1981–1986 and 1987–1992). There was little difference between the two time periods: about 30% of candidate drugs were discontinued for "commercial" reasons, between 30% and 40% were discontinued for lack of efficacy, and about 20% discontinued because of adverse safety findings. Similar data from 1991 and 2000 are presented by Kola and Landis [13]. They showed some differences between the two years but still about 30% of treatments failed due to lack of efficacy, just over 10% because of adverse safety findings and 11% (1991) and 20% (2000) failed for adverse toxicology findings. Interestingly, they report that in 1991 only about 5% of products were withdrawn from development due to commercial reasons but this rose to 20% in 2000. Of course, insufficient efficacy or excessive side effects may impact on commercial viability – but even setting aside the commercial reasons for discontinuing, in both studies (which cover the period from the early 1980s to 2000), adverse benefit-risk accounted for more than 50% of attrition. Put another way, more than half the experimental drugs offered in clinical trials to patients have a benefit-risk profile that is *worse than placebo*.

A second reason often put forward (more often on behalf of patients rather than by patients) is that of "no other treatment options." In many cases this will, indeed, be true. But does that mean it is therefore unethical to carry out a randomised controlled trial – even against placebo control? If a general standard of care exists (whether that be evidence-based or not, whether it be based on controlled clinical trials or not) then it would likely be unethical to withhold such care. (We should note, however, that there are cases where even the "assumed" best care has been shown to be harmful [23].) Where there is not even a general consensus of best care placebo would be an ethically justified control. The argument is put forward that patients randomised to placebo are being disadvantaged and denied the new therapy but what would happen to these patients if they were not in the proposed trial? They would either receive no treatment or, at best, would receive the (assumed) best standard of care. So no patient is worse off by being in the trial than if they were not. Actually, some patients might be worse off being in the trial: as noted above, more than half the experimental treatments trialled on patients are worse than placebo. Spodick [28] has even argued that patients deserve the chance to get the best therapy – which might mean *not* to get the new medicine:

> [it is always possible to do a randomized trial]. . . in the search for a real answer, and ensures an ethical approach that gives every patient a 50–50 chance to get best treatment, that is, not to get the new medicine at a time when its precise effects and risk-benefit ratio are not understood.

I put this argument aside, at least here, and rest on the fallback position that it is not an obviously unethical approach to randomise patients to not receive a new experimental medicine when no other treatment options exist. As Sir Austin Bradford Hill [11] noted:

> . . .frequently, we have no scientific evidence that a particular treatment will benefit the patients and . . . we are often, willy-nilly, experimenting upon them. It may well be unethical, therefore, *not* to institute a proper trial.

A third reason in favour of carrying out randomised controlled trials (although strictly it applies to getting reliable evidence, not necessarily from trials) is the importance of the question and the importance of answering it properly. There is an irony in this. All of us like working on important issues; all of us like (or would like – for many of us never manage) to work on the development of truly new and beneficial therapies. So why would anyone want to introduce a treatment that, in fact, did not work? Yet this is the very risk from poor quality evidence. The risk is partly that useful therapies will be missed but also that useless, or even harmful therapies will not be seen for what they are. Some people may still fall back on the argument of "nothing to lose", even if – in fact – a new treatment does not work as well as we thought it did. Sadly, there is plenty to lose. First and foremost, it gives very desperate patients false hopes. This matters little for a new treatment for relief, say, of mild headache. Patients will not be harmed and they will soon find something else to use instead. But it matters a lot when the treatment might be an only hope and possibly where use of the treatment may preclude use of any alternative treatment (in cases where patients have one chance left for success). It also (partly because of legislative incentives around market exclusivity but also when directing research effort to needed areas) prevents or discourages other researchers – including those who might (but don't know) have a treatment that works – from entering the research arena. It is harder to justify using experimental treatments in patients when an existing treatment already exists than when there is no alterative. It may become impossible for follow-on researchers with genuinely useful (but unknown) treatments to test them and so patients continue to use ineffective treatments, realising they are not "wonder cures" but still holding on to hope that they are believed to be better than nothing. Chalmers has addressed this point in a series of three articles [2–4] (first questioning, then stating, then demanding) that even the very first few patients who try experimental treatments should do so in a randomised trial, before hints of evidence, grossly exaggerated in uncontrolled settings, become assumed common knowledge. Uncontrolled trials are notoriously unreliable. Booth et al. [1] in writing about development of anti-cancer compounds refer to the "dramatic unpredictability of single-arm, uncontrolled Phase II trials. . .". Arguments to short-cut or circumvent well-established means of finding out *if* treatments work, *if* they are sufficiently safe, *how much* they work and *how safe* they are, (such as has

been attempted in US Federal regulations [8]) are undoubtedly based on compassion for desperate patients. The consequential dangers need to be thoroughly understood [27, 18].

3.4 Other Forms of Evidence

Accepting that clinical trials are very important and extremely useful in evaluating therapies (they have often been refereed to as the gold standard for doing so), how else might we evaluate benefits and harms of therapies? We might consider what there is *in addition* to trials; we might consider what there is *instead*.

Regarding, particularly, *additions* to trials the most obvious addition is more trials and, hence, the use of meta-analyses (see, for example, Sutton et al. [29], Whitehead [32]). This poses a potential problem when researching treatments in rare diseases when it may be very difficult to get enough patients for even one adequate trial, let alone more than one. Such constraints, however, can be used to advantage. Ideally, it seems that complete world-wide cooperation to recruit enough patients into a trial might be desirable but that is, of course, very difficult. Good international collaboration does exist (paediatric cancer trials perhaps being one of the highlights of this collaboration) but it is not easy and not universal. Whilst competition between trialists [25] is probably counterproductive, replication of evidence is of enormous value. Meta-analyses, particularly pre-planned meta-analyses, of more than one trial can be particularly helpful.

It is often questioned whether it is better to have one "large" study, or a meta-analysis of two (or more) smaller studies. As a particularly special case, it is debated whether one trial of 100 patients (say) is better than two trials of 50 patients, or five trials of 20 patients. This is then seen as a statistical question relating to efficiency, power, and so on. But there is a broader (although perhaps still statistical) issue about the value of replication of evidence. Probably every clinical trial ever carried out has some degree of bias inherent in it. Often the biases will be small and inconsequential – but typically we may have little idea of how large they might be, often we cannot even guess in which direction they might go. So, immediately, two different, independent trials would seem to protect us to some degree over just one trial. Similarly, several trials might protect us even more. Different trials, organised by different research groups in different regions of the world offer some protection against something going wrong with "the one and only" trial. But meta-analysts and clever statisticians cannot mix apples and oranges (despite the fact that computer software can!) This is why pre-planning a meta-analysis is so beneficial. It means we can plan independent studies knowing that, although they may have differences, they are also sufficiently similar that combining their results can lead to a conclusion that is clinically interpretable and useful. In this context it is noteworthy that in a hierarchy of evidence described by the Committee for Medicinal Products for Human Use [5], although meta-analyses were put above individual randomised controlled trials, the phrase actually used was "Meta-analyses of good quality randomised

controlled trials that all show consistent results", this being to stress that poor meta-analyses are not useful. Meta-analyses do not automatically give the "right" answer and there are many poor meta-analyses published. The full hierarchy described by CHMP was:

- Meta-analyses of good quality randomised controlled trials that all show consistent results
- Individual randomised controlled trials
- Meta-analyses of observational studies
- Individual observational studies
- Published case-reports
- Anecdotal case-reports
- Opinions of experts in the field.

Similarly, twenty years earlier, Green and Byar [10] listed a suggested hierarchy. Although the "other way up" from that of CHMP, it corresponds very closely:

- Anecdotal case reports
- Case series without controls
- Series with literature controls
- Analyses using computer databases
- Case-control observational studies
- Series based on historical control data
- Single randomized controlled clinical trials
- Confirmed randomized controlled clinical trials.

The obvious difference is the lack of explicit mention of meta-analyses by Green and Byar. Although the term was relatively new in 1984, the concept was not and Green and Byer's highest (or strongest) level of evidence – "confirmed randomized controlled clinical trials" – is really the equivalent non-technical term for CHMP's meta-analysis.

Both of these hierarchies stress the value of meta-analyses but also include other, much less stringent, types of evidence (i.e. the "what else *instead* of trials"). Both have, for example, anecdotal case reports low (or bottom) of the hierarchy; CHMP went a step further and listed expert opinion as of even less value – but not of *no* value at all. Note there are no solid lines cutting off "acceptable" from "unacceptable" levels of evidence (or, at least, none published) and nor should there be but many people do have their own unpublished doted lines; their own (private) thresholds of what level of evidence is convincing. However, different treatments in different indications (and particularly considering different expectations of disease progression and different degrees of observed efficacy) warrant different considerations of what types of evidence are adequately convincing. Note though, that to make things even more difficult, the pattern of expected prognosis may change over time as diagnosis improves and background standard of care improves. So the value of one type of evidence may change with time.

"Strength of evidence" is only the first part of the problem. What matters more is what we actually do with that evidence and how we make decisions [6]. To consider this, it is helpful to look, for example, at the views of the GRADE Working Group [9] on "Grading quality of evidence and strength of recommendations" and Schünemann et al. [26] on "Interpreting results and drawing conclusions." They give an analytical breakdown of how evidence of different strengths might lead to recommending implementation of a treatment (or diagnostic or screening procedure) but also discuss clearly how different people (or agencies) might legitimately make different decisions based on the same evidence (or same data). The GRADE approach is summarised in Tables 3.1 and 3.2.

Unfortunately, in summary form they can be misleading and may get used as *criteria* rather than as *guidance*. For example, a series of uncontrolled cases seemingly offering symptomatic relief for a naturally self-remitting disease (or at least naturally fluctuating disease) might, indeed, be seen as very low quality evidence (classed as level 3) and, consequently only a grade D recommendation. In contrast, substantially extended survival in a similarly uncontrolled series of patients with a confirmed diagnosis of an acutely life-threatening condition may be seen as much more convincing than simply a grade D recommendation, yet the evidence level would still only be level 3.

Further on what else might there be in some situations instead of randomised controlled trials, it is also helpful to consider what constitutes useful evidence from an observational (or as some might say, epidemiological) point of view. For this, the classic text and continually re-quoted "criteria" come from Bradford Hill in 1965 [12]. The comment made here about continuously "re-quoted *criteria*" is apposite, for Bradford Hill never considered them as *criteria*. In the paper in which he first published them, he wrote:

> What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None

Table 3.1 Levels of evidence

Level	Description
1++	High quality meta-analyses or systematic reviews of randomised controlled trials (RCTs) or of RCTs with very low risk of bias
1+	Well conducted meta-analyses or systematic reviews of RCTs or of RCTs with very low risk of bias
1–	Meta-analyses or systematic reviews of RCTs or of RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal
3	No analytic studies; only case reports, case series
4	Expert opinion

Table 3.2 Grades of recommendation

Grade	Description
A	At least one meta-analysis, systematic review or randomised controlled trial at 1++ and directly applicable to the target population; Or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated 1+, directly applicable to the target population and demonstrating overall consistency of result
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; Or Extrapolated evidence from studies rated 1+ or 1++
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; Or Extrapolated evidence from studies rated 2++
D	Evidence level 3 or 4; Or Extrapolated evidence from studies rated 2+

> of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer which is more likely than cause and effect?

The nine items, "viewpoints" in his terminology (listed below) were not to be used (and should not be used today) in a simple tick-box approach to causality (either of an environmental factor causing disease or of a therapeutic agent "causing" relief of illness).

1. Strength of association
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy.

Bradford Hill's nine viewpoints should also not be used as excuses to "make do" with lesser levels of evidence when better evidence is necessary. Difficulty and necessity are separate. Difficulty may be a reasonable *excuse* but it is never an adequate *substitute* for higher levels of evidence when they are needed. We should always strive for high quality (or high grade) recommendations, but the

levels of evidence (as detailed above) need not always be the same across different therapeutic options, to make those same high grade recommendations.

Any new study should usefully add to the existing evidence base. If there is a lot of evidence already, new studies need to be bigger or better than those that already exist. If very little evidence exists, then even small studies will add useful information and it is possible to explicitly and analytically determine, before a study starts, what benefits such a study might bring. Tan et al. [30] have done this from a scientific perspective; Phillips [20] has done it from an economic perspective. Small clinical trials (however "small" is defined – and it will differ in different situations) are not necessarily bad or of no value although arguments for and against can be found in, for example Matthews [16] (in their defence) and Piantadosi [21] (citing concerns). Importantly, "How much evidence already exists" does *not* equate to the current *sample size* of all existing studies, even though the two issues may be linked. But equally important is that there probably is an ethical case for objecting to a "small" study when a "usefully larger" one *could* be achieved.

3.5 Quality Always Matters

Perhaps a foremost approach should be that any data are better than none and good and reliable quality data are better than poor quality and unreliable data. Avoidance of bias (particularly in the way in which data are collected) is possibly one of the most critical features. Bias is very difficult to measure (although its existence is often easy to identify). So, some bias may exist but having no idea of its size (sometimes not even its direction) leaves us in very uncertain terrain.

Bias and precision are often illustrated in introductory statistics texts in pictures of arrows or bullets fired at a target, as in Fig. 3.1. Clearly the most desirable situation is in caption d where all the bullets are close to each other (there is high precision) and they are all just about on target (no apparent bias). Note that "close to each other" is measured by the size of the target; it is closeness in a relative sense, not necessarily in an absolute sense. Of course, the situation in caption a (all the bullets are close to each other so there is high precision but there is an obvious bias) could be of use to us. If we know how far off target our gun fires, then we can correct for that with our aim. But this illustration is only of any value if we know where the target is – that is, we know the "right answer". When we collect data – whether it be in a cohort of patients receiving a treatment (perhaps to try to determine an absolute response rate), or in a randomised controlled trial (to establish a relative effect, over and above the standard of care) – we do not know what the answer is; we do not know where the truth lies; we do not know where the target is. So, by analogy, the situation we have is more like that in Fig. 3.2. We can see the data (the bullets) but instead of assessing how close to the target we shot, we are using these bullets to try to infer *where the target is*.

We need an instrument (in this case a study of some type) that we can rely on to be sufficiently precise and unbiased. Good clinical trials can often eliminate biases but it is not always necessary to perform randomised controlled trials to get useable evidence. The United States Code of Federal Regulations [31], for example,

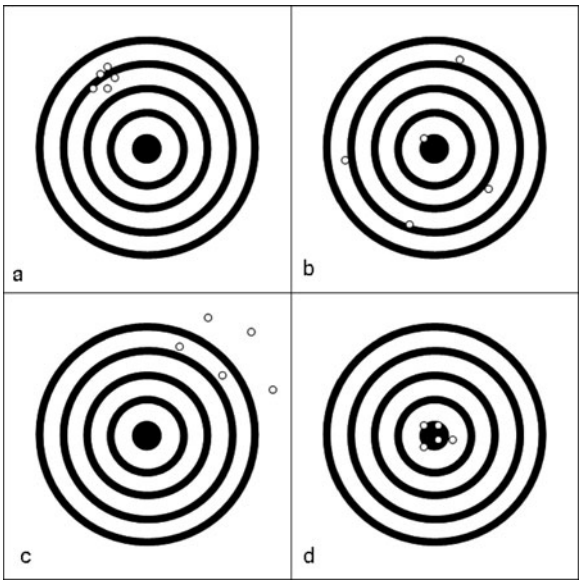

Fig. 3.1 Illustration of bias and (lack of) precision. **a** – high precision (low variance) but biased; **b** – low precision (high variance) but no overall bias; **c** – low precision (high variance) and biased; **d** – high precision (low variance) and no bias

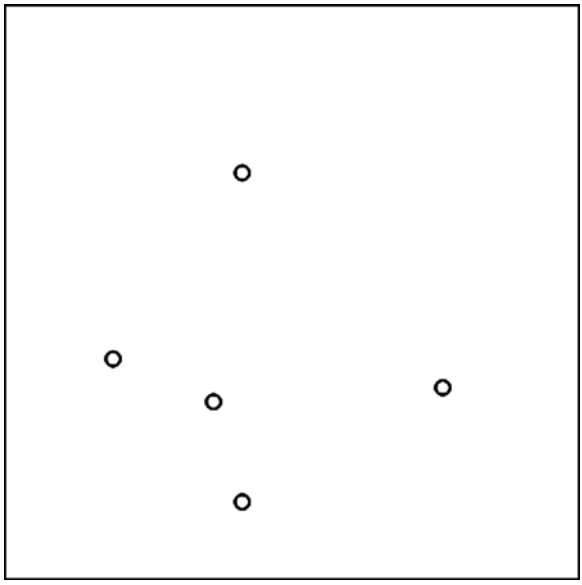

Fig. 3.2 Illustration of real situation of collecting data. We have no idea if the bullets (the "data") are on target or not (no idea of bias); and we have no idea if the bullets are closely packed relative to the size of the target (no idea of relative precision)

lists "...placebo concurrent controls, dose comparison concurrent controls, no treatment concurrent controls, active treatment concurrent controls, historical controls" as acceptable control groups – not all situations necessarily need randomised controlled trials. But clearly, in Fig. 3.2 we have no idea where the target is. We do not even know its size, so we cannot even determine if we have (relatively) high or low precision.

3.6 What Else Matters? The Place of Personal Experiences

We turn finally, albeit briefly, to two elements of evidence-based medicine (encompassed in its definition) that often get forgotten. These are the expert opinions of the treating physician relating to the individual patient and – perhaps most importantly – the opinions and wishes of that patient.

As illustrated above, most new treatments in early phases of clinical development are probably worse than placebo. This is a sad fact but a realistic one. Of course, every patient will have a different perspective on treatment options and what matters to them. Some of us will clutch at any straw of hope; others will feel the emotional and physical burdens of an experimental toxic treatment (possibly after several earlier options have failed) are too much to bear. A patient suffering with a life-threatening disease, might argue that nothing can be worse than the inevitable disease prognosis. Put in slightly more scientific terms of benefit-risk assessment, if survival is the efficacy endpoint, then almost any and all adverse effects tend to be of secondary importance to mortality (of course, in less severe conditions, the adverse effects can easily outweigh the clinical benefits).

Patients' wishes, therefore, may often over-ride the data. To what degree should this be respected? The easy answer is "always" but in some cases those wishes cannot be respected: unlicensed medicines are simply not available and often the only means of access will be in a trial (when there may be less than a 100% chance of being allocated to that treatment anyway). In other situations, patients may need to be protected against their own over-enthusiasm. The understanding of risk is generally poor and similar risks are interpreted differently depending on the context – both by patients [14] and professionals [15]. Hope in desperate situations is important but the distinction between hope and expectation is blurred. Even in randomised controlled trials, randomisation is not well understood and many patients enter trials knowing there may be a 50/50 chance of receiving placebo but still believing that *they* will get the (supposedly) active treatment.

Finally, recall from the definitions of evidence-based medicine that although treatment choices (and the name suggests this) should be driven by *evidence*, expert insight should not be ruled out completely. Often it is very difficult to formerly combine all sources of information and knowledge to arrive at a formal decision-making procedure. The school of Bayesian statistics tries to amalgamate all sources of knowledge and expert experience [6] – but it is not straightforward. Expert opinion of experienced physicians should not be ruled out completely because it is anecdotal opinion and not well controlled and objective data.

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Chapter 4
Prevention, Diagnosis and Services

Eva Bermejo and María Luisa Martínez-Frías

Abstract This chapter summarizes how *prevention*, *diagnosis* and *services* can result from the activities of a research programme on the group of rare diseases constituted by congenital anomalies. The Spanish Collaborative Study of Congenital Malformations (ECEMC) is a research programme based on a case-control registry of consecutive newborn infants with congenital anomalies. Its aim is the prevention of this group of rare diseases, through the research on their causes and pathogenesis, combined with the translational activity to transfer the benefits of this knowledge to the general population and health care providers. Its experience could be applied to the research on other rare diseases. The different levels of prevention (primary, secondary, tertiary and quaternary) are briefly defined, and the way in which these levels are being applied or can be applied to congenital defects prevention is reviewed. The main primary prevention measures regarding congenital anomalies are also detailed. To this respect, the benefits derived from the activity of Teratology Information Services (TIS), for the general population as well as for health care providers, are explained. It is finally emphasized how the epidemiological data can contribute to the prevention of that group of rare diseases.

Keywords Prevention · Diagnosis · Services · Congenital defects · Teratology information services

Abbreviations

RD	Rare disease(s)
CD	Congenital defects

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TIS	Teratology information service(s)
ToP	Termination(s) of pregnancy
ECEMC	Spanish Collaborative Study of Congenital Malformations
ENTIS	European Network of Teratology Information Services
OTIS	Organization of Teratology Information Specialists

4.1 Introduction

Prevention, diagnosis and services are three of the objectives that are set up regarding research on most rare diseases (RD). There could be diverse reasoning to put these 3 terms into different orders. Certainly, one could consider that *prevention* is first and, if the preventive efforts have failed, a *diagnosis* is necessary and some *services* will be required to get such a diagnosis. After getting a *diagnosis* some other *services* will be needed for an adequate attention. Additionally, *prevention* is also possible when patients get their *diagnosis*, as will be explained in this chapter, and *services* for *prevention* (and not only for *diagnosis*) are more and more frequent in the field of RD.

There is a group of RD, constituted by congenital defects (CD), with some special characteristics that enhance the interest of their study and research within the area of RD. Indeed, most of the CD fall individually into the category of RD, given their low frequency, with only a few exceptions. On one hand, many CD substantially increase morbidity and the risk for early death, and frequently confer diverse grades of disability and dependence to affected people, with a considerable damage of their quality of life and that of their families. On the other hand, unlike other RD with later onset, CD are already present at birth, which implies that they and their consequences have to be faced from that point. It has been estimated that 7.9 million infants are born worldwide every year with severe CD, and 3.3 million affected children die before the age of 5 years [96]. These eloquent figures and the burden of disease that CD usually cause, make them priority targets for research.

In this chapter, it will be summarized how *research* on CD can contribute to those three previously mentioned aims of *prevention, diagnosis and services*. More concretely, this will be illustrated through the experience of ECEMC (Spanish Collaborative Study of Congenital Malformations), since many of the facts regarding CD apply to the other types of RD.

4.2 A Research Programme for *Prevention, Diagnosis and Services* Regarding Congenital Defects: An Example Applicable to Other Rare Diseases

ECEMC is a research programme based on an on-going case-control registry and surveillance system of consecutive newborn infants with congenital anomalies, born

in hospitals from all over Spain. The major aim of this programme is the primary prevention of this group of RD, through the identification of their causes and pathogenesis, with a translational approach in order to transfer this knowledge to health care providers for their clinical practice, and thus to the patients and general population. The evolution of the programme over time has been marked by the specific needs at each moment. ECEMC was founded in 1976 by one of the authors of this chapter (María Luisa Martínez-Frías), initially as a response to the need for a surveillance system of congenital anomalies in Spain, after the disaster produced by the drug thalidomide causing thousands of infants with severe CD worldwide [25]. However, ECEMC was not merely conceived as a surveillance system, but also as a research programme, given the wide potentiality of the data obtained and the general lack of knowledge on the causes of CD at that moment. ECEMC's system registers data on newborn infants with CD (*cases*) and healthy *controls*, in more than 60 collaborating hospitals throughout Spain, although along its history it has attained data from more than 145 hospitals. At present, it covers more than 21% of births in the country [7, 19]. The network of ECEMC is made up of 2 main teams. The first one, the *Peripheral Group*, is integrated by more than 400 participating physicians in the collaborating hospitals, who, having an interest in the problem of congenital defects, join the ECEMC programme after accepting to follow its common and strict methodology. The second one is the *Coordinating Group*, which is multidisciplinary and integrated by physicians and biologists (with expertise in dysmorphology, clinical genetics, cytogenetics, molecular genetics, clinical teratology and CD epidemiology), as well as by specialists in computer science and biostatistics. For each infant included in the registry, whether case or control, a total of more than 312 pieces of data are gathered. This information covers reproductive and family history, obstetrical data, and exposures during pregnancy such as acute and chronic maternal diseases, maternal pharmacological treatments, maternal consumption of illicit drugs, alcohol, tobacco and caffeine, maternal and paternal occupation, paternal chronic diseases and treatments, among others. The Coordinating Group performs the coding of congenital anomalies of the cases, the data-processing, the cytogenetic studies (with high-resolution bands and FISH techniques) and the molecular analysis, makes the clinical study and diagnosis of the cases in collaboration with the participating paediatricians of the Peripheral Group, and carries out the epidemiological analysis and research. From the collaboration of both groups of ECEMC, several hundred joint publications have been released during the last 3 decades in the fields of Epidemiology, Dysmorphology, Clinical Genetics, Cytogenetics (high resolution and molecular), Clinical Teratology, Paediatrics and Obstetrics. The remarkable multidisciplinary approach of the joint research carried out by the group enhances the power and perspective of the programme, and is essential in a field in which there are so many areas involved. ECEMC's methods have been published previously [30, 39]. Between April 1976 and December 2008, ECEMC programme surveyed a total population of 2,592,906 consecutive live born infants, of whom 39,231 had major and/or minor CD detectable during the first 3 days of life. Since 1980, it has also surveyed a total of 14,207 stillborn infants, 671 of whom presented with CD.

4.3 Making Research on Congenital Defects Useful for Their *Prevention*

As it has been mentioned, in the early 1960s, a lot of concern was generated by the identification of thalidomide, an apparently safe drug according to pre-marketing studies, as a potent teratogen causing severe CD to thousands of infants in many countries. This made it clear that there was a need for surveillance systems capable of the early detection of risk factors introduced in a specific area. As a result of that experience, many countries developed their own registries of CD with surveillance purposes, and these structured several international organizations for collaboration [14, 18], in order to optimize efforts and resources.

However, while in many of the registries of CD the main objective was the surveillance of frequencies, others perceived the importance of these systems to obtain information useful for investigating the causes of CD and to prevent them [30]. On one hand, registries with *high-quality clinical information* about the cases, are an *exceptional source of experience for the diagnosis* of very uncommon (and other not so rare) conditions. As it will be explained later in detail, the diagnosis is the first step to elaborate the information to be provided to the patients and/or their families, and to establish possible preventive measures. On the other hand, if that clinical data is complemented with *information on exposures and diverse types of variables*, the study of risk factors can be carried out. Otherwise, any finding of the surveillance system, in terms of unusual increases (or decreases) of the frequency, can not be investigated for causal (or preventive) agents. It is clear that just knowing that the frequency is increasing will not generate prevention. On the contrary, to exert prevention it is necessary to previously identify the factors related with the disease, and for these purposes, information on a minimum set of data regarding possible hazardous exposures or characteristics must be gathered, as recommended by, for instance the National Birth Defects Prevention Network (NBDPN) [80]. In this sense, as it has been explained in the paragraph 4.2., ECEMC programme gathers information on more than 300 variables. This means that a huge amount of information can be analyzed in 2 ways:

(a) *For each individual entered in the registry:* Taking into account all the information available for each patient registered in ECEMC programme, after a thorough assessment performed by its multidisciplinary team of researchers, the identification of the specific causes of the defects that each particular case presents is attempted. This activity has enabled the cause of the defects to be determined in 42.3% of the cases in the registry [32] and, as it will be explained in the next heading, that identification of causes can be the first step for prevention.

(b) *Pooling data on many patients:* This aggregated information is ready in order to perform analytic studies, searching for the causes of congenital defects or risk factors involved in its origin. This type of analysis has generated many interesting results which have been released in many publications of the group

(some of them are included in the references list) [8, 9, 15, 16, 21–24, 26–30, 33–37, 41, 52, 58–62, 64–70, 72, 73, 76, 85–89, 94, 95]. This new knowledge has important implications for the prevention of congenital anomalies.

These 2 ways of analysing the information gathered, are in fact the 2 approaches of the research carried out by the ECEMC programme, with the aim of preventing congenital anomalies.

4.4 How a *Diagnosis* Can Be the Beginning of *Prevention*

Getting a diagnosis is one of the objectives of physicians taking care of patients with CD and other RD, and also for patients and their families. However, it is not intended just to have a "label"; on the contrary, a diagnosis is a concept full of content. Indeed, it provides access to extremely useful information, since for many conditions their natural history is fairly well known, and this allows the physician to:

(a) quickly establish the best known specific treatment for each condition, which apart from the advantage of bringing forward the benefits of the correct treatment, also prevents undesired consequences of inadequate treatments;
(b) predict a probable prognosis, based on the previous experience in other affected patients;
(c) have an anticipatory attitude, foreseeing possible complications and establishing the best preventive measures accordingly;
(d) obtain some specific aids and assistance from social and health services.

But there are also other benefits derived from having a diagnosis, since this means that the patients and/or their families can be informed regarding the absence of risk or the recurrence risk, as well as the possibility of other relatives being carriers of the genes causing the disease when it has a genetic origin. Moreover, it is possible to diagnose other relatives with milder manifestations of the disease and establish their risk of transmitting it to their offspring. Clearly, all these actions have an intrinsic preventive value. Furthermore, if the diagnosis is known, it is possible to outline a plan focused on the early diagnosis (not only in the postnatal life, but even before the implantation of the embryo) in future pregnancies of the same couple, or to offer alternatives through assisted reproduction with gamete donation, thereby preventing the disease.

4.5 How a Research Programme Based on a Registry Can Provide a *Service* for *Diagnosis*

It is patent that one of the main objectives of research programmes on health problems is to identify their causes. The first step is to classify the patients according to their diagnosis, in order to get tidy study groups. For RD, and CD are not an

exception, it is quite common that the diagnosis is delayed until advanced ages of the patients, since these conditions are largely unknown. Therefore, it is common that the cases entered in a registry are initially recorded without a definite diagnosis, and this is an important challenge for research. This means that, before performing any analysis of data, considerable efforts have to be addressed to get such a diagnosis, not only for the benefit of the patients (by avoiding unnecessary analyses) and their families, but also in order to constitute homogeneous study groups for research. As a consequence of this, some research registries establish themselves as true and powerful services for diagnosis, since they have the opportunity to examine patients with extremely rare conditions, and this provides an exceptional expertise. Such capability is difficult to achieve by other means, and can be useful for the diagnosis of other cases registered in the programme and having the same conditions. This is even more remarkable in programmes based on networks surveying large samples or populations. In the ECEMC programme, for instance, there have been more than 130 syndromes for which there is only one affected case identified in the series of about 2.6 million births surveyed [32]. This has led to some publications of ECEMC's group regarding several of those infrequent syndromes or defects [2–6, 38, 40, 42–50, 53–57, 63, 71, 77, 91–93] and, according to the most recent advances in molecular genetics, various molecular aspects of some of them [1, 12, 74, 78], even allowing to identify new responsible loci or mutations [1, 12].

Figure 4.1 shows the algorithm followed in ECEMC for the clinical analysis of infants with CD, which is performed previously to any of the other research activities of the group.

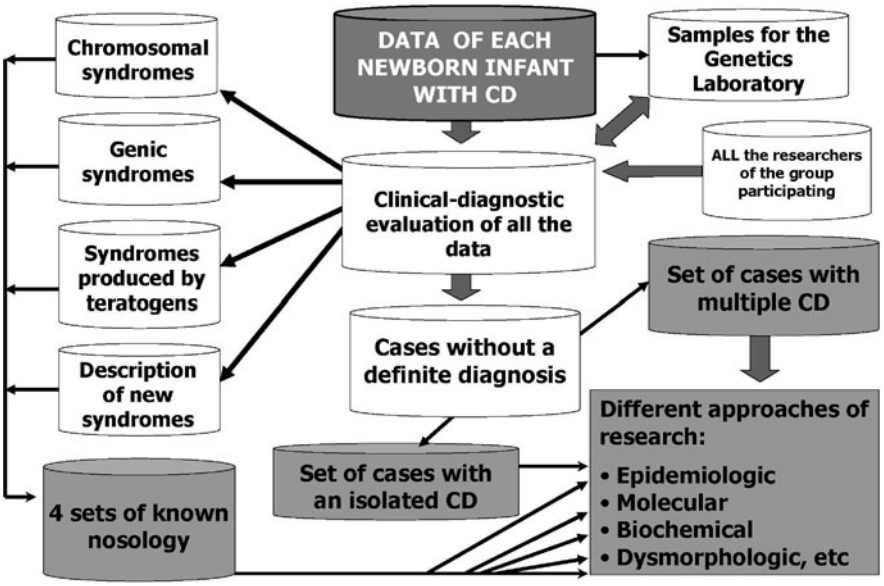

Fig. 4.1 Algorithm for diagnosis, previous to the other research activities of the ECEMC programme (modified from Martínez-Frías et al. [75])

This is an essential process, since it results in several homogeneous groups, providing the basis for further investigations. First, data and samples of each infant with CD are received, processed, and evaluated by all the researchers of the group. From that evaluation, in some cases a syndrome can be diagnosed (whether chromosomal, genic, produced by teratogens, and even some new syndromes, as have already been identified in the ECEMC group [42, 46, 47, 92]). Therefore, 4 sets of known nosology and a group of cases without a definite diagnosis result from the evaluation. In this last group, which represents about 60% of all infants with CD, 2 subgroups can be distinguished: those with isolated defects, and those with multiple CD. Most efforts of research, in its different approaches are addressed to this broad group without a definite diagnosis. To sum up, the main objective of all the research developed by the programme, is to identify causes by which CD are produced. Indeed, if it is possible to get a diagnosis, the cause can be identified in many cases. If such diagnosis is not achieved, different types of analyses (epidemiological, molecular, etc) can be applied in order to search for causes. But those analyses have to be applied to homogeneous groups of cases, and to define those groups, a good clinical definition of each case is essential. That good clinical definition allows establishing possible pathogenic mechanisms (and groups built on them) by which all the defects in each infant must have been produced.

Based on ECEMC's experience on this work plan, it is important to again underline the benefits of, first, establishing multidisciplinary teams for the study of rare conditions, and last, but not least, building collaborative networks.

Another aspect that has more and more importance refers to molecular studies performed on patients. These studies are used for getting a diagnosis for those conditions for which a specific test exists, but if a test is not available molecular studies can be undertaken in order to investigate possible genetic alterations that could be related with the presence of CD. Therefore, it is crucial to have groups of similar cases for which biological samples must be obtained to perform genomic analysis aimed at identifying common molecular changes that could be etiologically relevant. To this respect, there is a quite new discipline, the so-called *genetic epidemiology*, which focuses on the genetic determinants of disease and the joint effects of genes and non-genetic determinants [10], but to take on studies in the field of genetic epidemiology, it is essential to gather samples from a considerable number of patients. This is why it is encouraged to obtain samples from any patient with CD, with or without a known diagnosis.

4.6 *Services* for *Prevention* Derived from Research

It is quite normal that when a research programme stands out in a field related with health problems, some people, whether from the general population or professionals, want to contact the researchers in order to get some information regarding particular cases, and even soliciting some study which can contribute to the diagnosis. In some instances, these requests become quite numerous, and it can be difficult to manage since research groups generally are not structured to attend to them.

However, answering those questions frequently requires a high degree of specialization and expertise, which are uncommon out of these research groups. Therefore, the ability of these groups to provide answers, taking advantage of their background and knowledge, has led to some research groups on congenital anomalies developing services to inform the population and/or health care providers about risks for the embryo and foetuses derived from different exposures or circumstances. These services are generally designated under the denomination "Teratology Information Services (TIS)". This kind of service provides accurate evidence-based, clinical information to health care professionals and patients about exposures during pregnancy and prior to it. This information, following a thorough assessment, can substantially contribute to the prevention of birth defects, and especially to primary prevention of these conditions, promoting actions or attitudes (in the *childbearing age population* and *health care providers*) favouring a correct prenatal development. At present there are 2 international organizations of TIS, one in Europe, the so called ENTIS (European Network of Teratology Information Services) [13], and OTIS (Organization of Teratology Information Specialists) [84] in USA and Canada. In Spain, ECEMC programme has the Spanish Teratology Information Service [51], called *SITTE* (Spanish Teratology Information Service by Phone) for health professionals, and *SITE* (Service for Information to Pregnant Women by Phone) for the general population. Every year, an average of 4,000 calls are received and answered by SITE and about 1,000 by SITTE. The issues of interest for which the consultation is performed, are quite varied, but the calls are mostly focused on maternal use of drugs, maternal acute or chronic diseases, physical agents used in diagnostic procedures (X-rays, ultrasound, magnetic resonance, etc), chemical agents (whether occasional exposures or in the workplace), exposure to physical agents (other than the former) and biological agents (also occasional or continued exposures), exposure to agents linked to lifestyles (alcohol consumption, tobacco, caffeine, illegal drugs, food) and others. For many of the cases for which the consultation is performed, a follow-up is also available, thereby becoming a new source of information for research, given that some of the exposures of interest are rather infrequent and there is no experience or any published data worldwide. On the other hand, the international participation in the above mentioned organizations (ENTIS and OTIS) facilitates that when a very infrequent consultation is received in a TIS, a query can be addressed to TIS in other countries in order to gather all the unpublished available information, according to their experience. Therefore, the answer and report provided are based on the most up-to-date information.

4.7 Different Types of *Prevention,* and Their Application to Congenital Defects

Prevention is an usual concept in Medicine, trying to avoid diseases and their end results.

The prevention can be exerted at different levels. First, it aims at avoiding the onset of the disease. Nevertheless, if it is already established, the prevention can

be applied in function of the phase of the natural course of the disease. Prevention can be achieved by reducing, limiting or controlling the risk factors, or stopping the progress of the disease and attenuating its consequences or disabilities once it has been established. The following types or levels of prevention have been distinguished:

- *Primary prevention*: This category includes the set of actions addressed to avoid the occurrence of a particular disease, or to diminish the probability of suffering it. The objective of primary prevention is to diminish the incidence of the disease, that is, the occurrence of new cases. These types of actions are carried out in the pre-pathogenic phase of the disease, before the onset of the stimuli induced by the etiologic factors capable of generating the disease. These actions include those addressed for the protection of health (essentially performed on the environment) and for the promotion of health (concentrated on individuals).
- *Secondary prevention*: Actions starting once the disease has already established. Their purpose is to stop or ameliorate the evolution of the disease in the pre-clinic phase, that is, when signs and symptoms are still not apparent, but the disease has already established, or it is in its initial phases. These actions are mainly developed through screening tests, which will favour an early diagnosis. The success of this type of prevention is the reduction of mortality and morbidity, or a reduced frequency of the disease after such early diagnosis.
- *Tertiary prevention*: This includes the treatment and rehabilitation of an already established and apparent disease, as well as amelioration of its consequences, so that its progression is delayed and the appearance of complications or deterioration and disabilities can also be prevented. Tertiary prevention is also achieved through social actions that increase quality of life, rehabilitation and reinsertion.
- *Quaternary prevention*: This type of prevention refers to avoiding or attenuating the excessive unnecessary medical intervention which can generate some damage or even a previously inexistent disease [20]. This is the result of applying the principle of precaution, for diagnosis, therapy or prevention. In some circumstances, it is better to do nothing, even when the patients or their families are expecting for some intervention. As expressed by Newman [81], "If it's not worth doing, it's not worth doing well". This can be difficult to carry out when so many technologic advances are available, and it can be even more difficult to explain this to the families and patients. Also, the fear of judicial accusation can weigh on physicians' minds. Some clinical practice guidelines can be of limited help to this respect in certain cases. In fact, any guidelines should be assessed critically in order to avoid unnecessary over-medicalisation.

Prevention regarding congenital anomalies greatly depends on the knowledge of their causes, which is still quite limited. However, in spite of that limitation, it is paradoxical that some known, proven and easily applicable preventive measures to this respect are not well known by those who should apply them, including not only the childbearing age population but also some general practitioners and specialists.

This makes it clear that more diffusion, education of the population and formation of our health care providers are needed.

The main measures are widespread and can be found easily in many forums, although it is recommended to pay attention to the most trustworthy, such as, for instance, the CDC (Centers for Disease Control and Prevention), whose web page [11] offers some useful reliable links.

Next, we will go over the different levels of prevention detailed in the previous title, and the way in which these levels are being applied or can be applied to the group of RD constituted by CD.

4.7.1 Primary Prevention of CD and Other Adverse Perinatal Outcomes

This refers to measures favouring a correct prenatal development. Many of these measures for primary prevention of CD coincide with those just promoting healthy lifestyles. For instance, it is recommended to follow a quantitatively and qualitatively correct *diet* and *physical activity*, and avoid *toxic habits (alcohol, tobacco, illicit drugs)*. However, there are other measures that are less obvious and known at the level of the general population. These are the most remarkable preventive measurements, with proven health effects:

- *Planning pregnancy*: This is probably the best and most effective preventive measure regarding congenital anomalies. This allows scheduling pregnancy at the best parental ages (see below), avoiding harmful exposures from the time of gamete maturation through the periconceptional period.
- *Preconceptional medical consultation*: In general, this serves to review the physical condition, knowledge, attitudes and behaviours of both the father and the mother to assure the best medical conditions before getting pregnant, as the base for a healthy pregnancy and outcome. There are some specific issues to be checked at the preconceptional consultation: obstetric history; nutrition and weight; screening for disease; use of medications; infections and immunizations; tobacco, caffeine, alcohol, and illicit drugs consumption; occupational and environmental hazards; and family history, among others.
- *Special medical consultation in case of recurrent pregnancy loss or a long period of infertility*: These problems require a special search for health problems or other type of risk factors, whether environmental or genetic.
- *Preconceptional vaccination for rubella when women are not immune*: The determination of the immune status of childbearing age women regarding rubella, and vaccination in those who are not immune prevents infection during pregnancy, which is known to produce the congenital rubella syndrome in the newborn infant. This is a highly disabling condition, mainly affecting the central nervous system, vision and hearing, and the cardiovascular system.
- *Determination of immunization against toxoplasma*: If the mother has never had contact with this protozoa, which can be determined through a serologic study,

she should follow some simple hygienic measurements such as: avoiding contact with cats and handling cat litters; using gloves when gardening; and not eating undercooked meat without it being previously frozen at –20ºC (–4ºF). This precludes the foetal infection, which has serious consequences, mainly on the central nervous system.

- *Perform serologic HIV/AIDS and STD (sexual transmitted diseases) screening, and treatment if needed, for both partners*: This will allow timely treatment and planning of the pregnancy at the best health conditions, also minimizing the risks for the foetus, which otherwise can be damaged and suffer severe developmental disabilities, such as mental retardation, deafness and blindness.
- *Prevent Hepatitis B virus (HBV) infection through vaccination of men and women at risk and planning pregnancy*: The infection can be acquired through sexual transmission or through percutaneous or mucosal exposure to infected blood. This measure prevents transmission of the infection to infants and also the serious consequence of HBV infection in the parents.
- *Establish a proper medical management of diabetes (type 1 and 2) before conception*: This can reduce the risk for birth defects as well as for some obstetrical complications.
- *Get adequate treatment for maternal epilepsy before getting pregnant*: If proper control of the maternal disease allows changing the treatment to less teratogenic compounds, it should be achieved and the dosage adjusted, before conception. If that change is not possible, the adjusting of the dosage of antiepileptic drugs is still indicated, but always before conception. In any case, a careful medical follow-up during pregnancy is recommended.
- *Maternal high blood pressure*: This requires good medical control and treatment, which should start before the pregnancy, with the adequate medication if needed.
- *Maternal thromboembolic disease*: An adequate management should be programmed by the specialist, taking into account that some anticoagulants (coumarin derivatives) are teratogenic and must not be used during the pregnancy.
- *Proper management of maternal hypothyroidism*: A poor control of maternal hypothyroidism can cause a defective neurologic development of the foetus. Therefore, the dosage of levothyroxine has to be adjusted (usually increase it slightly) during the pregnancy in order to prevent mental retardation.
- *If the mother, or the father, suffers any chronic disease*, this and its treatment have to be assessed insuring the best control of the disease for the affected parent but not increasing the risk for the embryo and foetus. This can require changes in treatment and, for this purpose, it can be of great help to consult a teratology information service, which is specialized in this kind of assessment and has the most up-to-date information available, as already mentioned.
- *Use of teratogenic medications*: There are some drugs which are clearly contraindicated during pregnancy, since they have been shown to have teratogenic effects or induce irreversible damage in the foetus, and there are other safer alternatives, or the disease for which they are prescribed is not severe: *thalidomide, synthetic retinoids (isotretinoine, etretinate and tretinoin), coumarin derivatives (during the first and third trimester of pregnancy), misoprostol, ACE (Angiotensin*

Converter Enzyme) inhibitors, fluconazole (at high doses), retinol (at doses over 25,000 IU/day), androgens, diethylstilbestrol (DES) and estrogens, beta and dexamethasone (except if used for preventing the neonatal respiratory distress syndrome), and mycophenolate mofetil. If a woman is using some of these medications, effective contraception should be implemented to avoid unintended pregnancies and, when planning pregnancy, these treatments should be discontinued, according to the indications of a doctor who could request a teratology information service for updated information on the adequate use of drugs regarding pregnancy.

- *Avoid selfmedication when planning a pregnancy and after conception*: Do not use any medication or herbal product (they are also medications) which has not been prescribed by a doctor. During these periods, the principle "What is not indicated, is contraindicated", should prevail over any other rule.
- *Have a complete diet and try to get the ideal weight (not overweight or underweight) before getting pregnant*: During pregnancy it is specially important to insure an adequate supply of proteins, iodine, iron, calcium, other minerals, and vitamins. Significant deviations from the ideal weight have been related to adverse perinatal outcomes.
- *Women with phenylketonuria (PKU) should follow a low phenylalanine diet before conception and during pregnancy*: This measure has the effect of preventing mental retardation in their infants.
- *Insure an adequate supply of folic acid*: Folic acid supplements have been demonstrated to reduce the risk for neural tube defects by about 2 thirds with daily doses of 400 micrograms [79]. These should be provided from the time of pregnancy planning. On the other hand, it is recommended to eat a healthy diet including foods specially rich in folates such as green leafy vegetables. However, getting prevention policies universally implemented is quite difficult, and there are many countries which still have not established any measures for promoting an adequate supply of folic acid for the prevention of neural tube defects [82].
- *Cease intake of alcoholic beverages during pregnancy and while the planning of a pregnancy*: Alcohol can cause the condition known as "Fetal alcohol syndrome", in which almost any organ or system (including the central nervous system) can be affected. This is considered to be the main known environmental cause of mental retardation, and no dosage can be considered safe regarding the prenatal development. Therefore, the most effective preventive measurement to this respect is eliminating alcohol consumption from before conception, when planning a pregnancy.
- *Quit smoking before getting pregnant*: Some adverse perinatal outcomes, including several congenital defects (such as oral clefts, limb reduction defects, or gastroschisis), have been related to maternal tobacco consumption, even a passive consumption. Therefore, smoking cessation is recommended when planning a pregnancy and also has to be extended to the father.
- *Limit the daily amount of caffeine to a maximum of 3 cups of coffee or their equivalent*: Although this exposure probably does not bear a significant increase

of risk for congenital anomalies, it has been linked to spontaneous abortion as well as various obstetrical complications and adverse outcomes.

- *Do not use illicit drugs while pregnant or when planning pregnancy.*
- *Avoid or limit contact or exposure to toxic substances*: We are all exposed to many kinds of toxic agents (cleaning substances, paints, solvents, insecticides, products used in agriculture, etc) daily. These exposures should be avoided whenever possible, or at least restricted to the minimum. Occupational exposures should also be limited by respecting legislations and using protective equipment, or changing to another activity when pregnant.
- *Keep away from high temperature environments during pregnancy*: The use of saunas, hot tubs or steam rooms during more than 5–10 minutes is contraindicated during pregnancy, since hyperthermia can have harmful effects in prenatal development. Likewise, workplaces should maintain an adequate temperature. When a pregnant woman suffers fever, she should contact a doctor as soon as possible in order to establish proper therapeutic measurements, and meanwhile take an antipyretic drug (particularly acetaminophen if not contraindicated in specific cases).
- *Avoid unnecessary X-rays exposure*: Physicians should be informed by women if they are pregnant or planning pregnancy, in order to limit this exposure and establish special protection of the foetus.
- *Parental ages*: It is generally well known that the advanced maternal age increases the risk for Down syndrome, as well as the global risk for CD. It is less known that younger mothers have a higher risk for some congenital defects such as gastroschisis, and that the advanced paternal age also increases the risk for conditions produced by autosomal dominant mutations, like achondroplasia or thanatophoric dwarfism [38]. Taking into account all the accumulated experience, it can probably be recommended to establish the reproductive life plan for the less risky ages: between 22 years and 35 years.
- *In cases with some relative presenting congenital defects, or when the parents are related:* It is advisable to get counselling from a genetics service, where the possibility of performing genetic testing (if available) can be assessed according to the family history.
- *Prenatal care should be supervised by a physician,* who will appoint regular controls, and any incidence, acute disease or doubt regarding the pregnancy should be discussed.

Apart from all these measures, it is important to take into account the most recent information regarding epigenetic changes that can be induced by environmental agents. These can act by influencing gene expression and cell specification at different stages of development, both in males and females. This would mean that there could be new avenues for primary prevention if current preventive measures regarding birth defects are followed by both parents from three months before attempting to become pregnant, and during the entire pregnancy by the mother [31].

4.7.2 Secondary Prevention of CD

When primary prevention has failed, there is a role for *Secondary prevention*. Nevertheless, this is still very difficult to be achieved regarding CD. For some congenital defects (such as congenital diaphragmatic hernia, hydrops fetalis, some congenital heart diseases, congenital cystic adenomatoid malformation of the lung, myelomeningocele, obstructive uropathy, and placental vascular anastomoses in twins, among other), surgical treatment can be performed in highly specialized services before birth with some success and benefits [17]. However, this is really exceptional. In fact, secondary prevention of CD, with some controversy, is being mainly exerted through the interruption of pregnancy after the detection of foetal anomalies. This is having a considerable impact on the birth frequency of some congenital defects, especially those more easily detectable prenatally. Given that the ECEMC programme has operated since before the passing of the law permitting terminations of pregnancy (ToP) in Spain after the prenatal detection of congenital defects, the evolution of frequencies along the time can be analysed, thereby estimating the impact of ToP on the birth frequency. As an example, Fig. 4.2 shows the time distribution of the birth frequency of anencephaly in Spain, according to data of ECEMC for the period 1980–2008. A statistically significant decrease has been detected, and it is mainly attributable to the impact of ToP. This decreasing trend affects the frequency of many congenital anomalies worldwide, and makes clear the need for research on the causes of congenital defects, in order to exert primary prevention measurements rather than this secondary "prevention".

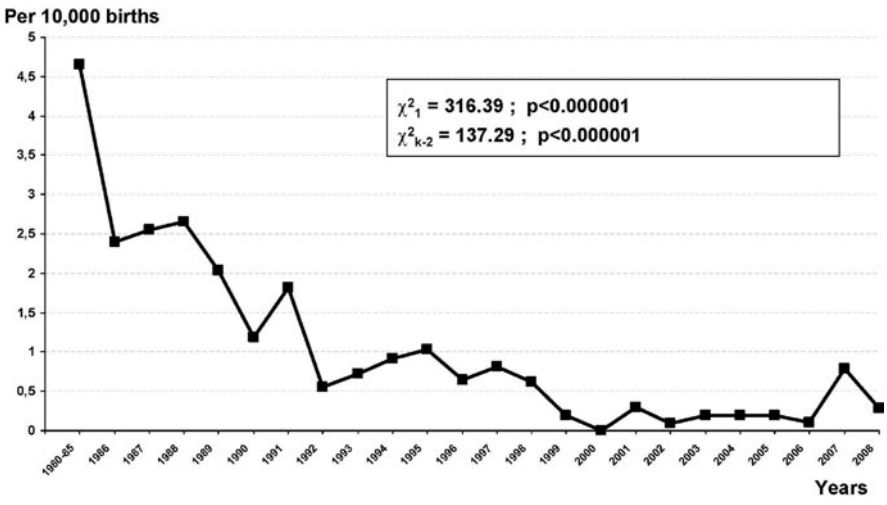

Fig. 4.2 Anencephaly: time distribution of its birth frequency in Spain

4.7.3 Tertiary Prevention of CD

In the last decades, considerable efforts have been dedicated to this issue, and important results have been obtained in the palliative treatment and rehabilitation of patients with some congenital defects, also increasing the social inclusion and consideration of patients.

4.7.4 Quaternary Prevention of CD

In order to avoid unnecessary medical interventions, as promoted with *quaternary prevention*, it is primarily important that all the specialists involved in the diagnosis and treatment of patients with congenital defects provide the patient with, at least, a detailed report of all the already applied procedures and their results. Therefore, these can be assessed by other specialists who may be in charge of that patient later.

Another way to get *quaternary prevention* regarding congenital defects, as well as any other rare diseases, is the specialization of medical groups and services, whether in the diagnosis or treatment of these conditions, so that these pivotal processes can be shortened and unnecessary interventions can be avoided. Of course, this must be accompanied by the proper arrangements in order to facilitate the flow of patients to be addressed to those specialized services. In this sense, it is important to constitute networks which can facilitate providing such specialized medical care, and contribute to a better use of resources.

An issue that deserves some reflection regarding quaternary prevention is *genetic testing.* At the present time, the patients and their families can access a huge amount of information regarding rare diseases, and the research performed in this field. In fact, their inquiries are contributing to promote this research, since they demand more results for diagnosis and treatment. This means that sometimes they want to undergo tests, which do not clearly contribute to rectify, treat, or prevent anything. This situation is especially critical when the undesirable consequences of performing the test may be significant, the risk of disease is minimal, and the benefit of early diagnosis is small.

4.8 Epidemiological Data as the Basis for Congenital Defects and Other Rare Diseases *Prevention*

Along this chapter, an overview has been presented on how a research programme on CD, based on a registry of newborn infants, can contribute to *prevention* and *diagnosis* as well as provide some *services*, the 3 topics heading the chapter. Most programmes on CD worldwide arose as a response to the need for epidemiological data and surveillance after the disaster of thalidomide in the late 1950s and early 1960s. This means that these programmes were organized many years before a general interest had risen about rare diseases, and this has provided them with an

advantage of more information and useful experience. Recently, some authors [90] underlined the medical and social importance of rare diseases, and manifested the lack of epidemiological data for most of the RD. They denounced the absence of a universally recognised coding system as an obstacle for reliable registration of patients in databases that could generate such epidemiological data, as well as the low consistency between sources of information and poor methodological quality. All this makes it difficult to estimate the true burden of rare diseases. In this sense, it has been shown in this chapter how a registry of CD covers research on a wide group of RD for more than 34 years, with data on more than 40,000 infants with CD after having surveyed a total population of more than 2.6 million births, demonstrating that it is able to produce epidemiological data and etiological hypotheses, as well as perform analytical studies that have contributed to the research and knowledge of causes of CD. As expressed by Oakley [82], "The reason we do epidemiology is the expectation that we will improve the health of the public". Moreover, according to new achievements in the field of molecular genetics and anticipating the possibility of performing whole genome studies for larger groups of patients, as they are more easily available, it must be encouraged that biological samples are stored in order to incorporate genomic data to epidemiological studies, which will enhance the possibilities of research on causes in this field, and will help getting prevention.

There are authors with more than 50 years experience [83], who are absolutely categorical and affirm that "Preventing birth defects is urgent!". They claim for more efforts and organization to implement the known preventive measurements, and consider that "Every child who develops a preventable birth defect is a failure of the medical care and public health systems that ignore preventive measures that are available but not implemented". This can be extended to foetuses (not only children), and also applies to other rare diseases. It is important to underline that the known preventive measures should be complemented with research, looking for *primary prevention* rather than secondary or tertiary prevention, in order to avoid the morbidity, disability, dependence and early death associated with rare diseases.

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Chapter 5
The Importance of Case Reports in Advancing Scientific Knowledge of Rare Diseases

John C. Carey

Abstract Case reports are defined as the scientific documentation of a single clinical observation and have a time-honored and rich tradition in medicine and scientific publication. Case reports represent a relevant, timely, and important study design in advancing medical scientific knowledge especially of rare diseases. While there are clear limitations to the methodology of case studies in determination of treatment and establishment of new tests, the observation of a single patient can add to our understanding of etiology, pathogenesis, natural history, and treatment of particularly rare diseases, and to the training of potential junior investigators. In recent years this class of scientific publication has come under scrutiny and disfavor among some in the medical scientific publication community and case studies are frequently relegated to the lowest rung of the hierarchy of study design. In this chapter the author will review and summarize the debate around the scientific publication of case reports in the context of the study of rare diseases and will present a taxonomy that ideally will encourage further dialogue on the topic. Future research on the importance of case reports in advancing knowledge of rare diseases is recommended.

Keywords Case report · Taxonomy · Impact factor · Etiology · Pathogenesis · Study design · Rare diseases

5.1 Introduction

Case reports, the scientific documentation of a single clinical observation, have a time-honored and rich tradition in medicine and scientific publication dating back to the 17th century [9]. This class of published papers often represents the initial account of what later becomes recognized as a highly relevant side effect

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for a specific drug or the original description of a novel human disease [27]. In particular, case reports occupy an important place in the investigation of rare diseases, especially those of genetic causation: Many – if not most – genetic conditions that are currently categorized as "rare" (the topic of this book), were initially documented as single clinical observations or small series. Numerous examples from medical genetics illustrate this tenet: The early reports in the 19th and 20th centuries of neurofibromatosis (now called NF1); the documentation of most human syndromes of chromosomal etiology (e.g. trisomy 18/Edwards syndrome, 5p deletion/cri-du-chat syndrome), and the majority of disorders due to inborn errors of metabolism.

Having said this, case reports have come under scrutiny and disfavor among some in the medical scientific publication community. They are frequently relegated to the lowest rung of the hierarchy of study design [22]. In an investigation designed to examine the frequency of journals publishing this class of article in selected medical journals, Carey [9] documented that 32% of journals did not publish case reports and another 36% published them in some modified format (e.g. on-line only, two issues per year). The purpose of this chapter is to summarize and discuss the issues surrounding the publication of case reports in the context of the investigation of rare diseases.

5.2 Definition of the Case Report

For the purposes of this chapter, I will propose a working definition of the case report that is compiled from various sources: A Case Report is the publication in the medical scientific literature of a single clinical observation whose principal purpose is to generate hypotheses regarding human disease or provide insight into clinical practice [8, 16]. As pointed out by Hunter in her comprehensive treatise on narrative structure in medical knowledge [16], case reports include an "implicit claim to generalizability." The best of this genre usually contain a "single message," generate "surprise" in the reader, and are involved in the "discovery aspect" of the advancement of knowledge in medicine (not in the quantifiable confirmation):

> Evidence-based medicine is exclusively concerned with finding the best evidence for clinical decisions; for example, should we apply a particular therapy or a diagnostic test for a particular patient? Hence a hierarchy of evidence with a randomized trial on top serves one purpose admirably: The final evaluation of therapies or tests, especially when their clinical value is not easily clearcut. Case reports and case series, however, have other aims that are equally important in the progress of medical science and education. These aims are a necessary complement to the aims of evidence-based medicine [27].

Case reports underscore observations, the first step in the scientific method; the subsequent hypotheses generated from the report are the tentative explanations for the observation and deserve further investigation. Picking up on this point, I will provide a working taxonomy of case reports below (see Table 5.1).

Table 5.1 A proposed taxonomy of case reports

I. *Astute observations of etiology and pathogenesis*
Recognition of new disease
Determination of the etiology of a disease
Study of mechanisms of disease
II. *Observations that add to the understanding of patients with a rare disorder*
Recognition of rare manifestations of disease
Detection of drug side effect
Treatment of rare disease based on a few or one case
Addition a patient with a rare disease to the literature
III. *Observation providing lessons in differential diagnosis or in decisions regarding diagnostic testing*

Adapted from Vandenbroucke [27] and Carey [9].

5.3 Possible Reasons for the Recent Decline in Publication of Case Reports

As mentioned above, there has been a notable decline in recent years in the publication of case reports by some journals [8, 9]. The reasons for this may be many, but I will posit two: 1.The notion that case reports represent a lower quality of evidence in the design hierarchy of studies, and 2. The increasing application of the impact factor (IF) in medical scientific publications as a metric. I will address these two explanations separately. In the above quote by Vandenbroucke [27], the issue of the hierarchy of evidence with randomized controlled trials (RCT) at the top was suggested. Various austere bodies in medicine have developed a listing of the quality of evidence with the RCT invariably at the peak and observational epidemiologic studies in between, and case series, case reports, and expert opinion at the lowest rung. Take, for example, the example in *Obstetrics and Gynecology* where Dauphinee et al. [11] showed a recent increase in the number of published articles of an analytical nature in that journal and suggested that the subsequent decrease (anecdotal reports) was an "improvement." The American College of Obstetrics and Gynecology, who publishes *Obstetrics and Gynecology* as their society journal, had adopted the design hierarchy alluded to above.

This particular view clearly has merit: Case reports and “smaller case series” represent investigations that primarily present a numerator with no denominator. No reasonable clinician would determine the use of a successful treatment of a condition or the adoption of a new test based simply on a single patient, i.e. on $N = 1$ [8]. Clearly the issue of chance enters into the decision-making equation and lowers the value of a case report determining management or decisions around choice of testing; however, as will be underscored below, their use in decision making of this nature is rarely the purpose of a case report.

The second issue relates to the now commonly visible and utilized metric, the IF [8]. The Institute of Scientific Information (ISI) calculates and distributes an IF for about 4,000 scientific medical publications on an annual basis. The IF is calculated

by counting the number of cites to articles published in a particular journal in a two-year period over the total number of citable articles published in that same period during the course of the third year. Thus the Impact Factor for a particular journal published in 2009 reflects the citations during the year 2008 from papers published in the journal in 2006 and 2007 (see Carey [8], Dong et al. [12] and the online entry of Wikipedia, www.wikipedia.org). The IF is now used by many libraries in the determination of renewal of subscriptions and is sometimes utilized by promotion and tenure committees in universities to evaluate the potential importance of a faculty member's academic productivity. There are many limitations to interpretation of Impact Factors in relation to the importance of a journal in its field. I refer the reader to the above mentioned reviews where these factors and the limitations of the IF are summarized comprehensively. Suffice it to say here, case reports likely decrease a journal's Impact Factor. In the seminal paper in *JAMA* by Patsopoulos et al. [19], the authors investigated citations for various study designs and found that case reports rarely generated citations as high as 10 during the two-year evaluation period. Patsopoulos et al. [19] found that less than 1% of case reports

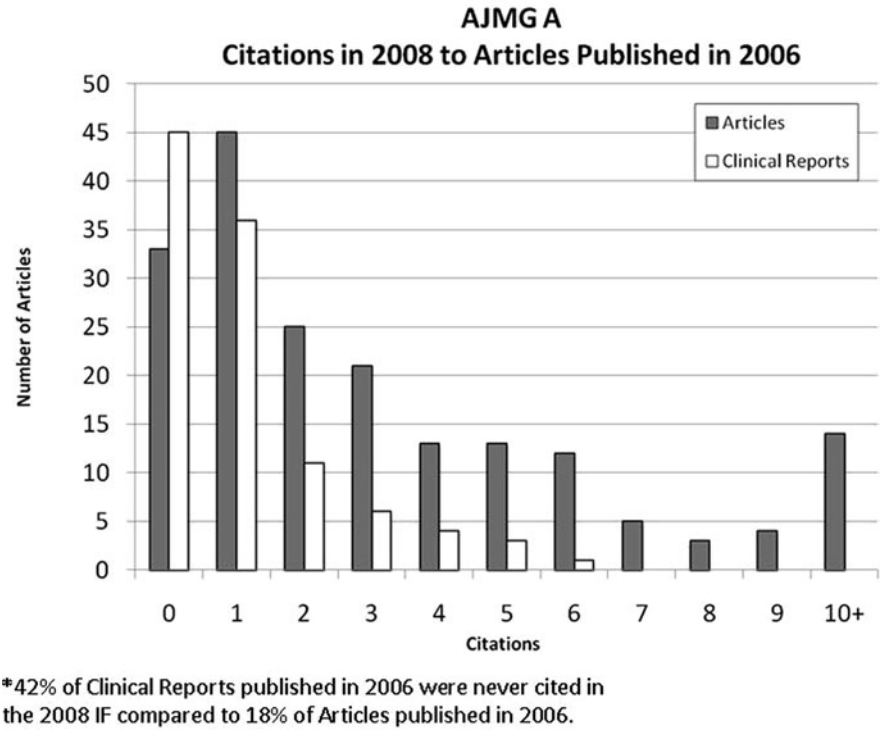

Fig. 5.1 This bar graph displays citations in 2008 by the types of publications of 2006 in the *American Journal of Medical Genetics*. Note that almost 50% of 2006 Clinical Reports were never cited in 2008, which is a much higher rate than Research Articles, several of which had more than 6 citations (figure and data courtesy of Kevin Jeannette and Colette Bean, Wiley-Blackwell)

had greater than 10 cites, compared to 43% of meta-analyses and 29% of clinical trials. I evaluated recent data of this nature for the *American Journal of Medical Genetics Part A*; the Publisher, Wiley-Blackwell, was gracious enough to provide 2008 citation data for papers published in 2006 (see Fig. 5.1). During that period of time 42% of clinical reports published in 2006 were never cited in 2008, while only 18% of research articles in 2006 were not cited in the 2008 year. No case report published in 2006 received greater than six citations in 2008 while many research articles did (Fig. 5.1). Therefore, it is easy to understand why journals who recognize that this metric has importance to academicians and librarians would hesitate to publish papers using this study design.

Biesecker [4] has written an important commentary discussing this issue of the publication of case reports and their potential importance in scientific knowledge. This author advocated two changes based on the concerns about the case reports mentioned above: Discontinuation in the practice of most case reports and the deposition of individual cases in a data repository to facilitate the analysis and pooling of cases. Biesecker's premise was that most reports of individual patients were primarily adding another observation on the condition and are best accessible through international registries rather than peer-reviewed publications. This proposal has definite merit but assumes two things: First, that most case reports are primarily additional patients with a previously defined conditions, and second, that such registries or repositories exist and are available and accessible. As I will point out below in the working taxonomy, additional patients of a known disorder represent only one category of case reports and likely the one that best lends itself to such registries. Secondly, while registries of rare diseases do exist on an international basis, these databases are not easy to fund and not always accessible to all investigators.

5.4 The Importance of Publication of Case Reports in the Study of Rare Diseases

There have been numerous publications in the last decade in defense of continued publication of case reports [8, 22, 27]. From these and stated examples, I will address the benefits of publication and the importance of the case report study design in advancing scientific knowledge of rare diseases.

First, the documentation of astute clinical observations has a long and rich tradition in medicine. The case study relates the story of a patient. The stories of patients comprise the essence of the culture of medicine [16]. This analysis of stories of our patients has evolved into a particular discipline in medical science now called "narrative medicine" [14].

Secondly, single case reports often determine the cause of a human disorder based on a small number of observations. For example, a paper published in the *New England Journal of Medicine* by Feldman et al. [13] describes two infants with the symptom complex of inappropriate excretion of antidiuretic hormone. Based

on the biochemical findings in these two infants, the authors postulated that the basic defect here was a vasopressin receptor defect and proved it by finding disease-causing mutations in the patients. Genetics periodicals regularly publish the causal basis of rare diseases (often of only a few cases) where the discovered mutation defines the cause of the disease; simply peruse the table on contents of any recent issue of the *American Journal of Human Genetics* and this point is illustrated. Novel syndromes of rare diseases (usually comprising a single pair of sibs or one kindred) are published by the major medical genetics journals and often pediatrics journals on a regular basis. The *American Journal of Medical Genetics* features a type of publication called "New Syndrome" and such a paper appears in almost every issue. In the field of clinical teratology, it is often the observation of only a few cases of patients with quite distinctive outcomes associated with particularly rare exposures in pregnancy that leads to the inference of causation, i.e., the exposure causes the syndrome (see Aleck and Bartley [1]). This approach is termed the astute clinician model [10], and is exemplified by the recent determination that mycophenolate mofetil is a human teratogen based on individual case reports [20]. Notably two of the most prestigious and high impact journals in the field of medicine, *The New England Journal of Medicine* and *Lancet*, recognize the potential of a single observation and publish case reports of this nature on a periodic basis (*Lancet* publishes a one-page case report weekly in the journal). In the field of clinical cytogenetics, the observation of a single patient (or two) with a particular chromosome abnormality establishes causation and exemplifies this point. For example, Van Bever et al. [25] determined that the cryptic deletion of subtelomeric 1q characterized a recognizable syndrome (see Table 5.2).

Thirdly case reports provide the clinical foundation for clinicians and scientists to postulate on the pathogenesis of the condition at hand. For example, South et al. [23] described an interesting child with a distal deletion of 5p who had the so-called cri-du-chat syndrome. The mother of the child had a paracentric inversion of the 5

Table 5.2 Proposed classification of cytogenetic case reports in the human/medical literature (with examples)

I. *Astute observations of etiology and pathogenesis*
  A. Etiology –
    1. Novel duplication or deficiency associated with discrete phenotype (Van Bever et al. [25]).
    2. Localization of a candidate gene due to a chromosomal rearrangement (Bocian and Walker [5]).
  B. Pathogenesis –
    1. Insight into a basic mechanism (Boyd et al. [7], South et al. [23]).
    2. Genotype –Phenotype correlation: Delineation of a critical region for a syndrome (Rodriguez et al. [21]).
II. *Observations that add to the collection of patients with a rare disorder*
  A. Novel manifestation/important complication in a known condition (Böhm et al. [6]).
  B. Additional Patient with an established condition/registry-type patient (Balci et al. [3]).
III. *Observation providing lessons in differential diagnosis or in decisions regarding diagnostic testing* (Takagishi et al. [24])

Modified from Carey [9].

short arm, a finding not usually considered to cause imbalance in offspring. These authors demonstrated quite elegantly that this maternal paracentric inversion led to the deletion in the child and elucidated a novel pathogenetic mechanism for chromosome 5p deletions.

In the context of rare diseases, a case report can add an important and relevant new manifestation of a disorder and thus characterize its natural history or can suggest a therapeutic option that could not occur otherwise since in rare diseases the opportunities to develop a RCT does not occur. In the former example, Al-Rahawan et al. [2] described a patient with hepatoblastoma who had the cardio-facial -cutaneous syndrome (CFC) and thus suggested that there may be a low but definite tumor risk in this syndrome. This observation is relevant since other conditions in the ras pathway are conditions with significant neoplastic risk (NF1, Costello syndrome). In regards to treatment, Hoffman et al. [15] documented improvement in the rickets of a patient with linear nevus sebaceous syndrome with octreotide, not only demonstrating the improved course but also proposing pathogenesis.

The exercise of publishing an important clinical observation in the literature often provides a rich opportunity to students, residents, fellows, and junior faculty who have an interest in or are beginning their career in academic medicine [18]. Thus the process of writing a case report can have a teaching and training function as well as providing a scientific contribution.

There are two other benefits of publication of case reports: the addition of cases to the ongoing collection of patients with a rare disease and the case observation that provides lessons in diagnosis or testing. The former of these two observations is primarily what Biesecker [4] was referring to in his paper, and I will refer to as the" registry" type of case report (Table 5.2). The other is the report that represents a surprise in the practice of medicine which provides a lesson. An example in medical genetics is the patient with an intellectual disability who has a relatively normal phenotype yet has a chromosome abnormality (e.g., Takagishi et al. [24], Table 2).

One of the areas where case reports have had the most amount of discussion relates to the so-called "anecdotes" of suspected adverse drug reactions in a single patient. These reports are common in the medical literature and more than 1,000 such observations were cited in one annual report of side effects of drugs [17]. Here the issue of a single observation determining management mentioned above enters. Some argue that case reports are of extremely limited value and it would be very premature to translate the information to clinical practice without better evidence, while others have argued that these observations in drug side effects have excellent predictive accuracy for bona fide drug reactions (for an excellent discussion of this topic see Loke et al. [17]).

5.5 Proposed Taxonomy of Case Reports

In two seminal papers Vandenbroucke [26, 27] proposed a taxonomy for case reports. Carey [9] suggested a hierarchy of reports indicating that certain astute observations had more value and importance in advancing medical scientific

knowledge than others. A classification of cytogenetics reports was used as an example of the concept [9]. In Table 5.1, I have combined the previous proposals of Vandenbroucke [27] and my paper [9] to suggest a working taxonomy of case reports in a hierarchical fashion. The point here is that those at the top (like RCTs at the top of design hierarchy) have more relevance and importance to medical scientific knowledge than those at the bottom. This taxonomy is meant to be a dynamic proposal with the aim that this represents a tentative set of guidelines meant to encourage future dialog on this theme.

Table 5.2 is an updated and expanded version from the prior publication [9] utilizing this hierarchy in the context of clinical cytogenetic reports. As mentioned, most reports describing conditions of chromosomal etiology fall into the rare disease category. The format in Table 5.2 can be applied to any class of rare disease, e.g., the description of single gene mutations.

5.6 Summary and Conclusions

Case reports represent a relevant, timely, and important study design in advancing medical scientific knowledge. While there are clear limitations to case reports in determination of treatment and establishment of new tests, the observation of a single patient can add to our understanding of etiology, pathogenesis, natural history, treatment of particularly rare diseases, and the training of potential junior investigators. Interestingly, interest in the publication of case reports seems to be rising in this decade. Two new journals produced by BioMed Central are devoted entirely to the open access publication of single clinical observations: The *Journal of Medical Case Reports* and *Cases*. Both periodicals have separate editor-in-chiefs, editorial offices and scopes. In addition, the prestigious high-impact journal, *Lancet*, continues to publish important and relevant single clinical observations in a one-page paper on a weekly basis. Recently, the *British Medical Journal* announced an interest in publishing appropriately documented case reports. Finally in the light of this discussion it is important to acknowledge a noteworthy journal in the field of clinical genetics, *Clinical Dysmorphology*, who continues to focus on the documentation of single case reports and astute clinical observations despite the potential effects on impact factor.

For future directions, I have three recommendations: 1. The continued establishment of clinical data repositories and registries; these should be developed in a systematic and standardized way and will require creative approaches to securing funding; several genetic support groups throughout North America and Europe, have established patient registries (e.g. Support Organization for Trisomy 18, Trisomy 13, and Related disorders [SOFT], the Joubert Syndrome and Related Disorders Foundation, and CFC International), and these databases could provide starting points; 2. Further dialogue on the proposed taxonomy of case reports; 3. The encouragement of future research on the importance of case reports in advancing knowledge of rare diseases.

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Chapter 6
Patient Registries: Utility, Validity and Inference

Rachel Richesson and Kendra Vehik

Abstract Patient registries are essential tools for public health surveillance and research inquiry, and are a particularly important resource for understanding rare diseases. Registries provide consistent data for defined populations and can support the study of the distribution and determinants of various diseases. One advantage of registries is the ability to observe caseload and population characteristics over time, which might facilitate the evaluation of disease incidence, disease etiology, planning, operation and evaluation of services, evaluation of treatment patterns, and diagnostic classification. Any registry program must collect high quality data to be useful for its stated purpose. Registries can be developed for many different needs, and caution should be taken in interpreting registry data, which has inherent biases. We describe the methodological issues, limitations, and ideal features of registries to support various rare disease purposes. The future impact of registries on our understanding and interventions for rare diseases will depend upon technological and political solutions for global cooperation to achieve consistent data (via standards) and regulations for various registry applications.

Keywords Registries · Public health surveillance · Clinical research · Epidemiology · Rare diseases

6.1 Patient Registries in Rare Diseases

6.1.1 Definition

In this chapter, we define patient registry as an organized program for the collection, storage, retrieval, and dissemination of a clearly defined set of data collected on identifiable individuals for a specific and specified purpose, as well as the collected

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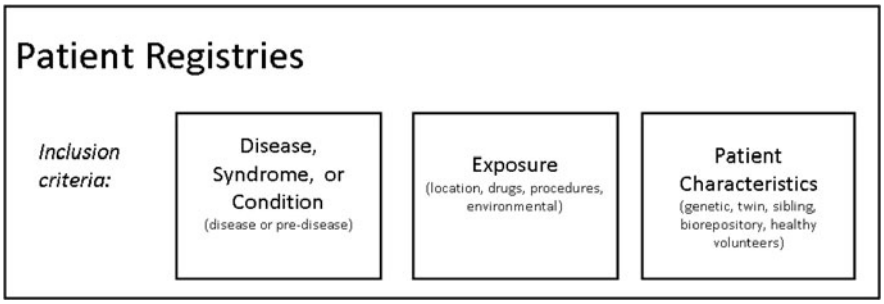

Fig. 6.1 Types of patient registries

data. This extends previous registry definitions by viewing a registry as not only a database, but also a systematic data collection program [13–36]. We deliberately exclude other registry types that inventory non-human entities such as orphan drug products, medical devices, clinical trials, or trial results. Although there are various definitions for patient registries in the public health literature, there is a general consensus that the term registry implies follow-up and change in status of cases over time [4, 5, 19].

As shown in Fig. 6.1, patient registries have 3 broad types of inclusion criteria: disease (or condition or syndrome), exposure (e.g., medical or surgical treatment, medical devices, environmental), and patient characteristics (e.g., genetic, twin, sibling, healthy controls). Disease and exposure registries are the most common types of registries, but the number of Patient Characteristics-based registries is increasing each year due to a surge of new genetic registries. The annotated data records associated with biological repositories ("biobanks") also can be thought of as registries of patient characteristics (usually genetic) with a biological data collection component– and the presence of these collections is growing rapidly.

6.1.2 History

The first known disease registries go back at least several hundred years with registries in leprosy and tuberculosis [21–22, 47]. The emergence of chronic diseases as a public health problem sparked a persistent proliferation of patient registries (which continues today) in the 1950s [19]. A recent review article found over 43,000 articles in the scientific literature (2000) referring to registries [10]. Cancer-specific registries grew explosively from thirty-two registries in 1966 to 449 cancer registries representing five continents in 2006 [27].

For rare diseases, patient registries are often the first step in estimating prevalence or incidence, and building a cause for future research and facilitating enrollment in trials. Genetic sequencing has lead to the identification of new diseases, which in turn has spawned the creation of numerous disease-specific patient advocacy groups which are demanding and funding new disease-specific registries in rare diseases.

While registries were first born from government departments to support core public health functions, many successful and large registries have since been established by patient-driven organizations. The creation of a registry is not merely a rite of passage to get a rare disease "on the map" for funding priority, but has become a fundamental early step in the understanding of the natural history of disease and the development of clinical endpoints, patient reported outcomes and baseline data to support formal evaluations of therapeutic interventions. In the United States, the NIH and the FDA are actively charging rare diseases special interest groups to develop registries in parallel to the identification of disease assays and drug compounds [39].

Concerns about the safety of new drugs (especially biologics with uncertain long term outcomes – e.g., thalidomide, human growth hormone), and desire for large-scale, real-world safety and efficacy data on marketed drugs (as well as combination therapies), have fueled the proliferation of patient registries for use in post-marketing activities. The use of registries for post-market monitoring (Phase 4 studies) of approved drug products has also increased in recent years. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA) in the United States, the FDA can mandate post-approval requirement studies and Risk Mitigation and Evaluation Systems (REMS) as a condition of approval for new products with potential safety issues [15].

6.1.3 Characterization of Registries, Their Uses, and General Requirements

The unending proliferation of registries and the need for global cooperation for rare disease research create a situation desperate for standards and best practices for patient registry projects. The large number of registries, and the various purposes and stakeholders for each, complicate any attempts to inventory, standardize, or prescribe good design features for patient registries in general. There have been a few attempts to characterize types of registries by their data source (local hospital, regional (∼multiple hospitals), and population-based (∼multiple data sources) [28] or by the database and data characteristics [10]. Characterizations of registries by purpose may simply delineate registries as either clinical or research [19]; or by more detailed purposes [6] which inspired the characterization we present in this chapter. Others consider the manifold impact of registries as supporting the classic medical school triad of research, service, and teaching [42].

We present a characterization of registries by purposes, and suggest some essential requirements to support various purposes. As displayed in Table 6.1, registry uses can fall into 6 (non-exclusive) categories of usage: Public health, health services research, health promotion, patient care, clinical research, and regulatory (public safety). Registries can be developed to serve multiple purposes. Based upon the primary purpose of the registry, the columns depict whether the selected primary registry function necessarily dictates an *absolute* requirement for: completeness of case ascertainment, extensive clinical data, verification of data validity, and follow-up. The table is designed to indicate which types of registries need this

Table 6.1 Purpose of registry and essential requirements

Purpose	Essential requirements			
	Completeness of Case Ascertainment	Clinical data *(beyond diagnosis or procedure)*	Verification of Data Validity	Follow-up Data
Public health ("population-based")				
• Population surveillance	Yes	No	Yes	No
• Contact notification	Yes	No	No	No
• Patient compliance (for management of infectious diseases)	Yes	Yes	Yes	Yes
• Planning (community and service)	Yes	No	No	No
• Policy	Yes	No	No	No
Health services research				
• Evaluation of health care/education delivery	Yes	Yes	Yes	No
• Facilitate health utilization, treatment patterns	Yes	No	Yes	Yes
• Monitoring health services	Yes	No	No	No
• Measuring healthcare quality	No	Yes	Yes	Yes
Health promotion tools and education				
• Patient education notifications	No	No	No	No
• Physician education notifications	No	No	No	No
• Aggregate data for patient education/support	No	No	No	No
Patient care				
• Chronic disease management	No	Yes	Yes	Yes
• Vaccination	Yes	No	No	Yes
Clinical research – funding and support				
• Research funding decisions	No	No	No	No
• Research planning and design	No	No	No	No
• Cohort selection	No	Yes	Yes	No
• Recruitment – outreach to patients	No	No	No	No
Clinical research – scientific inquiry				
• Cross-sectional	Yes	Yes	Yes	No
• Longitudinal	Yes	Yes	Yes	Yes
Regulatory				
• Safety of agents (post-marketing)	Yes	Yes	Yes	Yes
• Efficacy of agents (post-marketing; phase 4)	Yes	Yes	Yes	Yes

[a]Clinical data – additional data beyond the data elements required for determining eligibility for the registry. Eligibility is determined either by disease, exposure, or patient characteristics.

to fulfill stated functions in any capacity. For example, while clearly verification of data validity and completeness of case ascertainment is a desirable feature for any registry, for some purposes (e.g., the use of registry for scientific or epidemiologic investigation), the verification of data and assurance of complete case capture

is of utmost importance, where as in other applications, for other purposes, such as advertising for clinical trials, the lack of data verification or incomplete case ascertainment does not impede the registry objectives.

There are many data quality and bias issues, mostly related to case ascertainment, data validity, and follow-up, which limit the utility of registry data for various purposes. These must be clearly understood by registry users and considered in the design of any registry. In the next section, we describe the major limitations and biases associated with patients registries.

6.2 Data Quality, Bias, and Limitations of Patient Registry Data

Developers of registries and potential users of registry data must be keenly aware of the inherent limitations of certain registry designs for certain functions, particularly in the exploration of research questions involving treatment evaluation. A registry must have high quality data to be useful for any research purpose. Two fundamental concerns related to gauging the quality of registry data include completeness of case ascertainment and validity of values for each data point [19]. Timeliness of data has also been noted as a quality indicator [27]. For registries requiring follow-up data, the proportion of follow-up obtained and the nature of cases lost to follow-up must be provided.

6.2.1 Completeness of Registry

Disease registries for epidemiologic purposes are largely designed to ascertain cases of a specific disease for public health surveillance and planning. The primary metrics used are incidence and prevalence of a disease. Completeness of case ascertainment for infrequent or rare disorders is an essential measure to determine the accuracy of the true incidence or prevalence in a population. The idea behind any registry endeavor is that the registry is a tool to either count or characterize health or disease characteristics in a *sampled* population, with the intent to extrapolate those results back to a larger or different population. The completeness of case ascertainment (i.e., the inclusion of all cases in the sample area time or place) therefore has implications for the conclusions and the extrapolations made to the general population.

The capture-recapture methodology has long been the “gold standard” for determining completeness of case ascertainment. Originally, this method was first used in wildlife biology to study fish and wildlife populations [35, 36]. The simplistic model was used to estimate the unknown size of ecological populations. In human populations, the capture recapture methodology still utilizes the two-mode ascertainment model (e.g., physician provider versus hospital data); although, multiple models can be employed [9]. Cases are identified from multiple sources, where a source is defined as any location where a case was reported. Using the various sources, cases are matched to identify duplicate ascertainment across sources.

The sources are grouped into "modes" of ascertainment. The capture-recapture method is used to estimate the size of the unknown total population with a specific disease (condition or exposure) by capturing them in one mode and recapturing them in another mode(s). Based on the assumption that the probability of capturing cases in both modes would be equal to the probability of capturing cases in each mode, the number of missed cases can be estimated and the completeness assessed [40]. The percent completeness of ascertainment is defined as the number of observed cases divided by the estimated number by capture-recapture methodology.

6.2.2 Types of Error and Biases Associated with Registry Data

There are two types of measurement error that can affect the accuracy in estimation: random and systematic. Random error is unpredictable and is associated with precision. It often leads to inconsistency in repeated measures. This type of error is usually due to chance alone. Systematic errors are biases in a measurement that distort the measured values from the actual values. There are many sources of systematic error, such as instrument calibration, environmental changes, and procedure changes. Methods for the collection of certain data, such as anthropometric or genetic, may change over time and introduce error based on a specific time period of collection. The error would be considered systematic in that time period leading to differential misclassification. Alternatively, if a specific genetic test with inaccuracy is used to determine a case for all subjects in a registry, there still would be error, but the error would be constant. In any registry application, including for rare diseases, it is important to identify the possible sources of error and assess the impact the error will have on interpreting the results.

Bias is "any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease" [33]. Selection and information bias are the two main biases that affect registries. Selection biases are distortions that result from procedures used to select subjects for the registry or from factors that influence participation or inclusion [32]. One example is *self-selection bias* (also called healthy-worker/volunteer effect), where "healthier" participants disproportionally enroll in the registry, creating a false impression that the burden of disease is less or that the survival is increased. For epidemiological purposes, it is difficult to use registries to estimate population-based rate estimates for rare disease, because most rare disease registries are based on self-selection or hospital-based data collection. In this situation, it is difficult to determine a denominator of "at-risk" subjects because only those cases seen at the hospital or through self-selection are included in the registry. This type of bias will create distorted characteristics of the case population when looking at registry data. *Information bias* results from systematic errors in the measurement of either the exposure or the disease. Sources of this bias include poor questionnaire/survey design, data collection procedures ("interviewer bias"), selective recollection of exposures ("recall bias"), and imprecise diagnostic procedures.

Although both selection and information biases impact the estimates produced from registry data, the degree of their affect depends on how the data were collected. If the degree of inaccuracy of the registry selection (i.e., inclusion) or the data collection is uniform across the sample, then it is non-differential in that it affects the entire monitoring process rather than just a specific piece of the process. This type of bias predominately underestimates the result. However, if the inaccuracy of the data differs across the population, such that for example, those who are selected differ from those that are not included in the registry, then the bias is differential and can impact any interpretations of the registry data as a whole. These impacts are difficult to disentangle without using methods to control for confounding.

Misclassification is a type of bias generally associated with categorical or discrete variables. This type of bias is usually introduced into registries by inaccuracies or variation in methods of data acquisition and case/exposure definitions, as mentioned above. This bias can be differential or non-differential depending on how it affects the values of other variables associated with the variable of interest. Differential misclassification is dependent upon the values of other variables (e.g., a case defined in a hospital would not be defined the same in an outpatient setting). This type of bias can skew any summary data from the registry. Non-differential misclassification does not depend on the values of other variables, such that the misclassification of an exposure, for example, is not dependent upon the disease status.

Changes in the diagnostic criteria for a disease can affect the comparability of cases in a registry over time. *Lead-time bias*, for example, results from advances in testing (e.g., disease-specific genetic screening and testing) that lead to an earlier identification of disease. Patients can theoretically join a registry before symptoms even begin and represent "healthier" individuals than in previous years. Any examination of data characteristics (types of treatment, symptoms, survival time) could show an improvement over time that is not necessarily attributable to effective medical care but rather to the fact that the cases are being identified earlier in the disease process. Similarly, technologies that can identify diseases non-invasively or earlier in the course of disease can influence the number of cases detected, and markedly inflate the number of new cases, creating the false impression that the incidence of the disease is increasing.

Variability is a random bias that may attenuate true associations in epidemiologic measures, but is not intrinsically fatal to certain registry objectives. With-in subject variability tends to average out for repeated measures (e.g., blood ammonia test for urea cycle disorders); whereas, observer/measurement variability can vary on its overall effect on the measure of interest. This variability is usually random but can be systematic if different observers or instruments are introduced or not properly trained or calibrated. To reduce systematic bias it is important to make sure that observers or data collection instruments observe or measure data consistently from all subgroups of the sampled population.

Sensitivity estimates how successful a registry is at identifying all of the events, cases, or exposures in the target population. Sensitivity is the probability that a subject who is truly diseased (or exposed in case of exposure registries) will be classified as such by the method used for ascertainment. The level of sensitivity is

based on the purpose of the registry. If the registry is purely to monitor trends in disease then a low sensitivity is satisfactory. However, if the purpose is to assess the distribution or impact of a therapy then high sensitivity is needed.

6.3 Best Practices for Patient Registries in Rare Diseases Research

The unending proliferation in registries is driving a need for registry best-practices. Based upon the limitations mentioned above we can adopt some general guidelines, mostly from the public health practice literature [36], for first determining the appropriateness of a patient registry for a given purpose, and best practice for developing and maintaining various types of patient registries. Foci should be on methods that maximize and quantify the level of case ascertainment, and limit (or measure) the presence of the biases discussed earlier.

6.3.1 Evaluate Alternatives

Before even considering a registry, the motivations and long-term commitment must be thoroughly explored. Costs for even a simple administrative registry can be expensive. Long term, multi-national registries that capture clinical data can employ dozens to hundreds of people at tremendous expense. More efficient and cheaper alternatives to registries, such as cross-sectional surveys or short-term or limited catchment studies, should always be considered before establishing a new patient registry. Particular caution should be exercised in opening new registries when the primary motivation is epidemiological. The epidemiologic usefulness of a registry increases the longer it has been in existence, often meaning that data collection, documentation, and quality control activities be conducted for many years before a register becomes fully productive for epidemiological purposes [46]. As a general rule, patient registries require continual funding and long-term commitment, and should be undertaken only with strong assurance that the registry will be needed and will be funded for years or decades into the future. As summarized by Wedell in a 1973 review: “The critical question is: can this be done any other way?” If the answer is “yes”, then registry planners should consider them heavily [44].

6.3.2 General Methodology and Best Practices

Based upon the intended purpose, certain functionality and best practices will be required. Broadly, the functionalities relate to those presented in Table 6.1: completeness of case ascertainment, type of data collected, verification of data validity, and patient follow-up. The development of registry procedures and data

specifications depend upon the goals of the registry and the stakeholders involved. General stages in the development of a registry projects are presented below.

6.3.2.1 Develop and Document Explicit Goals for the Registry

The ideal design and scope of a registry data collection system is determined by its intended purpose and funding. Once decided that the development of a new registry is warranted, the first step is to develop clarity and consensus on the goals for the registry. Any registry endeavor should start with a clear description of the purpose, which should be vetted through and consensually agreed upon by various stakeholders. Stakeholders for patient registries include patients and families, clinicians, genetic counselors, industry, patient advocacy groups (often multiple), and regulatory agencies – especially if the registry is being developed to support future drug development and approval. The U.S. FDA has encouraged researchers and patient groups to incorporate "regulatory sufficiency" into registry design, with the assumption that the data collected in registries will support the evaluation of treatments in therapeutic trials. Of particular importance is the development of clinical endpoints that will be acceptable to regulatory agencies at the time of pre-marketing drug research. Therefore it is beneficial to engage in dialogue with regulators regarding the appropriateness of various proposed registry data points for future phase 2 and 3 trials in a given disease area.

It is particularly important to note the differences between etiological and therapeutic research, as well as the inherent limitations of registries and observational research designs for the latter [20]. For any comparison of treatment effectiveness, the randomized clinical trial remains the ideal, and perhaps the only credible, means for conclusion – despite the logistic and ethical challenges [31, 24]. The need for randomization emerges from the likely presence of patient or care-related characteristics that are subtle, complex, and unknown, and not easily subject to quantification. These characteristics, then, act as confounders and potentially mask any attempts at comparison. In practice, whenever a rational indication for intervention exists, confounders are likely [24].

6.3.2.2 Develop Leadership Structure and Policies for Data Storage, Protection, and Access

Once the purpose and goals of the registry are clearly defined, then issues of data ownership and security need to be addressed. These issues affect the enrollment of individuals in the registry, and need to be clearly disclosed to all potential registry participants, as part of the informed consent process. Before any data is collected, a data sharing and release policy needs to be developed and documented, and a governance structure for the registry will be required. It is critical to have this in place to ensure that registry data is protected, but also disseminated to trusted parties for review and action. Technical solutions for registry transactions and relevant data security should be driven by the policies and requirements set forth by registry leaders.

6.3.2.3 Develop Adequate Infrastructure

A registry should be conceptualized as a multi-disciplinary endeavor, and the skills of a multi-disciplinary team are crucial. Registry efforts should include active involvement of epidemiologists and biostatisticians as well as technical and informatics specialists. The multi-disciplinary team should engage in discussions on the best approach to capture the most valid data on the most cases (or the most representative cases) possible. The goals of the registry will be both the driver and the benchmark for measuring success, and will drive iterative discussions on the design and operation of the registry.

6.3.2.4 Identify Data Sources

The scope, purpose, and funding commitment of the registry also influence decisions about data source (e.g., medical record abstraction, patient self-report) and the aggressiveness of follow-up. The limited resources that are true of any registry project are weighted against the strengths and weaknesses of various data sources. All possible data sources, including existing sources such as death records, related registries or epidemiologic studies, and healthcare records, should be listed and considered at this phase. Small pilot investigations or review of previous work can help determine the suitability of the data source to meet the purpose of the registry will be required. Some data sources that are suitable for applications in prevalent diseases will have particular limitations for rare diseases. For example, although mortality data is often a good data source for chronic disease epidemiology, these data are not suitable for rare diseases, many of which are undiagnosed, or "lost" in the death certificate coding system that lumps various rare diseases under a more general heading "other". For epidemiological prevalence studies in general, the use of multiple data sources is preferred to fully understand the disease activity in a given region, and might be required for many rare diseases. For most rare disease registry projects, there may not be any existing data collection sources that are appropriate, and new organizational mechanisms for recruitment, enrollment, data collection, and follow-up will need to be devised. If the registry data is to be used as if it was collected from a prospective longitudinal hypothesis-driven study, then the rigor, documentation, enforcement, and validation of registry data collection should be subject to the same methodological consideration as a rigorous natural history study. In this regard, registry developers should consult established clinical research methods and best practices [12]. A detailed research protocol is required for registries developed specifically for post-market approval studies [15].

6.3.2.5 Identify Inclusion/Exclusion Criteria, Including Case Definitions

Standardization of data definitions and clinical diagnostic criteria is critical to ensure valid and reliable data for all registry purposes. More detailed examination of representative subsamples might be conducted to validate large survey results, and feedback of the results of validity tests are the primary objectives for

registry developers. For exposure-based registries, the length or circumstances of the exposure, and the method for determining it (e.g., patient-report, public records, pharmacy data) will need to be outlined. With genetic registries, the test method will need to be specified clearly. It is particularly important to standardize and document in registries employing follow-up. As diagnostic methods change over time, combining cohorts becomes difficult because the case populations have changed. In these cases, analysts are forced to use the "weakest" case definition that can be derived for all registry cohorts.

6.3.2.6 Sampling and Surveillance Methods

Passive and active surveillance are two alternative approaches to identifying cases. Passive surveillance is the approach where the registry does not contact possible reporters directly but rather leaves the reporting to others, such as, mandated or systematic monitoring system (i.e., physician's are mandated to report cases of influenza or cancer). Active or epidemiological surveillance is an approach where the party conducting ascertainment initiates procedures to obtain data through telephone calls, mailers or visits with physicians or hospitals. Based on the method of surveillance, bias can be introduced. Passive surveillance is most likely affected by systematic error due to its standard monitoring process; whereas, active surveillance is most affected by selection bias. Internet-based registries where patients self-select to enroll are considered passive surveillance, and are affected by both systematic bias and selection bias. When doing surveillance, whether active or passive, it is important that the approach used is consistent and documented in detail.

In registries designed for epidemiologic research, it is necessary to check regularly the completeness of case ascertainment – both to evaluate the effectiveness of the outreach and to understand any biases that will affect data interpretation. Eligibility and data collection from each registry case must be collected in a standard manner. Observations on the characteristics of (diseased) cases should be compared with data on the general population (from census, special population surveys, or by matched control studies) [46]. With genetic registries, the test method will need to be specified clearly, with the understanding that tests will change, metrics of the tests are questionable, and variability between labs will exist.

6.3.2.7 Design Data Collection Instruments

The most basic and important piece of all registries is the design of the data collection tool, which usually is a data collection form or patient-directed survey. The content of the form (i.e., the data collected) is, of course, driven by the goals and resources of the registry. Most registries capture disease, exposure, demographic, severity and treatment information, as well as some identification number or means to uniquely identify patients and prevent duplicate records in the registry. Important data to include for rare diseases are genetic factors to establish genotype-phenotype correlations, family history, concomitant medications, and medical or surgical interventions. The data to be collected in a survey tool must be specific to the objectives

of the study and associated analyses to be conducted. One tendency that investigators should be deterred from is trying to collect or measure too much. Data collection is a tedious and time-consuming process, so it is important to limit metrics that are of secondary importance.

Each variable included for measurement should have an operational definition and guide for collection to allow for standardized collection and comparison across registries. It is the nature of sampling tools that measurement collection will vary across reporting organizations and it is necessary that the technique used is comparable to what would be used in a clinical or laboratory setting. This will reduce bias and increase validity and repeatability of the findings from an analytical standpoint. Important characteristics of a metric in the context of a survey include its acceptability to subjects and researchers (i.e., minimal response burden), validity (i.e., does each data element truthfully measure what it is supposed to?), and reliability (i.e., can the instrument yield replicate metrics or estimates?). It is very important that the survey tool used is standardized across settings or regions (e.g., countries) and that the definitions used to identify a case is the standard used in the reporting community.

Procedures for data quality and completeness should be developed before data collection begins and evaluated regularly. This might include training and testing of observers/data entry staff, and the use of standard or clinical reference material which all data collection centers can calibrate to. Periodic review of the data can identify data elements or system features that need refinement to produce quality or complete data.

The costs for clinical data collection are huge, and many registries are considering patient-reported data as an alternative. Future studies will illuminate which types of data can be reliably reported by patients (e.g., quality of life, functioning, family history). Additionally, future studies might provide insight regarding methods for verifying patient-reported data, thereby increasing the validity of the data while still utilizing economically viable data sources [25].

6.3.2.8 Plan Follow-Up Data Collection Procedures

Perhaps one of the most expensive registry activities is the collection of follow-up data. The frequency and method of follow-up are influenced by both the purpose of the registry and the resources available. A statistical analysis plan should be developed at the design phase of the registry. Inconsistent follow-up procedures and success can lead to significant bias and affect the interpretation of registry data. In addition to aiming for complete patient follow-up, registry developers will need to characterize those lost to follow-up.

6.3.2.9 Continually Re-evaluate Purpose and the Registry

Communication between registry stakeholders and registry leadership (both governance and implementers) is vital to a registry, and there should be continuous dialog between all interested parties throughout the life of a registry. There is an inevitable

trade-off between limited time and resources and the amount and quality of the data, and this must be recognized by registry stakeholders and leadership. The value of a registry must be re-examined periodically to ensure that the objectives are still relevant and obtainable [44]. A plan or criteria for closing the registry should be specified at the start of the project [15].

6.4 Data Standards

Standards should certainly be given priority and consideration at the design of any registry project. Because data standards are continually evolving, there is current opportunity for rare disease investigators and activists to engage in standards development activities. There are currently no standards for developing registry programs, systems, or data collection instruments. A critical and largely unaddressed problem for registries is the need for tools that allow registry data collection forms and their component questions and answers to be encoded in such a way that they can be retrieved for re-use (e.g., to support the rapid development of another related rare disease registry) or that the collected data can be interoperable with other data sources (e.g., Personal Health Records or Electronic Medical Records.)

Broad areas of standardization that need to be considered when developing a registry include the choice of data content and structure. Specifically, a data model (~data fields) and associated controlled terminologies must be selected. These of course must address the objectives of the registry, but also enable any interoperability needs that might conceivably emerge in the future, and follow standard regulations where applicable. Both of these requirements are vague and dynamic so it is impossible to prescribe a universal set of standards. The dominant discussion forums for moving toward clinical research data standards that support applied uses are the Clinical Data Standards Interchange Consortium (CDISC) and the Regulated Clinical Research (RCRIM) Technical Committee of Health Level Seven (HL7). Compelling use-cases for shared clinical and research data drove the development of the BRIDG domain analysis model as a shared model to harmonize both sets of standards [17]. New and forthcoming pilot projects sponsored by HL7 and CDISC that demonstrate the use of common data elements and the BRIDG for specific therapeutic areas (e.g., cardiovascular, tuberculosis, and diabetes) should be monitored and explored as a source of standardized questions for rare disease registries [3, 7, 45]. Similarly, the most recent CDASH recommendations are promising in terms of standardizing form and section names (e.g., Patient Characteristics Form, Concomitant Medication Form, Medical History Form) [16].

Useful standardization of registry data collection forms should enable unambiguous, consistent, and reliable re-use of questions, answers, and groups of question/answer sets among different registries. Standards for the representation of common sets of questions and answers are maturing (e.g., CDISC, caDSR/caBIG), though implementation is still not common, and their encoding with standard terminologies is not done consistently [26, 30]. Semantic encoding of data elements (i.e., question + answer + definition) is very prone to inter-coder variability

[2, 29], and makes consistent querying based on these "standard" codes difficult and unreliable.

Previous research and the current U.S. federal standard for standardized assessment instruments have shown that a combination of standards (specifically LOINC® & SNOMED CT) are ideal to represent first the structural and generic features of questions and then the clinical content [8]. Promising feasibility studies have been conducted on small samples of questions in nursing, mental health, and public health [3, 7, 45]. Other standards, such as a recent (December 2008) standards recommendations put forth by the American Health Information Community's (AHIC) Family Health History Multi-Stakeholder Workgroup to the Office of the National Coordinator (ONC) can identify data elements for family history data collection, although controlled terminology such as SNOMED CT has not yet been incorporated into the standard [16].

One of the most important constraints for rare disease registries is coding and classification – both for finding related registries and linking them to other relevant data sources. There is no global "master index" of registries, so it is hard to know if a new registry is duplicating work or could be an extension of an existing program. Registry participation could be increased if people/physicians could be aware of all registry opportunities, and not asked to submit data to separate but related registries. There is a need for standards to "organize" or inventory registries. The Orphanet project in Europe (http://www.orpha.net/consor/cgi-bin/ResearchTrials_ParticipateClinicalResearch.php?lng=EN) maintains a database of rare disease registries in European and surrounding countries, although it is unclear how perfect the inventory is considering the need for continuous data collection, and the fact that the system is voluntary.

6.5 Ethical and Policy Issues

The notion of a physician-controlled registry (e.g., the "shoe-box of index cards") is a thing of the past due to availability of information technology and increasing proportions of privately funded medical research. The first activity of any registry effort is to define stakeholders, data policies, and a governance structure. If there is any possibility that a registry will be used to support research, then institutional review board (IRB) approvals will eventually be needed for planned research, and likely for the registry program itself. This will require documented procedures that ensure the integrity of the registry data and the protection of the individual participants.

There are several important ethical and policy considerations that need to be explored for registries that will operate in a multi-national context. This is especially clear in the EU, where a mix of policies – at the regional, national, and European level, regarding consent and data sharing are difficult to navigate [13]. The variety of disparate regulations govern not only general consent, research, data collection methods, and privacy issues, but dictate which data elements can be collected and how patients can be recruited. Because of the confusion, several groups have gotten

together to assimilate these resources [13, 11, 18, 41], though we must point out that is a dynamic area in need of continuous re-examination.

Rare diseases, some with very visible phenotypes, dismal prognoses, and small numbers of affected individuals, are especially vulnerable to possible identification. The increasing availability of electronic data with which to link to individuals in a registry has enabled the capture of data beyond the registry data set. This has been demonstrated in cancer by combining registry data with treatment and clinical data from health insurance records [43] and hospital data [6], and socio-economic status from census data [23]. In *de-identified data*, all explicit identifiers, such as Social Security number, name, or address, are removed or replaced with an alternative. De-identifying data does not guarantee that the result is anonymous however.

Anonymous data implies that the data cannot be manipulated or linked to identify any individual [37]. "Privacy" is emerging as a scientific discipline that includes mathematics and computer science to help address today's privacy-technology conflicts – including the prevention of re-identification from combining multiple seemingly "innocent" data sources [37, 38]. The creation and use of special algorithms, techniques, and qualified oversight is especially critical for rare diseases to prevent the identification of cases by association with other data sets.

An outstanding question that remains unanswered is the identification of who is best suited to "own" the registries. The notion of patients (via patient advocacy organizations) "owning" their data collection is gaining popularity and with some good reason. However, the resources, expertise and governance structure of these groups vary tremendously, and all might not be ready for the demands and responsibilities of data stewardship. There has been little work to explore the nature and organizational characteristics of different patient organizations. Patient organizations are exempt from some regulations such as HIPAA, although the use of registries for research purposes does constitute research involving human subjects and is subject to those regulations. The summary of a recent multi-perspective and EU-wide meeting on the topic of registries (funded by the European Commission Public Health Directorate), called for a code of conduct for patient organizations, academic researchers, policy makers, and the industry regarding the use of health information in biomedical research [13].

6.6 Future of Registries

The future of registries will continue to be shaped by technological advances, changing roles of registry stakeholders, and development of policy to support global cooperation in medical research. The availability of computer technology has contributed to the proliferation of registries, and influenced their evolution. Over the past decades, there has been more direct use of registries for patient care including, chronic disease management, delivery of best practice guidelines to both patients and providers, and quality care on both institutional and community levels [1]. In addition, we are seeing computer technology impact the nature and scope of registry data by affecting the collection (i.e., new sources), the volume, the quality (e.g.,

verification by using multiple sources), the promotion (e.g., social networking) and follow-up (e.g., customized reminders for data updates or corrections).

The transparency of systems and processes enabled by information technology can enable patients to consent to their information being part of a registry and allow them to specify preferences regarding how their data is used over time. Implied in that consent, and enabled by information technology, is the monitoring and control of the data. Patients can remove consent any time, leaving registry holders continuously accountable. New technologies, if designed to support thoughtful and proactive patient-oriented policies, can enable patient-controlled sharing of Electronic Health Record (EHR) data direct from health care providers or from patient-managed Personal Health Records (PHR). PHRs might someday contribute a rich source of patient-reported information to registries that would include various disease-specific outcomes and measures of functioning and quality of life – arguably of central importance to rare disease research. One assumption of PHRs is that they provide data that is complete and closest to the patient. Data streams from physiologic or device measures could also be incorporated.

Social Networking tools (e.g., MySpace, Facebook) are playing a growing role in the promotion and recruitment of registries. In rare diseases, coping with multiple languages will be a growing challenge. New applications are enabling patients to view aggregate data from similar patient communities, creating emergent needs for guidance on the presentation and appropriateness and utility of these ventures. Patient advocacy groups and vendors can analyze data to share with patient communities, but should be cautioned as to how the data are displayed or used. As mentioned earlier, registry data are generally inappropriate for comparing treatments, and any presentation of registry data for this purpose could be misleading and perhaps dangerous.

Advances in technology, standards, global communication, and policy will be needed to support expanded use and functionality of patient registries in the future. Technology and tools are needed to enable the rapid development of registries and to maximize participation by reducing response burden and enabling high quality data collection. Standards are required to enable sharing of content and technology across registry efforts and to enable the re-use of data from clinical settings or patient reports. In that sense, registry standards must be compatible with healthcare, though we are likely to see a certain synergy of standards as the eligibility criteria for clinical trials begin to drive the type and strategy of data collection in EHRs and healthcare settings. Global communication and cooperation are needed within rare diseases to enable consistent or complementary policies for data stewardship and patient privacy.

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Chapter 7
Biobanking in Rare Disorders

Hanns Lochmüller and Peter Schneiderat

Abstract Biobanks are collections of biomaterials with associated data. Biobanking is an essential tool to provide access to high quality human biomaterial for fundamental and translational research. Research for rare disorders benefits from the provision of human biomaterials through biobanks, and each human sample from a person with a rare disorder has a high value as it may hold the key to answer an important research question. Transnational cooperation in biobanking is an important catalyst to share limited resources and achieve optimal outcomes as in other areas of rare disorder research. Networks of biobanks aim to assure common practices and quality standards, and facilitate access to rare disorder biomaterials for the scientific community.

Keywords Biomaterial · Biobanking · Rare disorders · EuroBioBank · Biological resources centres

7.1 What Are Biobanks and What Are Their Benefits

There is no generally accepted definition of biobanks and existing definitions often have slightly different meaning. Following the definition of the Organisation for Economic Co-Operation and Development, OECD, a biobank is "A collection of biological material and the associated data and information stored in an organised system, for a population or a large subset of a population" [12]. Especially in rare disorders this definition is problematic as rare disorders are usually not considered a "large subset of the population", although about 6–8% of the population will be affected from a rare disorder during life [14]. Biobanks may be defined as structures collecting biomaterial and associated data either for specific disorders or for a group of disorders, in some instances restricted to a specific type of biomaterial, or for a specific subset of the population. In our view, the activity of a

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biobank should not be limited to the collection of biomaterial, but should involve the processing, cataloguing and distribution of samples to the scientific community. Additional characteristics of biobanks are the adherence to quality and ethical standards, the level of detail and accuracy of associated data, and the long-term sustainability [13].

There is a huge diversity of biobanks related to the different volumes and types of biological materials stored (human, animal, tissues, cells, blood, DNA), the variety of the specific goals of the biobank (service structure for scientists, diagnostic purposes, forensic reasons) and their different systems of governance (participating parties e.g. industry, hospitals, patient organisations).

Usually we distinguish two major categories of biobanks, also very different in terms of size: the Population based biobanks and the small "Disease-specific" biobanks. The Population biobanks, with a focus on epidemiology, have been created in the last decade and are typically large "industrial" collections of blood samples or DNA. One example is the Estonian Genome Project, a collection of DNA and medical data from the Estonian population [2]. By May 2009 this bank collected samples from 35,000 donors.

A large number of small biobanks and collections for human biomaterials, including numerous disease-specific biobanks were built by individual scientists or research centres. In this context, several networks of biobanks have been created with a common interest in a group of disorders. For example, EuroBioBank is a European network of biobanks in 8 different countries dedicated to rare disorders with a strong interest in neuromuscular diseases (www.eurobiobank.org). Some other networks are the Central Research Infrastructure for molecular Pathology (CRIP; www.crip.fraunhofer.de/en), a central database infrastructure of available specimens and data throughout the partners ĵnstitutions with a wide range of diseases or the Danubian Biobank Consortium (www.danubianbiobank.de), a initiative of biobanks situated along the Danube river between Ulm in Germany and Budapest in Hungary with a main interest in the field of non-cancer aging disorders, i.e. vascular disease, metabolic disease and neurodegenerative disorders.

The Biobanks have an important role in research as they provide material that is otherwise difficult or impossible to access for scientists. In many fields the lack of biological material and biological models are major bottlenecks for the ongoing research. Often animal models are missing or not suitable to answer a certain research question, in these cases cell culture based models can help to test therapeutic options or diagnostic procedures before being applied to humans (for example [6]).

The importance of biobanks as fundamental tool for research has been noted by national bodies and the European Commission [4]: In the past framework programs, the European Commission funded various disease-specific networks and biobanking projects in many areas of research. Similarly, in the framework of national plans, biobanking activities were also included as national initiatives were considered more likely to obtain a critical mass of biomaterial as compared to the individual scientist.

Sometimes centralized service structures are aimed for: For example a central service structure may process data from samples from all partners and store them

centrally. This may ensure improved data organization within the network and easier access to samples. One example is the Italian Telethon biobanking project. The Telethon Genetic Biobank Network (http://www.biobanknetwork.org/) is constituted by all biobanks supported by Telethon Foundation, whose purpose is to collect, preserve and offer biomaterials to the scientific community and to Telethon-funded investigators in particular. This includes biological samples and related clinical data from individuals affected by genetic diseases, from their relatives or from healthy control individuals. The aim of the Network is to coordinate and manage the biobanks' activities in order to enhance synergy and to provide scientists with an efficient service responding to the highest quality standards, according to rigorous ethical principles complying with Italian laws [1]. Once a sample is processed locally, the data is online a few moments later in the central database and visible to the whole network.

Recently, the EC created a Pilot Project for a Biobanking and Biomolecular Resources Infrastructure (BBMRI; www.bbmri.eu) to identify already existing biobanking infrastructures, as well as to evaluate the need and the prospect for a Pan-European infrastructure (see also links).

7.2 Ethics and Governance

Ethical issues are crucial to biobanks as the use of human material for research implies ethical and legal issues and is strongly regulated. There is no common European law and every country has its own regulations and restrictions. A detailed collection of different regulations in European countries can be found in [9]. As there are no internationally binding regulations and with increased international collaboration between researchers and biobanks, some recommendations for biobanks have been developed by OECD, for example Recommendations for Biological resources centres (BRC) related to ethical issues and best laboratory practice [11, 13].

In addition, many biobanks and biobanking networks have already developed common best practice guidelines and charters. Biobanks holding human biomaterial are usually subjected to local or national IRB or ethics board approval. The fundamental ethical and legal issues for all biobanks are the informed consent of the donors with the right to withdraw their permission, data protection issues and procedures in the case of anonymised or pseudonymised biological material for research. Currently, the biomaterial is considered a donation of the individual person to research. Therefore, the donor does not retain any rights over the biomaterial even if an important discovery or commercial success is based on the biomaterial. There are unsolved ethical aspects left, for example the participation of minors in biobank research [5]. As patients with rare disorders often play a very important and proactive role in biobanking in addition to be donors of biological material, the concept of "benefit sharing" has been developed in this medical area. This may include regular information to patients and patient organizations on the activities of the biobank, and on the results of the research based on the

biomaterial provided. Besides ethical and legal issues, quality assurance is of high importance for biobanks as scientists need to trust the information on the characteristics of the provided samples [8]. The need for harmonized procedures of good quality laboratory practice is pivotal to get standardized reliable and comparable results in research. To reach this goal, harmonized standard operation procedures are needed. For example the EuroBioBank pan-European network of biobanks, harmonized and implemented common procedures for all biobanks of the consortium, and made its standard operating procedures available to the public on its website (see "Useful links"). Moreover, a standardized subset of linked data including clinical data, genetic data, or classification of the disease either with ICD-numbers, OMIM-numbers or ORPHA-Code (www.orpha.net/), is essential to ensure comparability of samples from different biobanks.

The governance of biobanks is highly diverse [10]: There are for example scientist-led biobanks, institutional biobanks and biobanks governed directly or indirectly by patient organisations. Many biobanks have a steering committee or scientific advisory board for granting of access for the utilisation of samples. Scientist-led biobanks often emerged from individual research collections and changed their proceedings over the years towards more openly accessible biobanks. In institutional biobanks a project goal may determine the structure and services of the biobanks suitable to fill the needs of the institution or the research project. Patient initiated biobanks are often disease specific with the defined goal to develop diagnostic or therapeutic tools for the disease.

7.3 Specifics of Rare Disorder Biobanks

Many features of rare disease biobanks are similar to larger common-disease or population biobanks. However, some considerations are of particular importance to rare disease biobanking. In contrast to more common conditions such as diabetes mellitus or cancer, there are small donor numbers and a limited number of biological samples available for most rare disorders. Every rare disorder sample is unique and has to be processed with care as it may not be easy to obtain a new sample. Furthermore, due to new diagnostic procedures (e.g. genetics), in some diseases such as muscular dystrophies the availability of biopsy material through diagnostic or therapeutic surgical procedures has diminished over recent years.

On the other side, scientists have developed an increasing demand for biological material to develop therapeutics or diagnostic procedures for rare disorders. For rare disorders it is often not enough to establish collaborations on a national level. In order to gain a critical mass of samples to be beneficial for research, international collaboration is often required.

Exact molecular diagnosis is often difficult in rare disorders, and may only be available through highly specialized centres and a handful of dedicated experts. Molecular diagnostic data are highly relevant to correctly characterize a sample in the biobank. Only if this data is linked to the sample and made available to the scientist, the sample can be optimally used for research. Therefore, biobanks for rare

disorders need to closely link and receive information from specialised diagnostic centres and disease experts.

It is difficult to estimate the exact number of biobanks for rare disorders as they are often located within small institutions and there is no official registration at the moment. Visibility to the public is low and better efforts are required to bring rare disorders biobanks to the attention of scientists, clinicians and patients. In September 2009, on the BBMRI website there are 26 networks of biobanks and 247 individual biobanks listed in the catalogue of biobanks. Many of these biobanks deal with rare disorders. Although this list is likely to be incomplete even for Europe, it gives an impression on the enormous quantity and variety of biobanks in this field and the different action plans of scientists, patients organisations, industry and governments to overcome fragmentation in this field.

Funding of rare disorder biobanks is different from population and common disease biobanks which are usually supported by public money or even industry. Most of the rare disorders biobanks are financially supported through short-term research grants, funding from patient organisations, private donations, membership fees or fees for services. In addition to financial support, there is often enormous support from patients or patient organisations with regard to internal practices for managing the access to and the use oft he samples and ethical aspects or in the field of public relations.

7.4 Existing Biobanks in Rare Disorders

A few examples for existing rare disorder biobanks are given below. One example is the Munich Tissue Culture Collection (MTCC), situated in Munich, Germany. It is a biobank with special interest in the field of neuromuscular diseases, in particular muscular dystrophies and other inherited myopathies. MTCC was started in 1998 and up to 2008 about 2,500 different cultures of neuromuscular patients have been processed and stored (Fig. 7.1). MTCC processes muscle biopsies to primary myoblast cultures. Primary myoblast cultures are suitable for neuromuscular research as myoblasts are viable, easy to differentiate and a starting point for a variety of experiments. Research with myoblasts may include transcriptomics, proteomics, genomics, patch clamping or pharmacological testing. The biopsy samples are collected after individual informed consent of the patients from diagnostic material. After being collected, the sample is sent in a special solution via post to the central service structure where it is processed within a few days. Once frozen and stored in liquid nitrogen the samples remain ready for utilisation for many years. Scientists can apply for samples for research projects. The samples are available upon request including scientists from outside the network. Technical counselling and support as well as onsite technical hands-on teaching is offered. MTCC was initiated and originally sponsored by the German Muscular Dystrophy Association (DGM) and consecutively funded by the German ministry of education and research (BMBF) in the frame of a network for rare disorders (MD-NET, www.md-net.org) and by the EC in the frame of TREAT-NMD (www.treat-nmd.eu), a network of

Fig. 7.1 State-of-the art liquid nitrogen storage for rare disorder biomaterials

excellence for translational research in neuromuscular disorders. Research with myoblasts from MTCC led to important results in fundamental research [7] or translational therapeutic research [15].

A second existing biobank for rare disorder is the DNA and cell bank at Genethon, situated in Evry, France. Since 1990 DNA, tissue and cells are processed stored and distributed, mainly with genetic disorders. Genethon is funded by the French Association against Myopathies (AFM; www.afm-france.org) and is both a service structure for scientists and a non-profit organisation with an "in house" research portfolio. In addition, AFM also funded a second biobank, Myobank-AFM, collecting and distributing tissues mainly of neuromuscular rare disorders.

7.5 Existing Networks of Biobanks in Rare Disorders

The EuroBioBank network (www.eurobiobank.org) was the first operating network of biobanks in Europe providing human DNA, cell and tissue samples as a service to the scientific community conducting research on rare diseases. It is still the only network fully dedicated to rare disease research in Europe. A total of approximately 170,000 samples are available via the online catalogue – 145 cell collections, 544 DNA collections and 282 tissue collections. The network is currently composed of 15 members from 8 European countries (France, Germany, Hungary, Italy, Malta, Slovenia, Spain and Israel): 13 academic or private biobanks, one expert in biobanking management and Eurordis (European Organisation for Rare

Diseases) who has coordinated the network since its creation. Originally funded by the European Commission between 2003 and 2006, EuroBioBank has received funding through grants from AFM and DGM and through membership fees. Since January 2007, the network participates in the European Network of Excellence TREAT-NMD as leader of biobanking activities. The EuroBioBank network was established by patient organisations and researchers to facilitate research on rare diseases by guaranteeing quick and easy access to samples via an online catalogue. The catalogue lists the sample collections available in the EuroBioBank network. To find the required biological samples, a multi-criteria search engine is used. Samples can be selected by disease (name, ICD, MIM number or ORPHA-Code), by type of biological material (DNA, tissue or cells) or by biobank. The catalogue is regularly updated by the biobanks. Once the requested sample is located in the catalogue, an e-request form can be sent directly to the biobank by simply clicking on the biobank's email address next to the sample. Responsible for the samples is the individual biobank. This way, access to biological material is facilitated and accelerated, thus speeding up rare disease research. Within the last 5 years about 150 scientific papers emerged from the use of biomaterials provided through EuroBioBank which may be taken as evidence of the potential benefit of biobanking for rare disorder research. To improve standards, the network aimed to harmonize its practices by creating standard operating procedures (SOP) which are made available to the public. All members of EuroBioBank adhere to a common charter where basic regulations and goals of the network as well as core ethical issues are laid out. Annual meetings are used to discuss new developments and topics.

In the U.S.A. two biobanking networks have emerged that include rare disorders. The Genetic Alliance BioBank (www.biobank.org) is an advocacy owned repository for biological samples and clinical data. Centralized, standardized collection and archiving, highest biorepository and participant protection standards, open access for all organization approved researchers and advocacy organization control are provided. The National Rare Disease Biospecimen Resource (NRDBR) created by the National Resource Center (NDRI; www.ndriresource.org) is also involved in rare disorder biobanking. Since 2002, 2,000 tissues representing 101 rare diseases were procured. NDRI has a strong interaction with patient organisations for specific rare diseases.

7.6 Future Perspectives

Biobanking will remain important for rare disorder research, and in particular translational research. Results from laboratory research need to be translated into clinical applications ("from bench to bedside"). Human biomaterial is often required to validate findings from animal models or heterologous cell lines. To develop treatments in the next step, collaboration and cooperation with pharmaceutical industry is needed [3]. In the field of rare disorders a strong collaboration between the different groups and centres is required to overcome fragmentation and to reach a critical mass of patients and samples. Standardization, quality control, and sustainability

are major challenges for rare disorder biobanks. Participation of patients and patient organizations were instrumental in developing these resources. Therefore, continued involvement of patients and benefit sharing are key principles to retain and improve acceptance within society. Networking across national boundaries and among all stakeholders will remain important to get closer to the goal: Cure rare disorders!

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Useful Links

AFM: www.afm-france.org
BBMRI: www.bbmri.eu
CRIP: www.crip.fraunhofer.de/en

Danubian Biobank Consortium: www.danubianbiobank.de
EuroBioBank: www.eurobiobank.org
Genetic Alliance BioBank: www.biobank.org
OECD: www.oecd.eu
ORPHANET: www.orpha.net
Telethon Biobanks: www.biobanknetwork.org
TREAT-NMD: www.treat-nmd.eu

Chapter 8
Evaluation of the Validity and Utility of Genetic Testing for Rare Diseases

Scott D. Grosse, Lisa Kalman, and Muin J. Khoury

Abstract The conventional criteria for evaluating genetic tests include analytic validity, clinical validity, and clinical utility. Analytical validity refers to a test's ability to measure the genotype of interest accurately and reliably. Clinical validity refers to a test's ability to detect or predict the clinical disorder or phenotype associated with the genotype. Clinical utility of a test is a measure of its usefulness in the clinic and resulting changes in clinical endpoints. In addition, the utility to individuals and families of genomic information, or personal utility, should be considered. This chapter identifies methodological and data issues involved in assessing each type of validity or utility. The validity and utility of a test must be considered in a specific context, which include diagnostic testing, newborn screening, prenatal carrier screening, and family or cascade screening. Specific rare disorders addressed include cystic fibrosis, fragile X syndrome, Duchenne and Becker muscular dystrophy, spinal muscular atrophy, Huntington disease, as well as cancer associated with BRCA mutations.

Keywords Population screening · Genetic screening · Public health genomics · Rare disorders · Clinical utility

8.1 Introduction

The number of diseases for which genetic tests are available is growing rapidly; a voluntary international genetic test registry listed more than 600 diseases for which genetic tests were available in 1998, more than 900 in 2003, and almost 1700 in

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2008 [25]. Most of these diseases are rare disorders caused by mutations in a few genes, and the increasing availability of tests for them poses a challenge to assessing the tests' validity and utility. The major challenges are the lack of robust data on genotype-phenotype associations and gene-environment interactions for rare disorders. In addition, observational data cannot reliably assess penetrance, prevalence, and effectiveness of interventions or treatments that may follow genetic testing. Although genetic tests for rare diseases can be chromosomal, molecular, or biochemical [69], the focus of this chapter is on DNA-based tests for rare, heritable diseases of genetic origin. Biochemical genetic tests for newborn screening are covered in a separate chapter.

8.2 Evaluation of Genetic Tests

The criteria for evaluating genetic tests are summarized by the four components of the ACCE analytic framework: **A**nalytic validity, **C**linical validity, **C**linical utility, and associated **E**thical, legal, and social implications [36, 68]. The first two ACCE components relate to the existence of a safe, accurate test that can reliably detect disease or risk of disease. Analytical validity in the context of molecular genetic testing refers to a test's ability to measure the genotype of interest accurately and reliably. Clinical validity refers to a test's ability to detect or predict the clinical disorder or phenotype associated with the genotype. Clinical utility of a test is a measure of its usefulness in the clinic and resulting changes in clinical endpoints, including the balance of benefits and harms. Ethical, legal, and social implications are sometimes considered part of the clinical utility of genetic tests [6, 34, 69] and sometimes considered separately [58].

The evaluation of genetic tests first requires the specification of the test setting and the intended use of the test [7]. A given genetic test can be used in a variety of settings, such as clinical work-up, population screening, prenatal diagnosis, and cascade screening. A key distinction between screening and other genetic testing applications is that screening involves offering (and promoting) testing to a population or subgroup as opposed to ordering a test for a patient seeking care [30, 58]. The potential uses of genetic testing include providing information salient to the care of the patient or family members, reducing morbidity or mortality, or providing information for reproductive decision making [7].

The validity and utility of a test must be considered in a specific context. The ACCE project developed a set of 45 questions and applied them to *CFTR* carrier testing in prenatal care, *BRCA*1/2 mutation testing for women with increased risk of breast or ovarian cancer, *HFE* mutation testing for population screening, testing for mismatch repair gene mutations associated with Lynch syndrome (hereditary nonpolyposis colorectal cancer), and testing for prothrombin or Factor V gene mutations associated with thrombophilia [36].

The US Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative was established by the US Centers for Disease Control and

Prevention (CDC) in 2005 to develop a systematic process for evidence-based assessment of genetic tests. EGAPP methods [76] draw on the experiences in the previous ACCE model project as well as the US Preventive Services Task Force. Methodologic challenges specific to genetic testing include a lack of randomized trials, low power of observational studies because of inadequate numbers for rare diseases or genotypes, and limited numbers of interventions of demonstrated efficacy. An independent EGAPP working group selects genomic applications for consideration, commissions systematic reviews, grades the evidence according to acknowledged criteria, and issues practice recommendations depending on the magnitude of net benefit, the certainty of evidence, and consideration of other clinical and contextual issues. EGAPP reviews include an analysis of laboratory data needed to assess analytic validity, including, when available, results from proficiency testing schemes that distribute standardized specimens to multiple laboratories to assess average analytic sensitivity and specificity for assays. For the most part, EGAPP has prioritized its consideration of testing applications to pharmacogenomics and genes involved with common diseases, although it recently addressed genetic testing for Lynch syndrome [20].

8.2.1 Analytic Validity

Analytic validity is defined by how accurately and reliably the test measures the genotype of interest. This measure depends not only on laboratory analysis of the specimen but also the pre- and post-analytic phases of the testing process. Proper and comprehensive quality assurance practices are critical to establish and ensure accurate and reliable genetic tests.

A number of initiatives to improve the quality assurance of all phases of the genetic testing process are underway. CDC has ongoing projects to address shortcomings in ordering, reporting, and use of clinical genetic tests [45, 46] and proficiency testing. In addition, the CDC-based Genetic Testing Reference Materials (GeT-RM) Coordination Program was established to improve the supply of publicly available genomic DNA reference materials [11]. Organizations such as the American College of Medical Genetics (ACMG), the International Organization for Standardization, the Clinical and Laboratory and Standards Institute, CDC, and the Organization for Economic Cooperation and Development have produced guidance and policy documents designed to help laboratories achieve and maintain high standards of quality. The Collaboration, Education, and Test Translation Program for Rare Genetic Diseases developed by the US National Institutes of Health, Office of Rare Diseases Research, promotes the assessment and translation of genetic tests for rare diseases from research laboratories to clinical practice [22, 53]. EuroGentest is a European Union Network of Excellence with 5 units that look at all aspects of genetic testing – quality management, information databases, public health, new technologies, and education. The particular focus is on DNA-based testing for heritable disorders with a strong genetic component (usually due to the action of a single gene) [39].

Some rare genetic disorders are caused by a few mutations in a single gene. An example is Fanconi anemia, in which one mutation is present in 99% of patients of Ashkenazi Jewish ancestry [81]. Genetic testing for this disorder in the Ashkenazi population is typically performed by targeted mutation analysis. Other disorders may be caused by one of hundreds or thousands of mutations in a single gene, a status described as allelic heterogeneity. For example, more than 1600 mutations have been identified in the cystic fibrosis (CF) transmembrane conductance regulator (*CFTR*) gene that contributes to CF [18]. Many genetic tests for CF include targeted mutation analysis for common *CFTR* alleles. Some of these targeted assays in the United States include only the most common 23 alleles recommended by the ACMG for CF carrier screening [82], while others incorporate additional, less common *CFTR* alleles. Testing for CF can also include DNA sequence analysis of the entire *CFTR* gene, sequence analysis of targeted exons, and deletion analysis. The choice of test depends on the reason for testing and other factors specific to the patient and his or her family. Finally, for most rare disorders, no common mutations have been identified and testing must be performed by DNA sequence analysis of specific disease-associated genes.

Almost all genetic tests for rare genetic disorders are developed in individual laboratories (laboratory-developed tests). Each laboratory is responsible for designing the assay, determining which mutations to detect, selecting the genotyping method, and validating the performance characteristics of the assay, including accuracy, precision, sensitivity, specificity, limits of detection, and assay range. After an assay has been developed and validated, the laboratory is responsible for ongoing quality assurance activities, including daily quality control, proficiency testing, calibration, correlation with clinical findings, interpretation, and documentation. Quality assurance activities are a particular challenge for ultra-rare diseases that affect only a few patients; testing for these diseases is typically only performed by a single laboratory [27]. Clinical laboratories that report results to patients and physicians must also meet regulatory requirements. These requirements are mandated to provide oversight for performance and qualification criteria and applicable international standards, including quality control and validation of assays.

The ACCE framework lists four aspects of analytic validity: analytic sensitivity, analytic specificity, quality control, and assay robustness. Analytic sensitivity is a measure of how well the test can detect mutations present in the sample. Analytic specificity refers to the ability of the test to correctly identify samples that do not have mutations. These parameters can be assessed through proficiency testing programs in which laboratories are sent blinded reference materials of known genotype [12, 69]. Published analyses of proficiency testing data for specific mutations indicate that sensitivity is typically approximately 98.5% and specificity is more than 99.0% [19, 55, 56].

Assessing the analytic validity of gene sequencing for diagnostic purposes is more difficult [20], although specific guidelines outline procedures and criteria laboratories should adopt to ensure the quality of the sequencing results. A recently instituted European external proficiency testing program addresses sequencing methods [57].

The third component of analytic validity is quality control. Reference materials, typically genomic DNA, can be used to develop and validate new genetic tests, as routine quality controls to assure satisfactory performance of all aspects of the assay, and as proficiency testing samples. Assay robustness is a measure of how resistant the assay is to changes in pre-analytic and analytic variables such as variation in samples, reagents, or assay conditions. These parameters are considered during the development and clinical validation of the assay.

Analytic validity depends not just on the accuracy of the laboratory analysis but also on pre- and post-analytic procedures, including use of the appropriate test and result interpretation and reporting. Most incorrect reports in laboratory medicine typically result from pre- and post-analytic errors, such as incorrect documentation, specimens, or reporting [5]. The same is true of proficiency testing for molecular genetic tests.

8.2.2 Clinical Validity

The clinical validity of a genetic test defines how well test results correlate with clinical outcomes. This can be divided into two distinct components, genotype-phenotype association and test performance [6]. Test performance can only be evaluated in the context of a specific clinical scenario and target population. For example, tests for *CFTR* mutations can be conducted as part of newborn screening, in a diagnostic work-up for persons suspected of having CF, or for carrier testing in either preconception or prenatal care. In each of these situations, the test is used for different purposes, and the results must be interpreted in the context of these indications or symptoms.

Clinical validity can be assessed by using the following measures: clinical sensitivity (or the clinical detection rate), clinical specificity, and positive and negative predictive values. These measures depend on the prevalence of the specific disorder, its penetrance (cumulative incidence of a defined phenotype among persons with a specified genotype), and modifiers (gene or environmental) in addition to the analytic validity of the test. Clinical validity is well defined for diagnostic tests, but these measures are difficult to apply to predictive genetic tests because of the need to allow for the fact that disease phenotypes develop gradually. Consequently, analysis of data on a sample of people assessed at one point in time will typically overestimate the number of false-positives because some persons who will develop disease as a result of the genotype have not yet developed symptoms [68].

Clinical sensitivity measures the proportion of people with a defined phenotype who have a positive test result. For disorders associated with a small number of pathogenic mutations, a genetic test is likely to have high clinical sensitivity. Conversely, a mutation panel for a disorder caused by numerous mutations will have lowered clinical sensitivity even if analytic sensitivity for those mutations is 100%. A challenge in correctly estimating clinical sensitivity is the need for complete case ascertainment in the population to identify false-negative or missed cases.

Clinical specificity is the proportion of negative test results among people who do not have disease. For example, if 1,000 people without a disease are tested and 1 is incorrectly identified as having the disease (false-positive result), the specificity is 99.9%. Clinical specificity is a function of the penetrance and prevalence of a genotype in a population. For example, if a genotype has a penetrance of 50% for a specific phenotype and the analytic specificity is 99%, the clinical specificity is 98% if the prevalence in the population is 1% and 97% if the prevalence is 2%.

Estimates of penetrance often vary among studies because of differences in the type of endpoint assessed to define the disease phenotype. For example, the penetrance of mismatch repair gene mutations depends in part on whether the endpoint is defined specifically as diagnosis of colorectal cancer or as any cancer associated with Lynch syndrome [54]. Penetrance estimates are prone to ascertainment bias resulting from clustering of cases in highly-affected kindreds, although there are methods to adjust for ascertainment bias [60].

A more intuitive measure than specificity is the positive predictive value (PPV), which is the probability that someone with a positive test result will have or eventually develop a disorder or clinical phenotype. The negative predictive value (NPV) is the probability that someone who tests negative will not develop the disorder. PPV and NPV vary with the prevalence of the disorder as well as clinical and analytic specificity. The rarer the phenotype of interest, the lower the PPV will be for a given level of specificity. One way to increase PPV is to target the test to an enriched population sample with a higher frequency of the phenotype.

The clinical validity of a genetic testing strategy depends on the analytic and clinical validity of each test that is used in series, e.g., nonmolecular preliminary tests used to determine who should receive more expensive molecular tests. This is true for both screening and diagnostic strategies. For example, it is not economical to directly sequence genes of patients with colorectal cancer to test for a mutation on a mismatch repair gene; instead, a preliminary test should be conducted with either microsatellite instability or immunohistochemistry testing [20]. The overall sensitivity of a sequence of tests is the product of the sensitivities of each test. The same is not true for specificity; the test with the lowest specificity determines the overall specificity of the combined testing. Screening strategies commonly combine a nonmolecular screen that has a relatively low specificity with a highly specific molecular test. Performing both tests on the same specimen can identify false-positive results from the less-specific, preliminary test.

8.2.3 Clinical Utility

Clinical utility in the narrowest sense relates to how test results inform the clinical management of patients and resulting changes in health outcomes, including the balance of medical benefits and harms [34, 69]. The balance can depend on both the efficacy of interventions that follow a positive test result and the subsequent adoption of and adherence to these interventions. For example, a recent evidence-based review concluded that testing patients with venous thromboembolism for

a predisposing mutation, factor V Leiden (FVL) or prothrombin G20210A, was of low clinical utility despite high analytic and clinical validity for FVL because of lack of evidence that generic test results appropriately change clinical management or improve outcomes [70]. Discussions of clinical utility should distinguish between the potential benefits of a test and associated services and the feasibility and acceptability of the test and services [6].

Clinical utility, like clinical validity, depends on the relative true-positive and false-positive test results. The latter depends on disease prevalence among the population being tested. Thus, the clinical utility of a genetic test may vary by whether it is used for population screening (low prevalence) or testing people with a strong family history (high prevalence). For example, the clinical utility of BRCA testing is established for women with a close relative with a known deleterious mutation in the *BRCA1* or *BRCA2* gene or women with a strong family history of breast or ovarian cancer, but these tests are not recommended for testing for breast cancer susceptibility in the general population [79].

Diagnostic testing is the most common application of molecular genetics. When a person has symptomatic disease, an etiologic diagnosis can allow for clinical management to be tailored to the disease, which is one of the two classical definitions of clinical utility. Molecular genetic testing is not required to diagnose many rare diseases; the diagnosis can be established on the basis of a unique constellation of signs and symptoms. Molecular diagnostic testing is most likely to be valuable for highly-penetrant genotypes or genes with very high expressivity for a given phenotype [6]. Diagnostic tests are typically not held to an evidentiary standard of improvements in health outcomes, as is the case for screening tests [34, 75].

8.2.4 Personal Utility

Personal utility encompasses multiple dimensions, such as relieving anxiety, providing reassurance, family planning, and lifestyle modification. Reassurance for persons who have a family history of disease and test negative is valid only if they are tested for the specific mutations identified in their family. Conversely, genetic testing can result in anxiety and potentially unnecessary treatments if a positive result is identified in an asymptomatic person. It can also result in discrimination in hiring or insurability. Another dimension of personal utility is the use of genetic information to make decisions about housing, career, or childbearing. Because results of genetic testing can inform personal decisions, evaluations of genetic tests that end with available clinical endpoints, e.g., cost-effectiveness analyses, are insufficient to fully inform policy decisions [32]. New metrics are needed to assess personal utility, including quantitative methods to assess people's preferences over various aspects of the genetic counseling and testing processes and both medical and non-medical outcomes [31, 61].

The perceived value of genomic information, independent of its use in clinical care, is receiving more attention in the scientific literature [24, 31]. This subject was also the topic of a recent workshop cosponsored by the National Institutes of Health

and CDC, where the focus was on direct-to-consumer genomic testing profiles for susceptibility to common diseases [41]. Predictive genetic tests for rare diseases are also included in some direct-to-consumer panels. The challenge is to show that genomic test information is useful to consumers.

The value of predictive genetic testing for rare diseases that lack effective treatments has long been debated. In addition to the psychological implications for the person being tested, which can be positive or negative, genetic testing also has implications for biologically related family members. In particular, DNA-based test results reveal information about carrier status as well as disease-causing genotypes for autosomal recessive and X-linked disorders. The utility of revealing carrier status in recessive disorders is often uncertain. Typically, there is little or no clinical utility to the carrier since most heterozygotes are not clinically affected, but knowledge of carrier status can be used for reproductive decision making.

8.2.5 Examples

Molecular genetic test findings for rare diseases are often used for diagnostic purposes. For example, a child who has serious developmental delay will often be referred to a clinical geneticist for a series of evaluations. A clinical and family history and complete physical examination that focuses on dysmorphology may be followed by testing for chromosomal abnormalities through karyotyping, newer assays such as array-based comparative genomic hybridization [67], or molecular genetic testing for genetic disorders such as fragile X syndrome that can cause intellectual impairment and disability. Similarly, a child with progressive muscle weakness with an elevated creatine kinase level will often be tested for mutations associated with Duchenne or Becker muscular dystrophy (DBMD). Prompt diagnosis of DBMD permits the initiation of evidence-based management strategies such as steroid therapy and cardiologic monitoring [9]. An inherited DBMD mutation also has implications for family reproductive decision making and the cardiac health of the mother.

The use of genetic testing for screening or risk assessment in asymptomatic people can be controversial, depending on the age group and availability of effective treatments. Such testing can be done as a screening test in the general population, among apparently healthy relatives, or on request for people concerned about a particular disease.

8.2.5.1 Newborn Screening

Newborn screening is the classical form of testing for rare diseases of genetic origin, although almost all newborn screening tests are biochemical rather than DNA-based. A few newborn screening tests use molecular testing to confirm presumptive positive screening results. Thus, newborn screening for hemoglobin variants associated with sickle cell disease (SCD) or thalassemia, which has been adopted

nationwide in the United States and England, is typically performed with a protein-based assay that can reliably identify hemoglobin variants associated with specific gene mutations [72]. Some screening programs conduct molecular confirmatory testing for certain disorders in newborn infants who test positive or who had a blood transfusion before a dried blood spot specimen was collected [49].

Newborn screening for CF is commonly conducted by using a multiple-tier strategy in which immunoreactive trypsinogen (IRT) is used as a biomarker, and the same dried blood spot specimen is tested for *CFTR* mutations if an elevated IRT value is detected. If one mutation is detected, the child is referred for diagnostic sweat chloride testing. If the child has normal sweat chloride levels, the child is typically classified as an unaffected carrier. Certain US state screening programs routinely collect a second dried blood spot specimen more than one week after birth and conduct a repeat IRT assay [66]. Most screening programs in Europe and North America use mutation testing as a second-tier test to minimize the need to collect a second specimen [10, 14]. This IRT/DNA screening approach identifies a subset of children with one *CFTR* mutation, approximately 10 carriers per confirmed case of CF [15]. Although identifying carriers through newborn screening can be considered a benefit to many families, for others it may be unwanted information. A few screening programs use IRT/IRT screening in part because of concerns about the ethics of unnecessarily revealing carrier status [66]. Although newborn hemoglobinopathy identifies more carriers, approximately 25 per diagnosed case [72], the difference with IRT/DNA screening for CF is that there is no other way to screen for SCD that does not also identify carriers. The utility of molecular testing in newborn screening for CF needs to be assessed in comparison with alternative, nonmolecular testing strategies.

The clinical utility of screening newborns for CF has been assessed on the basis of epidemiologic evidence relating to both child health outcomes (nutritional status, lung function, survival) and psychosocial outcomes among parents. One analysis concluded that evidence of net benefit was sufficient to justify screening infants for CF [35]. The review of epidemiologic data sources and methods has recently been updated [29]. Two randomized trials of CF screening were conducted, but the numbers enrolled were small. In addition, the external validity of randomized trials can be problematic if the level of care provided differs substantially from settings outside the trial. One of the studies reported no deaths in unscreened children younger than 10 years, which differs from usual experience and could have resulted from the close monitoring of children in that study [33]. A substantial number of observational cohort studies provided confirmatory evidence of nutritional and survival benefits from screening newborns for CF [29, 33, 35].

CF is an instructive model to consider the challenges in assessing the utility of population screening for genetic disorders. Assessments of the utility of newborn screening tests are commonly based on comparisons with unscreened and inadequately treated historical cohorts. For example, evidence-based reviews of newborn screening for phenylketonuria (PKU) contrasted the near-universal serious intellectual disability, typically associated with institutionalization, among unscreened cohorts with PKU with the normal IQ scores of screened cohorts who underwent

dietary protein restriction as evidence of the effectiveness of screening newborns for PKU [23, 80]. However, such comparisons overstate the effectiveness of screening. Studies of groups of people with PKU in advanced economies who were not identified by screening but who began adequate treatment before age 7 years have reported average IQ scores in the low-normal range [28]. In contrast to PKU, evidence for screening newborns for CF was based on a number of observational studies in which children in screened and unscreened cohorts received comparable treatments after diagnosis [29].

Testing asymptomatic children for mutations associated with untreatable diseases, that is, those lacking treatments that prevent or delay major clinical endpoints, is not endorsed by professional organizations [78]. A recent survey of parents showed that opinion was sharply divided as to whether they would choose predictive genetic testing for a hypothetical disorder [74]. Screening newborns for DBMD with a biochemical creatine kinase assay is feasible, reasonably accurate, and inexpensive, but the inability to prevent the onset of disease has deterred its widespread use [40]. Indeed, the only North American public screening program for DBMD, in Manitoba, Canada [26], was recently discontinued [Cheryl Greenberg, personal communication, March 8, 2009].

Pilot screening for fragile X syndrome with a molecular assay is currently being conducted to demonstrate feasibility and assess the potential benefit of early diagnosis [4]. In addition, the assay being piloted identifies premutation carriers, and families can use that information for future childbearing decisions, although the knowledge may have negative psychological ramifications. The identification of carriers could have clinical value as well, if recent findings that children who are premutation carriers for *FMR1* mutations may also be at elevated risk of adverse behavioral outcomes [3] are corroborated by other researchers. Although adult premutation carriers are at risk for premature ovarian insufficiency in women and fragile X-associated tremor/ataxia syndrome [64], predictive testing for adult-onset disorders in children is controversial [78].

8.2.5.2 Prenatal Carrier Testing

Carrier testing for *CFTR* mutations during pregnancy is recommended in some countries, including the United States and United Kingdom, although there is no systematic approach to deciding which carrier tests should be recommended at the population level [16]. The ACMG and American College of Obstetricians and Gynecologists (ACOG) in 2001 jointly endorsed prenatal carrier screening for CF in the United States [17]. The clinical validity of carrier screening for CF is limited by the large number of mutations on the *CFTR* gene. The detection rate of carrier testing varies from 94% in the Ashkenazi Jewish population and 88% for other non-Hispanic Caucasians to 49% for Asian Americans [17]. Because the sensitivity of couples testing is the product of the detection rate for each person, the detection rate of affected US couples of the same background who are both tested varies from less than 80% for Caucasians to approximately 25% for Asian Americans. High uptake of carrier testing since 2001 has been linked to a marked drop in the number of US

infants born with CF [37]. In the United States, prenatal carrier testing for SCD has long been offered to at-risk women, but the prevalence of SCD has not changed [44]. Beta thalassemia major has been the focus of premarital, preconception, or prenatal carrier screening in a number of countries [50, 83].

The lack of a systematic approach to policy decisions on carrier screening can lead to controversy [16]. In the United States, carrier testing for spinal muscular atrophy (SMA), which tests for the homozygous absence of exon 7 in the survival motor neuron (*SMN1*) gene, is the subject of conflicting recommendations by the two US professional organizations that had previously jointly recommended CF carrier screening [16, 59]. An advocacy organization for SMA carrier testing pointed out that although the frequency of SMA carriers is modestly lower than that of CF, the severity (lethality) is greater and age of onset of serious disease is lower for SMA [13]. In addition, analytical validity is higher for SMA carrier testing (approximately 95% sensitivity) [59].

8.2.5.3 Cascade Screening/Testing

Cascade screening (reflexive testing) of relatives of patients with clinically diagnosed Mendelian disorders is often proposed. The strongest case can be made to offer screening or testing to first-degree relatives of probands with autosomal dominant disorders, since the relatives have a 50% chance of inheriting a disease-causing mutation. In particular, carrier testing of people with a family history of Huntington disease (HD) is one of the most studied genomic applications in rare diseases. The genetic test for HD has almost perfect clinical validity, with 100% penetrance of an autosomal dominant disease, but little clinical utility because of the lack of an efficacious treatment. Although offering HD testing is not controversial, there is lack of agreement as to its personal utility. Most people in HD families who are tested report reduced psychological distress, regardless of whether they tested positive or negative, although a few reported adverse psychological events such as depression [1]. Despite what appears to be a generally positive net balance of utility after testing, most (76–96%) members of HD families typically decline to be tested [77]. The potentially negative psychological effects of testing are given more weight by people who choose not to be tested [77]. In other, similar disorders, uptake of predictive testing may be even lower [62].

For dominant disorders with effective interventions, one can make the case for systematic carrier screening of relatives. For instance, a population cascade screening program for familial hypercholesterolemia has been in operation in the Netherlands since 1994 and has reduced morbidity among affected patients [38]. Because of this evidence of clinical utility, a similar program has been recommended for the National Health Service in England and Wales [52]. Cascade testing has been recommended for relatives of colorectal cancer patients who have mutations associated with Lynch syndrome [20]. Cascade screening for autosomal recessive disorders is less promising as a population intervention because it detects a much smaller percentage of cases [51], although it may be cost-effective compared with population-wide screening [65].

Cascade carrier screening may follow newborn screening for autosomal recessive disorders, particularly CF and SCD. Parents of infants diagnosed with disease can be tested for carrier status, even though they are obligate carriers, in part because of rare uniparental disomy (one parent contributing two disease-causing alleles) or nonpaternity [47]. The purpose of such testing is to inform reproductive decision making, so it is most often offered to relatives of carrier patients who are adults of childbearing age [63]. In the United States, experts recommend that nondirective genetic counseling be offered, and carrier testing should be made available only if parents desire it, in part because revealing nonpaternity may have negative consequences [14]. The uptake of genetic counselling and testing by parents is often low, even when active follow-up by telephone is conducted [42], and few investigators have attempted to assess the utility of cascade testing of relatives.

A major challenge in assessing the clinical validity of cascade screening or population screening is the calculation of penetrance in the face of allelic heterogeneity and genetic and environmental modifiers. For example, *BRCA1* and *BRCA2* mutations were first reported to have a penetrance for breast cancer of approximately 85% by age 70 on the basis of data on women with mutations who belonged to kindreds with several affected members. Subsequent studies of unselected women yielded considerably lower estimates, 30–70% [8]. In reality, penetrance is likely to be highly variable, depending on the location of a given mutation, which can also affect the age-related expressivity of the gene [2]. Also, evidence suggests that penetrance is higher in more recent birth cohorts, which could reflect environmental exposures to hormones [21].

Similar uncertainty exists with regard to the penetrance of mutations associated with Lynch syndrome. The probability of a carrier developing colorectal cancer by age 70 was first estimated to be higher than 80% on the basis of high-risk kindreds, but adjustments for ascertainment bias have lowered this estimate to a range of 25–55% [54, 60, 71].

The clinical utility of detecting mutation carriers for autosomal dominant familial cancer syndromes has been well established by prospective cohort studies. For BRCA gene mutation carriers, prophylactic surgery reduces the risk of developing breast or ovarian cancer [43, 48]. For Lynch syndrome mutation carriers, frequent (every 1–2 years) surveillance colonoscopy reduces the incidence of colorectal cancer by approximately 60% and death rate by more than 80% [73].

8.3 Conclusions

Assessment of the validity and utility of genetic testing for rare diseases must be considered in its various contexts depending on clinical scenarios (indications for testing) and the population targeted for testing. Genetic testing for diagnostic purposes is generally assumed to have clinical utility, and the chief issue is analytic validity. Analytic validity for molecular genetic tests is generally high, and most errors are associated with pre- and post-analytic phases, as is typical of laboratory

medicine in general. General quality assurance procedures are crucial for all steps of the testing process. The usefulness of genetic testing for carrier or population screening or testing depends on the establishment of clinical validity and clinical utility. In addition, it is important to consider the personal utility of knowledge of carrier status or genotype, including potential benefits and harms.

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Chapter 9
Population-Based Surveillance for Rare Congenital and Inherited Disorders: Models and Challenges

Jodi M. Jackson, Krista S. Crider, and Richard S. Olney

Abstract Worldwide, an estimated 7.9 million children are affected by congenital and inherited disorders. Some disorders are relatively common, affecting tens of thousands of newborns annually; others are rare, involving disorders that, in extreme cases, can affect less than 30 infants per year. However, this infrequency does not reduce the impact or burden on individuals and their families. Congenital defects can cause long-term disability, have a lifelong impact on health, and cost billions of dollars in care. Collection of population-based surveillance data ideally enables the discovery of etiologies for rare congenital disorders of unknown cause, allows for examining outcomes, and evaluating treatments and interventions for children with all types of congenital and inherited disorders. Many challenges are associated with performing population-based surveillance, such as difficulty in ascertaining appropriate diagnoses and frequent unavailability of necessary resources. This chapter focuses on the importance of population-based data and uses national and international surveillance systems as models for how these rare disorders can be better understood.

Keywords Population surveillance · Rare diseases · Congenital abnormalities · Genetic diseases

9.1 Public Health Importance of Rare Congenital and Inherited Disorders

This chapter focuses on rare congenital and single gene disorders, with specific discussions about birth defects and inherited hematologic, neurodevelopmental,

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functional, or metabolic disorders. In particular, this chapter will discuss the value of population-based data and surveillance systems as models for how these rare disorders can be better understood.

By definition, a major birth defect is a congenital abnormality that requires medical or surgical treatment, has a serious adverse effect on health or development, or has significant cosmetic impact. This category of disorders includes malformations, deformations, or disruptions in one or more parts of the body [46]. Birth defects are the leading cause of infant mortality, and structural defects and chromosomal abnormalities collectively affect approximately 3% of births annually in the United States [34, 44, 75]. Inherited hematologic, neurodevelopmental, and metabolic disorders affect function and are not classically defined as birth defects, but they are equally devastating. Combined, an estimated 7.9 million children (6%) worldwide are affected by abnormalities of structure or function [12].

More than 7,000 congenital and inherited disorders have been identified [12]. Some categories of disorders, such as congenital heart defects, are collectively relatively common, while others (e.g., maple syrup urine disease, homocystinuria, or beta-ketothiolase deficiency) are very rare (Table 9.1). The National Institutes of Health's Office of Rare Diseases Research (ORDR) defines a rare disorder as one that has a prevalence of less than 1 in 1,500 births and thus affects fewer than 200,000 individuals in the United States. For congenital conditions, prevalence is affected by survival and other factors such as variability in age of diagnosis, but even some of the more common conditions, such as sickle cell disease and spina bifida, have estimated U.S. prevalence rates well below the ORDR threshold (approximately 50,000 and 25,000 affected individuals, respectively) [61, 62].

Congenital defects can have a lifelong impact on health, causing long-term disability and costing billions of dollars in care, and the infrequency of rare disorders does not reduce their collective impact or burden on individuals and their families [10]. Additionally, research on these rare familial disorders increases our general understanding of genetics and human biology.

Table 9.1 Prevalence of selected birth defects and disorders in U.S. children

Disorder	Approximate number of infants born in the United States per year[a]	Rate per 100,000
Congenital heart defects [58]	35,000	814
Down syndrome [6]	5,000	118
Orofacial clefts [70]	7,500	77
Spina bifida [2]	1,440	34
Sickle cell disease and other hemoglobinopathies [11]	1,150	27
Maple syrup urine disease [11]	27	0.63
Homocystinuria [11]	12	0.27
Beta-ketothiolase deficiency [11]	7	0.16

[a]Based on live birth occurrence data for 2008 ($n = 4{,}247{,}000$) [67].

Birth defects can be caused by both genetic and environmental factors and have a wide variety of manifestations and related co-morbidities. Some are detectable through physical examination, while others require specialized testing. Case definitions are used to determine whether a person has a certain birth defect, syndrome, or other health condition. The criteria within each case definition consist of clinical information such as laboratory results, signs, and symptoms. They are specific and standardized to allow for uniform classification across different investigators, locations, and time periods. Case definitions are necessary for proper quantification and surveillance of any health event and for the prevention of disease [60]. As part of the guidelines for birth defect surveillance, both the National Birth Defects Prevention Network and the Metropolitan Atlanta Congenital Defects Program have created specific criteria for each birth defect of interest for abstractors to use while reviewing medical charts and for case classification during the clinical review process [46, 16]. Finally, it is important to note that surveillance systems are distinct from patient registries, which are usually specific to one disorder and tend to disproportionately include only the more severe clinical manifestations. Population-based surveillance systems are designed to detect all severities of multiple disorders and thus have the potential to provide more accurate prevalence estimates.

9.2 Establishing Birth Defects Surveillance as the Prototype and Entry Point for Rare Congenital Disease Studies

Global birth defect surveillance is composed of hundreds of well-established programs and can potentially be used as a conduit for studies of rare congenital diseases. Surveillance data can be used for epidemiological studies to support prevention activities, health policy decisions, health services, and education planning. Surveillance is not only the tracking and measuring of events or trends but also the analysis of that data and reporting back to the community at large. Surveillance and epidemiology link an individual clinical encounter and population-level information that, in turn, can be used in the next clinical encounter.

9.2.1 Brief History of Birth Defect Surveillance

Many of the birth defects surveillance programs around the world were created in response to the tragic effects of the drug thalidomide. Originally developed as a sedative, thalidomide was prescribed during the 1950s for conditions such as anxiety, insomnia, headaches, and colds. The drug grew in popularity when it was found to also greatly reduce nausea in pregnant women. The drug was marketed widely around the world under at least 37 different names and taken by thousands of pregnant women (though, interestingly, use in the United States was extremely limited as it did not have approval from the Food and Drug Administration). In 1961, a significant increase in the number of infants born with severely malformed or missing limbs was observed that was linked to the use of thalidomide during pregnancy.

Thalidomide was estimated to have affected more than 10,000 children [24]. In response to this experience, many countries established birth defects surveillance programs to act as early warning systems for other such toxins and teratogens.

9.2.2 Current Surveillance of Birth Defects: State, National, and International Programs

9.2.2.1 Metropolitan Atlanta Congenital Defects Program

The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based surveillance system that uses active case ascertainment to identify birth defects from birth and pediatric hospitals, clinical laboratories, and vital records. The program, the first of its kind in the United States, was established in 1967 by the Centers for Disease Control and Prevention, Emory University, and the Georgia Mental Health Institute. To be included in MACDP, the infant or fetus must have a gestational age greater than or equal to 20 weeks, the mother must have lived in the five-county metropolitan Atlanta area at the time of birth, and the infant must have been diagnosed with an eligible birth defect before 6 years of age. MACDP ascertains structural and genetic defects through the fifth year of life because some defects do not manifest signs until early childhood and therefore are not diagnosed until then. Especially for rare disorders, with which many clinicians are unfamiliar, a correct diagnosis may be delayed by several years after signs first appear. There are currently approximately 50,000 births per year in the metropolitan Atlanta area, with a birth defect prevalence rate of approximately 2.7%. MACDP has provided guidance to many other surveillance programs and the data from this program have been used in numerous studies. For example, MACDP data were used to ascertain cases for a study designed to estimate the risk of fathering a child with major structural birth defects among veterans of the Vietnam War [23]. Currently, MACDP data are included in the National Birth Defects Prevention Study (NBDPS), an ongoing case-control study of major structural birth defects being conducted at nine study sites and covering an annual birth population of approximately 500,000 [76].

9.2.2.2 National Birth Defects Prevention Network

The National Birth Defects Prevention Network (NBDPN) is a nonprofit organization that focuses on surveillance, research, and prevention of birth defects. Established in 1997, NBDPN is composed of epidemiologists and public health workers at the local, state, and national level. The NBDPN currently collects population-based surveillance data from 35 states, which are used to calculate prevalence estimates for 45 specific birth defects by attributes such as state, maternal age, race and ethnicity, and pregnancy outcome [57]. The NBDPN fosters collaborative projects between researchers, hosts an annual meeting, and produces educational materials with the goal of informing parents, medical providers, and officials and

helping to shape prevention strategies. Through this collaboration, studies gain patient numbers and statistical power and researchers are able to compare subjects with a wider range of demographics. For example, a study of clubfoot that combined data from 10 states covered a surveillance population of more than 900,000 births per year, which represents one quarter of all births in the United States [53]. By using pooled data from 13 states, representing 30% of U.S. births, a study of the association between major birth defects and preterm birth was able to utilize representative subjects with the same maternal age and racial and ethnic distribution as the total U.S. births for the same time period [32].

9.2.2.3 International Clearinghouse for Birth Defects Surveillance and Research

The International Clearinghouse for Birth Defects Surveillance and Research (frequently referred to simply as the Clearinghouse and formerly known as the International Clearinghouse for Birth Defects Monitoring Systems) was founded in 1974 to coordinate international data sharing and surveillance. It began with 10 countries monitoring 22 birth defects and has grown to more than 40 countries and 40 defects. The Clearinghouse's purview has similarly expanded to now include collaborative research on possible causes of and prevention strategies for birth defects, as well as program development and education [4, 35].

9.3 Use of Surveillance Programs to Initiate Long-Term Follow-Up Studies of Inherited Metabolic and Hematologic Conditions

A vital part of surveillance is the analysis of data and communication of findings to support prevention activities, health policy decisions, health services, and education planning. A primary way surveillance programs can accomplish these objectives is through long-term follow-up activities. The goals of long-term follow-up are to assess access to and quality of care across populations, increase knowledge of the natural history of a disease, evaluate preventive treatments, and, ultimately, improve outcomes. Newborn screening programs provide a model opportunity to track individuals with disorders from diagnosis through treatment.

9.3.1 Newborn Screening in the United States

Newborn screening (NBS) is a public health program that tests babies for genetic, endocrinologic, metabolic, and hematologic diseases. Screening began in the 1960s with one disorder, phenylketonuria (PKU). PKU is a metabolic disease that can potentially cause mental retardation; this complication can be prevented by placing the baby on a specialized diet. However, to be effective, this intervention must

be started within the first few days of life while the child is still asymptomatic. To facilitate early detection, Dr. Robert Guthrie developed a test for blood obtained by pricking a newborn's heel and dried onto filter paper [13, 29]. With the discovery of more disease pathways and treatments and advancements in high-throughput laboratory technology, a newborn's dried blood spot can now be screened for a panel of disorders.

Decisions about which disorders to include on screening panels are currently made in each individual state, resulting in state-to-state differences. Factors that can be considered in determining which disorders to screen for include the likelihood that diagnosis of the disease can be missed clinically at birth, the frequency of the disease, the existence of a known treatment or cure, the consequences of delayed diagnosis on treatment outcome, the reliability of the test, the cost of the test, and availability of resources. As a result of concerns about variability in state screening practices [49], the American College of Medical Genetics (ACMG) recommended that all states screen for a core panel of 29 conditions, which includes hearing screening [50]. Approximately 4 million babies are tested each year in the United States [9]. If all 50 states screened for the ACMG panel of 29 disorders, nearly one third more cases would be identified annually, thus reducing the adverse health consequences for children with these conditions [11].

In addition to operating at the individual state level, there is also a regional system in place to help support newborn screening efforts [47]. Previously, the Council of Regional Networks for Genetic Services (CORN) helped support newborn screening efforts at the regional level [47]. This group was founded in 1985 to facilitate collaboration between regional and federal genetic services, and in 1987 CORN formed the Newborn Screening Committee. CORN created a set of broad guidelines regarding organization and administration, selection of disorders, communication, quality assurance, and funding for NBS programs to use as a operational framework [69]. CORN also annually produced national newborn screening reports with data such as what disorders were being screened for in each state, laboratory procedures, screening results by race and ethnicity, and definitions of conditions.

In 1999, national reporting became the responsibility of the National Newborn Screening and Genetics Resource Center (NNSGRC). The NNSGRC provides resources to individual state programs and to consumers, health care workers, and government officials. In 2004, the Genetic Service and Newborn Screening Regional Collaborative Groups (RCs) were formed along with a National Coordinating Center (NCC). The seven RCs are the New England Genetics Collaborative, New York–Mid-Atlantic Consortium for Genetics and Newborn Screening Services, Southeast Newborn Screening and Genetics Collaborative, Region 4 Genetics Collaborative, Heartland Regional Genetics and Newborn Screening Collaborative, Mountain States Genetics Regional Collaborative Center, and Western States Genetic Services Collaborative. The NNSGRC, RCs, and NCC are funded by the U.S. Health Resources and Services Administration, Maternal and Child Health Bureau (MCHB) with the goal to increase coordination between programs, to avoid duplication of effort, and to address universal issues.

9.3.2 Newborn Screening and Long-Term Follow-Up

Ideally, newborn screening includes more than just detection of rare disorders; it is a system of screening, diagnosis, education, treatment, follow-up, and disease management. Historically, however, funding and resources have ended after the "short-term" follow-up of diagnostic confirmation. In 2000, the American Academy of Pediatrics called for increased long-term follow-up in NBS programs [49]; similar recommendations were also made by several other groups. Despite these recommendations, a 2007 study found that fewer than half of NBS programs collected any long-term follow-up data, and two thirds of programs did not use such data at all or used the data only minimally [30]. In 2008, the U.S. Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children released a statement with the goal of improving the long-term follow-up component of newborn screening [38]. The statement calls for efforts to shift beyond data management to include activities related to improving the quality and delivery of care, research into new pathophysiology and treatment options, and active surveillance and evaluation of care and outcomes data.

9.3.2.1 Regional Studies

Many of the RCs have long-term follow-up programs in place to collect data such as diagnostic and clinical laboratory results; information on the types of physicians, services, and treatments used; and patient outcomes [47]. For example, the Region 4 Genetics Collaborative formed the Inborn Errors of Metabolism Information System (IBEM-IS) to monitor differences in clinical practices and determine the most effective treatment strategies for metabolic disorders. The New England Genetics Collaborative has focused on improving care for patients with medium-chain acyl-CoA dehydrogenase deficiency (MCADD) and cystic fibrosis.

9.3.2.2 Sickle Cell Disease: An Example of Long-Term Follow-Up

Sickle cell disease (SCD) is a hemoglobinopathy characterized by red cells that have a sickle shape. These cells have decreased flexibility and other abnormal characteristics, and the disease is associated with conditions such as anemia, susceptibility to life-threatening infections, severe pain, stroke, and events of respiratory compromise. In 1972, Congress passed the National Sickle Cell Anemia Control Act which called for grant support for hemoglobinopathy screening programs. It took until the late 1980s, however, for most states to adopt newborn screening for SCD, and it was not until the mid 2000s that every state universally screened for the condition. The shift during the 1980s was prompted by results of a randomized trial demonstrating that oral penicillin prophylaxis was effective in preventing SCD-related infections, thus encouraging early diagnosis [26, 51].

As a means to measure the effectiveness of screening and treatment, several SCD long-term follow-up studies have used mortality as a quantifiable outcome. Analyzing national death certificate data from 1968–1992, Davis et al. concluded

that death rates had significantly declined [21]. During roughly the same study period, two studies out of the U.S. Cooperative Study of Sickle Cell Disease also reported declines in SCD mortality rates [27, 41]. Concomitant improvements in health care, development of new vaccines, and increases in the number of states performing SCD newborn screening make it difficult to determine the primary driving force(s) behind the improved survival rate.

The effect of newborn screening for SCD was specifically analyzed in a study of children born in California between 1975 and 1985, before SCD screening had become universal in the state [72]. One cohort received a diagnosis of SCD via newborn screening, while the other cohort was not diagnosed until a mean age of 21 months. The use of prophylactic penicillin was not yet general practice, and there was no difference in the number of life-threatening events between groups, yet those that were diagnosed at birth had an overall mortality rate of only 1.8%, compared with 7.8% in the group receiving a later diagnosis. Additionally, in studies of states with universal SCD newborn screening programs, mortality rates in black children with SCD was slightly less than that for black children without SCD [7, 52]. Parental education programs and early recognition of SCD-related complications, both products of newborn screening, in addition to early institution of penicillin prophylaxis, have been proposed to have caused the marked decline in mortality.

9.4 Incorporating Single Gene Disorders into Population-Based Surveillance Programs

Single gene disorders are conditions caused by a change in a single gene. There are more than 6,000 single gene disorders. Although individually rare, together they occur in approximately 1 in 300 births. To improve patient outcomes, surveillance for many of these disorders can be incorporated into population-based surveillance systems that are already well established.

9.4.1 Hemophilia

Hemophilia is a congenital disorder that results from a deficit in a protein necessary for normal blood clotting, which leads to spontaneous and/or excessive bleeding from trauma or surgery. Repeated bleeding into joints leads to a chronically painful and disabling arthritis. Treatment for bleeds in the form of intravenous infusions with concentrates of the missing protein manufactured from pooled blood donations became available in 1970. In 1975, Congress provided support for a network of hemophilia treatment centers to provide comprehensive preventive care for individuals with hemophilia and other bleeding disorders. Newborn screening for hemophilia is not routinely performed unless there is a family history of the disorder, which is present in about two-thirds of cases. Therefore, the exact number of individuals with hemophilia in the United States is not known. To capture the prevalence and incidence of hemophilia in the U.S., along with demographic, clinical, and

resource use data, from 1993 to 1998, CDC operated an active surveillance system composed of six states: Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma [63]. All individuals with hemophilia in the states were identified utilizing sources such as hemophilia treatment centers, general medical care facilities, patient advocacy groups, physicians, clinical laboratories, and Medicaid claims data. Trained data abstractors collected detailed information from medical records documenting clinical characteristics, complications and mortality over the 6-year period. These data have subsequently been used to determine the occurrence of the disorder (13.4 per 100,000 males) [63]; efficacy of treatments [64]; and rates, causes, and predictors of mortality [65] and other complications.

9.4.2 Duchenne and Becker Muscular Dystrophy

Duchenne and Becker muscular dystrophy (DBMD) are the two most common dystrophies – diseases that cause progressive weakening of muscles – and are caused by mutations in the X chromosome gene *DMD*. The clinical signs of DBMD are generally not present in young infants, and the disorder is not routinely ascertained by birth defect surveillance programs. The Muscular Dystrophy Surveillance Tracking and Research Network (known as MD STARnet) was started in 2002 by CDC with the goal of establishing a population-based surveillance system for DBMD. MD STARnet currently consists of surveillance programs in Arizona, Colorado, Georgia, Hawaii, Iowa, and 12 counties in western New York; it includes affected individuals born on or after January 1, 1982, and diagnosed before 21 years of age. Active case ascertainment is conducted by review of medical records from sources such as neuromuscular clinics, physicians, birth defect surveillance programs, hospitals, and service sites for children with special health care needs. For each case ascertained in the 6 states, every month the certainty of the diagnosis is classified by 6 neurologists – one from each state – by applying standardized criteria and definitions to abstracted data for that case. After the initial abstraction, cases are re-abstracted annually to follow disease progression. MD STARnet data are used to ascertain prevalence estimates across racial and ethnic groups and to study treatment use, secondary conditions, and long-term health outcomes.

Ultimately, population-based surveillance for single gene disorders such as DBMD might best be accomplished through universal newborn screening, but there has been ongoing debate regarding whether to include this disorder in newborn screening panels. Presymptomatic treatment for the disorder is still on the horizon, prompting some to argue that testing offers no direct benefit to the newborn. It has also been argued that the course of the disease varies across individuals, making parental counseling difficult and possibly exposing affected individuals to genetic discrimination. Arguments for its inclusion in newborn screening include allowing families to become knowledgeable and to develop support networks before the manifestation of symptoms, informing future reproductive decisions, and beginning supportive care (such as optimized nutrition and corticosteroid use) as early as possible [39]. Another justification for newborn screening is identifying the mothers

of affected boys. Carriers of the DBMD X-linked mutation have a high risk for cardiomyopathy and their risk can be reduced by timely cardiac therapy [33, 56]. The only newborn screening program for Duchenne muscular dystrophy currently in operation is in Wales [5]. CDC-funded investigators are studying its inclusion in the United States as part of either newborn or infant (6–15 months) screening.

9.4.3 Fragile X Syndrome

Fragile X syndrome (FXS) is the most common inherited cause of mental retardation. Population-based research studies have shown that it affects approximately 1 in 4,000 males and 1 in 6,000–8,000 females [17, 71]. It is caused by an increase in the number of CGG trinucleotide repeats in the *FMR1* gene, located on the X chromosome. Depending on the number of repeats, individuals are said to be unaffected, to have premutations, or to have full mutations. Individuals with the full mutation have varying clinical manifestations, including developmental and learning disabilities, speech and language delays, behavioral problems, and autism spectrum disorders [25]. A DNA blood test can determine the number of repeats present, but because of the wide range and non-specificity of the clinical presentation, currently, testing and diagnosis usually do not occur until a child is approximately 3 years of age [1]. As with DBMD, population-based newborn screening has been debated as a means of universal early identification. The suggestion of newborn screening for fragile X syndrome has been met with resistance because of the concomitant detection of the premutation. Because premutation-associated health problems such as ataxia and infertility are not experienced until adulthood, newborn diagnosis raises multiple ethical concerns. A recent study of Georgia newborn dried blood spots, however, was able to detect epigenetic changes in the *FMR1* gene specific only to the full mutation [14]. More than 36,000 newborns were sampled for this analysis, and the detected incidence rate of 1 in 5,161 males is consistent with previous estimates, proving the feasibility of its use for population-based testing. It remains to be seen whether this test will be adopted as part of state newborn screening panels.

9.5 Assurance and Quality of Rare Disease Management

Population-based health data can be used in myriad ways to improve the management of rare congenital and inherited diseases. Improving the speed and accuracy of diagnoses through new technology and genetic studies, ascertaining the actual utilization and effectiveness of preventive treatments, and the sharing of data are just a few of these ways.

9.5.1 Improvements in Diagnostic Practices

The goal of NBS is to minimize morbidity and mortality by early detection and treatment of clinically important disorders. The development of high-throughput

tandem mass spectrometry (MS/MS) in the 1990s enabled population-based screening of a wide range of rare metabolic disorders that had not been screened for previously. MS/MS can detect amino acid, organic acid, and fatty acid oxidation disorders such as maple syrup urine disease, methylmalonic acidemia, and medium-chain acyl-CoA dehydrogenase deficiency. Analysis is rapid (approximately 20 metabolites in 2 min) with a low false positive rate, making it ideal for NBS programs [9].

An Australian study found that children with one of 29 metabolic disorders diagnosed through MS/MS had fewer deaths and fewer clinically significant disabilities than children who received a later diagnosis [74]. Wilcken et al. compared outcomes such as death, intellectual and physical condition, school placement, growth, treatment, diet, hospital admissions, and other medical problems. More than 2 million children were followed for up to 6 years, with birthdates from before MS/MS screening was available, during the transition when MS/MS technology was performed only regionally, and after nationwide screening via MS/MS was implemented. The rate of MS/MS diagnosis was twice that seen clinically (15.2 per 100,000 compared with 7.5 per 100,000), making a clear case for increased detection and improved outcomes.

9.5.2 Value of Genotype/Phenotype Clarification

Each disease presents its own challenges for management; the more accurate the diagnosis, the more tailored the treatment plan can become. Understanding the genetics behind the disease can provide insight to the mechanism of illness and offer guidance in treatment. Even before the biologic pathways are fully understood, however, if specific forms of the causative gene (the genotype) can be linked to a set of specific physical characteristics (phenotypes), disease progression can be better predicted and managed.

9.5.2.1 Sickle Cell Disease Genotype-Phenotype

Possibly the first disease outcome to be linked to specific genotypes was sickle cell disease (SCD). In 1949, Linus Pauling demonstrated that it was an abnormal form of the hemoglobin molecule (Hb) that caused disease, calling the typical form A and the disease-causing variant S [54]. Other variants have subsequently been discovered and linked to SCD prognosis. Individuals with homozygous sickle-hemoglobin mutations (written as Hb SS) have the most severe form of SCD while those with Hb SC-disease (compound heterozygotes) have a milder form. Data from the U.S. Cooperative Study of Sickle Cell Disease showed the median age of death for Hb SS males was 42 years, compared with 60 years for Hb SC males. Hb SS and Hb SC females had similarly disparate life expectancies of 48 and 68 years, respectively [55]. This study was based on a group of individuals ascertained through clinical centers, however, and there is a need for population-based genotype/phenotype data.

9.5.2.2 Cystic Fibrosis Genotype-Phenotype

Cystic fibrosis (CF) is a lethal disease associated with altered chloride ion transportation that results in recurrent respiratory infections and reduced nutrient absorption. The gene responsible for CF was discovered in 1989 [59], and more than 1,600 mutant alleles have been identified [20]. There is a wide range of clinical manifestations of patients, which has been shown to be the result of the extreme genetic variation. The most common mutation is ΔF508, and patients who are homozygous for this allele have the most severe outcomes [40]. McKone et al. [45] further investigated this relationship by using the Cystic Fibrosis Foundation National Registry; though it is not population-based, it includes data from accredited CF care facilities on a large proportion (as high as 80%) of individuals with CF in the United States [18]. Clinical outcomes and mortality database were used to analyze the genotype-phenotype relationship in approximately 18,000 patients. Significant clinical differences were found in the 24 genotypes analyzed and findings showed that in compound heterozygotes, mortality and other outcomes are primarily determined by the non-ΔF508 allele.

Findings such as these for SCD and CF have strong prognostic implications and can be used for disease management. Both disorders are ascertained through NBS; currently, SCD is universally included in screening panels, and CF screening will become universal in the United States by the year 2010 [19].

9.5.3 Utilization of Preventive Treatments

The goal of early diagnosis is to begin treatment as quickly as possible and to prevent as many complications as possible. Sickle cell disease and medium-chain acyl-CoA dehydrogenase deficiency (MCADD) both serve as classic examples of the benefit of preventive treatments.

9.5.3.1 Sickle Cell Disease

Individuals with SCD have an increased susceptibility to bacterial infections, particularly *Streptococcus pneumoniae*. In 1986, Gaston et al. [26] conducted a multicenter, randomized trial of oral penicillin prophylaxis and saw results so overwhelmingly positive that the trial was terminated 8 months early. There was an 84% reduction in infection and no deaths with penicillin treatment, compared with three deaths in the placebo group. A daily dose of penicillin is the current standard of care for children aged 2 months to 5 years with SCD. In a study done by the New Jersey Division of Family Health Services, physicians reported that 96.5% of infants with SCD were treated with penicillin within the first 5 months of life [22]. What is not clear, however, is what proportion of patients continues to adhere to this recommendation. In a study conducted in California, Illinois, and New York, survey results from physicians reported that 44% of patients complied with penicillin prophylaxis, while surveys completed by parents of the same patient

group reported 93% adherence [8]. A study using Tennessee and Washington State Medicaid data analyzed the number of days during a 365-day period that a child had a filled prescription for prophylactic medication [66]. Results indicated that 10.3% of children younger than 4 years old with SCD had no penicillin prescriptions filled in a one year period, and only 21.5% had their prescriptions filled for more than 270 days. However, this study did not attempt to measure the rate of the second step of adherence, taking the medication.

9.5.3.2 Medium-Chain Acyl-CoA Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is a rare metabolic disorder occurring in 1 in 10,000–20,000 newborns [9]. Children with MCADD cannot properly process fatty acids, resulting in hypoglycemia, hypotonia, lethargy, seizures, and death. Adverse effects can be prevented, however, by avoidance of lengthy fasting and increases in the intake of carbohydrates during times of stress such as infection or recent immunization [28]. Left undiagnosed or untreated, though, approximately 20% of patients die during their first metabolic crisis, and about 40% of those who survive such a crisis show neurological impairment [43]. A population-based study in Australia found a reduction in morbidity and mortality among patients 4 years of age and younger who were diagnosed via newborn screening [73]. The same authors performed a long-term follow-up study of patients up to 10 years of age and showed that early diagnosis and an increased number of hospitalizations were associated with higher verbal, communication, and socialization skills [37]. Because metabolic crisis can be avoided, and the prognosis can be improved through early detection and monitoring, MCADD is now a part of the newborn screening panel in all 50 states.

9.5.4 Dissemination of Information

The ability to share information and results increases the pace and breadth of research. In 2005, the National Institutes of Health (NIH) first enacted its public access policy. This policy requires all scientific researchers who receive federal funding to post their results in the National Library of Medicine's online archive, known as PubMed Central. Full texts of these peer-reviewed articles are publicly searchable and available within 12 months of publication. The NIH public access policy is not the only one of its kind, however. The Massachusetts Institute of Technology, the Faculty of Arts and Sciences at Harvard University, advocacy groups such as Autism Speaks, Britain's Wellcome Trust, the Italian National Institute of Health, the European Research Council, and all seven United Kingdom research councils have all enacted similar guidelines.

There is also a trend to make national data publicly available. The National Birth Defects Prevention Network publishes an annual report in the journal *Birth Defects Research Part A: Clinical and Molecular Teratology* that provides state-by-state data, and the NNSGRC operates a national newborn screening data-collection

system that provides "real-time" information self-reported by state and territorial newborn screening programs [48]. Several states also have publicly accessible birth defects surveillance databases. The Iowa Registry for Congenital and Inherited Disorders has data available on its website, and both the Colorado Department of Public Health and Environment and the Texas Department of State Health Services have online databases that can be queried by characteristics such as year of birth, maternal county of residence, and maternal race and ethnicity [36, 15, 68].

9.5.5 Challenges

There are many challenges associated with performing high-quality, population-based surveillance, particularly for rare disorders. Frequently, the necessary resources and infrastructure are unavailable. For example, in a 2007 survey of NBS programs, 87% of respondents reported insufficient financial resources as a barrier to long-term follow-up [31]. Providing security for electronic data storage to ensure the privacy and integrity of large amounts of data with identifiable information is another challenge, as is reporting such data in a way that will prohibit the identification of small cells of individuals with rare disorders. Additionally, when abstractors are employed to perform active case ascertainment, they must have specialized training because of the technical aspect of reviewing medical records of children with rare conditions [16]. And finally, birth defect prevalence studies and measurements of the effectiveness of primary prevention practices can both be skewed by terminations of affected pregnancies, as these procedures often occur in settings such as outpatient clinics that are not typically included in surveillance systems [3].

In the absence of newborn screening or a family history that would alert clinicians to a particular diagnosis, single gene disorders affecting children, such as fragile X syndrome and DBMD, are typically diagnosed well beyond infancy. Variations in the age of diagnosis provide inherent challenges for population-based ascertainment, which ideally should capture all affected individuals in a given geographic area. With uncommon conditions, missing individuals can skew prevalence rates substantially. Even birth defects, which by definition are present on the day of delivery, can be challenging to ascertain completely. Some birth defects are internal and do not present signs in the birth hospital. In certain countries, this limitation has led to systems of ascertainment that focus on external anomalies [42]. For both internal birth defects and chromosomal or single gene disorders that rely on laboratory tests for diagnosis, surveillance systems should ideally rely on multiple sources that include diagnostic and referral centers for complete case ascertainment.

9.5.6 Conclusions

Collection of population-based surveillance data is a first step in the discovery of etiologies for rare congenital disorders of unknown cause and in examining outcomes of children with all types of congenital and inherited disorders. For these rare

disorders, a very large study population is often necessary, and still may be insufficient, to observe enough affected individuals for studies such as those that examine genotype-phenotype relationships and environmental etiologies. While clinical trials are necessary for evaluating the efficacy of therapies, population-based studies provide data across subpopulations to demonstrate the effectiveness of interventions in the "real world." By starting in local communities and building a wider surveillance area through state, regional, and national data, it will be possible to further study and hopefully understand the etiologies and treatment of these serious conditions.

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Chapter 10
Statistical Methods for the Geographical Analysis of Rare Diseases

Virgilio Gómez-Rubio and Antonio López-Quílez

Abstract In this chapter we provide a summary of different methods for the detection of disease clusters. First of all, we give a summary of methods for computing estimates of the relative risk. These estimates provide smoothed values of the relative risks that can account for its spatial variation. Some methods for assessing spatial autocorrelation and general clustering are also discussed to test for significant spatial variation of the risk. In order to find the actual location of the clusters, scan methods are introduced. The spatial scan statistic is discussed as well as its extension by means of Generalised Linear Models that allows for the inclusion of covariates and cluster effects. In this context, zero-inflated models are introduced to account for the high number of zeros that appear when studying rare diseases. Finally, two applications of these methods are shown using data of Systemic Lupus Erythematosus in Spain and brain cancer in Navarre (Spain).

Keywords Disease cluster detection · Disease mapping · Rare disease · Spatial scan statistic · Zero-inflated model

10.1 Introduction

Health authorities study the spatial variation of the incidence of disease because it is a matter of public concern. In addition to the study of the spatial variation, assessing whether cases tend to appear in small groups or clusters is also of interest. When information about possible risk factors is available, establishing a link between them and the distribution of the disease is of particular concern as well. This is why in many cases these agencies publish reports to describe the geographical variation of disease risk and other relevant data such as, for example, the location of a certain type of industries.

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Our aim in this chapter is to provide an introduction to the methods for mapping diseases, as a preliminary exploratory analysis, and the detection of disease clusters. In particular we will focus on rare diseases. Although there is no a single definition of rare disease, the European Commission (Health and Consumer Protection Directorate-General) considers that a disease is rare if its prevalence is lower than 50 cases per 100,000 habitants [14]. Hence, according to this definition, rare diseases will have very low observed cases in low populated areas. It should be noted that some types of cancer fall in this classification of rare diseases.

Some rare diseases have a strong genetic component and may have an even lower prevalence. If the disease is rare, many areas may have zero counts, which will cause additional problems in the statistical analysis due to the large number of zeros that appear. Although standard methods could be used, care should be taken and other statistical methods that account for the excess of zeros may be required [28].

Regarding the detection of disease clusters, many methods have been proposed so far and a comprehensive review can be found in Kulldorff [26]. These methods are often used for the study of common and rare diseases, but the underlying models may vary according to the prevalence of the disease.

As a previous step to the detection of disease clusters, displaying raw or smoothed estimates of the relative risks may help to provide a general description of the geographic variation of the disease risk. This can be regarded as an exploratory data analysis. Several risk estimators are discussed in Section 10.2.

Some methods for the detection of disease clusters are described in Section 10.3. Although these methods are suitable for rare diseases, they may not be appropriate for very rare diseases, such as many related to genetic factors because of the low number of observed cases [28]. This issue and possible solutions are treated in Section 10.4.

A short and non-comprehensive list of useful software is given in Section 10.5. Two examples based on the prevalence of Systemic Lupus Erythematosus in Spain and brain cancer in Navarre (Spain) can be found in Section 10.6. Finally, a summary and some final remarks are included in Section 10.7.

10.2 Disease Mapping

In order to display the geographical variation of the disease we will consider the scenario in which cases are aggregated at some administrative level. This means that counts of the disease are observed in a number of areas, which may be counties, states, etc., depending on the aggregation level. For each area the expected number of cases can also be computed using the population and some information about the incidence of the disease.

A common assumption for rare diseases is that the number of cases in a given region follows a Poisson distribution with mean the expected number of cases times the relative risk, which is our primary interest. The relative risk measures the variation of the disease in the area on top of the expected number of cases. The expected

number of cases is included to account for the variation of the disease due to the heterogeneous distribution of the population (i.e., the higher the population the higher the expected number of cases).

Usually, a relative risk of 1 means an average incidence, whilst values higher than 1 mean increased risk in the region. Hence, when trying to detect clusters we will be looking for groups of areas whose relative risks are all significantly higher than 1 (or any other relevant reference value).

To sum up, the distribution of the cases in region i can be written as

$$O_i \sim Po(E_i\theta_i)$$

where E_i is the expected number of cases in region i and θ_i the relative risk.

Once we have the observed and expected cases, the aim is to get reliable estimates of θ_i. This can be done in several ways. First of all, raw estimates can be obtained using the Standardised Mortality Ratio, which is

$$SMR_i = O_i/E_i$$

However, the variance of the SMR is O_i/E_i^2, which makes it very unreliable in low populated areas. Approximate 95% confidence intervals can be produced using a Normal approximation, so that they are

$$SMR_i \pm 1.96\sqrt{O_i/E_i^2}$$

These confidence intervals will provide a measure of the uncertainty about the actual relative risk in area i and an assessment of its significance. If the value 1 (or any other relevant reference value) is below the confidence interval we may consider it as significantly high.

A better approximate confidence interval can be obtained when working with the log-SMR. In this case, the aim is to obtain a confidence interval for $\log(SMR_i)$, whose standard error is $\sqrt{1/O_i}$. An approximate 95% confidence interval for the relative risk can be computed as

$$\exp\left\{\log(SMR_i) \pm 1.96\sqrt{1/O_i}\right\}$$

Notice that for the case of very rare diseases this can be problematic because in many areas the observed number of cases will be zero.

10.2.1 Smoothed Relative Risk

In general, plotting the SMR can be misleading because of its high variability. Furthermore, risk is usually assumed to vary smoothly between neighbours. Smoothed estimators have been developed by several authors [47], which provide estimates that show smoothed geographic patterns.

Smoothing is based on combining data from several areas to borrow information and reduce the noise in the estimates of a single region, similarly as how it happens in regression models. There are many ways of borrowing information. Clayton and Kaldor [10] discuss several methods in which they provide smoothed estimates of the relative risks using different models. Marshall [31, 32] uses a non-parametric approach, which can also account for spatial variation.

In order to allow for higher flexibility the relative risk can be modelled using log-linear models [34] of the form

$$\log(\theta_i) = \alpha + \beta X_i$$

to depend on a vector of covariates X_i. Furthermore, this model can be extended to include random effects so that the area-to-area variation can be accounted for. In principle, independent random effects can be considered, but other types of effects can be included as well. Given that accounting for spatial variation is a key issue when smoothing rates, spatially correlated random effects are of particular interest.

Besag et al. [7] proposed an approach which has been widely used and that models the relative risk as

$$\log(\theta_i) = \alpha + \beta X_i + u_i + v_i$$

where v_i represent a spatially correlated random effect and u_i independent random effects. This is considered within a Bayesian framework. Banerjee et al. [4] and Lawson [27] provide recent reviews on Bayesian methods for disease mapping.

Spatial correlation can be included by considering other types of models or smooth functions, such as splines [30]. Splines [39] are often used to model non-linear relationships between a response and a covariate, but they can easily be extended to the spatial case to produce smoothed surfaces.

Finally, all these models can be extended to produce space-time models that incorporate data from different years. They are useful because can be used to disentangle both spatial and temporal clusters [1]. For recent developments on spatio-temporal modelling of relative risks see Martínez-Beneito et al. [33] and Ugarte et al. [45] and the references therein.

10.3 Methods for the Detection of Clusters

The description of the geographical pattern of disease should be considered as a previous step to the detection of disease clusters. Regions of high risk will probably appear when displaying the relative risks in a map, but some other methods may be required to identify the actual location (and shape) of the clusters.

Wakefield et al. [46] describe some methods for the detection of disease clusters and show some examples of their use. Kulldorff [26] provides a comprehensive and recent summary of the methods for the detection of disease clusters available in the

literature. All the methods presented there are described for the general case, and no particular discussion is done for the case of rare diseases.

Besag and Newell [6] divide the types of methods for the detection of disease clusters in two groups:

- *General methods*: These methods provide a measure of the overall level of clustering in the whole of the study region. Most of these tests are based on looking for spatial autocorrelation [46]. However, if the cluster is very localised and the disease is very rare, these methods may fail to identify clustering.
- *Focused methods*: These methods look for clusters around a particular putative focus or pollution source. Usually, these methods are employed after a few cases of the disease are observed around the source, and care must be taken not to fall in the Texas sharp-shooter fallacy [see, for example, 5].

Another type of methods is that of scan methods. These methods are based on defining a window that is moved all over the study region. Every time the window is moved, the areas inside the window are tested for clustering. These methods are described in detail in Section 10.3.3.

10.3.1 Assessing Spatial Variation

Assessing spatial variation of the relative risks is the initial step for the detection of disease clusters. Wakefield et al. [46] and Gómez-Rubio et al. [17] describe several methods for the assessment of spatial variation in the context of disease mapping. The two main ways of approaching this problem are testing for spatial correlation and general clustering.

Moran's I [11] is a popular method to test for spatial correlation. In our case, we will try to assess spatial correlation of the relatives risks using the SMR's and Moran's I statistic is defined as

$$I = \frac{n}{\sum_i \sum_j w_{ij}} \frac{\sum_i \sum_j w_{ij}(\hat{\theta}_i - \overline{\hat{\theta}})(\hat{\theta}_j - \overline{\hat{\theta}})}{\sum_{i=1}^{n} (\hat{\theta}_i)^2}$$

where $\hat{\theta}_i$ is the SMR in area i, $\overline{\hat{\theta}}$ is the mean of all SMR's and w_{ij} are spatial weights that measure spatial dependence. Bivand et al. [8] describe many ways of defining these weights, but it is common to take them as 1 if areas i and j are neighbours and 0 otherwise.

Moran's I can be regarded as a (spatial) correlation coefficient, because its values range from –1 to 1. Values close to 1 mean high spatial correlation, which may imply the presence of clusters (i.e., areas with high relative risks tend to have neighbours with high relative risks).

A statistical test can be performed to assess the significance of the observed value of the statistic using a Normal approximation to the distribution of Moran's I statistic

[11]. A Monte Carlo test can also be performed under different assumptions for the distribution of the observed number of cases in the areas [17].

Geary's c statistic [16] is another popular method to assess spatial autocorrelation. It is defined as

$$c = \frac{(n-1)\sum_i \sum_j w_{ij}(\hat{\theta}_i - \hat{\theta}_j)^2}{2\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij} \sum_{i=1}^{n} (\hat{\theta}_i - \overline{\hat{\theta}})^2}$$

The spatial weights w_{ij} are similarly defined as for Moran's I before. However, Geary's c statistic relies on the pairwise differences between the relative risk estimates. Values of Geary's c range from 0 to 2, with small values indicating spatial autocorrelation. In order to assess for significant spatial autocorrelation similar Monte Carlo tests as for Moran's I exist.

10.3.2 General Clustering

Moran's I and Geary's C are generic statistics than can be used to test for spatial autocorrelation of any (spatial) variable, not necessarily the relative risk. Other authors have developed tests for global clustering that have been proposed taking into account the sort of data that we find in spatial epidemiology.

Whittermore et al. [48] have proposed a method based on comparing the observed cases in one area to those of its neighbours. The statistic that they use is

$$W = \frac{n-1}{n} r^T D r$$

where $r = [O_1/O_+,...,O_n/O_+]^T$ and D is a matrix whose elements d_{ij} are the distances between the centroids of areas i and j.

The main drawback of this method is that it only takes the observed cases into account, and completely ignores the expected number of cases. In order to investigate the geographic variation of the risk we would need to account for the expected cases as well.

Tango [42] proposed a similar statistic that compares the observed to the expected number of cases in each area. This new statistic has the following form:

$$T = (r-p)^T A (r-p)$$

where r is as before, $p = [E_1/E_+,...,E_n/E_+]^T$ and A is a matrix so that its elements A_{ij} measure dependence between areas i and j. This dependence can be defined in several ways. Tango [42] suggests using a smooth function based on the distance between the area centroids, for example, $A_{ij} = \exp\{-d_{ij}/\varphi\}$. d_{ij} is the distance between the centroids of areas i and j and φ is a smoothing parameter that controls the scale of the dependence between areas.

Clustering is related to small values of the T statistic and significance can be assessed by using a Monte Carlo test.

10.3.3 Scan Methods

Once we have assessed that there is evidence of clustering in the study region we should aim at finding the location of the disease clusters. This involves selecting a list of possible clusters and performing a statistical test on each of them. Scan methods provide a suitable framework for this since they are based on a moving window that looks for localised clusters. The elements of every scan method are the following:

- Locations of putative cluster centres. Area centroids are a common choice, but regular grids can also be used.
- Size of the cluster. This usually refers to the number of cases in the cluster. However, size may also mean the number of areas in the cluster or the radius from the cluster centre.
- Test for clustering. A test is performed around every cluster centre in order to assess its significance. In general, different scan methods will use different tests.

The size of the cluster is used to define the window, whilst the cluster centres indicate how this window should be moved. Sometimes it is worth using different types of windows, in size and shape, so that different cluster structures can be detected.

10.3.3.1 Geographical Analysis Machine

The Geographical Analysis Machine [GAM, 36] uses a regular grid on the study region and considers a circular window of fixed radio (based on geographical distance). Following the procedure of a scan method, the circular window is centred at each point of the grid and a test is performed for all the areas whose centroid is inside the window. The clustering test is based on comparing the total observed (O_+) and expected (E_+) number of cases in the regions in the window by means of a Poisson distribution.

Hence, for each possible cluster, a p-value can be computed using a Poisson distribution (and assuming a relative risk equal to 1) as follows:

$$\text{p-value} = Pr(O_+ > E_+) = 1 - Pr(O_+ \leq E_+) = 1 - \sum_{i=0}^{O_+} \exp\{-E_+\} \frac{(E_+)^i}{i!}$$

Once all possible clusters are tested, those which turned out to be significant are reported and highlighted in a map. A surface can be constructed by using a kernel smoothing using on the centres of the clusters detected. This will give an overview of the cluster locations all over the study region.

The problem with this approach is that we need to define the grid and the radius of the window. This may be problematic and it is usually a good idea to try several values of the step of the grid and the radius of the window. Circular windows are constructed by default, but other shapes may be considered if appropriate.

From a statistical point of view, there is also the problem of multiple testing because of the high number of tests that are performed. In order to correct for this, clusters are reported when their p-values are very small and the level of significance to report a cluster is smaller than the usual 0.05.

10.3.3.2 Spatial Scan Statistic

The Spatial Scan Statistic [SSS, 25] is based on comparing the risk inside a cluster to the risk outside it. This can be expressed as the following statistical test:

$$H_0 : \theta_c = \theta_{\bar{c}}$$
$$H_1 : \theta_c > \theta_{\bar{c}}$$

where θ_c is the relative risk in the cluster and the $\theta_{\bar{c}}$ the one outside the cluster.

Using the usual Poisson distribution for the observed number of cases, the value of the likelihood ratio for the previous contrast is given by

$$T_c = \left(\frac{O_c}{E_c}\right)^{O_c - E_c} \left(\frac{O_{\bar{c}}}{E_{\bar{c}}}\right)^{O_{\bar{c}} - E_{\bar{c}}}$$

For a given cluster centre, Kulldorff [25] considers the set C of all possible clusters that include up to a fixed proportion of the total population, to avoid testing for the same cluster many times. Instead of testing for all possible clusters in C, Kulldorff [25] takes the most likely cluster and then assess its significance using a Monte Carlo test. Hence, the test statistic is the maximum of all T_c:

$$T = \max_{c \in C} \{T_c\}$$

The Monte Carlo test is based on redistributing the cases at random proportionally to the expected number of cases in each area and recomputing the value of T. By doing this many times we can get the sampling distribution of T under the assumption that there is no cluster around that centre.

We can call $T^{(0)}$ the value of T for the real data set and $\{T^{(i)}\}_{i=1}^{K}$ to the values of the test statistic when we redistribute the cases K times. If l is the number of these values higher than $T^{(0)}$, the p-value can be computed as $(l + 1)/(k + 1)$.

This procedure is repeated considering each area as a possible cluster centre so that, in the end, we will have a list with all the significant and most likely clusters found in the study region. Among them, the one with the highest value of the test statistic can be selected as the main cluster. Other secondary clusters may appear as well.

The Spatial Scan Statistic is recommended by the European Surveillance of Congenital Anomalies network (EUROCAT) [15].

10.3.3.3 Shape of the Cluster

So far, we have assumed that the cluster has a circular shape around its centre. However, this may not always be the case. For example, some diseases are related to the proximity of certain pollution sources (e.g., roads) that may have a shape but circular. For the scan methods, the way the areas are put together around the cluster centre can be changed to allow for other shapes. Kulldorff et al. [24] proposed a version of the spatial scan statistic with elliptic windows.

If the real shape of the cluster is not circular, this will reduce the power of the methods to detect the cluster. Although, the main cluster may not be detected as a whole, it may be possible to detect smaller parts of it with a circular shape.

Tango and Takahashi [41] propose a method that allows for flexible shapes of disease clusters. Similarly, Assunçao et al. [3] describe a procedure for fast detection of disease clusters of arbitrary shape.

The Spatial Scan Statistic can be extended to detect clusters in space and time. Kulldorff et al. [22] consider a moving temporal window so that data are aggregated over small time periods and then the usual test is performed. The temporal window is moved in a similar way as in the spatial case, so that it starts with short time periods up to a certain proportion of the whole time period.

As Kulldorff et al. [22] point out, it may be necessary to adjust for temporal trends before merging the data in the temporal window. This is done so that the temporal differences are properly accounted for. Furthermore, prospective detection of disease clusters using a modified Spatial Scan Statistic is addressed by, for example, Kulldorff [21] and Kulldorff et al. [23].

10.3.4 Model-Based Methods

Although these methods are very useful to find the actual locations of disease clusters, there are other important issues that these models are not able to tackle. To mention a few, how relevant risk factors can be included or how to adjust for secondary clusters.

Zhang and Lin [51] and Jung [20] propose an approach to cluster detection based on the use of Generalised Linear Models. In this approach, clusters are introduced by means of dummy variables as follows:

$$\log(\theta_i) = \alpha + \gamma c_i$$

The dummy variable c_i associated to a cluster is defined so that it is 1 for the areas in the cluster and 0 otherwise. Many different clusters can be considered, in a similar way as in the Spatial Scan Statistic.

Note that with this formulation it is also possible to include other covariates in the model. Given that the covariates may explain part of the spatial variation, their effect will be estimated first and they will be introduced as an offset in the model:

$$\log(\theta_i) = \hat{\alpha} + \hat{\beta} X_i + \gamma c_i$$

This will ensure that the effect of both the covariates and that of the clusters are not distorted by any confounding between them. By doing so the cluster variable will account for any residual cluster remaining after adjusting for the effects of the covariates.

In this context, the cluster will have a significant increased risk if its associated dummy variable has a coefficient which is significantly higher than 0. A likelihood ratio test can be proposed to compare the model with a cluster variable to another model without any cluster variable. This is essentially equivalent to the likelihood ratio test of the Spatial Scan Statistic [20]. Alternatively, significance of the cluster can be done by computing a statistical test on the associated coefficient γ, such as a score test or providing confidence intervals for γ.

In a more general framework, many different cluster variables can be considered as it was done with the scan methods. The most likely cluster can be selected by taking the one with the highest value of the likelihood ratio statistic. Adjustment for several clusters can be easily done by including their respective cluster covariates, with different coefficients, in the model.

As a final remark, we would like to highlight the fact that when exploring many possible clusters, we can follow other general methods for covariate selection in the context of GLMs.

10.3.5 Mixed-Effect Models

Assuming that the distribution of the observed number of cases follows a Poisson distribution may prove difficult in practice. A common problem when analysing epidemiological data is that they are over-dispersed, that is, $Var[O_i] > E[O_i]$. However, when using a Poisson distribution, it should hold that $E[O_i] = Var[O_i] = \theta_i E_i$.

Over-dispertion may occur for different reasons. A common one is when there is a (spatial) structure in the data which is not properly accounted for with appropriate covariates included in the model. A simple and general test for over-dispertion is provided in Dean [12].

The main problem of using a Poisson model with over-dispersed data is that clusters may appear simply because of the higher variability of the data, which may lead to wrong conclusions. Gómez-Rubio et al. [17] propose sampling from a Poisson-Gamma model [10] in a Monte Carlo test to account for over-dispertion. Loh and Zhou [29] also discuss specific modifications to the Spatial Scan Statistic to deal with over-dispertion.

In a model-based context, over-dispertion can be accounted for by including random effects [10, 7] in the lineal predictor. Hence, the model for the detection of clusters will look like:

$$\log(\theta_i) = \alpha + \gamma c_i + u_i$$

u_i are random effects, which may take different structures. Assuming that the distribution of the random effects is Normal with zero mean and variance σ_u^2 is probably the simplest case of modelling over-dispertion, i.e.,

$$u_i \sim N(0, \sigma_u^2)$$

This means that the random effects are independent. Zhang and Lin [50] describe a method to include spatially-correlated random effects and perform cluster detection at the same time. However, cluster variables aim at modelling spatial (or clustering) effects and there may be some conflict between the fixed and random effects [38].

10.3.6 Spatio-Temporal Clusters

Gómez-Rubio [18] discuss an extension of model-based cluster detection for spatio-temporal data. Temporal trends can be included in the linear predictor in the following way:

$$\log(\theta_{i,t}) = \alpha + f(t) + \gamma c_{i,t}$$

$f(t)$ is a function that models the temporal trend and it can take several forms. For example, it can be a linear trend, a smooth spline or simply an intercept to account for the average temporal change at time t.

Cluster detection can be performed as we did before by means of dummy variables, but now these need to be defined to take into account the temporal dimension as well. In general, the same approach discussed in Section 10.3.3 can be followed so that $c_{i,t} = 1$ if area i at time t is in the cluster and 0 otherwise. The temporal window can be moved as well to allow for different spatial clusters.

10.4 Clusters of Rare Diseases

Although all the methods presented so far have been widely used in the analysis of health data, they may not be suitable for very rare diseases. The main reason is that some diseases have a very low prevalence and the number of cases is very low, even over large populations, and it is zero in most areas. This may cause a bias in the estimation of the models if these high number of zeros are not properly accounted

for. Hence, new types of models that can account for the excess of zeros that appear in the data set are needed.

When the disease appears due to genetic factors, it is clear that part of the population may not be exposed and will not develop the disease. This is what is known as a 'true zero'. But even if the population is exposed, it may also be the case that no cases are observed because of the low prevalence. This is what is often called a 'false zero', because the disease is present but it has not developed. Hence, when estimating risk factors it is important to distinguish between these two types of zeros because they come from two different sources.

10.4.1 Zero-Inflated Models

In order to deal with this high number of zeros, several authors [2, 43] have proposed the use of zero-inflated models. These models assume that some zeros appear because the population is not exposed to the disease whilst the others come from a Poisson distribution. The fact that some part of the population is not exposed to the disease can be very controversial but it may be appropriate when dealing with diseases induced by genetic factors. Not being exposed to the disease will mean that the population is free from the genetic anomalies that cause the disease under study.

The formulation of these models can be written assuming that the observed number of cases comes from a mixture of two distributions. The first one is the 'true zero' and has all its mass at zero, whilst the other distribution is a Poisson with mean $\theta_i E_i$ (as described earlier). We will assume that in each area there is a probability π_i of observing a 'true zero', and $1-\pi_i$ of observing some cases of the disease (which could also be a 'false zero').

The probability of observing n_i cases can be expressed as:

$$Pr(O_i = n_i) = \begin{cases} \pi_i + (1-\pi_i)Po(0|\theta_i E_i) & n_i = 0 \\ (1-\pi_i)Po(n_i|\theta_i E_i) & n_i = 1, 2, \ldots \end{cases}$$

The relative risk θ_i can be modelled using a log-linear model to depend on some relevant risk factors. In principle, we should expect differences between the estimates coming from a Poisson model and those obtained with a zero-inflated Poisson model [28].

Furthermore, π_i could be modelled to depend on covariates using a logistic regression:

$$\text{logit}(\pi_i) = \alpha' + \beta' x_i'$$

For example, information about the ethnic composition of the areas can be included as a proxy of the genetic variation of the population in the area. If no covariates are available then we have that π_i is equal for all areas, i.e., $\pi_i = \pi, \forall i = 1, \ldots, n$.

Regarding cluster detection, a likelihood ratio test similar to that of the spatial scan statistic may be difficult to develop in close form but cluster selection can

still be performed by looking at the changes in the likelihood of the model for the different clusters proposed. Böhning et al. [9] use this approach to select the best covariates in a zero-inflated Poisson model.

From an epidemiological point of view focusing on π_i may also be of interest because it will describe the susceptibility of the population to develop the disease. Although no risk assessment can be performed this analysis can be used to map the distribution of potential population at risk.

10.5 Software

In addition to appropriate methods for the detection of clusters of disease, suitable software is required to put these methods into practice. Major statistical packages provide general data analysis tools but many fail to provide specific tools for the analysis of clusters of disease.

The Spatial Scan Statistic is implemented in the SatScan™ software, which is freely available and can be downloaded from http://www.satscan.org. SatScan™ also implements several additional features, such as adjustment for secondary clusters, covariates and a multivariate scan statistic (see web page for a full list of features).

GeoSurveillance [49] is another interesting software that implements several methods for the detection of disease clusters. It is available from http://www.acsu.buffalo.edu/~rogerson/geosurv.htm. GeoSurveillance implements the spatial scan statistic and other methods for the detection of clusters in space and time. It can also handle maps (in shapefile format) to import data and region boundaries.

The commercial software ClusterSeer®; [19] includes a number of methods for the detection of disease clusters. ClusterSeer® is part of a more ambitious GIS system called TerraSeer®.

Similarly, the Pan American Health Organization (PAHO) has developed SigEpi (available from http://ais.paho.org/sigepi/index.asp) to provide some disease mapping and cluster detection capabilities to the commercial software ArcGIS.

R [37] is a statistical package that includes functions to deal with disease mapping and the detection of disease clusters. **R** also includes methods to perform GIS-like analysis, such as importing, managing and producing maps. The examples included in this Section have been produced using **R**. It can be downloaded at no cost from http://www.r-project.org.

10.6 Examples

10.6.1 Mortality by Lupus in Spain

In order to illustrate how all these different methods for the detection of disease clusters work, we will show an example based on the mortality by Systemic Lupus Erythematosus (SLE) in Spain. This disease comprises ICD-10 codes

M32.1+ (Systemic lupus erythematosus with organ or system involvement Libman-Sacks disease), M32.8 (Other forms of systemic lupus erythematosus) and M32.9 (Systemic lupus erythematosus, unspecified).

The data set has been provided by Dr. Manuel Posada (Instituto de Salud 'Carlos III', Madrid, Spain) and it comprises all cases of SLE for both genders in 2005. There were 89 cases of this disease out of a population of 44,108,530 (according to the Spanish Office for National Statistics). No cases of SLE M32.8 were observed and drug-related SLE was excluded as well.

This means that the overall incidence of the disease was 0.2 cases per 100,000 habitants, which is very low. Boundaries of the provinces in Spain have been obtained from the Spanish Office for National Statistics.

Cases are available at the province level, and the expected number of cases was computed using internal standardisation with the population records and national incidence rate of the disease. Raw risk estimates (SMR) and their standard error are shown in Fig. 10.1. As we have already mentioned, the SMR is not very reliable in low populated areas. The highest SMR is found in Melilla (7.57), which also has the highest standard error (7.57). The total population of Melilla was 65,488 in 2005, which makes it the lowest populated province in Spain.

The Geographical Analysis Machine was run using a grid of step 10 km and three different radii of 10, 50 and 100 km. This will provide an assessment of clusters at three different geographic scales. In order to avoid problems because of the high number of tests that are carried out, only those clusters with a p-value lower than 0.005 are reported. Figure 10.2 shows the centres of the clusters detected for a radius of 100 km.

In a similar way, Fig. 10.3 shows the most likely cluster detected by the Spatial Scan Statistic. It spans three provinces in the north of Spain: Oviedo, León and Zamora. The total number of cases in the cluster is 10 with 3.57 expected cases, which gives a raw relative risk of 2.8 in the cluster. Note that there are other regions with a higher SMR that have not been identified as a cluster. The reason for this is that the SMR is very unreliable in low populated areas, and its estimate will have a high variance. Hence, confidence intervals for the relative risks will be very wide and risk in areas with a high SMR may be non-significant.

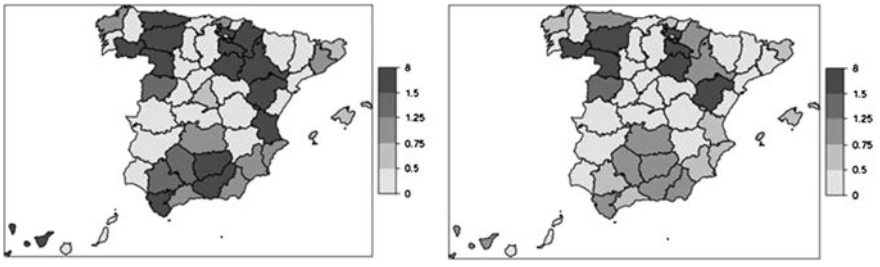

Fig. 10.1 Standardised mortality ratio (*left*) and its standard error (*right*) at the province level of the incidence of SLE in Spain

Fig. 10.2 Centres of clusters of SLE detected using the geographical analysis machine

Fig. 10.3 Cluster of SLE detected with the spatial scan statistic

Model-based cluster detection based on a Poisson model has been performed as well. As we suggested before, the results are essentially equivalent to those obtained with the spatial scan statistic. However, it should be noted that this approach allows for the inclusion of covariates.

There are 21 provinces (out of 52) with zero observations, around 40% of them, so it may be worth using a zero-inflated Poisson model instead of a purely Poisson model. In order to test for the adequacy of a ZIP model, we have tested for zero-inflation using the test described in Deng and Paul [13] but the test showed no signs of zero inflation despite the high number of zeros. This may happen when the expected number of cases is very small, as it happens now.

We have carried out model-based cluster detection based on a ZIP model. As explained before, the aim is to account for the high number of zeros in the data. First of all, we have considered all the probabilities π_i to be equal, i.e., $\pi_i = \pi, \forall i = 1, \ldots, n$ (model ZIP1). The most likely cluster in this case is the same one detected earlier with other methods.

Secondly, we have allowed for different probabilities π_i in the mixture for each area (model ZIP2). In this case the most likely cluster detected has size 7 and contains the one detected with the other methods. Some of the new areas have zero observed cases. Hence, the effect of allowing for different π_i is that areas with no cases can be included in the cluster. The reason is that by including individual π_i's the zeros are accommodated better in the model.

Table 10.1 Summary of main clusters detected with different methods

Method	O_i	E_i	Size	SMR	$\hat{\gamma}$	$se(\hat{\gamma})$	Log-likelihood
SSS	10	3.573	3	2.799	–	–	–
GLM	10	3.573	3	2.799	1.108	0.336	–71.241
ZIP1	10	3.573	3	2.799	1.107	0.336	–71.241
ZIP2	12	6.368	7	1.884	0.874	0.336	–52.787

Cluster selection using any of the model-based methods is based on choosing the cluster which maximises the likelihood and whose associated variable has a significant positive coefficient. Significance can be assessed by looking at the difference in the likelihood of the cluster model and a null model, computed with no cluster covariates at all.

It is worth mentioning that when scanning the regions using ZIP models, we can ignore the clusters centred at areas with no cases. This is partly because the model is not identifiable if only areas with no cases are in the putative cluster and because having a cluster with no cases does not make any sense.

If we want to choose between the Poisson, ZIP and ZIP2 models we may look at their likelihoods and pick the one with the highest one. However, the complexity of the model should be taken into account too, particularly for the ZIP2 model. Although this model has the highest likelihood, it is also the most complex of all and there is some risk of over-fitting the data. The results are summarised in Table 10.1.

Given that the suspected main cause of SLE is genetic, the presence of clusters should not be linked to any environmental risk factor as often happens in other public health studies. However, it may happen that the increased incidence of SLE is triggered by some environmental risk factors [35, 40]. The two northern-most provinces in the cluster are known for its mining activities. In any case, further insight should be taken on the cases found in these regions in order to confirm any environmental triggers.

10.6.2 Brain Cancer in Navarre, Spain

Ugarte et al. [44] have studied the incidence of brain cancer in men in Navarre, north of Spain. Cases are available at the health district level, of which there are 40 in Navarre. This data set is available in Ugarte et al. [43], and boundaries have obtained from the Navarre Health Department web site. This is another example of zero-inflated data set, with 129 cases in total and 13 health districts with zero cases (out of 40). The Standardised Mortality Ratio of the incidence of brain cancer in the health areas in Navarre is shown in Fig. 10.4.

The men population in Navarre was 296,587 individuals in 2005. This means that the overall incidence of the disease is 42 cases per 100,000 habitants. Hence, it is rare according to the guidelines discussed in the introduction but not as rare as SLE.

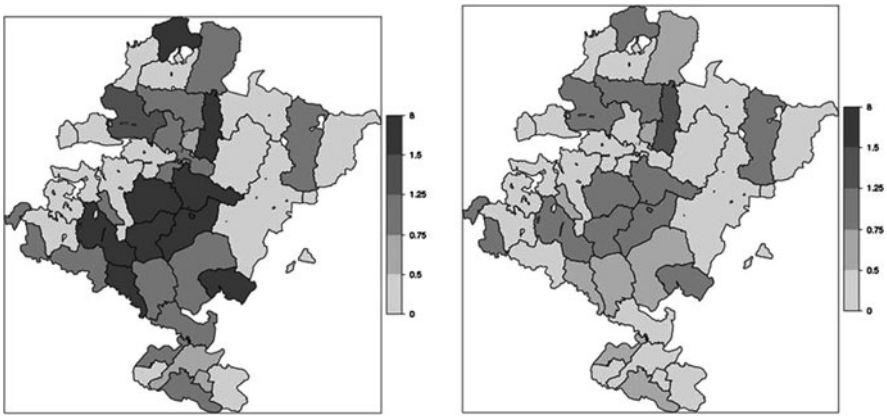

Fig. 10.4 Standardised mortality ratio (*left*) and its standard error (*right*) of brain cancer in Navarre, Spain, at the health district level

However, in this case we have a better resolution and we are able to work at a more detailed aggregation level such as the health district.

Ugarte et al. [43] assessed zero-inflation in this data set using several tests. Hence, a zero-inflated Poisson model should be better than a purely Poisson model. In order to compare the results, we have used a model-based spatial scan statistic using both a Poisson and a zero-inflated Poisson models.

Regarding zero-inflated models, we have used the same two approaches as in the previous example. The first one (model ZIP1) considers that $\pi_i = \pi, \forall i = 1, \ldots, n$,

Fig. 10.5 Cluster of brain cancer detected using the geographical analysis machine

and the second one (model ZIP2) that there are different probabilities π_i for each area.

First of all, we have used the Geographical Analysis Machine to look for clusters at different scales. For this, we have used a regular grid of step 0.5 km and radius of 20, 10 and 2 km. Only clusters with a p-value lower than 0.005 are considered. This gave no clusters when a 10 and 2-km radius were used. The cluster centres for the case of 20-km radius are shown in Fig. 10.5.

Figure 10.6 shows the different clusters computed with each method. The Spatial Scan Statistic finds a cluster of 78 cases in 9 areas, which includes several areas with no cases. The cluster detected with the Poisson and ZIP1 models is the same.

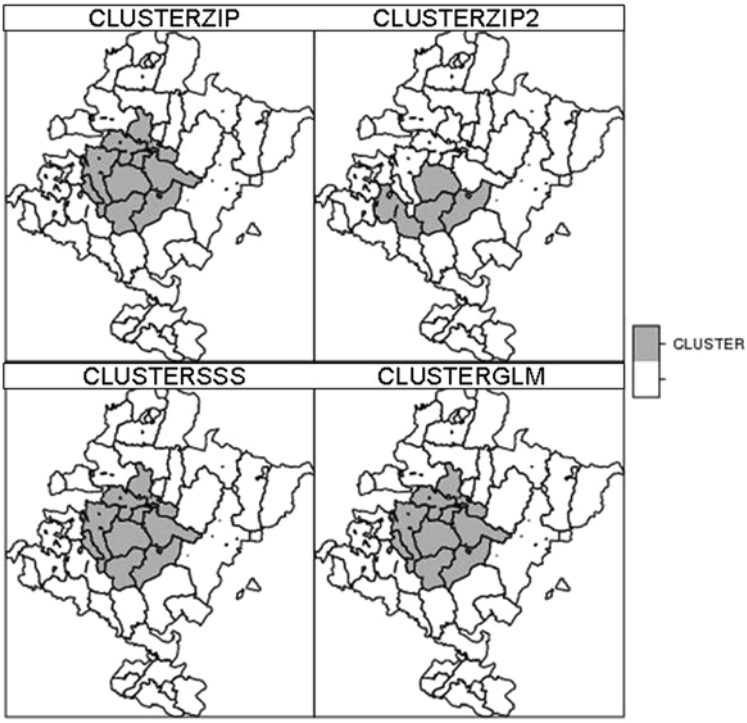

Fig. 10.6 Cluster of brain cancer detected using different methods

Table 10.2 Summary of main clusters detected with different methods

Method	O_i	e_i	Size	SMR	$\hat{\gamma}$	$se(\hat{\gamma})$	Log-likelihood
SSS	78	60.366	9	1.292	–	–	–
GLM	78	60.366	9	1.292	0.553	0.180	–66.663
ZIP1	78	60.366	9	1.292	0.471	0.197	–66.116
ZIP2	17	8.508	4	1.998	0.294	0.180	–48.428

However, model ZIP2 detects a cluster which is a subset of the former and only includes areas with observed cases. The results are summarised in Table 10.2.

10.7 Discussion

As we have described in this chapter, the detection of disease clusters plays an important role in Public Health. In every epidemiological study of the geographic variation of disease, the first step is to assess whether there is spatial dependence between the relative risks, which can usually be done by testing for spatial autocorrelation. However, small clusters may not be detected by testing for spatial correlation or general clustering.

Scan methods have proven useful to find the location of disease clusters. These can be formulated as model-based methods, which are based on fitting a model that accounts for the cluster and other covariates related to possible risk factors. Hence, it is possible to estimate not only the significance of the cluster but also its risk, which is often disregarded by traditional methods.

For the particular case of very rare diseases, these methods can still be applied. However, the underlying model assumption that the distribution is Poisson can be extended to a zero-inflated Poisson to account for the large number of zeros that appear. The adequacy of this model can also be assessed by performing different tests. Although we have not considered it here, these methods can be extended to detect clusters in space and time.

Although all the methods presented here are likelihood-based, Bayesian inference also offers a wide range of methods for smoothing disease rates and perform disease cluster detection [18].

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Chapter 11
Clinical Trials and Rare Diseases

Joachim Werner Otto Gerß and Wolfgang Köpcke

Abstract Whenever possible, standard methodological approaches should be applied in the design and analysis of a clinical trial that warrant adequate informative value. However, there are circumstances when the number of experimental subjects is unavoidably small. In such circumstances it is justified to consider abandoning standard statistical methodology in place of alternative approaches. Performing a small clinical trial however it should be pointed out, that a such trial can never be as meaningful and provide as much evidence as a larger trial. In the present text, basic concepts are presented, that apply to small clinical trials in general. Moreover, several specific methodological approaches are presented, that either enhance the efficiency of standard statistical procedures or evolve from the idea of abandoning classical paradigms in the design and analysis of clinical trials. Within the scope of the former approach, (Bayesian) adaptive randomisation, group sequential (adaptive) designs, repeated measurement designs for longitudinal data, and meta-analyses are illustrated and discussed. The latter approach comprises alternative strategies such as (non-randomised) risk-based allocation designs, statistical prediction designs, ranking and selection designs, as well as the application of Bayesian statistics.

Keywords Rare disease · Small clinical trial · Methodological approaches · Design · Statistical analysis

11.1 Introduction

In a clinical trial in general three basic requirements are demanded to be satisfied [6]. First, the trial should examine a valuable and important biomedical research question; second, it must be based on a rigorous methodology that can answer the

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basic research question posed; third, it must be based on ethical considerations and assure that risks to individuals are minimised. Conducting a clinical trial in the context of a rare disease, almost necessarily one main feature is implicated. Due to a low number of patients in the basic population, the number of patients recruited in a trial is limited and conducted trials naturally involve fewer patients compared to a more common disease. In a small clinical trial (SCT) of course the three above basic requirements apply as in any clinical trial in general. Satisfying the requirements however arises specific problems, that concern especially the second item. Defining a valuable research question and satisfying ethical demands can be accomplished in any kind of trial regardless of the sample size equally well. However validly answering the basic research question in a SCT naturally is more difficult than in a larger trial. The present text deals with methodological approaches, that can be applied in SCT in order to maintain scientific significance. Three main problems especially arise. The validity of results may be questionable, i.e. derived findings and conclusions may be biased and do not apply to the basic population. Moreover a SCT carries a risk of failing to demonstrate an intervention effect when one is really present, i.e. it is likely to be able to detect only large effects with adequate statistical power. Beyond the inherently low power, a SCT is more prone to variability than a large trial and thus the intervention effects under study often can only be estimated with low precision.

Besides the above problems, certain advantageous features of SCT in rare diseases should not be omitted to be mentioned. In SCT it is more likely that the sample population will share several unique characteristics (e.g., with respect to disease characteristics, exposures, or environment surroundings), yielding homogeneous outcomes with low variability. Moreover in a SCT, the relationship of patients and investigators may be more close, sometimes almost familial. Hence participants can be more practically involved in the design of the trial and the likelihood of compliance, adherence to the regimen, and willingness to participate in monitoring and follow-up activities is increased. Opportunities for community discussion and conversation among patients exist. This last feature however not necessarily proves to be advantageous. In a blinded trial, conversation among patients may cause interventions to be unblinded. Furthermore, problems of data protection and privacy may arise in a SCT.

Before presenting methods to be applied in the context of SCT in the following text, it shall be emphasised articulately that whenever possible, standard methodological approaches should be applied in clinical trials. Among other requirements, investigators should strive to design clinical trials that contain adequate statistical power. However, there are circumstances when the opportunity to perform a trial with adequate statistical power is not possible and the number of experimental subjects is unavoidably small. In such circumstances – instead of refraining from inductive statistical evaluation of study results at all – it is justified to consider abandoning standard statistical methodology in place of alternative approaches.

In the second chapter of the present text, general concepts of clinical trials are reviewed. Additionally, basic considerations and recommendations are given, that apply to SCT in particular. Chapters 3 und 4 deal with methodological approaches

in the context of SCT. Two different main strategies may be pursued. The first strategy consists of approaches, that are embedded in the framework of classical statistical theory. In order to utilise respective methods in SCT, innovative features are integrated, providing enhanced efficiency of statistical analyses. The presented approaches in Chapter 3 are not limited to SCT, but can be applied to increase efficiency of larger trials as well. In Chapter 4, a different strategy is pursued, i.e. the basic paradigm of statistical methodology is shifted. Presented methods are not consistent with classical methodology and hence are usually not accepted to be applied in standard clinical trials. In SCT however, application of such non-standard methods may represent the only possible way to perform appropriate analyses and provide at least a low degree of scientific evidence. In Chapter 5 the contents of the present text are summarised and final conclusions are drawn.

11.2 General Concepts of (Small) Clinical Trials

In clinical trials in general, certain basic methodological concepts are required to provide valid scientific evidence. If all of the following requirements are satisfied, the primary statistical significance test provides confirmatory evidence and results are top-ranking in terms of evidence-based medicine (see [11]). Methodological key concepts of clinical trials are (see e.g., [3]):

11.2.1 External Validity

In a clinical trial, one of the most essential steps is to define the basic patient population. Which specific disease pattern the trial is targeted to investigate? The definition of the basic population is performed by framing inclusion and exclusion criteria of eligible patients to be recruited. Defining the potential patient population of the trial however does not necessarily ensure that the set of actually recruited patients in fact constitutes a representative sample of the basic population. A practical way to check for representativeness is to establish a screening log. In a screening log, any eligible patient is documented, including those who finally participated in the trial as well as those who refused to participate. If no systematic differences between both subgroups of patients emerge, representativeness usually is assumed to be warranted. In case a representative sample is drawn, external validity of study results is provided. Consequently performing inductive statistical analyses, study results can be generalised from the sample to the total population.

11.2.2 Internal Control Group

Regarding the basic design of a clinical trial, inclusion of a concurrent internal control group is agreed to represent the gold standard approach. The control intervention

may constitute a placebo treatment, an active reference treatment, no intervention, or dose-comparison treatments. Based on mean results observed in the internal control group, the respective results of an active intervention group can be evaluated most validly. If differences emerge, it can be concluded with high confidence, that the intervention of interest took action in fact. On the other hand using external controls (i.e., historical or retrospective controls), biased conclusions may be drawn. The intervention group may differ from the control group not only with respect to the intervention of interest, but also in other aspects, such as the severity of illness, concomitant treatment, accurateness of data collection, compliance of the patients, and others.

11.2.3 Internal Validity

In the above mentioned concept of external validity, the study population as a whole is considered in relation to the basic population. The concept of internal validity relates different patient groups within the study population among each other. It has to be warranted that the active intervention group differs from the control group in fact only with respect to the intervention of interest and no other concomitants. In order to provide internal validity of study results, interventions should be allocated at random and patients as well as trial personnel should be kept blinded whenever possible. Matching can be used in order to warrant balanced baseline covariates in several intervention groups.

11.2.4 Pre-specification of Outcomes

Primary and secondary outcomes of a clinical trial should be carefully chosen and have to be specified prior to the start of the trial. Appropriate outcomes satisfy requirements of validity. Does the outcome measure what is intended? Is the result unbiased and relevant? Moreover outcomes should provide reliability, responsiveness or sensitivity to change, and have to be feasible. Can the measure be applied easily, given constraints of time, money, and interpretability [6]?

11.2.5 Pre-specification of the Primary Analysis

Usually the primary statistical analysis of a clinical trial is performed applying a statistical significance test. In order to provide valid evidence, the basic null- and alternative hypothesis of the test need to be specified in advance. That means it has to be determined, if a two-sided or a one-sided problem is tested and if the test is applied in order to prove superiority or non-inferiority. Beyond specification of the test problem, the applied statistical test procedure needs to be determined exactly. This involves considerations e.g., if data are regarded normally distributed

or a nonparametric approach without specific distributional assumptions is applied instead.

11.2.6 Controlled Risk of False Positive Results and Provision of Sufficient Power

Any applied significance test is at risk of possibly yielding false positive results. While a type I error can never be ruled out definitely, all that can be done is to reduce and strictly control the respective risk. Usually the false positive rate of an applied test is limited by an upper bound of $\alpha=5\%$. A further quality criterion of a significance test is associated with the risk of false negative findings. In an applied test, provided that an effect under study in fact exists, the likelihood (power) of detecting it should be sufficiently high. The power in turn is directly related to the sample size. The larger the number of recruited patients in a clinical trial, the higher is the power of the applied test.

Performing scientific research in the context of rare diseases, large clinical trials often are not feasible and trials can only be conducted with a limited number of patients. In Small Clinical Trials (SCT) of course basically the same requirements are demanded as in any clinical trial in general. But undoubtedly research in rare diseases and corresponding SCT represent exceptional cases of clinical trials that require special consideration [2]. Although trying to keep as many of the above requirements as possible, often certain curtailments can not be avoided. Finally it has to be accepted, that quality criteria can not be satisfied as strictly as in larger trials. If basic quality criteria of statistical analyses are abandoned or relaxed, one should be aware that there is an important difference between retrospectively estimating the extent to which requirements are relaxed on the one hand and prospectively controlling respective (relaxed) limits on the other hand. Whenever possible, the latter approach is to be preferred. Otherwise possibly existing insufficiencies in the informative value of a conducted trial are revealed at a time, when it is too late to react.

The inherent lack of informative value is a highly important feature of a SCT. Investigators should be aware that a SCT can never provide as much scientific evidence as a larger trial. Consequently, interpreting and publishing the results of a SCT, researchers should articulately account for the relatively low level of scientific evidence provided, frankly revealing and accentuating the limitations of the trial. Eventually it should be admitted that results do not provide confirmatory but rather exploratory statistical evidence. However, the above facts do not implicate that a researcher conducting a SCT is constrained to capitulate with one′s fate and cannot actively intervene. It can consciously be considered and carefully decided, which sacred cows of quality criteria are most important and hence must not be slaughtered. Other requirements may be more easily tolerated to be abandoned or relaxed to some extent. A solution to this problem of decision cannot be given universally. Which one of the below-mentioned approaches is applicable in a certain research project, has to be decided individually. Amongst others as the case may be, the

phase of drug development of present research has to be taken into account. In early phases of drug development usually a larger risk of false positive results is tolerated compared to late phases.

Before presenting specific approaches to the design and analysis of SCT in the following sections, a few basic issues are presented in the remainder of this section. It is known that different types of outcome variables exhibit different levels of accuracy in measurability. In this respect, continuous outcome variables are advantageous compared to discrete variables. Using outcomes that provide higher accuracy generally causes increased statistical power.

Another important issue, that planning a SCT should be discussed refers to basic assumptions of statistical analyses, that may or may not be applied. The issue in particular refers to the decision if either parametric or nonparametric statistical approaches are applied. Nonparametric approaches are robust in so far as no distributional assumptions of observed data are required, e.g. the normality assumption. This proves to be advantageous especially in case of small samples, that do not allow to check for the basic data distribution validly. The feature is important, as particularly in case of small samples the central limit theorem of mathematical statistics does not hold. Approximate normality of aggregate sample characteristics results from asymptotic theory that does not apply to small samples. However on the other hand, albeit the above arguments pro nonparametric approaches, normality of observed random variables might be satisfied in fact. In that case, parametric approaches are justified to be applied and naturally are advantageous compared to corresponding nonparametric approaches due to a higher statistical power provided. This yields a strong counter-argument to the above argument. Applying a parametric approach (if it is justified), one main drawback of a SCT – its inherently low power – may be diminished at least to some extent. To sum up these considerations it can be stated, that it is a crucial issue to decide if the normality assumption is satisfied or not. Pros and cons of either corresponding approach – a parametric or a nonparametric approach – have to be discussed accurately. If finally a nonparametric approach is chosen, it should be noticed that most nonparametric significance tests can be performed in two different variants, i.e. calculating either exact or asymptotic p-values. Due to the lack of applicability of asymptotic theory in SCT it generally is recommended to apply exact methods (see [4]) instead of asymptotic approaches.

Besides the above considerations, another related issue refers to the choice and extent of another kind of assumptions, that one may be willing to implement in the applied approach of statistical analyses. Again two different basic strategies may be pursued. One possible general strategy may be to perform model-based analyses. In a model-based approach, the impact of an intervention is not evaluated by means of a global significance test, simply comparing mean results of different intervention groups. Instead of that, analyses are adjusted for further prognostic co-variables, applying multivariate regression models or analyses of variances. The established model may not only include co-factors used in stratified randomisation, that are recommended to be accounted for anyway. Moreover any other co-variable that is known to impact the response may be included in the model. If the established

model is correct, the power of the applied model-based significance tests is increased compared to the above mentioned global test. This is intuitively comprehensible, if one considers the fact that the detection of differences between intervention groups is naturally hampered by random variation inherent to the response variable. In a model-based approach, part of the variation of the response variable is attributed to prognostic co-variables. Thus the remaining unexplained random variation is reduced. Reduced random variation generally leads to an increased statistical power.

The above considerations show the general impact of statistical approaches, that are based on certain model assumptions to a certain degree. Any assumption in principle is at risk of being violated, so that finally incorrect findings result. Consequently, findings are robust in this respect, if only few and/or weak model assumptions are established. A such general strategy is usually pursued in large clinical trials. In SCT however, another strategy may be appropriate, establishing stronger model assumptions. The risk of possibly violating the assumptions may be accepted, taking advantage of the resulting increase in power of applied significance tests.

11.3 Advanced Approaches to Classical Clinical Trial Designs

11.3.1 Adaptive Randomisation

In a clinical trial applying adaptive randomisation, the allocation of patients to intervention groups is not predetermined as it is common in the classical approach. Instead of this, the probabilities of allocation change, based on baseline covariates or based on efficacy response that is observed in different intervention groups. A covariate-adaptive approach is advantageous in a clinical trial, as it positively affects internal validity especially in small samples. Different intervention groups are ensured to coincide with respect to important patient characteristics and possible differences can validly be attributed to the intervention under study. In a response-adaptive randomisation approach, probabilities of allocation change based on accrueing efficacy response data. If one intervention is beginning to emerge as better, new patients entering the study are more likely to be allocated to that intervention. Response-adaptive designs are sometimes called play-the-winner designs. The main advantage compared to a classical design with fixed allocation rates is that the number of patients receiving the superior intervention is increased. Thus during the conduct of the trial already, more patients take profit of a possibly superior intervention.

An example of a response-adaptive randomisation procedure is presented in Giles et al. [10]. In a prospective randomised study, patients with adverse karyotype acute myeloid leukemia (AML) were randomly allocated to one of three treatments, i.e. either Idarubicin plus Cytarabine (IA), or Troxacitabine plus Cytarabine (TA), or Troxacitabine plus Idarubicin (TI). The primary efficacy end point was defined as

a complete remission, without nonhematologic grade 4 toxicity by day 50. Initially the randomisation was balanced, with a probability of 1/3 of random assignment to each of the three arms. As efficacy data accrued, assignment probabilities shifted in favour of arms that were performing better. After 24 patients were recruited and patient 25 presented for randomisation, the success rates were five in nine patients (55%) with IA, three in seven patients (43%) with TA, and zero in 5 patients with TI. Responses were yet unknown in two patients treated with IA and one patient treated with TA. At this time, due to the poor success rate, the probability of random assignment to TI became 0 (i.e., the TI arm dropped out). When the 34th patient was recruited, the success rates were seven in 12 patients (58%) with IA and three in eight patients (37%) with TA. Due to the poorer performance of the TA arm at this time, it was dropped. Recruitment of further patients was stopped because the only remaining treatment was IA. When the efficacy results of all treated patients were available, the final success rates were 10 in 18 patients (55%) with IA, three in 11 patients (27%) with TA, and zero in five patients with TI. Thus the authors draw the conclusion that neither troxacitabine combination (TA or TI) was superior to IA in patients with adverse karyotype AML.

11.3.2 Group Sequential (Adaptive) Designs

In group sequential designs in contrast to the classical approach, the total sample size is not predetermined at the beginning of the trial. Instead, several stages of recruitment are conducted with fixed sample sizes of a certain number of patients each. After every stage of recruitment, an interim analysis is performed. The trial is stopped as soon as the information is sufficient to conclude. Planning a trial it is not foreseeable for sure, but is subject to randomness to some degree, how many patients will finally be recruited in total, until the trial is stopped. However under certain assumptions, the expected value of the sample size can be calculated. Typically, it is smaller than the required size of a comparable fixed sample design. This is the reason why group sequential designs are advantageous in research in the context of rare diseases [12]. Group sequential designs can be extended to so-called adaptive designs [1]. In both a fixed sample design and a group sequential design, power analysis and associated sample size estimation is performed based on assumptions on treatment effects and the amount of random variation, that are established prior to data collection. Respective expected quantities are not ensured to be estimated correctly. Incorrect assumptions however (e.g., over-optimistic estimation of the treatment effect) may lead to underpowered statistical tests in the final analysis of a clinical trial. This main drawback is overcome in an adaptive design, that admits design modifications after interim analyses. For example, according to the observed results of yet collected data at a certain time, the required sample size of further stages of recruitment is assessed anew. By this means, the study power is ensured to meet given requirements, even if original assumptions regarding treatment effects or measurement error of the response variable turn out to be incorrect.

11.3.3 Repeated Measurement Designs

In standard clinical trials with parallel group design, one single response measurement is obtained from each patient. Statistical analysis is performed comparing mean responses between patient groups, i.e. between-subject comparisons are performed. In repeated measurement designs, not only one but multiple observations of response variables are obtained from each patient. Measurements may be collected either repeatedly over time or at the same time from several different body regions of a patient. The approach has two advantages. First, not only between-subject comparisons are performed, but also within-subject comparisons. This allows any patient to provide his/her own control data, leading to optimal internal validity and thus a maximal chance of establishing valid intervention effects. A second advantage of a repeated measurement design is that compared to a single measurement design with the same number of patients, the number of elementary data values is increased. A larger sample size naturally causes an increased statistical power of significance tests. Both issues implicate that repeated measurement designs are likely to be useful especially in SCT. Statistical data analysis is performed using advanced approaches that explicitly account for intra-subject correlations among repeated measurements collected from the same patient, i.e. generalised estimating equations (GEE, see e.g., [5]) or hierarchical linear or nonlinear models (mixed effects models, see [17] and [13]).

The following exemplary sample size estimation in a hypothetical clinical trial shows the resulting reduction of sample size, if a repeated measurement design is applied instead of a single measurement design. Two treatments are compared, using a dichotomous primary outcome. Response rates are assumed to amount to p_0=0.5 and p_1=0.75 under the control and active treatment, respectively. The primary (two-sided) statistical significance test is to provide a maximum type I error α=5% and – in case expected response rates turn out to be correct in fact – an 80% power of detecting treatment differences. In a standard clinical trial with parallel group design, the required total number of patients is calculated to amount to n=116, i.e. 58 patients per group. Alternatively, a repeated measurement design may be applied. Patients are allocated a certain treatment that is administered throughout the study, assuming a constant impact on response over time. Table 11.1 shows the required number of patients in the repeated measurement design, calculated on the basis of generalised estimating equations (GEE, see [14]). Several possible scenarios are considered, that vary with respect to the number of measurements collected from each patient, the correlation between successive measurements as well as the (conditional) loss to follow-up rate of patients.

Table 11.1 shows that in a repeated measurement design, the required number of patients may be reduced considerably. The sample size compared to a single measurement design is reduced all the more, the more measurements are obtained from each patient and the lower successive observations within patients are correlated. Loss to follow up of patients in the course of the trial naturally causes the required number of recruited patients to increase. One more conclusion can be drawn from Table 11.1. Consider a designed trial with k=3 measurements per

Table 11.1 Sample size estimation in a clinical trial with repeated measurement design [14]

	$k=3$	$k=5$	$k=5^a$	$k=5^b$
$\rho=0.5$	$n=82$	$n=74$	$n=78$	$n=84$
$\rho=0.6$	$n=90$	$n=84$	$n=88$	$n=94$
$\rho=0.7$	$n=98$	$n=94$	$n=100$	$n=104$

Patients are allocated a certain treatment that is administered throughout the study, assuming a constant impact on response over time. Response rates in two treatment groups are assumed to amount to $p_0=0.5$ and $p_1=0.75$, respectively. The primary (two-sided) statistical significance test is performed on a significance level $\alpha=5\%$ and with a required 80% power, applying generalised estimating equations (GEE). k, number of measurements collected from each patient.

[a]5% conditional loss to follow-up rate.

[b]10% conditional loss to follow-up rate; ρ, correlation between successive response measurements; n, total number of patients.

patient, that exhibit successive correlations ρ=0.6. Table 11.1 shows that if 90 patients are recruited and hence 3×90=270 elementary data values are observed in total, the resulting power amounts to 80%. This power value may be compared to a single measurement design with 270 elementary data values, i.e. in that case, 135 patients per group. The latter design results in a 99.1% power, considerably larger than 80%. The conclusion to be drawn is that collecting more (than one) measurement of the response variable per patient, the power will not be as large as if the corresponding number of additional patients would be recruited. This results from the quite comprehensible fact that the informative value of say x (positively) correlated elementary data values expectedly is lower than the information of x independent values from different patients.

A special and extreme case of a repeated measurement design is a clinical trial with a so-called n-of-1 design. In a classical n-of-1 design, only one single trial patient is recruited. The patient undergoes treatment for several pairs of periods. During one part of each pair the experimental treatment is applied, and during the other part an alternative treatment. The order of the two treatments within each pair is randomised. The final outcome of a n-of-1 trial is a conclusion about the best treatment for the particular patient under study. Results of series of n-of-1 trials may be combined, applying meta-analytic methods (see below).

11.3.4 Meta-Analysis

The term meta-analysis refers to a set of statistical procedures used to summarise the results of two or more independent studies, in order to yield an overall answer to a question of interest [15]. The rationale behind this approach is to provide a test with more power than that provided by the separate studies themselves. Usually an applied meta-analysis starts with a systematic review of literature, trying to find all studies that have been performed and published in the context of a specific research

question. Single studies not necessarily need to share the same basic design and outcome or assessment measure. The only requirement is that a common observed outcome metric of each study is provided. A such study-specific effect may be e.g. the odds ratio of a certain endpoint comparing an active intervention with a control treatment. Quantitative synthesis of the observed study-specific effects is performed accounting for the differences in precision, typically by weighting in proportion to sample size. Finally a pooled effect estimate is established. In the pooled analysis, the power naturally is increased and the effect of interest can be estimated more precise than in single studies. Beyond the pooled analysis, available total information can also be used in a sense to update the observed study-specific effects. In observed study-specific effects, observational and measurement error inherently is contained, that leads to relatively less accurate estimates. Applying a fitted meta-analytic model, observed effects are estimated anew, eliminating observational and measurement error. The obtained model-based effect estimates show which treatment difference would have been observed in a single study, if no empirical data had been evaluated, but theoretical data of the respective total population instead.

One methodological key issue of meta-analytical techniques is the treatment of heterogeneity of several study-specific effects. In many cases, the effect of interest obviously varies among studies, due to differences in study population, the year of conduct of the study, slight differences in therapeutic regimen, or others. One way to cope with this variability methodically is to establish a random-effects model, assuming random variation of study-specific effects. In an alternative more informative approach, a prognostic model is established. E.g., the different mean age of several study populations is specifically accounted for, explicitly modelling the resulting systematic impact on observed study effects. If by this means, variability of data is modelled systematically, a meta regression approach finally is more powerful than a corresponding random-effects model. Another advanced approach can be applied to increase the performance of classical meta-analytic models. In the classical approach, the elementary source data are summary data of several studies. Obviously summary data however necessarily is less informative than individual patient data. This might be the exact age of each patient in a study, instead of the average age across all study patients. Accounting for individual patient data methodically leads to the establishment of hierarchical models, that represent a flexible tool of advanced meta-analysis.

11.4 Alternative Strategies in the Design and Analysis of Clinical Trials

11.4.1 Risk-Based Allocation Designs

In certain research situations it may not be possible to perform a randomised trial. Imagine the following exemplary situation. In a clinical trial, patients with a certain disease are under study. A metric measure of patients' disease severity exists,

that allows classification into low-risk and high-risk patients. Medication may be administered either in a high or a standard dose. Now outside the study protocol, information is available, that suggests a benefit of high dose treatment. Especially in case of high-risk patients, the standard dose is expected to result in stagnation of patients' condition, that can not be compensated subsequently any more. Due to this information, it is considered unethical to administer standard treatment to high-risk patients. Anyhow, how can the (expected) benefit of high dose compared to standard treatment be evaluated? In this specific situation, if a randomised trial indisputably is not possible to be conducted, a nonrandomised design using risk-based allocation might be applied (see [8, 9]). In a risk-based allocation design, low-risk as well as high-risk patients are recruited. Low-risk patients are randomised to receive either high dose or standard treatment; all high-risk patients however deterministically receive high dose treatment. In the final analysis of efficacy response data, the treatment effect in the subgroup of low-risk patients is estimated applying standard statistical procedures. Moreover, using data of low-risk patients, a risk-responsive prognostic model is established. The fitted model allows to predict the expected additional benefit of high dose treatment, that emerges depending on the given disease severity. High-risk patients finally are evaluated by extrapolating the prognostic model from low-risk to high-risk patients. Subsequently, the observed efficacy response under high dose treatment is combined with the predicted additional benefit of high dose treatment. Finally the benefit of high dose compared to standard treatment has been estimated in high-risk patients. The main advantage of the risk-based allocation design is that all patients with greater disease severity benefit from a potentially superior high dose treatment already during the conduct of the trial. Validity of results primarily depends on the risk-response model established and in particular on the possibility of extrapolating the treatment effect from low-risk to high-risk patients.

11.4.2 Statistical Prediction Designs

The application of statistical prediction designs in clinical trials represents a paradigm shift in that it departs from the more commonly used paradigm of hypothesis testing. The approach involves characterisation of the distribution of control measurements of an observed condition. The control distribution allows to establish an expected normal range of future measurements. If future experimental measurements are contained within the established prediction limits, it is concluded that the experimental intervention does not have an impact on the observed condition. On the other hand if future measurements exceed prediction limits, the experimental intervention has been shown to take effect. The methodology is applicable especially if the number of potential endpoints is large and the number of available subjects is small.

The design is illustrated on the basis of a research project, that was initiated by the National Aeronautics and Space Administration (NASA) (see [6]). During long missions in space, astronauts or cosmonauts are exposed to environmental stresses

(e.g., microgravity), that could be deleterious or even fatal during space travel, on landing on another planet, or after the return to Earth. In order to prevent potentially life-threatening conditions, countermeasures against accelerated bone mineral density (BMD) loss must be taken. Naturally, a study in this situation would have to rely on data of only a few individuals, i.e. astronauts or cosmonauts during space missions. The following design of a clinical trial is proposed to evaluate the efficacy of a certain countermeasure, that is expected to prevent BMD loss. A series of 50 control astronauts are exposed to microgravity in a simulated weightless environment on Earth, not taking part in a countermeasure program. Measurements of BMD at a certain body location are collected from each individual. Using control data, prediction limits are established, that allow evaluation of future experimental data. Experimental data are collected in 6 future space missions. In each mission, 5 astronauts take part and the countermeasure program is applied to all astronauts. The median observed BMD is calculated across 5 astronauts of each mission, respectively. Thus experimental data are reduced to 6 median BMD values. Data are evaluated as follows. If a certain number of median BMD values lies outside of the prediction interval of control data, the countermeasure program is concluded to be efficacious. Otherwise its inefficacy is concluded. The approach can be elaborated in detail either parametrically or nonparametrically. Its performance can be increased if multiple responses are obtained at each individual (e.g., BMD measurements at different body locations). Moreover, a sequential approach can be applied. The basic idea is that in the presence of an initial experimental value that lies outside the prediction interval, another sample for independent verification is obtained. A true exceedance is indicated only if both the initial value and the verification resample are outside the interval.

11.4.3 Ranking and Selection Designs

Ranking and selection designs are another alternative approach, that can be applied beyond the classical hypothesis test. Suppose there are k treatment groups in a clinical trial with expected mean responses μ_i for i=1,. . .,k, respectively. Without loss of generality, large values of the response measure are assumed to be preferable compared to small values. Some of the goals that can be accomplished by a ranking and selection design are (see [6]):

- selection of the one best treatment;
- selection of the t best treatments (t≥2), in an either ordered or unordered manner;
- selection of those treatments that are superior to a standard control treatment;
- selection of a set of treatments, that certainly include the best treatment;
- ordering of all treatments (or alternatively, a subset of treatments) from best to worst.

One of the ways in which ranking and selection methods can be of help in a clinical trial is by ruling out poor competitors. Suppose that investigators must choose

the best of five interventions. With small sample sizes the investigators may not be able to choose the best. But instead of that, he/she might be able to assert that the best is among a group of three of the interventions, although they are not sure which one is the best. Subsequent studies can then focus on choosing the best of the three interventions.

It is possible to view a certain kind of selection trials as equivalent to classical hypothesis testing with a type I error rate of 50% (rather than the usual rate of 5%). From this relationship it naturally follows, that selection trials generally require much smaller sample sizes than those required for usual hypothesis tests. It represents an advantage of the selection paradigm over the confirmatory hypothesis testing paradigm, but on the other hand shows that in the former approach a considerably lower level of scientific evidence is provided.

11.4.4 Bayesian Statistics

This final section in a sense is outstanding in relation to the above sections of the present chapter. Not a single method is reported, that may be useful in a specific research situation or type of available data. Instead of that, the Bayesian approach represents a comprehensive framework or school of statistical theory, that exhibits fundamental differences to classical (so-called frequentistic) statistics (see [16]). Almost any existing method of statistical analysis can be performed alternatively either in a classical or in a Bayesian way. So in many of the design and analysis approaches described above, Bayesian methods can be applied and are extremely useful especially in SCT.

The main difference of both schools traces back to the basic notion of probability. While in the classical approach, e.g. an 20% event probability expresses that – if the underlying experiment would be repeated sufficiently frequently – in every 5th instance the event will be observed on average. In contrast to this frequentist approach, the Bayesian notion of probability represents a more direct way of modelling knowledge or uncertainty. A 20% event probability expresses the fact that already in a single realisation of the experiment one can be 20% sure that the event of interest will be observed.

The attraction of the Bayesian approach lies in its simplicity of concept and the directness of conclusions. Whereas basic concepts of the frequentist school are somewhat abstract constructs such as significance levels, p-values and confidence intervals, in Bayesian statistics, questions can be more directly addressed such as:

- How large is the probability of a certain active treatment exceeding the adverse event rate of placebo?
- To what degree is the hypothesis of a beneficial effect of an active treatment more likely than the opposite hypothesis of its inefficacy?
- How strong is the evidence in favour of a substantially enhanced benefit of an active treatment, defined e.g. by an enhancement of the success rate by more than factor 2 compared to a control treatment?

One important feature of the Bayesian approach is that it naturally allows to incorporate prior knowledge into statistical analysis. Performing a classical hypothesis test, an investigator in a sense starts from scratch. If two interventions are compared with respect to efficacy, a completely non-informative starting point of statistical analysis is applied, i.e. the hypothesis of no existing treatment differences. This may not always be appropriate. Suppose a certain drug is already known to take effect in adults. Now a paediatric trial is planned to be performed, in order to evaluate efficacy in children. It may be argued that the paediatric trial should be performed in a way, somehow using the knowledge about the drug effect in adults, instead of completely ignoring the respective information. In this situation, a Bayesian analysis proceeds as follows. Before the investigator has observed any data in children, a subjective distribution of the treatment effect is formulated, resulting from any kind of existing experiences and knowledge (e.g., knowledge about the treatment effect in adults). The subjective distribution is called the prior distribution of the treatment effect in children. After data are collected in the paediatric trial, these will influence and change opinions about the treatment effect. The combination of observed data and prior opinion provides an automatic update of the investigator's subjective opinion. Application of Bayes' theorem finally yields a new subjective distribution for the treatment effect in children, called a posterior distribution. The posterior distribution can be interpreted to represent a kind of weighted average of prior opinion and observed data. Weights are determined according to the precision of both components of information. E.g., the use of highly precise prior information and sparse data finally leads to a posterior distribution, that is similar to the prior distribution. On the other hand in case of less informative prior information, the initial subjective opinion is overwhelmed and revised considerably according to empirical data information.

Incorporating prior knowledge may be appropriate and advantageous in situations like the one described above. One main drawback one has to be aware however is the fact, that some degree of subjectivity is introduced in statistical analysis. Results in part rely on an investigator's subjective opinion. In other words, if several persons analyse the same data, it is not warranted that all investigators obtain the same objectively reproducible results.

Bayesian methods can be applied in many instances in the design and analysis of a clinical trial. However in a few special applications the approach turns out to be particularly powerful. This concerns the early phases of drug development, e.g. dose finding phase I trials, that can be performed exclusively using Bayesian methods. In later phases of drug development, Bayesian methods are not (yet) accepted to replace classical approaches completely. However certain supplementary tasks can be addressed successfully. Adaptive randomisation as described above relies on a Bayesian approach. Moreover in sequential clinical trials, its flexibility is especially valuable. This is shown in Fayers et al. [7], who illustrate a Bayesian data monitoring approach. It is argued that in a clinical trial, interim analyses should be performed in order to monitor accruing results. Approaching this problem in a Bayesian way, one starts with a supposed prior distribution of the treatment effect of interest. The prior distribution is chosen to be either clinically uninformative, sceptical or

enthusiastic, according to an investigator's subjective opinion. In the first interim analysis of accrued clinical trial data, the posterior distribution of the treatment effect is obtained, combining observed data with initial prior knowledge. Derived results are still relatively unreliable, as they depend on the investigator's subjective opinion to a large extent. In subsequent interim analyses, the approach can be interpreted as if the posterior distribution is updated repeatedly, using each successive posterior distribution as the prior distribution for the next update. Pursueing this approach successively, the subjective influence of the initial prior distribution more and more declines. Finally evidence is obtained regarding the treatment effect of interest, that largely relies on empirical data instead of the investigator's original subjective prior opinion. One main advantage of sequential Bayesian monitoring is that in interim inspections no significance tests are performed, but the posterior distribution of the treatment effect is only estimated and inspected instead. This implicates that no adjustment for multiple testing has to be applied, as would be the case in interim analyses that are performed within the scope of a classical group sequential design.

11.5 Summary and Conclusion

Whenever possible, standard methodological approaches should be applied in the design and analysis of a clinical trial. Investigators should strive to design clinical trials that warrant adequate informative value. However, there are circumstances when the number of experimental subjects is unavoidably small. In such circumstances – instead of refraining from inductive statistical evaluation of study results at all – it is justified to consider abandoning standard statistical methodology in place of alternative approaches. Performing a Small Clinical Trial (SCT) however it should be pointed out clearly, that a such trial can never be as meaningful and provide as much evidence as a larger trial. Limited resources naturally implicate a reduction of the informative value of scientific research.

Consequently almost unavoidably, certain requirements of standard clinical trials have to be abandoned or relaxed to some extent. It is important to carefully consider and decide, which specific requirements are tolerated to be relaxed. This allows to choose an approach to the design and analysis of a planned SCT that optimises the efficiency of given resources. However one should be aware that certain limits of scientific quality must not be under-run. If this is the case in a certain situation, one should consider to refrain from conducting a clinical trial at all. Possibly, instead of conducting a clinical trial it may be more efficient to spend (human and/or financial) resources in different research activities. One alternative to a clinical trial may be the establishment of an observational registry of the medical condition under study, including as many patients as possible. Evaluating data from the registry may provide a solid basis for a future clinical trial.

Several methodological approaches exist, that either enhance the efficiency of standard statistical methods or abandon classical paradigms. It is important to note that none of the presented approaches can be regarded a gold standard. Instead of

that, any single approach has potential utility in specific settings and none is advocated above all others. Alternative approaches of design and analysis have to be carefully considered. Finally it has to be decided on a case-by-case basis, which approach is useful in a specific research situation. Given the variety of existing approaches it is recommended to perform several alternative statistical analyses in order to evaluate the consistency and robustness of results. Of course this does not mean that the basic concept of pre-specifying one approach to be the primary one is abandoned. Publishing the results of a SCT, caution should be exercised in the interpretation before attempting to extrapolate or generalise vague results. Applied methods and results should be reported in detail and unbiased, in order to allow for subsequent aggregation of several study results in a future systematic review or meta-analysis.

All above considerations finally lead to the conclusion that planning and conducting a SCT represents a particular challenge regarding the applied statistical methodology. In a sense, a reciprocal relationship exists between the sample size and the effort of (especially the statistical) personnel involved. Planning a SCT, generally not less than more and also more sophisticated work has to be done compared to larger trials.

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Part III
Pharmacoepidemiology

Chapter 12
A Regulatory Overview About Rare Diseases

Jordi Llinares

Abstract Rare diseases attract very little interest for drug development. To create more favourable conditions, incentives for development (scientific advice, research grants) and marketing of medicines (market exclusivity, regulatory fee reductions) are offered by several orphan legislations. These incentives have proven to be a valuable stimulus for research and development for new products for treatment, prevention and diagnosis of rare diseases. In the US almost 2000 products have been designated as orphan medicines and about 340 have received marketing authorisation. Rare diseases have also gained attention from regulators in the last years. Nowadays it is acknowledged that rare diseases deserve specific attention and individual regulatory guidance. Also, regulatory authorities have developed different mechanisms to put products on the market considering specific limitations of data availability (conditional marketing authorisation, exceptional circumstances authorisation). In the future more initiatives will have to address the need for networking scientific knowledge and research capabilities to address the difficulties to generate data in rare diseases.

Keywords Orphan regulation · Incentives · Orphan designation · Drug development · Conditional marketing authorization · Exceptional circumstances

12.1 Regulations for Orphan Medicines

12.1.1 Origin and Justification

Usually, diseases that affect very few patients (rare diseases) attract very little interest with regards to drug development. The reasons for this can be multiple: small drug market that does not justify investment, insufficient patients to perform appropriately powered trials, lack of knowledge about the disease mechanisms, low

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awareness and lack of critical mass. All these reasons can be associated to the rarity of the disease as the underlying factor.

In different parts of the world rare diseases have been the object of specific legislative initiatives aimed at stimulating the research and development of drugs to treat, prevent or diagnose such conditions. Drugs for rare diseases are known as orphan medicines in allusion to the lack of support from those that in general would take care of their development.

Legislation for orphan medicines establishes a system of recognition of the special status of individual products justified by their potential to diagnose, prevent or treat a rare disease. Those compounds that fulfil predefined criteria gain access to incentives for development (e.g. financial, regulatory, scientific). Some regulations also set up measures to protect against competitor products in an attempt to modify the market conditions that otherwise would affect them due to the small number of patients that constitute the market. Overall, the regulations for orphan medicines are a combination of push (development and regulatory incentives) and pull incentives (market exclusivity, tax incentives).

12.1.2 Main Orphan Regulations

Currently orphan regulations are in place in different parts of the world such as the United States of America, Australia, Japan and the European Union (Table 12.1).

12.1.2.1 United States

The first orphan regulation in the world was adopted in the USA in 1983. The Orphan Drug Act has its origins in an initiative from parents of patients affected

Table 12.1 Legal references for some of the existing orphan drug regulations

	Year of adoption of regulation	Legal text
United States	1983	Orphan Drug Act SEC 525 Recommendations SEC 526 Designation of Drugs for Rare Diseases or Conditions SEC 527 Protections for Drugs for Rare Diseases or Conditions
Japan	1993	Japanese Medicines Act; Articles 77-2 and 77-6
Australia	1997	Therapeutic Goods Regulations 1990; Part 3B Regulations 16H, 16 I and 16 J
European Union	1999	Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

by rare diseases. These families had to overcome great difficulties to import drugs for the treatment of rare diseases and raised the problem with representatives in the US Senate. This initiative resulted in the first attempt for a regulation that offered incentives for development of drugs for rare diseases. Initially the regulation defined the lack of profitability of products for rare diseases as the criteria for designation; to receive orphan designation a sponsor was requested to estimate the absence of profitability for 7 years after FDA approval. The Act was amended in 1984 to include a prevalence threshold as criterion for the definition of a rare condition to obtain orphan designation.

The US Orphan Drug Act [24] defines rare diseases, or conditions, as those affecting less than 200,000 persons in the US. As an alternative to the prevalence criterion, the US Act also offers the possibility to designate those drugs for which the necessary investment for their development will not be recovered by the return from the sales of the product. The designation provides incentives for sponsors in the form of 7-year market exclusivity, tax incentives, access to a dedicated development grant program, access to protocol assistance for the development and fee waivers for regulatory activities (Table 12.2).

The Orphan drugs act, is implemented in the US by the Office for Orphan Product Development (OOPD) of the Food and Drug Administration.

So far more than 1990 products have been designated by the OOPD and 340 designated drugs have been marketed in the US (Fig. 12.1). In the ten years preceding the entry into force of the Orphan drugs act fewer than ten products were authorised for rare diseases [22].

In the US orphan designation is also possible for medical devices (humanitarian use devices) under the Food Drug and Cosmetic Act. Humanitarian use devices are intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are present in fewer than 4,000 individuals in the United States per year.

Table 12.2 Incentives for orphan drug development

	Incentives offered	
	Economic	Regulatory/development
USA	Market exclusivity (7 years) Tax credit for clinical trial costs Fee waiver for regulatory activities	Protocol assistance Access to orphan grants programme
Japan	Market exclusivity (10 years; 7 for devices) Tax credit on any studies Funding for R&D costs	Advice on development
Australia	Fee waiver for regulatory activities	Priority review
European Union	Market exclusivity (10 years) Fee reductions for regulatory activities	Protocol assistance Access to Framework Program grants National incentives for development (compiled in EC inventory)

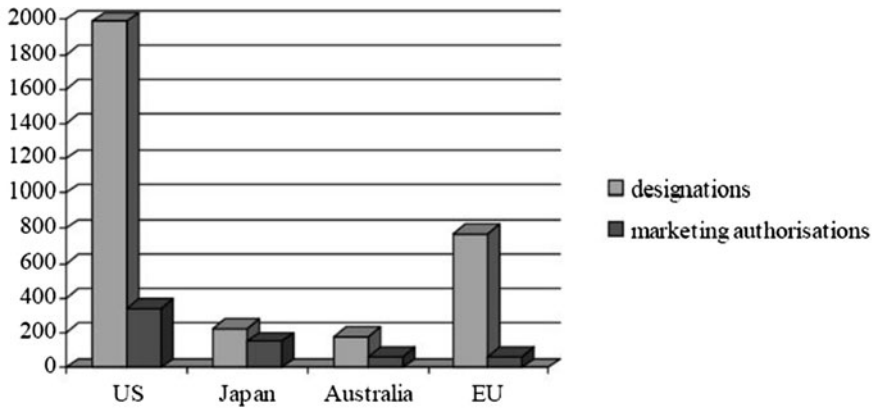

Fig. 12.1 Designations and marketing authorisations pursuant to implementation of orphan legislation

The OOPD gives support and advice for the approval process of designated devices. About 50 humanitarian use devices have been approved for very rare diseases and conditions.

One of the additional incentives provided for drug development by the OOPD is the Orphan Product Grants Program. The program supports research projects that investigate safety and efficacy of new drugs and devices for rare diseases. The program is competitive and the projects are selected according to scientific merit and viability, after assessment by external experts. Normally the funding granted is for up to three years for Phase I trials, and up to four years for Phase II and III trials. Up to date 43 products approved by the FDA have benefited from development support from the Orphan Grants Program. Some examples are treatments for Fabry disease, mucopolysaccharidosis type II, infant botulism, or a titanium expandable rib prosthesis for thoracic insufficiency syndrome.

12.1.2.2 Japan

In Japan a package of incentives for research and drug development for rare diseases was established in 1993. The Pharmaceutical and Medical Devices Agency (PMDA) is responsible for the promotion of orphan dugs in Japan. For the recognition as orphan drug in Japan it is necessary to fulfil a prevalence criteria (patients affected must be fewer than 50,000) plus two additional criteria. Firstly, the condition subject of the designation should not have suitable alternatives of treatment, otherwise the efficacy and safety of the drug to be designated must be better than available drugs or interventions. It is also required that the potential for development is justified and high (i.e. justification for the use of the drug and a feasible development plan) [21].

The economic incentives offered in Japan are rather comprehensive and include grants for drug development for up to 50% of the research and development cost per year for a maximum of 3 years after designation; tax deductions and market

exclusivity (extension of the registration validity period). Also sponsors can apply for advice on development and have access to fast track review for authorisation.

At the end of 2009, 147 products had been approved in Japan as orphan medicines for new indications and 277 products have been designated as orphan medicines (Fig. 12.1). Some of these products have been authorised for conditions such as acute promyelocyte leukaemia, idiopathic pulmonary fibrosis, and mucopolysaccharidosis type I.

12.1.2.3 Australia

The Therapeutic Goods Regulation, which regulates pharmaceuticals in Australia, introduced in 1997 the principles for orphan designation [23]. Part B of the Therapeutics Goods Regulation recognises as orphan medicines those intended to treat, prevent or diagnose rare diseases. The prevalence criteria is defined for certain products (vaccines or in vivo diagnostic agents) so they are recognised as orphan products if their administration in a year is restricted to not more than 2,000 people after it is registered for use for the disease or condition.

So far the Australian regulation does not offer marketing protection for designated products; instead, it offers a priority review system for marketing authorisation of designated orphan medicines and fee waivers and exemptions for regulatory activities. To date 177 medicinal products have been designated in Australia and 62 have obtained marketing approval (Fig. 12.1).

12.1.2.4 European Union

In the European Union the orphan legislative initiative came after the approval of the regulations in the US, Australia and Japan, therefore it was able to benefit from the precedents in other regions, mostly from the US. In December 1995, the Council of Ministers adopted a Resolution [3] asking the European Commission to look into the situation of orphan dugs and propose necessary actions to improve access to dugs for rare diseases. The resolution identified the need to define rare diseases, set up criteria for designation and propose incentives to promote research, development and marketing authorisation of such drugs. A Resolution is a first necessary step towards introducing new legislation. The European Commission carried out a wide consultation on the subject and submitted a proposal to the European Parliament and the Council on an orphan regulation. The European regulation [4] on orphan medicinal products was adopted in December 1999 and was implemented in 2000.

In the European Union orphan drug designation is based on three elements: (i) prevalence or economic criteria, (ii) seriousness and (iii) existence of satisfactory alternative medicines.

The prevalence threshold for the recognition of a disease as rare is defined by a maximum of 5 in 10,000 people in the EU. As in the US orphan designation can also be granted based on economic criteria. In this latter case it must be shown that without incentives it is unlikely that the marketing of the medicinal product in the EU will generate sufficient revenue to justify the investment that drug development requires.

Secondly, for orphan designation it is required to justify that the disease is life-threatening or chronically debilitating.

Finally, before designation it has to be established whether there are satisfactory methods of diagnosis, prevention or treatment of the condition. If such methods exist a justification of the clinically relevant advantage or major contribution to patient care that the medicinal product may offer is required. Guidance on the concept of significant benefit, the legal term for a clinically relevant advantage or a major contribution to patient care, is available in different documents such as the Commission Communication on rare diseases [6] and other regulatory texts [9]. The concept of significant benefit has been applicable to more than 60% of the positive opinions adopted on orphan designation.

The main incentives offered by the EU regulation are a period of 10 years of market exclusivity, scientific advice on the development of products in the form of protocol assistance, regulatory fee reductions and automatic access to the Community marketing authorisation procedure or centralised procedure. In addition, since entry into force of the EU Paediatric Regulation, the market exclusivity period for designated orphan medicinal products can be extended by two additional years if the product is authorised after complying with an pre-agreed investigation plan (Paediatric investigation plan) [7].

The European Medicines Agency does not provide direct funding or grants for the development of orphan medicines. However, orphan designated products may apply for funds from the Community 7th Framework Programme, which offers grants for preclinical and clinical research, with special focus on natural history and pathophysiology of rare diseases and on development of preventive, diagnostic and therapeutic interventions. In the European Union, orphan designation facilitates access to the Community 7th Framework Programme grants.

So far the EU regulation has resulted in 744 positive opinions on drug designation and 62 authorised products. More than one third of the designated products (36%) are related to orphan diseases affecting less than 1 in 10,000 patients in the EU (i.e. less than 50,000 patients) and a high proportion of the designated products (30%) are for very innovative active substances for the treatment of rare diseases (e.g. monoclonal antibodies, gene therapy, cell therapy) [2].

After more than twenty five years of incentives for drug development and marketing it is obvious that there is still a significant need for continuous incentives and support for drug development for rare diseases. Even if difficult to quantify, the success of the measures offered to stimulate drug development for rare diseases has nevertheless been reported upon by various sources [19, 25].

12.2 Drug Development and Drug Approval

The requirements for marketing authorisation and the principles that regulate the marketing authorisation procedure for drugs for rare diseases are the same as those applied for other drugs. As stated in the EU Orphan Regulation, patients affected by rare diseases “deserve the same quality, safety and efficacy in medicinal products

as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process" [4].

The marketing of a drug is possible only after a positive outcome on the assessment of the balance between the therapeutic benefits that the product provides and the risks derived from its administration. These risks have to be defined in relation to the patients, public health and the environment [5].

12.2.1 Fundamental Aspects of Drug Development for Orphan Medicines

12.2.1.1 Non-clinical Development

Non-clinical development refers to the studies that are performed before the start of the clinical studies. The main objectives of these studies are the study of the toxicology and pharmacology of a drug. Most but not all toxicology studies necessary for marketing authorisation are generally performed before the investigation in humans. Toxicology studies may include: single-dose and repeated dose toxicity, reproductive toxicity, genotoxicity tests, carcinogenicity and immunotoxicity. Also studies of local tolerance and of environmental risk may be required.

The internationally accepted guideline ICH M3 [17] and the Committee for Human Medicinal Products (CHMP) Guidance on first-in-human clinical trials [15] provide guidance on the non-clinical safety studies required for the conduct of clinical trials. No specific provisions for orphan medicines are included in those guidelines, and they are applied taking into account the characteristics of the product and the nature of the disease treated.

Studies on the environmental risk that a product can generate can be subject to special consideration for rare diseases as the need for the studies is determined by the extent of exposure to the drug by the environment, which could be extremely low for very rare diseases [13].

12.2.1.2 Clinical Development

Classically, clinical development has been divided in four different phases that are defined both in relation to time needed for the total development of the product and to the objectives of each phase. Even though this classification is very useful from a theoretical point of view and helps understanding the different characteristics and difficulties of drug development history, in reality there are many overlaps between phases (Table 12.3).

The objective of the clinical development is to provide the basis for the assessment of the benefit-risk balance. This can be done only after a correct determination of the appropriate dose in the intended indication, the demonstration of the efficacy of the product and the description of the safety profile. For reference, the ICH E8 "Note for guidance on general considerations for clinical trials" (CPMP/ICH/291/95) provides more information on clinical development [11].

Table 12.3 Main characteristics of the different phases of clinical drug development

	Main objectives	Approximate number of participants	Subjects
Phase I	Pharmacokinetics Pharmacodynamics First data on safety	Tens	Healthy volunteers Patients (exceptionally)
Phase II	Dose finding Definition of treatment schedule Preliminary data on efficacy	Tens to hundred	Patients (highly selected)
Phase III	Efficacy Safety	Large (hundreds)	Patients
Phase IV	Safety New indications Promotion of prescription/use Economic aspects of use	Large-very large (hundreds to thousands)	Patients (prescription of drug)

This section is not intended to provide a comprehensive discussion on the different phases of development but a short description of the main characteristics of the clinical development phases in relation to orphan medicines.

Phase I: this early phase of clinical development usually consists of small studies (tens of subjects) in which the drug is administered for a first description of its tolerability, pharmacokinetics and basic pharmacodynamic characteristics. Phase I studies provide the first information about the toxicity of a product in humans.

The first time a product is administered to humans constitutes a very specific situation of phase I study. These studies are done in very small groups, normally with sequential administration of the product to one volunteer at a time and under strict conditions of monitoring.

Other examples of phase I studies are bioequivalence studies, those that study the pharmacokinetic properties in healthy populations or in special populations (e.g. renal insufficiency) and some drug interaction studies.

In some situations phase I studies are performed in patients. This is particularly common when the toxicity of the product is such that it precludes administration to a healthy volunteer. In this case patients, normally in advanced stages of the disease, volunteer to participate to contribute to the development.

Phase II studies typically include tens to a hundred of patients and have as main objective to define the most appropriate dose and schedule for the treatment of a disease. The ICH E4 "Note for guidance on dose response information to support drug registration" [10] provides a discussion on dose escalation studies, a specific study design for phase II studies aimed at finding the dose of a drug.

These studies also provide preliminary data on the efficacy of the drug in humans, typically using endpoints of limited clinical relevance compared with those used in later phases of development. Due to the rare nature of the diseases, phase II

studies have been provided to support marketing authorisation of orphan medicines on many occasions, and in some cases constitute the only evidence that can be provided.

Phase III studies include large number of patients based on very strict design and methodological considerations. Phase III studies aim at generating enough data to define the future therapeutic use of the product. The main objective of phase III studies is to confirm efficacy in patients, preferably in experimental conditions that are as close as possible to the real conditions of use. Data on the safety profile of the drug are prospectively recorded in phase III trials and normally this constitutes the core data that regulatory authorities will have to assess the safety of the product at the time of licensing.

An example of the flexibility of clinical development phases, particularly in the field of rare diseases, is discussed in the Reflection paper on methodological issues in confirmatory Clinical trials planned with an adaptive design [16]. In the paper it is stated that in some circumstances a study combining phase II and III can be performed. The necessary circumstances are a well-established therapeutic dose, and the inclusion of a population in the phase II study similar to the phase III population. If in this case the phase II endpoints are relevant for phase III studies, then a combination study could be proposed. In this case it is necessary to discuss and justify why sufficient evidence is expected from the phase II / phase III combination trial compared to a classical strategy (second phase II followed by a phase III). Further considerations are included in the reflection paper. The paper explicitly identifies rare diseases as the situation that may justify performing a single phase II / phase III combination trial to provide the totality of available information, rather than another design using a limited number of patients.

Phase IV studies are performed after marketing authorisation and may have different objectives such as studying the safety of the product, efficacy in other indications, market promotion or analysis of economical aspects of the prescription. Importantly, some phase IV studies are generated by the requirements from the regulatory authorities to fulfil post-marketing commitments.

12.2.1.3 Scientific Advice in Orphan Drug Development

Scientific advice on drug development (called protocol assistance in the EU) is one of the most important incentives available for products designated as orphan medicines. Any aspect of drug development can be addressed in scientific advice, including quality, non-clinical and clinical aspects, and also issues relevant to orphan status and the incentives, such as discussion on similarity or demonstration of significant benefit. In Europe it is also possible to receive advice on non-product related issues, such as on a new statistical approach or validation of a scale, and also on qualification of genomic and other biomarkers for use in the clinical development.

Scientific advice helps the sponsor to ensure that the appropriate tests and studies are performed during the drug development. This avoids performing insufficient or unnecessary studies. This prevents major objections during evaluation of the

marketing authorisation application and has been associated with a higher rate of success of the authorisation procedure [20].

12.2.2 Drug Approval for Orphan Medicines

Sometimes orphan drugs challenge the marketing authorisation paradigm, mainly due to the difficulties in generating sufficient data for a conventional assessment [1]. It is expected that there will be some situations where despite the fact that not all data will have been generated at the time of marketing authorisation the public health interest in marketing the product is extremely high. There exist regulatory mechanisms to authorise products in these circumstances, and they are particularly relevant for orphan medicines: authorisation under exceptional circumstances and conditional approval [8, 12].

The critical difference between conditional approval and authorisation under exceptional circumstances is the presence or absence of the possibility to generate the data that are unavailable at the time when the authorisation is recommended.

If comprehensive evidence cannot be reasonably generated with regards to the safety and efficacy of a product, it is possible to grant a marketing authorisation to the product under exceptional circumstances. Marketing authorisations granted under exceptional circumstances are also appropriate when, according to scientific knowledge comprehensive information cannot be provided, or when generating such data would be contrary to the generally accepted principles of medical ethics. The guideline on exceptional circumstances [12] states that orphan drugs are not expected to be approved automatically under exceptional circumstances.

The specific characteristics of this marketing authorisation include a yearly reassessment of the benefit – risk balance and certain specific post-approval obligations, very often associated with the generation of additional data for safety purposes. To date, in the European Union 40% of the marketed orphan medicinal products have been authorised under exceptional circumstances (Fig. 12.2).

On the other hand, a conditional marketing authorisation may be possible for products where only preliminary evidence is available at the time of marketing authorisation but additional data can be generated, submitted and assessed. If the data contained in the marketing authorisation application is sufficient to predict a clinical outcome after a comprehensive development, then the product can be

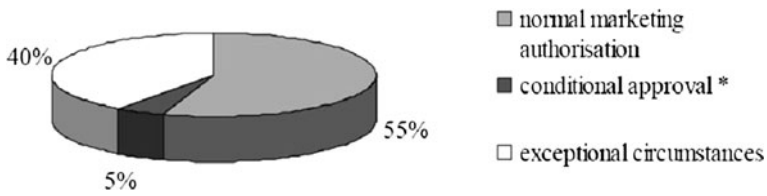

Fig. 12.2 Types of marketing authorisation applied in the EU for orphan medicinal products; *conditional approval applied since 2006 only

authorised conditionally. The Guideline on procedures for the granting of a marketing authorisation as a conditional marketing authorisation [8] specifically refers to orphan drugs.

For a conditional marketing authorisation to be granted it is necessary that the risk-benefit balance of the medicinal product is positive; the unmet medical need derived from the condition is fulfilled; and there is a benefit to public health of the immediate availability on the market of the drug and this outweighs the risk inherent to the need for additional data. Importantly, the incompleteness of the data in the submission leading to a conditional marketing authorisation should be restricted to clinical aspects of the application. Only for those products to be used in emergency situations it is foreseen that an incomplete non-clinical and/or quality package can be accepted after fully justified.

A conditional marketing authorisation will be reviewed once a year and may be renewed. The marketing authorisation can become a "normal" marketing authorisation once the data required for confirming the positive benefit-risk relationship are provided. Five per cent of the orphan medicinal products currently authorised have reached the market in the EU through conditional marketing authorisation (Fig. 12.2).

12.3 Regulatory Guidelines and Other Regulatory Activities Which Also Feature Rare Diseases

12.3.1 Regulatory Guidelines that Address Rarity

The focus on rare diseases by regulators is a relatively recent phenomenon. Nevertheless, in Europe there are already different examples where rare diseases have been addressed in regulatory guidelines. Good examples of this are the "Guideline on clinical trials in small populations" [14] and the "Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design" [16].

The Guideline on clinical trials in small populations [14] addresses the problems of performing clinical trials in small populations, and by analogy rare diseases. This Guideline recognises the inherent problems of conducting clinical trials when the number of patients is limited. For rare diseases "conduct, analysis, and interpretation of studies (. . .) at times may be constrained to varying degrees by the prevalence of the disease."

The document states that there are no methods specific for small populations. However, it is recognised that in situations where the population is small or very small less conventional methodological approaches may be acceptable if fully justified. In these cases protocol assistance is strongly recommended. To date, the majority of products currently authorised as orphan medicinal products have been authorised with data generated by studies following classical methodologies.

The reflection paper on methodological issues in confirmatory Clinical trials planned with an adaptive design [16] refers to particular aspects of drug development in rare diseases. The combination study phase II /phase III has been discussed above. Moreover, the document also refers to rare diseases with regards to the difficulties to provide evidence:

> The term "difficult experimental situation" has been used in this document to describe diseases, indications, or patient populations, where it is common knowledge that clinical trials will be difficult to perform. Examples include(. . .)(ii) small populations or orphan diseases with constraints to the maximum amount of evidence that can be provided, (. . .)

By addressing the specificity of rare diseases, both documents show regulators increasing understanding of rare diseases and identify the need for a flexible approach.

The International Conference on Harmonisation (ICH) provides a multinational and multidisciplinary framework for regulatory requirements for data for marketing of products. It brings collaboration between Regulatory authorities from Europe, Japan and the United States and experts from pharmaceutical industry. ICH also includes observers from the World health Organisation (WHO), Canada, and the European Free Trade Area (EFTA) countries. The ICH guidelines constitute recommendations on how to harmonise the interpretation and application of technical guidelines and requirements for marketing authorisation. These guidelines have not yet addressed specifically the issues affecting drug development for rare diseases. The final goal of harmonisation is to build an efficient system of drug development across different geographical areas. Recognising that drug development for orphan medicines is a global project. Therefore, it seems reasonable to expect that some of the principles that have already been accepted in regional guidelines will be put forward in the future for harmonisation.

12.4 The European Network of Centres for Phamacoepidemiology and Pharmacovigilance (ENCePP)

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is an initiative led by the European Medicines Agency.

The main objective of the ENCePP is to network the available expertise and research experience in the fields of pharmacoepidemiology and pharmacovigilance across Europe. A network of excellence has been created, including relevant research centres, University hospitals, owners of healthcare databases and/or electronic registries and existing European networks covering certain rare diseases, therapeutic fields and adverse drug events of interest.

All ENCePP partners are included in the ENCePP Inventory of research centres [18]. This database is available at the ENCePP web portal to the general public and offers sources of information, expertise and research experience across Europe.

By bringing collaboration between experts and networking, ENCePP offers the structure that can benefit areas such as rare diseases. Epidemiological studies after

marketing authorisation may help addressing scientific questions that only at this point in time may be answered with appropriate methodologies.

12.5 Conclusions

Rare diseases attract very little interest for drug development from pharmaceutical industry, due to the limited market for those medicines.

To create more favourable conditions for development and marketing of drugs for rare diseases several legislations have been approved in the last 25 years in different parts of the world, including the United States, Japan, Australia and the European Union. The regulations combine push and pull measures aimed at offering incentives for development (scientific advice, research grants) and marketing of medicines (market exclusivity, regulatory fee reductions). These incentives have proven to be a valuable stimulus for research and development for new products for treatment, prevention and diagnosis of rare diseases.

Rare diseases have gained attention from regulators in the last years. These have recognised the extreme difficulty in developing products in rare diseases in different documents, including ICH guidelines and single Regulatory Agencies guidelines. Currently it is generally acknowledged that the development of products for rare diseases generates specific challenges and that it deserves specific regulatory guidance. In addition, regulatory authorities have developed different mechanisms to put products on the market considering specific limitations of data availability (conditional marketing authorisation, exceptional circumstances authorisation), which apply to rare diseases.

In the future more initiatives will have to address the need for networking scientific knowledge and research capabilities to address the difficulties in generating data for rare diseases. Only collaboration can overcome the problems that the rarity of the diseases and the dispersion of patients put on the development of medicines for rare diseases.

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Part IV
Economics and Social Epidemiology

Chapter 13
Economic Considerations in the Provision of Treatments for Rare Diseases

Christopher McCabe, Richard Edlin, and Jeff Round

Abstract Orphan Drug legislation in the USA, Europe and elsewhere has been incredibly successful in promoting the development of new treatments for rare diseases. Historically, payers have constructed special schemes that have facilitated patient access given the small total budget impact of these treatments. However, whilst each disease is rare, the number of licensed orphan drugs is growing rapidly. This, in conjunction with the high prices claimed for these treatments, has increased the total budget impact of orphan drugs. In the medium term, the feasibility of omitting orphan drugs from value for money type assessments is doubtful. The arguments for a special status for orphan drugs in reimbursement processes are reviewed in this article, and it is concluded that these arguments do not generally stand up to critical assessment. A new paradigm for the development and purchase of orphan drugs may be required. Given the strong parallels between the challenges of neglected diseases in developing countries and orphan diseases in developed countries, policy tools developed for neglected diseases; such as Public Private Partnerships and Advance Market Commitments, might be fruitfully applied in the orphan drug arena.

Keywords Market access · Budget impact · Sustainability · Public private partnerships · Advance market commitments

13.1 Background

Over the last two decades access to biopharmaceutical treatments for rare diseases has become one of the most high profile challenges facing health care systems in developed nations [4]. Orphan drugs can be costly and as an increasing number of such treatments arrive on the market the total expenditure on these drugs is likely

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to increase dramatically [17]. Providing these treatments may be problematic for health care systems as the budget impact may simply become too great to be sustainable. A framework for the development and provision of treatments in a sustainable manner is a matter of urgency.

Three decades ago these treatments did not exist, as market conditions did not provide the appropriate incentives for the for-profit pharmaceutical manufacturers to develop them. To stimulate development of such treatments, the introduction of the United States' Orphan Drugs Act in 1983 provides for both tax incentives and protected periods in which competition is prevented for seven years within the USA [10]. Similar incentives were introduced in Europe by the Orphan Drugs Regulation [20]. These measures have proven a highly effective incentive for the development of a large number of new treatments for rare diseases [17]. However, the premium prices requested for these products means that many wealthy nations struggle to make treatments available to all patients who may benefit from them.

Whilst some payers approve unrestricted access to these treatments, others have responded with regulation ranging from requiring individual patient approvals to blanket bans. Faced with variation in access within and between health care systems, advocates for the affected patients have advanced a number of arguments for treatments for rare diseases to be afforded special status in reimbursement decision processes.

This chapter provides the reader with a critical understanding of the arguments that have been advanced to support a special status for treatments for rare diseases, to describe the different types of scheme that have been used to implement them, and to consider whether alternative incentive and regulatory structures could be effective in ensuring sustainable, development of new treatments for rare diseases. Section 13.2 considers the arguments for a special status for rare diseases, including both efficiency and equity arguments, alongside those suggesting specific difficulties within standard health technology appraisal processes. Section 13.3 then describes alternatives to standard health technology appraisals, through a selection of patient access strategies from the USA, Canada, United Kingdom and Australia, identifying the pros and cons of each. Finally, Section 13.4 considers whether methods currently used for developing and funding other neglected diseases (Public Private Partnerships and Advance Market Commitments) offer alternatives incentives for the development and funding of future treatments for rare diseases.

For the sake of simplicity in the remainder of this chapter, we use the term "orphan drug" to refer to any biopharmaceutical developed to treat a rare disease. We do not rely on any specific definition of orphan, as the principles we consider are not dependent upon a particular incidence or prevalence threshold.

13.2 Arguments for Special Status

The arguments advanced for giving treatments for rare disease a special status in reimbursement decision making fall neatly into those considering how efficiently the market functions (Section 13.2.1), those considering how equity considerations

can be balanced against issues of efficiency (Section 13.2.2), and those that speak to whether or not such issues can be explored within a standard health technology appraisal process (Section 13.2.3). These arguments are considered in turn.

13.2.1 Efficiency-Based Arguments

Under standard economic theory, consumers are willing to pay up to the amount that the good is worth to them, with any excess of value over the price paid (i.e. without subsidies) called "consumer surplus". Correspondingly, any excess of price received (i.e. including subsidies) over average costs is called the "producer surplus" from that unit. The total surplus from a market is typically equal to the sum of producer and consumer surplus minus any net payments from government. It is efficient for a market to exist when this total surplus is positive, and a free market is often argued to maximise this total surplus.

However, a key issue for rare diseases is that it may be more efficient that treatments not be produced due to a negative total surplus. In general, efficiency appears to rely on three issues: (1) Whether producers receive enough return to convince them to invest; (2) Whether it is efficient to produce under conditions generous enough to induce supply; and, (3) Whether the reimbursement authority can justify spending enough money to induce this supply.

Producer surplus measures the difference between the amount of money a company receives and its total costs. Within producer surplus, these (economic) costs are higher than accounting costs and include a standard rate of return that reflects the cost of raising capital to fund investments. Economic costs include an apportioned cost for unsuccessful research and development, with positive producer surpluses implying that companies receive more than they could expect when investing elsewhere.

The patent and other protections given to the pharmaceutical companies may allow them to make excessive profits across their product range. If the internal policy of industry is to require the same return on investment in orphan drugs as in other areas, and this return is excessive, then the small size of the market for an orphan drug makes provision unlikely in some cases where it is efficient (non-negative producer surplus and positive total benefit). That is, whilst the average cost of an orphan drug will be higher than for drugs treating common diseases (due to fixed costs within research and development and low numbers of potential patients), the claims made by industry with respect to their costs may be excessive. If industry demands returns *beyond* those which are possible in other industries, their policies may actually prevent drugs from reaching the market and thus contribute to the problem of orphan drugs.

Subsidies, in the form of reimbursement payments, cannot normally resolve this issue. Whilst they increase the return that the drug companies receive, they tend to reduce total surplus, as the producer and consumer surplus tend to increase by less

than the total subsidy. In this way, excessive demands from industry may render some orphan drugs inefficient. Even where this is not the case, higher prices are harder for reimbursement authorities to justify.

For efficiency's sake, the reimbursement authority must consider whether the benefit (or health) produced by the orphan drug is greater than the benefit (or health) foregone from spending the same resources on other health care interventions for the same or different patients. The high costs of orphan drugs mean that reimbursement authorities would normally need to move beyond simple market-based arguments to fund them. We begin by considering arguments that the costs or the benefits of the treatment are mis-specified – that is, there are market failures that lead to inefficiency.

Efficiency-based arguments for market failure can include cases where taxation policy and risk may lead to manufacturers assigning too high a cost to investing in orphan drugs, or where the manufacturer believes protection of intellectual property is inadequate to stop them recouping the cost of investments (as distinct from requiring protection to allow excessive profits). In these circumstances, the public funding of research and legislative action could be justified; it is arguable that these are exactly what the authorities in the USA and elsewhere aim to do. These types of interventions do not typically offer a higher price for orphan drugs but instead change the environment in which decisions are made. More generally, these concerns are not unique to orphan drugs and cannot provide a basis for their special status in reimbursement unless: (1) The type and extent of these market failures are different for orphan drugs; or, (2) These issues are insufficiently addressed by the subsidies and protections provided as part of the research and development and licensing processes.

Costs or benefits can also be mis-specified where the provision of a treatment has effects beyond those directly concerning either the company or the reimbursement authority – or "externalities". An example that has been increasingly argued for orphan drugs is the economic value of innovation to society; i.e. when the introduction of a technology creates opportunities for other socially valuable activities that did not previously exist. These opportunities, if taken advantage of, will increase economic activity. However, such considerations apply equally to all interventions, and their application will be case specific. Therefore, the value of innovation argument does not provide a general argument for special status, although it is possible that these arguments will apply more frequently to orphan drugs.

Mis-specification may also occur when either party is unable to accurately measure the benefits of treatment. For example, there are concerns that currently available health related quality of life instruments (benefit measures) are inadequate in scope and/or sensitivity to adequately capture the benefits of new treatments for rare diseases. This argument is frequently and effectively advanced for common disease areas, and for groups including those with mental health problems, children, and the elderly. Whilst one might recognise the potential value in more robust measures of health, it is not clear that rare diseases are a specific priority.

13.2.2 Equity and Decision Making Within Health Care Systems

If the development and reimbursement of an orphan drug remains inefficient even after appropriate regulatory action and taking any other factors into account, then a positive reimbursement decision must be based on equity considerations. That is, it requires that the value placed on treating rare diseases is deemed to be higher than on treating other diseases in cases where each option provides the same (or less) benefit to those treated.

The way that value is assigned within a health care system depends on what that system has been designed to accomplish, such as equality of access or equality of health outcome. Yet, regardless of the objective used in a particular system, a minimum requirement for equity is universality, in the sense that the same processes and criteria are applied to all claiming for treatment within that system. As it is impractical to consider treatments on an individual-by-individual basis, equity is likely to mean that all treatments must be assessed within the same system based on the same objective (or set of objectives, weighted in a consistent way).

For example the use of cost effectiveness analysis in a single-payer health system, without modification for other factors, is consistent with an objective of health gain maximisation. Under cost-effectiveness analysis, each treatment is assessed on the same basis with the effect that some, more efficient, treatments are more likely to be funded than other, less efficient, treatments. In a similar way, a pure market system would require that those treatments that people are willing (and able) to pay for are more likely to be funded than those that people are unwilling or unable to pay for.

In terms of equity, a range of other objectives are potentially feasible including equality of health outcome, equality of resource utilisation or the allocation of resources according to the severity of individual's ill-health. However, if the way that the health care system values health flows from its objectives, then changing the way the system values health means also changing the core objectives of the system itself. We cannot, therefore, make a special case for rare diseases without also changing the way that other technologies are assessed.

It must be noted that such changes would not necessarily favour allocating more resources to orphan drugs than the status quo. If a system placed more weight on equal resource allocation across individuals (e.g. by advocating individual lifetime health budgets), then it is clear that this would make it less likely orphan drugs will be funded.

13.2.2.1 A Special Weight on Rarity?

Drummond and colleagues have argued that the Orphan Drug regulations demonstrate that societies have an objective of equal access to biopharmaceutical treatments for rare diseases as compared to common diseases [7,8]. This argument would be more convincing if the US Orphan Drugs Act had provided for coverage of orphan drugs under a Medicare or Medicaid like system; or if the European Orphan Drugs Regulation had established a Pan-European health care financing scheme for treatments licensed with an orphan designation. As neither regulation addressed the

issue of financing, the strong implication is that the legislators wished to correct for potential supply-side efficiency failures rather than to suggest that treating very rare diseases is more valuable than treating more common, or even slightly less rare, diseases.

If Drummond's argument is specific to rarity (rather than access), it appears to lack validity. It appears implausible that a system can be equitable whilst making arbitrarily-defined special cases, or using principles that cannot be easily justified when applied at an individual level. The applicability of a principle at an individual level provides a useful test of the value of that principle at a treatment level. From an equity position, treatment-based groups are considered because we cannot consider allocation decisions for individuals in isolation. Here, rarity per se – as the size of groups – appears to make little sense at this individual level. As each individual can make a limited claim to uniqueness, every person is ultimately in a subgroup of one. A claim for rarity must ultimately be justified by saying that treating *individuals* with rare diseases is more important than treating *individuals* with common diseases.

Such arguments can be made, however, by considering issues which are more likely, but not uniquely, related to rarity. For example, placing weight on severity may favour orphan drugs over treatments for common mild diseases, but there are many common severe conditions which would have an equal claim on resources. Likewise, placing weight on reducing health inequalities may favour orphan drugs for those who are unlikely to obtain a "fair innings" of health throughout their life, [21] but again only when also giving priority to other groups who are also unlikely to obtain a fair innings of health. As it appears intuitively reasonable (to the authors, at least) that those who are in worse health and those who are expected to have less opportunity over their lives could receive priority, both arguments have some merit at the individual level.

13.2.2.2 A Lack of Alternatives?

A specific argument advanced for orphan treatments is that when there is no existing therapy, the act of treatment itself has a value to the patient and society at large, independent of its effect on the disease. In developed countries' health care systems, no alternative treatment actually means no alternative, effective, and biologically active treatment. Individuals are not normally abandoned by the health care system simply because there is no biologically active treatment available.

In effect, this suggests that in the context of orphan drugs, health improvements produced through modifications to the patient's biochemistry, should be valued more highly than improvements in health that are achieved through other means such as best supportive care. It is unclear why health gain should be ascribed a differential value according to a physician's intent when prescribing a treatment. However, this is a hypothesis that can be subject to empirical testing and if empirical research found evidence for a differential value by mode of action, this could legitimately be applied to treatments for rare and common diseases. Whilst orphan drugs would be more likely to benefit from this differential value, it would not provide the basis of

a special status for all orphan drugs; only those for whom the mode of action of the current treatments attracted a lower value.

13.2.3 Issues for Health Technology Appraisals in Rare Diseases

A number of authors, including Drummond et al; and Hughes et al have argued that the evidence base for some orphan drugs, especially ultra-orphan drugs close to licensing is such that it is not feasible to subject them to standard methods of health technology appraisal [7,12]. In the UK, the National Institute for Health and Clinical Excellence were so concerned about this issue that they conducted a feasibility study of applying the standard methods to an ultra orphan drug, Cerezyme® [18].

The most frequently advanced arguments for the inadequacy of current methods of health technology appraisal are that: (a) randomized controlled trials of orphan drugs are frequently impossible; (b) it is not possible to be as certain of the effectiveness of an orphan drug as for a conventional therapy; (c) the methods used to value health gain in conventional health technology appraisal are not appropriate for orphan conditions.

13.2.3.1 Randomised Controlled Trials of Orphan Drugs

In general, whilst some orphan drugs (e.g. beta interferon) [2] have been evaluated in a randomised control trial, licenses have been granted for treatments dealing with extremely rare conditions (e.g. lysosomal disorders) on the basis of remarkably small observational cohort studies [3]. The acceptance of this type of data by licensing authorities has been justified on the grounds that the number of patients is simply too few for RCTs to be feasible. This may be true in practice, although the example of Gaucher's Disease provides a cautionary tale. Ceredase® was licensed as a treatment for Gaucher's on the basis of an observational cohort study which recruited 12 patients and followed them up for six months. Subsequently over 10,000 patients have received the therapy and provided data to the Gaucher's Disease Registry [13]. The true prevalence of an orphan disease may be much higher than presumed before a potential treatment becomes available; and therefore claims that randomised controlled trials are not feasible should only be accepted after substantial efforts to identify patients have failed.

13.2.3.2 Uncertainty in the Evidence Base for Orphan Drugs

McCabe and colleagues observed that the degree of uncertainty in the evidence base was necessarily greater when the evidence base was small [15]. However, given the evidence base a quantification of the decision uncertainty is a key outcome of methodologically robust HTA, rather than an impediment to it being undertaken. Further, the study team observed that a positive reimbursement decision remains efficient under cost-effectiveness analysis at much higher levels of uncertainty than would be the case for conventional treatments. This is because the consequences of

making the wrong decision are much smaller with an orphan drug, all other things being equal, than for a conventional therapy. The opportunity cost of treatment is the amount of health benefit that could have been achieved if the same resources were put towards an alternative treatment. As orphan drugs have by definition small target populations, even if treatment were possible and more costly than conventional treatments, the total number of patients to be treated would remain low thereby keeping the total cost of treatment lower. However, as the budgetary impact of the orphan drug increases, through increases in the cost of the drug itself or an expanding, previously unidentified patient population (see above discussion on Gaucher's Disease), the opportunity cost of making the wrong decision increases and the value of requiring more research increases [1].

From an efficiency perspective, rarity appears to have two effects on uncertainty – it firstly increases the level of uncertainty about the treatment's effects, and secondly to increase the tolerance of uncertainties by the decision maker. It is not clear exactly which of these effects is expected to dominate and when. Further research may consider this issue.

Finally, even where these issues are fully captured within an efficiency perspective, it is possible that there are relevant equity considerations. This may particularly be the case where uncertainty cannot be effectively reduced given the small numbers of those affected in rare disease, although it must be noted that this is an issue of the type of uncertainty (the degree to which it is reducible) rather than rarity per se. If such uncertainties do exist then it would be unfair to require their reduction before making a reimbursement decision. However, establishing that an uncertainty is truly irreducible represents an extremely high hurdle, and one that treatments for common diseases could also call upon.

13.3 Patient Access Strategies for Orphan Drugs

The price of orphan drugs has proven to be the single greatest barrier to patient access. Many health care systems have developed special systems to ensure patient access whilst managing the budget impact. Australia has introduced the rule of rescue criteria within the Pharmaceutical Benefits Scheme. The UK (in)famously introduced the MS Risk Sharing Scheme for treatments for Multiple Sclerosis; [6] and subsequently established a national funding agreement for treatments for Enzyme Replacement Therapies in Lysosomal Disorders [19]. In the United States, manufacturers often operate their own Patient Assistance Programmes to facilitate access for those who do not have adequate (or any) health insurance coverage and insufficient personal wealth to buy them [9]. Both France and Italy have instituted approved provider systems to control access and thus budget impact [14].

These different schemes represent quite different philosophies. The MS Risk Sharing Scheme is designed to achieve two different objectives. It aims to ensure both that the drugs are purchased at a cost effective price, and also that the uncertainty regarding their effectiveness is reduced through the generation of new evidence. This scheme aimed to improve efficiency and the health gain for patients

with rare diseases is not given a differential weight. It is notable that the scheme has yet to report the results of any analyses although there is a report that analyses have been completed. The possible explanations for this failure are discussed elsewhere [16].

The subsequent policy to fund enzyme replacement therapies for lysosomal disorders appears to reflect the principle of equity of access [19]. However, this agreement has not been extended to other orphan drugs indicating the lack of a coherent policy framework in this area. Whether the UK can sustain its current ad hoc approaches to reimbursement of orphan drugs as the volume of such drugs increases is open to question. It is notable that the organisations that deals with specialist commissioning was recently brought within the NHS organisational framework – moving out of the Department of Health – and thus made subject to the same legal duty to balance the books and promote population health as other NHS bodies. The lack of a coherent framework means that any future decision not fund a particular orphan drug will be at risk of successful judicial review.

The Australian scheme accepts that not all health gain is valued the same; specifically that health gain for individuals with a severe, rare condition for which there is no other treatment and a significant mortality burden, is valued more highly than health gain to others. The Australian scheme values some health gain more highly but is only willing to do so when the total budget impact is expected to be small because the total number of patients is small. Whilst not intellectually coherent; the value premium is not applied consistently, the policy is a pragmatic response that avoids a blanket ban [5]. However, whether the policy will be financially viable as the volume of qualifying therapies increases in the next few years, is a moot point [17].

The French and Italian systems are different again, focussing on promoting appropriate use as a means to cap the budget impact; whilst maintaining equity of access to treatment for patients with rare diseases [14]. Again, this approach is probably sustainable as long as the total budget impact of orphan drugs is small. However, the evidence reported by Miles et al suggests that this is unlikely to remain the case. How these systems will respond to rapid increases in the total budget impact remains to be seen.

The Patient Access Schemes operated by manufacturers in the US also reflect a principle of equity of access. This approach is at odds with the prevailing ethos of US health care, where access to conventional treatments is dependent upon the ability to pay, as with any other commodity. The degree to which these schemes are sustainable in the long term is largely a function of how large a premium the insurance companies and other payers are willing to fund for these treatments, as it is this revenue that allows the companies to finance their Patient Access Schemes.

13.4 Orphan Diseases and Neglected Diseases

There are two categories of so-called non-commercial diseases where national governments and international organisations have concluded that there is a need for special provisions in research and development and regulation if new treatments

are to be developed. The first of these is Orphan Diseases, the second Neglected Diseases. Whilst the focus of this chapter is the former, there are useful insights into some of the challenges in access to orphan drugs, from considering actions to achieve the same objectives in the neglected diseases arena.

The orphan drug regulations have been incredibly successful in overcoming barriers to developing new treatments. However, the pricing strategies of the for-profit companies that have been supported to develop orphan medicines are such that the gap between the neglected diseases and orphan diseases is narrowing. As the number of treatments for rare disease increases, their total budget impact begins to approach the point where even developed health care systems may not have the willingness and the ability to pay the current prices. As Drummond observes, all the incentives to promote research and development will be worth nothing if they treatments are not provided to patients once licensed [7]. If the current model for developing treatments for rare diseases is not sustainable, are there lessons to be learnt from the neglected diseases arena?

In orphan diseases, it was the prevalence of the disease rather than the ability to pay that meant companies were unwilling to invest in order to invest in developing new treatments. Neglected diseases are diseases that are prevalent in markets where there is insufficient ability to pay for commercial companies to believe that treatments can be profitably developed.

New treatments for neglected diseases are being developed through product development partnerships and Advanced Market Commitments. Product development partnerships have been described by Grace (2006) as virtual not-for-profit companies that bring together civil society (represented by academia), the public sector (government) and the private sector. PDPs leverage in private sector technology and expertise and combine these with direct research funding from the public sector [11]. Grace reports that PDPs have achieved superior development timelines and greater cost – efficiency compared to either purely public or purely private endeavours. However, as PDP technologies have moved to the later stages of development, the focus is starting to move onto ensuring access to these technologies. Advanced Market Commitments (AMCs) attempt to address this concern.

The AMCs have been developed in the context of new vaccines for neglected diseases such as malaria. The objective of an AMC is to create a market of sufficient value to stimulate research and development and manufacturing of new treatments in developing countries. Sponsors make legally binding financial commitments of a pre-agreed value. There is an ex ante specification of the product including efficacy, duration of effect, target population and presentation. The companies commit to supply a pre-agreed initial price and a tail price. The tail-price is considerably lower than the initial price, reflecting the marginal cost of production. The Sponsors top-up initial price for a specified volume of treatments, up to the full value of the AMC.

Importantly, the payout is based upon demand for the product. If there is no demand from developing countries there will be no payout. All qualifying companies can compete for sales and this maintains an incentive to develop better products.

AMCs encourage industry to invest in manufacturing scale up as technologies approach the market. They also provide developing countries with the security of supply as a foundation for planning the large scale introduction of the new technologies. The parallel between the challenges to developing and implementing treatments for neglected diseases in developing countries and treatments for orphan diseases in developed countries is obvious – the question is whether the solutions developed in the former can be adapted for the latter.

13.5 Conclusion

Orphan Drug legislation in the USA, Europe and elsewhere has been incredibly successful in promoting the development of new treatments for rare diseases. However, the prices that manufacturers of these treatments wish to charge are such that health care systems are finding it extremely difficult to make them available to all patients who could clinically benefit. Arguments for a special status for orphan drugs in reimbursement processes do not generally stand up to critical assessment. However, as the total budget impact of these treatments has been small, payors have constructed special schemes that have facilitated patient access. However, whilst each disease is rare, rare diseases are not and the number of licensed orphan drugs is growing rapidly. In the medium term their budget impact is likely to be substantial and the feasibility of excepting orphan drugs from value for money type assessments is doubtful [17]. A new paradigm for the development and purchase of orphan drugs is needed. There are increasingly strong parallels between the challenges of neglected diseases in developing countries and orphan diseases in developed countries. It may be that policy tools developed for neglected diseases; such as Public Private Partnerships and Advance Market Commitments, can be fruitfully applied in the orphan drug arena [11].

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Chapter 14
Rare Diseases Social Epidemiology: Analysis of Inequalities

Anna Kole and François Faurisson

Abstract Rare disease patients experience particular obstacles in accessing high quality healthcare. These obstacles include but are not limited to: (i) lack of scientific knowledge of their disease, (ii) lack of access to correct diagnosis, (iii) delays in diagnosis, (iv) lack of appropriate multidisciplinary healthcare, (v) lack of quality information and support at the time of diagnosis, (vi) undue social consequences, (vii) inequities and difficulties in access to treatment, rehabilitation and care, (viii) dissatisfaction with and loss of confidence in medical and social services, (ix) denied treatment by health professionals and (x) lack of availability of orphan drugs. Three surveys and their subsequent analysis, conducted by the European Organisation for Rare Diseases (EURORDIS), a non-governmental patient driven alliance of European patient organisations, demonstrate several of these obstacles by describing the experience of rare disease patients across 18 rare diseases and over 24 European countries as well as highlighting inequalities that exist between them.

Keywords Rare disease patients · Diagnostic delay · Access to care · Orphan medicinal products availability

14.1 Introduction to Obstacles Faced by Rare Disease Patients

As documented in the WHO constitution, "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without the distinction of race, religion, political belief, economic or social condition", where health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [15]. In reality, rare disease patients are denied this right and are confronted with similar obstacles in attaining the highest possible standards of health including: (i) lack of scientific knowledge of their

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disease, (ii) lack of access to correct diagnosis, (iii) delays in diagnosis, (iv) lack of appropriate multidisciplinary healthcare, (v) lack of quality information and support at the time of diagnosis, (vi) undue social consequences, (vii) inequities and difficulties in access to treatment, rehabilitation and care, (viii) dissatisfaction with and loss of confidence in medical and social services, (ix) denied treatment by health professionals and (x) lack of availability of orphan drugs [7].

The difficulty in obtaining the correct diagnosis is the first dramatic hurdle for rare disease patients and may take years or even decades to overcome. Late diagnoses delay the beginning of adapted treatments and can have severe, irreversible, debilitating and life-threatening consequences. When seeking diagnosis, patients frequently consult numerous doctors, undergo multiple examinations and often receive various incorrect diagnoses resulting in inefficient and even harmful treatments. Additionally, relatively common symptoms can hide underlying rare diseases, leading to misdiagnosis. The individual consequences of improper diagnosis include the worsening in clinical status [1, 3, 14], psychological damage [12] often related to medical denial of the undiagnosed disease, and in some cases death [11]. In addition, families endure other consequences, including lifelong feelings of guilt due to inappropriate behaviour towards the affected person prior to diagnosis or the possible birth of additional affected siblings [2]. Without a diagnosis, a patient's medical or social needs may not receive due attention and the patient may be considered a complainer who, as a result, progressively looses confidence in medicine [10]. Also, the accumulation of consultations, examinations, tests and inefficient treatments are a major financial burden for both families and society.

Barriers in access to care for rare disease patients include barriers in scientific knowledge, organisations barriers, financial barriers and personal barriers. Lack of publically driven research has resulted in a delay in the establishment of fundamental scientific knowledge needed to establish the causes and mechanisms for the majority of rare diseases thus resulting in underdiagnosis, misdiagnosis, delays in diagnosis and lack of appropriate treatment whether drug therapy or other medical attention. Health professionals' unfamiliarity with rare diseases also leads to a lack of referral to specialised services due to an inability to identify what is appropriate but also a lack of knowledge about what potential services may be need or available. Even if correctly diagnosed, no good clinical practice guidelines exist for the vast majority of rare diseases. Where they do exist, their practice varies from country to country. Additionally, the segmentation of medical specialities is a barrier to the multidisciplinary care of a patient suffering from a rare disease. Services required by rare disease patients are often inadequately available and unadapted due to the fact that they are not covered by their respective health care systems (i.e. psychotherapy, occupational therapy, dental care, optics, nutrition). This is especially true for social services. Social security systems are usually designed around frequent diseases and are not flexible enough to take into consideration unprecedented health needs. This is also true for adjusting reimbursements. The financial costs of caring for rare disease patients are often higher than those for common diseases on which most home healthcare services are based. Having to stop working either as a patient or to take care of an affected family member creates further financial burdens. Physical

barriers to access often affect rare disease patients with physical or mental disabilities. As services are not abundant, patients have to travel far for care or endure long periods of waiting. As a result of the aforementioned difficulties in obtaining correct diagnoses or appropriate care, patients experience frustration with the medical field in general, feeling rejected by their health care providers and eventually losing confidence in the medical system.

As previously highlighted, due to a lack of a single aetiological treatment for most rare diseases their management most often results in a piecemeal approach to the treatment of symptoms. These treatments often include off-label medicinal products for which it is particularly difficult to account for or identify their uses. To address these insufficiencies, the European Commission Regulation on Orphan Medicinal Products [13] was introduced in 1999 to offer incentives for development of drugs unprofitable under normal conditions of marketing given the small number of patients concerned with each treatment. The EU Orphan Drugs Regulation has stimulated research and development of orphan medicinal products in the EU, through centralized authorisation at the European level in which advantages for the development of a drug (e.g. scientific advice) as well as their marketing (e.g. ten-year market exclusivity) are included. The regulation is also intended to improve availability of existing orphan medicinal products in all member states in a timely manner. Despite the introduction of centralized authorisation, equitable and timely access to approved orphan medicinal products for rare diseases patients remains an issue [8]. In addition to investigations by the European Organisation of Rare Diseases (EURORDIS) into such disparities in the availability of orphan medicinal products across Europe, other studies have echoed the reality of strong variation between and even among countries in Europe [5]. These conclusions have again been underlined by the final conclusions and recommendations on Pricing and Reimbursement of the EU High Level Pharmaceutical Forum [6].

To investigate the experience of rare disease patients faced with these obstacles as well as the inequalities that remain amongst patients in the rare disease community, EURORDIS conducted three surveys under its EurordisCare Survey Program. The EurordisCare2 survey (conducted Sept 2003–June 2006), focused on delays in diagnosis and subsequent consequences of such delay and included the participation of 5,980 patients or patient carers (response rate of 33%) representing eight rare diseases and 17 European countries.[1] The EurordisCare3 survey (conducted as part of a larger EURORDIS European Commission-funded project, Rapsody, between May 2006 and April 2008) followed by focussing on issues concerning access to medical and social services with participation from 5,995 respondents

[1] Diseases included: Chron's disease (CD), Cystic fibrosis (CF), Duchene muscular dystrophy (DMD), Ehlers-Danlos syndrome (EDS), Fragile X syndrome (FRX), Marfan syndrome (MFS), Prader-Willi syndrome (PWS), Tuberous sclerosis (TS); Countries included: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Ireland, Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, United Kingdom.

(response rate 30%) representing 17 rare diseases and 22 European countries.[2] EurordisCare2 and EurordisCare3 surveys were distributed to rare disease organisations willing to distribute them to their patient, patient-carer, and family of patient members. Completed surveys were anonymously returned to EURORDIS directly from respondents. Finally, the 4th EURORDIS Survey on Orphan Drug Availability was conducted in 2006 to compile an inventory of the availability and price of orphan drugs receiving market authorisation. This survey represented responses from 28 countries about the availability of 21 orphan medicinal products.[3] The number of available orphan medicinal products, the date of availability of each orphan medicinal product in each country and the price were compiled from the following sources: pharmaceutical companies having obtained market authorisation for their products, the competent national authorities, rare disease patient organisations, and national agencies responsible for drug reimbursement. The findings of these three surveys serve as the basis for conclusions described in this paper.

14.2 Difficulties in Obtaining a Correct Diagnosis

For many rare disease patients, the quest for a correct diagnosis signifies a long and significant challenge. To obtain a correct diagnosis they must consult many specialists, undergo numerous medical exams and often received incorrect diagnoses along the way. This journey is not only troublesome and taxing as patients often travel long distances and used their own savings, but also often lead to deleterious consequences for patients and their families. Overall, patients are left with no choice but to seek answers on their own initiative with little help from healthcare systems in many cases. Even if obtained, diagnoses are often announced under inappropriate circumstances where the gravity of the announcement and the subsequent consequences for the patients and their families were not considered.

14.2.1 The Quest for Diagnosis

When presented with a symptom or set of symptoms, it is logical that a rare disease is not the first proposed cause by a health professional. For the same reason,

[2] Diseases included: Alternating Hemiplegia (AH), Aniridia (ANR), Ataxia (ATX), Chromosome 11 disorders (Ch11), Cystic fibrosis (CF), Ehler-Danlos syndrome (EDS), Epidermolysis bullosa (EB), Fragile X syndrome (FRX), Huntington's disease (HD), Marfan syndrome (MFS), Myasthenia gravis (MG), Osteogenisis imperfect (OI), Prader-Willi syndrome (PWS), Pulmonary arterial hypertension (PAH), Tuberous sclerosis (TS), Williams syndrome (WS); Countries included: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway, Romania, Slovakia, Spain, Sweden, Switzerland, United Kingdom.

[3] Countries included: All MS of the EU as well as Norway, Iceland and Switzerland; OMP included: 21 orphan drugs having been market authorized for at least 6 months prior the start of the study January 1st, 2006.

Table 14.1 Median time elapsed between the first symptoms and a correct diagnosis. Minimum times for reaching a correct diagnoses reported by respondents

Disease	Delay in diagnosis for 50% of patients	Delay in diagnosis for 75% of patients
CF	1.5 months	15 months
TS	4 months	3 years
DMD	12 months	3 years
CD	12 months	5.8 years
PWS	18 months	6.1 years
MFS	18 months	11.1 years
FRX	2.8 years	5.3 years
EDS	14 years	28 years

it is not surprising that the time to diagnose a rare disease may be longer and more difficult than a common one. With each clinical event, the time to reach a diagnosis will depend upon the disease in question and the complexity of diagnostic needs. These delays, difficult enough to accept for individuals with common diseases (let alone healthy individuals) represent only the first obstacle for rare disease patients. The delays in diagnosis for the eight diseases investigated in the EurordisCare2 survey (Table 14.1) varied greatly. A small percentage of respondents experienced very short delays in diagnosis and another small percentage of respondents experienced very long delays. However, the majority of patients within each disease group experienced delays somewhere in between.[4] As a result of this range in delays, the median delays in diagnosis were calculated based on the responses of 50% of the respondents in each disease group as well as for 75% of respondents in each disease group. These results not only illustrate the great differences in delays between disease groups but also between patients with the same disease.

As the aim of this survey was not to criticise the diagnosis process in general, but rather to investigate the consequences and factors associated with longer delays, these aspects are explored in order to help propose solutions that can ultimately lead to an improvement in health and quality of life for rare disease patients.

14.2.1.1 Prenatal and Neonatal Diagnosis

The neonatal and infancy periods are very unique periods and for certain diseases, specific symptoms are only apparent during this time. For all patients, it is a time when contact with healthcare professionals is particularly frequent. As such, this period presents ideal circumstances for diagnosis of a disease. For many

[4]For example, for 50% of respondents affected by CF diagnosis was determined 1.5 months after the first appearance of symptoms. When including the 25% of respondents with CF that experienced the longest delays, the median increased dramatically, to at least 15 months of delay following the first appearance of symptoms (Table 14.1).

Table 14.2 Median time elapsed between the first symptoms and correct diagnosis for all patients and for patients not diagnosed during or before the first 3 months of life

Disease	Delay in diagnosis for 50% of all respondents	Delay in diagnosis for 50% of respondents excluding those diagnosed during neonatal period (% of patients not diagnosed during 1st three months of life)
CF	1.5 months	9 months (63%)
PWS	1.5 year	4 years (66%)
TS	4 months	6 months (90%)
MFS	1.5 year	2 years (92%)
DMD	12 months	16 months (95%)
EDS	14 years	14 years (96%)
FRX	2.8 years	3 years (97%)
CD	12 months	12 months (100%)

rare diseases, neonatal screening represents an undeniable opportunity to minimise diagnostic delays and therefore warrants further investigation (Table 14.2).

Missing such an opportunity to minimise severe and harsh consequences is an unacceptable reality. For certain rare diseases, an early diagnosis is realistic when clinical signs can be observed during pregnancy or just after birth; if a specific diagnostic test exists and is systematically proposed at birth; or in the case of prior family cases. In the EurordisCare2 survey, the relatively high percentages of PW and CF patients diagnosed in the first three years of life could serve as a source of encouragement for other patients. At the same time, although relatively high, these percentages are low considering the consistently observed clinical signs of the disease (ex. hypotonia) in PWS neonates and the existence of reliable genetic tests for CF (systematically provided in France, Belgium and Italy). With correct screening, the number of patients reporting early diagnosis for these diseases could approach 100%. A significant variation in early diagnosis is observed across country groups (Fig. 14.1).

Fig. 14.1 Percentage of respondents obtaining a diagnosis with the first three months of life

14.2.1.2 Initial Misdiagnosis and Inappropriate Treatment

Initially receiving incorrect diagnoses is a common experience for many rare disease patients. Of the total number of survey participants, 41% received at least one such misdiagnosis before obtaining the correct one. The diversity in responses was more apparent among respondents affected by diseases with onset during adulthood: 25% of respondents with MFS compared to 51% of respondents with CD and 56% of respondents with EDS reported receiving an initial misdiagnosis (Fig. 14.2). The trend in responses across country groups showed less frequent reports of misdiagnosis from patients from France, the United Kingdom, Spain, the Netherlands and Finland (Fig. 14.2).

It is only logical that an incorrect diagnosis be followed by inappropriate treatments. These include surgery (Fig. 14.3) and psychological and psychiatric treatment including psychological therapy, psychiatric hospitalisations, and psychiatric medication (Fig. 14.4). Overall, 7% of survey participants reported inappropriate such psychological and psychiatric treatments, though responses varied between disease groups. Across countries, patients also reported varied experiences. More than 15% of Polish respondents reported inappropriate psychological or psychiatric treatment. Finnish, German, Danish and Dutch respondents reported these treatments less than 5% of the time, suggesting that the phenomenon is related to cultural factors in addition to disease-related factors.

Fig. 14.2 Percentage of respondents reporting initial misdiagnosis

Fig. 14.3 Percent of patient reporting surgery as a result of initial misdiagnosis

Fig. 14.4 Psychological and psychiatric treatments in the case of the misdiagnosis of a rare disease between disease and country groups

14.2.1.3 Misdiagnosis and the Quest for Diagnosis

Misdiagnosis of rare disease patients not only leads to inappropriate treatments but may also be followed by the cessation of the quest for another diagnosis. Although, it cannot be concluded that misdiagnosis directly causes the cessation of the quest for another diagnosis, relationships between the type of misdiagnosis and delays in obtaining a correct diagnosis are observed. Patient testimonies strongly suggest that misdiagnosis introduces an additional barrier in obtaining a correct diagnosis. Table 14.3 describes the percent of overall misdiagnoses and the percent of psychological or psychiatric diagnoses for each disease investigated. It also displays the delays in diagnosis reported by survey participants as a function of the type of misdiagnosis they received. Longer delays in diagnosis were experienced by patients who initially received a false psychological or psychiatric diagnosis, suggesting that this type of diagnosis introduced yet an even greater barrier for patients before the quest for correct diagnosis could be resumed.

Table 14.3 Misdiagnoses and delay in diagnosis in relation to the type of misdiagnosis

	Delay in diagnosis for 50% of patients (% of respondents)[a]		
Diseases	Without misdiagnosis	With non-psychological or non-psychiatric misdiagnosis	With psychological or psychiatric misdiagnosis
TS	3 months (62%)	12 months (33%)	3.5 years (5%)
CF	3 months (52%)	12 months (47%)	24 months (1%)
DMD	1 year (69%)	2 years (22%)	3 years (9%)
CD	1 year (49%)	2 years (44%)	6 years (7%)
MFS	1 year (74%)	9.5 years (24%)	14 years (2%)
FRX	2 years (58%)	3.6 years (24%)	4.6 years (18%)
PWS	2.5 years (66%)	5 years (30%)	10 years (4%)
EDS	16 years (44%)	16 years (45%)	22 years (11%)

[a]Patients diagnosed during the prenatal and neonatal periods are excluded from this analysis.

14.2.1.4 Factors Leading to a Correct Diagnosis

In the absence of an ideal system of diagnosing rare diseases, the motivation and personal initiatives of rare disease patients themselves are often the crucial factors in obtaining a correct diagnosis. These initiatives can include the suggestion of the possibility of a rare disease to the diagnosing physician, the location of diagnostic laboratories, the cost of obtaining a diagnosis, and travel to such diagnostic structures outside the patients region or country.

For many patients, arriving at a correct diagnosis requires the passage through a crucial step: the suggestion by either the patient, a member of their family, or a healthcare professional that their disease is not one frequently encountered but possibly a rare disease. Once introduced as a possibility, the arrival at a correct diagnosis is often accelerated. In 18% of cases, patients reported making this suggestion themselves (Fig. 14.5). The sources from which they obtained the possibility of a rare disease varied: their family and friends, media, other patients, the Internet, among others. Even when the possibility of a rare disease is suggested and a specific disease may even be suspected, patients need to be directed to a diagnostic laboratory or centre to perform tests to confirm a diagnosis. Very often, patients reported having to identify these structures themselves (Fig. 14.6).

Fig. 14.5 Percentage of patients who reported introducing the possibility of a rare disease to their healthcare professional

Fig. 14.6 Percentage of patients having reported identifying a diagnostic structure from a non-health professional source

Table 14.4 Delays in diagnosis in relation to raising the possibility of a rare disease and the location of a diagnostic structure provided a health professional or non-health professional source

	Delays in diagnosis for 50% of patients when the possibility of a rare disease was raised by*		Delays in diagnosis for 50% of patients when the diagnostic structure was identified by*	
Disease	A health professional (months)	A non-health professional (months)	A health professional (months)	A non-health professional (months)
TS	6	11	7	4.8
CF	9	17	11	6
CD	12	30	12	32
DMD	15	18	14	24
MFS	24	36	24	51
FRX	31	41	33	41
PWS	48	108	50	57
EDS	156	227	144	240

*Patients diagnosed during the prenatal and neonatal periods are excluded from this analysis.

For almost all the investigated diseases, longer delays in diagnosis were reported if the suggestion of a rare disease or the identification of a diagnostic laboratory or centre came from a non-health professional source (Table 14.4).

Despite the fact that universal access and coverage to healthcare is largely practiced across countries in Europe, some rare disease patients reported that obtaining a diagnosis was only possible with a "high" or "very high" personal financial contribution though this varies across country and disease groups (Fig. 14.7). The final step in reaching a correct diagnosis includes testing at private or public diagnostic structures. The process begins, however, with consultations many health professionals before receiving referral to a diagnostic centre. Each consultation, exploratory, and diagnostic test introduces financial burdens on patients that can create barriers to obtaining a correct diagnosis.

Fig. 14.7 Percentage of patients reporting "high" or "very high" personal financial contribution

14.3 Consequences of Diagnostic Delay

14.3.1 Consequences of Delays in Diagnosis

From a medical perspective, a delay in correct diagnosis is primarily regarded as a cause of delaying appropriate treatment, unnecessarily worsening the disease state. In the day to day lives of patients and their families, however, the same delays in diagnoses can lead to numerous equally deleterious consequences, which include but are not limited to medical consequences: physical consequences, psychological consequences, cognitive consequences, and death; as well as non-medical consequences: birth of another affected child, unadapted family behaviour or loss of confidence in medicine. Patient responses regarding these consequences varied significantly across disease and country groups (Fig. 14.8).

Rarely recognised by the medical community, non-medical consequences were reported by survey participants as frequently as medical ones (Fig. 14.9). When considered by type, these non-medical consequences most often included the unadapted

Fig. 14.8 Cumulative percentage of reported medical consequences of delayed diagnosis. In the EurordisCare3 survey medical consequences were defined as physical, psychological, cognitive, or death. As this percentage represents a summation of all medical consequences of which patient may have experienced several, the total may exceed 100%

Fig. 14.9 Cumulative percentage of reported non-medical consequences of delayed diagnosis. In the EurordisCare3 survey non-medical consequences were defined as birth of another child suffering from the disease, unadapted family behaviour, loss of confidence in medicine. As this percentage represents a summation of all medical consequences of which patient may have experienced several, the total may exceed 100%

Table 14.5 Delays in diagnosis in relation to medical consequences and non-medical consequences

	Delay in diagnosis for 50% of patients (% of respondents)[a]		
Disease	Without misdiagnosis	With medical consequences (physical, psychological, cognitive, death)	With non-medical consequences (birth of another child suffering from the disease, unadapted family behaviour, loss of confidence in medicine)
CF	3.9 months	18 months	18 months
TS	2.7 months	12 months	22 months
DMD	1 year	2.4 years	2.5 years
CD	1 year	2 years	3 years
PWS	2 years	6 years	5.9 years
MFS	1.1 years	4 years	6 years
FRX	1.5 years	4 years	3.3 years
EDS	2.5 years	19 years	20 years

[a]Patients diagnosed during the prenatal and neonatal periods are excluded from this analysis.

behaviour of the patient's family (21%) and loss of confidence in the healthcare system (19%). Unadapted behaviour most often includes the lack of recognition that certain characteristics in the patient are symptoms of their disease and are mirrored in a lack of recognition by physicians. A loss of confidence in the healthcare system (reported by 19% of respondents overall), may steer patients or their families toward alternative, potentially less effective if not harmful forms of treatment.

Respondents reporting non-medical consequences reported the longest delays in diagnosis (Table 14.5).

14.3.2 Confirmatory Diagnosis

The announcement of a rare disease diagnosis marks a significant turning point in the life of a patient and their family. It is understandable, therefore that a patient and their family would seek a confirmatory diagnosis from a second physician or diagnostic structure. It follows that motivation for seeking a second opinion is even stronger for patients or families who initially received misdiagnoses. As patients with EDS frequently reported receiving a misdiagnosis, it is not surprising that the same respondents most frequently reported seeking a confirmatory diagnosis.

The varied distribution of patients having reported seeking a confirmatory diagnosis across country groups suggests that the motivation to seek a second opinion is also culturally determined. Less than 10% Dutch and British respondents reported seeking a confirmatory diagnosis, whereas more than 33% Spanish respondents reported the same action (Fig. 14.10).

Fig. 14.10 Percentage of patients reporting seeking confirmatory diagnosis across disease and country groups

14.4 Access to Medical and Social Services

14.4.1 Outpatient Medical Services

In the absence of a single aetiological treatment for most rare diseases, their management usually involves a piecemeal approach to the treatment of symptoms. In addition, most rare diseases are complex requiring a comprehensive, multidisciplinary approach to their care. The medical services required include specialised medical consultations (e.g. cardiology, neurology), medical exams (e.g. MRI), and additional care services (e.g. dental care, physiotherapy). The extent to which this multidisciplinarity is required varies from patient to patient within a disease group, from disease group to disease group, and varies depending on place of residence, income level, educational level, and gender.

When comparing between disease groups, a greater number of medical services are required by patients with more complex diseases (e.g. Ehler Danlos Syndrome) than by those with less complex diseases (e.g. Fragile X Syndrome) (Fig. 14.11). Within disease groups the number of medical services needed varies

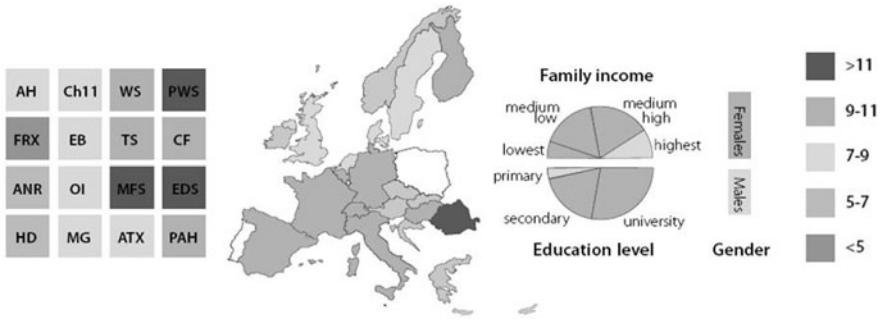

Fig. 14.11 Number of medical services required during the 2-year period preceding the survey

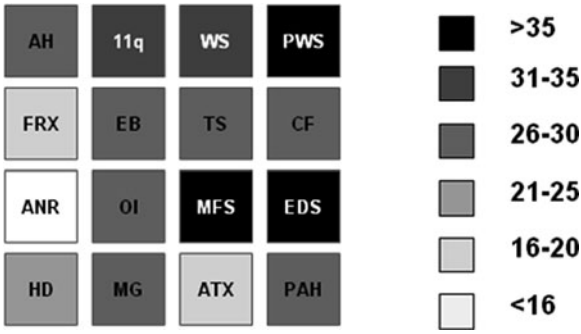

Fig. 14.12 Number of medical services required by at least 10% of patients in each disease group

depending on the severity of the disease with less severe forms or cases (e.g. Epidermolysis Bullosa simplex) requiring fewer medical services than more serious ones (e.g. dystrophic Epidermolysis Bullosa, recessive type). Some respondents of the EurordisCare3 Survey with Epidermolysis Bullosa reported more than 25 required services in the 2-year period preceding the survey (Fig. 14.12). Some variation exists in the need for medical services depending on area of residence, where residents of country capitals seek more services as compared to residents of smaller cities and towns. The differences are restricted to consultations and medical exams, as additional care services are usually provided by local professionals throughout a country. The need for consultation and medical exams decrease with increased levels of income and no significant variation occurs for additional care services. A relationship between need for medical services and educational level has also been observed where the number of services sought is greater amongst patients and families with university level education than those with primary level education. Disparities between men and women are observed with women seeking all three types of medical services more frequently (Fig. 14.11).

14.4.2 Hospitalisations

Rare disease patients may require hospitalisation not only for ambulatory care (acute problems related to the disease), but also for further exploration (radiology, ultrasound, biological testing, etc.), routine check-ups or for specialised care only available in a hospital setting. Hospitalisation is heterogeneous amongst the different rare disease groups. Slight differences were also observed across country groups, with more frequent hospitalisations in Germany, Italy, Hungary and Romania (Fig. 14.13).

Survey participants not only reported on the number of hospitalisations, but also on the total number of days spent in hospital (Fig. 14.14). Patients with Huntington's Disease reported the highest number of days spent in hospital as a result of disease-specific needs that required longer stays. Patients with Pulmonary Arterial Hypertention reported the least number of days spent in hospital as a result

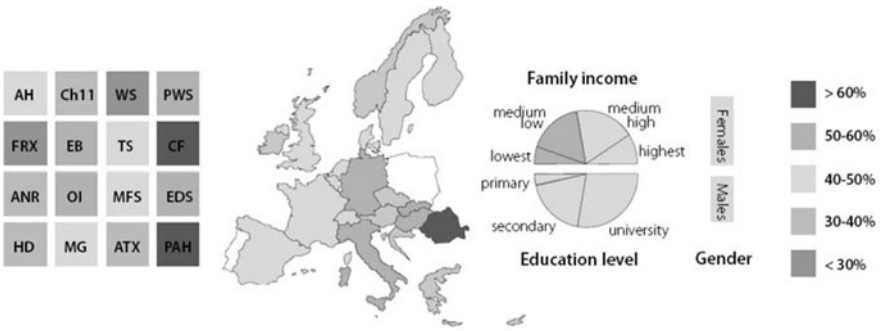

Fig. 14.13 Percentage of patients hospitalised during the two-year period preceding the survey

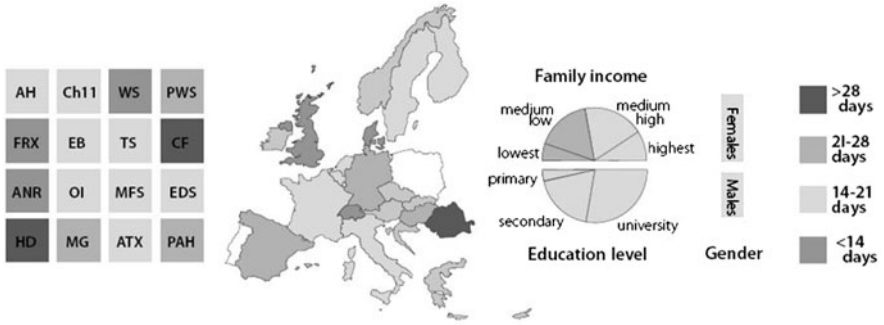

Fig. 14.14 Number of days of hospitalisation during the two year period preceding the survey

of the fact that disease-specific needs required shorter but more frequent hospital visits. Patients from the United Kingdom, Switzerland and Denmark reported the least number of days spent in hospital. Although no general trends were observed across disease or country groups, these data should be considered in policy shaping discussions concerning the organisation of care. For patients with diseases requiring frequent hospital visits, local services would be more appropriate. Some variations in the number of patients requiring hospitalisation and the duration of their stay were observed across demographic groups. A slightly larger percentage of patients from small towns required hospitalisation compared to patients living in large cities and capitals. More respondents from households with lower incomes required hospital stays for a longer period of time than respondents from households with the higher incomes.

14.4.3 Denial of Treatment

Rare disease patients are subject to marginalisation in classic healthcare systems designed for non-rare diseases and confronted with unequal obstacles in attaining

the highest possible standards of health they deserve. Strong anecdotal evidence gathered from patients suggests the frequent denial of treatment of rare disease patients by their healthcare providers such as:

- A Prader-Willi Syndrome patient unwelcome in a general practitioners office because of the inability to accommodate her in the waiting room due to her weight
- A Tuberous Sclerosis patient asked to leave a physician's office because her behaviour made other patients uncomfortable
- A patient with a metabolic disorder diagnosed with tonsillitis was sent home with no treatment due to the reluctance of a ear-nose and throat specialist to prescribe any treatment that may be contradicted

Understanding the dynamics of denial of treatment by healthcare professionals is a controversial subject. Patients' perception of denial of treatment can be viewed as subjective and therefore unreliable by some critics. Among many explanations, acts by healthcare professionals experienced as denial of treatment by patients may be unintentional, a result of prudence with the intention of protecting the patient, a result of the health professionals limited knowledge of the obstacles faced by rare disease patients or a limited capacity of the healthcare structure in accommodating rare disease patients with needs that may differ from others in the practice. Even the investigation of such a phenomenon can elicit controversy amongst all stakeholders. Many healthcare professionals and health authorities are unaware of the problem, or greatly surprised by its scale. The intentions of investigating experiences of denial of treatment by patients is not to criticise healthcare professionals or to justify the legitimacy of feelings of patients, but rather to quantify the magnitude of their existence investigating the reasons for denial of treatment, in order to help adjust the structure and approach in healthcare settings to more appropriately accommodate rare disease patients.

The first and most striking aspect of the denial of treatment experienced by patients is its scale. Overall, one out of five survey respondents of the EurordisCare3 survey (18%) reported being denied treatment by a healthcare professional with a great variation reported across disease and country groups (Fig. 14.15). In general, patients report experiencing denial of treatment either as a result of the disease itself (its complexity) or as a result of characteristics associated with the disease (physical appearance, communication, behaviour). In many cases patients reported experiencing a denial of treatment for several reasons even during the same encounter with a health professional. Overall, the reluctance of health professionals to treat patients is most frequently reported due to the complexity of their disease (in 85% of situations of denial of treatment). Responses across disease and country groups reflected the same trend. However, respondents concerned with diseases including psychological difficulties (Huntington's Disease, Fragile X Syndrome, Williams Syndrome, Prader-Willi Syndrome, 11q chromosome disorders) also report denial of treatment due to personal characteristics associated with the disease such as physical appearance (in 11% of situations of

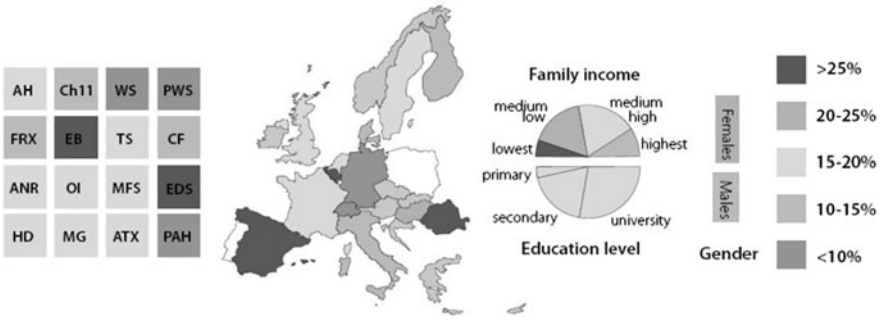

Fig. 14.15 Frequency of situations in which patients were denied treatment by health professional

denial of treatment), disease-related behaviour (in 11% of situations of denial of treatment), and difficulty in communication (in 16% of situations of denial of treatment).

The rate of overall denial of treatment is closely linked to the income level of families where patients and their families with higher incomes report it less frequently than those with low income levels (Fig. 14.15). These differences become more dramatic when investigating the differences across economic groups for reasons of denial of treatment. Denial of treatment of respondents with the lowest income level compared to respondents with the highest income level was reported in twice as many situations due to the complexity of the disease, in three times as many situations due to disease-related behaviour, in four times as many situations due to communication problems and in ten times as many situations due to a physical aspect. Given the direct correlation between income level and level of education, it could be expected that denial of treatment would be more frequently experienced by respondents with a lower level of education than those with a higher level. This trend, however, was only observed in cases of denial of treatment related to the physical appearance of the patient (in 16% of situations for respondents with a primary level of education, 14% of situations for respondents with a secondary level of education and 8% of situations for respondents with a university level of education). In the case of denial of treatment due to the complexity of the disease, however, the opposite trend was observed where patients with higher levels of education more frequently reported being rejected by a health professional (denial of treatment in 13% of situations reported by patients with a primary level of education, 15% of situations reported by patients with a secondary level education and 16% of situations reported by patients with a university level of education). These differences may be explained by the fact that more highly educated respondents were more sensitive to situations of denial of treatment, or that health professionals are more likely to explain the reason of denying treatment to more educated patients. Considering all types of denial, males less frequently reported being denied treatment compared to female respondents (15 and 20% respectively).

14.4.4 Social Services

In addition to the numerous medical services rare disease patients require, social services are at times equally important. Consultation with a social worker can provide the opportunity to seek (i) information on social, legal and financial rights, (ii) assistance with financial paperwork (assistance of financial liability or reimbursement, allowance, etc.), (iii) information on specialised technical support, (iv) assistance with social integration (school, leisure, professional, etc) (v) help in getting personal assistance at home, (vi) referral to other services (psychological support, home care, etc), and (vii) assistance for obtaining exceptional financial support, amongst other assistance.

Nearly one third of respondents to the EurordisCare3 survey reported the need for social services. This need varied dramatically from country to country as well as disease group to disease group (Fig. 14.16). It is important to consider, however, that the decision to seek (or report) social assistance, may not only be influenced by direct needs resulting from the disease, but also the availability of social services and cultural norms regarding social assistance.

Despite a greater need for social services, respondents from lower income groups experience greater barriers to access than those from higher income groups. In addition, respondents from lower income groups more frequently report being "not at all" satisfied with the social services they receive even after overcoming any barriers to access. The limitations in access and satisfaction with social services is illustrated in Fig. 14.17 where, for a given 100 lower income respondents, 34 required social services. Of these 34, only 30 were able to access services. Of the 30 able to access social services 13 were "not at all" satisfied with the services they obtained. In the end, of the 100 respondents 17 were either unable have their initial social service needs met. In contrast, fewer higher income group respondents reported a need for social services, of which a greater number reported being satisfied with the social services they received. Overall, an inadequate organisation of the social service systems seems to exacerbate social inequalities rather than improve them.

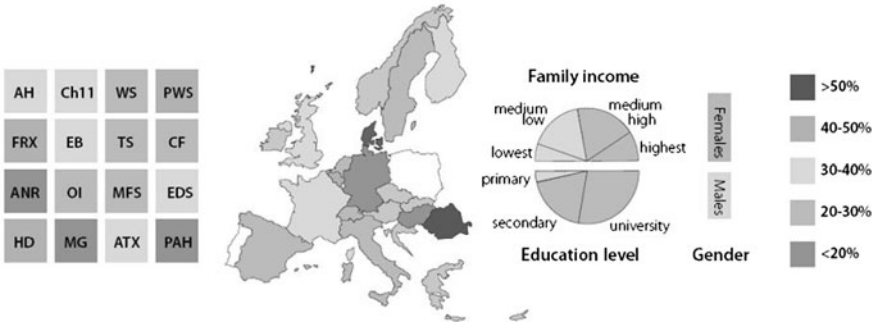

Fig. 14.16 Percent of patients reporting the need to meet a social worker in the 12 months preceding the survey

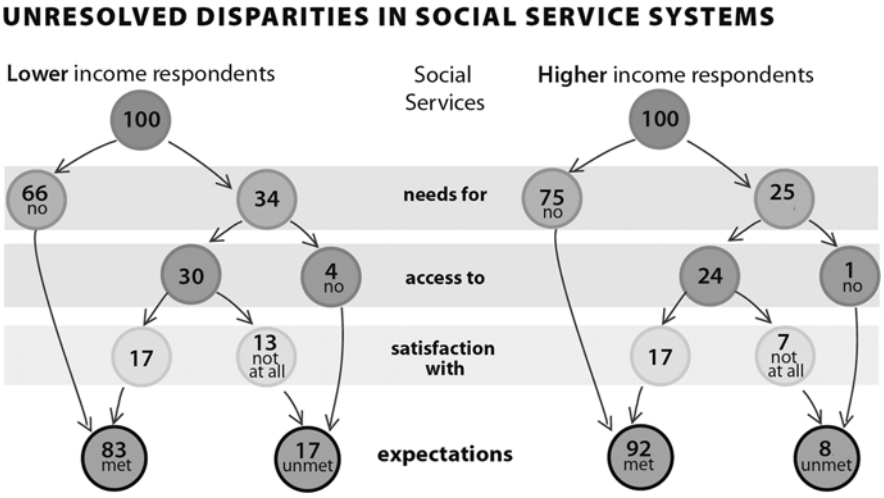

Fig. 14.17 Comparison of needs, access, and satisfaction with social services between lower and higher income groups

14.5 Availability of Orphan Medicinal Products

The provision of orphan medicinal products can be described as a dynamic where increased delays between the market authorisation of a product and its actual availability to patients results in a decrease in the number of orphan medicinal products available at a given point in time. The delays may be due to a reluctance of manufacturers to distribute their products (especially in small countries or those with low national incomes) or a result of resistance on the part of competent authorities in the practical implementation of their distribution (such as a delay in setting a price for technical or financial reasons). Furthermore, some drugs are never made available in some European countries, despite being a violation of the European Commission Regulation on Orphan Medicinal Products.

14.5.1 Access to Information

Despite the multiplicity of sources, the first important observations of the 2006 investigation were the extreme difficulties of obtaining the information sought. For a total of 588 cases (21 orphan medicinal products in 28 countries) only 352 data were able to be documented. Further, the disparity in transparency was not uniform where certain sources were more willing to provide information than others. The countries in which obtaining information from national authorities was most difficult were Cyprus, Estonia, Greece, Spain, Iceland, Lithuania, Norway, Poland, Portugal, Slovakia, and Switzerland. It can be concluded that this lack of transparency is not related to the country's national income (and therefore the means available to control the distribution of drugs) as countries in this group include both those with

Fig. 14.18 Countries in which data on availability of orphan medicinal products for the survey was provided

high (e.g. Switzerland) and low national incomes (i.e. Latvia) at the time of the study (Fig. 14.18).

Barriers in access to information from companies seemed to be related to aspects other than the economic size of the company. Difficulties in obtaining information were experienced more often for chemical (59%) than for biological therapies (25%), for companies located in EU member states (70%) than non-EU member states (33%). Differences in difficulties obtaining information were not great between major (46%) and small or medium sized companies (56%).

14.5.2 Analysis by Country

14.5.2.1 Number of Orphan Medicinal Products

The percentage of orphan medicinal products available during the execution of the 4th Eurordis survey varied significantly (Fig. 14.19). In only four countries across Europe (Finland, France, Germany, and Sweden) nearly all of the existing orphan medicinal products were available at least six months after marketing authorisation. However, in eleven of the investigated countries (Belgium, Cyprus, Greece, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Poland, Portugal, Slovakia) at least 40% of existing orphan medicinal products were not available at the time of the study. Among countries with 60% or less availability of existing orphan medicinal products, most were either small in population or had a low gross national product.

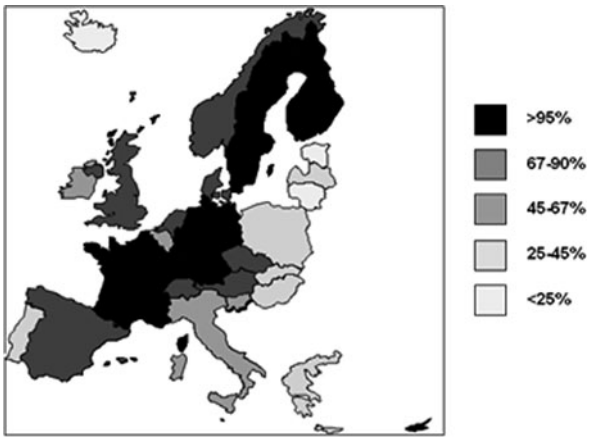

Fig. 14.19 Percent of orphan medicinal products available in Europe

14.5.2.2 Delays in Availability

Delays between the time of marketing authorisation and actual commercial availability present a barrier limiting patient access to treatment. In the 2006 study, it was observed that in Belgium, the Czech Republic, Slovakia, and United Kingdom, the time from marketing authorisation to commercial availability was on average longer by at least one year than in all the European countries investigated overall. Conversely, in Greece and Germany, and to a lesser extent in Austria, Denmark, France, Ireland, Spain and Sweden this time was calculated to be shorter than the average across all investigated countries in Europe (Fig. 14.20).

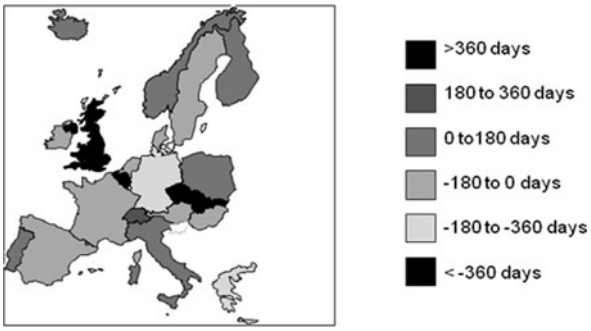

Fig. 14.20 Number of days delay between market authorisation and availability at the national level

14.5.2.3 Price

The ex-factory prices of orphan drugs are very similar from one country to another, differences remain within the range of ±10% in all European countries regardless of significant differences in the gross national product. Variation in user prices

is slightly more significant. The price of orphan medicinal products investigated was highest for users (10% higher than the average in European countries investigated overall) in Italy, the Czech Republic, Norway and Slovakia. The price for users in Spain, the United Kingdom and Hungary was 5% lower than the average in European countries investigated overall. Altogether, these price differences are considered minimal.

14.5.3 Analysis by Orphan Medicinal Product

14.5.3.1 Number of Products

In comparing the availability of orphan medicinal products, it is observed that the number of countries where a given drug is available is extremely variable. In over 90% of countries two products (Wilzin and Pedea) are available. In less than 36% of countries six products (Lysodren, Nevaxar, Revatio, Xyrem, Prialt, and Photobar) are available. Overall there is a relationship between the time from which the market authorisation has been granted and the number of countries where the drug is available: on average, a drug is readily available in six countries and extends its availability to three new countries per year ($N = 5.7 + 0.24$ months, $p < 0.02$, where N is the number of countries in which an orphan medicinal product is available).

By observing the kinetics of availability of orphan medicinal products across Europe, it is observed that that the nature of the product and/or the company that produces it significantly affects its availability (Fig. 14.21). Across Europe, availability of biological products was available in 90% of countries and only 63% for chemical molecules. Depending on the type of pathology concerned, there is also inequality of access: 87% of the investigated countries reported availability of products for metabolic diseases, 73% for cancers and 53% for other diseases. The relationship between the size of the company producing the product and availability is observed as less strong where 76% of investigated countries reported availability of orphan medicinal products produced by small to medium sized enterprises as compared to 66% of products produced by major companies.

14.5.3.2 Delays in Availability

The average time elapsed between the market authorisation of an orphan medicinal product and its availability at the national level is influenced by the type of product and the size of the company that produces it. With a delay of 341 days overall, a delay of 246 days was observed for chemical products as compared to 461 for biological molecules. Differences were also observed depending on the pathology: 445 days of delay were observed for metabolic disease products, 202 days of delay for cancer products, 296 days for products for other diseases. Products developed by SME's were delayed less (278 days) than those developed by major companies (371 days). Finally it is worth noting that delays observed for products developed

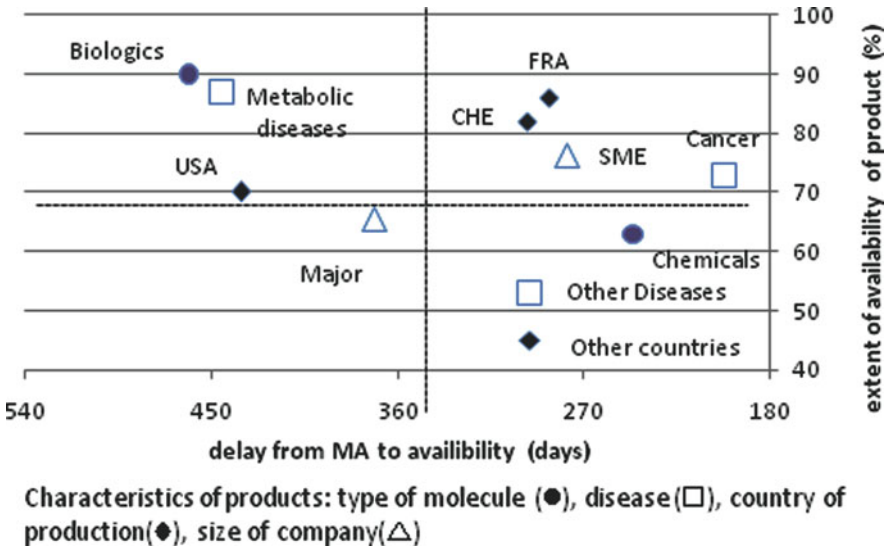

Fig. 14.21 Summary of availaibility of orphan medicinal products according to charachteristics of country of production, size of company of production, disease designation, and type of molecule

by companies in the United States are significantly longer (436 days) than their European counterparts (290 days).

14.5.4 Summary

The situation of the availability of orphan medicinal products (according to the characteristics of country of production, size of company of production, disease designation, type of molecule) that have received market authorisation can be summarised by describing the extent of their distribution and the speed of their availability at the national market level. By calculating the average of i) of the population with access to the medication (69% of European population) and ii) the delay between market authorisations and availability in a country (341 days) one can distinguish four types of categories for the availability of the orphan medicinal products investigated (Fig. 14.21):

1. Products that are both widely available (73–86% of countries investigated) and quickly available (2.5–10 month delay after market authorisation) such as those for cancer, those produced in France or Switzerland, or those produced by SMEs.
2. Products widely available (70–90% of countries investigated) but less quickly available (approximately 15 months delay after market authorisation)
3. Products that are less widely available (45–63% of countries investigated) a rather quickly available (8–10 months delay after market authorisation) such

those for metabolic disorders, in European countries excluding France and Switzerland, and chemical products.
4. Products that are less widely available (in 66% of countries investigated) and less quickly available (12 months delay after market authorisation) such as those produced by large companies.

Biological molecules, those designated for metabolic diseases, and to a lesser extent those produced by companies in the United States are fairly widely available, but have a much longer delay (over 14 months) after market authorisation.

14.6 Conclusions

14.6.1 Eliminating Delays in Diagnosis

It is well established that late diagnoses delay the beginning of adapted treatments leading to severe, irreversible, debilitating and life-threatening consequences. Furthermore, treatments applied in a misdiagnosed disease may be inappropriate, ineffectual or even harmful, further compounding the adverse effects on the health of the patient and further delaying a correct diagnosis.

However, the initial misdiagnoses and delayed eventual diagnoses of patients have even further negative repercussions for the general medical knowledge of a rare disease. Delays in diagnosis and inadequate care create a vicious cycle in the treatment of rare diseases. When patients are diagnosed in late stages of a rare disease, the body of knowledge about the disease fails to include key early symptoms or manifestations. Very frequently, clinical descriptions of rare diseases are based on advanced stages of the disease observed after an absence of intervention. Diagnoses based on these descriptions are consequently and not surprisingly, late. To use the example of PWS, moderate to severe mental retardation can develop, particularly in cases with no treatment. Early diagnosis can provide PWS patients the opportunity to optimise their learning environment and improve cognitive development while their cognitive capacity is still flexible. With repeated documentation, such benefits of early intervention could be included in clinical descriptions, be put into practice, and break the vicious cycle allowing for earlier diagnosis and more robust treatment.

Non-medical consequences resulting from excessive delays in diagnosis such as the birth of another affected child or the inappropriate treatment of an affected child profoundly affect patients, but are seldom if ever taken into account in the implementation of many healthcare policies. In the case of screening policies, many health authorities argue that the availability of diagnosis should only be offered in cases where specific treatment exists. From this survey as well as countless patient testimonies, it is well established that not knowing ones illness is not only a psychologically frustrating and tiring experience, but also one that can lead to inappropriate treatments and other severe and unacceptable consequences. Prior to the publication of these results, these consequences were not well known by policy makers, health

care professionals and other healthcare authorities. The consequences were rarely recorded in medical records as they were considered to fall outside the sphere of the patient's acute medical needs and relevant medical information, and were not considered as relevant medical history. The issue of the right to diagnosis remains a significant debate in the rare disease community. The majority of patients feel they have a right to know their diagnosis, whether treatment for their disease exists or not. Many healthcare professionals feel that it is unethical to announce to a patient, the diagnosis of a disease for which nothing can be done. What is certain is that the continued collection of experience and expectations on this topic (as well as all others related to rare diseases) can only help all stakeholders make informed decisions.

14.6.2 Overcoming Barriers in Access to Medical and Social Services

Rare disease patients are subject to marginalisation in classic healthcare systems designed for non-rare diseases. They are confronted with unequal obstacles in attaining the highest possible standards of health they deserve (as agreed upon in the WHO Constitution [15]. Patients and their families are often forced to educate themselves about rare diseases when the health professionals they consult are not able to. They are often the ones to introduce the possibility that their illness may be a rare disease to their health care professionals. In 18% of cases, patients reported making this suggestion themselves. The sources from which they obtained the possibility of a rare disease varied, including family and friends, media, other patients and the Internet, amongst others. It is often because of this suggestion that the correct diagnosis is finally reached. Even when the possibility of a rare disease is suggested and a specific disease may even be suspected, patients need to be directed to a diagnostic laboratory or centre to perform tests to confirm a diagnosis though, very often, patients also reported having to identify these facilities themselves.

The restructuring of the classic system designed for the management of frequent diseases can be accomplished through the establishment of Centres of Expertise. Although the specific functions and implementation of Centres of Expertise may differ from country to country or disease group to disease group, the concentration of expertise in a place where the (i) management of the disease is multidisciplinary and coordinated, (ii) accurate diagnosis can be provided, (iii) access to social assistance can be facilitated, iv) research and knowledge about the disease can be shared on the national and European levels, and (v) patients can feel welcome, safe and included in decisions related to their disease management and evaluation, can help rare disease patients attain the "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [15], to which they are entitled.

It may be surprising, however, that rare disease patients' perception of the quality of their lives is linked more to the quality of care provided, than to the gravity of the illness, or the degree of the associated disabilities. Overall, respondents of this survey emphasised the importance of the quality of services they expected in a

Centre of Expertise rather than quantity of services available. Patients did not frequently report the expectations that Centres of Expertise be highly technical centres of knowledge. They did not emphasise the importance of the need for Centres of Expertise to follow a high threshold of patients to maintain the skills and experience of its professionals, nor the need that they monitor patient needs through surveys or patient registries. More frequently, survey participants emphasised the importance of improving the way in which existent care and therapy was provided through better coordination and communication between professionals within the Centers of Expertise, with professionals in other Centers of Expertise, and local professionals (such as the patients general practitioner, social workers, caregivers).

Given these priorities expressed by survey participants, it follows that Centers of Expertise should not focus on a disease, but rather on the patients with the disease. This is not so much a question of changing the care that is given but rather the frame of mind in which it is given. When considering the patient as a whole not just their disease, the need for integration of social services and medical services in a single facility becomes very obvious.

Prescription of a treatment is only helpful if it is correctly adhered to. Such adherence is often associated with transportation to a distant care facility, significant costs, accompaniment by another person; each taking time away from work. Not all rare disease patients have the necessary support systems at hand to correctly adhere to their treatment and may, rightly so, require social assistance to meet these needs. It is especially for this reason that social services should be accessible in the same care facilities as medical services and offered in parallel, systematically to all who need them. The integration of such services in Centres of Expertise and making their availability transparent should eliminate disparities across socioeconomic groups rather than reinforcing them as is currently the case. Patients should not have to be more educated or have a higher income to better navigate social services or have them more frequently offered.

14.6.3 Improving Availability of Orphan Medicinal Products

A good medication for rare disease patients is a medication that is both available in the country where they live and affordable. If one of these two factors is missing, the drug is of little use. Despite obvious limitations in the 4th EURORDIS Survey on the Availability of Orphan Medicinal Products such as a lack of complete responses from participants, the survey findings strongly suggest this unfortunate situation for rare disease patients is unfortunately a reality in some Member States and for certain market authorized orphan medicinal products. Several areas of concern have been highlighted:

- The reluctance of various stakeholders to provide the information sought
- The heterogeneity in availability of orphan medicinal products across Europe
- Longer delays in countries with smaller populations and lower gross national products

- Unexpected longer delays in countries with higher gross national products such as Belgium and Ireland

Several factors have been identified as contributing to lack of universal availability of orphan medicinal products with market authorisation in Europe. Orphan drug designation, protocol assistance and marketing authorisation are centralised processes, but therapeutic value assessment, pricing and reimbursement for these innovative products remain the Member states' responsibility. Due to the lack of a centralised source of information and therefore a lack of transparency of information on each market authorised orphan medicinal product in each country, it is impossible to conclude where the responsibilities of delays in access lie. Companies are not financially motivated to provide products in countries with small populations or low gross national products. Smaller enterprises may also not have the resources to apply for registration of their drug according to a different procedure for each country. Many times, national authorities do not have the expertise to conduct an adequate therapeutic value assessment or may postpone negotiations to delay the required reimbursement of a product once it has been made available. Such negotiations could promote favourable conditions for both parties. In reality, many companies begin negotiations with countries that grant a higher price (then used as a reference price in further negotiations) and hesitant member states end up paying higher prices. Reluctant companies lose years of their market exclusivity when negotiations take months or even years.

EURORDIS has been denouncing this situation since its first survey on orphan drug availability [8], as mentioned in the Commission's report on five years of the Orphan Drug Legislation [4]. To improve patient access to orphan drugs, interested parties have identified the creation at the EMEA of a Working Party for the assessment of the clinical added value of Orphan Drugs as being a key instrument for an increased collaboration between Member States and EU-level authorities [9]. The objective of the collaboration is to facilitate the national pricing and reimbursement decisions in order to minimise delays to access orphan medicinal products for rare disease patients, while fully respecting national competences to make their pricing and reimbursement decisions within their respective healthcare and economic environment. The success of this newly proposed collaboration will depend on carefully, precisely and realistically defined role, mandate and composition of the Working Party. The link between the Working Party and the EU Member States needs to be explicitly stated. It has to be ensured that any newly created process does not interfere with the normal regulatory approval process as this might create additional delays in access to innovative therapies for patients, which would result in the exact opposite of the desired intent.

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Chapter 15
Quality of Life and Rare Diseases

Luis Rajmil, Lilisbeth Perestelo-Pérez, and Michael Herdman

Abstract HRQOL assessment in patients with rare diseases can help to identify health needs, to evaluate the impact of disease and treatments, and to assess the evolution in health status through the natural history of disease. Several studies have shown that although some rare diseases do not necessarily affect life expectancy, the majority lead to physical, emotional and/or psychosocial limitations with a wide range of disabilities. Reliability as well as content, criterion, and construct validity, and also responsiveness should be taken into account in selecting the instrument to be used assessing individuals with rare diseases. The use of proxy-report may be essential in some cases where the patient is cognitively impaired or unable to communicate. Criteria for selecting a HRQOL instrument, as well as the more common strategies proposed help interpret scores on HRQOL instruments are addressed in the chapter. Given the impact of rare diseases on the quality of life of both patients and carers, it is likely that interest in its measurement will continue to increase among professionals, patients, and the general public. Improving the quality of life of people with rare diseases should be one of the most important goals of any health care intervention or multidisciplinary approach.

Keywords Children · Health-related quality of life · Rare disease · Reliability · Validity

15.1 Introduction

In recent decades, the increased prevalence of chronic disease and the need for ever more sensitive, patient-oriented outcomes measures has led to a growing emphasis

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on the development and use of reliable self-rated measures of health and well-being [26]. "Patient reported outcomes" (PROs) are now commonly used in many areas of clinical research and are even making inroads into clinical practice. They have been found to be useful in many areas of research including studies of treatment effectiveness, comparisons of alternative interventions for the same condition, monitoring changes in health status over time, predicting relevant clinical events, or describing population health.

Patient-reported outcomes have been defined as the "direct subjective assessment by the patient of elements of their health including: symptoms function, well-being, health-related quality of life (HRQOL), perceptions about treatment, satisfaction with care received, and satisfaction with professional communication" [56]. In such measures, the patient is required to "summarize his or her evaluation of the disease, treatment, or health-care system interactions through various modes, providing perceptions related to the condition, its impact, and its functional implications" [56].

Patient reported outcomes can therefore range from relatively simple measures of, for example, pain intensity, to measures of much more complex constructs such as quality of life (QOL). Instruments measuring QOL or, more specifically, health-related quality of life (HRQOL) are some of the most widely used PROs and there has been an exponential rise in their development in recent years. Although earlier definitions of HRQOL were arguably quite limited and tended to address patient satisfaction with activities of daily living and functional status [17], the construct has been refined and broadened over time into a multidimensional concept covering the physical, psychological, and social domains of health. The aim of modern instruments, then, is to assess the way these domains are influenced by illness and its treatment while taking into account a person's experiences, beliefs, expectations, and perceptions [60].

Though there is increasing consensus around the definition of HRQOL, within the overarching idea of measuring disease and its treatment in terms of its impact on physical, psychological, and social health [71] the measurement approach can vary substantially, from the use of single index instruments to multidimensional profile measures. Likewise, the concepts included in such measures can range from negatively valued aspects of life, including death, to the more positively valued aspects such as role function or happiness [43].

15.1.1 Basic Concepts and Measurement Issues

In the development of any PRO instrument, it is important to first define what the instrument is intended to measure. As mentioned earlier, the target concept can range from a complex construct such as health-related quality of life, to specific symptoms such as pain or fatigue, or concepts such as satisfaction with care or with treatment. Carefully specifying the target construct will help to guide the development process. For example, measurement of more complex constructs such HRQOL or satisfaction with care may require numerous items distributed over several domains all of which will need to be tested for reliability, validity and,

potentially, sensitivity to change. Although an apparently less complex concept, scales to measure fatigue can also vary in complexity depending on whether, for example, the aim is to measure simply the intensity of fatigue or a broader concept encompassing not only the intensity of fatigue, but also its impact on daily activities and well-being.

Once the concept to be measured has been defined it is necessary when developing or selecting an instrument to specify both the target population and the setting and type of study it will be used in. For instance, instrument characteristics are likely to vary considerably both in content and format depending on whether they are intended for use in adults or children. Recent development of a child version of the EQ-5D, for example, indicated the need for a change in wording in the emotional well-being dimension from "I am extremely anxious or depressed" to "I am very unhappy, sad or worried". In other cases and conditions, such as stroke or dementia, proxy instruments (instruments completed by caregivers) may be essential, and special care may be required in instruments intended for the very elderly.

The setting and type of studies the instrument will be used in will also influence content and format. For example, an instrument designed to be used in clinical practice will usually have to be relatively brief, as well as being easy to complete and to score. It may, then, be necessary to sacrifice some degree of reliability and precision for the sake of brevity (in general, multi-item scales tend to be more reliable and precise than single item scales). On the other hand, instruments to be used in clinical research can potentially be longer which could, given an adequate development process, help to ensure a higher degree of precision and reliability. A further issue is whether the instrument will be used primarily in cross-sectional, survey-type settings or longitudinal studies, where they will be required to capture changes in patients' health status or to assess the impact of a health care intervention. The items that would be included in a measure for inclusion in longitudinal, evaluative studies, where responsiveness is of prime importance, may be very different to those that would be included in a measure intended for use in cross-sectional studies or population surveys.

Apart from these issues, instrument developers and users also need to consider practical issues such as the type of response options and the instrument's time frame (the present, the past week, the past month, etc), again bearing in mind the nature of the target population and particular study objectives. For example, younger children may have difficulty discriminating over a scale using 7 response options and may be more comfortable with pictorial response options such as smileys. Instrument developers also need to provide evidence of scale variability, including missing values, score distributions, and ceiling and floor effects, among others as well as investigating the instrument's psychometric properties as described in Section 15.4 of this chapter. Finally, both users and developers should be aware of current guidelines regarding development and use of PRO measures. For example, whilst instrument content may be derived from a range of sources, for example literature reviews or clinical experts, it is increasingly recognized that members of the target population should be involved in instrument development through focus groups

or in-depth interviews. Indeed, current recommendations from some regulatory agencies place considerable emphasis on this aspect as a requirement for achieving content validity [62].

15.2 HRQOL in Rare Diseases

It is clear that many rare diseases have an extraordinary impact on many or all of the domains making up HRQOL instruments, though the relative impact on the different domains is obviously disease dependent. Many of these diseases involve substantial disabilities, implying a considerable burden not only for the patient but also for carers and the health care system. HRQOL in individuals with rare diseases, and their caregivers, may depend on disease progression, premorbid characteristics (e.g., personality or demographics), or idiosyncratic effects (e.g., life event unrelated to the disease). Furthermore, effects may differ for patients and caregivers; physical decline may impact the caregiver more than the patient [37, 54], specific domains of HRQOL may be differentially affected by the disease and treatment. For example, whereas the domains of Physical Functioning, Role Physical, and Social Functioning may deteriorate with disease progression, Mental Health and Role Emotional domains may be largely unaffected [13].

Comparisons with levels of HRQOL in the general population have shown diverging results [13, 18]. Some studies have shown a deteriorating physical health but stable mental health [13]. Likewise, monitoring of patients with neurodegenerative diseases over time has shown how passage of time did not affect QOL in patients, but total HRQOL and particularly HRQOL related to physical symptoms declined over time in caregivers [36, 37, 40, 54]. Other studies have demonstrated the potentially positive effect of treatment in some cases [4, 22].

In rare diseases, HRQOL measures have been used primarily in clinical trials, though also in observational studies [4, 18, 36, 37, 54]. Although several studies have indicated that some rare diseases do not necessarily affect life expectancy, use of disease-specific instruments have shown that the majority lead to physical, emotional and/or psychosocial limitations with a wide range of disabilities. Consequently, HRQOL assessment in patients with rare diseases can help to identify health needs, to evaluate the impact of disease and treatments, and to assess the evolution in health status through the natural history of disease.

15.3 Generic and Diseases – Specific HRQOL Instruments

In rare diseases as in other areas of research, two basic approaches to HRQOL measurement may be used in research and practice: generic instruments and disease specific instruments [28, 36, 37, 39]. Generic instruments measure HRQOL domains which are universally important across diseases and are multi-item problem lists that are meant to be independent of sex, age and disease and which can be

applied in different populations or diseases. These may also be useful in predicting health outcome by considering several direct effects and mediators [25, 44]. Among the generic HRQOL measures, there is a distinction between health profiles and preference-based measures. Health profiles assess different domains of HRQOL resulting in scores for each of these domains (i.e., "physical function", "emotional function", "mental health") though some health profiles also provide a composite (or index) score. Preference-based measures are especially designed for use in health economics studies and provide a single index score which usually ranges between 0 and 1 and which is based on empirically measured preference weights [12].

Disease specific instruments measure the impact of disease and treatment on domains which are of particular relevance in a given condition. They may be more sensitive in detecting treatment effects or changes in patients' health status over time than generic measures. They tend to be multi-item inventories derived from interviews with patients with the condition and / or clinical experts in the condition. A common approach in many studies of HRQOL is to combine a generic and a disease-specific instrument to optimize the ability to detect important HRQOL changes and to avoid missing unexpected effects [18, 25, 44]. Including a generic measure also allows for comparisons with results from studies in patients with different conditions if the same instrument is used.

15.4 Psychometric Properties of HRQOL Instruments

The results of studies using PROs may be used to guide clinical decisions and to develop care plans. The quality of the information provided by outcome measures depends, in part, on the psychometric properties of those measures. Before using an HRQOL instrument, it must undergo psychometric assessment of reliability, validity, and responsiveness [15, 23].

Reliability is the consistency of the results delivered by a test. Reliability is an assessment of the measurement error of scores or correlations among items or subscores [15]. There are four general classes of reliability estimates*: internal consistency* is a measure of the similarity of an individual's responses across items within a test, indicating the homogeneity of a scale. Internal consistency coefficients can take values from 0 to 1 with higher values representing higher levels of internal consistency. *Inter-rater or inter-observer* reliability is used to assess the degree to which different raters give consistent estimates of the same phenomenon. *Test–retest* reliability is a measure of response stability over time. It is assessed by administering an instrument to patients or individuals at two separate time points and then evaluating the two scores for consistency. It is usually performed in patients or individuals in which clinical or health status is expected to remain relatively stable. *Parallel-forms* reliability is used to assess the consistency of the results of two tests constructed in the same way from the same content domain. In general, the statistic used to quantify the *internal consistency*, or unidimensionality of a scale is the Cronbach's coefficient alpha, and the Intraclass correlation (ICC) is used to

measure *inter-rater* reliability for two or more raters. It is also now the most widely used method for assessing *test–retest* reliability.

Reliability is a necessary but not sufficient characteristic of a HRQOL measure. An outcome measure can produce consistent findings and still not provide the required information. Validity refers to whether a questionnaire measures what it is intended to measure. Three types of validity are usually evaluated in scales and instruments: content validity, criterion validity, and construct validity. Content validity is the degree to which a test includes all the items necessary to represent the concept being measured. An approach to assessing the content validity of an instrument is to select a panel of judges based on their expertise in a given research area, and then use them to conduct and independent "confirmatory content validation". However, it is a descriptive approach and has limited ability to test alternative hypotheses about the structure of an instrument systematically. Confirmatory factor analysis (CFA), in contrast, provides a more precise estimate of the degree to which necessary aspects of a construct are well represented within a particular measure. CFA can be used to assess the instrument's structural validity, which is a specific form of content validity that assesses whether the conceptual components hypothesized to make up an instrument actually underlie people's responses to the instrument.

Criterion validity is a more quantitative approach to assessing the performance of scales and instruments and is the degree to which an instrument can be used to predict a relevant, external outcome. The validity of an outcome measure is tested by comparing the results of the outcome measure or target test to a gold standard or criterion test. If the target test measures what it is intended to measure, then its results should agree with the results of the gold standard criterion test. There are two different types of criterion validity: *concurrent validity* and *predictive validity*. Concurrent validity is achieved when the criterion measures are obtained at the same time as the test scores. Predictive validity occurs when the criterion measures are obtained at a time after the test.

Construct validity reflects the ability of a test to measure the underlying concept of interest to the clinician or researcher. Construct validity is a comparison of the new index score and a reference score (i.e., convergent validity) or a construct of what the new index is measuring (i.e., discriminant validity), such as a prediction that patients with more severe disease will have poorer HRQOL scores (construct validity) [24, 44]. Convergent validity is demonstrated when scores on the test being examined are highly correlated to scores on a test thought to measure similar or related concepts and discriminant validity is demonstrated when scores on the test being examined are not correlated to scores on a test meant to measure a very different construct. Known groups validity is another form of construct validation in which the validity is assessed by determining the degree to which an instrument can demonstrate different scores for groups known to vary on the variables being measured.

Responsiveness is the ability to reflect important clinical changes. Two types of responsiveness have been identified [31]. Internal responsiveness is defined as the

ability of a measure to change during a pre-specified time frame. Internal responsiveness is often examined by administering a measure before and after a treatment of known efficacy. External responsiveness reflects the extent to which changes in a measure relate to changes in other measures of health status.

15.5 Special Populations

15.5.1 Children and Adolescents

A systematic review of the literature on available instruments of HRQOL for children and adolescents found 96 published instruments, 30 generic and 66 specifics measures [57, 58]. This review highlighted the rapid development in HRQOL measurement in children and adolescents. In particular, the number of disease-specific instruments available was noted to have grown exponentially in recent years.

Table 15.1 shows selected generic and disease-specific instruments which are potentially useful in assessing HRQOL in children and adolescents with rare diseases. Among generic instruments, the Child Health and Illness Profile (CHIP) [59] was one of the first to be published and children with rare diseases, such as cystic fibrosis, were involved in its development and validation. Another widely used instrument in young people is the PedsQL, for which several disease-specific modules are available, including asthma, rheumatology, diabetes, cancer, cardiac conditions, and cognitive functioning. Finally, the KIDSCREEN instrument is interesting as it is one of few available instruments to be developed cross-culturally by taking into account the views and opinions of parents and children in several countries in its development. It is designed for use in the general population of children 8–18 years-old and has been used to assess HRQOL in children with cerebral palsy and to compare the HRQOL of this group with a representative general population sample of children of the same age [16, 19]. Interestingly, the authors found that children with cerebral palsy had similar QOL to children in the general population in all 10 of the KIDSCREEN domains except, possibly, schooling and physical wellbeing. Based on those results, they concluded that most children aged 8–12 years with cerebral palsy will have similar QOL to other children and that the findings should orientate social and educational policy towards full participation of disabled children in society. On a methodological note, they also found that 39% of the sample could not self-report because of severe intellectual impairment.

As regards disease-specific instruments for children with rare diseases, relatively few are available if we take into account the large number of such diseases. For the (generic and disease-specific) instruments which are available, furthermore, there is little available evidence of their sensitivity to change in these populations. Consequently, studies to evaluate treatment effects are also scarce so that the vast majority of studies into HRQOL in rare diseases have been cross-sectional and descriptive.

Table 15.1 Description of selected generic and disease-specific health-related quality of life instruments for use in children with rare diseases

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
Generic							
Child health and illness profile (CHIP) [52, 53, 59]	US	1993–2004	12–18	Adolescent Edition	183 (6)	Satisfaction, comfort, resilience, risks, achievement, disorders	R (2); V (2); S (1). http://www.chip.jhu.edu/
			6–11	Child Edition child report form	45 (5)		
			6–11	Child Edition parent report form	76–45 (5)		
KIDSCREEN [49, 50, 55]	13 European countries	2006	8–18	Child, parent	52 (10), 27 (5),10 (index)	Physical well being, psychological well being, moods and emotions, autonomy, self perception, parents and home life, peer relationships, school environment, social acceptance, financial resources	R (2); V (2); S (1). http://www.kidscreen.org

Table 15.1 (continued)

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
PEDSQL [65, 66]	US	1999–2001	5–18	Child	23 (4)	Physical functioning, Emotional functioning, Social functioning, School functioning	R (2); V (2); S (1). http://www.pedsql.org/about_pedsql.html
			2–18	Parent			
Disease-specific							
Disabkids [2, 7, 46]	Austria France Germany Greece Netherlands United Kingdom	2005	4–16	Child, parent	6, 12, 37 (6)	Medication, limitation, emotion, independence, social inclusion, social exclusion	R (2); V (2); S (0). http://kidscreen.diehauptstadt.de/disabkids/master/index.html
Cerebral palsy							
CP Qol Child [69]	UK	2007	A: 9–12	A: Child	A: 52 (4)	A: Physical, social, and emotional well-being, acceptance by others	R (2); V (1); S (0). http://www.deakin.edu.au/hmnbs/chase/cerebral-palsy/downloads/cp_qol_manual_final.pdf

Table 15.1 (continued)

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
			B: 4–12	B: Parent	B: 66 (6)	B: Physical, social, and emotional well-being, acceptance by others, access to services, primary caregiver health	
Congenital cardiac diseases							
ConQol [38]	UK	2006	A: 8–11	Child	A: 31 (3)	A: Symptoms, ability to do activities, relationship w/others	R (1); V (1); S (0). http://www.cardiacrehabilitation.org.uk/conqol.htm
			B: 12–16		B: 39 (4)	B: Symptoms, ability to do activities, relationship w/others, control and coping	

Table 15.1 (continued)

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
Cystic fibrosis0							
CFQ [29, 30]	France	1996	A: >14 B and C: 8–13	A: Adolescent and adult B and C: Child and parent	A: 33 (9) B and C: 44 (7)	A: Physical functioning, emotions, social limitations, energy/well-being, treatment burden, embarrassment, body image, role, eating disturbances	R (2); V (2); S (1). http://www.atsqol.org/sections/instruments/ae/pages/cfq-cfq-r.html
Bleeding disorders							
Hemo-QOL [8, 9, 47]	France Germany Italy Netherlands Spain UK		A: 4–7 B: 8–12 C: 13–16	Child and parent	A: 21 (10) B: 64 (10) C: 77 (10)	Physical health, feelings, attitude, family, friends, other people, sports and school, coping, treatment, future, relationship	R (1); V (1); S (0), except for version A where no data is available. http://www.haemoqol.de
ITP [3, 33]	Canada	2003, 2007	A: ? B: 1–17	A: Child	26 (5 child, 6 parent)	A: treatment side effects, intervention, disease, activity, family	R (2); V (1); S (1). http://www.flintbox.com/technology.asp?page=3979

Table 15.1 (continued)

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
				B: Parent		B: concerns related to diagnosis, treatment/disease monitoring, child's activity, interference with daily life, disease outcomes, emotional impacts	
Digestive disorders							
Children with Crohn's disease quest. [48]	UK	1996	A: 8–12 B: 12–17	Child	88 (6)	Disease and treatment, family, social, emotional, education, future	R (0); V (0); S (0).
IMPACT [41, 45]	Canada	2002, 2008	9–18	Child	33 (4)	General well-being and symptoms, emotional functioning, social interactions, and body image	R (0); V (2); S (0). http://www.proqolid.org/instruments/impact_iii_impact_iii

Table 15.1 (continued)

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
Neuromuscular disorders							
Neuromuscular disorder (LSIA) [51]	Canada	1994	12–19	Child	35 (5)	General well being, interpersonal relationships, personal development, personal fulfillment, leisure/recreation	R (1); V (1); S (0) http://www.proqolid.org/instruments/life_satisfaction_index_for_adolescents_lsia
Spine deformities							
BrQ [67]	Greece	2006	9–18	Child	34 (8)	General health, physical functioning, self-esteem and aesthetics, vitality, school activity, bodily pain, social functioning	R (1); V (1); S (1) http://www.proqolid.org/instruments/brace_questionnaire_brq
QLPSD [10]	Spain	1995	10–20	Child and parent	21 (5)	Physical functioning, sleep disturbances, body image, back flexibility, back pain	R (2); V (1); S (0)

Table 15.1 (continued)

Measure (acronym)	Country of origin	Year of publication	Age range	Version(s) and respondent(s)	No items (dimensions)	Dimensions	Psychometric properties*. Web site information when available
QOL in Spina bifida Q [42]	Canada	1997	5–20	Child and parent	44/47 (10)	Social, emotional, intellectual, financial, medical, independence, environmental, physical, recreational, vocational	R (2); V (1); S (0)
SQLI [20]	US	2005	10–18	Child	5 (5)	Physical activity performance, back pain, self-esteem, moods and feelings, satisfaction with management	R (2); V (1); S (0)

* R: reliability; V: validity; S: sensitivity to change. Reliability, validity and sensitivity to change were scored (0) when no results were available and/or were negative; (1) when the results were satisfactory in at least one aspect of the analyzed property and (2) when almost all of possible aspects were satisfactorily measured according to international recommendation on PRO's measurement.

Examples of such studies include assessments of HRQOL in children with diseases such as skeletal dysplasias [1], cystinosis [63], or galatosemia [5]. All these studies analyzed a relatively small number of individuals (n= 19, 9 and 75, respectively), and administered generic questionnaires such as the 17D or the TACQOL. All of them indicated significant impairment in psychosocial adjustment, family living conditions, and intellectual and motor performance, indicating the considerable impact of such disorders on HRQOL, although to different extent depending on the disease. In summary, the study of HRQOL in children with rare diseases is a promising area for future research and will undoubtedly be helpful in gaining a more precise and systematic understanding of how these diseases and their treatment affect important aspects of children's lives.

15.5.2 Patients Cognitively Impaired or Unable to Communicate

Another aspect of HRQOL research in rare disease which may be very relevant is the use of proxy measures, i.e. measures completed on behalf of a patient by a caregiver or health professional who knows the patient well. This approach may be helpful when it can be anticipated that patients may become too ill to complete a questionnaire or to respond to an interviewer in longitudinal studies [62], in individuals or groups with mild to severe cognitive impairment, or in very young children who are unable to answer a questionnaire themselves. Rare diseases where this approach might be necessary for example include Rett syndrome, Pick disease or some acquired or degenerative brain injury [68]. Although such an approach clearly contradicts the PRO "philosophy" of relying on self-report, it may be essential in some cases and makes it crucial to assess wherever possible correlations between proxy and self-report. One example would be that of the study in cerebral palsy mentioned above, where almost 40% of the sample were unable to self-report.

15.6 Selecting a HRQOL Instrument

When selecting a HRQOL instrument, it is important to consider whether the questionnaire fits the study objectives, whether, for example, the dimensions covered are relevant, and whether the questionnaire is available for the age group and country of interest. Clearly, only instruments with demonstrated reliability and validity should be used, and if the aim is to evaluate the effectiveness of an intervention, or monitor the evolution of health status over time, then the instrument should have demonstrated sensitivity to change.

It will often be advisable to use both a generic and a disease-specific instrument, or to use a questionnaire which integrates both generic and disease-specific modules.

In longitudinal studies, the number and frequency of assessments to detect changes on HRQOL will depend on the natural history of the disease, and also on characteristics of the instrument used to assess HRQOL. Figure 15.1 represents

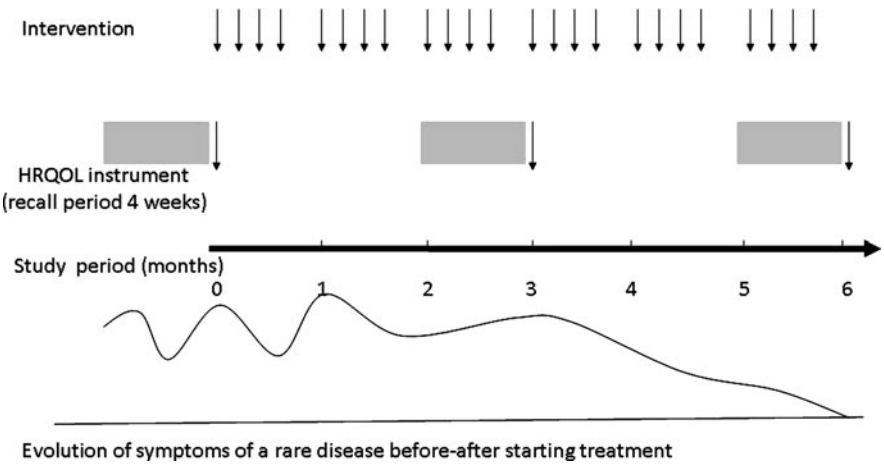

Fig. 15.1 Hypothetical example of an intervention study using HRQOL as the outcome measure

a hypothetical example of evaluating treatment of rare disease using repeated measures of HRQOL. It should bear in mind that sometimes several measures will be necessary along the study given that the recall period of the instrument could be longer than changes on symptoms or effects of treatment on patient's well-being until a clear improvement is achieved.

15.7 Interpreting Scores on HRQOL Measures

One of the main challenges in using HRQOL as an endpoint is how to interpret the results, and to translate these results into conclusions and recommendations. Clinicians, policymakers, and health professionals responsible for making recommendations based on results obtained with HRQOL measures need to understand the meaning of scores and score changes and be able to weigh the benefits of a given treatment against its adverse effects [27].

Several strategies have been proposed help interpret scores on HRQOL instruments, based either on changes in scores before and after treatment or between groups in a cross-sectional analysis [6]. For example, distribution-based approaches may use the difference between scores before and after treatment, while taking into account score distributions, to estimate the effect size or magnitude of change. Effect sizes are conventionally interpreted as no change (<0.2), small change (0.2–0.5), moderate changes (0.51–0.8) and large changes (>0.8) [11].

In anchor-based approaches the change observed in the HRQOL measure is assessed in relation to an independent standard that is easy interpretable. This "anchor" may be some external criteria such as a shift between categories on a well-known clinical classification, for example an index of severity of heart disease. Alternatively, an internal anchor can be used. Patients might, for example, be asked

to report the degree of change on the parameter of interest (for example changes in the frequency of dyspnea) using a scale from very much worse to very much improved. Changes on the HRQOL measure can then be correlated to changes on the global rating scale.

The key issue using either strategy is to establish the magnitude of change that determines the minimal important difference (MID), that is the "smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in a patient's management" [32]. Although they have some limitations, these approaches have proven useful in interpreting and translating scores from HRQOL measures into meaningful results.

An illustrative example on the comparison of different approaches was published by Kulkarni [35]. They administered the Hydrocephalus Outcome Questionnaire (HOQ) [34], a 51-item questionnaire covering 3 health domains (Physical, Social-emotional, and Cognitive) and which provides a global score from 0 (worse health) to 1 (the best possible health), to mothers of children with hydrocephalus. Mothers and physicians also completed a global rating scale of the child's impairment (in six categories, from severely impaired to not at all impaired). The authors determined that the HOQ's MID using the distribution approach was 0.03 points (for an ES = 0.2) compared to 0.10 points using the anchor-based approach. The latter was the difference in mean HOQ scores between children rated as "Not at all impaired" versus those classified as "Very mildly impaired".

A complementary and/or alternative to the distribution-based approach is to compare scores for the population of interest to those of the general population or other reference group. This can only usually be done when a generic measure of HRQOL is used, however. In the case of the hydrocephalus study, Health Utility Index (HUI-2) [21, 61] scores were also collected from the mothers, making it possible to compare scores in those children with those of children included in other studies using the same instrument. In the hydrocephalus sample, the mean utility score was 0.77 which compares to 0.85 for pediatric survivors of Hodgkin disease [64].

15.8 Challenges and Limitations to Measuring HRQOL in Rare Diseases

Although some rare diseases have received a relatively large amount of attention in terms of QOL measurement, with several HRQOL instruments available to assess HRQOL in multiple sclerosis or cerebral palsy patients for example, disease-specific instruments are still lacking for most rare diseases. Although generic instruments can be used when disease-specific instruments are not available, the former nevertheless have a higher degree of content validity (i.e. they are more relevant for the population they aim at) and tend to show better known-groups validity as well as being more sensitive to changes in health status. There is thus a strong argument for developing disease-specific instruments where these are not available. One obstacle

to developing new instruments may be the lack of sufficient numbers of patients for the various stages of instrument developing and testing. The involvement of patient activist groups and associations and government bodies and/or simultaneous development of measures in several countries could help to overcome this limitation.

A further challenge in this context is to assess how caring for children and/or adults with a rare disease impacts on the HRQOL of the carers. The high levels of disability associated with many rare diseases means that carers' HRQOL can be considerably affected, though relatively few studies have been performed in this area to date. Examples include that of a study which compared the HRQOL impact of caring for children with hemophilia, type I diabetes or juvenile idiopathic arthritis. The authors found that parents of children with hemophilia experienced less impact on their quality of life and lower psychosocial strains than parents of children with type I diabetes or juvenile idiopathic arthritis, though they also reported a need for more information on managing the condition [70]. A Swedish study which used generic HRQOL instruments to analyze the effect of an intervention addressed to increase family competence in children with rare diseases found high levels of parental stress, and physical and emotional strain among mothers, especially single mothers [14].

15.9 Final Remarks

Although in the last decade substantial progress has been made in the development, use, and interpretation of HRQOL measures in rare diseases, there is still an enormous amount of work left to do. The development of sound, valid and reliable instruments in those areas that have not as yet received attention, and efforts to improve the interpretation and clinical application of the instruments are required. Given the impact of rare diseases on the quality of life of both patients and carers, and the importance of quality of life as a clinical outcome, it is likely that interest in its measurement will continue to increase among professionals, patients, and the general public. Ultimately, of course, this interest stems from the fact that improving the quality of life of people with rare diseases should and will be one of the most important goals of any health care intervention or multidisciplinary approach.

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Chapter 16
Cost of Illness and Economic Evaluation in Rare Diseases

Julio López-Bastida and Juan Oliva-Moreno

Abstract Rare diseases are a major cause of morbidity and mortality in high income countries and have major repercussions on individuals and health care systems. This chapter examines the health economy of rare diseases from two different perspectives: firstly, the study of the economic impact of rare diseases (Cost of Illness studies); and, secondly, cost-effectiveness evaluation, which evaluates both the costs and results of the health care technologies applied in rare diseases. From the point of view of economics, health resource allocation is based on the principle of scarcity, as there are not – and never will be- sufficient resources for all worthy objectives. Hence, policy makers should balance costs and health outcomes. Rare diseases may well represent a significant societal burden that should rightly receive appropriate prioritisation of health care resources. As new and seemingly expensive health care technologies are developed for rare diseases, it will become increasingly important to evaluate potential and real impact of these new technologies in both dimensions: social costs and health outcomes.

Keywords Rare diseases · Health care technologies · Health economics · Costs of illness · Economic evaluation

16.1 Introduction

Continuously rising health care costs have been a cause of growing concern among governments since the 1970s. Some reasons for this increase are the ageing population, the care given to terminally ill patients, and the increase in chronic diseases

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coupled with the continuous care that these require. Pressure from demands for more services made by society and health care workers also plays a part, as does variability in clinical practice, which leads to inappropriate use of health resources.

Nevertheless, a substantial part of health care costs is considered to be caused by the proliferation of new technologies. Accordingly, it is not enough for these health care technologies to be safe and highly specific: the main questions to be addressed are whether they result in better health outcomes and for which patients they are useful.

If it is agreed that implementation of new technologies is to be deemed the main cause of the rising cost of health care [7, 13], then the factors that determine the use of such technologies can never be routine but rather the balance between clinical efficacy and cost-effectiveness [1].

Rare diseases are a major cause of morbidity and mortality in western countries and have major repercussions on individuals and health care systems [10, 11]. These burdens and economic impacts must be calculated in order to appraise the problems of health care and indicate how to allocate human, health and material resources and thus reduce the undesirable effects which these rare diseases have on patients, health care systems, and society in general.

From the point of view of economics, health resource allocation is based on the principle of scarcity, as there are not – and never will be- sufficient resources for all worthy objectives. Hence, choices must continuously be made as regards where to increase spending. To this end, and to be able to judge what health benefits such additional spending yields, economic analysts use the concept of opportunity cost, which is the value of resources in terms of their most favourable alternative use. In the context of health technology, opportunity cost would be applied by evaluating the benefits generated by implementing one type of intervention instead of another, and the repercussions that this would have in terms of health. Given the demands on health resources, the only principle to follow is to compare costs and choose what will afford the maximum benefit to the health of the population.

Methods of economic evaluation of health technology have been developed and improved over the last 10 years [5, 8]. While it is true that this evaluation is not perfectly adjusted to the requirements for making clinical or management decisions, it does provide valuable information for deciding which technology should be financed or which one affords better patient care. Choosing involves contrasting and comparing alternatives, and economic evaluation rationalises this choice, thereby rendering resource allocation more efficient.

This chapter examines the health economy of rare diseases from two different angles, namely: the first is cost of illness, which does not analyse results; and the second is cost-effectiveness, which evaluates both the costs and results of the technologies applied in rare diseases. In many cases the term “pharmacoeconomics” is used as a synonym when the economic evaluation of drugs is involved.

16.2 Cost of Illness

Cost-of-illness studies furnish information that is relevant *per se* and, moreover, represent a preliminary phase or first approximation to a full economic evaluation. The cost of an illness in any given period can be interpreted as the benefit obtained by society if the disease does not exist or has previously been eradicated by means of a preventive program. Studies into the cost of illness seek to emphasise the negative effects of disease on welfare, by quantifying this though a monetary valuation.

Rare diseases have a series of negative effects on the well-being of those who suffer them and on society, including effects on the use of health care and other resources, indirect effects on productivity through changes in health status, and, finally, effects on health, such as a reduction in quality of life (anxiety, incapacity, pain, etc.) and/or premature death (years of life lost).

Thus, calculating the cost of illness is essential for appraising the magnitude of a particular health problem, and for allocating health care, human and material resources directed at reducing the undesirable effects that rare diseases have on patients, the health care system and the society that maintains it [15].

A distinction must be drawn among different types of costs. Firstly, direct medical costs are the value of the resources used in the treatment of patients, and so correspond to the use of the health care system's resources, including costs of inpatient care (general hospitals, day hospitals and emergency-room care), outpatient care (specialists and primary care consultations) and drugs.

Secondly, direct non-medical costs are those that correspond to informal and formal (non-health) care. Both cases involve support activities provided to persons with limited autonomy, i.e., people with problems in basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Consequently, formal and informal care comprise a diverse range of activities, such as: feeding, dressing/undressing, grooming, helping to walk through the house, helping to move (disability); changing diapers for incontinence of urine or stool; helping to get into/out of bed; helping with bathing/showering; helping to use toilets/bathroom in time; helping with the shopping, preparing meals, doing other chores; helping to take medication; helping to use the phone; helping to go out/move down the street or use public transport; managing money; and helping to take steps, go to the doctor, tie or buckle shoes. The difference between formal care (whether publicly or privately funded) and informal care is that the latter is provided by people who usually belong to the emotional environment of the person with limited autonomy and do not charge for it, or at least are paid, not for providing such care as an occupation, but rather for providing it unselfishly. While informal care usually takes place within the household of the person with disability, formal care can be given at the person's home (home-care provider, meals and laundry services, telecare) or elsewhere (day centres, homes).

Thirdly, loss of productivity (so called indirect costs) consists of the decrease or loss in productivity due to early death and/or sick leave (temporary and permanent disability) attributable to a certain illness.

Obviously, welfare losses caused by diseases are not exclusively restricted to the three cost items identified. There is a fourth type known as "intangible costs", which are those related to the pain and suffering caused by the disease. In rare diseases, intangible costs may be substantial and will be measured by comparing patients' health-related quality-of-life scores to those of an age- and gender-matched sample of the general population. A widely used instrument to assess health-related quality of life is the EQ-5D questionnaire [2]. Summary scores (utilities) are calculated from the answers and are anchored between 0 (death) and 1 (perfect health). The difference in quality-of-life scores of patients and the general population can thus be used to calculate the loss of quality-adjusted life years (QALYs), by multiplying life years by their quality weight [16]. By assigning a social value (or social willingness to pay) to a QALY, the intangible costs of rare diseases can be estimated.

Studies conducted to estimate the cost of illness are important because they help: (a) define the dimensions of the disease in monetary terms; (b) justify and assess intervention programs; (c) allocate research resources; (d) provide a baseline for planning policy in relation to prevention and new initiatives; and (e) furnish an economic framework for evaluation programmes.

In theory, direct costs (health care and non-health care costs) and labour productivity costs are quantifiable. Health care and formal costs can be calculated from the public and private resources invested, provided that the retrospective information – including data collected prospectively- is accurate and precise. The unit cost of these resources should reflect the opportunity cost of their use. In practice, it is usual for these to be valued at market price (where there is such a market) or book value, or on the basis of publicly agreed or set rates and prices. Informal care is more complex to assess, though in practice there are several techniques, such as the opportunity- and replacement-cost methods and contingent valuation for estimating social value [14, 17]. Finally, in the case of job losses, usually computed on the basis of wages lost during the period of incapacity (temporary or permanent) as an approximation to lost productivity, their calculation requires accurate and precise information on incapacity (permanent and temporary) and rates of premature death.

Moreover, direct costs which are incurred by the patients and their families (caregivers) and are not health-related should be included in the estimates of the costs of an illness. Examples of these are extra costs and time involved in the care of, say, patients with degenerative cerebellar ataxia or amyotrophic lateral sclerosis [10, 11].

When a cost-of-illness study solely considers health care costs, other costs that are relevant from a social stance remain invisible. Lopez Bastida et al. estimated that in Spain the mean annual cost per patient with degenerative cerebellar ataxia was €18,776 (€26,789 and €9,962 for patients in the high- and low-severity groups respectively). For patients in the high-severity category, direct medical costs accounted for 11%, direct non-medical costs accounted for 59% and labour productivity costs accounted for 30% of the total cost. The most important cost

categories were informal care, followed by early retirement (permanent disability), medications and orthopaedic devices [10].

For amyotrophic lateral sclerosis, Lopez Bastida et al., estimated that in Spain the mean annual cost per patient was €36,194 (€42,728 and €17,000 for patients in the high- and low-severity groups respectively). For patients in the high-severity category, direct medical costs accounted for 21%, direct non-medical costs accounted for 60% and labour productivity costs accounted for 19% of the total cost. The most important cost categories were informal care, followed by health care costs (medications and orthopaedic devices) and early retirement (permanent disability) [11].

It is true to say that resources should be allocated, not according to the impact of a certain disease, but rather according to where intervention yields the greatest health benefit. Cost-of-illness studies frequently enable the real dimension of a health problem to be seen, furnishing valuable information in this respect for society and society's policy makers. However, this information can be complementary to epidemiological data on the morbidity, mortality and disability caused by a given disease. In this respect, cost of illness is just one indicator of the consequences of an illness, expressed in monetary terms. As Knapp pointed out, "These often substantial non-health care costs are not decorative embellishments in obscure academic studies. Nor are they the chartings of obsessional researcher intent on costing anything and everything. They are real burdens on resources which have to be carried by some individual or some part of society". He went on to say, "However . . . cost-of-illness calculations merely describe what is, not what we should do about it, let alone providing guidance to decision-makers on how to get the best out of their limited resources" [9].

16.3 Economic Evaluation

Economic evaluation aims at determining which technology is efficient, i.e., which produces better health outcomes according to the resources invested, once the costs, risks and benefits of the programmes, services or treatments have been properly identified, measured and compared. On the basis of this definition, and in contrast to what might be supposed, economic evaluation not only considers the cost of comparative technologies, but also tries to relate these costs to their effects (benefits/outcomes): in other words, efficiency of alternatives is analyzed. Thus, within an overall appraisal of technology, clinical evaluation based on efficacy/effectiveness and safety can be distinguished from economic evaluation based on efficiency, in which costs as well as effectiveness are calculated.

In a global context, initial efforts by Australia and Canada have found support in a number of European countries, which similarly acknowledge that information obtained from economic evaluations is a useful tool for allocating available health resources coherently. Although health care technology assessment agencies have been operating in Europe since the 1990s, it was the experience of the National

Institute for Health and Clinical Excellence (NICE) that marked a turning point in the role and influence of these agencies in the decision-making process. European health-policy makers are responsible for ensuring that advances in medical technology which improve quality of life and life expectancy are made available to patients, and for investing in measures aimed at prevention. There can be little doubt, however, that such improvements usually require an increase in spending, and the indiscriminate adoption of these measures would pose a serious risk to the health system. Debate and cultural changes centred around the creation of NICE and the work it has carried out since its inception have undoubtedly contributed to a new perception of the responsibilities of health technology assessment agencies, and underscore the potential benefits of their recommendations.

In addition, the recent growing interest in economic evaluation of health technology is reflected by its increasing appearance in medical journal articles. For these reasons, it is essential to become familiar with the methodology, apply it appropriately, and use and interpret the terminology correctly. Some authors have proposed guidelines for conducting economic evaluation studies, insisting on the need for readers, researchers, and journal editors to apply the principles systematically [4].

There are several types of economic evaluation techniques [5, 8].

16.3.1 Cost Minimisation

This type of analysis is used to compare interventions of identical clinical effectiveness and safety. Each option's cost is compared and the most economical is then chosen. Evidence must be shown of the equivalence in health outcomes of the options compared. This type of analysis is the simplest to apply but is also the one calling for the most caution.

16.3.2 Cost-Effectiveness Analysis

In this analysis the health benefits of the treatment options compared are measured in the same units. The results of these analyses are expressed in terms of costs, measured in certain units, and effects, measured in physical or natural units (e.g., lives saved, life years gained, days of pain prevented, etc.). This is undoubtedly the most common type of analysis in the current literature. The main drawback is that its use is limited to the comparison of similar interventions (or technologies), the health benefits of which are measured in the same clinical units. The analysis involves calculating the increases in costs and effectiveness (incremental cost-effectiveness ratio), and evaluating whether the extra benefit offsets the additional cost.

16.3.3 Cost-Utility Analysis

This analysis is used to measure the effects of an intervention using units which combine quantity and quality of life, by calculating the life years gained through

an intervention and weighing up the quality of life achieved. The units obtained are quality-adjusted life years (QALYs) gained. This allows for a much more advanced analysis of effects than do cost-effectiveness studies because indices which take into account subjective aspects, such as patients' quality of life, are included [16]. The main advantage lies in being able to compare different types of interventions or health care programmes and integrate the patients' quantity and quality of life.

16.3.4 Cost-Benefit Analysis

In this kind of analysis, the costs of both the treatment options and the effects of such options are measured in monetary units. Results are expressed as cost-benefit coefficients or the net difference between cost and benefit. This type of analysis is the most orthodox from an economic standpoint. The main advantage lies in being able to compare several options, the results of which would be expressed in different terms in any other type of analysis. The main drawback, however, resides in the difficulty of measuring health in monetary terms and the ethical problems to which this gives rise.

Drummond et al., make the point that, historically, patients with rare diseases have been underserved by commercial drug development. In several jurisdictions, specific legislation has been enacted to encourage the development of drugs for rare diseases (orphan drugs), which would otherwise not be commercially viable [6]. McCabe et al., contend that the cost-effectiveness of orphan drugs should be treated in the same way as for other technologies [12]. Yet, owing to the small market, these drugs are often very expensive. In this regard, Drummond et al., argue that, under standard health technology assessment methods which incorporate economic evaluation, orphan drugs do not usually prove to be cost-effective, and this, coupled with their high cost, means that funding and patient access may be limited. Nevertheless, these restrictions may not be in line with societal preferences [6].

16.4 Establishing Priorities

Cost-of-illness assessment cannot be used to establish priorities, as these can only be set after careful evaluation of the costs, benefits and all the technological options to be compared. Given that public health service budgets are limited, not all technologies can be financed. Priority must thus be given to those which generate the greatest improvement in health per unit cost incurred, in comparison with other options for the care of rare diseases and other technologies in all health care fields. Over the last few years, economic evaluation of health technologies has become a major tool used by health policy decision-makers to create strategies for prioritising allocation of health resources and approval of new technologies. This exercise calls for data, not merely on cost, but on both cost and effectiveness, i.e., to establish priorities in this way, economic evaluation techniques such as cost-effectiveness, cost-benefit and cost-utility are needed rather than cost of illness alone.

Economic analysis is most used in health service decision-making. Politicians, managers, clinics, drug companies, nursing staff and others are increasingly obliged to examine the evidence concerning the cost and effectiveness of technologies, in order to decide which of these should be recommended and to include such information in clinical practice guidelines and therapeutic protocols. Bearing these possibilities in mind, rapid advances are thus needed in the validation of economic evaluation methods. Those who remain aloof from the type of economic analysis that has been developing over the last few years will find themselves at a considerable disadvantage in the near future.

16.5 Conclusions

Analyses of the economic costs of many types of illness have been used to assist a variety of national and local health policy decisions. The economic burden of rare diseases has not been extensively studied, however, because of the difficulty of finding sufficient data and because the cost impact of any single rare disease on society is thought to be small. Nevertheless, rare diseases often have a chronic, intensive pattern of health care use, with extended periods of morbidity and early mortality [10,11]. Viewed collectively, rare diseases may well represent a significant societal burden that should rightly receive appropriate prioritisation of health care resources. As new and seemingly expensive technologies are developed for rare diseases, it will become increasingly important for both the cost of such diseases and the potential impact of these new technologies to be ascertained.

The resources available to meet the demands of any given society are always limited, making it necessary to decide on the best way of allocating them. Although cost-of-illness studies have a more limited role in decision-making than do economic evaluation studies, they provide information for mathematical models on the relative consequences of different rare diseases and, in addition, show the economic impact of a certain illness. Such input can be invaluable when managers have to make decisions and do not have information on the potential treatments and their cost.

Health policy makers are responsible for ensuring that advances in medical technology which improve quality of life and life expectancy are made available to patients, and for investing in measures aimed at prevention. There is little doubt, however, that such improvements usually require an increase in spending, and indiscriminate adoption of these measures would pose a serious risk to the public health system (affordability).

Within Europe, numerous countries have witnessed the growing use of economic evaluation as a common tool in the health care policy decision-making process. The formulae are varied, ranging from the creation of information units for centralised decision-making on the public funding and price setting of drugs on the one hand, to local information centres on the other, and also include agencies that draw up guides and recommendations on the adoption and use of health technologies. Secondly, and

partly as a result of the previous considerations, a change in health care culture has been underway for years and is beginning to take hold on the main actors. This change takes into account the fact that the resources used in a certain situation are relevant because their use reflects an inherent opportunity cost, in the form of the best alternative which is forgone. This cost may be clearly visible (the time that a health care professional devotes to each patient's visit) or somewhat less visible (the taxes from which public health system funding is obtained). At all events, health care professionals should accept the idea that paying exorbitant amounts for insignificant therapeutic benefits is unacceptable.

Nonetheless, the inflation generated by the introduction of new technologies and the replacement of old by ever newer technologies have made economic evaluation crucial for making decisions in a world where the most modern tools must be paid for. Moreover, the use of economic evaluation greatly increases the degree of transparency in the decision-making process [3].

Economic evaluation of rare diseases is essential in order to provide a baseline that ensures that patients are treated with efficiency and equity.

The greater presence of economic studies in health care should be aimed at encouraging the adoption of decisions and actions based on cost and effectiveness, thereby reducing the arbitrary prioritisation that currently underlies the financing of health care programmes.

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Part V
Epidemiology of Group of Rare Diseases

Chapter 17
The Burden of Rare Cancers in Europe

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Abstract The burden of rare tumors in Europe is still unknown and no generally accepted definition of them exist. The Surveillance of Rare Cancers in Europe project (funded by the European Commission) aimed at providing a definition of "rare cancer", a list of cancers and rare cancer burden indicators, based on population-based cancer registry data, across Europe. An international consensus group agreed that incidence is the most appropriate indicator for measuring rare cancers frequency and set the threshold for rarity at 6/100,000/year. The list of rare cancers was based on the International Classification of Diseases for Oncology (ICD-O 3rd edition) and it was hierarchically structured in 2 layers based on various combinations of ICD-O morphology and topography codes: layer (1) families of tumors (relevant for the health care organisation) and layer (2) tumors clinically meaningful (relevant for clinical decision making and research). The burden indicators were estimated and are provided in this chapter.

Keywords Rare tumor · Population based cancer registry · Incidence · Prevalence · Survival

17.1 Introduction

According to the European Union (EU) definition, cancers are classified in the group of rare diseases when their prevalence in the general population is less than 50 out of 100,000 persons [4]. Patients with rare cancers are faced with the same challenges as other patients living with a rare disease just because their condition is rare. Rare cancers are often misunderstood, misdiagnosed, or poorly investigated, and there are usually few treatment options [17].

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Rare cancers are a challenge to clinical practice. Delay in diagnosis and suboptimal treatment outcomes are common for rare cancers due to a lack of knowledge among physicians and pathologists, a limited expertise in the management of rare cancers (also because of the limited number of cases), a poor referral rates from general practitioners and pathologic misdiagnosis. Outcomes for rare cancers could be improved through the establishment of reference networks however, few networks or centers of expertise exist across the EU and funding is not available to cover the increased costs associated with the organization of these networks [6].

Exchange of experience, information and data on rare cancers is low. Information about rare cancers, their treatment options and where to obtain appropriate treatment is in many cases not readily available to patients.

Clinical studies are more difficult to conduct in rare cancers due to the low number of patients. This makes it difficult to demonstrate the effectiveness of different therapeutic options and build a comprehensive evidence-base for practice. For many rare cancers, research is confined to case reports or small retrospective series, for which substantial selection bias occurs and total experience is commonly too limited for any firm conclusions on management to be made. Therefore, medicines have to be often used off label.

Population-based survival study [10] reports large variations in survival over time and across Europe, with poorer outcome among older patients and in eastern European countries.

In spite of these problems, substantial advances in the treatment of some rare cancers have occurred in the recent past. Childhood lymphatic leukaemia was practically invariably fatal until the years 1970s, while nowadays has a cure proportion of 80% or more [8]. For adult cancers, gastrointestinal stromal sarcomas have increased their survival rate from 30 to 75% [16]; anal squamous-cell carcinoma have improved outcome in the 1980s thanks to the introduction of fluorouracil and radiotherapy in the protocol of treatment [15].

Since the EU Orphan Drug Regulation [5] entered into force, 20 of the 46 medical products that have been designated as orphan drugs have received marketing authorisation for a rare cancer indication [6].

These results are due to international efforts aimed at strengthening scientific excellence in research and treatment, promoting incentives for research and development of orphan drugs, clinical trials and collaboration in the field of rare cancers.

The European LeukemiaNet (http://www.leukemia-net.org) and the Scandinavian Sarcoma Group (http://www.ssg-org.net/), are good examples of the benefits of such efforts and networks in the field of rare tumors. The LeukemiaNet integrates the leading leukemia trial groups (CML, AML, ALL, CLL, MDS, CMPD), their interdisciplinary partners (diagnostics, treatment research, registry, guidelines), industry and Small and Medium Enterprises (SME) across Europe to form a cooperative network for advancements in leukemia related research and health care. It cares for some ten thousand patients. The Scandinavian Sarcoma Group (SSG) was formed in 1979 by physicians and scientists from the Scandinavian countries with a primary interest in tumors of connective tissues. The goal of the SSG is to advance the care

of patients with sarcoma and to increase knowledge of all aspects of the biology of these tumors, including basic and clinical research. The SSG has developed treatment protocols for different sarcoma types and participates in international clinical trials.

These networks, as many others, provide good examples of what works for rare cancers:

1. integration of local, national and European centres of expertise into European reference networks in order to provide the necessary *organisational structures for clinical research*, *early transfer of research data into clinical practice* and *clinical management of rare cancers*;
2. exchange of experience, information, data and best practices;
3. development of consensus guidelines on multi-disciplinary treatment;
4. engagement of all stakeholders including representatives of patients.

In this context, to start addressing rare cancers challenges, it is essential to have a clear picture of which are the rare tumors as well as to have information on their frequency and outcome figures. Considering that the burden of rare tumors in Europe is still unknown and no generally accepted definition of them exist, the aims of this chapter are:

1. to provide a definition and a list of rare tumors;
2. to estimate the indicators of rare tumors in Europe: incidence, prevalence, survival. Estimates will be provided for rare malignant tumors diagnosed during the period 1995–2002.

17.2 Criterion for Defining Rare Tumors

According to the official EU definition, rare tumors are identified in the same way as rare diseases, i.e. as those conditions whose prevalence is lower than 50/100,000.

However, prevalence has shortcomings as a measure for rarity for tumors, although we acknowledge its appropriateness for non-neoplastic diseases. Many of these are chronic conditions, so prevalence, which reflects the total number of cases at any given time in a population truly renders the burden that a disease poses at a population level. On the contrary, tumors are subacute diseases in which everything tends to happen once. In the natural history of a tumor, there will be one potentially eradicating surgery, one local radiation therapy, one first chemotherapy and each of these will take place in a definite time intervals. Thus, the total amount of resources that tumors mobilize are proportional to the yearly rate of new diagnoses (incidence) and not to the total amount of persons with previous cancer diagnosis (prevalence), some of them been cured. Incidence, which reflects the yearly number of new cases occurring in a population might thus be a better indicator to describe the burden posed by a tumor.

The prevalence of a disease depends on two time-dependent characteristics which are independent of one another: incidence and survival. With the prevalence threshold adopted as a definition, some commonly-occurring diseases for which the survival is very poor, such as most cancers of stomach, pancreas, lung will be defined as rare since the proportion of the general population who are survivors is very low. By contrast, some neoplasms that occur very infrequently ("rare" in the sense of incidence) but which have very good survival, such as cancer of testis, will be defined as common on the basis of prevalence, because although they occur infrequently, most people who develop the disease survive for long periods.

For these reasons, incidence seems to be a more useful indicator to select a threshold for rarity in the case of tumors, as opposed to non-neoplastic diseases. In addition it is worth stressing that:

- the incidence of tumors tends to change in a more predictable manner than prevalence and it is more closely connected to the cause of the diseases;
- the incidence is a direct measure of the burden imposed by the need for the first line cancer treatment;
- the number of patients amenable to enter a clinical study is reflected by cancer incidence.

It should be clear, however, that the conventional definition of rare diseases has regulatory implications, including those on orphan drugs. In addition, evolution of therapies may well affect the definition of rare cancers in the future. For example, if oncologists will manage to deliver anticancer therapies in a chronic way, overcoming the currently limiting factor of tumor resistance, prevalence would become a much more useful indicator of frequency. At the moment, this is not the case, although an evolution towards more chronic anti-cancer therapies is in place. Thus, in this chapter, we will consider incidence as the frequency indicator of tumors' rarity.

17.3 List of Rare Cancers

Usually, cancer statistics are provided for broad cancer categories, based on the anatomic site of the malignancies as defined by the International Classification of Diseases (ICD) codes. Rare tumor entities, because of their specific problems related to the health care organisation and to the clinical management, might be more appropriately defined as a combination of topographical and morphological characteristics, as defined by the International Classification of Diseases for Oncology (ICD-O) [13].

The ICD-O list of tumor entities have a pathologic basis however, to have a clinical meaning the tumor entities have to be grouped. This grouping exercise, necessary to identify a list of clinically relevant rare tumor entities, was carried out in the framework of the EU funded project Surveillance of Rare Cancers in

Europe (RARECARE) by an international group of experts, including oncologists (European Society for Medical Oncology – http://www.esmo.org/), epidemiologists, pathologists and organizations of patients (European Cancer Patient Coalition – http://www.ecpc-online.org/). The group had the possibility to estimate incidence and prevalence for different combination of tumor entities from the RARECARE project database including data from all the European CRs participating to the project. The group of experts met three times drawing a provisional list of rare tumors, that was subsequently validated with the engagement of local and international experts by e-mail exchanges and through the project web site. The complete list of rare cancers, including the topography and morphology codes that define the entities, is available on the RARECARE project website (www.rarecare.eu).

17.3.1 The Structure of the Rare Cancers List

A rare tumor will be problematic per se, i.e. due to its low frequency, under the perspective of clinical decision-making and the perspective of the health care organization.

Clinical decision-making is more problematic in the case of a rare tumor because clinical studies on that tumor are more difficult to carry out so the quality of available evidence tends to be limited. Under this perspective, a liposarcoma or a bronchioloalveolar lung carcinoma are similar because the feasibility of clinical studies on both conditions is equally affected by their low frequency.

Also the *organization of health care* is more problematic in the case of a rare tumor because the direct clinical expertise of any oncologist will be limited in comparison to the one that they have on common cancers so some kind of centralized patient referral needs to be implemented (towards centres or networks of excellence). Under this perspective a liposarcoma and a bronchioloalveolar lung carcinoma are not alike because the former belongs to a family of tumors which are rare as such, while the latter is a lung tumor i.e. it belongs to a family of common tumors. Any community oncologist deals everyday with lung tumors and will be aware of bronchioloalveolar carcinoma while this will not be the case for any sarcoma. In fact, centralized patient referral is generally recommended for sarcomas but not for lung tumors. A bronchioloalveolar carcinoma will be rare under the clinical decision-making but not the health care organization perspective while any sarcoma will be rare under both perspectives.

In order to respond to these issues, the list of rare tumours was hierarchically structured in two layers based on various combinations of ICD-O morphology and topography codes. The *first layer* denotes the main families of tumors identified according to a consensus-based clinical perspective. This partitioning should be mainly useful for patient referral purposes i.e. it is relevant under the health care organization perspective. A family of tumors generally finds its own referral pattern.

The *second layer* denotes tumors relevant from the clinical, mainly the therapeutic, decision-making perspective (ICD-O coded entities have been grouped on the basis of their similar clinical management). This partitioning should be

mainly useful for clinical purposes, e.g. for clinical studies, etc. The two layers simply group the ICD-O codes in a clinically sound fashion at a different level of depth. Under the clinical decision-making perspective, tumors partitioning have to be as detailed as required by the diversity of treatments. Under the health care organization perspective, the level of detail may be lower.

17.3.2 First Layer: Families of Cancers Relevant for the Health Care Organization

The first criterion for grouping tumor entities was the referral pattern. According a list of the major tumors families useful for patient referral purposes was developed by the international experts involved. Thus, entities included in the first layer of the list are those relevant under the health care organization perspective (Table 17.1). As a first step, the two large groups of epithelial and not epithelial tumors were disentangled and, within them, broad anatomic categories were identified. The long list of the epithelial group of tumors, that are usually treated by different oncology specialists, is closely related to the organization of health care. For instance the epithelial tumors of nasal cavity and sinuses, of nasopharynx, of major salivary glands, of hypopharynx and larynx, of orpharynx and of oral cavity and lip are treated by the head and neck oncologists even if they have different prognosis and will need different medical and surgical approaches. Similar considerations are suitable also for tumors of the digestive organs, tumors of the respiratory system and intra-thoracic organs, female/male genital organs, urinary tract, hematologic malignancies, and so on. In all these cases, the expertise is defined by the anatomical group of sites and the treatment will be more or less centralized depending on the rarity of tumors.

Table 17.1 Crude annual incidence rates, 5-year relative prevalence proportion and survival by first layer of malignant tumor entity

Crude incidence rate × 100,000	Tumor entity	5-year relative survival (%)	15-year prevalence × 100,000
>50	Epithelial tum of breast	81	594
	Epithelial tum of lung	11	85
>20–50	Epithelial tum of skin	98	474
	Epithelial tum of prostate	75	474
	Epithelial tum of colon	53	233
	Lymphoid malignant diseases	55	172
	Epithelial tum of bladder	66	133
>10–20	Epithelial tum of stomach	22	46
	Epithelial tum of rectum	53	102
	Malignant skin melanoma	84	135
	Epithelial tum of pancreas	4	8
	Epithelial tum of kidney	57	65

Table 17.1 (continued)

Crude incidence rate × 100,000	Tumor entity	5-year relative survival (%)	15-year prevalence × 100,000
>10–20	Epithelial tum of corpus uteri	80	100
>7–10	Epithelial tum of ovary and fallopian tube	38	48
	Epithelial tum of esophagus	11	8
≥6–7	Epithelial tum of hypopharynx and larynx	55	36
	Epithelial tum of liver and intrahepatic bile tract (IBT)	6	9
	Epithelial tum of cervix uteri	67	58
≥5–6	Glial tum of Central Nervous System (CNS) and pineal gland	20	15
≥4–5	Epithelial tum of oral cavity and lip	59	29
	Soft tissue sarcoma	56	43
	Epithelial tum of gallbladder and extrahepatic biliary duct	13	7
	Carcinoma of endocrine organs	85	41
≥2–4	Acute myeloid leukemia and related precursor neoplasms	20	8
	Tum of testis and paratestis	95	43
	Myeloproliferative neoplasms	60	29
	Epithelial tum of oropharynx	37	12
	Neuro endocrine tumors	51	19
≥1–2	Epithelial tum of vulva and vagina	61	13
	Malignant mesothelioma	6	3
	Epithelial tum of pelvis urether and urethra	54	10
	Myelodisplastic syndrome	37	4
	Epithelial tum of major sal glands and sal gland type tum	65	10
	Epithelial tum of anal canal	56	7
<1	Bone sarcoma	61	6
	Epithelial tum of small intestine	25	2
	Malignant melanoma of uvea	73	5
	Epithelial tum of penis	72	5
	Malignant melanoma of mucosa	30	2
	Epithelial tum of nasopharynx	49	2
	Mixed epithelial and mesenchymal tum of uterus	38	?
<1	Epithelial tum of nasal cavity and sinuses	48	2
	Non epithelial tum of ovary	63	3

Table 17.1 (continued)

Crude incidence rate × 100,000	Tumor entity	5-year relative survival (%)	15-year prevalence × 100,000
	Kaposi sarcoma	64	2
	Extragonadic embryonal neoplasms	77	4
	Myelodisplastic myeloproliferat diseases	23	1
	Adnexal carcinoma of skin	87	3
	Non glial tum of CNS and pineal gland	53	2
	Epithelial tum of thymus	57	1
	Epithelial tum of eye and adnexa	80	1
	Malignant meningiomas	62	1
	Epithelial tum of trachea	12	< 1
	Extragonadal germ cell tum	69	2
	Non-glial tum of nerves, autonomic nervous system and paraganglia	64	2
	Gastrointestinal stromal sarcoma	71	< 1
	Histiocytic and dendritic cell neoplasms	72	< 1
	Epithelial tum of middle ear	42	< 1
	Trophoblastic tum of placenta	90	< 1
	Glial tum of nerves, autonomic nervous system and paraganglia	87	< 1

Tum = Tumor; Sal = Salivary.

17.3.3 Second Layer: Cancer Entities Relevant for Clinical Decision Making and Research

Within each of the first layer entities, a set of second layer entities was defined according to their relevance from the clinical (basically the therapeutic) decision-making perspective. For instance among the epithelial tumors of the oesophagus, which may be considered a relatively common tumor, few entities (see Table 17.2) can be identified with different natural history and different therapeutic approaches. These are: the squamous cell carcinomas, the adenocarcinomas, the salivary gland type tumor and the undifferentiated carcinoma.

Under the clinical decision making perspective, all the epithelial tumors of the oesophagus are rare. For all of them, effective curative treatment does not exist also because the majority of patients get a diagnosis when the disease is already at an advanced stage. The surgical ablation is indicated for localised lesion. Radiotherapy, as well as multi-chemotherapy, have been proposed alone or in combination with surgery. Prognostic factors include stage at diagnosis, patient's general health, morphological and molecular feature of the tumor. For squamous cell carcinoma

Table 17.2 Crude annual incidence rates, 5-years relative survival prevalence proportion and for three groups of tumor entities

Layer	Tumor entity	Crude incidence rate × 100,000	5-year relative survival (%)	15-year prevalence × 100,000
1	Epithelial tumors of oesophagus	7.49	10.65	11.1
2	Squamous cell carcinoma and variants of oesophagus	3.39	10.67	4.9
2	Adenocarcinoma and variants of oesophagus	2.83	11.74	5.2
2	Salivary gland type tumors of oesophagus	0.01	9.56	0.01
2	Undifferentiated carcinoma of oesophagus	0.07	7.28	0.07
1	Epithelial tumors of liver and intrahepatic bile tract (IBT)	6.28	8.8	5.5
2	Hepatocellular carcinoma of liver and IBT	3.1	11.7	3.5
2	Cholangiocarcinoma of IBT	0.83	5.5	0.7
2	Adenocarcinoma and variants of liver and IBT	0.21	5.4	0.2
2	Undifferentiated carcinoma of liver and IBT	0.02	3.6	0.01
2	Squamous cell carcinoma and variants of liver and IBT	0.01	9.6	0.01
2	Bile duct cystadenocarcinoma of IBT	0.00	12.1	0.00
1	Epithelial tumors of cervix uteri	6.07	66.6	58.9
2	Squamous cell carcinoma and variants of cervix uteri	4.28	67.3	41.9
2	Adenocarcinoma and variants of cervix uteri	1.01	66.7	9.0
2	Undifferentiated carcinoma of cervix uteri	0.03	34.1	0.2

the depth of invasion and for adenocarcinoma the presence of lymphatic metastasis should also be considered. Clinical trials should be conducted taking into account the different histotypes [12, 14].

17.3.4 Limitations and Advantages of the Proposed Cancer Entities Grouping

The list of entities described in this chapter is based on tumor entities classified using topography and morphology. We are aware that this is just a subset of many

other possible features that contribute to the clinical presentation of a clinical case. In addition to being affected by a given tumor, a patient will have a specific stage of the disease, which, along with his/her sex, age, genetic patrimony, and several other factors (including concurrent diseases), will eventually determine treatment. In the era of molecular targeted therapies, the molecular profile will be relevant as well. We can foresee that disease entities will be increasingly defined on the basis of other features in addition to conventional pathologic aspects. It follows that many different clinical presentations may tend to become rare even when the tumor is common, simply because the number of characteristics which define the case will be high.

The choice of basing the definition of rare tumor only on topography and morphology was made for two reasons. The first reason is *to follow existing tumor classifications*. Any list of rare tumors will always be a subset of a standard list of tumors. International agencies preside over such classifications, constantly updating them, and genetic and molecular profile is more and more relevant to tumor partitioning in such classifications. This list of rare tumors is based on the ICD-O (3rd edition) classification [13] because this is the worldwide recognized classification of tumors. The second reason is *data availability*. Cancer registry data, the only data available to calculate population-based incidence and prevalence indicators, refer to cases classified only according to ICD-O. Other, even attractive, classification criteria such as biomarkers or gene expression cannot be used for any quantitative description of cancer burden.

17.4 Definition of the Cutpoint

Clinically defined cancer entities are classified as rare if their frequency falls below a given threshold level. As discussed in the previous paragraph, there is unanimous agreement among oncology specialists and epidemiologists that the most appropriate frequency measure for cancer is the crude incidence rate in the general population. The definition of an incidence threshold value, under which a given entity should be considered as rare is necessary arbitrary. However, several practical and important decisions depend on the threshold or cut point value. From the point of view of the health care organization, the management of rare cancers is different from the one of common tumors since rare entities should have a centralized treatment. From the research perspective, innovative clinical study designs should be considered when well-powered randomised trials are not feasible due to the low incidence. In addition, according to the EU Directive on orphan drugs [5], specific incentives are available to promote research and development of rare cancers.

Therefore, the choice of an appropriate cut point has been accurately considered on the basis of several issues. A brief description of the main issues considered follow.

17.4.1 How Many Cancer Diagnoses Refer to Rare Cancers?

In order to be of practical use, the concept of rare cancer cannot include the majority, or even a large proportion, of all cancers. In a setting of limited resources, provision of incentives for the study and management of a subset of cancers is as more effective as more precisely targeted and smaller is the number of affected patients. Using the RARECARE database (see paragraph 17.5), Fig. 17.1 provides the proportion or rare cancer patients over all cancer patients that would be selected as a function of the incidence cut point. For instance, an incidence cut point of 1 × 100,000 per year would select a subset of cancer entities affecting about 5.5% of all cancer patients. With a cut point of 10 × 100,000 per year, a wider set of entities would be classified as rare, corresponding to a proportion of 27% of all cancer diagnoses. A well chosen cut point should provide a balance between being too selective (i.e. less that 10% of patients) and too inclusive (more than 30% of patients). This balance could be provided choosing an incidence threshold between 3 and 12 × 100,000.

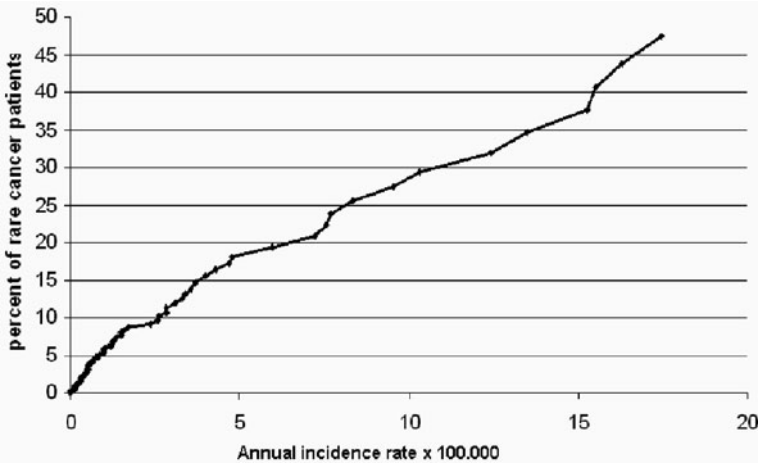

Fig. 17.1 Percent of cancer patients diagnosed with rare cancers, according to the definition of rarity

17.4.2 Does Rarity Affects the Possibility to Carry Out Effective Research?

Randomised clinical trial (RCT) is the standard study design required for research on new treatments. The number of patients included in the study, and the related statistical power, is one of the crucial characteristic for a good trial. The possibility to enrol a high proportion of all the incident cases is therefore of major importance to decide on the feasibility of a clinical trial. Unfortunately, with the exception of childhood cancers, it is usually very difficult to enrol more than 10% of the eligible patients in a given population. If the treatment under study regards a rare cancer, a

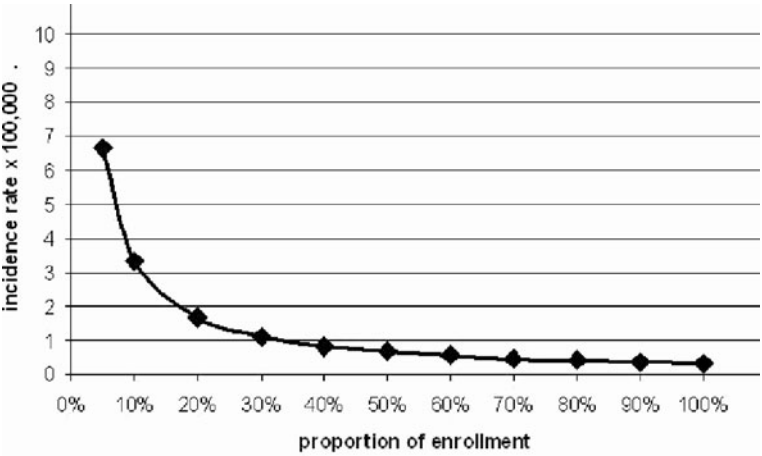

Fig. 17.2 Annual incidence rate necessary to recruit at least 500 patients in 3 years in a 50 million country

single hospital would take too much time to enrol a sufficient number of patients to ensure the required statistical power, and multicentre studies have to be planned. These are generally more difficult than single-centered studies, since common protocols for treatment and data collection and analysis have to be previously agreed on. This process is even more difficult for large multinational studies, because legal constrains arise on the circulation of data and biological material. The possibility to carry out a RCT for a given cancer, with enrolment of 500 patients in three years within a large country of 50 million inhabitants has therefore been considered to support the discussion on the decision of the cut point value.

In Fig. 17.2, the minimum incidence level required to make possible such a study was plotted against the expected proportion of enrolment. With incidence of 1 × 100,000 per year, an enrolment proportion of 33% should be reached in order to carry out the study. With an incidence below 6 × 100,000, a proportion of at least 5% would be necessary. Cancers with incidence greater than 10 × 100,000 do not create particular problems under this point of view. This criterion suggest an incidence cut point ranging between 3 and 6 × 100,000.

17.4.3 Is Clinical Decision Making More Difficult?

Assessing in an objective way the minimum rate of new diagnoses necessary to reach a sufficient experience in the clinical management of patients is difficult since it depends, among others, on the complexity of the disease and of the treatment and on the individual response variability. On the basis of the developed list of cancer entities the experts of the RARECARE group have systematically discussed their experience and their perception of the problems in the clinical management of

the various entities. This analysis has been particularly addressed to cancers with incidence rate between 3 and 10 × 100,000.

In conclusion, *an incidence cut point of 6 × 100,000 has been identified as the appropriate value to define rare cancers or a group of rare cancers*. This means (Fig. 17.1) to consider as rare about 20% of all cancers that arise in the general population. Almost all cancers defined as rare on the basis of the incidence based criterion are rare also according to the European prevalence-based definition of rare disease. Five cancers: poorly differentiated endocrine carcinoma of lung, adenocarcinomas of lung, squamous cell carcinomas of lung, adenocarcinomas of stomach and pancreatic adenocarcinoma are classified as common (according to their incidence) while, due to their low survival have a prevalence rate below 50 per 100,000.

17.5 Assessing Rare Cancers Burden

Information and health care statistics for cancer are better than for most other diseases, both because there is a long history of epidemiological studies and because population-based cancer registries (CRs) have provided an invaluable source of information for decades. Epidemiologic indicators of frequency such as incidence, prevalence and mortality, and indicators of outcome like relative survival are all available from population-based cancer registries and disseminated by the scientific literature, web sites and electronic tools. Incidence and survival figures based on CRs data are routinely available in the Cancer Incidence in Five Continents (CI5C) published by the International Agency for Research on Cancer (IARC http://www.iarc.fr) and through the EUROCARE (Survival of Cancer Patients in Europe) project monographs. Survival for the European patients has been provided by the EUROCARE project (http://www.eurocare.it/) since 1995. Prevalence was estimated by the Globocan software [9] to which contributed also the EUROPREVAL project [2]. However, all these projects describe the burden of broad cancer categories defined on the basis of anatomic site of the malignancy as defined by the ICD-O codes for topography [13]. On the contrary, specific objective of the RARECARE project is to provide basic epidemiologic indicators for rare cancers based on morphology and topography. This project, based on the data collected from 90 CRs in 21 European countries, gives a unique opportunity to study the epidemiology of rare tumors in a large population from various countries. RARECARE gathered CRs data on patients diagnosed from 1978 up to 2002, with vital status information available up to 31st December 2003 or later. To our knowledge, no similar large-scale analyses of rare tumours have been reported. A systematic presentation of rare cancer indicators is provided in Table 17.1 which includes only cancer groups listed in layer 1. Those included in layer 2 were removed for brevity however, few examples of layer 1 and 2 entities are reported in Table 17.2. The full list of rare cancers is available on the RARECARE project website: www.rarecare.eu.

17.5.1 Indicators of the Burden of Rare Cancers: Incidence, Survival, Prevalence

All the frequency indicators were calculated by the RARECARE project and expressed as crude rates. The frequency of each gender specific cancer was assessed in the general population. Therefore incidence rates were estimated as the number of new cases occurring in the considered period 1995–2002 over the total number of person years lived by the general population in the same period. Relative survival was estimated by the Hakulinen method [11]. Prevalence is expressed as the proportion of patients alive at the index date of 1 January 2003 with a diagnosis of tumour received any time in the last 15 years over the total population. It was estimated by the counting method [2], based on CRs incidence and follow-up data from 1988 to 2002. Only 22 CRs covered the entire period and were therefore included in the analysis.

Figure 17.3 shows the distribution of incidence rates of all the groups of tumors belonging to the first layer, those relevant for the health care organization, ranked from the highest to the lowest. As expected, the two most frequent tumors are (Table 17.1) the epithelial tumor of breast and of the lung, with annual incidence rates higher than 50 per 100,000. By contrast, slightly less than half of the tumor entities have their annual incidence rates lower than 1 per 100,000.

All the common entities are epithelial tumors of the most common sites, with the exception of skin melanoma and the group of lymphoid disease, including lymphomas and lymphatic leukemias. All the other entities are rare.

For almost all common entities, 5-year survival was more than 50%, exception were the epithelial tumors of pancreas (5-year survival 4%), oesophagus (5-year survival 11%), lung (5-year survival 11%), liver (5-year survival 8%), ovary (5-year

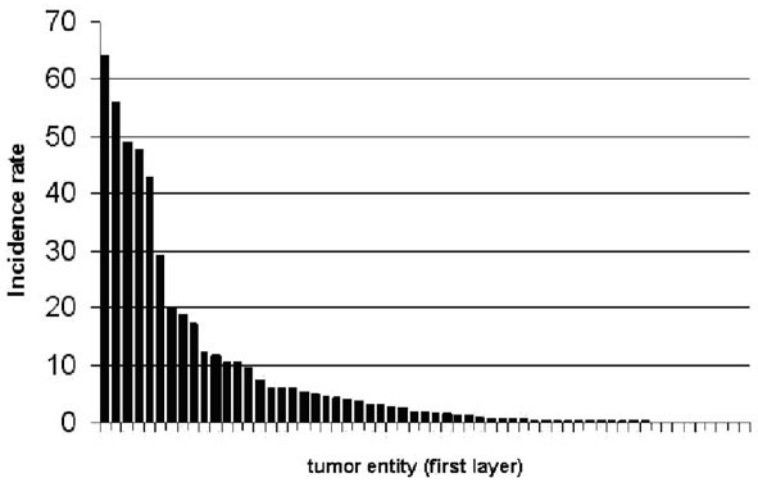

Fig. 17.3 Annual incidence rates ranging of groups of tumor entities (first layer)

survival 38%), and stomach (5-year survival 22%). For the rare entities survival variation was larger and many tumors had a poor prognosis: 5-year survival was less than 50% for the majority of rare entities. Fifteen-year prevalence (per 100,000) ranged between slightly less than 600 (epithelial tumor of breast) to less than 1.

The data in Table 17.1 clearly show how much prevalence of a specific cancer depends on prognosis. Within rare tumors, the highest prevalence was observed for testicular cancers (prevalence 43, 5-year survival 95%), soft tissue sarcomas (prevalence 43, 5-year survival 56%) and carcinomas of the endocrine organs (prevalence 41, 5-years survival 85%). There are very few rare tumors with prevalence higher than 50 per 100,000 i.e. the threshold of the EU definition of rare diseases [4], and few common tumor entities have a prevalence under 50 due to their poor prognosis.

It is worth mentioning that groups of common cancers might include rare tumour entities which are relevant for the clinical decision making perspective. Three examples of this situation are presented in Table 17.2. The oesophageal tumors as well as the liver and cervix epithelial tumors, have an incidence rate close to the threshold adopted of 6 per 100,000. However, the epithelial tumors of the oesophagus includes four rare clinically defined entities. Five-year survival figures vary from 9% for the adenocarcinoma to 6% for the undifferentiated carcinoma. The epithelial tumors of the liver and intrahepatic bile tract include different rare tumor entities relevant from the clinical management. The most frequent histotypes are the hepatocarcinoma and the colangiocarcinoma. These two different clinical entities have both a bad prognosis, lower for the cholangiocarcinoma. Adenocarcinomas of liver have low survival similar to that observed for cholangiocarcinoma. The other three entities present very few cases and can be considered as exceptional.

Epithelial tumors of cervix uteri comprise 2 rare tumor entities relevant from the clinical perspective: squamous cell carcinoma and adenocarcinoma.

17.6 Final Considerations and Future Directions

The RARECARE project, on the basis of population based cancer registries data provided an operative definition of rare cancer, a list of tumour entities from which is possible to select rare entities and the most important epidemiologic indicators (incidence, prevalence and survival) of rare tumors in Europe. The RARECARE project assured a wide engagement of oncologists, pathologists, cancer epidemiologists and patients advocacy groups in all its activities thus the conclusion of the project were extensively discussed and agreed on. We proposed a definition of rare cancer based on incidence and we developed a list of rare entities, using an incidence threshold of 6/100.000. However, we also acknowledge the importance of prevalence for health planning purposes, therefore this important measure was provided for all the tumor entities included in the rare cancer list. No important differences were found in identifying rare tumors on the basis of the incidence rate as opposed to the European definition of rare diseases based on prevalence [4].

This is the first time that CRs data are used to estimate epidemiologic indicators for rare tumors thus, the results obtained should be consolidated and widely utilised.

Bias in our results might arise because of variations in data quality and comparability. However, the analysis of the major indicators of the quality of cancer-registry data [3] – i.e., proportion of cases reported as death-certificate only, microscopically verified, and lost to follow-up – suggest a high-quality dataset. Information on morphology is commonly available from CRs, however in depth quality control should be done on the validity and completeness of such data. This important task was included among the aims of the RARECARE project. Actually, we are working on data quality revising a sample of selected rare tumors to assess the effect of such revision on incidence and survival rates. We hope that the results of rare cancer data quality analyses will contribute to increase the awareness on this critical topic among CRs.

Another important task is the dissemination of the results. These data should reach all the relevant stakeholders in order to support the best effective research into rare cancers and the best provision of care to patients. The list of rare cancers could be important for:

- establishing networks on rare cancers (European reference network),
- identifying tumor entities where a focus on treatment and timely diagnosis is essential,
- investigating the off-label use in rare cancers,
- supporting a greater involvement of disease-oriented research communities in the mechanisms developed by regulatory bodies to provide advice to the pharmaceutical industry on the development of new agents for use in rare cancers,
- developing alternative methodologies for rare cancer research,
- involving patients in the clinical decision-making process.

What will be the future of such experience?

Although information on patients access to care in the different European countries is not widely available, previous studies reported substantial regional differences in survival from rare cancers, particularly for those that respond well to treatment. Furthermore, a survey on the availability of orphan drugs in Europe, conducted by EURORDIS (European Organisation for Rare Diseases) in 2007, showed that access to recently approved orphan drugs is very limited and it varies significantly across the EU member states [7]. These results are of great concern and further investigations are needed to understand the reasons of survival differences across the European countries. Population-based studies may contribute to address this critical issue and it is our intention to carry out additional survival studies also to contribute to ameliorate the equity of care in rare cancer. Accurate population-based information on cancer patient survival is indispensable for effective cancer control. While clinicians need survival from clinical series to evaluate the efficacy of their treatments, only population-based survival comparisons can provide information on the effectiveness of health care systems. Population-based cancer registration is also necessary for monitoring cancer incidence and for estimating cancer prevalence

which are required for health care planning and resource allocation [1]. Policy and economic investments to ensure equal access to care to rare cancer patients have to be foreseen and we will work for providing evidence on which base such important decisions.

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Chapter 18
Hereditary Channelopathies in Neurology

Karin Jurkat-Rott, Holger Lerche, Yvonne Weber, and Frank Lehmann-Horn

Abstract Ion channelopathies are caused by malfunction or altered regulation of ion channel proteins due to hereditary or acquired protein changes. In neurology, main phenotypes include certain forms of epilepsy, ataxia, migraine, neuropathic pain, myotonia, and muscle weakness including myasthenia and periodic paralyses. The total prevalence of monogenic channelopathies in neurology is about 35:100,000. Susceptibility-related mutations further increase the relevance of channel genes in medicine considerably. As many disease mechanisms have been elucidated by functional characterization on the molecular level, the channelopathies are regarded as model disorders for pathogenesis and treatment of non-monogenic forms of epilepsy and migraine. As more than 35% of marketed drugs target ion channels, there is a high chance to identify compounds that counteract the effects of the mutations.

Keywords Epilepsy · Ataxia · Migraine · Pain · Neuromyotonia · Myasthenia · Myotonia · Periodic-paralysis

18.1 Introduction

The implication that ion channels may play a causal role in disease pathogenesis came first from the observation of abnormal ion conductances from muscle biopsied from myotonic goats [9] and patients with paramyotonia congenital [55] and periodic paralysis [56]. In the 1990s the term ion channelopathies was coined and defined for disorders that are caused by malfunction or altered regulation of ion channel proteins. Therefore, they may be either hereditary (for example by mutations in ion channel genes) or acquired (for example by auto antibodies). In neurology, channels of both the nervous system and skeletal muscle are involved. The channel disturbances result in changes of excitability which one would expect

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to be present constantly in EEG or EMG. However, this is not the case. Clinical symptoms mainly appear episodically, provoked by an out-of-the-normal situation, so-called trigger. Compensatory mechanisms often allow spontaneous and complete remission following an episode. These mechanisms show an age-dependency which causes symptoms to be present mainly in a specific phase of life (only childhood or only adulthood with onset from puberty). In addition to the episodes, progressive manifestations with neuronal or muscular degeneration are present in ~50% of patients. Main phenotypes include epilepsy, episodic ataxia, migraine, neuropathic pain, myotonias, and muscle weakness including myasthenia and periodic paralyses.

The prevalence of a hereditary neurological channelopathy is only ~0.1–4 in 100,000 individuals of the general population each. However, because there are so many of them, the total prevalence of channelopathies in neurology is 35 of 100,000. Based on the mechanisms of genetics and pathogenesis of these rare disorders, we can expect that ion channel susceptibilities are involved in the frequently occurring, not strictly hereditary variants of epilepsy, migraine, pain, and muscle weakness. Therefore, at least 5% of the population may either carry a disease-causing or a susceptibility-related mutation in an ion channel of muscle or nerve. Based on this observation, channelopathies are regarded as model disorders for pathogenetic mechanisms [43, 54]. Conveniently, more than 35% of marketed drugs target ion channels, so that channelopathies also provide model disorders for therapeutic strategies.

18.2 Hereditary Channelopathies of the Central and Peripheral Nervous System

18.2.1 Epilepsy

Epilepsy is one of the most common neurological disorders affecting ~3% of the world's population during lifetime [36]. The disease is characterized by recurring epileptic seizures resulting from synchronized electrical discharges of neurons within the central nervous system. With regard to the complicated nature and the many different functions of the brain, there are a number of clinically differentiable seizure types. The symptoms of a seizure depend on age, the underlying cause and the brain region involved. Accordingly, epileptic semiology can include only mild sensations of the patient himself that are not visible for other individuals (such as seen with an epigastric aura), but also transient black outs (such as known for absence or complex-partial seizures), or severe generalized tonic-clonic convulsions. The most important features used to classify epileptic seizures and epileptic syndromes are (i) the origin of the seizure/epilepsy which can be focal or generalized and (ii) the underlying cause which can be symptomatic (for example due to cortical malformations, brain tumors or stroke) or idiopathic, i.e. genetic. In the following, idiopathic epilepsy syndromes are described for which ion channel mutations have been identified as a genetic cause.

18.2.1.1 Idiopathic Partial Epilepsy

Autosomal dominant nocturnal frontal lobe epilepsy includes frequent brief seizures occurring in childhood with hyperkinetic or tonic manifestations, typically in clusters at night. Ictal video-electroencephalographic studies have revealed partial seizures originating from the frontal lobe but also in parts of the insula, suggesting a defect of a broader network. The penetrance of the disease is estimated at approximately 70–80%. A mutation was identified in the gene *CHRNA4* encoding the α4-subunit of a neuronal nicotinic acetylcholine receptor as the first ion channel mutation found in an inherited form of epilepsy [89]. Altogether, five mutations in *CHRNA4* and two in *CHRNB2*, which encodes the β2-subunit of neuronal nicotinic acetylcholine receptor, have been reported [88]. Recently, another mutation in *CHRNA2*, encoding the neuronal nicotinic acetylcholine receptor α2-subunit, was detected. Most mutations reside in the pore-forming M2 transmembrane segments. Different effects on gating of heteromeric α4β2 channels leading either to a gain- or a loss-of-function were reported when most of the known mutations were functionally expressed in *Xenopus* oocytes or human embryonic kidney cells. An increased acetylcholine sensitivity is thought to be the main common gating defect of the mutations [60, 88].

In one patient with cryptogenic partial epilepsy that was classified as pharmacoresistant because of non-response to carbamazepine or oxcarbazepine, a Nav1.3 mutation, K354Q, was identified that was not present in 295 neurological normal controls [39]. Functional analysis of this mutation demonstrated an increase in persistent current, a gain-of-function. The phenotype was purely focal with no structural brain abnormality to account for the symptoms. The role of Nav1.3 for epilepsy is yet to be established.

18.2.1.2 Idiopathic Secondarily Generalized Epilepsy

Benign familial neonatal seizures (BFNS) are dominantly inherited with a penetrance of 85%. The seizures manifest within the first weeks of life and typically disappear spontaneously after weeks to months. Seizures may have a partial onset, often with hemi-tonic or -clonic symptoms or with apnoe, or may appear primarily generalized. Accordingly, ictal EEGs showed focal and generalized discharges. Interictal EEGs are mostly normal. The risk of seizures recurring in adulthood is ∼15%. Although psychomotor development is usually normal, an increasing number of cases with learning disability have recently been described [6]. Mutations have been identified in Kv7.2 and Kv7.3 potassium channels which interact with each other and constitute the so-called “M-current”, an important current in the regulation of the firing rate of neurons. Co-expression of heteromeric wild-type and mutant Kv7.2/Kv7.3 channels usually revealed a reduction in the resulting potassium current of ∼20–30%, which is apparently sufficient to cause BFNS [81]. Even subtle changes in channel gating restricted to subthreshold voltages of an action potential are sufficient to cause BFNS, proving the physiological importance of this voltage range for the action of M-channels in a human disease model [62, 108].

Clinically similar epilepsy syndromes that are genetically different from BFNS are BFNIS and BFIS, benign familial (neonatal-)infantile seizures. The phenotype also displays partial epileptic seizures with or without secondary generalization, but they occur between the age of 3 and 12 months (BFIS) or more variable between the neonatal and infantile periode (BFNIS). Ictal EEGs can show focal epileptic discharges in different brain regions. BFIS can be associated with other neurological disorders, such as paroxysmal dyskinesia or migraine. Mutations in the *SCN2A* gene encoding one of the α-subunits of voltage-gated sodium channels expressed in the mammalian brain have been identified in BFNIS [38]. Functional investigations revealed predominant small gain-of-function effects or reduced channel activity predicting increased neuronal excitability. The age dependence of this syndrome could be explained by a transient expression of the respective Nav1.2 channels in axon initial segments of principal neurons in cortex and hippocampus during development, and replacement later on by Nav1.6 at these sites. A few *SCN2A* mutations with severe effects such as non-functional, truncated proteins have been described in patients with intractable epilepsy and mental retardation [60a].

18.2.1.3 Idiopathic Primarily Generalized Epilepsy with Febrile Seizures

Generalized epilepsy with febrile seizures plus (GEFS+) is a childhood-onset syndrome featuring febrile convulsions and a variety of afebrile epileptic seizure types within the same pedigree. The penetrance is ∼60%. Two-thirds of affected individuals were diagnosed as having febrile seizures (FS) which may be combined with either FS persisting after the sixth year of life or with afebrile generalized tonic–clonic seizures (FS+). Additional seizure types such as absences, atonic, or myoclonic–astatic, or focal seizures may occur. Vaccination and its associated fever may trigger the first episode of a hitherto unsymptomatic GEFS+ [5]. More than 20 different mutations were subsequently identified in GEFS+ patients, accounting for 10% of cases. GEFS+ is caused by missense mutations in α and β1 subunits of the neuronal sodium channel, encoded by *SCN1A* and *SCN1B* respectively. Mutations may increase persistent sodium current but loss-of-function mutations have been observed as well [2]. Reduced channel function is considered to be more significant than gain-of-function changes [76], leading to an overall loss-of-function phenotype at the neuronal level. Therefore, sodium channel blockers exacerbate symptoms in many GEFS+ patients.

Next to *SCN1A*, also GEFS+ is associated with mutations in the homologous sodium channel α subunit genes encoded by *SCN2A* in a single family [94] and by *SCN9A* in potentially up to 5% of the patients with febrile seizures [84]. The latter show a high penetrance of 95%. Functional expression has not yet been performed. Finally, several mutations in genes coding for different GABA-A receptor subunits, *GABRG2* and *GABRD*, have been identified. Dominant *GABRG2* mutations produce decrease of GABA-activated chloride currents thus reducing inhibitory currents which results in hyperexcitability. The decrease in inhibition has been observed in the cortex, as shown in a knock-in model carrying one of the human mutations [72].

Severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome is characterized by clonic or tonic–clonic seizures in the first year of life that are often prolonged and associated with fever. During the course of the disease, patients develop afebrile generalized myoclonic, absence, or tonic–clonic seizures, but simple and complex partial seizures also occur. Cognitive deterioration appears in early childhood. In contrast to GEFS+, the syndrome is resistant to pharmacotherapy in most cases, but stiripentol seems to have a significant positive effect in patients with SMEI. Cranial magnetic resonance imaging in patients with SMEI found focal and generalized internal and external atrophy, which is discussed as a result of the brain encephalopathy; the rate of hippocampal sclerosis is not increased. Because patients with SMEI sometimes have a family history of febrile or afebrile seizures, and in some families GEFS+ and SMEI overlap, SMEI may be regarded as the most severe phenotype of the GEFS+ spectrum [85].

Similar to SMEI, intractable childhood epilepsy presents with generalized tonic–clonic seizures (ICEGTC) [31]. Onset and clinical course including learning disability are as in SMEI, except that myoclonic seizures do not occur. Families with some instances of ICEGTC in other family members affected by GEFS+ have been described. Therefore, we may conclude that the GEFS+ spectrum extends from simple febrile seizures to a variety of severe epilepsy syndromes of childhood such as intractable ICEGTC and SMEI, as also confirmed by genetic results described below [60].

For SMEI and ICEGTC, mutations in *SCN1A* encoding Nav1.1 have been identified [13]. Together with GEFS+, more than 100 *SCN1A* mutations have been identified, accounting for 70% of cases [64]. Mutation hotspots, such as sites of CpG deamination, account for 25% of de-novo mutations [48]. Genetic screening for *SCN1A* is standard for diagnosing early-onset childhood seizures. Most SMEI mutations cause loss of function due to nonsense mutations demonstrating that haploinsufficiency of *SCN1A* is pathogenic.

18.2.1.4 Idiopathic Primarily Generalized Epilepsy Without Febrile Seizures

Genetic mutations were also identified in families with classical idiopathic generalized epilepsies, namely childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures on awakening (EGTCA). Absence seizures in ECA manifest typically around the sixth year of life are of short duration, ~10 s, and typically occur in clusters of up to 100 seizures a day. In adolescence, generalized tonic–clonic seizures can occur. Myoclonic jerks are the clinical hallmark of EJM, particularly of the upper extremities, which appear without loss of consciousness. They can be clinically subtle and escape clinical recognition. The disease also manifests during puberty, with seizures typically developing after awakening and being provoked by sleep deprivation. Generalized tonic–clonic seizures occur in about 75% of patients. The idiopathic generalized epilepsies may overlap within individuals and are typically associated with generalized spike-wave or poly-spike-wave discharges on EEG. Brain imaging is unremarkable.

For juvenile myoclonus epilepsy, a mutation in *GABRA1*, the gene encoding the α1-subunit of the GABA-A receptor, was identified in a single family [15]. The mutation leads to loss-of-function of the GABA-A receptor i.e. a decrease of inhibitory chloride currents and hyperexcitability [15]. Larger studies suggest that GABA-A receptor mutations are extremely rare [20]. Two EJM mutations have been described in the calcium channel β subunit gene *CACNB4*, but they were not examined functionally and not much can be deduced about prevelance in the small population studied [26]. Recently, a few EJM mutations were found in the gene *CLCN2* encoding a neuronal voltage-gated chloride channel [34, 78]. This channel may play a role in neuronal inhibition. Owing to its specific gating properties, it constitutes a chloride extrusion pathway keeping the intracellular chloride concentration at low levels, which is important for the inhibitory action of the GABA-A receptor. Because the segregation with the phenotype was incomplete, the role of *CLCN2* as susceptibility gene for EJM is still a matter of debate [66].

For childhood absence epilepsy, a mutation in the γ2 subunit of the GABA-A receptor encoded by *GABRG2* has been described [102] which decreased GABA-activated chloride currents. This reduction of inhibitory currents results in hyperexcitability. Due to trafficking changes and endocytosis increase upon temperature elevation in-vitro, and occasional reports of FS in-vivo, the differentiation to GEFS+ is rather difficult (and in agreement with this statement, the features of this family resemble GEFS+). Three ECA mutations were reported in the β3 subunit of the GABA-A receptor encoded by *GABRB3* that showed reduced penetrance and hyperglycosylation-induced reduction of inhibitory chloride current [96]. For completeness of the expression data: a *GABRA1* mutation associated with absence epilepsy revealed a loss of trafficking and a loss of channel current. Functional co-expression of the wild-type suggested that haploinsufficieny is the pathogenetic mechanism [61].

Finally, variants in childhood absence epilepsy and other subtypes have been described in *CACNA1H* encoding a neuronal voltage-gated T-type calcium channel. They were suggestive of gain-of-function by several different alterations in channel gating which can explain a neuronal hyperexcitability [72].

18.2.2 Ataxia

Episodic ataxias (EA) are characterized by episodic spells of cerebellar ataxia that can be triggered by stress, startle, or heavy exertion such as exercise. Symptoms can first appear in infancy. There is a phenotypic overlap with migraine, spinocerebellar ataxia, and epilepsy.

EA1 is associated with myokymia (neuromyotonia) i.e. continuous muscle movement and usually presents with paroxysmal truncal and limb ataxia and dysarthria lasting seconds to minutes. Nystagmus is absent. Typically, episodes are triggered by strong emotion or exercise and last seconds to minutes. The syndrome usually presents in childhood or adolescence and often improves spontaneously in the third decade. About 10% of patients also have epilepsy. Inheritance is autosomal dominant. Approximately 20 mutations have been described, almost all of which are missense mutations of the *KCNA1* gene that encodes the voltage-gated potassium

channel Kv1.1 [7]. Most involve highly conserved amino acids such as those in the transmembrane segments. If the functional changes mainly show a slowing of the time course of activation, the phenotype may be primarily neuromyotonia without ataxia, if the threshold of activation is shifted or the current reduced, the ataxia is more prominent. Reduced penetrance can occur.

EA2 is caused by mutations of *CACNA1A*, the gene encoding the neuronal voltage-gated P/Q-type calcium channel α1 subunit, Cav2.1 [67]. The ataxia last longer and mild interictal nystagmus and ataxia are present. Vertigo, nausea and vomiting precede the episodes in over half of the patients. Over 50% have migraine as well. For diagnosis, interictal gaze-evoked nystagmus with features typical of rebound nystagmus may be elicited. Spontaneous vertical nystagmus, particularly downbeat nystagmus, is seen in ∼30% of cases. Penetrance is 80–90%. Acetazolamide and 4-aminopyridine are effective in controlling or reducing the frequency and severity of attacks. More than 50 Cav2.1 EA2 mutations have been described of which the majority represents nonsense mutations leading to premature truncations of the protein with loss of function. The prevalence has been estimated at lower than 1:100,000 population.

EA5 has been described in a single family with a mutation in the calcium channel ß4 subunit encoded by the *CACNB4* gene [26]. This is a subunit that interacts with Cav2.1. The family had clinical features similar to EA2, but mutations in *CACNA1A* were excluded. However, the same mutation was found in a German family with generalized epilepsy without ataxia, so that the associated phenotype must be regarded with care. Functional studies showed only minimal changes in calcium channel function.

Spinocerebellar ataxias (SCA) are characterized by progressive degeneration of cerebellum, brainstem and spinal cord. Of these, SCA6 is a channelopathy that is caused by a CAG repeat expansion in the calcium channel *CACNA1A* gene [110]. It makes up 6% (in Japan) to 30% (in Australia) of SCA cases [80, 91, 103]. In most families, patients show permanent dysarthria, oculomotor deficits, and gait ataxia although there may be a phenotypic overlap with EA2. Depending on the splice variant which is translated into proteins, the mutation elongates a poly-glutamine stretch in the C-term which is thought to form intracellular aggregations. The longer the repeat expansion the earlier is the disease onset. Patients with longer expansions present with disease symptoms at an earlier age.

In a 9-year-old boy with mental retardation, pancerebellar atrophy, and ataxia, a heterozygous nonsense mutation in exon 4 of the *SCN8A* gene was identified [98]. It introduced a stop codon into the pore loop of domain 4 resulting in a prematurely truncated loss-of-function channel. Three additional heterozygous family members exhibited milder cognitive and behavioral deficits, but not the full phenotype. For this reason, *SCN8A* was considered a susceptibility gene for the phenotype.

18.2.3 Migraine

Migraine with and without aura has a 1-year prevalence of 12–15% in North America and Western Europe. Migraine occurs in some 6% of children, and becomes more common in females after puberty, reaching a peak at age 41 when

three times more females than males have migraine [83]. The current pathogenesis models of migraine with aura suggests cortical spreading depression which consists of an initial brief spike of increased neuronal activity followed by long-lasting suppression of excitability spreading across the cortex at 1–3 mm/min. The depression wave is associated with long-lasting depolarization and changes in ion concentration gradients i.e. elevation of extracellular potassium and intracellular sodium. Its progress correlates to the succession of symptoms during the aura initiating the migraine attacks.

Familial hemiplegic migraine (FHM) is a monogenic subtype that enables to study the pathogenesis of the cortical depression wave. FHM presents with characteristic unilateral migrainous headaches accompanied by nausea, phono- and photophobia. Episodes are typically precipitated by an aura with symptoms of both hyper- and hypo-excitability such as aphasia, dysarthria, vertigo, homonymous hemianopsia, cheiro-oral paresthesias, and some degree of mainly unilateral paresis. FHM prevalence has been estimated in Denmark. It is approximately 0.005% with a male to female sex ratio of 1:3. Of the various FHM forms, up to 50% of cases are FHM1 and 20–30% FHM2 [45].

FHM1 includes sporadic hemiplegic migraine with progressive cerebellar ataxia. The aura may be prolonged and confusion and loss of consciousness may occur. In the interval, some families additionally present with epilepsy, retinal degeneration, hypakusis, and persistent cerebellar dysfunction with Purkinje cell atrophy. Over 20 missense mutations have been described, that are primarily located in the pore region or transmembrane segments and result in gain of Cav2.1 function [67].

FHM2 is an autosomal dominant disease, caused by mutations in the *ATP1A2* gene on chromosome 1q21–23 encoding the alpha2 subunit of the astrocytic Na^+/K^+-ATPase 3 [18, 87]. Well over 20 missense mutations have been detected that all lead to loss of ATPase function by blocking ion transport pathways or the Mg-ATP binding region. As FHM2 is not a channelopathy it has not been included in Table 18.1.

FHM3 is caused by mutations in the *SCN1A* gene on chromosome 2q24 encoding the neuronal voltage-gated sodium channel alpha1 subunit, Nav1.1. As just a few families with a Nav1.1 mutation are known, FHM3 is not yet distinct clinically [21]. Functional expression of the three known mutations demonstrated reduced channel activity in two cases and gain-of-function features in the third case [11, 46]. The presence of seizures in addition to migraine in the third family demonstrates the potentially close relationship between these migraine and epilepsy.

18.2.4 Neuropathic Pain

In the peripheral nervous system, Nav1.7 channels are expressed in sympathetic neurons, sensory neurons, and their axons, whereas Nav1.8 and Nav1.9 are exclusively expressed in sensory neurons, including peripheral terminals, axons, and cell bodies. Recent studies have linked Nav1.7 to three pain disorders: inherited

Table 18.1 Overview of hereditary channelopathies in Neurology. The diseases or the susceptibilities are listed in column 1, their acronyms in column 2, the responsible genes and their chromosomal locations in columns 3 and 4, and the ion channels and their specific protein names in columns 5 and 6. The inheritance is given in column 7 (D = dominant, R = recessive), and the disease prevalence in the last column

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Nocturnal frontal lobe epilepsy EFNL	EFNL1 EFNL3 EFNL4	*CHRNA4* *CHRNB2* *CHRNA2*	20q13.3 1q21 8p21	Cation channel	nAChRα4 nAChRβ2 nAChRα2	D	>5 families <5 families <5 families
Cryptogenic pediatric partial epilepsy		*SCN3A*	2q24	Sodium channel	Nav1.3		1 patient
Benign familial neonatal seizures BFNS	BFNS1 BFNS2	*KCNQ2* *KCNQ3*	20q13.3 8q24.22–24.3	Potassium channel	Kv7.2 Kv7.3	D	
BFN/Infantile seizures	BFNIS	*SCN2A*	2q24.3	Sodium channel	Nav1.2	D	
Generalized epilepsy with febrile seizures plus GEFS+	GEFS1 GEFS2 GEFS7 GEFS4 GEFS5	*SCN1B* *SCN1A* *SCN9A* *GABRG2* *GABRD*	19q13.1 2q24 2q24 5q31.1–33.1 1p36.3	Sodium channel GABAAγ2 GABAAδ	Navβ1 Nav1.1 Nav1.7 D	D	
Severe myoclonic epilepsy of infancy	SMEI	*SCN1A*	2q24	Sodium channel	Nav1.1	D	
Childhood absence epilepsy	ECA2 ECA4 ECA5	*GABRG2G* *ABRA1* *GABRB3*	5q31.1–33.1 5q34–35 15q11.2–q12	Chloride channel	GABAAγ2 GABAAα1 GABAAβ3	D	
Susceptibility to ECA	ECA6	*CACNA1H*	16p13.3	Calcium channel	Cav3.2	D	
Juvenile myoclonus epilepsy	EJM5	*GABRA1*	5q34–35	Chloride channel	GABA-A	D	
	EJM6	*CACNB4*	2q22–23	Calcium channel	Cavβ4	D	

Table 18.1 (continued)

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Susceptibility to EJM	EJM8	*CLCN2*	3q26	Chloride channel	ClC2	D	
Ataxia and migraine							
Spinocerebellar ataxia	SCA6 SCA13	*CACNA1A* *KCNC3*	19p13.1 19q13.3–4	Calcium channel Potassium channel	Cav2.1 Kv3.3	D	
Episodic ataxia Susceptibility to EA	EA1 EA2 EA5	*KCNA1* *CACNA1A* *CACNB4*	12p13 19p13.1 2q22–23	Potassium channel Calcium channel Calcium channel	Kv1.1 Cav2.1 Cavβ4	D	10 mutations <1:100,000 1 patient
Familial hemiplegic migraine	FHM1 FHM3	*CACNA1A* *SCNA1*	19p13.1 2q24	Calcium channel Sodium channel	Cav2.1 Nav1.1	D	1 family
Susceptibility to ataxia, mental retard.		*SCN8A*	12q13	Sodium channel	Nav1.6	D	1 patient
Neuropathic pain and others							
Inherited erythromelalgia	IEM	*SCN9A*	2q24	Sodium channel	Nav1.7	D	
Paroxysmal extreme pain disorder	PEPD						
Congenital insensitivity to pain	CIP	R	~30 families				
Hyperekplexia	STHE	*GLRA1* *GLRB*	5q31.3 4q31.3	Chloride channel	GlyRα1 GlyRβ	D/R R	
Neuromyotonia isolated myokymia	MK1	*KCNQ2* *KCNA1*	20q13.3 12p13	Potassium channel	Kv7.2 Kv1.1	D	3 mutations 3 mutations
Epilepsy,ataxia,deafness,tubulopathy	EAST	*KCNJ10*	1q22–23	Potassium channel	Kir4.1	R	

Table 18.1 (continued)

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Paroxysmal dyskinesia	GEPD	*KCNMA1*	10q22.3	Potassium channel	KCa1.1	D	
Dominant deafness		*KCNQ4*	1p34	Potassium channel	Kv7.4	D	
Deafness Jervell and Lange-Nielsen		*KCNQ1*	11p15.5	Potassium channel	Kv7.1	R	
Congenital stationary night blindness		*CACNA1F*	Xp11.23	Calcium channel	Cav1.4	R	
Retinitis pigmentosa		*CNCG1*	4p12–ce	Cation channel	CNCG1	R	
Motor endplate and skeletal muscle							
Congenital myasthenic syndromes	CMS	*CHRNA1* *CHRNB1* *CHRND* *CHRNE*	2q24–32 17p12–11 2q33–34 17p13.2	Cation channel	nAChRα1 nAChRβ1 nAChRδ1 nAChRε1	D/R	
		SCN4A	17q23.1–25.3	Sodium channel	Nav1.4	D	1 patient
Myotonia congenita	MC	*CLCN1*	7q32-qter	Chloride channel	ClC1	D R	1:400,000 1:25,000
	SCM	*SCN4A*	17q23.1–25.3	Sodium channel	Nav1.4	D	1:400,000
Paramyotonia congenita	PMC	*SCN4A*	17q23.1–25.3	Sodium channel	Nav1.4	D	1:200,000
Hyperkalemic periodic paralysis	HyperPP	*SCN4A*	17q23.1–25.3	Sodium channel	Nav1.4	D	1:200,000
Hypokalemic periodic paralysis	HypoPP1 HypoPP2	*CACNA1S* *SCN4A*	1q31–32 17q23.1–25.3	Calcium channel Sodium channel	Cav1.1 Nav1.4	D	1:100,000 1:500,000
Andersen-Tawil syndrome	ATS	*KCNJ2*	17q24.2	Potassium channel	Kir2.1	D	1:1,000,000

Table 18.1 (continued)

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Susceptibility to thyrotoxic PP	TPP	*KCNJ18*	17p11.1	Potassium channel	Kir2.6	D	0.07%Asian
Central core disease Multiminicore disease	CCD MmD	*RYR1*	19q13.1	Calcium channel	RyR1	D R	
Malignant hyperthermia susceptibility	MHS	*RYR1*	19q13.1	Calcium channel	RyR1	D	1:50,000

erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and Nav1.7-associated congenital insensitivity to pain (CIP) [19, 27, 33]. Dominantly inherited gain-of-function mutations in *SCN9A*, the gene encoding Nav1.7, cause the painful neuropathy IEM, characterized by episodes of burning pain, erythema, and mild swelling in the hands and feet, which are triggered by mild warmth or exercise. Symptoms of IEM can start as early as at age of 1 year or in adulthood, and both types have been described in families and in sporadic cases. Recently, a familial case from Taiwan has been reported with symptoms first appearing in the feet of affected teenagers and with almost a decade delay in the involvement of hands. Although early- and delayed-onset IEM have been linked to mutations in Nav1.7, the etiology of adult-onset IEM remains a mystery.

A different set of gain-of-function mutations has been identified in Nav1.7 in patients with PEPD, previously referred to as familial rectal pain [28]. Severe pain in PEPD patients along with flushing are induced by bowel movement or probing of the perianal areas and are sometimes accompanied by tonic non-epileptic seizures and cardiac deficits. In contrast, recessively inherited loss-of-function mutations in Nav1.7 have been identified in individuals with complete inability to experience pain coupled with impaired sense of smell [16]. These studies provide complementary and compelling evidence for a central role of this channel in pain signaling.

PEPD mutations in Nav1.7 change amino acids that have been implicated in fast inactivation of sodium channels. The voltage dependence of steady-state fast inactivation of PEPD mutant channels is shifted by 20 mV in a depolarizing direction, and inactivation is incomplete, resulting in a persistent and a socalled resurgent current [40]. Impaired channel fast inactivation and the persistent current produced by the mutant channels would be expected to increase frequency of action potential firing. Indeed, expression of PEPD mutant Nav1.7 channels renders neurons of dorsal root ganglia (DRG) hyperexcitable [19]. The favorable response of the patients to carbamazepine, a use-dependent sodium channel blocker, is consistent with the impaired inactivation of the mutant channels.

Loss-of-function mutations invariably truncate the channel protein, resulting in Nav1.7-related CIP and impaired sense of smell [16]. These mutations do not produce functional Nav1.7 channels when expressed in mammalian expression systems [16]. Patients do not experience pain from normally painful acts, such as puncture wounds, bone fracture, tongue and lip biting, or walking on hot surfaces (including burning coals), but do not suffer from other sensory, motor, or cognitive deficits. Heterozygous parents are asymptomatic, indicating that a null mutation on one allele does not lead to haploinsufficiency.

18.2.5 Hyperekplexia

Hyperekplexia, also known as hereditary startle disease or stiff-baby syndrome, is a rare nonepileptic disorder characterized by excessive startle response to acoustic, visual, or other stimuli [109]. Hypertonia and apneic spells, nocturnal myoclonus,

startle-induced falls and accumulation of injuries occur. It is predominantly an autosomal dominant disease with few autosomal recessive and sporadic cases. It mainly affects Northern European descendants, but has been reported from many other countries as well. Of the various responsible genes, those for the inhibitory glycine receptor (GlyR), a hetero-pentameric, ligand-gated chloride channel, are typically affected. Mutations in *GLRA1* encoding the ligand-binding GlyR alpha1 subunit and less frequently those in *GLRB* coding for the GlyR beta subunit cause the syndrome. GlyRs facilitate the fast-response, inhibitory glycinergic neurotransmission in the brainstem and spinal cord. Certain mutations inhibit the occurence of higher conductance states [53].

Symptoms are present from birth, as infants display muscular rigidity, which increases with handling and disappears during sleep. It may lead to potentially fatal spells of apnea (sudden-infant death). The diagnosis is clinically confirmed by demonstrating an exaggerated head-retraction reflex in tapping the infant's nose-bridge or chin. Muscular hypertonia decreases gradually during the first year of life whereas excessive startling persists throughout life. Even so, affected young children and adults tend to walk stiff-legged, with a mildly wide-based gait, but without signs of spasticity. The head-retraction response continues to be readily elicited. Other clinical features are periodic limb movements in sleep and hypnagogic myoclonus. The hallmark is the excessive startling in response to unexpected stimuli, which results in short-lasting generalized stiffness causing the patient to fall forwards "as stiff as a stick" while fully conscious but unable to protect himself. This may result in serious injuries. Clonazepam is the treatment of choice, which potentiates the inhibitory transmitter GABA. During the first year of life infants need to be fitted with an apnea monitor.

18.2.6 Neuromyotonia

It is heterogeneous in terms of symptoms, signs, severity, pattern, and rate of progression and is also termed peripheral nerve hyperexcitability (PNH). Its association with a variety of disorders adds to the diversity. Motor features of spontaneous and continuous skeletal muscle overactivity usually dominate the clinical presentation and are common to all variants. Muscle twitching (fasciculations and/or clinical myokymia – undulation of the muscle causing rippling of the overlying skin) and painful cramps are the commonest, and in many patients the only, presenting features. In the fully developed syndrome, however there can also be stiffness, pseudomyotonia, pseudotetany (for example, Chvostek's and Trousseau's signs with normal calcium homeostasis), and weakness. All of these features tend to be triggered or worsened by muscle contraction. Muscle overactivity characteristically continues during both sleep and general anesthesia. Muscle hypertrophy, usually affecting the calves, can develop in severe cases. Conversely, distal muscle wasting can be seen, especially in those patients with an associated peripheral neuropathy. Growth retardation can occur in severely affected children.

Two of the three hereditary neuromyotonias are channelopathies whereas the third is caused by a mutations in a peripheral myelin protein (PMP22), also called hereditary motor sensory neuropathy type 1a (HMSN type 1a) or hereditary liability to pressure palsies. The two channelopathies are caused by mutations in voltage-gated potassium channels, Kv1.1 and Kv7.2 [17, 107]. Patients with Kv1.1 mutations show continuous muscle overactivity that can be visible as myokymia or detectable only on EMG as regular bursts of high frequency discharges. Only few families only show myokymia while the majority of patients present with additional ataxic episodes (see above EA1). Recently a family with a Kv1.1-N255D mutation revealed hypomagnesemia as a new phenotypic characteristic [32]. Patients with certain Kv7.2 mutations show muscle twitching affecting the limbs and trunk and myokymic discharges on the EMG whereas the majority of patients with present with Kv7.2 mutations present with benign familiar neonatal seizures (see above BFNS).

For the other neuronal channelopathies such as EAST syndrome (epilepsy, ataxia, deafness, and tubulopathy) and the paroxysmal dyskinesias, as well as the sensory diseases such as sensorineural deafness and blindness (dominant deafness, deafness Jervell and Lange-Nielsen, congenital stationary night blindness, and retinitis pigmentosa), we refer to Table 18.1.

18.3 Hereditary Channelopathies of the Motor Endplate and the Skeletal Muscle

18.3.1 Congenital Myasthenic Syndromes (CMS)

CMS are a heterogeneous group of inherited disorders with defective transmission of neuromuscular excitation resulting in muscle fatigue [25]. Weakness is usually evident at birth or within the first year or two of life, and is characterized by feeding difficulties, ptosis, impaired eye movements, and delayed motor milestones. Strength sometimes improves during adolescence, and does not exhibit a progressive course. Reflexes are usually brisk and muscle wasting does not occur. CMS can lead to congenital arthrogryposis multiplex involving reduced fetal movement and multiple joint contractures in the neonate [8]. Electromyography in CMS patients reveals a characteristic decrement of compound action potential amplitude on repetitive stimulation, and single fibre recordings show an increased variability in the synaptic transmission time (“jitter”) and transmission blocks [51].

CMS result from defects in presynaptic, synaptic, and postsynaptic proteins. Only postsynaptic CMS are known to be caused by mutations in ion channels like the nicotinic acetylcholine receptor (nAChR) that conducts monovalent cations [24]. Loss-of-function mutations of AChR subunits lead to compensatory expression of fetal δ subunits yielding AChR complexes which differ functionally from the adult type. Rarely mutations alter the kinetic channel properties. These kinetic mutations

result in the slow- or fast-channel syndromes. The low-affinity, fast channel syndrome is caused by loss-of-function mutations that have similar effects as AChR deficiency but is much rarer. Mutations at different sites lead to fewer and shorter channel activations. In contrast to all above CMS, the slow-channel syndrome presents in childhood, adolescence or adult life with upper limb predominance and contractures, does not respond to anticholinesterase, and is progressive. CMS patients with a slow-channel syndrome show increased synaptic response to ACh with characteristic repetitive discharges in response to a single supramaximal stimulus. The syndrome results from gain-of-function mutations in the ion-conducting pore M2 [22]. The leaky AChR exert an excitotoxic effect and cause endplate myopathy via focal caspase activation [99].

18.3.2 Non-dystrophic Myotonia

Myotonia is an involuntary slowed relaxation after a forceful voluntary muscle contraction which is experienced by the patient as muscle stiffness. Situations requiring rapid motor control may provoke severe generalized stiffness causing the patient fall to the ground without being able to protect themselves, and liable to be injured or rendered unconscious. This has previously led to the misdiagnosis of epilepsy, prompting the use of antiepileptic drugs, particularly sodium channel blockers, which improved the myotonia. After making a forceful fist closure the patients are unable to open the hand immediately. Electrical hyperexcitability of the muscle fiber membrane is the basis of myotonia which is apparent in the form of repetitive action potentials in the EMG. Needle insertions in the resting muscle elicit myotonic bursts, i.e. bursts of action potentials with amplitude and frequency modulation that sound like dive bombers). Curare cannot block this activity. This differentiates the symptom from neuromyotonia, which is caused by spontaneous motor unit activity due to hyperexcitability of the terminal motor nerve branches.

18.3.2.1 Myotonia Congenita (MC), A Chloride Channel Myotonia

The two classical forms of myotonia, i.e. dominant myotonia congenita (or Thomsen myotonia) and recessive myotonia congenita (or Becker myotonia) are caused by mutations in *CLCN1*, the gene that codes for the chloride channel of skeletal muscle, ClC1 [49]. For this reason, they are also referred to as chloride channel myotonias. The muscle stiffness slowly progresses during childhood and adolescence whereas it typically decreases with continued exercise, a phenomenon called “warm-up” although it is not really related to temperature. It lasts for several minutes. The usually more severely affected Becker patients often exhibit hypertrophic leg and gluteal muscles and, due to muscle shortening as result of the continuous contractions, tend to toe-walk and develop a compensatory lordosis. The stiff, hypertrophic leg muscles cause gait problems. Very disabling is a peculiar transient weakness which lasts a few seconds following initial contractions [57, 97]. The pathomechanisms of the warm-up phenomenon and the transient weakness remain unclear.

Functionally, the ~15 dominant mutations exert a dominant-negative effect on the homodimeric channel complex as shown by co-expression studies, meaning that mutant/mutant and mutant/wildtype complexes are malfunctional. The most common feature of the resulting chloride currents is a shift of the activation threshold towards more positive membrane potentials almost out of the physiological range [71, 101]. As a consequence of this, the chloride conductance is drastically reduced in the vicinity of the resting membrane potential. Interestingly, both testosterone and progesterone rapidly and reversibly exert a similar effect on the channel [29]. The ~100 recessive mutations do not functionally hinder the associated subunit. This explains why two mutant alleles are required to reduce chloride conductance sufficiently for myotonia to clinically develop in Becker myotonia. Heterozygous carriers of a recessive mutation are healthy but may exhibit some myotonic runs in the EMG.

The prevalence of Thomsen disease is now estimated at ~1:400,000 [57], i.e. much lower than 1:23,000 as thought in the premolecular era [4]. This is owing to the fact that many families with dominant myotonia are now identified with sodium channel mutations which result in a different disease with very similar symptomatology. Other families were found to have Becker myotonia with pseudodominant inheritance. Conversely, the prevalence of Becker myotonia is now thought to be 1:25,000 [57], much higher than Becker's original estimate of 1:50,000 [4].

The frequency of patients carrying two such mutations in Europe may be estimated to be roughly 6:100,000 [3, 95, and our own data]. To deduce the positive predictive value of a *CLCN1* mutation in a myotonic patient, the ratio (true positives)/(true positives + false positives). When considering the fraction of RMC patients with at least one mutation of 67%, the true positives are 67%*0.00006 = 0.00004. Based on our testing, we can say that false positives in non-*CLCN1* myotonic disorders were 5/123 = 4% of patients. The prevalence of non-*CLCN1* myotonias taken together is 1:10,000 = 0.01% [4, 82]. Thus, the rate of false positives is: 4%*0.01% = 0.0000004. We can conclude that the positive predictive value of one recessive *CLCN1* mutation to identify a Becker myotonia mutation is approximately 0.00004/(0.00004+0.000004)~91%.

18.3.2.2 Sodium Channel Myotonia (SCM)

Autosomal dominantly inherited myotonia can be caused by mutations in *SCN4A*, the gene encoding the voltage-gated sodium channel of skeletal muscle, Nav1.4, The channel is essential for the generation of the muscle fiber action potential. SCM includes myotonia fluctuans, myotonia permanens, acetazolamide-responsive myotonia, and painful myotonia, i.e. a spectrum of diseases with overlapping clinical features which have in common that, in contrast to the allelic disorders paramyotonia congenita, hyperkalemic periodic paralysis and hypokalemic periodic paralysis, no weakness occurs [50, 69, 93]. The prevalence of SCM is estimated at ~1:400,000 [57].

At the first glance, *myotonia fluctuans* and moderate SCM are clinically very similar to the well-known Thomsen myotonia, so that this diagnosis usually is made.

However in contrast to Thomsen and Becker patients, SCM patients become stiff 10–30 min after strenuous work. This *delayed* and sometimes painful stiffness may hinder the patient's movements for several hours. It should not be confused with *paradoxical* myotonia, i.e. myotonia worsening with repeated contractions. Usually, most limb muscles show the warm-up phenomenon, and paradoxical myotonia is restricted to the eyelid muscles. Furthermore, potassium and other depolarizing agents (and sometimes cold) aggravate the myotonia, a reaction that is not observed in Thomsen and Becker patients. Therefore we have coined the term *potassium-aggravated myotonia* [37, 65]. SCM responds much better than chloride channel myotonia to sodium channel blockers like the flecainide.

A gating defect of the sodium channels destabilizes the inactivated state so that the channel inactivates slower and incomplete and conducts more sodium [58, 65, 106]. Despite the resulting sustained membrane depolarization, this increased sodium inward current generates repetitive action potentials because the mutant channels show less accommodation.

18.3.2.3 Paramyotonia Congenita (PMC) – Myotonic Stiffness and Flaccid Weakness

Also PMC is caused by *SCN4A* missense mutations with dominant effects on the sodium channel. Signs are present at birth and often remain unchanged throughout life. The cardinal symptom is cold-induced muscle stiffness that increases with continued activity (paradoxical myotonia). In the cold (or even in a cool wind), the face may appear mask-like, and the eyes cannot be opened for several seconds or minutes. On intensive cooling, in most families the stiffness gives way to flaccid weakness or even to paralysis. Families with R1448 substitutions PC also have episodes of generalized periodic paralysis [57]. Such attacks occur spontaneously and can be triggered by rest or potassium. They are of short duration (an hour or less) in comparison to the cold-induced weakness which usually lasts for several hours even when the muscles are immediately re-warmed after a short bout of exposure to cold. During a severe paralytic attack, the muscle stretch reflexes are diminished or absent. Under warm conditions, most patients have no complaints because impaired muscle relaxation improves at higher temperatures. Muscle atrophy or hypertrophy is not typical for the disease. PMC is considered an extremely rare disorder, though little epidemiological work has been done. Prevalence is generally higher in European derived populations and lower among Asians. Epidemiological estimates have been provided for the German population. Here, it was estimated that the prevalence of PC is between 1:350,000 and 1:180,000 [64a]. It should be noted, however, that the German population of patients with PC is not uniformly distributed across the country. Many individuals with PC herald from the Ravensberg area in North-West Germany, where a founder effect seems to be responsible for most cases [4a, 64a]. The prevalence here is estimated at 1:6,000.

Most PMC mutations are situated in protein parts relevant for channel inactivation, in the inactivation gate itself (i.e. the intracellular loop connecting domains III and IV like T1313M), in the outermost arginine of the voltage sensor in domain IV

(R1448H/C/S/P), in intracellular S4–S5 loops of domain III or IV (e.g. F1473S), or in the C-terminus [106]. During cooling to 27°C in-vitro, PMC muscle fibers slowly depolarize from -85 mV to about -45 mV whereas normal muscle fibers depolarize by not more than 5 mV. The depolarization is associated with a long-lasting burst of action potentials which stop as soon as the membrane potential approximates values of –40 to –50 mV [55, 59]. At this voltage, also the mutant sodium channels fibers are inactivated and therefore the muscle fibers become inexcitable and paralyzed. Functional expression of mutant channels revealed slowed fast inactivation and accelerated recovery from the inactivated state and an uncoupling of *fast* inactivation from activation [12, 54]. As also *slow* sodium channel inactivation should be incomplete to maintain depolarization-induced paralysis [74], several groups examined the effects of temperature on slow inactivation of the mutant channels [10, 75, 104]. The results were not uniform and difficult to interpret since entry into slow inactivation was already changed by the strikingly slowed fast inactivation.

18.3.3 Periodic Paralysis

Patients with muscle paralysis resulting from diseases associated with permanent electrolyte abnormalities are seldom misdiagnosed. In contrast patients with periodic paralysis may not have any interictal signs or symptoms and are often thought to suffer from a conversion reaction, and this may cause them to suffer needlessly. The weakness spells occur episodically with varying intervals of normal muscle function. Apparently, the underlying ion channel defects are usually well-compensated and an additional trigger is often required for channel, cell and tissue malfunction. Two dominant episodic types of weakness with or without myotonia are distinguished by the serum potassium level during the attacks of tetraplegia: hyper- and hypokalemic periodic paralysis. Due to release of potassium from muscle in the hyperkalemic form and uptake of potassium by muscle in the hypokalemic form, the resulting dyskalemia can be so severe that cardiac complications arise. During an attack, death can also occur due to respiratory insufficiency. Independently of the severity and frequency of the paralytic episodes, many patients develop a chronic progressive myopathy in the forties, an age at which the attacks of weakness decrease.

18.3.3.1 Hyperkalemic Periodic Paralysis (Hyperkalemic PP)

The disease is transmitted as an autosomal dominant trait with full penetrance, a male-to-female ratio of 1:1, and a prevalence of 1:200,000 [57]. It is characterized by attacks of flaccid weakness associated with an increase in serum potassium. Potassium-rich food or rest after exercise may precipitate an attack. A cold environment, emotional stress, fasting, and pregnancy provoke or worsen the attacks. Between attacks, the disease is often associated with myotonia, which is mild and does not impede voluntary movements but may exacerbate at the beginning of

an attack of weakness. Patients without interictal myotonia are much more prone to develop progressive myopathy and permanent weakness than individuals with myotonia. This becomes especially obvious in individuals with the most common T704M mutation which is not associated with EMG myotonia in half of the patients, and about half of the T704M patients develop permanent myopathy. The second most frequent mutation, M1592V, always is associated with EMG myotonia and permanent myopathy has never been reported.

Also hyperkalemic PP is caused by mutations in the voltage-gated sodium channel Nav1.4 [73]. Most Nav1.4 mutations are situated at inner parts of the transmembrane segments or in intracellular protein loops and affect structures that form the three-dimensional docking site for the fast inactivation particle, and any malformation may reduce the affinity between the "latch bar and the catch". The mutant channels avoid the inactivated state and, in contrast to normal sodium channels, reopen or flicker between the inactivated and the open state, corresponding to a gain-of-function defect [35, 100]. As a result, sodium influx is increased as shown in vitro [56] and in vivo [105]. This inward current is associated with a sustained membrane depolarization that increases the electrical driving force for potassium, and potassium released from muscle elevates the serum potassium level. Sodium influx into muscle is accompanied by entrance of water into the fibers, causing hemoconcentration and further increase in serum potassium. This is a vicious cycle which spreads out and affects the surrounding muscle fibers. Starting point is the elevation of extracellular potassium due to ingestion or exercise.

18.3.3.2 Hypokalemic Periodic Paralysis (Hypokalemic PP)

The disease is transmitted as an autosomal dominant trait with reduced penetrance in women (the male to female ratio is 3 or 4–1) and is the most common of the primary PP (prevalence of 1:100,000) [57]. It differs from hyperkalemic PP in the sense that a spontaneous attack is associated with hypokalemia, potassium is a remedy, and carbohydrate- and sodium-rich food triggers an attack, and the EMG does not show myotonia. In general, the attacks last longer and are more severe. Usually, the patients are weakest during the second half of the night and in the morning, and become stronger as the day goes by.

Hypokalemic PP is caused by voltage sensor mutations in Cav1.1 (hypokalemic PP type 1) and Nav1.4 (hypokalemic PP type 2) [30, 44]. Results on sodium and calcium channels indicate that voltage sensor mutations may create an accessory ion pathway generating a hyperpolarization-activated cation leak independent of the main channel pore [47, 86, 92]. This membrane leak opens under hypokalemic conditions and depolarizes the muscle fibers to -50 mV and renders them inexcitable [47]. As muscle fibers are depolarized at potassium levels in the low normal range, this membrane leak might also be responsible for the progressive myopathy patients with certain mutations suffer from. About 80% of the patients in whom a mutation was identified harbor the R528H or the substitution in Cav1.1 while R1239H seems to predispose to the progressive myopathy in all of them.

18.3.3.3 Dyskalemic Periodic Paralysis Caused by KCNE3/MiRP2 Alteration?

In 2001, an R83H substitution in a K+ channel beta subunit, MiRP2, was suggested to cause dyskalemic periodic paralysis because it showed a loss of function in vitro and was found in 2 of 100 of such patients but in none of 120 unaffected controls [1]. By later studies, the substitution was identified in 1 of 104 and 1 of 138 patients, but also in 8 of 506 and 3 of 321 controls [42, 90]. Taken together, the substitution is present in 1.17% of patients and in 1.16% of healthy controls, which does not support disease causality and shows that the common lab practice to exclude a novel mutation in approximately 100 healthy controls is insufficient.

18.3.3.4 Andersen–Tawil Syndrome (ATS)

ATS is a periodic paralysis with cardiac arrhythmia and dysmorphic features. The prevalence is estimated to <1,000,000. Patients may experience a life-threatening ventricular arrhythmia independent of their PP, and long QT syndrome is the primary cardiac manifestation. The syndrome is characterized by the highly variable clinical triad of dyskalemic PP, ventricular ectopy, and potential dysmorphic features [79]. The paralytic attack may be hyperkalemic or hypokalemic and accordingly, the response to oral potassium is unpredictable. Mutations of the Kir2.1 potassium channel, an inward rectifier expressed in skeletal and cardiac muscle, are causative of the disorder [70]. Kir2.1 channels are essential for maintaining the highly negative resting membrane potential of muscle fibers and accelerating the repolarization phase of the cardiac action potential. The mutations mediate loss of channel function by haploinsufficiency or by dominant-negative effects on the wildtype allele and may lead to long-lasting depolarization and membrane inexcitability.

18.3.3.5 Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis (TPP) resembles familial HypoPP with respect to changes in serum and urinary electrolytes during attacks and in its response to glucose, insulin, and rest after exertion. However, it differs from familial HypoPP in the adverse effect of thyroid administration and that the male to female ratio in Japanese is about 6:1 and the onset is usually after the age of 20 years. Forty-five percent of the patients develop the syndrome in the third decade, another 35% in the fourth, and the rest in the fifth decade of life. More than 75% of the cases occur in Orientals suggesting a predisposing racial factor (Chinese, Japanese, Korean, Vietnamese). The attacks occur much more frequently in summer than in winter. A geographical component is not likely, because Chinese or Japanese immigrants in North or South America have same disease frequency as in their country of origin. Reports of cases in Caucasians and Blacks indicate that the disease rarely occurs in non-Orientals as well. An unusual association with Hashimoto's thyroiditis has been reported familial in one Chinese family.

The thyrotoxicosis precedes or appears simultaneously with the periodic paralysis in more than 80% of the TPP patients [23] but the thyrotoxic signs are relatively mild at the time of the initial attack (no palpitations, goiter, or exophthalmus). Typical are sudden paralytic attacks of proximal limb muscles after strenuous exercise or at rest following high-carbohydrate meals in the evening or during the night, and hypokalemia during the attacks. The serum potassium falls to levels below 3.5 mM in 80% of the patients. In some patients it may be as low as 1.2 mM and cause life-threatening arrhythmias or sino-atrial block. As the hypokalemia is the result of an insulin-induced shift of potassium from the extracellular space into the muscle, potassium is released from muscle at the end of an attack to cause rebound hyperkalemia. During an attack, both the arrhythmia and the acute paralytic attack are relieved by administration of potassium.

More than 75% of the cases occur in Asians, suggesting a predisposing racial factor. Statistically, the incidence of thyrotoxic PP in Asian men with hyperthyroidism (Graveś disease) has been estimated at between 13 and 24% [57]. In contrast to TPP, Graves' disease shows a 5:1 female to male predominance with a prevalence of 2% in the general population. In Kir2.6, an inwardly rectifying potassium channel that is transcriptionally regulated by thyroid hormone, mutations were identified in 4 of 30 unrelated TPP patients [77].

18.3.4 Disorders of Excitation-Contraction Coupling

Muscle contractures as well as flaccid weakness are characteristic features of disturbed muscle excitation-contraction coupling. Two allelic forms are well studied: central core disease (CCD) and multiminicore disease.

18.3.4.1 Central Core Disease

Central core disease (CCD) is a congenital myopathy clinically characterized by muscle hypotrophy and weakness and a floppy infant syndrome, often alongside other skeletal abnormalities such as hip displacement and scoliosis. The clinical severity of CCD and the number of cores can vary with age: there is also variability between and within families. The serum CK is normal or mildly elevated. Pathognomonic is the abundance of central cores devoid of oxidative enzyme activity along the predominant type 1 muscle fibers. Usually the mode of inheritance is dominant. The disease is caused by mutations in mutations in the C-terminal region of the ryanodine receptor RyR1 of skeletal muscle which is located in the membrane of the sarcoplasmic reticulum (SR). Some mutations decrease the open probability of the channel so that it loses the ability to release calcium from the SR, thereby causing muscle weakness. Other mutations increase the open probability of the channel, leading to depleted SR calcium stores and weakness.

18.3.4.2 Multiminicore Disease

Multiminicore disease (MmD) is considered a recessively inherited congenital myopathy with a pattern of weakness that differs from central core disease in that

there is often severe axial involvement, while respiratory, bulbar and extra-ocular muscles are commonly affected. As with CCD, the condition is stable or minimally progressive, and the serum CK is normal or only mildly elevated. MmD is characterized by cores lacking oxidative enzyme activity on histochemical analysis. However, in contrast to CCD the cores in MmD are usually multiple, are poorly defined and do not extend along the axis of the fiber. Of the four clinical subtypes of MmD, the moderate form is a channelopathy. It presents with generalized muscle weakness that affects predominantly the pelvic girdle and may lead to scoliosis. This form can involve the hand muscles and lead to amyotrophy and muscle hyperlaxity. This form and another one, associated with ophthalmoplegia, are most often associated with *RYR1* variants [41] which can be homozygous, compound heterozygous or heterozygous with mono-allelic expression and which are spread across the whole RYR1 protein. Furthermore, there are myopathic patients with histological cores in whom mutations of RYR1 and the other MmD-responsible genes such as *ACTA1* and *SEPN1* have been excluded.

18.3.4.3 Susceptibility to Malignant Hyperthermia

Susceptibility to malignant hyperthermia susceptibility (MHS) is an autosomal dominant predisposition of clinically inconspicuous individuals to respond abnormally when exposed to volatile anesthetics, depolarizing muscle relaxants or extreme physical activity in hot environments. During exposure to triggering agents, a pathologically high increase in myoplasmic calcium concentration leads to increased muscle metabolism and heat production resulting in muscle contractures, hyperthermia associated with metabolic acidosis, hyperkalemia, and hypoxia. The metabolic alterations usually progress rapidly and without immediate treatment, up to 70% of the patients die. Early administration of dantrolene, an inhibitor of calcium release from the sarcoplasmic reticulum (SR) has successfully aborted numerous fulminant crises and has reduced the mortality rate to less than 10%.

Malignant hyperthermia occurs worldwide and affects all racial groups. Most cases occur in children and young adults for unknown reason. Incidence of MH crises during general anesthesia varies age-dependently from 1:15,000 in children to 1:50,000 in adults [68]. As the triggering substances elicit an event only in a fraction of anesthesias, the true prevalence of MH susceptibility may be higher than the very low clinical penetrance. In accordance with the varying severity of the clinical picture, non-anesthetic MH-like episodes triggered by overheating, body exertion, and infections have been described. Evidence for a relation to the sudden infant death syndrome is rather weak. MH-like crises have also been observed in patients with myopathies such as myotonia fluctuans, Duchenne/Becker progressive mucular dystrophy, myotonia congenita and myotonic dystrophy. It seems very likely that the molecular mechanisms underlying these MH-like events differ from those of true MH susceptibility, e.g. in the myotonic diseases as increased myotonic reactions to anesthetic agents. This different pathogenesis, of course, does not obviate the need for caution when considering general anesthesia in these disorders.

In up to 70% of MHS families, variants in the skeletal muscle isoform of the ryanodine receptor gene *RYR1* have been identified. In contrast to the CCD mutations,

most of the MHS variants are situated at the N-terminus of the protein. Only 29 of the more than 200 sequence variations in *RYR1* have been investigated for their functional effect and meet the criteria to be included in the guidelines for molecular genetic detection of MH susceptibility. In the absence of a "high-throughput" method to investigate novel variants for being causative, these functional analyses remain laborious and they have not kept pace with the detection rate of novel variants in this large gene. Although it is likely that many of the currently uncharacterized *RYR1* variants associated with MH susceptibility will have pathological significance, until this is proven they have no diagnostic utility. In these circumstances patients with a personal or family history suggestive of MH should be considered at risk of the condition until proven otherwise by normal responses of muscle biopsy specimens to in vitro contracture tests.

18.4 Conclusion

As ion channels constitute one of the only protein families that allow functional examination on the molecular level, expression studies of putative mutations have become standard in supporting the disease-causing nature of mutations. While this is quite helpful, one must not over-interpret functional changes that a mutation produces because these changes may not necessarily indicate a disease-causing mutation but a functional polymorphism instead. Additionally, functional polymorphisms are *not* the equivalent to susceptibility mutations [52]. The confusion of these two does not only lead to circulating errors in the scientific community that take years to correct, but many patients will be falsely diagnosed and treated as well. Therefore, functional studies do not alleviate from the need for the genetic screening of large and adequately matched control populations for the putative mutations. Association analysis is essential to prove disease association or causality. Two reports have proposed the typing of 150–200 controls (300–400 chromosomes) for putative mutations with a prevalence of 1% by power analysis [14, 63]. A more general equation that simply allows to calculate the number of required controls for such studies [42]. The number depends on the prevalence of the change of interest: rare changes require quite a large number of controls. Likewise, scientists must exercise utmost care in the interpretation of genetic epidemiologic results including reviews of the status quo as in the present text.

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Chapter 19
Osteochondral Diseases and Fibrodysplasia Ossificans Progressiva

Antonio Morales-Piga and Frederick S. Kaplan

Abstract Osteochondrodysplasias like thanatophoric dysplasia, osteogenesis imperfecta, achondroplasia, and other genetic skeletal disorders like fibrodysplasia ossificans progressiva are infrequently seen in clinical practice. In cases of sporadic achondroplasia as well as in fibrodysplasia ossificans progressiva, there is a strong association with paternal age, a relationship that is less evident in other genetic osteochondral diseases. No other constitutional or environmental factor has proven to be associated with these disorders. The use of prenatal ultrasonography as a routine component of prenatal care is crucial in the early suspicion of osteochondrodysplasias whereas definitive diagnosis is usually obtained by pre-natal molecular analysis. In the case of fibrodysplasia ossificans progressiva, recognition of congenital great toe malformations associated with rapidly–appearing soft tissue swelling is sufficient to make the proper clinical diagnosis, which can be confirmed by genetic testing. Large regional centres will improve diagnosis performance, provide accurate genetic counselling, and ensure an integral assistance for these often severe and incapacitating conditions.

Keywords Constitutional disorders of bone · Osteochondrodysplasias · Fibrodysplasia ossificans progressiva · Paternal age effect · Prenatal ultrasound · Pre-natal molecular analysis · Early clinical and radiological detection · Genetic counseling

19.1 Scope and Definitions

The complexity of the skeleton, the diverse origin of its components, and the heterogeneity of its physiology provides a basis for understanding the broad diversity of ways in which bone, cartilage and related tissues may become damaged.

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Historically, skeletal disorders are often described eponymously, descriptively or pathologically.

In an attempt to develop an operative and universally accepted classification, a group of experts met in 1970 and proposed an International Nomenclature called "Constitutional (or Intrinsic) Disorders of Bone" [24]. This classification was subsequently revised. The latest revision incorporates recognized disorders and reflects new molecular and pathogenetic concepts [36]. Three hundred seventy-two different conditions were included and placed in 37 groups defined by molecular, biochemical and/or radiographic criteria. Of these conditions, 215 were associated with one or more of 140 different genes.

A comprehensive description of the epidemiology of these diseases, many of which lack consistent data, is beyond the aim of this chapter. Epidemiological studies based on total populations are expensive and difficult to perform. The scant reports available on skeletal dysplasias are heterogeneous and incomplete, so that critical data are missing or are not comparable. In addition, many of these disorders are difficult to diagnose and thus often misclassified. Moreover, they might remain undiagnosed, especially in stillborn babies and in children dying shortly after delivery. As a consequence, here we briefly review the data on the disorders usually recognizable at birth that cause the most relevant clinical involvement, and on which there is reliable information about frequency, determinants and consequences. We will address separately the osteochondrodysplasias from fibrodysplasia ossificans progressiva, a genetic disorder of ectopic skeletogenesis.

19.2 Epidemiology of Osteochondrodysplasias

Osteochondrodysplasias are a heterogeneous group of more than 200 disorders characterized by abnormalities of cartilage and bone growth and development resulting in abnormal shape and size of the skeleton and disproportion of the long bones, spine, and head [34]. Classically, this concept includes: achondrogenesis, achondroplasia, chondrodysplasia punctata, camptomelic dysplasia, congenital lethal hypophosphatasia, perinatal, lethal type of osteogenesis imperfecta, thanatophoric dysplasia, and short-rib polydactyly syndromes, among other important disorders [24, 34].

19.2.1 Frequency Measurements, Gender, Parental Age, and Familial Occurrence

Table 19.1 summarizes data of the major epidemiological studies on osteochondrodysplasias [1–3, 6, 7, 10, 16, 25, 27, 30, 35]. In these studies the point prevalence rates (at delivery) vary from 1.1 [7] to 9.46 [1], per 10,000 births. Although ethnic and geographic variations can not be discounted, differences in case ascertainment, definition, and classification criteria account for the largest part of this variation. The highest prevalence rate corresponds to the most recent survey, performed in an

Table 19.1 Summary of main epidemiological studies on osteo-condral diseases (in chronological order)

References (year) [Area; country]	Setting Years of study	Population targeted and period of ascertainment	No. of cases (female/male)	Rate per 10.000 deliveries (95%CI, when provided)
Gustavson [10] (1975) Uppsala (Sweden)	Hospital-based Feb 1970–Aug 1974	Osteochondrodysplasias in newborns	7 (4/ 3)	4.7
Camera [6] (1982) Italy (90' hospitals)	Hospital-based (multicenter)	Osteochondrodysplasias in newborns (first 7 days)	53	2.4 (1.8–3.2)
Connor [7] (1985) West Scotland	Population-based 1970–1983	Lethal neonatal Osteochondrodysplasias	38	1.1
Orioli [25] (1986) [20 cities; 9 South American countries]	Hospital-based (multicenter) 1978–1983	Osteochondrodysplasias in newborns (first 3 days)	80 (47/ 32) (+ 1 intersex)	2.3
Stoll [35] (1989) [Strasbourg; France]	Population-based Jan 1979–Dec 1986	Osteochondrodysplasias in newborns (first 8 days)	34 (18/16)	3.22
Andersen [2] (1989) [Fyn; Denmark]	Population-based Jan 1970–Dec 1983	Lethal Osteochondrodysplasias	12	1.5
Andersen [3] (1989) [Fyn; Denmark]	Population-based Apr 1973–Dec 1983	Generalized bone dysplasias (any age)	59	7.6 (5.9–9.3)
Sánchez [30] (1991) [Ciudad Bolívar; Venezuela]	Hospital-based (monitoring system) Apr 1978–Aug 1990	Osteochondrodysplasias in newborns	25	3.5
Källén [16] (1993) [International]	Monitoring systems: – 3 hospital-based – 4 population-based	Osteochondrodysplasias (age no specified)	1,500	1.6

Table 19.1 (continued)

References (year) [Area; country]	Setting Years of study	Population targeted and period of ascertainment	No. of cases (female/male)	Rate per 10.000 deliveries (95%CI, when provided)
Rasmussen [27] (1996) [Boston , USA]	Hospital-based	Neonatal Osteochondrodysplasias (first 5 days)	27 (14/11) [+ 2 undetermined]	2.14
Al-Gazali [1] (2003) [United Arab Emirates]	Hospital-based (multicenter) Jan 1996–Dec 2000	Osteochondrodysplasias in newborns (first 7 days)	36 (23/13)	9.46

area with high risk of inbreeding [1]. The second highest point prevalence – 7.6 per 10,000 births – corresponds to the only study performed on generalized bone dysplasias including cases detected in both the neonatal period and later in life [3]. The majority of these studies include cases detected in the perinatal period, which probably underestimates the true rate of osteochondrodysplasias. Milder cases are seldom recognizable in this period because they do not manifest until short stature, joint symptoms, or other skeletal complications arise during childhood. Importantly, incomplete investigation of the cases could mask the true frequency at birth. This fact could lead one to underestimate the true prevalence of bone dysplasias, especially when the diagnosis is retrospective.

One of the most controversial issues in this field is the association between parental age and the occurrence of osteochondrodysplasias. Some general studies report that a higher paternal age exists in sporadic achondroplasia [25, 35], consistent with that of other previous [23] and subsequent work [39]. In contrast, Al Gazali did not observe statistical differences between the ages of fathers and mothers of the newborns with either sporadic achondroplasia or thanatophoric dysplasia, compared to the controls [1]. In one study specifically designed to address this aspect, paternal ages of nonfamilial cases of achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta from both an Italian and a South American series, were compared with matched controls [26]. The degree of paternal age effect on the origin of these dominant mutations differed among the three conditions. Thus, in achondroplasia mean paternal age was elevated in both the Italian (36.30 ± 6.74 years) and Latino American (37.19 ± 10.53) series. In thanatophoric dysplasia, mean paternal age was also elevated in both series, although less consistently. In osteogenesis imperfecta, paternal age was only slightly elevated in the South American cases whereas in Italian cases paternal age did not differ from controls. Increased maternal age or "birth order" in these conditions disappeared when corrected for paternal age. Approximately 50% of achondroplasia and thanatophoric dysplasia cases and only 30% of osteogenesis imperfecta cases were born to fathers above age 35 years. For achondroplasia and thanatophoric dysplasia, the increase in relative incidence with paternal age fit an exponential curve. Taken together, these data suggest a strong relationship between an older paternal age and the appearance of sporadic achondroplasia, an association that is less evident in other genetic osteochondral diseases.

The frequency of parental consanguinity, which also was rarely addressed in depth, ranges widely between 4% [25] and 72% [1], reflecting variations in ascertainment as well as in methods of study. Family history was occasionally reported, being remarkable in isolated cases of proven achondroplasia [25], ostopetrosis [35] and osteogenesis imperfecta [27]. No indications of geographical cluster were communicated.

Only six studies have a sample size large enough to allow a reliable disclosure between subtypes of osteochondrodysplasias [1, 3, 6, 25, 27, 35] (Table 19.2). However, it should be noted that setting, design, and research methods were quite different between these studies (Table 19.1), making their results heterogeneous and difficult to compare. In addition, in the pre- and peri-natal period, the differentiation

Table 19.2 Relative frequency (point prevalence at birth/10,000) of osteochondrodysplasias (outsiders values are in bold)

Condition	Author (References)					
	Camera [6]	Orioli [25]	Stoll [35]	Andersen [3]	Rasmussen [27]	Al-Gazali [1]
I. Usually frequent (in order of frequency)						
Thanatophoric dysplasia	0.69	**0.09**	0.28	0.38	0.40	0.78
Osteogenesis imperfecta	0.36	0.43	0.64	**2.2**	0.40	0.78
Achondroplasia[a]	0.37	0.46	0.46	**0.13**	0.24	1.04[b]
Achondrogenesis	0.23	**0.03**	0.28	0.64	–	–
II. Usually rare (in alphabetical order)						
Achondrogenesis or Thanatophoric dysplasia	–	0.11	–	–	–	–
Asphyxiating thoracic dysplasia (Jeune)	0.14	–	0.09	0.26	–	0.26
Campomelic dysplasia	0.05	0.09	0.09	0.13	0.16	0.26
Cereebro-costo-mandibular Dysplasia	–	–	–	–	–	0.26
Chondrodysplasia punctata (all types)	0.09	0.06	0.27	0.13	–	**1.04**
Chondroectodermal dysplasia	0.05	0.06	0.09	–	–	–
Cleidocraneal dysplasia	–	0.03	–	–	–	–
Desbusquois syndrome	–	–	–	–	0.08	–
Diastrophic dysplasia	–	0.03	0.09	–	–	–
Ellis van Creveld syndrome	–	–	0.09	–	–	**0.52**
Engelman disease	–	–	0.09	–	–	–
Fibrochondrogenesis	–	–	–	–	–	**1.05**
Fibrous dysplasia	–	0.03	0.09	–	–	–
Hypochondroplasia	–	–	–	0.13	–	–
Hypophosphatasia	–	0.03	–	–	–	–
Larsen syndrome	0.05	–	–	–	0.08	–
Melnick-Needles (Ostodysplasty)	–	–	–	–	0.08	–
Metaphyseal chondrodysplasia (Schmid type)	–	–	–	0.13	–	–
Micromelic dysplasia with Cloverleaf skull	–	–	–	0.26	–	0.26
Multiple cartilaginous exostoses	–	–	0.18	1.28	–	–
Multiple epiphyseal dysplasia (tarda)	–	–	–	0.9	–	–

Table 19.2 (continued)

Condition	Author (References)					
	Camera [6]	Orioli [25]	Stoll [35]	Andersen [3]	Rasmussen [27]	Al-Gazali [1]
Osteopetrosis	–	–	0.18	**0.51**	–	0.26
Schneckenbecken dysplasia	–	–	–	–	–	0.26
Schwartz-Jampel syndrome	–	–	–	–	–	0.52
Short rib polydactyly (any type)	–	–	–	–	0.16	0.52
Spondyloepiphyseal dysplasia	–	–	–	0.26	0.24	–
Stickler syndrome	–	–	–	–	–	**0.52**
Without specific diagnosis	0.23	0.37	No specified	0.26	0.32	No specified

[a]Only "true" cases of Achondroplasia are considered; some authors' added some "questionable" cases.
[b]Original data are presented disaggregated by pattern of inheritance. The frequency of achondroplasia was 0.78 for sporadic cases and 0.26 for inherited ones. As per osteogenesis imperfecta, sporadic cases represent 0.52 whereas inherited cases account for the remaining 0.26.

between bone dysplasias is often difficult and in most instances a sensible proportion of cases, reported from 16% [27] to 42% [25], did not fit into a specific diagnostic category. Although these limitations oblige caution, it is possible to make some general observations. Four conditions appear to predominate: Thanatophoric dysplasia, osteogenesis imperfecta, achodroplasia and achondrogenesis (Table 19.2). One exception is the report of Orioli et al. [25], a multicenter hospital based study performed in 20 cities of nine South American countries, in which thanatophoric dysplasia shows a frequency that is unusually low. The other confounding data are that of Al Gazali et al. [1], which report on a population with a huge proportion of consanguinity and, therefore, prone to develop autosomal recessive disorders.

The birth prevalence of sporadic achondroplasia shows a wide variation ranging from 0.13 [3] to 0.78 [1]. However, most authors provide values near to the lower limit (0.46 [25, 35], 0.37 [6], 0.24 [27]), well below the expected prevalence. Consequently, there is an agreement that this represents the recognised tendency to over-register achondroplasia, mostly due to the misdiagnosis of cases of thanatophoric dysplasia and achondrogenesis [3, 8, 25].

Apart from these general studies, few investigations have ascertained the prevalence of specific osteochondrodysplasias. In a population based study on achondroplasia and thanatophoric dysplasia performed in selected regions of the US the prevalence of achondroplasia ranged from 0.36 to 0.60 per 10,000 livebirths (1/27,780–1/16,670 livebirths) and the prevalence of thanatophoric dysplasia ranged from 0.21 to 0.30 per 10,000 livebirths (1/33,330–1/47,620 livebirths) [39]. These results were consistent with previously reported general studies on osteochodrodysplasias [1, 3, 6, 25, 27, 35] (Table 19.2).

19.2.2 Early Detection and Specific Diagnosis

The increasing use of prenatal ultrasound is changing the surveillance of skeletal dysplasias [27, 35]. Although, diagnostic specificity is difficult with this procedure, a high proportion of chondrodysplasias can be suspected early in gestation with its appropriate use. From an epidemiologic viewpoint, prenatal diagnosis may prevent the delivery of a stillborn infant or of an infant destined for early death, but does not appear to change the frequency of delivery of liveborns likely to survive more than a month [27].

The increasing trend of prenatal diagnosis has altered the birth status of cases of osteochondrodysplasias which, with a growing frequency, are the products of pregnancy terminations after ultrasonographic identification. As a consequence, making an accurate diagnosis by traditional clinical means could be difficult, and in some cases impossible. In spite of this, clinical manifestations and radiological investigations remain a cornerstone in the diagnosis of generalised bone dysplasias. As a rule, the radiological findings in these disorders are so characteristic that an exact diagnosis can be made, even after destructive pregnancy termination procedures [27]. Nevertheles, with the increasing use of ultrasonography, the role of biochemical and molecular techniques in diagnosis of some osteochondrodysplasias appears to be

crucial, especially in order to provide appropriate genetic counselling [4, 5, 11, 29, 31, 37]. Their implementation has the potential for assisting in the specific diagnosis of cases of osteochondrodysplasias, and could allow for earlier and more accurate prenatal diagnosis in future pregnancies [27]. This is important because, even in cases where the therapeutic possibilities are few or non-existent, a correct diagnosis is crucial for valid genetic counselling and evaluation of clinical prognosis.

19.2.3 Temporal Trends

In diverse geographical areas, an increasing temporal trend has been reported in the occurrence of generalised bone dysplasias [1, 16]. Thus, the birth prevalence of osteochondrodysplasias in the United Arab Emirates seems to have doubled in the last 2 years of the 5-year observation period (6.74/10,000 in 1996 vs. 12.86/10,000 in 1999, and 13.45/10,000 in 2000). Although such tendency could be explained by changes in ascertainment methods [16], it is not possible to rule-out increased parental exposure to either environmental or domestic teratogenic agents [1].

19.2.4 Mortality Rates

With the exception of achondroplasia, there is a paucity of data about mortality in osteochondroysplasias. In the few general studies in which this aspect is mentioned, the data are scant and fragmentary. Thus, in one of these studies, the overall frequency of skeletal dysplasias among peri-natal deaths was 9.1 per 1,000 [6]. In Orioli's series, the peri-natal mortality rate for skeletal dysplasias was as high as 44% (with no deaths among the 16 proven achondroplasia cases), and rated at 40% for the osteogenesis imperfecta cases [25].

An additional difficulty concerns the low quantity and poor quality of available information on this topic. Further, it is important to analyse mortality data attributable to osteochodrosysplasias in the context of general causes of death in children. Results from a Canadian study showed that infant deaths caused by major congenital anomalies have decreased substantially from 3.11 per 1,000 live births in 1981 to 1.89 per 1,000 live births in 1995 [40]. Because the decrease in major congenital anomaly-attributed infant mortality paralleled the decrease in infant mortality due to other causes, the percentage of infant deaths attributable to major congenital anomalies remained constant at about 30% during the 15 years of study. Reductions varied according to specific forms of anomalies. Cause-specific infant mortality rates (per 1,000 live births) for musculoskeletal anomalies and multiple congenital anomalies were of 0.22 and 0.13 respectively, in 1981–1983, whereas corresponding rates were 0.12 and 0.06 in 1993–1995. By contrast, during the same time period, there were only moderate non-significant decreases or even a tendency to an increase in infant deaths due to urinary system, respiratory system, and chromosomal anomalies. This substantial decrease in infant mortality related to certain congenital anomalies, particularly in skeletal dysplasias and multiple congenital anomalies, seems to be the result of increased prenatal diagnosis [40].

The only exception to the scarcity of mortality data on specific osteochondrodysplasias is achondroplasia, perhaps because premature death, particularly in young adults, has been a big concern [13]. Studies performed on large cohorts of proven cases revealed that the overall mortality and age-specific mortality at all ages remained significantly increased [13, 41]. Moreover, rates of death were similar across all 42 years of follow-up suggesting that higher death rates were still occurring in the contemporary achondroplasia population. Overall survival and the average life expectancy for this population were decreased by 10 years. Compared to the general population, accidental, neurological, and heart disease related deaths were increased in adults with achondroplasia. Specifically, heart disease-related mortality, between ages 25 and 35, was more than 10 times higher than the general population. These results demonstrate that despite advances in the knowledge of the natural history of achondroplasia and improvements in health care, mortality remains increased in this disease. The high rate of heart disease related deaths illustrates the need to identify specific risk factors and, accordingly, develop treatment interventions.

19.3 Epidemiology of Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva, the most severe and disabling disorder of extraskeletal ossification in humans, is a genetic condition characterised by congenital malformation of the big toe and progressive heterotopic ossification following specific anatomic patterns [9, 20]. The worldwide prevalence is, approximately, one in two million of individuals [9, 20].

There appears to be no ethnic, racial, gender, or geographic predisposition [18, 19, 32]. Most cases arise as a result of a spontaneous new mutation and a paternal age effect has been reported [28]. Fewer than ten small multigenerational families are known [32]. When inherited, the pattern of transmission is autosomal dominant. The condition can be inherited from either mothers or fathers [17, 32]. Maternal mosaicism has been described [15].

Phenotypic heterogeneity has been observed in fibrodysplasia ossificans progressiva [14, 38] and, both, genetic and environmental factors affect the phenotype of the disease. A study of three pairs of monozygotic twins found that within each pair, congenital toe malformations were identical. However, postnatal heterotopic ossification varied greatly depending on life history and environmental exposure to viral illnesses and to soft tissue trauma. Genetic determinants strongly influence disease phenotype during prenatal development while environmental factors strongly influence postnatal progression of heterotopic ossification [12].

Diagnostic errors are common in fibrodysplasia ossificans progressiva [9, 20, 21]. Most patients are misdiagnosed before the appearance of heterotopic ossification and undergo unnecessary diagnostic and therapeutic procedures that alter the natural history of the disease, causing permanent harm [21, 22]. However, an accurate diagnosis of the disease can be made early in life on the basis of the clinical findings of tumor-like swellings in association with characteristic malformed great toes [22].

The recent identification of the genetic cause of fibrodysplasia ossificans progressiva represents a real hope for a better control of this disorder [33]. After identifying linkage of fibrodysplasia ossificans progressiva to chromosomal region 2q23–24, a recurrent mutation in the gene encoding activin A receptor, type I (ACVR1), a BMP type I receptor, was demonstrated as the cause of all classically-occurring inherited and sporadic cases [33]. The identification of this gene, also known as activin like kinase 2 (ALK2), allows a reliable confirmatory diagnoses before ectopic ossification appears [20, 22]. Recognition of highly specific diagnostic features of the disease – particularly congenital great toe malformations associated with rapidly–appearing soft tissue swelling, should prompt early genetic consultation and testing. Such proper diagnosis can avoid harmful diagnostic and therapeutic procedures. The identification of fibrodysplasia ossificans progressiva provides a specific target for the development of therapeutic agents that block overactive ACVR1/ALK2 signaling, and thus may eventually prevent the progression of the disease [20, 22].

19.4 Implications of Epidemiological Findings: Conclusions and Recommendations

Generalized bone dysplasias are more frequent than generally assumed, with thanatophoric dysplasia, osteogenesis imperfecta, achondroplasia and achondrogenesis, accounting for the majority of cases. True Achondroplasia is less common than expected, perhaps because many bone dysplasias are often erroneously classified as achondroplasia. Thus, it is important to emphasize correct diagnosis for prognosis, treatment, and genetic counselling.

In sporadic achondroplasia as well as in fibrodysplasia ossificans progressiva, there is a strong association with paternal age, a relationship that is less evident in other genetic osteochondral diseases. No other constitutional characteristic has proven to be associated with generalised skeletal dysplasias. Similarly, no environmental agents, either chemical or biological, have been demonstrated, although more research should be done to determine the possible role of these exposures in the etiology of osteochondrodysplasias. Environmental agents, by increasing the rate of mutation, might explain the increasing occurrence observed in different countries, although changes in ascertainment methods can not be excluded.

Clinical and radiographic features are crucial for diagnosis of osteochondral diseases and fibrodysplasia ossificans progressiva since radiological findings are often definitive. In suspected cases of skeletal abnormalities and dwarfism, it is important to obtain skeletal surveys as soon as possible in order to secure the correct diagnosis. In the case of fibrodysplasia ossificans progressiva, recognition of congenital great toe malformations associated with rapidly–appearing soft tissue swelling early in childhood is sufficient to make the proper diagnosis, which can be confirmed by genetic testing. Such proper diagnosis can avoid substantial iatrogenic harm.

The use of prenatal ultrasonography as a routine component of prenatal care can aid in the suspicion of osteochondrodysplasias earlier in pregnancy. However, as a specific diagnosis is required for the counselling of families, additional methods

are needed. Definitive diagnosis is most often achieved by pre-natal molecular analysis.

Although osteochondrodysplasias and other genetic skeletal disorders are relatively frequent in general practice, individually they are rare. As a consequence, it is difficult for most hospital and primary care services to obtain experience in managing these disorders. These facts emphasize the need for large regional centres which will improve diagnosis performance and provide the integral assistance for these often severe and incapacitating conditions.

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Chapter 20
The Prevalence of Congenital Anomalies in Europe

Helen Dolk, Maria Loane, and Ester Garne

Abstract EUROCAT (European Surveillance of Congenital Anomalies) is the network of population-based registers of congenital anomaly in Europe, with a common protocol and data quality review, covering 1.5 million annual births in 22 countries. EUROCAT recorded a total prevalence of major congenital anomalies of 23.9 per 1,000 births for 2003–2007. 80% were livebirths. 2.5% of livebirths with congenital anomaly died in the first week of life. 2.0% were stillbirths or fetal deaths from 20 weeks gestation. 17.6% of all cases were terminations of pregnancy following prenatal diagnosis (TOPFA). Thus, congenital anomalies overwhelmingly concern children surviving the early neonatal period, who have important medical, social or educational needs. The prevalence of chromosomal anomalies was 3.6 per 1,000 births, contributing 28% of stillbirths/fetal deaths from 20 weeks gestation with congenital anomaly, and 48% of all TOPFA. Congenital heart defects (CHD) were the most common non-chromosomal subgroup, at 6.5 per 1,000 births, followed by limb defects (3.8 per 1,000), anomalies of urinary system (3.1 per 1,000) and nervous system defects (2.3 per 1,000). In 2004, perinatal mortality associated with congenital anomaly was 0.93 per 1,000 births, and TOPFA 4.4 per 1,000 births, with considerable country variation. Primary prevention of congenital anomalies in the population based on controlling environmental risk factors is a crucial policy priority, including preconceptional care and whole population approaches.

Keywords Congenital anomalies · Prevalence · Registers · Perinatal mortality

20.1 Introduction

Collectively, congenital anomalies present an important public health issue in terms of (a) impact on the quality of life of affected children and adults and their families

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(b) contribution to fetal and infant mortality, both in terms of loss of potential years of life and wellbeing of the family (c) provision, quality and financial cost of medical, social and educational services to improve the participation and quality of life of affected individuals and their families and (d) provision, quality and financial cost of prenatal screening in the population and its psychological cost to pregnant women.

This paper will concern the prevalence of major congenital anomalies diagnosed prenatally or in the first year of life, focusing on structural defects (malformations, deformations, disruptions and dysplasias) and chromosomal anomalies. "Major" congenital anomalies are those which are lethal or carry high mortality or have other serious medical or functional consequences. "Congenital anomalies" or "birth defects" are sometimes defined more widely, for example including inborn errors of metabolism or conditions where a large proportion of cases have a congenital origin (e.g. cerebral palsy, specific learning disabilities) but we use here a narrower definition.

The congenital anomalies we see in livebirths are those that have survived intrauterine life. Congenital anomalies are a major cause of early spontaneous abortions, and some malformations and patterns of malformation are incompatible with in utero survival.

Congenital anomalies are a group of Rare Diseases where environmental factors have an important aetiologic role, and there is thus potential for primary prevention [14]. The last few decades have not seen increasing success in congenital anomaly prevention, as evidenced by a lack of decline in total prevalence. Implementation of current knowledge with effective policies, as well as research into causes of congenital anomalies, have the potential to change this situation.

Prenatal screening and diagnosis have seen rapid development. The near future will bring less invasive technologies for the detection of chromosomal anomalies, and greater sensitivity and specificity of diagnosis of anomalies. However, the challenge for European countries is to reduce the number of women having to consider termination of pregnancy as an option by achieving effective primary prevention by addressing environmental risk factors, and by improving the outcome of affected surviving children and their families in terms of health and quality of life.

20.2 Genetics and Environment in the Causation of Congenital Anomalies

Both genetic and environmental factors are involved in the causation of congenital anomalies. Genetic syndromes, where a genetic abnormality can be diagnosed by the clinician with the help of genetic tests or family history and is sufficient to explain why the child is malformed, account for less than one fifth of cases. Genetic abnormalities can be chromosomal anomalies (e.g. trisomies such as Down Syndrome), microdeletions, single gene mutations (monogenic syndromes), or genetic imprinting disorders. Many of the monogenic syndromes are inherited from the parents, but some are new mutations where environmental factors may have

been involved [40]. However, there is as yet no convincing evidence that differences in radiation exposure or mutagenic chemicals have been associated with differences in the prevalence of genetic congenital anomaly syndromes in humans. On the other hand, some of the variation in expression of genetic abnormalities may be due to a vulnerability to the effects of environmental exposures. For example, research on why some children with Down Syndrome have cardiac defects and others not, have suggested that maternal smoking may have a role [38].

Some environmental exposures, such as maternal rubella and certain teratogenic medications, confer a high risk of congenital anomaly if exposure is in early pregnancy, but taken together these known strongly teratogenic environmental exposures probably account for less than 5% of congenital anomaly cases. In the vast majority of cases of congenital anomaly, the cause cannot be identified as one single factor. These include congenital anomalies of multifactorial origin, with many genetic and environmental factors contributing additively such that the individual embryo/fetus surpasses a "threshold" beyond which it can no longer self-regulate to follow the normal developmental pattern [30]. As genetic research progresses however, the main emphasis is not only on the additive accumulation of many genetic and environmental factors, but on the interaction between genetic factors and environmental factors, such that specific environmental exposures are only teratogenic in the presence of specific predisposing genetic factors.

Environmental causes of congenital anomaly, whether a sufficient or contributory cause, include maternal infection (such as rubella), nutrition (such as low levels of periconceptional folic acid intake), maternal disease (such as diabetes and obesity), medicinal drugs (such as antiepileptics), exposure to recreational drugs including smoking, alcohol and cocaine, and occupational exposure to chemicals [9]. Congenital anomalies are also associated with assisted reproduction [34], particularly in relation to epigenetic effects. Pollution sources such as drinking water disinfection byproducts [4] and hazardous waste landfill sites [39] have been implicated.

Primary prevention of congenital anomalies in the population in the medium term future will come from controlling environmental risk factors. A particular challenge for prevention is the fact that development of the major organs, the sensitive period for environmental exposures, starts before the pregnancy is recognized. Thus there is a need for specific preconceptional care strategies for primary prevention of congenital anomalies. These can be combined with whole population approaches such as rubella vaccination, folic acid food fortification, regulation of pharmaceutical, occupational and environmental exposures, and measures to tackle use of recreational substances.

20.3 Population-Based Congenital Anomaly Registers in Europe

EUROCAT (European Surveillance of Congenital Anomalies) is the principal source of information on the epidemiology of congenital anomalies in Europe [13]. EUROCAT is a network of population-based congenital anomaly registers, using

multiple sources of information to collect high quality data (both in terms of case ascertainment and diagnostic detail). Registries cover affected livebirths, stillbirths and fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis.

The member registries of EUROCAT vary from regional to national registries, the national registries mainly in small countries like Malta, or Scandinavian countries with well developed health information systems with legal mandates. The emphasis in EUROCAT is on data quality rather than complete population coverage. There are registries in 22 countries, together covering a geographical area with approximately 1.5 million annual births. 28% of annual births in the European Union are covered by a EUROCAT register [29].

"Population-based" means that a register covers residents of a defined geographical area. This is important to avoid the selection bias (e.g. referral for prenatal diagnosis) inherent in "hospital-based" registers, which cover one or several selected hospitals and, if tertiary centres, may result in artificially high prevalence rates.

20.4 Definition of Prevalence Rates and Perinatal Mortality Rates

It has become a convention to refer to the frequency of occurrence of congenital anomalies as a "prevalence" rather than an "incidence". This is in recognition of the high loss rate as early spontaneous abortions of affected fetuses, so that the "prevalence" represents survival to late pregnancy or birth of the fetus. Counts of early spontaneous abortions (malformed and non-malformed) are generally not available in health data, and diagnosis of congenital anomalies in early spontaneous abortions is very incomplete.

With increasing availability of prenatal screening and diagnosis, followed in many countries by the option to terminate an affected pregnancy, terminations of pregnancy for fetal anomaly (TOPFA) have been included in prevalence rates, on the premise that the vast majority would have survived to live or stillbirth had it not been for the termination, and thus they arise from the same population described by the births denominator. This assumption would need to be questioned if the proportion of early TOPFA, with a higher natural spontaneous abortion probability, were to increase.

The EUROCAT definition of a prevalence rate is a compromise to achieve the least biased estimate of prevalence at 20 weeks gestation. In the numerator are included all affected livebirths (LB), fetal deaths from 20 weeks gestation (FD), and TOPFA of any gestational age. In the denominator is the number of livebirths and stillbirths in the population. The mismatch between numerator and denominator concerns the fetal deaths between 20 weeks and the national lower limit for official registration of stillbirths (most commonly 24 weeks), and TOPFA. It can easily be calculated that whether or not all such fetal deaths and TOPFA are included in the denominator does not make an important difference to the prevalence rate, as their numbers are small.

The measure used by EUROCAT to represent "risk" is the "total prevalence rate" including TOPFA.

Total Prevalence Rate = No. Cases (LB + FD + TOPFA) /No. Births (live and still)

Changes in total prevalence rate over time, or geographical differences or differences between population subgroups, are of interest in relation to differences in underlying environmental and genetic risk factors. However, they may also represent differences in diagnostic services, differences in the methods of collecting or coding registry data, and chance differences.

The Prevalence Rate at Birth is the same as the Total prevalence rate, but not including TOPFA. The two measures are equal if there are no TOPFA in the population. Differences in Prevalence rates at birth over time or between regions may indicate the same factors as above, but also differences in the frequency of termination of pregnancy following prenatal diagnosis.

The Livebirth Prevalence Rate is based on liveborn cases as a proportion of all livebirths in the population. This is particularly useful for health service purposes, as it measures cases needing health care.

The Perinatal Mortality Rate (PMR) as defined by EUROCAT includes all fetal deaths from 20 weeks gestation as well as deaths within the first week of life in the numerator, and all births (live and still) in the denominator. Inclusion of fetal deaths from 20 weeks gestation to the lower limit of stillbirth registration in each country makes this measure a little different from those produced by national statistics which include only stillbirths, though the difference is small. Another difference is that the EUROCAT PMR counts all cases with a major congenital anomaly who die in the defined period, whether or not the congenital anomaly is the main cause of death, whereas national mortality statistics may concern the main cause of death,. A further problem of definition relating to the PMR, is whether TOPFA at gestational ages within the stillbirth range are included. EUROCAT PMR excludes all TOPFA, whatever the gestational age. Some national statistics include late TOPFA as stillbirths.

According to EUROCAT guidelines [24], each individual can have up to eight malformations and one syndrome diagnosis coded according to the International Classification of Disease version 10 (ICDv10) with the British Paediatric Association one digit extension. These codes are regrouped into 75 congenital anomaly subgroups [24]. Defects that are seen as consequences of other defects i.e. "sequences" (e.g. hydrocephaly when associated with spina bifida) are counted only under the primary defect in many of these subgroup definitions.

Cases with only "minor" anomalies are excluded [24] – this is of course an arbitrary distinction, but is standardised across all registries. Included in the exclusion list are patent ductus arteriosus associated with prematurity, and pyloric stenosis, neither of which are always a congenital anomaly. There are however problems with implementing such a list – some minor anomalies do not have their own code to distinguish them from major anomalies, so necessitating text descriptions. Syndactyly can vary from slight webbing of the skin between two fingers to fusion of the bones

between two fingers, and polydactyly can refer to the addition of a tiny digit to a fully formed digit – minor forms can only be excluded if enough information is available to registries in their information sources. Other anomalies range in size, such as microcephaly, microphthalmia, microtia, and it is not possible to impose size criteria which can be reliably found in medical records.

A major division into "chromosomal" cases (with abnormal karyotype) and "non-chromosomal" is made, since this is a readily available aetiological distinction, and the epidemiology of these two groupings is very different. It is more difficult to classify monogenic syndromes (many of which do not have a unique ICD code) and multiple malformations, and this is done by a panel of medical geneticists for special studies rather than routine publications.

In EUROCAT Prevalence rate or PMR calculations, a baby/fetus with several anomalies is counted once within each relevant rate. A baby with spina bifida and omphalocele, for example, will be counted once within the spina bifida prevalence rate, once within the omphalocele prevalence rate, and once within the "All Anomalies" prevalence rate. Prevalence rates for different congenital anomaly subgroups therefore cannot be added to reach the "All Anomaly" prevalence rate.

EUROCAT updates prevalence rates on its website annually (http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables). The most recent update of total prevalence rates for all EUROCAT congenital anomaly subgroups, choosing all full member registries covering the period 2003–2007, is shown in Table 20.1. Numbers of cases by type of birth (LB, FD, TOPFA), by registry and country, and by year, can be found on the website.

Table 20.1 Total prevalence per 1,000 births of congenital anomalies in full member EUROCAT registries[a] 2003–2007, by congenital anomaly subgroup

	All	Excl Chromosomal
Anomaly subgroup	LB+FD+TOPFA Rate	LB+FD+TOPFA Rate
All Anomalies	23.95	20.39
Nervous system	2.54	2.28
Neural tube defects	0.94	0.90
Anencephalus and similar	0.32	0.31
Encephalocele	0.12	0.11
Spina Bifida	0.51	0.48
Hydrocephaly	0.59	0.53
Microcephaly	0.29	0.26
Arhinencephaly/holoprosencephaly	0.14	0.09
Eye	0.35	0.31
Anophthalmos/micropthalmos	0.10	0.08
Anophthalmos	0.02	0.02
Congenital cataract	0.10	0.09
Congenital glaucoma	0.03	0.03
Ear, face and neck	0.19	0.17
Anotia	0.04	0.03
Congenital heart disease	7.32	6.46

Table 20.1 (continued)

Anomaly subgroup	All LB+FD+TOPFA Rate	Excl Chromosomal LB+FD+TOPFA Rate
Common arterial truncus	0.08	0.06
Transposition of great vessels	0.32	0.31
Single ventricle	0.07	0.06
Ventricular septal defect	3.04	2.75
Atrial septal defect	2.27	2.05
Atrioventricular septal defect	0.38	0.17
Tetralogy of fallot	0.29	0.25
Tricuspid atresia and stenosis	0.06	0.05
Ebstein's anomaly	0.05	0.05
Pulmonary valve stenosis	0.34	0.32
Pulmonary valve atresia	0.08	0.07
Aortic valve atresia/stenosis §	0.08	0.07
Hypoplastic left heart	0.29	0.27
Hypoplastic right heart §	0.04	0.04
Coarctation of aorta	0.32	0.28
Total anomalous pulm venous return	0.05	0.05
Respiratory	0.45	0.40
Choanal atresia	0.08	0.07
Cystic adenomatous malf of lung §	0.07	0.06
Oro-facial clefts	1.51	1.39
Cleft lip with or without palate	0.94	0.86
Cleft palate	0.58	0.56
Digestive system	1.66	1.50
Oesophageal atresia with or without tracheo-oesophageal fistula	0.24	0.21
Duodenal atresia or stenosis	0.12	0.08
Atresia or stenosis of other parts of small intestine	0.09	0.09
Ano-rectal atresia and stenosis	0.31	0.29
Hirschsprung's disease	0.12	0.11
Atresia of bile ducts	0.03	0.03
Annular pancreas	0.02	0.02
Diaphragmatic hernia	0.28	0.25
Abdominal wall defects	0.57	0.49
Gastroschisis	0.25	0.24
Omphalocele	0.30	0.22
Urinary	3.21	3.06
Bilateral renal agenesis including Potter syndrome	0.12	0.11
Renal dysplasia	0.46	0.44
Congenital hydronephrosis	1.09	1.06
Bladder exstrophy and/or epispadia	0.07	0.07
Posterior urethral valve and/or prune belly	0.10	0.10
Genital	1.95	1.90
Hypospadias	1.60	1.58
Indeterminate sex	0.08	0.07

Table 20.1 (continued)

Anomaly subgroup	All LB+FD+TOPFA Rate	Excl Chromosomal LB+FD+TOPFA Rate
Limb	0.40	3.81
Limb reduction	0.61	0.57
Upper limb reduction	0.43	0.40
Lower limb reduction	0.22	0.21
Complete absence of a limb	0.02	0.02
Club foot – talipes equinovarus	1.14	1.09
Hip dislocation and/or dysplasia	0.62	0.60
Polydactyly	0.98	0.93
Syndactyly	0.56	0.52
Arthrogryposis multiplex congenita	0.07	0.07
Musculo-skeletal	0.86	0.80
Thanatophoric dwarfism	0.03	–
Jeunes syndrome	0.01	–
Achondroplasia	0.05	–
Craniosynostosis	0.17	0.16
Congenital constriction bands/amniotic band	0.05	0.05
Other malformations	0.66	0.61
Asplenia	0.02	0.02
Situs inversus	0.06	0.06
Conjoined twins	0.02	0.02
Disorders of skin	0.22	0.19
Teratogenic syndromes with malformations	0.12	–
Fetal alcohol syndrome	0.04	–
Valproate syndrome	0.01	–
Maternal infections resulting in malformations	0.06	–
Single gene syndromes + microdeletions	0.55	–
Chromosomal	3.56	–
Down Syndrome	2.05	–
Patau syndrome/trisomy 13	0.19	–
Edward syndrome/trisomy 18	0.50	–
Turner's syndrome	0.21	–
Klinefelters syndrome	0.10	–
Cru-du-chat syndrome	0.01	–
Wolff–Hirschorn syndrome	0.02	–

LB, Live Births; FD, Fetal deaths/stillbirths from 20 weeks gestation; TOPFA, Termination of pregnancy for fetal anomaly following prenatal diagnosis.

[a]Styria (Austria), Antwerp (Belgium), Hainaut (Belgium), Zagreb (Croatia), Odense (Denmark), Isle de la Reunion (France), Paris (France), Saxony-Anhalt (Germany), Dublin (Ireland), SE Ireland, Emilia Romagna (Italy), Tuscany (Italy), Malta, N Netherlands (NL), Wielkopolska (Poland), Vaud (Switzerland), East Midlands & South Yorkshire (UK).

Source: EUROCAT Website Database: http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables (data uploaded 07/12/2009).

20.5 Congenital Anomaly Prevalence and Perinatal Mortality: An Overview

EUROCAT recorded a total prevalence of major congenital anomalies of 23.9 per 1,000 births for 2003–2007 (Table 20.1). Eighty percent were livebirths. Approximately 2.5% of livebirths with congenital anomaly die in the first week of life [29]. In 2003–2007, 2.0% were fetal deaths/stillbirths from 20 weeks. 17.6% of all cases were TOPFA [19]. Thus, congenital anomalies overwhelmingly concern children surviving the early neonatal period, who have important medical, social or educational needs. According to data from one of the registries (Odense, Denmark) for 2005–2007, 1.2% of all livebirths have surgery for a congenital anomaly in early childhood.

The prevalence of chromosomal anomalies was 3.6 per 1,000 births 2003–2007 (Table 20.1). This group contributes 8% of livebirths with congenital anomaly, 28% of fetal deaths/stillbirths from 20 weeks gestation with congenital anomaly, and 48% of all TOPFA.

Congenital heart defects (CHD) were the most common non-chromosomal subgroup, at 6.5 per 1,000 births, followed by limb defects (3.8 per 1,000), anomalies of urinary system (3.1 per 1,000) and nervous system defects (2.3 per 1,000) (Table 20.1).

PMR associated with congenital anomaly was 0.93 per 1,000 births in 2004 [29]. The main congenital anomaly subgroups contributing to perinatal mortality were CHD (26% of perinatal deaths with anomaly), nervous system anomalies (21% of perinatal deaths with anomaly), and chromosomal anomalies (25%). Perinatal mortality due to congenital anomaly varies by country. Among European Union countries, the highest rates of perinatal mortality associated with congenital anomaly in 2004 were recorded in Ireland (2.4 per 1,000) and Malta (2.6 per 1,000). These are both countries where TOPFA is illegal, and thus the perinatal mortality rate includes affected fetuses with a lethal or high mortality anomaly many of which in other countries would have been prenatally diagnosed followed by termination of pregnancy.

The rate of TOPFA per 1,000 births for 2004 averaged at 4.4 per 1,000 births, with a range from 0 (Ireland and Malta) to 10.7 (France) [29], outnumbering perinatal deaths. Differing prenatal screening policies and practices, differences in uptake of prenatal screening and diagnosis due to cultural and organisational factors, and differences in TOPFA laws, influence the rate of TOPFA in the population, as discussed in detail elsewhere [5, 25, 31, 32].

20.5.1 Down Syndrome and Genetic Syndromes

The average total prevalence of Down Syndrome recorded by EUROCAT registries 2003–2007 was 2.1 per 1,000 births (Table 20.1). Risk of Down Syndrome is strongly associated with advanced maternal age, and given the maternal age distribution of births one can quite accurately estimate the total prevalence of Down

Syndrome in the population without the need for a register. A more than twofold variation in total prevalence between regions and countries corresponds mainly to differences in maternal age profile. A trend towards delayed childbearing in Europe – according to EUROSTAT figures the proportion of mothers of age 35 and over doubled from 9 to 18% between 1990 and 2004 in the European Union – has led to substantial increases in the total prevalence of Down Syndrome in Europe [15].

Prenatal screening for Down Syndrome in many countries has led to large proportions of parents choosing to terminate the pregnancy after prenatal diagnosis [5]. This has counteracted the maternal age-driven increase in numbers, so that livebirth rates over time have remained relatively stable when averaged across Europe [15]. The average livebirth prevalence for 2007 was 0.97 per 1,000 [19]. There was a fourfold variation in livebirth prevalence between countries, a combined effect of variation due to maternal age profile and due to laws and practices regarding prenatal screening and TOPFA. The decline in livebirth rate would bring Down Syndrome within the definition of a "rare disease" in some countries of Europe (i.e. population prevalence below 5 per 10,000).

Other trisomies such as Trisomy 13 and 18 show a similar maternal age-related epidemiology to Down Syndrome, but are much rarer in late pregnancy (Table 20.1) and associated with high mortality.

Chromosomal anomalies are increasingly commonly diagnosed – 2.3 per 1,000 births in 1987 to 3.4 in 2007 [19]. Part of this trend is maternal age-related as discussed above. Part of the trend is the increasing detection during prenatal screening of anomalies that would not otherwise have been detected till later life, or not at all, such as sex chromosome anomalies. A further part of the increase is increased diagnosis and recording of chromosomal anomalies as a result of prenatal screening which were formerly associated with spontaneous abortion.

The prevalence of single gene syndromes and microdeletions in EUROCAT registries 2003–2007 was 0.57 per 1,000 (Table 20.1). This is however an underestimate, since syndromes are poorly coded in International Classification of Disease coding, microdeletions in particular are underdiagnosed, and skeletal dysplasias are not included (Table 20.1). Improving routine data on syndromes is an area of current development. It will remain true however that such syndromes represent a very small proportion of congenital anomalies in the population.

20.5.2 Congenital Heart Defects

The total prevalence of non-chromosomal congenital heart defects (CHD) in Europe is 6.5 per 1,000 in 2007 (Table 20.1). A more extensive analysis was made for the years 2000–2005, including 30 full member EUROCAT registries recording a prevalence of 7 per 1,000 births [20]. Eighteen percent of non-chromosomal CHD cases had other major congenital anomalies in addition to heart defects. 1.9 per 1,000 births were classified as severe non-chromosomal CHD, with high perinatal mortality (9%), a significant TOPFA proportion (15%), and the vast majority

requiring surgery. Ventricular septal defects (VSD), atrial septal defects (ASD), and pulmonary valve stenosis (PVS) were more common, accounting together for 4.8 per 1,000 births, with low perinatal mortality (1.7%), a low TOPFA proportion (2.3%, most of which are associated with multiply malformed cases) and only an estimated 10% of affected livebirths requiring surgery. CHD prevalence estimation is very dependent on whether registries have full access to information on cases detected after the neonatal period, on the level of prenatal and neonatal screening for detection of CHD, and on whether small defects which spontaneously resolve are recorded.

Infant mortality associated with congenital heart defects has improved considerably over recent decades [10]. Increasing sensitivity of prenatal diagnosis means that early preparation can be made for surgery, with the potential to improve survival. Improving survival from all the medical and surgical developments has brought with it a need for more service capacity for the continuing care of affected children and adults.

Unfortunately, progress with primary prevention of CHD through the identification and reduction of environmental exposures has been limited, although a few important interventions exist, including prevention of maternal infections such as maternal rubella and prevention of exposure to teratogenic drugs. The promotion of folic acid supplementation and fortification, primarily to prevent neural tube defects, may have beneficial effects in reducing CHD prevalence, but the evidence is as yet limited [35].

20.5.3 Neural Tube Defects

In 1991, results of a randomised trial of periconceptional folic acid supplementation established that raising folic acid status could be an effective measure to prevent neural tube defects such as anencephaly and spina bifida [37], potentially more than halving the prevalence in Europe. The prevalence of NTD in Europe has however not declined substantially over the subsequent decade [3, 6, 7, 26], a failure in preventive policy. The majority of women are either unaware of the benefits of supplementation, or start taking supplementation too late, after the pregnancy has been recognised [11, 26]. Many countries outside Europe have introduced mandatory folic acid fortification of staple foods [12], in order to overcome the problems associated with prevention by supplementation. Fortification has the support of most parent support groups contacted in Europe [1], but has met with concerns regarding whether scientific evidence for safety is sufficient [2, 17].

The total prevalence of neural tube defects averaged across EUROCAT registers was 0.9 per 1,000 births for 2003–2007 (Table 20.1). Traditionally, the United Kingdom and Ireland have been the areas within Europe of high prevalence of neural tube defects. However, during the 1980s total prevalence declined markedly in these countries, and continued to decline, though less steeply, through the 1990s. [6, 7, 28]. By the period 2000–2007, total prevalence in the UK and Ireland (1.0–1.3 per 1,000) was not higher than many continental European areas [18, 19].

In many European countries, the majority of cases of neural tube defects are prenatally diagnosed leading to TOPFA. In 2007, 59% of registered spina bifida cases were TOPFA averaged across EUROCAT registries (71% in countries excluding Ireland, Malta and Poland where TOPFA for spina bifida is not legal) and 83% of anencephaly were TOPFA [19]. It is possible that this is making neural tube defects a relatively "invisible" problem, with less attention being paid to primary prevention by folic acid in public health policy. Registration of terminations of pregnancy for neural tube defects is essential for the monitoring of the impact of primary prevention with folic acid, for monitoring prenatal screening policies, and for rendering neural tube defects "visible" in public health policy.

20.5.4 Orofacial Clefts

Cleft palate and cleft lip occurred in 1.4 per 1,000 births in Europe 2003–2007 (Table 20.1). Cleft lip with or without palate is aetiologically different from cleft palate without cleft lip and accounts for nearly two thirds of cases. Geographic variation within Europe has consistently been shown for cleft lip with or without palate [8, 27]. Some northern European countries have higher rates of cleft lip with or without palate, for example Belgium, Netherlands, Denmark and Norway with rates of 1.3 per 1,000 and over for 2003–2007 [19]. The large majority of facial cleft cases are liveborn infants, who require surgery within the first years of life and clinical follow-up until adult life.

20.5.5 Gastroschisis and Omphalocele

Gastroschisis is an anomaly of the abdominal wall, with an average prevalence of 0.24 per 1,000 2003–2007 (Table 20.1). It is associated with low socioeconomic status and young maternal age (less than 20 years). A strong increase in gastroschisis prevalence has occurred both in Europe [36] and elsewhere in the world. Particularly high rates and increases have been experienced in Britain, only part of which is associated with high rates of teenage pregnancy. In Italy however, rates are lower and an increase in prevalence has not been experienced [36]. The great majority of cases of gastroschisis are prenatally diagnosed [19], but TOPFA is infrequent as the prognosis is good with surgery. The strong variation in gastroschisis by age, time, geography and socioeconomic status suggests great potential for primary prevention by reduction of environmental risk factors, and research is ongoing into factors such as recreational drugs, smoking, low body mass index, environmental pollutants, and the interaction of these factors.

Omphalocele is often associated with a chromosomal anomaly (Table 20.1), but when non-chromosomal is of similar total prevalence to Gastroschisis. The livebirth prevalence rate for non-chromosomal omphalocele 2003–2007 was approximately 0.12 per 1,000 [19].

20.5.6 Hypospadias

Hypospadias, where the urethral opening in boys is misplaced, has a prevalence of a minimum of 1.6 per 1,000 births (Table 20.1). It is difficult to produce a valid prevalence estimate unless data regarding surgery in the first three years of life are accessed [16]. Criteria may vary over the diagnosis and treatment of milder cases. A previous EUROCAT guideline that glanular hypospadias should not be reported was found to be impractical to implement [16]. Hypospadias is of particular current interest in relation to exposure to endocrine disrupting chemicals. A high rate of hypospadias in Sicily is under investigation in relation to industrial and agricultural chemical exposures [3].

20.6 Data Quality and Data Quality Indicators

One of the frustrations in reviewing data on the prevalence of congenital anomalies is the difficulty of assessing data quality: Are cases of congenital anomaly being diagnosed early and accurately in the population? Are diagnosed cases all being ascertained by the register, and are registers recording full diagnostic information with accurate coding? Is database management thorough with regard to prevention of duplicate registrations and transcription errors?

Where it is not possible to improve data collection, transparency of data quality is essential. The EUROCAT strategy to improve data quality and make it more transparent involves three areas of activity:

(a) Standardisation and Guidelines mean that collective experience is readily available to less experienced registries, that specific expertise can be disseminated across registries, and that data from different registries can be meaningfully compared to analyse data quality issues. Guidelines [24] relate to case ascertainment methods, variable sets, variable coding schemes, and malformation coding. Standard computer software is used to implement the guidelines and carry out basic data quality checks.

(b) Registry descriptions and Data Quality Indicators aim at transparency. A standard format for member registry descriptions explains case ascertainment methods, including whether TOPFA and liveborn cases diagnosed after the early neonatal period are well ascertained, and sources of information for diagnostic detail. In the past, distinctions have been made between registries with “active” (registry searching records) and “passive” (registry receiving notifications) ascertainment methods, but this is no longer a useful distinction in Europe, where access to electronic health records blurs the distinction. Annual production of Data Quality Indicators (DQI, (http://www.eurocat-network.eu/ABOUTUS/DataCollection/DataQuality/DataQualityIndicators) compares the registry’s individual performance with the EUROCAT average, and with all other registries. DQI relating to ascertainment completeness include the total prevalence of congenital anomalies, the ratio of spina bifida to

anencephaly (a DQI relating to completeness of ascertainment of terminations of pregnancy), prevalence of selected anomalies usually diagnosed after the early neonatal period, prevalence of (non-chromosomal) genetic syndromes, and the prevalence of fetal deaths. DQI relating to diagnostic detail relate to the proportion of multiple malformations, the use of 5 digit ICD/BPA codes, the use of unspecified codes (e.g. unspecified congenital heart disease), and the proportion of autopsy and karyotypes for relevant cases. DQI for completeness of data relate to the full variable set and proportion of missing values.

(c) Annual statistical monitoring, and investigation of variation in prevalence over time and between registries allows more directed investigation of data quality for specific congenital anomalies. Annual statistical monitoring for trends and clusters [21, 22] is principally aimed at detection of increases that may indicate new teratogenic exposures. However, an important secondary aim relates to data quality, as investigations of trends and clusters often reveal underlying data quality problems that would not otherwise have come to light – these may either concern diagnostic methods (e.g. introduction of new screening policy) or registry methods. For example, 7 out of 17 temporal clusters occurring 2005–2006 were found on investigation to be due to diagnostic or data quality issues. Similarly, investigations of geographic differences in prevalence for studies of specific congenital anomaly subgroups also lead to a better understanding of data quality issues. For example, congenital hydronephrosis shows large differences in recorded prevalence in Europe [33]. These differences are explained both by different prenatal detection rates as unilateral hydronephrosis may not be diagnosed after birth if no ultrasound is performed, and differences in coding and definition of hydronephrosis. Investigation led to a recommended lower size limit and the recommendation that dilatation of the renal pelvis caused by reflux should not be coded and reported as congenital hydronephrosis. Implementation of these recommendations by the registry depends on access to full medical notes, and follow up of the child beyond the neonatal period.

Experience with capture-recapture analysis of ascertainment levels shows that it is very dependent on model assumptions concerning interdependence of information sources, and correct assignment of sources as notification or verification sources [23], and is resource intensive. We have chosen therefore not to use it. We recommend however that member registries code sources of information for each case, and monitor indicators such as the proportion of cases reported by a single notification source over time, and the proportion of cases notified by each notification source. This can help a registry analyse its case ascertainment.

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Chapter 21
Rare Autoimmune Diseases

Arrigo Schieppati and Erica Daina

Abstract Under the term "autoimmune diseases" are comprised a large number of disorders with variable clinical expression which have in common an autoimmune pathogenesis as defined by direct, indirect or circumstantial evidence. Autoimmune diseases may affect a single organ or may determine a multisystem involvement, and most of them cause significant and chronic morbidity and disability. Another important feature of autoimmune diseases is their propensity to affect more often females than males. Although few of them are quite common and well studied, the majority of autoimmune diseases are rare, and share with rare diseases lack of epidemiology data. The implementation of specific disease registries can help improve the knowledge on epidemiology of these conditions, a crucial step for evaluating health care interventions.

Keywords Autoimmune diseases · Epidemiology · Diseases coding · Off-label use of drugs · Disease registries

21.1 Introduction

The term "autoimmune disease" defines a large group of heterogeneous conditions, that recognise a pathogenic mechanism defined as autoimmunity. Autoimmunity means that the immune response is directed against an antigen within the body of the host. This response may be innate or acquired, and may be induced by a foreign or an autochthonous antigen [4, 15].

Autoimmune diseases are broadly divided in two categories: those affecting many organs (for example systemic lupus erythematosus), and those affecting a single organ or tissue (for example, autoimmune thyroiditis). This distinction however sometimes is not clear-cut, since the effects of localised autoimmune disorders

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extend to other organs. In general, autoimmune diseases show a great variability of symptoms and organ injuries. On the other hand, they have many common features and therefore are considered a family of disorders.

An autoimmune disease is often defined as conditions characterised by the presence of autoantibodies. However this definition is not completely satisfactory since autoantibodies may be naturally present and occurring without disease signs or symptoms, and they not establish a cause-effect relationship. According to the criteria suggested by Rose and Bona, an autoimmune disease is defined by the evidence of an autoimmune etiology at three different levels: direct, indirect, and circumstantial [14].

Direct evidence is demonstrated by the transmission of lesions of the disease from human to human, or human to animal. Examples of autoimmune diseases defined by this criteria of direct evidence are idiopathic thrombocytopenic purpura, hyperthyroidism and myasthenia gravis [1, 5, 13]. One demonstration of this kind of evidence is the transplacental transfer of autoantibodies and the transient appearance of symptoms of the disease in the infant.

Actually, there is another way to demonstrate the pathogenetic effect of autoantibody by in vitro experiments.

Indirect evidence is the reproduction of the human disease in animal models. For example there are several mouse models of systemic lupus erythematosus, with serological and pathological features closely resembling those of the human disease [18]. There are other example of this kind of indirect evidence, and the increasing availability of genetically manipulated animals that reproduce autoimmune diseases (with all the limits in extrapolating data from animal models to human pathophysiology) is greatly improving the understanding of these diseases.

Finally, circumstantial evidence are those clues that are suggestive but not proof of autoimmune disease. The presence of autoantibodies (within certain limits) belongs to this type of evidence. A positive family history of autoimmune disease, or the presence of another autoimmune disease firmly established with a positive diagnosis both increase the likelihood of an autoimmune disease.

Certain HLA haplotypes are more often associated with certain autoimmune disease [17]. Finally the response to empirical immunosuppressive therapies may be considered an indirect proof of autoimmune etiology of a condition.

The term autoimmune disease is applicable to a large number of conditions that satisfy the conditions described before. They include diseases which involve a single organ and diseases with multiple organ involvement, that are also called systemic autoimmune diseases. A partial list of autoimmune diseases divided into organ specific and systemic diseases is reported in Table 21.1.

For example, Graves' disease or autoimmune hyperthyroidism is caused by autoantibodies to the thyrotropin receptor (TSHR-Ab) that activate the receptor, thereby stimulating thyroid hormone synthesis and secretion as well as thyroid growth. The histology of the thyroid gland in patients with Graves' disease is characterised by follicular hyperplasia, multifocal lymphocytic infiltration and rare lymphoid germinal center. Other example of organ specific autoimmune diseases

Table 21.1 Example of autoimmune diseases according to prevalent organ involvement

Diseases with single organ involvement	Diseases with multiple organ involvement
Skin	*Connective tissue disease*
Pemphigus Vulgaris	Systemic Lupus Erythematosus
Pemphigus Foliaceus	Sjogren's Syndrome
Bullous Pemphigoid	Mixed connective tissue disease
Epidermolysis bullosa acquisita	Scleroderma
Erythema nodosum	Relapsing Polychondritis
Vitiligo	Ankylosing Spondylitis
Alopecia Areata	Polymyositis/Dermatomyositis
Endocrin system	Behçet's Syndrome
Type 1 diabetes mellitus	*Autoimmune Vasculitis*
Graves' Disease	Goodpasture's syndrome
Hashimoto's Thyroiditis	Wegener's granulomatosis
Autoimmune polyendocrine syndrome type 1	Takayasu's arteritis
Autoimmune polyendocrine syndrome type 2	Giant cell (temporal) arteritis
Autoimmune Addison's disease	Kawasaki's disease
Blood	Polyarteritis nodosa
Autoimmune Thrombocytopenic Purpura	Churg-Strauss syndrome
Autoimmune hemolytic anemia	
Autoimmune neutropenia	
Antiphospholipid syndrome	
Central and peripheral nervous system	
Guillain-Barre syndrome	
Myasthenia gravis	
Multiple sclerosis	
Autoimmune polyneuropathies	
Gastrointestinal and liver	
Celiac disease	
Crohn's disease	
Pernicious anemia	
Primary biliary cirrhosis	
Autoimmune Hepatitis	
Sclerosing cholangitis	
Kidney	
Primary Glomerulonephritides	

are hemolytic anemia, pemfigus, idiopathic thrombocytopenic purpura. A peculiar feature of several organ-specific autoimmune diseases is the tendency to develop other autoimmune diseases.

Systemic autoimmune diseases are characterized by the pathologic involvement of multiple organs and tissues. The prototypical systemic autoimmune disease is systemic lupus erythematosus, a disease that can involve almost all bodily organs and tissues, and is associated with a variety of autoantibodies.

Treatments of most autoimmune diseases is aimed to reduce the symptoms, since definitive cures are not available yet. In general, two approaches to treatment are currently available.

In general treatments are based on drugs that suppress the autoimmune response and several immunosuppressive drugs that reduce the overall immune response are

available and are used often in combination. The main problem with the use of immunosuppression is concomitant reduction of the individual's resistance to infections. Moreover, they often have several adverse side effects that may limit their use. In the recent past the effort of the research has been focused on the development of new drug therapies that target a specific step in the tissue-damaging inflammatory response rather than aiming to immunosuppression. Some of these new drugs are biologic agents that produce more targeted immunosuppression. Some are already available for clinical use (like etanercept or infliximab for rheumatoid arthritis), other are being studied in clinical trials.

One major issue concerning these new biologic drugs is their cost. For example one year treatment with etanercept, a monoclonal antibody which inhibits Tumor Necrosis Factor alfa (TNF alfa), can cost as much as $ 26,000, and the annual cost of Interferon beta for treatment of multiple sclerosis can reach $ 59,000 [7].

Another interesting aspect of biologic therapeutic agents is their extended off-label use. These agents are currently being use for an expanding number of autoimmune diseases, for which they are not licensed by Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). Physicians often recur to these new drugs to treat patients who are not responding or intolerant to conventional therapies and/or are in life-threatening conditions. Even though the rationale for their use in these conditions is usually sound, the indication for their off label use rarely relies on results of randomised controlled clinical trials (RCT), most often is suggested by observational studies or case reports. Recently, Ramos-Casals and colleagues [12] conducted a systematic review of the off-label use of biological therapies in systemic autoimmune disorders.

They made a systematic review of the published literature of RCT or case series on 16 systemic autoimmune diseases, which were treated with 5 biological agents (infliximab, rituximab, etanercept, anakinra, adalimumab). Most of the cases were of Sjögren syndrome, Wegener granulomatosis, sarcoidosis, systemic lupus erythematosus, Behçet disease. They found that the evidence on the use of biological therapies was mainly based on uncontrolled, observational data, and indeed no treatment could reach the highest level of scientific evidence in any condition. At the same time, they found that the overall reported rate of side effects was 27%.

This review shows that the off-label use of biologic agents for autoimmune diseases is relevant, although there is a substantial lack of evidence of their efficacy. With some exception autoimmune diseases are rare and heterogeneous in clinical presentation. These are the reasons for lack of interest from the part of the pharmaceutical company to adventure in registering a drug for any new indication that have a low prevalence.

21.2 The Epidemiology of Autoimmune Diseases

What is indeed the prevalence of autoimmune disease? Unfortunately there is a substantial lack of rigorous estimate of the incidence, prevalence, morbility of autoimmune diseases. This lack of knowledge undermines the possibility to

understand the implications of this group of diseases from the public health point of view. Autoimmune diseases are characterised by chronic, often severely disabling course, comprising phases of remission and relapses. Some conditions, such as systemic sclerosis, significantly reduce lifespan. Many diseases affect people in their working age, resulting in loss of productive years and limitation in earning capacity. In summary, a precise evaluation of the burden of autoimmune diseases on health is important for both the social and economic costs that they impose on society.

A landmark study in this field is the work published in 1997 by Jacobson and colleagues [9]. The authors selected a group of 24 autoimmune diseases, which all satisfied the criteria of Rose and Bona (described before) for being defined as such. Also the definition of each disease was carefully established in order to assure the highest possible homogeneity. Indeed many autoimmune diseases included in the analysis did not have a well-standardized definition criteria.

Medical literature from 1965 to 1995 was searched for articles pertinent to epidemiology studies. A careful selection of the retrieved papers was done in order to avoid bias in prevalence and incidence estimates.

A total number of 211 prevalence studies for 24 autoimmune diseases were selected. One-hundred and six studies reported data from Europe, 49 from North America (USA and Canada) and 56 from other countries of the world. The highest number of prevalence studies were for multiple sclerosis (80 studies), rheumatoid arthritis (38 studies), and systemic lupus erythematosus (23 studies).

Among the 24 selected diseases, only 8 diseases had at least 7 prevalence studies. For 6 conditions (Goodpasture's syndrome, idiopathic thrombocytopenic purpura, relapsing polychondritis, hemolytic anemia, myocarditis, and pemphigus) the authors could not find any published study on prevalence.

There were 188 incidence studies published during the study period. Again, most of the studies were from Europe, and for 5 diseases (Goodpasture's syndrome, idiopathic thrombocytopenic purpura, relapsing polychondritis, Sjogren's syndrome and vitiligo) no eligible incidence study could be retrieved.

For each disease, weighted mean incidence and prevalence rate was calculated with greater weight given to larger studies. Then the authors estimated the total population affected by each of the 24 diseases using the 1996 projected population by the U.S. Census Bureau. For each disease different age categories were applied, according to the age category most cited in the published studies.

Using the prevalence studies, it was estimated that nearly 8.5 million of people in US has one of the 24 autoimmune diseases, a prevalence of 1 in 31. The most frequent diseases are Graves' diseases (115.1/10,000), Type 1 diabetes mellitus (19.2/10,000), pernicious anemia (15.0/10,000), rheumatoid arthritis (86/10,000), thyroiditis/hypothyroidism (79.1/10,000).

In 16 of the autoimmune diseases considered in this study, the estimated prevalence was higher in the female sex, with rates that ranged from 6 females per 4 males, to 9–1. In 2 conditions (vitiligo and uveitis) the prevalence was equal in the two genders and in 2 (IgA glomerulonephritis, multiple sclerosis) the male was the most affected sex.

In this analysis there were at least 12 conditions that had a weighted mean prevalence that satisfied the criteria for defining these conditions as rare diseases according to the European (5/10,000) or American (less than 125,000 people in US) of rare disease [16].

There are several considerations that can be drawn from this important study. First, it demonstrates that there is a relative paucity of good epidemiologic studies on most of autoimmune diseases, and for some of them there are no study at all. This may lead to substantial underestimation of the burden that these diseases are posing on the health care, including the economic impact of their care.

Indeed, this study also highlighted the lack of uniform definition for many of these conditions, and suggested that better standardisation of diagnostic criteria is warranted. This problem is common to many rare diseases, which are often lacking an International Classification of Disease code. World Health Organization has established Topic Advisory Groups (TAG) that serve as the planning and coordinating advisory bodies in the update and revision process of the ICD for specific issues. One of these TAGs is working on a new coding for rare diseases. This is an essential tool for future epidemiologic studies, and it has a direct impact on health care, as it influences public health programmes, prevention, reimbursement and treatment [21].

The study of Jacobson et al. also showed that many autoimmune diseases are rare or at least uncommon disorders, and therefore share with other rare diseases the difficulty to define and ascertain cases.

Another important epidemiologic study was recently conducted by Eaton and colleagues in Denmark. They used data from the Danish Civil Registration System to identify all persons alive in Denmark on December 31, 2001 [6]. This population was linked with the National Hospital Register, which collects data on all hospital admission in Denmark since 1977, and since 1995 includes all contacts with emergency rooms and outpatient clinics. The diseases are coded according to ICD codes. The authors selected 31 autoimmune diseases for this study, for which lifetime prevalence was estimated. They also took particular care to estimate comorbidity, i.e. the occurrence of more than one disease in the same individual, and familial aggregation among siblings, parents and offsprings.

It was estimated that the lifetime prevalence proportion for the 31 autoimmune diseases in a population of 5,472,032 people was 5.29%. Among the 31 diseases there was a great variation in term of prevalence. The highest prevalence was found for insulin dependent diabetes (946 cases per 10,000 population), while the least prevalent disease was pemphigus (0.4 cases per 10,000). Among the 31 diseases, 15 had an estimated prevalence of less than 5 per 10,000 people, and can be defined rare entities.

The study found some discrepancy with other studies in estimated prevelance of autoimmune diseases. The reasons for such discrepancies are several. First, for some diseases there may be ethnic and national differences. Then, there may be biases in methodology of calculating prevelance among studies. Jacobson and collegues reported estimate derived from published literature, while the Danish study relied on official registry of hospital admission, based on a coding system, such as

ICD, that has advantages and disadvantages. This coding system does not include some condition, for example antiphospholipid syndrome is coded as "Other specified coagulation defect", or cannot distinguish autoimmune from non-autoimmune forms of a disease (diabetes mellitus in ICD 8th version).

An interesting aspect of the Danish study was the estimate of prevalence of comorbidity in autoimmune diseases. They found that in 31 diseases there were 465 combinations of two diseases.

For each of the 31 conditions it was possible to track down the number of comorbidities. Some of the disease, in particular connective tissue diseases, combined with a large number of other conditions. For example, systemic lupus erythematosus and Sjogren's syndrome cases were found in combination with 14 different other conditions.

They also examined the pattern of co-occurence in families, and found a considerable familial aggregation in almost all 31 conditions. The aggregation was strongest for individual diseases and weak across diseases. Purpura, psoriasis, multiple sclerosis and Crohn's diseases had the strongest evidence of familial aggregation. The odds ratios for familial aggregations was higher for siblings than for parent to child; for 10 diseases the siblings odds ratios were more than double the parent to child. The authors suggest that common environment influences over and above genetic transmission.

In summary, the Danish study concluded that while the prevalence of autoimmune diseases is low, as a group they have an overall prevalence of 5%.

Recently Cooper and colleagues [3] have examined more recent studies pertaining to the prevalence of autoimmune diseases. They considered the limitation of previous studies. For instance they noted that Jacobson et al. study considered reports which were 30 years old at the time the review was done. On the other hand, the Danish study was based on hospital registry data, which underestimate the prevalence of conditions that have a low hospitalisation rates. These considerations lead Cooper et al. to update the prevalence estimate, by reviewing more recent studies and use the data to correct for the underestimation of some diseases (Table 21.2).

Their analysis lead to a new estimate for prevalence, suggesting an estimated prevalence of 7.6–9.4% depending on the size of correction factor used. They also reviewed studies on co-occurrence of diseases within individuals and within families. They found that data support the tendency for autoimmune diseases to co-occur at a greater than expected rates, although not uniformly across all diseases.

All the epidemiologic studies that we have reviewed confirm the well established clinical experience that autoimmune disorders affect far more often women than men. That was noted since the first descriptions of systemic lupus erythematosus and multiple sclerosis. As shown in Fig. 21.1, Sjogren's syndrome, SLE and thyroid disease are almost exclusively found in females.

The reasons for the sex bias in autoimmune diseases are unclear but may include such factors as sex-related differences in immune responsiveness, response to infection, sex steroid effects, and sex-linked genetic factors [8, 20]

The burden of autoimmune diseases on women health is substantial, and probably is not fully estimated. Several autoimmune diseases have a high fatality rates, and

Table 21.2 Incidence (per 100,000 people per year) and prevalence (per 100,000) of some autoimmune diseases. Data are derived from Cooper and Stroehla [2]. The name of the condition is underlined when the prevalence of the disease is below the threshold defintion of rare disease in Europe (50 per 100,000 people)

Condition	Incidence	Prevalence
Addison	0.6	14.0
Chronic active hepatitis	0.7	0.4
Glomerulonephritis	3.6	40.0
Type 1 diabetes mellitus	12.2	192.0
Graves' disease/hyperthyroidism	13.9	1151.5
Multiple sclerosis	3.2	58.3
Mystenia gravis	0.4	5.1
Myocarditis	0.1	–
Pernicious anemia	–	150.9
Polymyositis/dermatomyositis	1.8	5.1
Primary biliary cirrhosis	0.9	3.5
Rheumatoid arthritis	17	148
Systemic sclerosis	7.3	23.8
Sjogren syndrome	3.9	14.4
Systemic lupus erythematosus	7.3	23.8
Thyroiditis/hypothyroidism	21.8	791.7
Uveitis	18.9	1.7
Vitiligo	–	400.2
Wegener granulomatosis	1.0	3.0
Primary systemic vasculitis	2.0	14.5

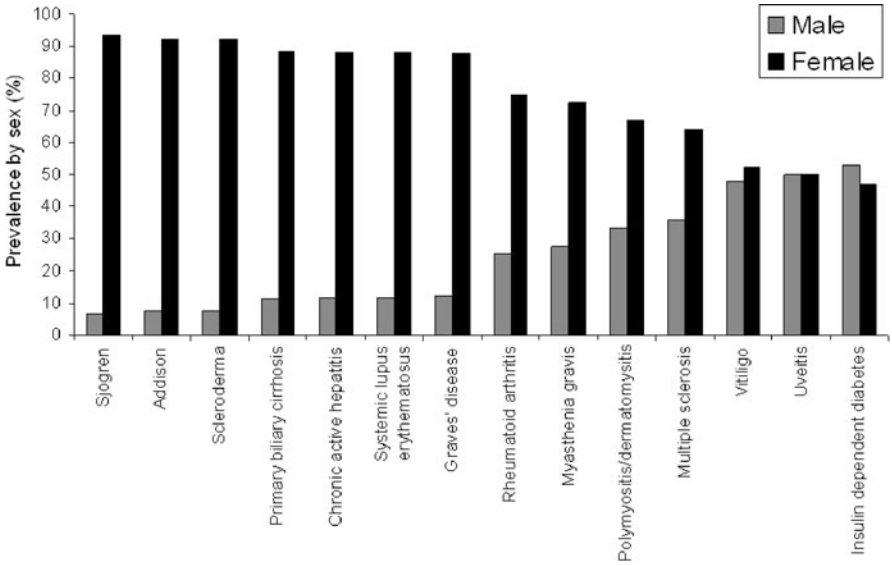

Fig. 21.1 Prevalence of autoimmune diseases by sex. Data of prevalence are derived from [9]

although as single entity may not rank high among cause of death, they do when considered together as a group. Walsh and Rau compared the counts of death for 24 autoimmune diseases pooled together with the counts of the 10 leading cause of death in United States as reported by the National Center for Health Statistics in 1995 [19]. They selected the 24 conditions that were object of analysis in the paper of Jacobson et al. They found that death count for autoimmune diseases (as a group) was always greater than the counts of the 10th leading cause of death among women of less than 65 years of age. These data confirm that autoimmune diseases constitute an important issue in women health.

Another important aspect that should be considered is the social and economic burden of autoimmune diseases. While there is a wealth of information concerning the socioeconomic impact of the most prevalent autoimmune diseases, such as rheumatoid arthritis and lupus [10, 11], fewer studies are avaiable for less frequent conditions and none for the rarest. This is an area of investigation which needs to be considered by health care authorities and funding agencies for future research.

Registries and databases of autoimmune diseases are available for most common autoimmune diseases but should be extended to the rarest form of diseases. They are a formidable tool to collect not only clinical data, but also information on the social aspects of the diseases.

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Chapter 22
Epidemiology of Rare Anaemias in Europe

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Abstract Registry and epidemiological data of Rare Anaemias (RA) in Europe is in general still incomplete and/or partially documented. One important issue is the increasing prevalence of haemoglobin disorders (HD) due to migrations from high prevalence areas. The size of the problem, particularly for sickle cell disease (SCD), is already having an impact on health services in many European countries. The best known cause of rare anaemias associated with congenital haemolytic anaemia (CHA) in Europe is Hereditary Spherocytosis (HS) a red blood cell (RBC) membrane defect with a prevalence of 1 to 5 cases per 10.000 individuals. Some other causes of CHA are extremely rare and only few individual cases have been described worldwide (i.e. some RBC enzymopathies). Congenital defects of erythropoiesis are less frequent Diamond–Blackfan Anaemia (DBA) and Fanconi Anaemia (FA) exhibit a very low prevalence ranging from 4 to 7 per million live births. Congenital Dyserythropoietic Anaemia (CDA), a genetically heterogenous group, is still less frequent and exhibits a large variability of frequency depending on the European region: 0.1–3.0 cases per million births In addition many cases are known from a large autosomal dominant family in Sweden. Although incidence of Paroxysmal Nocturnal Haemoglobinuria (PNH) in Europe is still unknown, data collection from different sources has given quotes of 1 case per 100,000 individuals to 5 cases per million births.

Keywords Anaemia · Red blood cells · Erythropoieis · Congenital red cell aplasia · Thalassaemia · Sickle cell anaemia · Paroxysmal nocturnal haemoglobinuria · Migrations prevention · Epidemiology · Genetic screening

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22.1 Introduction

Rare Anaemias (RA) are diseases with a prevalence of less than 5 cases per 10,000 individuals (rare diseases) associated with anaemia as the most relevant clinical manifestation. In Europe, many people, including some health professionals, don't know of the existence of RA because in the majority of cases the cause is unknown and there is no treatment, exception made of some special types of RA. More than 80% of RA are hereditary, and in dominant pattern, the gene defect can be passed on from parents to their children with the probability of 50%. In recessive hereditary cases, parents or other relatives can be healthy, because only the occurrence of two mutated genes causes the disease and the disease can occur with the probability of 25% in each pregnancy. As in other rare diseases (RD), due to the reduced number of patients, there is a need to mobilise resources and their study can be only efficient if done in a coordinated European way. Since the development of preventive plans and epidemiological surveillance require the knowledge of the distribution of patients with RA through the Member States and the creation of a European Registry, in October 2002, the European Commission (EC), through its Public Health and Consumer Protection Directorate (DG SANCO), approved for financing a Project entitled *European Network for Rare Congenital Anaemias* (ENERCA) addressed to improve the status of congenital RA in Europe. After 2005, ENERCA Project was extended to rare anaemias of acquired origin with another grant for a second phase entitled *European Network for Rare and Congenital Anaemias)* where the "and" indicated that acquired causes of anaemia were also included in the Project's scope [25]. Accordingly, one of the most important objectives of ENERCA is the improvement of epidemiological surveillance of RA in Europe. To achieve this goal, ENERCA partners and other experts in RA, have been invited to complete the epidemiological data from their personalized clinical registries, and/or to collect the required data from other sources to pursue its completion.

For obvious reasons, it has been impossible to include here all the known causes of RA because of their large number (www.enerca.org) and the unavailability of data, especially for some very RA such as some RBC enzymopathies [92]. Here, six different RA have been selected for epidemiological description on the basis of their relevant clinical and/or social impact in the European populations: Haemoglobin disorders (HD) Diamond Blackfan anaemia (DBA), Fanconi Anaemia (FA), Congenital dyserythropioetic anaemias (CDA) and paroxysmal nocturnal haemoglobinuria (PNH). Hemoglobin Disorders (HD), mainly sickle cell syndromes and thalassaemias, are the RA with higher prevalence in Europe (1 to 4 cases per 10.000 births). The *haemoglobinopathies* are characterized by structural defects of haemoglobin molecule leading to chronic or acute haemolytic anaemia and thalassaemias are due to inherited defects in haemoglobin synthesis. Their epidemiological interest is growing in Europe due to the increasing frequency of the severe clinical form sickle cell disorders (SCD) as a consequence of immigration. *Beatrice Gulbis*, from the ENERCA Consortium describe here the current situation of structural haemoglobinopathies and SCD epidemiology in Europe. *The thalassemias* are HD due to hereditary defects of haemoglobin

synthesis and, their interest in Europe is also growing due to immigration. The most severe clinical forms of thalassaemia are Cooley's anaemia (β-thalassaemia major) and haemoglobin Bart's (Hydrops Foetalis). *Androulla Eleftheriou and Michael Angastiniotis,* from the Thalassemia International Federation (TIF) and ENERCA Consortium, describe here the current situation of thalassaemic patient's health care services and social support in different European Countries, categorized according to known prevalence data. *Diamond Blackfan Anaemia (DBA)* is a very rare congenital failure of erythropoiesis where National registries indicate an incidence of 4 to 7 cases per million live births. Since DBA is sometimes difficult to identify, *Sarah Ball*, provides, in addition to the most recent knowledge of its epidemiology in Europe, a brief summary of most relevant clinical features. *Fanconi Anemia (FA)* is due to a genetic failure of haematopoiesis and its estimated frequency ranges from 1 to 5 cases per million newborns. FA differs from DBA in that the anaemia is associated with clinical manifestations due to the progressive bone marrow failure, congenital abnormalities and cancer predisposition. A very important research on FA is undertaken in Spain by *Jordi Surrallés and Maria Castella* with the participation of key organisms from the Spanish and Catalan Governments. *Congenital dyserythropoietic anaemias (CDA)* comprise a group of hereditary disorders of erythropoiesis firstly described by *Hermann Heimpel* and others in the late 60s. Despite 42 year cumulative incidence analysis, it is still impossible to determine the precise number of cases per live births, estimated to range from of 0.1 to 3.0 cases per million births. Finally, the incidence *Paroxysmal Nocturnal Haemoglobinuria (PNH)*, an acquired stem-cell disease associated with haemolytic anaemia, is still unknown. A local study performed by *Anita Hill*, an outstanding expert in this disease, found an incidence of 1.3 per million population.

22.2 Haemoglobin Disorders (HD)

Haemoglobin disorders are inherited disorders of haemoglobin and are the most common monogenic disorders in humans. The term "haemoglobin disorders" contains two main groups of disorders: the sickle cell disorders (SCD) and thalassaemias. SCD and thalassaemias are autosomal recessively inherited disorders and carriers are most often healthy. SCD are the consequence of the presence of an abnormal haemoglobin called haemoglobin S (Hb S). Its major clinical features are acute episodes of pain, stroke, priapism and acute chest syndrome and chronic organ damage, like osteonecrosis, renal failure and chronic haemolytic anaemia. There are several forms of SCD; the most frequent is due to haemoglobin S homozygosity, while compound heterozygosity lead to a more or less severe disease, eg Hb SC, Sβ-thalassaemia. Beta-thalassaemias are disorders characterised by a reduction of β-globin chains synthesis. There is a relationship between the reduction of β-chains synthesis and the severity of the disease. Individuals with β-thalassaemia are silent carriers, have a mild microcytosis, or a severe anaemia defined as β-thalassaemia major. Patients who come to medical attention in late infancy, or who do not require regular transfusion are said to suffer from β-thalassaemia

intermedia. Alpha-thalassaemias are disorders characterised most often by a reduction of α-globin chains synthesis. There is a relationship between the reduction of the α-chains synthesis and the severity of the disease – individuals with α-thalassaemia are silent carrier, have a mild microcytosis, or a severe anaemia defined as haemoglobin H disease. The most serious cases are observed when an absence of effective α-globin chains is observed; in that situation, the foetus died in uterus or early at birth, from hydrops fetalis.

The frequency of SCD and thalassaemias varies in different ethnic groups. Since the carrier condition confers a protection towards the severe forms of malaria, this is the reason why these disorders were first confined on the endemic countries for the malaria. For example the thalassaemias are endemic to the entire Mediterranean area and the frequency of the carriers reaches rates of 15% in Cyprus. Due to population movements those disorders are now encountered in almost every country in the world. Based on country prevalence estimation of haemoglobin disorders, a chart of the frequencies of the diseases by European (EU) country could currently be as follows: comparable frequencies of haemoglobin disorders throughout the EU with SCD more frequent than thalassaemias and more frequently encountered in Northern and Western EU countries [56]. Based on neonatal screening, other data have been obtained (Table 22.1) In the EU, five countries or capital-cities have adopted a neonatal screening program financed by local or national public health service: England, France, Belgium (Brussels, Liège), Spain (Madrid) and recently The Netherlands [8, 17, 31, 34, 84]. From those programs, the prevalence of SCD has been confirmed to be high in Northern and Western countries. Nevertheless, quite high SCD numbers have been demonstrated in Madrid [17]; other studies carried out in Spain have confirmed those results [55].

The last decade, there has been increasing immigration flows especially from Northern and sub-Saharan regions of Africa all over Europe. Those new immigrants allow explaining the data obtained by a recent prenatal screening study or those reporting the number of living patients in various EU countries [9, 23, 56]. Remarkably, the prenatal study conducted in Portugal reported a prevalence of

Table 22.1 Neonatal screening program financed by national authorities in Europe

Country	Systematic(S) targeted (T)	Number tested	Period tested	SCD (‰)	β-thal major (‰)	HbAX (‰)	References
Belgium[a]	S	191.783	1994–2007	0.64	0.025	17.2	[92]
England	S	1,95,614	2005–2007	0.54[b]	NA	14.5	[56]
France	T	2,622,87	1996–2007	1.48	NA	24.5	[84]
The Netherlands	S	180,000	2007	0.30	0.044	NA	[8]
Spain[c]	S	190,238	2003–2005	0.16	NA	5.6	[34]

[a]Brussels and Liège.
[b]SCD and homozygous for Hb E.
[c]Madrid.

4.2‰ carriers of HbS and 12.6‰ of β-thalassaemia carriers [9]. Around half of the immigrants in Germany come from countries where SCD and thalassaemias are frequent; the number of living patients with SCD and β-thalassaemia major is estimated to be around 1,250 and 450, respectively [23]. Those data confirm that SCD and β-thalassaemia should be recognized as a public health problem all over Europe.

Although facilities for control and management of haemoglobinopathies are available in European countries, providing national programs for prevention and clinical management of SCD as well as of β-thalassaemia major is a challenge. The reason is that haemoglobinopathies are not officially recognized as a significant health problem in all EU countries. However recently, haemoglobinopathies have been recognized as a public health priority by the World Health Organization [81] and European dedicated networks like for example the "Euromediterranean network of research centres conducting molecular and clinical research of thalassaemia and related haemoglobinopathies" (http://www.ithanet.eu), the "European Network for Rare and Congenital Anaemias" (http://www.enerca.org), the portal for rare diseases and orphan drugs "Orphanet" (hppt://www.orphan.net) and the European Organisation for Rare Diseases (http://www.eurordis.org) are supported by the European Commission. The distribution of immigrants at risk for haemoglobin disorders is very heterogeneous and differs in each EU country widely from one region to another. It seems reasonable to adapt the prevention strategy to the local situation encountered in each EU country. In those concerned by haemoglobinopathies a clear message should be delivered at a national level: an integrated program should be implemented. But one should be always aware that it outlines many challenges since it implies to implement effective procedures for primary and secondary prevention, diagnosis, education, information, and clinical care. The need for such integrated programs has introduced a challenge to the highly developed medical services which need to cope effectively with the newly imported chronic conditions. Concerning Thalassaemia for example experience has demonstrated that this challenge has been variously met and has left many thalassaemia patients in Europe unassisted and prevention services unable to effectively reach the population at risk.

Europe is a continent that goes beyond the EU, and cannot be regarded as a single unity with similar standards in patient care and responses to health problems. There is diversity in the frequency and prevalence of thalassaemia, as well as diverse, standards of care, health systems and ability to respond to the needs of thalassaemia as a health issue. In this respect the continent may be divided into different thalassaemia areas:

1. The high prevalence countries of the Mediterranean coast, typified by Italy, Greece and Cyprus. These countries have taken the lead in developing services and their results justify their characterisation as models for the control of thalassaemia and other genetic disorders. [58]
2. Lower prevalence countries (1–2% carriers) where thalassaemia has a regional distribution in the indigenous population. These are typified by Romania, Bulgaria, Russia, Portugal and Spain. The services in these countries, especially for prevention, are largely underdeveloped and unevenly distributed. Portugal

and Spain are regarded as advanced compared to the others of this group and are more able to respond to public health needs. The others have additional economic and public health handicaps which make service provision difficult. Portugal for example has a total population of 10.5 million with only 40 registered patients (a prevalence of 1/263400 of the population) [57].

3. Low prevalence countries (1/1000 carriers in the population) where migrants from high prevalence areas have settled in significant numbers, creating minority groups carrying a high risk for thalassaemia births. These are typified by Germany, Belgium, the Netherlands and Scandinavia. Prevalence in Germany for example is 450 patients (1/183333) and Belgium with 71 patients (1/145437). These countries have the ability to respond but face organisational and cultural problems inhibiting service delivery for this rare and relatively new disease [57].
4. Very low prevalence countries (1/1000 carrier rate) where the thalassaemia problem has not yet penetrated through migration to a significant degree, typified by Poland, Hungary and the Czech Republic. These are potential future targets which must not be forgotten but should be monitored as far as immigration is concerned.
5. The UK and France belong to category 3 but differ in that they received migrants many years ago and have responded to a great extent to the needs of the thalassaemia community and have accumulated experience and developed services which may serve as an example to the rest of Europe. Also they have taken the lead in research activities for many years [39].

Each of these groups presents different needs but explores similar solutions. The first category will not be discussed, except to point out that its experiences should be shared by all, even though they cannot be exactly imitated. Category 2 presents a challenge similar to that of many underdeveloped countries. The patient support associations are weak, inexperienced and under-funded. The services are poor and need development at a very basic level e.g. blood donation and banking. Planning for upgrading services with the support of international NGOs such as the Thalassaemia International Federation (TIF) includes:

1. Forming national support associations as members of TIF.
2. Identifying interested physicians.
3. Organising educational programmes for health professionals, locally or regionally. There is need for funding of these activities.
4. Gathering all available epidemiological information.
5. Presenting the necessary information to Health Authorities with a plan of action preferably drawn up by a medical advisory panel and with WHO confirmation.
6. Providing political support to local associations and physicians.
7. Encouraging the local associations to join other European groupings such as Eurordis so that a constant flow of information as well as advocacy may be attained.
8. Encouraging WHO regional office to support, morally or otherwise, all development efforts.

In category 3 there are countries which should learn from the experience of UK and France since basically the problems are very similar. They have a model on which to base their programmes and so a North Western European collaborating grouping may be appropriate. TIF has taken the initiative to form such a group, in order to unite the patient associations initially and then to encourage medical contacts by organising Pan- European conferences. These efforts are coordinated with other rare disease groups in Europe. It must not be assumed that this part of the world does not face difficulties in service provision and assume that they belong exclusively the so called underdeveloped world. Thalassaemia in the European setting is classified as an "immigrant" health problem and as a "rare" disorder. This creates the illusion of not being important in public health. Rare is defined arbitrarily as affecting less than 1 in 2000 citizens. The chronicity of thalassaemia and SCD and the need for multidisciplinary care with expensive medication, which is beyond the reach of individual families, also the need for prevention programmes and early detection (e.g. neonatal screening) and specialised laboratories, all contribute to making these disorders a major public health concern which the EU must recognise and deal with.

Countries of category 4, in which the immigration from high prevalence areas has not yet reached significant levels, should be closely monitored to detect demographic changes early. In conclusion Thalassaemia represents a major challenge to health services in Northern Europe even though the prevalence is not as high as it is in the Mediterranean coast.

22.3 Diamond–Blackfan Anaemia (DBA)

Diamond Blackfan Anaemia (DBA; OMIM 205900) is a rare congenital aplasia, classically presenting in infancy with profound aregenerative anaemia, often in association with growth retardation and congenital anomalies. Associated physical anomalies are present in 50% of affected children. Craniofacial abnormalities are most commonly described, with cleft or high arched palate, broad flat nasal bridge and hypertelorism. Abnormal thumbs may be present, ranging from flat thenar eminence to absent radii, and including the classic triphalyngeal thumb of DBA. The anaemia responds to treatment with corticosteroids in 60–70% of cases, but remission is usually associated with a residual erythropoietic defect, characterized by persistent mild anaemia and macrocytosis, and increased erythrocyte adenosine deaminase (eADA) activity. Patients with severe anaemia who do not respond to steroids enter a life-long transfusion programme, with chelation therapy to manage transfusion-associated iron overload, unless they have a suitable donor for haemopoetic stem cell transplant (HSCT) (reviewed in [3, 93]).

National registries indicate an incidence of classical DBA of 4–7 per million live births, with neither gender nor ethnic bias [7, 14, 65, 94, 102] In 20% of cases there is a clear family history, most commonly with an autosomal dominant pattern of inheritance. However, it is now accepted that the phenotypic spectrum of DBA encompasses a wider range of severity than originally described, and that an isolated

increase in eADA may be the sole manifestation of DBA [60, 101]. The true prevalence of DBA is thus likely to be higher than predicted from registry data. Similarly, a higher proportion of cases are now believed to be familial; haematological abnormalities were identified in 31% of otherwise phenotypically normal first-degree relatives of children in the UK with apparently sporadic DBA [60] The existence of clinically silent DBA complicates genetic counseling, and represents a particular hazard in donor selection for sibling HSCT [12, 59], especially in association with pre-implantation HLA-typing.

A definitive diagnosis of DBA may be confirmed on genetic testing if a mutation can be identified, currently possible in around 50% of cases. 25% of probands have a mutation affecting *RPS19* [102] the first DBA gene to be identified [24]. Mutations affecting a further four genes encoding ribosomal subunit proteins have subsequently been reported: *RPS17* [18] *RPS24* [30], *RPL5, RPL11* [29] and *RPL35a* [18, 28]. In all cases to date mutations have been heterozygous, affecting a single allele, consistent with an autosomal dominant pattern of inheritance.

The median survival in a longitudinal study of patients treated in Boston Children's Hospital over a 60-year period was 38 years [46], although with a significantly worse prognosis for patients presenting before the introduction of steroid therapy. A high proportion of deaths could be attributed to the consequences of transfusion-transmitted hepatitis or to iron overload [46], results echoed in French [103] and North American registry data [94] Neutropenia and thrombocytopenia often develop after the first decade, and patients with DBA are at risk of progression to severe global bone marrow failure (aplastic anaemia).

Acute myeloid leukaemia developed in 4 of 76 (5%) patients in the Boston study [46], with further cases reported in the literature (reviewed in [3, 93]. Possible reporting bias and incomplete registry data currently preclude an accurate assessment of the risk of malignancy, but a low median age for the development of cancer, and high proportion of cases of sarcoma [53] are consistent with the reported cases reflecting a true increased risk of cancer, in common with other inherited syndromes of bone marrow failure.

22.4 Fanconi Anaemia (FA)

Fanconi Anemia (FA) is a rare genetic disease characterized by congenital abnormalities, progressive bone marrow failure and cancer predisposition. It was originality described in the late twenties by the Swiss pediatrician Guido Fanconi. He reported 3 siblings of the same family with anemia, malformations, recurrent infections and bleedings, resulting in premature death [27]. Over thirty years later, the German geneticists Schroeder described spontaneous chromosome fragility and the recessive autosomal inheritance of this syndrome [78]. In 1969, Schuler and coworkers provided the first diagnostic test for FA based on chromosome fragility [79], which was later improved and extended by Auerbach and colleagues [6]. In 1992 the first FA gene, *FANCC*, was cloned by the Canadian geneticists Buchwald and his team [83]. *FANCC* was followed by 11 additional genes, the two latest ones

being reported in 2007. The diagnostic tests for FA relies of the fact that patient's cells are hypersensitive to the chromosome breaking activity of DNA interstrand cross linking agents like mytomicin C, diepoxybutane, photoactivated psoralens or cisplatin. The chromosome fragility test must be done in highly experienced laboratories and is usually performed on peripheral blood, but it can also be done on fibroblasts or amniocytes, if required. Interestingly enough, these same agents serve as important drugs in cancer chemotherapy, placing FA research in the center of molecular oncology.

FA is a very rare disease with an estimated frequency of 1–5 cases per million newborns [47]. The number of patients in western European countries ranges from hundred to few hundreds in Spain, Germany or France, up to over 1000 patients reported in the North American register. The estimated frequency of otherwise unaffected FA mutation carriers in the general population is close to 1/300. The incidence of FA is, however, abnormally high in some consanguineous ethnic groups such as the Spanish gypsies, where nearly all FA patients share the 295C>T mutation in the *FANCA* gene, in part explaining the overrepresentation of FA-A patients (>80%) in Spain [16] Another example are the Ashkenazi Jews, where all FA patients are homozygous for the IVS4+4 A>T mutation in *FANCC* gene [98] or the white Afrikaner of South Africa, all sharing a large deletion in *FANCA* [89].

Since 3 out 12 FA genes (FANCD1/BRCA2, FANCJ/BRIP1 and FANCN/PALB2) are intimately related to hereditary breast cancer proteins BRCA1 and BRCA2, the biochemical route defective in FA patients is currently known as the FA/BRCA pathway. The exact role of this pathway is not well understood but current models suggest that FA gene products are essential for repairing DNA lesions that stall DNA replication forks during DNA synthesis [13, 96]. Improperly processed stalled replication forks lead to DNA breaks that, when left unrepaired or misreported, are the cause of the above described chromosome fragility of FA cells. The 12 genes and their corresponding complementation groups are known as FANCA, -B, -C,-D1,-D2,-E,-F,-G,-I,-J,-L, and −N, being the FANCA gene the most frequently mutated in the majority of populations studied, accounting for almost 60% of all FA patients in USA, whereas FA-C, FA-G represent 10–15% and FA-D1, FA-D2 represent 5% for each one. The other subtypes are extremely rare [49].

Resembling the genetic basis, the clinical symptoms and disease evolution of FA patients are very heterogeneous and include haematological disorders, congenital defects, endocrine pathologies and cancer predisposition. Almost all FA patients suffer progressive bone marrow failure (BMF) with severe trombocytopenia or pancytopenia in the majority of cases. Although the time of onset of haematological disease is highly variable, the majority of patients experience hematopoietic defects during the first decade of life. Further haematological complication of FA patients are myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) with accumulative incidence of 33% by the age of 40 [15, 51]. The age of onset and progressive evolution of the haematological disease varies between complementation groups, being FAD1 and FAD2 patients more severe than FAA patients [48, 54]. Some patients undergo a spontaneous recovery of blood counts due to mosaicism.

Mosaicism is a very interesting phenomenon that affects from 15 to 25% of all FA patients. It appears when a single hematopoietic stem cell reverts the mutation present in one of the two alleles of the affected FA gene, thus reverting the FA cellular phenotype to a "normal" wild-type. Due to proliferation advantage of this reverted cell, it clonally expands and colonizes the bone marrow of the patient, resulting in clinical improvement in many mosaic patients. Mosaicisms can be detected by the chromosome fragility test when performed by well trained cytogeneticists.

Androgen treatment can delay the decline of blood counts, but the only cure of BMF is hematopoietic stem cell transplantation preferably with a related compatible donor as the outcome of unrelated transplants is still poor. However, the majority of patients do not have suitable donors and their only hope is a future implementation of novel therapies including gene therapy [68] and regenerative medicine based on disease-free hematopoietic progenitors derived from induced pluripotent stem cells, a therapeutic strategy first reported in FA by a consortium of Spanish teams [67].

Two out of 3 FA patients have congenital defects including skin hyperpigmentation with "café au lait" spots (55%), short stature (51%), upper limbs abnormalities, such us radius hypoplasia or abnormal thumbs (43%), abnormal gonads in males (32%), microcephaly (26%), microphtalmy (23%) and urinary tract malformations (21%). However, these defects are common in other genetic diseases and 1 out 3 FA patients do not present any congenital abnormalities at all, suggesting that congenital defects should be considered along other indicators when diagnosing FA [21, 74]. In addition, the extent of the malformative syndrome also varies among complementation groups. FANCD1 patients present many birth defects and almost 90% of FANCD2 patients are microcephalic and the VACTERL phenotype (vertebral defects, anal atresia, cardiac malformations, tracheoesophageal fistula with esophageal atresia, renal and radial dysplasia and limb malformations) is overrepresented in FA-D1, FA-E and FA-F groups [26]. Eighty percent of FA patients present some endocrinopathology. The most commonly observed are growth hormone deficiency (53%) leading to short stature, hypothyroidism (37%), abnormal glucose/insulin metabolism (39%), obesity (27%) and dyslipidemia (55%). 92% of adult FA patients also present osteopaenia or osteoporosis and 65% of them have gonadal dysfunction [32, 95].

Apart from above referred AMLs, FA patients have also an extremely high risk of developing solid tumours with an accumulative frequency of 35% by the age of 40. The most frequent cancers are squamous cell carcinomas (SCC) of head, neck, esophagus, and ano-genital region (42% of all solid tumors) and liver cancer (29% of all solid tumours), often as a side effect of androgen treatment [2, 51]. The incidence of SCC in FA patients is even increased in transplanted versus non transplanted patients, probably as a side-effect of graft-versus-host disease often seen after transplant [69]. Thus bone marrow transplant advances the age of onset of SCC up to 10 years in FA patients [91]. A recent study demonstrated that only 5% of FA SCCs are positive for human papilloma virus (HPV), at least in European cohorts, suggesting that, unfortunately, the newly developed vaccine against HPV will not prevent the majority of head and neck SCC in FA patients [91]. The spectrum and

age of onset of cancer is also influenced by the complementation group. An example is FA-D1 patients that present AMLs and solid tumours (medulloblastoma, Wilms tumor) during very early childhood [43].

22.5 Congenital Dyserythropoietic Anaemia (CDA)

Definition and classification: The congenital dyserythropoietic anaemias (CDAs, ICD-10 D64.4) comprise a group of rare hereditary disorders that are characterized by ineffective erythropoiesis as the predominant mechanism of anemia and by distinct morphological abnormalities of erythroblasts in the bone marrow. The term was first used by Crookston et al [19] for cases later classified as CDA II, and by Wendt and Heimpel [97], for cases later classified as CDA I. The working classification initially proposed by Heimpel and Wendt is still used in clinical practice. There are, however, families that fulfill the general definition of the CDAs, but do not conform to any of the three classical types [99] (Table 22.2).

In general, the diagnosis of the CDAs requires the presence of all of the four following criteria:

1. Evidence of congenital anemia/jaundice or a positive family history
2. Evidence of ineffective erythropoiesis
3. Typical morphological appearance of bone marrow erythroblasts, and Exclusion of congenital anaemias that fulfill criteria 1 and 2, but were classified according to the underlying defect, such as the thalassaemia syndromes, certain types of haemoglobinopathies or hereditary sideroblastic anaemias.
4. Exclusion of congenital anaemias that fulfill criteria 1 and 2, but were classified according to the underlying defect, such as the thalassaemia syndromes, certain types of haemoglobinopathies or hereditary sideroblastic anaemias.

Table 22.2 Characteristic features of different types of congenital dyserythropoietic anaemias (CDA)

CDA type	CDA I	CDA II	CDA III familial	CDAIII sporadic	CDA variants
Inheritance	Autosomal-recessive	Autosomal-recessive	dominant	Variable	Autosomal-recessive
Cases reported	~200	~450	3 families	~20	~70
Morphology	Abnormal chromatin structure, chromatin bridges	Multinuclearity of mature erythroblasts	Giant multinucleated erythroblasts	Giant multinucleated erythroblasts	CDA I-like CDA II-like Others
Gene	CDAN1 15q15.1.3	*Sec23B* 20p11.23	Unknown 15q (21–25)	Unknown	Unknown
Associated dysmorphology	Skeleton, others	Variable, rare	B-Cells Retina	Variable	CNS Others

All types of CDA share a high incidence of splenomegaly, cholelithiasis and iron overload. As in other forms of anemia with ineffective erythropoiesis, this is due to up-regulation of iron resorption, mediated by hepcidin. Extramedullary haematopoiesis presenting as paravertebral masses may be observed. Estimates on prevalence, either expressed as lifetime or affected birth prevalence are not available. Cumulative incidence for the time interval 1967–2009 of CDA I and II in Europe, including the member States of the European Union, Norway and Switzerland are to be published. The CDAs are not included in mortality or prevalence registries administrated by governments or NGOs such as scientific societies.

In most cases, CDA has no major impact on life expectancy, although being a serious problem for quality of life and social competence. Diagnosis depends on awareness of the medical community and access of the population to hematological diagnosis including bone marrow biopsy and advanced biochemical and/or molecular procedures. Therefore, all estimates on incidence of patients or frequency of mutations are minimal values and depend on the health system of the population studied. The distribution of the age when the correct diagnosis was made suggests that even today many cases had longtime an erroneous diagnosis or, in cases with moderate of only borderline anaemia, remained undetected. In addition, one has to assume that not all cases were the correct diagnosis was made were notified to one of the registries, or were published as case reports. Male/female ratios do not deviate significantly from one. Not only underreporting, but multiple publications of identical cases and multiple notifications in more than one registry or survey are serious methodological problems in as rare disorders as CDA. The reports from the registries mentioned above, and all papers containing patient's data from the same institution or with identity of at least one author were therefore cross referenced.

Source of data: *1. Publications*. All publications describing cases of CDA were systematically collected since the first description of CDA in 1967. Completeness was checked by review of online databases (National Library of Medicine, www.ncbi.nlm.nih.gov/pubmed) for key words "congenital dyserythropoietic anemia" or "CDA" last on 31. 07. 2009. All reports were analyzed for citations of previous case reports. In addition, early reports were retrieved from three monographs [52, 63, 76]. To identify the individuals reported in publications, the authors were asked for additional identifying data (see below) by correspondence, *2. Registries and surveys*. The German registry on CDAs collects all cases of CDA, and the International registry in Italy all cases of CDA II. These registries initially tried to recruit all cases from the German speaking countries (Germany, Austria, and Switzerland) and Italy by repeated queries in the National haematological societies, respectively. When the competence of these centers became known by publications, they received queries for diagnostic confirmation of suspected cases or were asked for advice for management of patients with CDA from many countries of the world. The same is true for the Department of Pediatrics and the French Center for Inherited Erythrocyte and Erythropoiesis Disorders at Hopital Bicetre (France) (J.D; BB), the Laboratory of the late S. Wickramasinghe, at Imperial College, London (UK), the Hematology Center at the Fundeni Hospital in Bucharest collecting cases from Romania (A.C.), the Oxford CDA Research

Initiative in Oxford (UK) and the IRCCS Ospedale Maggiore Policlinico, Divisione di Ematologia 2, Milano (Italy) and *3. Demographic data* were obtained from the United Nations Demographic Yearbook (UNDYB) 2008, and Consanguinity data Bittles [76] and www.consang.net

Cases reported worldwide: 712 cases from 614 families were included in the identified German CDA Registry from all sources mentioned above. CDA type, sex, date of birth (DOB), date of first diagnosis of CDA and country of residence were first order attributes. Any individual was pseudonymised using a code (three digits for family/ two digits for family member), which does not allow identification of personal data. Not all cases from the Bedouin tribe and of the large Västerbotten family are identified (see below).

Congenital dyserythropoietic anemia type I (CDA I, OMIM 224120): This was the first disorder described under the term CDA [37]. Definition is based on the general criteria shown above, and confirmed by the characteristic morphological aberrations seen by light of electron microscopy. The mutated *CDAN1* gene was mapped to the long arm of chromosome 15 between 15q15.1q15.3 in four Bedouin families with a high degree of consanguinity [88] From studies in unrelated patients of European, Bedouin, North-American and Asian origin altogether 36 different point mutations, distributed over 13 exons were detected [22, 33, 36, 73, 87]. In less than 10% of cases, only one or no mutations were detected, suggesting mutations of other genes [1]. Most families have been detected among Western Europeans, Arabs and other Mediterranean populations, but single cases have also been reported from the USA, India, Japan, Australia, New Zealand, Polynesia and China. Two cases of the latter countries had mutations previously found in European patients.

At present, 174 cases form 145 families are recorded. In addition, more than 70 cases from the original Bedouin tribes all being homozygote are known, not collated in the identified registry are known. The cases recorded in Europe are shown in Fig. 22.1. Total frequency is 0.24 per Million, with large variations between 0.01 and

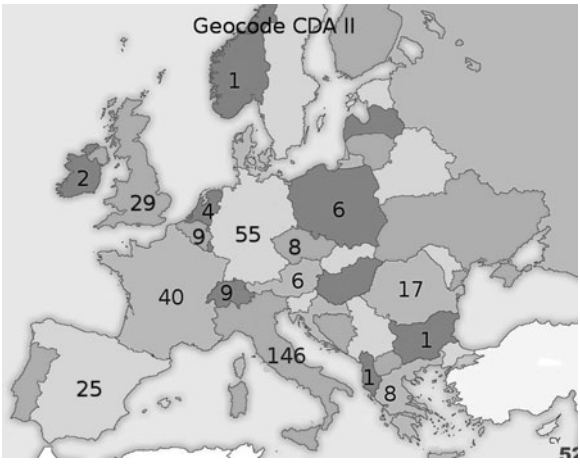

Fig. 22.1 Geocodes of CDA I in Europe. The indicated numbers are the number of cases

0.6 per million in different regions. No significant differences according to ethnic origin are observed.

Congenital dyserythropoietic anemia type II (CDA II, OMIM 224120): CDA II was the first described by disorder described under the term HEMPAS (Hereditary Multinuclearity with Positive Acidified Serum Lysis Test [19] and independently as CDA II [37]. Definition is based on the general criteria shown above, and confirmed by the characteristic morphological aberrations seen as well as by abnormalities of the red cell membrane [4, 44, 77]. The mutated *CDAN1* gene was mapped to the long arm of chromosome 15 between 20p11.23−20p12.1 and identified as *SEC23B* [11, 80]. All genotyped cases were homozygote or compound heterozygotes. Most families have been detected among Western Europeans, Mediterranean populations, but single cases have also been reported from the USA, Canada, India, Japan, Australia, New Zealand and South Africa. At present, 454 cases from 356 families are recorded. The cases recorded in Europe are shown in Fig. 22.2. Frequency is 0.71 per Million, with large variations between 0.1 and 2.5 per million births in different regions. A particular high prevalence is found in Southern Italy. No significant differences according to ethnic origin are observed. A non-significant trend of increased prevalence in some non indigenous ethnic groups may be explained by their higher consanguinity rate.

Congenital dyserythropoietic anaemia type III (CDA III, OMIM 105600): CDA III was first described in 1962 under the name of Hereditary Benign Erythroreticulosis [10] or "Västerbotten anomaly" in members of a large family living in Northern Sweden, and designated as type III after Types I and II were classified [38]. At present, the fifth generation of this family is being investigated, and most data on CDA III have been described by the investigators from Umea, Sweden [75]. There are two more families with similar haematopoietic changes and dominant inheritance living in North and South America, but only a few details are known, and it is not clear whether they share the same genetic basis. In addition, 25

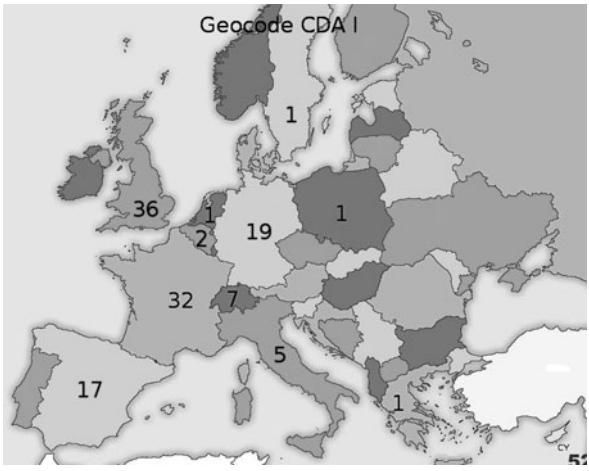

Fig. 22.2 Geocodes of CDA II in Europe. The indicated numbers are the number of cases

cases from 23 families are known with cases in only one generation, suggesting an autosomal recessive mode of inheritance. No genetic data are reported, and some of these cases may be misclassified.

Congenital dyserythropoietic anaemia type variant (CDA-variants): These patients fulfill the general definition of CDA, but represent an extremely heterogeneous group. Failure to attribute some of these cases to one of the three types may result from incomplete diagnostic workup. The mode of inheritance is generally autosomal recessive, but nothing is known about the genes possibly involved. There are 98 cases from 81 families known, the vast majority from Europe. Robust estimates of prevalence are not possible.

22.6 Paroxysmal Nocturnal Haemoglobinuria (PNH)

Paroxysmal nocturnal haemoglobinuria (PNH), first described as a distinct clinical entity in 1882 [20], is characterised by intravascular haemolysis, venous thrombosis and is associated with aplastic anaemia [42]. The characteristic symptoms of PNH, abdominal pain, dysphagia, erectile failure and intense lethargy, can be attributed to the intense intravascular haemolysis and the release of free plasma haemoglobin from its intra-cellular compartment [72]. PNH arises through a somatic mutation of the phosphatidylinositol glycan complementation class A (PIG-A) gene in a haematopoietic stem cell followed by a tremendous expansion of this abnormal clone [86]. The functions of the GPI-linked proteins are extremely varied. At least two are important in the control of complement. Decay accelerating factor (DAF or CD55) controls the early part of the complement cascade by regulating the activity of the C3 and C5 convertases. CD59 inhibits terminal complement by preventing the incorporation of C9 onto C5b-8 and therefore preventing the formation of the membrane attack complex (MAC). As a result of complement-mediated attack, the survival of PNH erythrocytes in vivo is shortened to about 10% that of normal red cells [100]. The brisk intravascular haemolysis commonly leads to haemoglobinuria, dysphagia, recurrent abdominal pain, severe lethargy and erectile failure. PNH is a chronic condition, frequently affecting young individuals, that may persist for many years and which often presents clinicians with difficult management problems. The symptoms associated with ongoing haemolysis and/or insufficient haematopoiesis have a major impact on the patient's well-being. Patients usually have acute exacerbations of haemolysis on the background of persistent lower levels of haemolysis. The acute exacerbations can occur either regularly or unpredictably, and have a further adverse impact on quality of life. Anaemia and the need for transfusions to sustain haemoglobin levels occur frequently. Haemolysis in patients with PNH can be monitored by levels of the enzyme lactate dehydrogenase (LDH) and levels are frequently elevated, exceeding 20 times the upper limit of normal during severe paroxysms [41, 62, 71, 85]. The most feared complication of PNH is venous thrombosis which occurs in ~50% of patients with haemolytic disease and is the cause of death in at least one-third [41, 42, 62, 71, 72, 82, 85, 86, 100]. PNH is known to be a rare disorder, but its incidence and prevalence have so far been poorly defined

[90, 70] with very few studies. It therefore remains of unknown frequency worldwide with little information on the incidence. Figures of incidence quoted by PNH information websites range between 1 per 100,000 to 5 per million population [35, 61, 66]. Increased prevalence is reported in some regions, e.g. Thailand and other countries in the Far East [50, 64, 70], possibly due to a higher incidence of aplastic anaemia [45].

In a study performed to accurately report the incidence and prevalence of PNH in a given population in a well-defined geographical area, survival data were collected on all patients diagnosed with PNH between January 1991 and July 2006 [40]. All patients were diagnosed by flow cytometry in one laboratory. This study did not include routine screening of normal individuals or patients with myelodysplastic syndrome (MDS) but only the routine diagnosis of all samples referred for exclusion of PNH. The population of the study region was 3,742,835. Seventy-six PNH patients were diagnosed giving an incidence of 0.13/100,000/year. Based on incidence and survival rates, the estimated 15-year prevalence of PNH is 1.59 per 100,000 resulting in a predicted prevalence of 59 patients in the study region. Levels of LDH were elevated in 82.5% of patients. Of the 59 patients in the study region, 33% reported haemoglobinuria. With a population of 57,105,375 (2001 census of Britain), Britain should have an estimated 75 new cases of PNH/year and a predicted prevalence of 908 patients. The U.S.A. will therefore have 4713 cases of PNH based on its July 1,2005 census bureau population estimate of 296,410,404.

The US definition of a rare disease is one that affects less than 1 in 200,000 individuals; the corresponding number in Japan is 1 in 50,000 and in Australia 1 in 2000. These numbers translate to prevalences of 1–8 in 10,000. The European Community definition is less than 5 in 10,000, and the World Health Organisation has suggested less than 6.5–10 in 10,000 [5]. PNH would certainly remain classified as rare regardless of whose definition was used.

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Chapter 23
Inherited Metabolic Rare Disease

Teresa Pampols

Abstract Inherited metabolic disorders (IMD) represent a vast, diverse and heterogeneous collection of around 700 genetic diseases. They are caused by rare mutations that affect the function of individual proteins and are a significant cause of morbidity and mortality, especially in childhood. Difficulties in ascertaining cases and the increasing number of new disorders have hampered efforts to accumulate exhaustive epidemiological data. Nonetheless, recent studies quote the cumulative incidence of IMDs at around 1 in 800 live births. To understand the epidemiology of IMD we will consider in this chapter two types of epidemiological approaches. The first type, or the Analytical approaches, includes the function of genetic factors in the natural history and clinical variability of the disease, as well as the role of epigenetic, stochastic and environmental factors. The second type, or the Descriptive approaches, comprises methods of case ascertainment through the diagnosis of symptomatic patients and population screening, mainly newborn and carrier screening, as well as measures of disease frequency and resources for disease control and prevention (primary, secondary and tertiary).

Keywords Diagnosis · Incidence · Inherited metabolic disorders · Population-based screening · Prevention

23.1 Introduction

Inherited metabolic diseases (IMDs), or inborn errors of metabolism, according to the name given in the paramount studies of Sir Archibald Garrod (1857–1936), are relatively rare conditions. However, as a group, they represent a vast, diverse and

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heterogeneous collection of genetic diseases that are a significant cause of morbidity and mortality, mainly in the childhood, showing an important presence of neurological syndromes.

Around 700 IMDs have been described, with the main groups of IMDs presented in Table 23.1. The cumulative incidence is usually quoted between 1/2,500 and 1/5,000 live births. However, owing to their extreme heterogeneity, the difficulties in ascertaining cases and the increasing number of new disorders, the real figure is underestimated and exhaustive epidemiological data on the overall occurrence are lacking. Indeed, in several recent studies the prevalence at birth has been found to be substantially higher, either 1/784 [81] or 1/813 [77].

IMDs are caused by mutations in highly penetrant nuclear genes with some contribution of mutations in mitochondrial DNA in a few specific conditions. As a consequence of the gene mutation, the corresponding gene product (protein) can be flawed and its function impaired, causing chemical imbalances in the organism that are related with the manifestation of clinical disease. For this reason, inherited disorders of metabolism have been defined by Rosenberg as "genetically determined biochemical disorders due to specific, congenital defects in the structure or function of protein molecules" [80].

IMDs are the most evident examples of genetic variation affecting health, but genotype does not always predict phenotype. In addition, the clinical features and

Table 23.1 Groups of inherited metabolic diseases

Disorders of amino acid metabolism
Disorders of urea cycle
Membrane transport disorders
Disorders of organic acid metabolism
Disorders of carbohydrate metabolism
Congenital defects of glycosilation
Disorders of fatty acid oxidation
Defects of Pyruvate dehydrogenase and Krebs cycle disorders
Mitochondrial respiratory chain disorders
Cerebral creatine deficiencies
Disorders of purine and pyrimidine metabolism
Lysosomal diseases
Peroxisomal diseases
Disorders of lipoprotein metabolism and other lipidaemias
Disorders of sterol metabolism
Disorders in metals
Disorders in porphirine and haemo group
Disorders concerning vitamins
Disorders concerning hormones
Disorders in neurotransmitter metabolism
Blood disorders
Others

In this classification, conditions are grouped together under common altered metabolites or metabolic pathways, while others are grouped under subcellular organelles. Despite these inconsistencies, this classification is commonly employed, sometimes with slight variations.

course of the disease can be modified by epigenetic and environmental factors, as well as by other variations in the causal gene and in the whole genetic background. It is therefore not surprising that most IMDs show some degree of complexity, even behaving sometimes as complex traits [86].

To understand the epidemiology of IMDs, we will consider in this chapter two types of epidemiological approaches. First are the Analytical approaches which include the function of genetic factors in the natural history of the disease and their interaction with epigenetic, stochastic and environmental factors. Secondly are the Descriptive approaches which include methods of case ascertainment, measures of disease frequency, disease control and prevention.

23.2 Analytical Epidemiology of IMDs

23.2.1 Causes of IMDs: Relationship Between Mutation, Altered Gene Product and Disease

Population genetics, as well as molecular and genetic epidemiology are a source of new concepts and methodological issues relevant to the knowledge and research of IMDs. Therefore, to reach a better understanding of IMD epidemiology, we will need to consider some fundamental genetic concepts, albeit in a simplified manner for the non-geneticist reader. However, readers who wish to go deeper into these concepts will find more supplementary information in the references. Firstly, we will consider what causes IMDs, which means an introduction to the concept of mutation and the molecular basis of gene expression, as well as to the relationship between the mutation and the altered gene product and disease. Secondly, we will discuss the variability of clinical expression due to both intrinsically determined factors, such as genetic heterogeneity, and extrinsically determined or environmental factors.

23.2.1.1 Mutations and the Molecular Basis of Gene Expression

IMDs are caused by *mutations.* The genetic information stored in DNA must be faithfully copied or replicated in each cellular division. Despite complex repair and protection mechanisms, changes or errors in the copying process sometimes occur. Those changes in the primary nucleotide sequence of DNA which are stable are called *mutations.* Alternatively, some mutations can be unstable. For example, the discovery of expanding triplet repeat mutations has explained the basis of Huntington's disease, Fragile X syndrome, Myotonic dystrophy and other monogenic diseases.

Mutations occurring in somatic cells may be relevant to cancer or aging, but otherwise may be of less phenotypic significance. In any case, mutations in somatic cells will only affect the individual, but not their descendents. For a mutation to have impact on the offspring of an individual it must be present in germinal cells (gametes).

The term *mutation* is only used for changes in the DNA that are disease causing, the other changes are called *Polymorphisms*, contributes to diversity and permit adaptation to environmental changes and are thus an important basis of evolution. In particular, single nucleotide polymorphisms (SNPs) have been revealed to be the main source of genetic and phenotypic variation in humans. Polymorphisms in a mutated gene (e.g. Gaucher's disease, Short-chain Acyl-CoA dehydrogenase deficiency) and, on occasions, combinations of polymorphisms (haplotype) can further modify the consequences of a disease-causing mutation and the clinical course of an IMD (e.g, Hurler's disease). To ascertain whether a gene variant is a neutral polymorphism or a "modifier variant" requires functional analysis. For example, with this approach it was demonstrated that the change C.10936G>A in the acid beta-glucosidase or GBA gene causing Gaucher's disease, decreases enzyme activity when found as a double mutant and is thus currently considered a "modifier variant" whereas formerly it was thought only to be a polymorphism [58].

Mutations are quite diverse and can involve even millions of base pairs, but IMDs are caused by minute mutations, called *point mutations*, involving deletion, insertion or replacement of a single base in a unique gene. Mutations can also involve larger deletions that may affect a portion of a gene, an entire gene or a set of continuous genes. In fact it is estimated that a 5% of all mutations related to simple Mendelian disease are currently ascribed to sub microscopic insertions or deletions [7].

In the genome there are structural variations (SVs) or genomic changes that are not single base-pair substitutions, but include insertions, deletions, inversions, duplications and translocation of sequences, in addition to copy number variations (CNVs), that, like SNPs, contribute to human phenotypic variation. Benign SVs exist widely in the healthy population, but others are pathogenic, contributing to phenotypic variability, disease susceptibility and drug responses. These pathogenic CNVs can result in changes in gene dosage, which can influence carrier phenotypes, or they may alter the location or effect of essential regulatory elements, as observed in thalassemias [9]. In another example, 40% of patients with haemophilia A, were found to have a recurrent 400-Kb inversion of the factor VIII gene [52]. The detection of these sub microscopic variants depends on the emergence of high-throughput and high resolution genomic technologies [105] and it is expected that these will provide more important information in the future.

Gene expression is the basis for cellular differentiation, morphogenesis and adaptability of any organism. Gene expression occurs according to the central theory of the molecular flow of genetic information. In this process, the information stored in our genes in nuclear DNA is first transcribed to make RNA (precursor RNA), that after a process of splicing is then transported from the nucleus in the form of mRNA (messenger RNA) where it is subsequently translated into protein in the cytoplasm. Once gene information is translated into a gene product, the protein can still be subject to post-translational modifications.

Although the central dogma of gene expression may be simple, "turning on" a gene at the transcriptional level is complex and regulated by many factors. In addition, regulation of gene expression even occurs at the post-transcriptional level, after the gene has been turned on, and involves processes such as alternative splicing

of precursor RNA transcripts, regulation and export of mRNA to the cytoplasm and stabilization of mRNA. Splicing in particular is an important process not only for regulating gene expression, but for creating diversity. Splicing is the process of eliminating intronic sequences from a precursor RNA when it is still inside the cell nucleus to make an mRNA transcript, Genes have sequences called exons which contain the code for the final protein which are interspersed with non-coding sequences called introns.

Alternative splicing makes it possible that a gene can be transcribed into different mRNAs and, in consequence, to be translated into more than one gene product. As a consequence, it is now well known that we have around 25,000 genes, but at least 200,000 proteins. The initial concept of one gene/one protein cannot always be applied and alternative splicing is one of the many possibilities for generating diversity by the complex mechanisms of transcription and gene expression control.

Regulation of gene expression also depends on mechanisms unrelated to the genomic DNA coding sequences called *epigenetics*- Some epigenetic processes include DNA methylation, RNA-associated gene silencing, histone modification and chromatin modification. Epigenetic mechanism also account for the random inactivation of one of X chromosome in early steps of female foetus development, contributing to the phenotypic variability in heterozygous females. The epigenome is also involved in human disease, such as in cancer, single gene disorders and common complex disorders and is an important target of environmental modification. Some monogenic disorders such as Rett, Angelman, Prader-Willi and Beckwitht-Wiedemann syndromes are epigenetic diseases [29].

Transcriptional silencing may also affect manifestation of an IMD, as has been described in Niemann-Pick disease types A and B which is caused by the deficiency of acid sphingomyelinase. The gene encoding this enzyme is paternally imprinted (silenced) and enzyme activity appears to be determined by the function of the maternally inherited gene copy. Niemann-Pick disease is autosomal recessive, but heterozygotes that inherit a mutation from the mother may sometimes develop symptoms [87].

The knowledge of these complex mechanisms can be useful for the understanding of formerly unexplained findings in Mendelian disorders in general, but it is also relevant in order to develop new therapies. For example, there are interesting therapeutic approaches based on transcriptional silencing of genes and inhibition or repair of RNA fragments. These therapies are mutation dependent and require a deep knowledge of the gene concerned and its status in the patient [1, 25, 51, 46].

23.2.1.2 Relationship Between Mutation, Altered Gene Product and Disease

Mutations in a gene are incorporated into the transcribed RNA, resulting in a change in the pattern of its specific gene product (polypeptide or protein), which can affect its function negatively. This loss of function alters physiological homeostasis (pathogenesis), inducing clinical manifestations and phenotype.

In IMD, very often the gene product is an enzyme and its loss of function can cause a blockage in a step of a metabolic pathway that can result in an accumulation

of metabolites prior to the blockage, deviations of the metabolic pathway towards the production of undesirable toxic compounds, deficiencies in the synthesis of relevant products, as well as combinations of these problems. Mutated gene products are not always an enzyme and in Table 23.2 there are several examples of IMDs caused by defects in other types of proteins.

Some examples of accumulation of metabolites prior to the blockage in a pathway include the lysosomal diseases, organic acidemias and disorders of amino acid metabolism. Although the intracellular accumulation of macromolecules in lysosomal storage disorders is tightly correlated to the generalized cellular lesion present in several organs, other secondary cellular and metabolic pathways must nevertheless be considered in order to explain the pathology. The massive increase of organic acids in the organic acidemias is related with metabolic acidosis and clinical signs of intoxication.

Defects in mitochondrial fatty acid β-oxidation as well as deficiencies in pyruvate metabolism and the mitochondrial respiratory chain manifest in clinical signs of energy deficiency.

Glycogenosis type I or Von Gierke's disease is a good example of an incapacity to produce a terminal compound, glucose, due to the deficiency of Glucose-6-phosphatase, causing severe hypoglycaemias and glycogen storage in liver.

Relationship between protein and symptoms can be very tight as in the case of the haemoglobin molecule where alterations reduce the capacity of blood to transport oxygen.

The spectrum of IMD disease mechanisms is wide and in order to find adequate therapies it is very important for research efforts to achieve a better understanding of the complex physiopathology of IMDs. Currently, it is estimated that successful treatment can only be offered for about 12% of IMDs, while a partial benefit can be obtained in 45% and for the remaining 34% of IMDs, there is no successful therapy [89]. Often, the success of a treatment relies on the early diagnosis of the condition.

Table 23.2 Some examples of inherited metabolic disorders in which the deficient gene product is not an enzymatic protein

Disease	Deficient gene product
X-Linked adrenoleukodystrophy	ABCD transporter protein
Zellweger syndrome	Several peroxines (at least 12)
Niemann Pick Type C disease (NPC1)95% of patients	Lysosomal membrane protease
Niemann Pick Type C disease (NPC2) 5%of patients	Soluble lysosomal protein that interacts with protease
Rhizomelic Punctate Chondrodysplasia autosomal recessive	Peroxine Pex 7
Cistinosis	Cystinosine (a membrane lysosomal transporter protein)
Gaucher disease caused bay Sap C deficiency	Sphingolipid activator protein Sap C
Congenital disorders of glycosilation caused by COG subunit deficiencies	Subunits of Conserved oligomeric complexes COG1, GOG4, GOG5, COG7 and COG8

IMDs are caused by mutations in highly penetrant genes, which means that the proportion of individuals with a given genotype presenting with phenotypic features of the disorder is very high. In some cases penetrance depends on environmental factors, for example exposure to drugs or fava beans in glucose-6 phosphate dehydrogenase deficiency. See Section 23.2.2.

IMDs are inherited in a monogenic or Mendelian form, due to the fact that one gene plays a predominant role in the determination of disease. Most IMDs (67%) are of autosomal recessive inheritance, 21% are of autosomal dominant inheritance, while 6% are X-linked and another 6% are associated with mitochondrial inheritance [42].

Whether a mutation generates a dominant or recessive disorder is determined by two factors: the effect of the mutation on the function of the gene product and the tolerance of the biological system to perturbation of that particular gene product. At the practical level, it means that in dominant IMDs, heterozygous individual are always symptomatic and homozygosity can be even lethal.

However, Mendelian traits are not quite as simple as sometimes assumed. Mutations affecting the same amino acid residue, or single amino acid deletions affecting adjacent residues, may be associated with different inheritance patterns. In X-linked diseases the terms dominant or recessive are perhaps more misleading than helpful as most X-linked disorders may give rise to at least some clinical symptoms in at least a minority of heterozygous females. Male individuals have only one X chromosome and they are therefore hemizygous (that is, neither homozygous nor heterozygous). Similarly, in females, random X-inactivation in each cell during foetal development results in usage of only one copy of most X-chromosomal genes, being thus a functional hemizygosity. An important factor of pathogenicity is skewed X-inactivation leading to expression of the non-functional mutated allele in a disproportionate number of cells. This is a stochastic event and it is therefore impossible to predict the clinical severity of, for example, ornithine transcarbamilase deficiency and pyruvate dehydrogenase deficiency when carrier status is found in prenatal diagnosis. For a review of these concepts in IMD see [107].

In the case of genetic disorders affecting mitochondrial function, many of the mitochondrial proteins are encoded in the nuclear genome and mutations are inherited with a Mendelian pattern. However, mitochondria also contain a small circular DNA genome (mtDNA) that encodes 2 ribosomal rRNAs, 22 transfer tRNAs and 13 peptide components of the multi enzyme complexes of the respiratory chain. Mutations in mtDNA display a distinct pattern of inheritance, called “maternal inheritance”, because embryo mitochondria are derived from the oocyte, with the contribution of sperm being insignificant. In consequence, mtDNA mutations can only be transmitted by woman carrying the mutation. There is wide variation in the number of mtDNA copies per cell (polyplasmy), with wild type and mutated mtDNA often coexisting within the same cell (heteroplasmy). Since mitochondrial mitotic segregation is random, it renders unpredictable the fate of daughter cells and confers a high tissue and phenotypic heterogeneity to mitochondrial inherited IMDs. These facts add special difficulties to the genetic counselling and prenatal diagnosis [27, 20].

23.2.2 Variability of Clinical Expression

Patients with a specific IMD are not a homogeneous group, and what is more intriguing, in some cases, even with the same mutation, siblings may show different clinical presentation.

The lack of homogeneity is due in great part to the *genetic heterogeneity* that can result from different mutations at a single locus (allelic heterogeneity) or from mutations at different genetic loci (non allelic or locus heterogeneity).

For example, the same bleeding disorder, haemophilia, can be caused by mutation at two different loci on the X chromosome, one of them causing factor VIII deficiency (Haemophilia A) and the other a deficiency of factor IX (Haemophilia B). The accumulation of ganglioside GM2 in GM2 gangliosidosis can be due to mutations in either the gene that codes for the α chain of hexosaminidase A (Tay Sachs disease), the gene that codes for the β chain of Hexosaminidase A and Hexosaminidase B (Sandhoff disease), or in the gene that codes for a specific activator protein (in activator-deficient protein GM2 gangliosidosis).

These diseases are examples of non allelic heterogeneity, but allelic heterogeneity is much more extensive such that it is almost universal with a great deal of clinical heterogeneity being due to different mutations at a single locus. Sometimes a good clinical correlation can be established between specific mutations and the clinical course. For example, it is well known that the mutation p.N370S in the *GBA* gene, either in homozygous or heterozygous individuals correlates with type I non-neuronopathic Gaucher's disease, whereas the allele p.L444P, in the absence of a mild mutation, is associated with the neuronopathic forms of the disease (Gaucher Type II and III) [91]. Similarly, the genotype p.D409H + p.D409H has been associated with a special type III phenotype, presenting severe cardiac involvement and oculomotor apraxia [18]. On the other extreme, there is the example of X-linked adrenoleukodystrophy, where patients have been described with an infantile cerebral phenotype or an adult adrenomyeloneuronopathic form with the same mutation in the *ABCD1* gene, that moreover, can co-occur in a single kindred or sibship [59].

Patients with autosomal recessive disorders seldom have the same mutant alleles; it occurs only when the patient is product of a consanguineous mating or when particular alleles are present in high frequency in the population, for example, sickle cell anaemia with a SS genotype, cystic fibrosis with a p.ΔF508/p.ΔF508 genotype or Medium chain acyl-CoA dehydrogenase deficiency (MCADD) with a p.A985G/p.A985G genotype. That means that very often the patients we call homozygotes are "*compound heterozygotes*" or "*genetic compounds*" that have inherited two different mutations, one from the father and the other one from mother. The compound heterozygote produces two different gene products or proteins contributing to the complexity of the clinical continuum.

Severe mutations, those which greatly impair the function of the gene product, are necessary and sufficient causes of disease, but there are many mutations that allow a residual function.

Similarly, there are many missense mutations that only impair the protein folding and under optimal conditions can show little effect on the protein function, while

under adverse conditions may result in a devastating clinical phenotype. The mutation in itself is a necessary major primary component, but its effect may be modified by environmental factors (temperature, metabolic stress), cellular conditions, and possibly by genetic variations in the cellular quality control systems (comprising chaperones and proteases) [33]. Disorders of fatty acid mitochondrial β-oxidation and many other IMDs belong to this category of protein misfolding disorders.

Clinical outcome of a genetic disease can also be modulated by other mechanisms, such the nonsense-mediated decay (NMD) pathway, an mRNA surveillance system that typically degrades transcripts containing premature termination codons (PTCs) in order to prevent translation of unnecessary or aberrant transcripts [49, 51]. Nonsense or frame shift mutations can generate a PTC and NMD has been shown in several IMD. Preventing translation of aberrant transcripts can have distinct effects, such as changing the inheritance pattern between recessive and dominant, protecting from the toxic effects of accumulated aberrant transcripts, or, on the contrary, increasing disease severity by eliminating any possible residual activity of the truncated protein. It is an important consideration to investigate these possibilities in order to improve prognostic and genetic counselling.

In general, the amount of functional gene product required to prevent clinical symptoms depends on other genetic and *environmental factors*. For example, an individual with benign methylmalonic acidemia is still at risk during major catabolic events, such that the designation "benign" is merely conditional. There are other IMDs that can be highly influenced by environmental factors. Drugs or fava beans induces important haemolytic crises in individuals with glucose-6-phosphate dehydrogenase deficiency; acute intermittent porphyry is also exacerbated by drug exposure; reducing iron intake and protocols favouring blood loss improves the course of hemochromatosis; smoking is especially devastating for individuals with α-antitrypsin deficiency; lengthy fasting in children with MCADD and other fatty acid β oxidation defects can be fatal.

In addition to genes at other loci which act as modifiers of the phenotype (e.g., the α-globine cluster on sickle cell anaemia), there is also the influence of epigenetic factors and stochastic factors. Therefore, it is not surprising the degree of complexity of many IMDs, which often behave more as complex traits, being at the border between monogenic and polygenic and multifactorial disorders.

It has already been discussed how protein diversity far exceeds that of nucleic acids, but an additional important consideration is how the organization of proteins into functional metabolic pathways further magnifies this complexity. The dynamic approach of "systems biology" has been critical to further understand the complex networks of interacting molecules that co-ordinately control their activities in the context of normal physiological function and reactions to stress. Recently, patients have been described with clinical evidence of energy metabolism disorders who exhibited concurrent partial enzymatic deficiencies in several energy generating pathways. Moreover, it was shown that some of them were heterozygous carriers for individual mutations in more than one gene involved in these functionally related pathways. In isolation, heterozygosity for each mutation was clinically irrelevant, but concurrent heterozygosity was synergistic, leading to clinically relevant

biochemical derangements. This model of "synergistic heterozygosity" can be very useful for the understanding of complex phenotypes [96].

23.3 Descriptive Epidemiology of IMDs

The Descriptive epidemiology approach will cover the methods for IMD case ascertainment, how to know frequency and distribution of the disease in the population, the description of the patterns of disease progression over time (natural history) and finally, aspects of disease control and prevention.

23.3.1 IMD Case Ascertainment (Case Definition and Diagnostic Criteria)

Cases of IMD can be ascertained through diagnosis of symptomatic patients or by means of population screening programs and further investigation. Cases of IMD can be defined on clinical grounds including using support technologies, such as imaging studies and anatomical pathology investigations, but as they are genetic diseases, laboratory investigations have become the gold standard for a definitive, unequivocal diagnosis. In order to perform epidemiological studies it is also useful to undertake systematic searches of case descriptions in Medline, as well searches of additional data available on the World Wide Web.

23.3.1.1 Diagnosis of IMD in Symptomatic Patients

The first step for the diagnosis of an IMD is the *clinical hypothesis* based on signs and symptoms. There are many factors that contribute to make the clinical diagnosis of IMDs very difficult for the physician, such as:

The vast, diverse and heterogeneous collection of disorders.

The above mentioned phenomenon of genetic heterogeneity is a very important source of variability of clinical and biochemical expression.

Signs and symptoms may be nonspecific, especially in the neonatal period.

Despite the fact that they are inherited disorders, IMD patients very often present as isolated cases due to the small size of many families. Consanguinity is not a common factor, except in specific cultures or ethnic groups.

Prejudices against their perceived rarity contributes to the fact that they are not taken in account in critical situations until other more frequent conditions have been discarded.

There is poor knowledge of symptoms that can be clues to diagnosis. Mild forms with delayed or adult presentation may be even more difficult to recognize.

Some IMDs present intermittent abnormalities and samples may be unrevealing if they are not collected during a crisis.

Several excellent publications have addressed the issues surrounding clinical diagnosis, including the generation of many helpful diagnostic algorithms [11, 22, 30, 64, 84].

In the *laboratory,* IMDs can be investigated at three different levels: (a) the gene, (b) the gene product and (c) the metabolic products or metabolites. Many IMDs have stereotypic presentations and *molecular genetics* is usually not suitable for the first approach to diagnosing the patient. It is called *biochemical genetics*, the laboratory discipline that covers the evaluation and diagnosis of patients and families with IMDs by metabolite and enzymatic analysis, or by other protein-based assays of biological fluids, cells and tissues, including monitoring of treatment, carrier identification and prenatal diagnosis [12].

Very often the first approach is at level (c) with a multicomponent analysis of the body fluids. High-resolution and extremely sensitive chromatographic methods combined with mass spectrometry in all its modalities produce extensive profiles and can give information on the functional status of many genes, especially those involved in pathways of intermediary metabolism. Often the identification and measurement of metabolic products leads directly to the diagnosis. In other cases, the metabolic profile allows a hypothesis to be proposed that must be then verified with other laboratory investigation, usually following flow charts, and sometimes functional tests are required.

Diagnosis at level (b) with direct analysis of enzymes and proteins is essential for many IMDs. This usually requires the use of cells or tissues, mainly leukocytes and cultured skin fibroblasts, but also erythrocytes and other tissue biopsies when it is necessary (muscle, duodena). An enormous variety of chemicals and substrates have been developed, including radioactively labelled or deuterated compounds. Cultured patient cells, mainly skin fibroblast, allow many kinds of "in vitro" assays to be carried out, including those to investigate the metabolic fate of relevant compounds.

Interpretation of results by the biochemical geneticist is necessary to make the results meaningful for the clinician. The biochemical strategy requires that the laboratory have been informed on clinical features of the patient and the success in the diagnosis relies to a great extend on the co-operation between clinician and biochemical geneticists. The consequence of a misdiagnosis concerns not only the patient, who could die or be deprived of the benefits of an early treatment, but also his family who might ignore the genetic risk. For these reasons, quality assurance requirements are very high. The European Research Network for Evaluation and Improvement of Screening, Diagnosis and Treatment of Inherited Disorders of Metabolism (ERNDIM) develops a specific Quality Assurance Programme for biochemical genetics laboratories including schemes with characteristics of diagnostic proficiency. See also *www.erndimqa.nl* and *www.Eurogentest.org*.

Once the disorder has been identified, the study of the gene can be critical for establishing genotype/phenotype correlations, more reliability in the assessment or excluding of heterozygous states (especially in X linked disorders), prenatal diagnosis (very often as a double methodology with biochemical genetics assays), future requests for pre-implantational genetic diagnosis as well as studies of population allele frequency and distribution. It can also be used in screening population programmes, especially in carrier screening and, in a few cases, in newborn screening.

Diagnosis of the patient requires prompt genetic counselling for the parents and other relatives, including information about reproductive options.

23.3.1.2 Population-Based Screening

According to Wald [101] "Screening is the systematic application of a test or inquiry to identify those individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder".

There are two main approaches and periods to screen population for IMDs. Screening during the newborn period is usually undertaken for severe treatable diseases with the aim of initiating a preventive medical intervention in individuals found positive. Screening during the pre-conceptional and prenatal period, is with the aim of identifying carrier couples at risk for severe untreatable diseases in order to offer genetic counselling, including information on reproductive options.

Screening can occur at other life stages for late-onset diseases such haemochromatosis or familiar hypercholesterolemia. The most heavily discussed is Type I hereditary haemochromatosis, due to its high frequency among individuals of European ancestry and the possibility to reduce or prevent iron load through regular phlebotomy [2, 72]. However, some evidence-based recommendations have discouraged its population wide screening [92] and for the moment it has not been endorsed. On the contrary, millions of newborns in industrialized countries from the five Continents are routinely screened for congenital hypothyroidism (CH), phenylketonuria (PKU) and a variable number of IMDs.

Newborn Screening (NBS)

NBS is a Public health activity that has "traditionally" been performed to detect metabolic or endocrine diseases that are severe, relatively frequent (<1:10,000–1:15,000) and treatable, according to criteria established in the late 1960s by the World Health Organization [103]. For several decades, there has been a universal agreement to screen for CH and PKU. Other important diseases, such as congenital adrenal hyperplasia due to 21 hydroxylase deficiency, hemoglobinopathies, cystic fibrosis, biotinidase deficiency and galactosemia, have also reached a variable degree of consensus.

The development of electrospray ionization tandem mass spectrometry (MS/MS) allows screening for several disorders of intermediary metabolism (disorders of fatty acid mitochondrial β-oxidation and some disorders of amino-acid and organic acid metabolism). This technology has contributed to diagnostic progress, but has also brought new controversies and the development of dozens of lists of new criteria. The controversy is mainly due to the lack of high quality observational evidence for most disorders and their very low incidences, in the range of >1:75,000–>1:100,000, except for PKU and MCADD with 1:17,000–1:25,000 [26, 94].

The screening for conditions with such low incidences generates a high number of false positives. For example, although the positive predictive value of MCADD screening is approximately 50%, the positive predictive values for a myriad of other conditions may be as low as 10%.

Positive predictive value is the proportion of patients with a positive test result that are really affected. This value depends on test Sensibility (S = The proportion

of affected individuals detected by the test), test Specificity (Sp = the proportion of affected individuals not detected by the test) and the Prevalence (P) of the disease in the population [PPV = S × P / S × P + (1− Sp) (1−P)]. What this means is that in spite of the high sensitivity and specificity of tests, the number of false positive may be necessarily very high [43, 88]. In addition, for some diseases, many of the true positive results may be destined to be asymptomatic ast occurs in MCADD and in 3-Methylcrotonyl-CoA carboxylase deficiency.

Effectively, mutational studies of MCADD have shown that 80% of homozygous patients present with the mutation 984A > G if diagnosed when they present clinical signs, but that this mutation is only found in 50–65% of children detected through newborn screening,as they harbour benign mutations much more frequently [34].

The rarity of these disorders contributes to the fact that the natural history is not always well understood. Outcome assessment, rarity, lack of standardized care and variability of clinical expression of the same defect in different patients are very important issues.

Consequently there is little agreement among countries as to which specific disorders should be included in screening panels [3, 13, 73, 102]. With some exceptions, screening policies have typically been determined by technological capability, advocacy groups, parents associations of concerned diseases and medical opinion, rather than through a rigorous, objective, evidence-based review process [37]. Nevertheless, virtually every developed country either had initiated expanded newborn screening with MS/MS, or was about to do so. In fact, MS/MS may be the tip of iceberg [16], with newborn screening for lysosomal storage disorders, adrenoleukodystrofy, Smith-Lemly-Opitz Syndrome and possibly others not far away.

At present in Europe, The European Commission (Executive Agency for Health and Consumers) have launched a Call for Tenders: Rare disease Newborn Screening, for the Evaluation of population newborn screening practices for rare disorders in Member States of the European Union. In the United States, the National Academy of Clinical Biochemistry have published Practice Guidelines and Recommendations reviewing US panels [26] that are summarized in Table 23.3.

From the disorders mentioned in Table 23.3, MCADD is the most frequent together with PKU, and for the moment, these are the disorders for which there is a more consistent agreement that screening is cost effective [21, 61, 62, 68, 69, 76, 95]. Nevertheless, taking into account the epidemiology of MCADD and a prevalence of 1 in 17,000, it would be necessary to screen 70,000–80,000 children to prevent one death or serious disability. In the U.S.A., screening 4 million births per year could prevent 50–60 premature deaths or cases of disability caused by MCADD [37].

In order to analyze the contribution of MS/MS to newborn screening, it is helpful to consider the estimated overall number of children who would have been identified with disorders in 2006 in the United States, using a screening panel of 29 disorders (Tyrosinemia Type I and hearing loss not included), based on incidence of these disorders in four state newborn screening programmes during 2001–2006 [17]. Life birth data for 2006 was 4,138,349 live births. With a total estimation of 6,618 cases,

Table 23.3 Disorders of intermediary metabolism detectable by MS/MS. Strength of evidence according to the National Academy of Clinical Biochemistry (NACB) [26]

Group	A. I	A. II	B.II
Disorders of amino acid catabolism and transport	PKU, benign PKU and disorders of biopterin cofactor synthesis or regeneration	Maple syrup urine disease Tyrosinemia type I	Argininsucccinic acidemia Citrullinemia Homocystinuria(CBS deficiency) Argininemia Citrullinemis Type II Hypermethioninemia Tyrosinemia Type II Tyrosinemia type III
Disorders of fatty acid oxidation	Medium-chain acyl-CoA dehidrogenase deficiency (MCADD)	Carnitine uptake defect Long-chain 3-OH acyl-CoA dehydrogenase deficiency Trifunctional protein deficiency Very-long-chain acyl CoA dehydrogenase deficiency	Carnitine palmitoyl-transferase Ia deficiency Carnitine palmitoyl-transferase II deficiency Cartitine/acyl-carnitine translocase deficiency

Table 23.3 (continued)

Group	A. I	A. II	B.II
Organic acidemias	Glutaric acidemia Type I Isovaleric acidemia	Methylmalonic acidemia, AB, mut and CblC and D Propionic acidemia 3-Hydroxy 3-methil glutaric aciduria Beta-ketothiolase deficiency	Glutaric acidemia type II 3-Methil crotonil-CoA carboxylase deficiency Multiple carboxylase deficiency 2-Methyl butyryl-CoA-dehydrogenase deficiency 3-methyl glutaconic aciduria Isobutyryl –CoA dehydrogenase deficiency Malonic aciduria

(A) The NACB strongly recommends adoption. There is good evidence that it improves important health outcome. Benefits substantially outweigh harms. (B) The NACB Recommends adoption. There is at least fair evidence that it improves important health outcomes. Benefits outweigh harms. Grade of quality evidence: I Evidence include consistent results from well-conducted studies in representative populations. II Evidence is sufficient to determine effects, but its strength is limited by the number, quality or consistency of individual studies. For eight other disorders NACB recommends against adoption. U.S. Incidence is >1:25,000 for PKU and MCADD, the rest are >1:75,000–<1:100,000.

five disorders would account for 5,605 cases: Primary congenital hypothyroidism (2,156), Hemoglobinopathies (1,775), Cystic fibrosis (1,248), Congenital adrenal hyperplasia (202) and Classical galactosemia (224).

The estimation for those disorders screened using MS/MS technology would be 951 cases, from which 215 would have been PKU and 736 cases would have belonged to a group of other 18 disorders of amino acid, organic acid and fatty acid metabolism. From these, the higher number of cases would have been biochemical phenotypes of MCADD (225) and 3-Methylcrotonyl–CoA carboxylase deficiency (100). The remaining 16 disorders would contribute with 421 cases.

It can be argued that PKU could have been detected with other technologies distinct from MS/MS, but it must be recognized that this technology has dramatically reduced the number of false positives for this disorder. Although it is also true that disorders screened with MS/MS other than MCADD constitute only a relatively low number of cases, due to their low individual prevalence, for those of them which are severe and treatable, it represents a highly valuable contribution and they therefore deserve to be screened.

Disorders of intermediary metabolism comprise a group of more than one hundred diseases very often with stereotypic clinical presentations. With MS/MS applied to blood spot samples, it is only possible to detect a limited number of them. A general paediatrician must be educated not only about new possibilities, but also about the limitations of newborn screening using this technology. This is in order to be well aware that a sick neonate urgently needs a much more broader search including more extensive metabolic profiling of amino acids and organic acids in plasma, urine or other biological material, than must be performed in the biochemical genetics laboratory.

The U.S. President's Council on Bioethics [90] in its recommendations reaffirms the essential validity of Wilson-Jungner criteria [103]. It insists that mandatory screening be recommended for those disorders that clearly meet the classical criteria and endorses the view that other conditions that fail to meet them may be offered on a voluntary basis under the research paradigm. Without entering into discuss the ethical aspects concerning to the mandatory character of programmes, the document deserves mention for its lucid analysis of the situation.

A newborn screening programme is a complex integrated system, comprising all the steps of the process: offer of this public health intervention to the targeted population, laboratory detection tests, confirmatory diagnostic tests, treatment and follow–up, quality assurance mechanisms, continuous programme evaluation, organization of genetic counselling and educational aspects. Social, ethical end legal issues are also very relevant [38, 90].

In order to include a disease in a newborn screening programme, we must have knowledge of its epidemiology in the full sense of the term. Conversely, however, newborn screening of rare diseases allows us to know with precision the frequency of the screened disorders in the population concerned and to gain knowledge of the disease. It is therefore very important that rigorous study and investigation on the results and outcome of the programmes be carried out.

Many dilemmas were solved in the past until the enormous effectiveness and benefits of newborn screening for CH and PKU were appreciated, but still, many more problems will need to be faced in order to reach a comparative effectiveness for other candidates IMDs.

Carrier Screening

Carrier screening is aimed to identify couples at risk of transmitting a genetic condition to their offspring in order to offer timely and appropriate genetic counselling, including information on reproductive options, such as avoidance of pregnancy, adoption, use of gamete donors, preimplantation genetic diagnosis and selective embryo implantation, foetal sex selection for X-linked disorders, prenatal diagnosis and selective abortion or acceptance of the birth of affected infants.

Carrier screening may therefore be offered to individuals at risk at different stage: The *pre reproductive age*. As early as possible in pregnancy during the *prenatal* period or during follow up of prenatal diagnosis for couples that are both heterozygotes. During the *preconceptional* period, offering carrier testing to couples planning a pregnancy. When possible, the last option is the best because it avoids confronting the parents with difficult decisions in the case of an affected foetus.

Carrier screening is usually undertaken only for severe diseases in targeted population groups showing high incidence of specific IMDs. Benefits and risks must be carefully considered and social and ethical issues are highly relevant.

In order to offer population-based carrier screening, we need an accurate method. Those which allow a binary discrimination, such as molecular testing for disease mutation, are the most frequently used. Due to the phenomenon of genetic heterogeneity, we need to know which are the most prevalent mutations in the population and to decide the percentage of alleles to cover. Mutations and allele prevalence may differ among countries or ethnic groups and an exhaustive characterization of the specific disease at mutational level is necessary before undertaking population-based carrier screening.

Policy strategies are established according to disease characteristics; see for instance the situation in United States. Table 23.4 shows the proportion of Delta F 508 mutations and the incidence of Cystic Fibrosis (CF) in different population groups. When the frequency and sensitivity (detection rate) are high, the test must be offered, but for lower risk populations there is a relatively lower sensitivity and limitation of testing, for instance, the lack of an ethnically adjusted mutation panel). Nevertheless, given the increasing difficulty in assigning a single ethnicity, testing for CF in the U.S. must be offered universally to all pregnant couples [4]. Carrier screening for CF is also offered universally in several countries such as the UK and France.

Another type of carrier screening universally offered in several countries, together with CF screening, is for Hemoglobinopathies (mainly sickle cell disease) and Thalassemias. Both have an increased frequency in some Mediterranean regions, the Middle East, South East Asia, Caribbean countries and South American countries and, for Thalassemias, in the Western Pacific region. Routine laboratory testing uses Hb electrophoresis and Hb HPLC, followed by additional molecular

Table 23.4 Cystic fibrosis (FQ). Proportion of allele delta F 508 and incidence of FQ in Several populations in the United States

Population group	% of Delta F 508 mutation	Incidence of FQ	Incidence of heterozygous
Caucasians	70%	1 in 3,300	1 in 29
African–Americans	48%	1 in 15,300	1 in 65
Hispanics	46%	1 in 8,000–9,000	1 in 46
Assian Americans	30%	1 in 32,000	1 in 90
Ashkenazi Jews	30%	1 in 3,300	1 in 29

More than 1,300 mutations in the CFTR (transmembrane conductance regulator) gene have been described. The most frequent mutations present in all populations is Delta F 508. The other 15–20 common mutations account for 2–15% of alleles, the remaining mutations are considered rare [36, 60]

studies when it is appropriate. As an example of excellent practical guideline,see the guideline for carrier screening in Canada [53].

Sometimes a carrier screening programme is targeted to selected population groups with an increased frequency of specific diseases, as is the case of several diseases in Ashkenazi communities [66]. The best example is Tay-Sachs disease for which carrier screening for 1.4 million individuals has been performed. More than 1400 heterozygous couples have been identified to be at risk; prenatal testing was performed in more than 3,200 pregnancies, over 600 infants with this fatal neurodegenerative disease have been prenatally diagnosed and 2,466 non affected children have been born [45].

Finally, *Cascade screening*, consists of expanding carrier testing to the relatives of previously identified carriers, under the hypothesis that we will succeed in finding more carriers than screening the general population. So far it has been performed for familial hypercholesterolemia and cystic fibrosis [24]. A careful estimation of the efficacy and efficiency of different strategies is crucial before decision making.

23.3.2 Disease Frequency

Population frequency information is difficult to obtain. This is in part due to the low incidence of individual IMDs, where most of them fall into the category of rare diseases, with 80% classified as very rare with frequencies <0.0001.

Population-based screening provides prospective frequency. Neonatal screening in addition to heterozygote screening are very important tools for direct measurement of frequency, but until now this has related to only a small number of IMDs even when considering the expansion of newborn screening to a group of inherited disorders of intermediary metabolism with MS-MS technology, as described above.

Disease frequency is usually estimated by extrapolation from the number of recognized cases, but patients whose phenotypes differs from the “classical” one, or those who are mildly affected or, on the contrary, those who die very early, are less likely to be recognized. Consequently there is an underestimation of cases and often

a bias towards a phenotypic severity. Clinical heterogeneity and misdiagnosis are additional difficulties and for very rare diseases, even a single missed diagnosis can make a large difference.

The method used to calculate incidence and prevalence figures may be different in individual studies and must be considered when comparing data. Confusion between nomenclature and the low level of consistency between studies are additional handicaps.

As a general and solid source of information, the FIND base [93] comprises a relational database recording the frequencies of genetic defects leading to inherited disorders world-wide, whereas Orphanet [65] performs an important systematic and periodically actualized survey of the literature in order to provide an estimate of the prevalence of rare disease in Europe. Classic genetic texts books [85] are also a good source of information.

The frequency of IMDs in the population depends on the mutation rate, inheritance pattern, disadvantages conferred by the mutation, as well as natural and social distorting events (such as patterns of migration and inbreeding).

Mutations may be induced chemically or by external radiation such as x-rays or ultraviolet light or they may occur spontaneously as a result of mistakes made during DNA replication in a germ cell, giving rise to a monogenic disorder.

When a mutation disrupts the function of a gene and leads to a disadvantage, the mutated version of the gene tends to disappear from the population. However, new mutations continuously arise within each generation and a balance is achieved between mutation giving rise to deleterious gene variants and selection removing them from the population. This is the source of IMDs and they are comparatively rare because mutation rates are generally quite small and their selective disadvantages important, which maintains very low the balance between mutation and selection.

In the absence of distorting events, deleterious gene variant frequency remains unchanged in next generations (it follows Hardy-Weimberg equilibrium law). For an overview of Population genetics see [14, 97].

Mutation rate is the term used to describe the chance of a mutation occurring in a gene in each generation and the rate varies across the different regions of the genome. Our ability to accurately measure mutation rates can contribute greatly to the understanding of medical genetics by providing a means of measuring factors that influence mutation rates. With new generation high throughput sequencing technologies able to directly measure the mutation rate of a gene on the Y chromosome, it was demonstrated that the mutation rate is one mutation in every 15–30 million nucleotides, which corresponds to 100–200 new mutation in the genome each generation [106]. It has been calculated that all of us carry 8–10 mutated alleles for known autosomal recessive disorders [63].

Assuming that, on average, the overall mutation rate per generation per gene is very low, in the order of 10^{-5} or 10^{-6} for a dominant lethal disorder and precluding affected individuals having any offspring, the gene frequency at equilibrium would be 1 in 100,000 or 1,000,000, respectively. However, for a recessive disorder, the mutant gene is present in healthy heterozygotes and the only elimination of the

mutation from the population occurs via affected homozygotes, which is a much less efficient selective process. With the same mutation rate of 10^{-6}, the frequency of homozygotes would be 1 in 1,000,000, but the gene frequency at equilibrium of the recessive mutant would be 1 in 1000. It must be emphasized that different mutations in a gene can have different mutation rates as well as different associated selective disadvantages. Aggregation of conditions must be taken into account in the calculations. In general, the larger the gene the higher the overall expected mutation rate, which explains the prominence of diseases like X-linked Duchenne muscular dystrophy (the dystrophin gene has a size of 2.4 Mega bases).

Sometimes, the frequency of a rare inherited recessive disease varies substantially by a factor of 10 or even 100 between populations. See Table 23.5 for some examples of IMDs with important differences in gene frequency in different population groups. These higher frequencies are associated with particular alleles that, by chance, have "*drifted up*" substantially compared to all other alleles present in the population with similar effects.

One form of chance effect is the called "*founder effect*". When populations have gone through a "bottle-neck", namely a severe reduction in size followed by a rapid expansion, mutations present in the reduced population will be retained when expanded, being only becoming apparent that it had drifted up in frequency more than would be expected in a larger heterogeneous population. This presumably accounts for the relative larger number of severe alleles for Tay-Sachs disease in Ashkenazi Jewish populations. For a review of the genetic profile of Jewish populations see [66].

A somewhat similar phenomenon is seen in Finns, Icelandics, Afrikaners, Dutch and Flemish, Swedes and French Canadians [70, 5, 44]. See also Table 23.5.

In recessive disorders, the equilibrium of gene frequencies depends on the relative extent to which the heterozygote is fitter than either of the two homozygotes (the homozygote for the deleterious mutation and the homozygote for the wild type (normal) gene). When there is a selective advantage for the heterozygote, it reaches and maintains a stable "balanced polymorphism". A good example is sickle cell trait, where the heterozygote shows differential resistance against malaria, while the anaemic homozygote or the homozygote for the normal gene are selectively disadvantaged. In thirty five generations, the frequency of sickle cell allele in East Africa rose from 0.1 to 45 %.

Other examples of balanced polymorphisms are Glucose-6-phosphate dehydrogenase deficiency (X linked G6PD), Phenylketonuria (PKU), Tay-Sachs disease and Cystic fibrosis [54].

Studies in African children with malaria show that heterozygous females and hemizygous males for X linked G6PD are under-represented. This suggests that inheriting the enzyme deficiency gene somehow protects from malaria. Therefore, it would be expected that the mutated allele would eventually predominate, but this do not happens because people with the enzyme deficiency are selected out of the population by anaemia. In this case, natural selection acts in two directions.

It has been observed that women who are carriers for PKU have a lower than average incidence of miscarriage. They have elevated levels of phenylalanine and

Table 23.5 Examples of IMDs with important differences in gene frequency in different groups of population

Higher frequency than in general Caucasian population		
	Incidence in Ashkenazi Jewish population	*General population*
Tay-Sachs disease	1 in 3,900 [71]	< 1 in 100,000
Gaucher disease type I	1 in 855 [10]	1 in 57,000
Canavan disease	1 in 6,700 [50]	Unknown
	Incidence in Finnish population	
Aspartilglucosaminuria	1 in 18,500 [8]	< 1 in 100,000
Infantil neuronal ceroid lipofuscinosis	1 in 13,000 [83]	< 1 in 100,000
Juvenil neuronal ceroid lipofuscinosis	1 in 21,000 [83]	< 1 in 100,000
	Incidence in Menonites (Amish) Pensylvania	
Maple syrup urine disease	1 in 800 [55, 75]	1 in 80,000 [55]
	Incidence in Amish, Ohio	
Cystic Fibrosis	1 in 569 [104]	1 in 2,500 (Northen Europe)
	Incidence in Quebec	
Tyrosinemia type I	1 in 12,500 [40]	1 in 100,000–120,000 [23]
Lower frequency than in general Caucasian population		
	Incidence in Assiatic population	
Cystic fibrosis	1 in 32,000	1 in 2,500 (Northen Europe)
	Incidence inYupik Skimos	
Congenital adrenal hyperplasia	1 in 490 [41]	1 in 10,000–25,000
	Incidence in Finnish population	
Phenylketonuria	1 in 100,000 [39]	~1 in 18,000
	Incidence in Japan	
MCADD	2 cases in 102,000 newborns	~1in 25,000
	Incidence in China	
Galactosemia (classical)	1 in 400,000 [19]	~1:50,000

the theory to explain this phenomenon is that this amino acid inactivates a poison, called ochratoxin A, produced by certain fungi that it is known to cause spontaneous abortion.

Carrying Tay-Sachs disease may protect against tuberculosis and the defect that underlines Cystic fibrosis protects against diarrhoeal illness, such as cholera or typhoid fever. Cholera opens chloride channels allowing chloride and water to leave the cells. The CFTR protein does just the contrary, closing chloride channels and trapping salt. Epidemiology of cystic fibrosis has been extensively studied and other theories have also been proposed [79, 99], though the protection from diarrhoeal illness is generally accepted.

The movement of alleles between local populations owing to migration of individuals, or *gene flow,* may have a role in determining distribution and frequency

of genetic disorders. One example is the role of demographic history in determining characteristics of transferase-deficient galactosaemia mutations [31].

Despite migration and physical separation, Jews have retained their genetic identity over thousands of years. Similar conservation of group genetic identity has been observed for the Roma (gypsies), another migratory people [35]. In our centre, we have observed high incidences of MCADD [56], Canavan disease and GM1 gangliosidosis [82] in Spanish gypsies.

There is a lot of information in the literature and in the World Wide Web on disease frequencies of specific IMDs. But it is a such a wide group that is impossible to include a review of all diseases in this chapter. In order to find information on an IMD of its interest, the reader can refer to the above mentioned resources FINDbase [93] and Orphanet [65].

Nevertheless, for a general understanding of disease frequency magnitudes, it is worthwhile summarizing the main relevant frequencies for the groups of IMD mentioned in Table 23.1, according to data obtained in four studies from different countries/regions: Spain [77], the West Midlands, UK [81], Italy [28] and British Columbia,Canada [6].

To define disease frequency, we need to define and calculate birth prevalence as an estimation of incidence, using methods previously described [6, 28, 57, 81]. Birth prevalence is calculated by dividing the number of diagnoses by the number of live births for a defined time period, assuming the hypothesis that the rate of post-natal diagnosis is equal to the birth rate for each disorder (complete ascertainment). See Table 23.6.

This approach is of course only approximative because we will never have the complete certitude that we can ascertain all the cases of IMD. Diagnostic facilities and techniques, coverage, medical awareness as well as the number of newly recognized diseases increase with time in any country. It is therefore not surprising that the overall incidences found in the more recent studies shown in the Table 23.6, from Spain (1 in 813) and West Midlands, UK (1 in 784), were very similar and higher than those from Italy (1 in 3,707) or British Columbia (1 in 2,500) that were published 5 year earlier. In any case, the newer studies imply a higher frequency in the former.

The number of diseases comprising each Group is different and, moreover, it can occur that not all the corresponding diseases were found in the period considered. For instance, during the 3 years of the REDEMETH survey in Spain, from a group of 50 Lysosomal diseases, only 27 of them were found in spite of the fact that there were resources available for the diagnosis of all of them. The same occured with the Organic acidemias which constitutes a group of more than 60 diseases, from which only 26 have been found. Urea Cycle disorders form a group of only of 6 diseases. Cerebral creatine deficiencies are a recently described group whereas Neurotransmitter defects are difficult to diagnose as cerebrospinal fluid is needed and samples need be taken under very strict conditions which adds difficulties to the diagnosis. In any case, comparing frequencies between different groups is a difficult matter.

Table 23.6 Frequency of inherited metabolic disorders in four studies in different countries/regions

Group of IMD	Spain 2003–2005 1,675 cases [77]	West Midlands UK 1999–2003 395 cases [81]	Italy 1993–1997 1935 cases [28]	Canada British Columbia 1969–1996 619 cases[6]
	Number of cases (birth prevalence Live births)	Number of cases (birth prevalence Live births)	Birth prevalence Live births (number of cases not recorded)	Number of cases (birth prevalence Live births)
PKU[a]	243 (1 in 5,608[b])	25 (1 in 12,420)	1 in 19,589	86 (1 in 13,290)
Aminoacids (exclududing PKU)	146 (1 in 9,334)	58 (1 in 5,354)	1 in 36,389	87 (1 in 13,137)
Urea cycle defects	72 (1 in 18,928)	14 (1 in 22,179)	1 in 41,506	18 (1 in 53,717)
Carbohydrate	41 (1 in 33,240)	19 (1 in 16,343)	1 in 19,532	–
Organic acids	227 (1 in 6,003)	39 (1 in 7,962)	1 in 21,424	29 (1 in 27,082)
Glycogen storage	147 (1 in 11,263)	21 (1 in 14,786)	1 in 34,056	24 (1 in 43,160)
Lysosomal storage	289 (1 in 4,715)	60 (1 in 5,175)	1 in 8,275	79 (1 in 13,112)
Purine and pirimidine	51 (1 in 26,722)	4 (1 in 77,628)	1 in 234,645 (Lesch-Nyhan syndrome)	–
Fatty acid oxidation	66 (1 in 20,649)	24 (1 in 12,938)	1 in 91,599	–
Peroxisomal	49 (1 in 27,813)	23 (1 in 13,500)	1 in 71,794	20 (1 in 28,960)
Mitochondrial	115 (1 in 11,850[c])	63 (1 in 4,929)	1 in 27,106[c]	7 (1 in 112,200[c])
Metals	2 (1 in 681,421. Wilson not recorded)	11 (1 in 28,228)	1 in 106,254 (only Wilson disease)	–
Lipids and steroids	26 (1 in 52,417)	20 (1 in 15,526)	–	–
Porphyrin and haemo	Not recorded	1 (1 in 310,510)		
Membrane transport	87 (1 in 15,664)	–	–	–
Congenital defects of glycosilation	40 (1 in 34,071)	–	1 in 156,256 (CDG type Ia)	–
Crerebral creatine deficiencies	6 (1 in 227,140)	–	–	–
Neurotransmitters	2 (1 in 681,421)	–	–	–

Table 23.6 (continued)

Group of IMD	Spain 2003–2005 1,675 cases [77]	West Midlands UK 1999–2003 395 cases [81]	Italy 1993–1997 1935 cases [28]	Canada British Columbia 1969–1996 619 cases[6]
Colagen	9 (1 in 151,427)	–	–	–
Miscelaneous	57 (1 in 23,909)	14 (1 in 22,179)		
Overall	1,675 (1 in 813)	396 (1 in 784)	1935 (1 in 3,707)	619 (1 in 2,500)

[a]PKU cases have been detected with National Newborn Screening Programmes.
[b]In Spain, the incidence for Classical PKU is 1 in 19,747, for Hyperfeninalaninaemias 1 in 12,422 and the overall incidence 1 in 7,549 (n= 8,062,512, years 1988–2007). Source: Asociacion Española de Cribado Neonatal (AECNE) (see www.aecne.es).
[c]Includes all congenital lactic acidemias.
Birth prevalence had been calculated by dividing the number of diagnoses by the number of live births for the defined time period, assuming the hypothesis that the rate of postnatal diagnosis is equal to the birth rate for each disorder. See Section 23.3.2. Data of Spain are unpublished, birth prevalence had been calculated using data obtained by REDEMETH survey [77].

In order to give some information on specific disease frequencies, we can refer to the results obtained by REDEMETH, the Spanish co-operative research network funded by FIS (Fondo de Investigación Sanitaria, Instituto de Salud Carlos III. Ministerio de Sanidad) that in three years collected 1,675 cases from 158 diseases [77]. Birth prevalences had been calculated dividing number of cases reported in the survey, by the number of live births in the three year period.

Amino acid disorders: Excluding PKU, the most frequent disorders are: Cystationine beta synthase deficiency (1 in 26,722), Maple syrup urine disease (1 in 32,448), Non-ketotic Hyperglycinemia (1 in 80,167) and Tyrosinemia Type I (1 in 97,345).

Urea Cycle: 55 of 72 cases were Ornitine transcarbamilase deficiency (1 in 24,778)

Organic acidemias: The most frequent disorders are Propionic acidemia (1 in 28,996), Glutaric acidemia type I (1 in 41,298) and Methylmalonic acidemia (CblA) (1 in 85,177). It should also be mentioned that Propionic acidemia and Glutaric acidemia type I showed higher frequencies than those mentioned in some Newborn Screening programmes.

Fatty acid beta oxidation: Half of the 66 cases are MCADD (1 in 85,177) and LCHADD (Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency) (1 in 75,713). The incidence of MCADD seems much more lower than the incidence (1 in 25,000) found through several newborn screening programmes, it can be due to a lower prevalence in Spanish population, but also to the fact that all the cases are symptomatic patients and newborn screening detects also benign forms that never present symptoms. See [37].

Lysosomal storage disorders: The most frequent LSD was Gaucher disease type I (1 in 22,714), Fabry disease (1 in 27,256), GM1 gangliosidosis (1 in 30,973) and Maroteaux-Lamy (MPSVI) (1 in 64,897).

Purine and pyrimidine metabolism: From 51 cases, 29 were Myoadenilate deaminase deficiency (1 in 46,994).

Peroxisomal diseases: The most frequent was X-linked adrenoleukodystrophy (1 in 40,083, approximately 1 in 20,000 males). Peroxisome biogenesis disorders were much less frequent (1 in 104,834).

In our centre, according to our experience in a group of 1,119 cases of 114 different diseases diagnosed between 1975 and 1996, the most frequently diagnosed diseases were Gaucher disease type I (78 cases), X-linked Adrenoleukodystrophy (72 cases), Hurler disease (MPS I) (52 cases) and Hunter disease (MPSII) (42 cases). In general, our results were in good agreement with results of the REDEMETH survey in which we also participated, except for the group of Lysosomal disorders, for which, besides the higher representation of MPSI and MPSII, we had a higher presence of cases of GM1 Gangliosidosis (34 cases), Tay-Sachs disease (32 cases), Metachromatic leukodystrophy (29 cases), Sanfilippo A (MPSIII) (29 cases), Mucolipidosis II/III (23 cases) and Niemann Pick C type (22 cases), but only 10

cases of Maroteaux-Lamy (MPS VI) and 15 of Fabry disease [67]. These figures for lysosomal diseases are more similar to those described by other authors [32, 57].

National surveys requires a lot of effort. Three to five years is a very short period for such rare diseases and in order to guarantee the continuity of data capture it is very important to have the support of health authorities.

Nevertheless, nowadays we have enough consistent data to propose changes to the cumulative incidence figures for IMDs, usually quoted as 1 in 2,500−1 in 5,000 live births, to around 1 in 800 (1 in 784 from [81] and 1 in 813 from [77].

23.3.3 Natural History of IMDs

The *Natural history* of a disease is the description of the patterns of disease progression over time. It is crucial in order to understand the impact of the disease on the individual, their family and care-givers as well as the society as a whole. Interventions are aimed to change the natural history for the better and the clinical and economic benefits of any intervention must be evaluated against the "untreated" natural history.

The knowledge of the natural history of a disease provides estimates of the expected disease progression for a representative cohort of patients, from diagnosis or onset of disease until death, that is the Biological onset, Preclinical phase, Clinical Phase and Outcome. It also gives an indication of the burden of morbidity at different stages of the disease in terms of the number of quality-adjusted life-years (QALYs) lived by the cohort for different progression states [74].

This allows evaluation of clinical assays with respect to the potential altering effects of treatment on disease progression and provides a theoretical estimate of the impact on the quality of life of patients. It is therefore also a very important tool in order to evaluate public health intervention. One of the problems inherent to the expansion of newborn screening programs towards disorders of intermediary metabolism is that for several of them, the natural history is generalyl poorly understood, mainly due to their very low frequency (> 100,000) and consequently it is very difficult to assess which would be the real benefits for affected children.

IMDs are rare diseases that can show large genetic and clinical heterogeneity which introduces additional difficulties. It is very difficult to reach a statistically appropriate cohort size and very often it is necesary to include cases reported in the literature via Medline searching and retrospective chart reviews by surveying physicians. This is, for instance, the approach followed in Infantile-Onset Pompe disease [47] and in MCADD [37].

It should be noted that most IMDs have different clinical presentations and that the Natural History must be studied for each one of the presentations. The preceding example is also useful to illustrate this problem. Pompe disease or Glycogenoses type II is a lysosomal storage disorder caused by the deficiency of acid maltase. Glycogen accumulates in many tissues with skeletal, cardiac and smooth muscle most prominently involved. Patients have a highly variable enzymatic activity and the severity varies according to the age of onset, organ involvement, including

degree and severity of muscular involvement and rate of progression. This means that there is a continuum of disease spectrum and for this reason classifications found in the literature may show some degree of inconsistence, with the terminology infantile, late infantile, childhood juvenile and adult onset forms being commonly used. The most clear classification is in two main groups: the infantile form (includes the classic infantile and the more severe forms with death in the first year) and the late-onset form, including childhood, juvenile and adult onset. For a review of Pompe disease see [48]. Therefore, it must be clearly established which is the form for which the natural history is studied.

Due to the rarity and dispersion of cases of IMDs, the creation of registries at national and international level is of great importance because they are valuable resources for many purposes including Natural history studies.

23.3.4 Control and Prevention of IMDs

In order to control and prevent disease we must take into account all the aspects considered in the precedent paragraphs: how to detect the cases, their frequency and distribution in the population and the description of the patterns of disease progression over time, which means to understand its Natural History.

Control and prevention options are available, but differ significantly between the Natural History phases of a disease, from Biological onset, Preclinical phase, Clinical Phase or Outcome. For example, preventive interventions could be directed to Promotion of health and Primary prevention in the phase of biological onset, to Secondary prevention (screening and early detection) at the preclinical phase or as early as possible when symptoms appear with the aim of beginning the therapy, and finally to Tertiary prevention comprising rehabilitation and support.

23.3.4.1 Primary Prevention

Primary prevention is aimed at reducing the prevalence of a disorder or dysfunction by reducing the number of new cases (incidence) that appear in a defined population.

In Section 23.3.2 we presented some elemental concepts of population genetics and how deleterious gene variant frequency remains unchanged in next generations in the absence of disturbing influences.

To create such disturbing influences in order to decrease the incidence of a specific IMD at general population level is impracticable. This is because new mutations arises in each generation and perpetuate in healthy heterozygous individuals. However, we can undertake measures for control of the disease in the families or in population groups at high risk.

When a case of IMD is diagnosed, *genetic counselling* must to be offered to the parents. Part of this process is the estimation of risk for future offspring, the offering of information on reproductive issues and the encouragement to the couple to communicate to the family relatives its genetic risk. There are many options available for primary prevention, including *heterozygote detection* in the family*, prenatal diagnosis* and *assisted reproductive technologies* which allows *preimplantatory*

genetic diagnosis with selective implantation of unaffected embryos, *preimplantatory selection of foetal sex* in X-linked diseases and also the possibility of recourse to a *heterologous gamete donors*. Nowadays prenatal diagnosis is possible for almost all IMDs and assisted reproductive technologies are accessible in several countries.

Nevertheless this approach is directed to the family unit and implies the knowledge of the genetic risk only after the diagnosis of the index case. There is still another approach at population level that applies when the frequency of a severe untreatable IMD is high in a concerned population which is *population-based screening for heterozygotes* in the pre-reproductive or prenatal period with the goal of identifying heterozygous individuals who could then gain access to reproductive counselling.

Programmes for heterozygote detection for Tay-Sachs and Gaucher disease in Ashkenazi communities worldwide and for thalassemias in Cyprus, Sardinia and Canada have had an important impact in the groups at risk (see paragraph on Population-based carrier screening).

Selective or targeted carrier screening implies selecting the individual participants with a question: does the individual belong to the at-risk group or not? This in itself is a screening process with false positives and false negatives [100]. The question can be a sensitive issue in our multicultural/multiethnic societies and the determination of ethnic origin can be complicated. Moreover, the general population has a lower risk, but it is a much bigger group and the total number of cases of the disease is therefore higher. In America there are currently more children born with Tay-Sachs disease to non-Jewish than to Jewish families, and therefore the preventive strategies for each IMD requires careful consideration from a global perspective.

Currently, the prenatal or preconceptional screening of carriers for Cystic fibrosis, hemoglobinopathies and thalassemias is universally offered in several countries (France, the United States, and the United Kingdom) to all couples independently of whether they pertain to a risk group or not. On the other hand, carrier screening for Tay-Sachs diseases is offered in several countries only to Ashkenazi communities together with other diseases for which they are at increased risk [66].

It is important that primary care physicians be well informed about all the screening population programs included in the health care system as well as about those IMDs and other genetic disorders that present with high incidence in specifics groups of population in order to offer preventive information to the families.

23.3.4.2 Secondary Prevention

Secondary prevention is aimed to reduce the prevalence of a disorder by reducing the duration of the disorder or associated dysfunctions in individuals who had expressed signs and symptoms of such disorders. This requires being able to provide an early intervention and treatment, which in turn implies having resources to make an early diagnosis.

For some IMDs, such as phenylketonuria, the success of treatment depends on detection before the clinical suspicion of the disease based on the symptoms,

being this fact the origin of the implantation of newborn screening programmes. According to the definition of population screening given above, screening applies to individuals that have not sought medical attention and this is the case for newborn screening for IMDs. For this reason *newborn screening* can be considered at an intermediate position as *early secondary prevention* or *late primary prevention.*

Taking the group of IMDs as a whole, the number of diseases screened in neonatal period is comparatively low even when considering the more extended programmes (29 disease in a primary panel plus a secondary panel of disorders that form part of the differential diagnosis of the primary panel disorders, encompassing 50 diseases overall). See also the paragraph on Newborn Screening. Ascertaining the bulk of IMD cases relies, therefore, on clinical suspicions and the correct laboratory diagnosis being made as early as possible. Good clinical services and expert laboratories of biochemical and molecular genetics with quality assurance policies are paramount elements in the secondary prevention of IMD patients.

The second issue to consider is the effectiveness of treatments. IMDs by definition are genetic and therefore chronic diseases. For only 12% of IMDs is there a successful treatment available, whereas for 45% of IMDs there are partial benefits and in a 34% of IMDs there is no response [89]. It is true that partial benefits should be considered positive achievements, but some therapies are still only the first step towards a cure and it often occurs that we are able to convert a fatal disease into a chronic one. Therefore, consideration must be taken to weigh the quality of life that these children are destined to have, versus early death.

It is very difficult to estimate whether we reduce the prevalence of IMDs, probably for those fully treatable diseases it is true, but in the case of partial benefits, it is more difficult to assess.

IMDs have individually very low incidence and most of them low prevalence because of the high mortality in childhood. However, we also have IMDs with a long life expectancy that can often be increased thanks to the benefits of treatment, which means that, paradoxically, the prevalence increases because of improved survival.

Certainly the development of novel treatments greatly contributes to a better and longer life expectancy, but at the same time they create a demand and there is a considerable and increasing need for specialist services for people with IMDs that can only be afforded by a careful organization of health services.

The lack of accurate and comparable epidemiological data is a handicap in order to know and quantify the effectiveness of secondary prevention. The set up of registries and the continuous collection of epidemiological data are very important tools towards resolving these issues.

23.3.4.3 Tertiary Prevention

Tertiary prevention is aimed at reducing disability and dependence as well as preventing handicaps despite the persistence of impairment. When the underlying impairment is well understood, then very specific medical interventions may be adopted to prevent the consequences. As well as medical treatment, tertiary prevention will therefore usually include psychosocial, educational and family and

social aspects. Primary care professionals need to be aware of what interventions are available for their patients and their families and will often be involved in these interventions themselves, or be well connected with tertiary care facilities and caring for the patient for additional concurrent diseases. General practitioners must be aware of the importance of continuing diets or supplements and be willing to support parents in maintaining them for many years. Depending on clinical features and the course of the disease, patients will need rehabilitation programmes including early cognitive stimulation, special education and rehabilitation to enhance affected function, community support programmes and continuous treatment for the chronically ill. IMDs are overwhelming diseases and palliative care, especially at the end of life, are also very important.

Better and longer life expectancy creates a demand on paediatric and adult services for continued management, including reproductive aspects concerning fertility/infertility and pregnancy. Thanks to all these progress, there is an effective increase in the number of women with IMDs who have reached child bearing age and with appropriate management, the outcome has been satisfactory in at least 14 Different IMDs. However, biochemical, hormonal and physiological changes occurring during and after pregnancy and labour may have consequences for the affected mother. Maternal disease may, in addition, have an adverse effect on the developing foetus and, on the contrary in rare cases, it is the homozygous foetus who may cause harm to his/her heterozygous mother [78, 98].

It is very important the needs-assessment of services for people with IMDs in order to provide them with comprehensive and equitable services. Patient groups become more and better informed and constitute active partners in the process. It is worth mentioning as a concluding remark the final recommendations proposed by Burton [15] after a rigorous study of resources and needs in UK: “There should be an overall strategy for inherited metabolic disease that commissions services to cover the whole population on an equitable basis”. “There should be reconfiguration of services bringing them into networks that can provide the following for their populations: Coordinated and integrated paediatric, adult and laboratory services. A critical mass of professionals as a multidisciplinary team to provide comprehensive services, including emergency access. Formal arrangements with supporting tertiary specialties. Formal arrangements to provide support and shared care with peripheral hospitals. Clinical and laboratory databases.”

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Chapter 24
The Contribution of Rare Diseases to Understanding the Epidemiology of Neurodevelopmental Disabilities

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Abstract Our objective is to describe the contribution of rare diseases to our understanding of the epidemiology of neurodevelopmental disabilities (NDDs) by comparing and contrasting the epidemiologic features of NDDs classified according to key characteristics of developmental delay or deviance in such areas as behavior or cognition (the phenotypic approach; autism spectrum disorders and intellectual disability as examples) versus classification based on the identification of an etiologic diagnosis (the etiologic approach; 22q11.2 deletion syndrome and fragile X syndrome as examples). We suggest specific applications in which consideration of rare etiology-based NDDs might further our understanding of NDD epidemiology overall; what is needed to integrate the two classification approaches; and identify practical challenges in achieving that integration. Understanding commonalities and differences in the epidemiologic features of the phenotypically and etiologically defined NDD classifications provides a useful framework for furthering our understanding of the prevalence, distribution, and causes of NDDs, as well as delivering appropriate diagnostic resources, appropriate treatments, accurate prognostic information, and estimates of recurrence risk for these disorders.

Keywords Neurodevelopmental disabilities · Rare disorders · Epidemiology · Autism spectrum disorders · Intellectual disability · Fragile X syndrome · 22q11.2 deletion syndrome

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24.1 Introduction

Neurodevelopmental disabilities (NDDs) have been defined as "a heterogeneous group of conditions that have in common the long-term effects of developmental delay and deviance that restrict one or more major life activities and result from damage to those neurological processes responsible for developmental functioning" [60]. Survey data indicate that 13–17% of children in the United States have an NDD [7, 8]. NDDs can be classified in a variety of ways depending on the purpose, such as classifications to aid diagnosis or the delivery of medical or educational services, with the result that individual cases might be assigned to multiple but overlapping categories (e.g., an individual with a single-gene disorder affecting cognition also would be eligible for classification in an educational program category for intellectual disability (ID)). One approach that often is adopted for epidemiologic purposes is to classify cases according to key characteristics of developmental delay or deviance in such areas as motor function, speech and language, cognition, or personal–social function. Examples of this classification approach (which for our purposes we label here as the phenotypic approach) include cerebral palsy, ID, communication disorders, specific learning disabilities, autism spectrum disorders (ASDs), hearing loss, vision loss, disorders of attention and activity level, mood disorders, chronic orthopedic conditions, and epilepsy. Following this approach, classification can be made without respect to etiology, which in many instances often is unknown. Despite classification based on shared characteristics of delay or deviance, it generally is recognized that each of these phenotypically classified NDDs is etiologically heterogeneous.

Another classification approach for NDDs is based on etiology. This classification scheme is based on the identification of an etiologic diagnosis such as a chromosome abnormality or single-gene disorder. Examples include Down syndrome, 22q11.2 deletion syndrome (also known as DiGeorge syndrome or velocardiofacial syndrome), and fragile X syndrome (FXS). Notably, for these types of disorders the associated symptoms often are variable (a characteristic known as variable expressivity) and phenotypic features such as cognitive or motor delay can be important early indicators in the diagnosis of individuals who are affected. The expression of certain phenotypic features among individuals with an etiologically defined condition might be sufficient to warrant an additional, co-occurring diagnosis of a phenotypically defined NDD, such as diagnosing an ASD for an individual with Down syndrome.

Among the conditions in the category of NDDs classified according to a single etiology are the so-called rare neurodevelopmental disorders. Although the definition of a rare disorder or disease varies between countries, there is a well-defined standard in Europe qualifying a disease prevalence as rare: United Kingdom, 1 in 50,000; Sweden and Denmark, 1 in 10,000; European Union, 1 in 2,000 [41]. For the United States, The National Organization for Rare Disorders defines a rare disease as one affecting fewer than 200,000 people. There are thousands of rare neurodevelopmental disorders and these disorders have diverse effects on the immune, endocrine, neurologic, hematologic, and other body systems.

Both the phenotypic and etiologic classification approaches have important scientific and clinical uses. The phenotypic approach identifies a group of individuals who share key characteristics of developmental delay or deviance and a clinical approach to diagnostic evaluation, possible medical requirements, therapeutic needs, required interventions, and individual or family challenges to participation and integration. A diagnosis identified by the etiologic approach often provides specific information about prognosis, recurrence risk, and the benefits of specific therapeutic and educational interventions. It is important to recognize that a focus on one approach versus the other will lead to very different epidemiologic patterns. For example, use of the phenotypic classification approach tends to yield categories of NDDs that are more prevalent (e.g., ID) than categories of NDDs classified according to a single etiology (e.g., Down syndrome). From the epidemiologic perspective, NDDs classified by phenotype are good candidates for routine public health surveillance because they are relatively common; on the other hand, individual rare NDDs typically are not amenable to routine population surveillance, with the exception of disorders that are monitored by newborn screening programs. Population-based birth defects surveillance programs also might capture some cases of individual rare NDDs if the study population is sufficiently large and surveillance is ongoing over time.

The purpose of this chapter is to describe the contribution of rare diseases to our understanding of the epidemiology of NDDs by comparing and contrasting the epidemiologic features of NDDs classified by phenotype versus etiology. Although there is an overlap in the conditions across categories in different classification approaches, we used these two classification approaches to illustrate possible approaches to defining NDDs for epidemiologic analysis. For our comparison, we focused on ASDs and ID as examples of the phenotype-defined approach and 22q11.2 deletion syndrome and FXS as examples of the etiology-defined approach. These examples illustrate both the concept of overlap of conditions between the two classification approaches and the contribution of rare NDDs to our understanding of the epidemiology of NDDs in general.

24.2 Concepts in the Epidemiology of Neurodevelopmental Disabilities

The epidemiologic features focused on for our comparison comprise case definition and co-occurring conditions, prevalence, population distribution, and risk or etiologic factors (Table 24.1). We first provide a brief overview of these epidemiologic concepts before making our specific comparisons.

Epidemiology is the study of the prevalence, distribution, and factors affecting health and illness with a focus on populations rather than individuals. Because of its population focus, a cornerstone of epidemiologic studies is the case definition, which specifies the characteristics of individuals with the condition of interest to be

Table 24.1 Epidemiologic features of phenotypically defined and rare etiologically defined classifications of neurodevelopmental disabilities

	Phenotype-defined neurodevelopmental disability	Etiology-defined neurodevelopmental disability
Case definition	• Complexes of key developmental characteristics; overlap in characteristics with other conditions. • No objective test using a biologic marker.	• Specific, biologic test permits more precise case definition. • Test accuracy or reliability may not be 100%.
Prevalence	• Not "rare". • Reported prevalence might be variable across studies due to differences in case definition, identification process or study methods, or a combination thereof.	• By definition, "rare". • Accuracy of prevalence might be uncertain due to lack of systematic surveillance; estimates typically based on referred cases to clinic-based populations; therefore, might be prone to both underestimation and overestimation of prevalence. • Variable expressivity might lead to underestimate of prevalence if milder affected cases are unrecognized.
Population distribution	• Distributions across subgroups (e.g., sex and age) are reported routinely, but might vary somewhat due to identification or study methods differences, or both.	• Distribution might be unknown or inaccurate due to small, clinic-based samples.
Co-occurring conditions	• Reported types of co-occurring conditions and proportion of affected cases might be variable across studies depending on identification and study methods to determine co-morbidity. • Usually co-occurs with multiple rare etiologically defined neurodevelopmental disabilities.	• Reported types of co-occurring conditions and proportion of affected rare disease cases with a given phenotype (such as a phenotypically defined NDD) might not be reliable due to lack of systematic assessment for the phenotype in all rare disease cases. • Variable expressivity of phenotype in a rare disease complicates estimates of phenotypic comorbidity with rare disease. ○ Might have ascertainment bias towards more severely affected cases with a rare disease.
Etiology	• Typically unknown but presumed to be hetereogenous; the uncertainty complicates etiologic investigations. • Reported distribution of specific causes is variable across studies. • Definition by phenotype masks multiple etiologies.	• Etiology well defined. • Rapid growth of new technologies makes for a dynamic, ever-shifting knowledge base of new etiologic discoveries.

included in the study. Ideally, the case definition is based on objective and standardized measures (e.g., a blood test or a bacterial culture) to confirm that people with suspected cases actually have the condition. However, if such confirmatory tests are not available, more subjective indicators – such as descriptions of symptom complexes – might be necessary. With the case definition in place, ascertainment of affected individuals can be achieved either through population surveys or through systematic examination of reports or records from medical, laboratory, or service providers serving the study population. This population-based approach for case ascertainment contrasts with clinical diagnosis of individuals, which requires patient and family histories, clinical examination for signs and symptoms, and diagnostic or laboratory testing to confirm or rule out diagnoses for that specific individual. Population surveys might incorporate individual clinical evaluations to confirm case status, but records-based approaches often might not. Thus, population surveys to ascertain cases might be thorough, but can be costly and time consuming, while records-based ascertainment is more feasible for large-scale or ongoing studies, but can be limited by the quality and completeness of the recorded information. Refusal to participate by some potential cases might bias results of a population survey. Records-based approaches that do not require individual consent will mitigate this participation bias. Thus, the depth and breadth of information on each case and the representativeness of the case sample for an epidemiologic study will be influenced by the ascertainment method. These methodologic factors of case definition and ascertainment, and success in their study implementation, in turn will influence the validity, reliability, and generalizability of results from epidemiologic studies, including estimates of prevalence and descriptions of the population distribution (e.g., demographic, socioeconomic, and biologic features of people who are affected). Finally, an important outcome of epidemiologic studies is the identification of potential etiologies. Etiologic findings from an epidemiologic study most often are based on statistical comparisons of collected risk factor data between persons with and without a disease, necessitating large sample sizes, in contrast to the clinical search for cause based on in-depth diagnostic evaluations of individual patients.

24.3 Phenotypically Defined Neurodevelopmental Disabilities

24.3.1 Autism Spectrum Disorders

ASDs are a group of developmental disabilities characterized by unusual development in socialization, communication, and behavior. The symptoms of ASDs typically are present before a child is 3 years of age and often are accompanied by abnormalities in cognitive functioning, learning, attention, and sensory processing [10, 60]. The term “spectrum disorders” is used to indicate that ASDs encompass a range of behaviorally defined conditions that are diagnosed through clinical observation of development. These conditions include autistic disorder (i.e., autism),

Asperger disorder, and pervasive developmental disorder – not otherwise specified. Autism now is considered to be one of several disorders clinically referred to as ASDs. Anticipated changes to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV)*, due out in 2012 as the *DSM-V*, indicate additional changes to the diagnostic classification of the ASDs. The complex nature of these disorders, the current lack of consistent and reliable genetic or biologic diagnostic markers, and a changing landscape in defining and identifying these conditions make evaluating ASD prevalence over time challenging.

Until the late 1980s, autism was thought to be rare, affecting approximately 1 in every 2,000 children [22, 38]. While the number of individuals receiving clinical or educational services for an ASD has increased markedly since the early 1990s, controversy remains over whether this increase reflects a true increase in risk for ASDs or is the result of other factors, such as changes in diagnostic criteria, expansion of the autism spectrum, increased provider awareness and availability of specialized services, or a combination thereof [21, 22]. Because services within communities are not available uniformly to all people with ASDs, studies that rely exclusively on single-source administrative datasets – such as disability service records or annual reports of special education counts – are likely to underestimate ASD prevalence and might not capture adequately population changes over time [9]. For this reason, and because ASDs are behaviorally defined conditions, the most complete prevalence estimates have been obtained from direct screening and case confirmation or multiple source record review methodologies. ASD prevalence estimates using the current diagnostic criteria are approximately 6–7 per 1,000 children, which is over 10 times higher than earlier estimates [22]. Some of the most recent studies have shown ASD prevalences of more than 1% in Japan, Sweden, the United Kingdom, and the United States [10], and up to 2.7% of children with symptoms of ASDs in Norway [40]. Recent research indicates that the core social traits of autism are distributed among populations along a continuum [13]; where the line is drawn between trait measures regarded as normal variants in behavior versus those labeled as impairment or disability will have a substantial effect on ASD prevalence estimates.

One of the consistently recognized factors related to autism risk is that boys are more susceptible than girls. The male-to-female ratio for males without cognitive impairment (5.5:1) has been found to be higher than the commonly accepted 4:1 ratio overall [22]. Although it is often stated that autism occurs among all racial and ethnic groups, the majority of prevalence studies have been done with relatively homogonous groups in industrialized countries. Therefore, the descriptive epidemiologic data on ASDs are limited in terms of diversity by racial and ethnic groups in the world and by variations in culture and geography, or by features such as level of industrialization. Studies from the United States have found a higher prevalence among White non-Hispanic children than among Black or African-American non-Hispanic or Hispanic children, with these differences attributed to ascertainment disparities rather than a true difference in risk [10, 38]. There also has been some evidence of an increased risk of autism among children who have at least one parent

who immigrated to that country; however, these data are not conclusive, and an etiologic mechanism has been difficult to identify [38]. Some studies have found an increased risk for ASDs among individuals of higher socioeconomic status as indicated by income and education level [21, 22, 38]. These findings might reflect a referral bias toward those families who are able to access diagnostic and clinical services [28, 48, 58]. When drawing conclusions about socioeconomic status and autism, it is important to sort out differential access to services, identification bias, and the colinear relationship between race or ethnicity and socioeconomic status.

ASDs often co-occur with other NDDs. Given the developmental features that form the diagnostic criteria for ASD diagnosis, most children with an ASD also will meet the criteria for another phenotypically identified condition, such as a language disorder, learning disorder, or attention-deficit/hyperactivity disorder (ADHD). Current diagnostic standards do not call for separate diagnoses of these types of conditions, as they are considered part of the core symptom complex of ASDs. ID typically is identified as a co-occurring condition and has been identified as a key feature predicting the long-term level of support needed [39]. Recent studies have indicated changes in the characteristics in the overall population distribution of co-occurring ID, with less than half of children with ASDs having co-occurring ID compared with the approximately 75%, previously reported [10, 38]. The recognition that ASDs can co-occur with other conditions such as cerebral palsy and Down syndrome has been recognized in the past 15–20 years. A recent study found that 5% of children with an ASD also had cerebral palsy, and 1% had hearing or vision loss [61]. It is estimated that 20–30% of people with an ASD have epilepsy, with peaks of first occurrence early in life and then during adolescence [21]. A number of other medical symptoms or disorders commonly are reported mong children with an ASD, including gastrointestinal symptoms, feeding challenges, and sleep difficulties [38].

The concordance rate for ASDs among monozygotic twins is 70–90% and up to 10% among dizygotic twins. The recurrence risk among siblings of affected children is 2–6% [2, 44] indicating a strong genetic component in the etiology of ASDs. In about 10–20% of children with an ASD, specific metabolic or genetic disorders might be identified [2, 31]. The exact frequency of the overlap in these conditions and ASDs is not known due to limited population-based data. In addition to metabolic diseases and other single-gene conditions, disorders of energy metabolism from mitochondrial dysfunction also have been associated with ASDs [63]. Identification of these conditions has been variable and dependent on the utility of screening protocols, length and frequency of follow-up, and symptom presentation. For ASDs, current clinical management guidelines focus on identification of the behavioral constellation indicative of an ASD, with additional medical evaluation based on the clinician's judgment of symptom presentation [20, 27, 46]. While there is much to learn about the relationship between ASDs and the genetic and metabolic diseases that co-occur with them, it is clear that the clinical management of individuals affected with metabolic conditions is linked inextricably to the many challenges associated with the diagnosis and management of ASDs [63].

In recent years, an ever-increasing number of nonsyndromic single-gene defects, genetic syndromes and de novo or inherited copy number variants have been identified among individuals with an ASD. Although the specific genetic abnormalities identified often are assumed to have a causal connection to the presence of an ASD, no one condition has accounted for more than 1–2% of ASD cases (Table 24.2). It also has been hypothesized that ID, not the specific rare syndrome, is the common link between many of the metabolic and genetic conditions identified and ASDs [36, 52]. In addition, the ASD phenotype is relatively common in multiple rare conditions identified by genotype (e.g., FXS and Angelman syndrome) [36]. The relative proportion of ASDs that are explained or associated only with rare or common genetic variants remains to be determined because this information is evolving. Although autism has a strong genetic component, specific environmental influences and gene–environment interactions are likely to contribute to the etiology of many forms of ASDs. Much more work needs to be done to understand the interplay between multiple, individual, and subgroup risk factors that lead to the development of an ASD.

24.3.2 Intellectual Disability

ID historically has been defined by many different classification systems, but the most recent consensus statement of the American Association on Intellectual and Developmental Disabilities (AAIDD), formerly the American Association on Mental Retardation (AAMR), defines "intellectual disability" as "a disability characterized by significant limitations both in intellectual functioning (reasoning, learning, problem solving) and in adaptive behavior, which covers a range of everyday social and practical skills. This disability originates before the age of 18" [1]. The term "intellectual disability" has emerged to replace "mental retardation", reflecting the current emphasis on functioning and social contextual factors and not solely on cognitive ability [47].

ID can be viewed as a complex of key developmental characteristics that at their core represent a defect or disorder in learning [51]. Because there is no physical or biologic marker for ID, objective identification of ID for epidemiologic purposes is subject to limitations in the availability of objective standardized tools for assessing adaptive behavior and the social context. Thus, very often, case definition is based only on results of standardized tests of cognitive ability, such as intelligence quotient (IQ) scores. Prevalence estimates for ID have been affected by variations across the different classification systems in definition and specific diagnostic criteria for ID, the degree to which the different domains of functioning (e.g., IQ scores and cut points, adaptive behavior, and social supports) are operationalized in case definitions, and methods of case ascertainment. These sources of methodologic variability in case definition and ascertainment could underlie much of the variability in ID prevalence estimates, which range from about 1 to 4% among school-aged children [30].

Table 24.2 Prevalence of specific genetic diagnoses among individuals with autism spectrum disorders or intellectual disability

Autism spectrum disorders (ASDs)				
References	Study purpose	Sample	Results	
[2]	Review current state of genetics and autism	Review	10–20%	Total estimate of ASDs with defined mutations, genetic syndromes, and de novo or inherited copy number variants
			1–2%	15q duplication (Angelman syndrome)
			1–2%	Fragile X syndrome
			About 1%	16p11 deletion
			About 1%	22q deletion
			About 1%	Tuberous sclerosis
			About 0.5%	Rett syndrome
			"Rare"	Cortical dysplasia-focal epilepsy syndrome, Joubert syndrome, Smith-Lemli-Opitz syndrome
			"Unknown"	Potocki-Lupski syndrome, Timothy syndrome
[12]	Review current state of genetics and autism	Review	2–5.5%	Fragile X syndrome
			2–5%	Down syndrome
			<5%	MECP2 mutations
			1–4%	Tuberous sclerosis
			1%	Angelman syndrome
			1%	Sanfilippo syndrome
			<1%	Smith-Magenis syndrome
			<1%	Adenylosuccinate lyase deficiency
			Unknown	Duplication of 15q11–q13, 22q13 deletion, phenylketonuria, Smith-Lemli-Opitz syndrome, Cohen syndrome

Table 24.2 (continued)

Autism spectrum disorders (ASDs)				
References	Study Purpose	Sample	Results	
[23]	Chapter reviewing "double syndromes" noted with autism	Book chapter review	Genetic conditions noted to co-occur with autism (prevalence of conditions in autism not reported): Angelman syndrome, anorexia nervosa, CHARGE association, Cohen syndrome, deLange syndrome, Down syndrome, Ehlers-Danlos syndrome, fragile X syndrome, Goldenhar syndrome, hypomelanosis of Ito, Joubert syndrome, Kleine-Levin syndrome, Lujan-Fryns syndrome, Moebius syndrome, mucopolysaccharidosis, neurofibromatosis 1, Noonan sydrome, peroxisomal disorders, phenylketonuria, Rett syndrome, Smith-Magenis syndrome, Sotos syndrome, Steinert's myotonic dystrophy, Tourette syndrome, tuberous sclerosis, unilateral cerebellar hypoplasia syndrome, velocardiofacial syndrome, Williams syndrome	
Intellectual disability				
[30]	Review of the epidemiology of ID; reported diagnostic yield across several studies	Review	4.7–20.3% 1.7–1.9% 1.7% 0.5–0.7% 0.3–0.7% 0.3%	Down syndrome Fragile X syndrome William syndrome Prader-Willi syndrome Angelman syndrome Noonan syndrome

Table 24.2 (continued)

Intellectual disability			
References	Study Purpose	Sample	Results
[54]	Diagnostic yield of global developmental delay	Clinic population: 261 consecutive patients <5 years of age referred for global developmental delay to community pediatric outpatient clinic	13.3% *Chromosomal abnormality:* fragile X ($n = 3$), XO Turner ($n = 1$), unbalanced trans X/Y ($n = 1$), 6/14 unbalanced trans ($n = 1$), isodicentric Yp chr ($n = 1$), 6q27 del ($n = 1$), 7q36 del ($n = 1$), chr 7 del_dupl ($n = 1$), 2 chr markers 13/21 ($n = 1$), 16q del ($n = 1$), 17p del ($n = 1$) 11.2% *Genetic syndrome*: Sotos syndrome ($n = 3$), epidermal nevus syndrome ($n = 2$), neurofibromatosis type 1 ($n = 1$), Brachmann-de Lange variant ($n = 1$), Silver-Russell syndrome ($n = 1$), hemifacial microsomia ($n = 1$), Dubowitz syndrome ($n = 1$), autosomal recessive spastic ataxia of the Charlevoix-Saguenay (ARSCAS) ($n = 1$)
[42]	Diagnostic yield of a variety of genetic diagnostic techniques applied in a clinical setting	Clinic population: 670 unselected patients referred for developmental delay or intellectual disability to cytogenetic or genetic clinics	9.2% Down syndrome 2.4% 22q11.2 deletion 1.3% Williams-Beuren syndrome 1.3% Fragile X syndrome 0.7% Cohen syndrome 0.6% Monosomy 1p36.3 <0.5% Variety of others

There is considerable variation in the population distribution of ID by age, sex, socioeconomic status, and race and ethnicity. Age-specific ID prevalence rates, typically based on cross-sectional rather than longitudinal data, tend to peak among children of primary school age and then decline into adulthood, although it has been argued that this partly might reflect differences in ascertainment at different ages [30]. ID is more common among males than females, with a male-to-female ratio of 1.4–1.9 depending on the level of ID severity. It also is identified more commonly among children of low socioeconomic status and among racial or ethnic minorities such as Black or African-American or Australian aboriginal populations [5, 15, 18, 29, 59]. While some of these differences might be due to biologic factors such as the vulnerability of males to X-linked genetic abnormalities, much of the variability likely results from racial or ethnic biases in methods of identification or diagnosis, or both, or is reflective of unmeasured potential etiologic factors such as maternal intelligence and adverse prenatal, perinatal, or postnatal environmental conditions [30]. ID can co-occur with other conditions. The proportion of individuals with ID who have a co-occurring condition and the type of co-occurring condition vary by IQ level, age of evaluation, the population or type of study sample under investigation, and the method by which co-occurring conditions are identified and documented. For example, in metropolitan Atlanta during the period 1996 through 2000, 14–17% of 8-year-old children with ID also had one or more other motor or sensory developmental disabilities [5], while a review of epidemiologic studies reporting psychopathology among people with ID reported a prevalence range of 10–70% [19].

The etiology of ID is highly diverse, although the reported proportion of individuals with ID with an identified etiology varies enormously (e.g., 22–77% was reported in one review [30]) depending on such factors as how "known etiology" is defined (e.g., limited to specific clinical diagnoses such as Down syndrome or more broadly defined to include less specific conditions such as birth asphyxia), as well as IQ level, population, and type of diagnostic data available. The largest and undoubtedly most rapidly growing group of specific etiologic factors for ID is genetic [30]. One systematic search of the Online Mendelian Inheritance in Man (OMIM) database entries and literature searches through September 2003 revealed 282 molecularly identified ID genes; more than 1,300 entries for ID appeared on OMIM in November 2006 [26, 57]. The rapid advance in genetic techniques and explosion in genetic studies have prompted recent systematic literature reviews to determine the yield and utility of different genetic laboratory diagnostic approaches for ID. As reported in these reviews, routine cytogenetic analysis – or karyotyping – has identified specific abnormalities such as Down syndrome among 4–10% of individuals; fragile X studies specifically have yielded a prevalence range of 3–5%; and molecular screening for subtelomeric rearrangments using fluorescent in situ hybridization (FISH) has yielded abnormal findings among 4–7% of individuals [50, 56]. As illustrated in Table 24.2, individual genetic conditions are rare and account for relatively few ID cases; however, ID is very common among those with several rare conditions [36]. Application of the newer array comparative genomic hybridization techniques to identify genome copy number abnormalities also might provide

substantial diagnostic yield (4.8–20%) and replace FISH investigations [33]. The pathogenicity of new genetic variants, however, might be unknown, and typically the variants are not linked to a known disorder or genetic lesion and might not be replicated across different studies [62]. Thus, making sense of the genetic diversity underlying ID is a challenge, but the reports of novel variants underscore both the genetic heterogeneity of ID and the contribution of individual genetic variants to the total pool of ID etiologies.

24.4 Etiologically Defined Neurodevelopmental Disabilities

24.4.1 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome is a highly variable disorder that is the result, in most cases, of a recurrent submicroscopic deletion of chromosomal material on the long arm of the 22nd chromosome. Associated features include cleft palate; hypoparathyroidism; thymic aplasia and associated immunological deficits; conotruncal heart defects; and a host of neurodevelopmental deficits, including ID, autism, obsessive compulsive disorder, bipolar disorder, and schizophrenia. As with most other syndromes, for 22q11.2 deletion syndrome early publications preferentially identified those patients with the most striking phenotypic features. These reports emphasized the tetrad of cleft palate, hypoparathyroidism, thymic aplasia, and cardiac defects, which was referred to as DiGeorge syndrome. A milder phenotype was recognized later, and included features of velopharyngeal incompetence, cardiac defects, and characteristic appearance, referred to as velocardiofacial syndrome. With the discovery that individuals with both DiGeorge syndrome and velocardiofacial syndrome had the same submicroscopic deletion at chromosome band 22q11.2, clinical diagnosis was supplanted by molecular cytogenetic diagnosis using FISH methods. Soon after the availability of FISH for diagnosis, the full spectrum of associated features began to emerge. Such testing made it possible to make a definitive diagnosis and precise case definition for all patients for whom there was clinical suspicion. It also allowed for full investigation of previously unrecognized familial cases, mildly affected individuals, and those with atypical phenotypes.

Most prevalence estimates for 22q11.2 deletion syndrome have relied on extrapolation from patient populations referred for evaluation of cardiac defects or possible chromosome abnormalities. Goodship et al. [24] examined a group of 170 children referred for a cardiac defect and derived a prevalence of 1 in 3,900, which must be regarded as an underestimate because many children with 22q11.2 deletion syndrome do not have a cardiac defect. By contrast, Devriendt et al. [16] found a prevalence of 1 in 6,395 by examining the number of positive tests for 22q11.2 syndrome in a busy clinical laboratory. Botto et al. [6] used a population-based, multiple-source surveillance system to examine prevalence over a 5-year period and found an overall prevalence of 1 in 5,950. The rate among different population groups was examined, and prevalence among Hispanics was higher (1 in 3,800)

than the prevalence among White, Black or African-American, or Asian populations (1 in 6,500 to 1 in 6,000). Almost all of these investigations are likely to have underestimated the actual prevalence of 22q11.2 deletion syndrome because the disorder is highly variable and the diagnosis might be missed among many mildly affected individuals as well as among those not served by the clinical populations under study.

The most consistent neurodevelopmental deficit identified in 22q11.2 deletion syndrome is cognitive impairment in the low borderline IQ range [3]. Expressive language skills are particularly low, even when considered in the context of low cognitive development [53]. Nonverbal learning disabilities also are seen frequently and probably represent the most common cognitive abnormality [35]. A general trend toward greater cognitive delay among younger children has been observed. The reasons for this trend are not well understood but might relate to a greater number of hospitalizations and medical complications among young children or an ascertainment bias toward more severely affected individuals for those who are identified during early infancy. Among affected adults, much attention has been given to the development of schizophrenia and the associated neurodevelopmental abnormalities that accompany this diagnosis. Up to 30% of adults with this syndrome can be expected to develop schizophrenia [37]. Autistic disorder and schizoaffective disorder also occur with increased frequency among this population when compared with other populations with NDDs. Again, some of this high frequency of associated problems might be attributed to ascertainment bias toward more severely affected individuals among study populations. To support this notion, McDonald-McGinn et al. [32] found that adults who were ascertained through diagnosis of an affected child generally were within the normal range of cognitive development, and only 1 in 19 had developed schizophrenia.

24.4.2 Fragile X Syndrome

FXS syndrome is a multisystem disorder caused by loss of function mutations of the *FMR1* gene, located on the long arm of the X chromosome. The molecular pathogenesis of FXS is complex and involves gene silencing from a trinucleotide repeat expansion and abnormal gene methylation. Individuals with up to about 200 trinucleotide repeats are considered to have what is known as a premutation, usually without significant phenotypic effects, whereas those with more than 200 repeats have the full mutation and associated developmental disabilities. There is great variability, however, in the expression of FXS. Because the gene is on the X chromosome, males are affected more commonly than females, and the clinical phenotype is more severe among affected males. Characteristic features include moderate ID, abnormal behavior, enlarged head circumference, a long appearing face, large ears, a prominent forehead and jaw, and enlarged testes in postpubertal males [55]. Affected females tend to have mild ID and milder growth and facial features than their male counterparts. Although the diagnosis of FXS might be

suspected from clinical features, molecular genetic testing for *FMR1* mutations is clinically available and reliable, and provides a definitive diagnosis and precise case definition. Prior to the era of molecular diagnosis, the estimated prevalence of FXS was almost 1 in 1,000 males. As molecular diagnostic techniques became more readily available and were applied to selected and relatively small samples, the prevalence estimate was closer to 1 in 6,000 to 1 in 3,000 males [14, 17]. The most comprehensive prevalence study to date examined dried blood spots of a population-based sample of 36,124 de-identified newborn males and found an incidence of 1 in 5,161 (95% confidence interval of 1 in 10,653 to 1 in 2,500) [11]. The female prevalence has been predicted to be half the male prevalence.

Co-occurring developmental diagnoses are common among those with FXS and include ID; ASDs; ADHD; depression; and a variety of abnormal behaviors such as self-stimulation, gaze avoidance, and temper tantrums [4]. ID is seen among virtually all affected boys and is usually moderate in degree. ASDs were found among approximately 25% of patients in one series [25], but were reported among 46% of 976 boys ascertained through a national parent survey [4]. Parents also reported attention problems among 84%, anxiety among 70%, hyperactivity among 66%, and depression among 12% of these boys, all of whom had the full *FMR1* mutation. In addition to functional abnormalities of the central nervous system, MRI examination of the brain also has identified structural abnormalities among some affected boys, including neuronal heterotopia and increased ventricular volume [34].

24.4.3 Implications

A summary of the epidemiologic features of the phenotypically and etiologically defined NDD classifications is presented in Table 24.1. Considering the differences outlined in Table 24.1, Table 24.3 suggests specific applications in which consideration of rare etiology-based NDDs might further our understanding of NDD epidemiology overall, suggests what is needed to integrate the two classification approaches, and identifies practical challenges in achieving that integration. For example, when one considers the effect of genotypically diagnosed disorders such as 22q11.2 deletion syndrome and FXS on the overall prevalence of NDDs such as ID and ASDs, their influence must be regarded as modest, at best. A disorder that affects perhaps 1 in 3,000–4,000 individuals is unlikely to make up a high percentage of the population of those with ID or ASDs, which are relatively more common (with a prevalence of 1% or more among the general population). It is clear, however, that children with genotypic diagnoses currently are overrepresented among populations with NDDs and that they represent a subgroup whose disabilities have a more clearly identifiable genetic association than those without such diagnoses. Thus, the large number of rare diseases – especially of genetic origin – associated with NDDs but individually accounting for a small proportion of NDD cases overall are etiologically important. It has been suggested that the genetic risk for common complex diseases such as asthma or heart disease might be conferred by

Table 24.3 Role of rare diseases in neurodevelopmental disability epidemiology

Epidemiologic concept	Role of rare diseases
Case definition	• Can enhance specificity of case definition, e.g., by permitting inclusion or exclusion of specific rare diseases in phenotypic-based case definition.
Prevalence	• Can potentially improve validity and reliability of prevalence estimate for a given phenotype by accounting for individuals with both a rare disease and the phenotype. • Effect on prevalence estimate for a given phenotype will depend on prevalence of co-occurring rare disease and specific phenotype.
Population distribution	• Potentially can improve validity and reliability of estimates of neurodevelopmental disability population distribution by accounting for the contribution of rare diseases to a specific phenotype. ○ Effect on validity and reliability of descriptions of specific NDD population distributions overall might be low. ○ Effect on the ability to identify and characterize specific vulnerable subgroups within a phenotype with the co-occurring rare disease might be high.
Co-occurring conditions	• Can improve the reliability and validity of descriptions of specific types of co-morbid conditions and estimated proportion of affected cases with a given phenotype. • By accounting for the co-morbid rare condition, might add important information regarding the source of variability in severity, clinical course, and prognosis of individuals with a given phenotype.
Etiology	• Can improve the reliability and validity of descriptions of specific etiologies and their proportional contribution to the total pool of individuals with a given phenotype • Can enhance etiologic investigations of a given phenotype: ○ Exclude individuals with a rare disease in order to focus on individuals with "unknown" etiology. ○ Focus on individuals with a rare disease to explore the specific etiologic mechanism (e.g., metabolic or neurochemical) exemplified by the rare disease that apparently leads to a given phenotype.
Overall	Consideration of rare diseases might have a great effect on understanding the sources of clinical, epidemiologic, and etiologic heterogeneity of a given NDD phenotype

Table 24.3 (continued)

Other points of interest	Role of rare diseases
What is needed to integrate phenotype- and etiology-based NDD classifications	• Specific clinical diagnostic work-up for rare disease or access to specific diagnostic data in records of each case with a given phenotype. ○ Ideally, diagnostic work-up is based on results of systematic screening. • Systematic assessment for phenotypic characteristics in each case with a rare disease. • Due to the relatively rarity of conditions in both classification schemes, study of their co-occurrence will require large sample sizes potentially requiring multisite or multinational collaboration.

Practical challenges to integration of phenotype- and etiology-based NDD classifications	• Recognition and diagnosis of rare disease associated with a given phenotype often driven by clinical judgment rather than systematic assessment which can lead to flaws and gaps in NDD information due to:
	  ○ Referral bias,
	  ○ Uneven clinical expertise and knowledge, and
	  ○ Search for a rare disease often motivated by need to recommend treatment.
	• Diagnostic capabilities for rare diseases rapidly changing with new technologies and discoveries.
	  ○ Uneven clinical access to new diagnostic techniques.
	• Variable expression of neurodevelopmental features in rare diseases complicates the recognition and diagnosis of rare diseases with a given phenotype.
	• Rapid growth of new technologies and etiologic discoveries make it challenging to keep current and integrate information.
	• Bioinformatic and analytic tools and techniques that can handle the large amounts of data that are being generated with new gene discovery technologies.
	  ○ Large data volume: ability to sort out the “noise” from the disease-causing variants.

many low-frequency alleles [43]. If this concept applies also to the etiologically heterogeneous, phenotypically defined NDDs, then the role of rare disease investigation similarly might provide better understanding of various NDDs by focusing on specific pathogenetic mechanisms.

The interrelationship between phenotype-based and rare genetic etiology-based conditions also has important implications for medical evaluation and diagnosis. Phenotypic diagnoses usually are recognized prior to the identification of their etiology, which has led to investigations of the most appropriate diagnostic evaluation for children referred for diagnoses such as ASDs and ID. Several large-scale studies have examined the likelihood of finding a definitive diagnosis after full evaluation of a child with global developmental delay or ID, which sometimes is referred to as the "etiologic yield" of the diagnostic evaluation. The etiologic yield has varied, depending on the characteristics of the study population, the availability of comprehensive testing modalities, and the methods used to classify children's disabilities. A recent review of etiologic yield, which considered the most recent retrospective and prospective studies, places the figure at around 50% [51]. Similar investigations among children with ASDs have found an etiologic yield of 15–40% [45, 49]. This underscores the considerable knowledge gap regarding the causes of ID and ASDs and provides a framework for the systematic diagnostic evaluation of at-risk children to uncover specific etiologic factors. Similarly, the medical evaluation of individuals with genotypic diagnoses should include systematic screening for known associations with NDDs such as ID and ASDs.

Despite the value in recognizing the contributions of rare genetic etiology-based diseases to NDD epidemiology overall, there is another important epidemiologic concept that warrants careful consideration. Although a rare disease might be reported to co-occur with a given phenotype, the exact nature of the co-occurrence might be unknown. It might be imprudent to assume that the co-occurrence is causal (e.g., the genetic abnormality in a rare disease is the cause of the entire array of abnormal features in a phenotype). A wiser approach would be to evaluate the likelihood of different explanatory scenarios for the co-occurrence. It might be possible that (1) the co-occurrence is truly causal, (2) the association actually is due to separate and independent etiologic factors arising in the same individual, (3) the two conditions share a common etiologic factor, (4) the association is an epiphenomenon (i.e., either the cause of the rare disease or the cause of the phenotype are intermediate features along a shared etiologic pathway), or (5) the rare disease increases the susceptibility for the phenotype in the presence of a second etiologic factor.

24.5 Conclusion

NDDs represent a diverse group of conditions. When considering this diversity at the population-level, it is important to be clear on how the categorization of the various NDDs is accomplished, because the classification methods can greatly affect epidemiologic results. In this chapter, we have used two different approaches to classify

NDDs. Understanding commonalities and differences in the epidemiologic features of the phenotypically and etiologically defined NDD classifications provides a useful framework for furthering our understanding of the prevalence, distribution, and causes of NDDs, as well as delivering appropriate diagnostic resources, appropriate treatments, accurate prognostic information, and estimates of recurrence risk for these disorders.

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Part VI
Policy and Ethics Issues in Rare Diseases

Chapter 25
Creating a European Union Framework for Actions in the Field of Rare Diseases

Antoni Montserrat Moliner

Abstract Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000). The specificities of rare diseases – limited number of patients and scarcity of relevant knowledge and expertise – single them out as a unique domain of very high European added-value. The legal instruments at the disposal of the European Union, in terms of the Article 152 of the Treaties of the European Union, are very limited. However a combination of instruments using the research and the pharmaceutical legal basis and an intensive and creative use of funding from the First Public Health Programme 2003–2008 and from the Second Health Programme 2008–2013 has permitted to create a solid basis that Member States have considered enough to put rare diseases in a privileged position in the health agenda. The adoption of the Commission Communication, in November 2008, and of the Council Recommendation, in June 2009, and the future adoption of the Directive on Cross-border healthcare, maybe during 2010, have created an operational framework to act in the field of rare disease with European coordination in several areas (classification and codification, European Reference Networks, orphan drugs, European Committee of Experts, etc.). In conclusion**,** Rare diseases is an area with enormous and practical potentialities for the European cooperation.

Keywords European policies · Neonatal screening · National plans · European reference networks · Patients organizations

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25.1 Introduction

Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. This definition appeared first in the European Union (EU) legislation in the Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products [3]. It was extended to the public health field by the Community action programme on rare diseases including genetic diseases, 1 January 1999 to 31 December 2003 [2], and most recently by the Commission Communication COMM(2008) 679 final on Rare Diseases: Europe's challenges [5] of 11 November 2008. It is estimated that between 6,000 and 8,000 distinct rare diseases exist today (currently 5,860 are described in the Orphanet database), affecting between 6% and 8% of the European population in total. In other words, between 27 and 36 million people in the European Union are affected by a rare disease. According to the World Health Organisation, a rare disease affects at most 6.5 out of every 10,000 individuals. Australia, Japan and the United States have set prevalences of 1.16, 4.07 and 6.68 per 100,000 individuals respectively for a given rare disease.

On the other hand, population prevalence should not be the sole criterion, as the incidence is also a very appropriate indicator to assess the issues related to diagnosis and expert care. This is particularly true for rare cancers. Rare Diseases which are rapidly fatal in general may have a low prevalence despite a high incidence. A more refined definition based on incidence, not prevalence only, will be analyzed using the European Union Health Programme resources and taking into account the international dimension of the problem.

The specificities of rare diseases – limited number of patients and scarcity of relevant knowledge and expertise – single them out as a unique domain of very high European added-value. There is probably no other area in health where collaboration between 27 different European approaches can be as efficient and effective. Coordination at European Union (EU) level is probably the best way of pooling the very limited resources available.

25.2 Rare Diseases European Policy

Based on Article 152 of the Treaty of the European Union, a Community action programme on Rare Diseases, including genetic diseases, was adopted for the first time for the period 1 January 1999 to 31 December 2003. As a first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases but this first programme was in reality a simple grant programme. The European Union's objective in the field of rare diseases is to bring

together the necessary elements for an efficient overall strategy, hence the adoption of Commission Communication COMM(2008) 679 final on 11 November 2008, setting out what the European Commission will do in this field, and the Council Recommendation on an action in the field of rare diseases [7], of 9 June 2009, advising the Member States on what they should do. The complementarity of objectives in both documents results in a clear strategy for European Union intervention in this field aimed at improving patients' access to appropriate and timely diagnoses, information and care. In this area, European action can be more effective than Member States acting on their own. This involves the following steps:

- **making rare diseases more visible** by developing proper identification and coding of rare diseases, many of which currently go unrecognised, leading to inappropriate treatment for individuals and lack of appropriate resources overall;
- **encouraging Member States to develop national rare diseases plans in their health policies** to ensure equal access to and availability of prevention, diagnosis, treatment and rehabilitation for people with rare diseases. More initiatives in terms of public awareness-raising in the Member States are needed. In addition to targeting public opinion, these efforts should also be directed at healthcare and social services professionals, decision-makers, health and social services managers and the media.
- **providing European support and cooperation**, such as ensuring that **common policy guidelines are developed and shared** everywhere in Europe. There should also be specific actions in areas such as research, centres of expertise, access to information, incentives for the development of orphan drugs and screening. Cooperation between existing European programmes also needs to be improved.

25.3 Building Capacity and Knowledge

Rare diseases also differ widely in severity and in expression. Rare diseases patients have a significantly lower life expectancy. Many are complex, degenerative and chronically debilitating, whilst others are compatible with a normal life – if diagnosed in time and managed and/or treated properly. They affect physical capabilities, mental abilities, behaviour and sensorial capacities, and generate disabilities. Several disabilities often co-exist, with many functional consequences (defined as polyhandicap or plurihandicap). These disabilities enhance the feeling of isolation and could be a source of discrimination and reduce any educational, professional and social opportunities.

According to available sources in medical literature [27], less than 100 Rare Diseases have a prevalence near the threshold of 5 per 10,000, such as Gelineau Disease, Triplo X Syndrome, Scleroderma or neural tube defects. Most RD are very rare, affecting one in 100,000 people or less such as Gaucher disease, Ewing

Sarcoma, Duchenne muscular dystrophy or Von Hippel-Lindau disease. Thousands of Rare Diseases affect only a few patients in Europe such as Pompe disease, Alternating hemiplegia or Ondine Syndrome. Patients with very rare diseases and their families are particularly isolated and vulnerable.

There is also a great diversity in the age at which the first symptoms occur: half of Rare Diseases can appear at birth or during childhood (such as Williams's syndrome, Prader-Willi syndrome, retinoblastoma). The other half of Rare Diseases can appear in adulthood (such as Huntington disease, Creutzfeld Jacob disease, Amyotrophic Lateral sclerosis). Most RD are genetic diseases, but they can also result from environmental exposures during pregnancy or later in life, often in combination with genetic susceptibility. Some are rare forms or rare complications of common diseases. Relatively common conditions can hide underlying RD, e.g. autism (major symptom in Rett Syndrome, Fragile X, Angelman, Adult Phenylketonuria, Sanfilippo disease, *etc*.) or epilepsy (Tuberous sclerosis, Shokeir Syndrome, Dravet Syndrome, etc.). Many conditions classified in the past as mental deficiency, cerebral palsy, autism or psychosis, are manifestations of RD still to be characterised. Many types of cancers, including all cancers affecting children, are RD, as well as most congenital malformations.

25.4 Orphan Drugs Policy in the EU

Under normal market conditions, the pharmaceutical industry is reluctant to invest in medicinal products and devices for rare conditions because of the very limited market for each disease. This explains why Rare Diseases are also called "orphan diseases": they are "orphans" of research focus and market interest, as well as of public health policies. Under the responsibility of DG Enterprise of the European Commission and the EMA (European Medicines Agency) the EU implements a policy on Orphan Drugs. The mentioned Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products) establishes criteria for orphan designation in the EU and includes a number of incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) for research into, and the development and marketing of medicines to treat, prevent or diagnose Rare Diseases. In 2008 [10] a total of 119 applications were submitted for designation as orphan medicinal products and the Committee for Orphan Medicinal Products (COMP) adopted 86 positive opinions and one negative opinion. The European Medicines Agency's Committee for Orphan Medicinal Products (COMP) reports a record-breaking number of applications for orphan designation in 2009. So far year, 150 applications for orphan medicinal product designation have been received, already representing an increase of 25% from 2008. As in previous years, cancer treatment was the most-represented therapeutic area for which the COMP adopted positive orphan-designation opinions. Almost two-thirds of designated orphan medicinal products were for conditions affecting children and

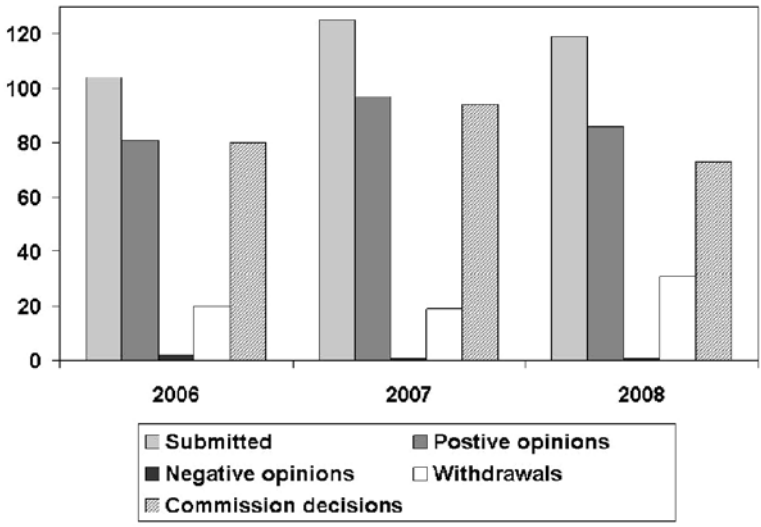

Fig. 25.1 Applications for orphan medicinal product designation by years

the COMP took on average 66 days to evaluate applications— the same as in the previous year (Fig. 25.1).

There are specific bottlenecks linked to rarity and the way forward is to increase collaboration at European level to scientifically establish the (added) therapeutic value of Orphan Medicinal Products. In this respect the COMP, which is part of the European Medicines Agency, in cooperation with the future EU Committee of Experts on Rare Diseases, could make a positive contribution to any future collaboration at European level on the scientific assessment of the (added) therapeutic value of such products. This input could be used by National Competent Authorities when appraising Orphan Medicinal Products for pricing and reimbursement purposes. Access to orphan medicines should be ensured and appropriately defined within all Member States. Administrative delays beyond the 180-days legal limit should be prevented. The aim should be to ensure that patients with rare diseases are not disadvantaged in any way compared to patients with more prevalent diseases.

The results of the Survey of the delay in diagnosis for 8 rare diseases in Europe ('EURORDISCARE 2') [19] carried out by EURORDIS (European Organisation for Rare Diseases) the most important patient′s platform for rare diseases in Europe, survey on orphan drug availability in Europe (supported by the European Commission), aimed at measuring real patient access to orphan drugs and identifying possible solutions for improving the situation, has surveyed 22 orphan drugs authorised before the 1st of January 2006 and the 25 EU countries before the last enlargement, as well as Iceland, Norway, and Switzerland. The results are quite telling. The countries with most orphan drugs available to patients (20 or 21 orphan drugs) are Finland, France, Germany, and Sweden. They are closely followed by

Austria, Czech Republic, Denmark, Italy, Netherlands, Norway, Spain, Switzerland, and United Kingdom (15 to 19 orphan drugs available). The worst contenders are Iceland, Latvia, and Lithuania, with only up to 4 orphan drugs available. In the Czech Republic, Italy and Slovakia, the price patients have to pay (or their national healthcare authorities) for orphan drugs is more than 110% the European mean price for all orphan drugs (Orphan drugs are often fully reimbursed to patients). On the other hand, patients from Hungary, Spain and the United Kingdom have to pay up to 94% of that price for the same drugs. Other main findings of this survey showed that 25% of patients had to wait between 5 and 30 years from early symptoms to confirmatory diagnosis of their disease, 40% of patients first received an erroneous diagnosis, others received none. This led to medical interventions (including surgery and psychiatric treatments) that were based on a wrong diagnosis. 25% of patients had to travel to a different region to obtain the confirmatory diagnosis, and 2% had to travel to a different country. In 33% of cases, the diagnosis was announced in unsatisfactory terms or conditions. In 12.5% of cases, it was announced in unacceptable ones. The genetic nature of the disease was not communicated to the patient or family in 25% of cases. This is paradoxical, given the genetic origin of rare diseases. Finally, there was genetic counselling in only 50% of cases.

25.5 European Research in Rare Diseases

Over the last two decades, collaborative and coordinated research projects supported by successive European Community Framework Programmes for Research and Technological Development (FP) have made a substantial contribution to advancing knowledge on rare diseases. The FP6 supported an important ERA-Net project dedicated to Rare Diseases (E-Rare) [13] for the development of joint and trans-national activities (survey on national programmes, identification of gaps and overlaps among national research programs and activities on Rare Disease). E-Rare foresees to set up sustained and long lasting cooperation between EU Member States partners, to coordinate national research programmes in order to overcome the fragmentation of research on Rare Diseases and promote interdisciplinary approaches, to harmonize and develop synergies among the national and/or regional research programs of the participating countries, to develop common research policy on Rare Diseases and to sustain a favourable competitive position with regard to research on Rare Diseases in other regions of the globe such as North America and Asia. The Rare Diseases activities in FP6 also allowed to duly involving representative patient organisations (by participation in projects – including co-sponsoring, agenda setting, workshops and conferences). This process was mutually cross-fertilising and permitted as such to start bridging the gap between science and the public and the patients.

In the current framework programme, FP7 [4], rare diseases have been designated a priority for research activities. Research on Rare Diseases has offers us a much better understanding of the mechanism of common conditions like obesity

and diabetes, as they represent a model of dysfunction of a biological pathway. Research on Rare Diseases has been fundamental to identifying most currently-known human genes and a quarter of the innovative medicinal products that have received market approval in the EU (orphan drugs). The FP5 programme supported 47 research projects on rare diseases (for a total of 64 million euros). There were 59 such projects in the FP6 programme (for a total of 230 million euros). The FP7 will give priority to Europe-wide studies of natural history, pathophysiology and the development of preventive, diagnostic and therapeutic interventions. This sector will include rare Mendelian phenotypes of common diseases and should help to identify and mobilise a critical mass of expertise to (i) shed light on the course and/or mechanisms of rare diseases, or (ii) test diagnostic, preventive and/or therapeutic approaches to alleviating the negative impact of the disease on patients' and their families' quality of life, as appropriate, depending on the level of knowledge concerning the specific disease or group or diseases under study.

25.6 European Reference Networks

In 2005, DG SANCO established the High Level Group on Health Services and Medical Care (HLG) to implement the recommendations of the reflection process on patient mobility and the future adoption of a Directive on Cross-border healthcare [6]. One of its working groups deals with reference networks of centres of expertise**,** in particular for rare diseases. In the Commission Communication and the Council Recommendation, high importance is given to the creation of European Reference Networks on Rare Diseases. Diagnosis of a rare disease is often delayed, and for the majority of rare diseases no appropriate treatment exists. Sometimes, knowledge and appropriate treatment of a disease may exist in another Member State but mobility of information is hampered by inefficiency and fragmentation of the limited resources available.

Rare diseases offer a prime example of the benefits of trans-national coordination. When diseases are rare, expertise is scarce as well. Certain centres have developed expertise which is widely used by other professionals from their country or even internationally. In some countries these centres are officially recognised, but in most they are only established by reputation. The Commission has decided to prioritise cooperation and knowledge sharing between them as the most efficient approach. Certain principles have been developed regarding European Reference Networks (ERN), including their role in tackling rare diseases or other conditions requiring specialised care, patient volumes and other criteria that such centres should fulfil. ERNs should also serve as research and knowledge networks updating and contributing to the latest scientific results, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. ERNs should also reflect the need for services and expertise to be appropriately distributed across the enlarged European Union. The EU rare diseases Task Force 2006 Report '*Contribution to policy shaping: For a European collaboration on health services and medical rare in the field of rare diseases'* [31] recommends that

Member States contribute to the identification of their expert centres and support them financially as much as possible. It also recommends that Member States organise healthcare pathways for their patients through the establishment of cooperation with all necessary expert centres within the country or from abroad when necessary.

The European Commission has selected for funding 10 pilot ERN projects [9] serving as examples and source of experiences and lessons in building these networks.

The European Reference Networks will have a strategic role in harmonising care and improving quality of treatment for all patients throughout the European Union. Within ERNs, knowledge and expertise will be shared across different Centres. If necessary at specific moments of the development of a disease, it will be considered as "normal and fair" to travel from one Centre to another within the same network to confirm a diagnosis or seek a second opinion, or for important medical procedures, such as surgical operations, transplantations and other invasive medical interventions. It should not be an administrative, legal and medical battle for a patient to travel abroad for involuntary medical reasons.

Both approaches (transfer of knowledge and patient mobility) are useful. A centrifugal approach to transferring knowledge from the central network to a broader periphery allows more local delivery of care/treatment to patients and the dissemination of information. The benefits are care close to the patient's home/environment and dissemination of knowledge to a wide community. This however does not guarantee that the knowledge is in the hands of experts or that the patient will have access to the latest treatment/technology. A centripetal approach favouring the concentration of patients in one expert centre increases the expertise/standard of care of the centre. The benefits are a high quality of care/treatment for the patients, access to the latest technology and the possibility for patients and their families to feel less isolated. However, it keeps the expertise in the expert's hand and requires patients to travel to the centre.

European Reference Networks should initially be evaluated at EU level via an agreed set of criteria (minimum set of standardised criteria and objectives) and then regularly assessed on common indicators using both soft and hard values. Methods and tools should also be developed for European reference networks to perform regular self-evaluation.

25.7 Improving the Classification and Information of Rare Diseases

The EU should cooperate closely with WHO in revising the existing ICD (International Classification of Diseases) to ensure a better codification and classification of rare diseases. The current ICD-version 10 should be replaced by a new ICD-version 11 to be adopted by the World Health Assembly in 2014 to be in force in 2015. All rare diseases should be adequately coded and traceable in all health

information systems, thus contributing to adequate recognition of them in national health care and reimbursement systems. Form the 5,860 rare diseases repertoried in Orphanet only 250 have an explicit code in the ICD-10. This constitutes a problem, not only from the statistical point of view, but for the affected persons themselves who, sometimes, are rejected by their national healthcare system because 'the disease not exists'. This statistical existence of the rare diseases constitutes a high challenge. This has required the creation of a working group on Classification and Codification of rare diseases, acting as an advisory working group to WHO in the current ICD revision process [32]. Once the ICD-11 becomes available, active cooperation of the EU Statistical Programme will be necessary to ensure that the new version, including new codes for rare diseases, is used in death certificates and hospital discharge tabulation systems in all Member States. Similar efforts should be made to ensure proper coding of rare diseases in the SnowMed and MedDRA coding systems. The ICD is always the basis for the Diagnosis Related Groups used to calculate hospital care disease costs.

Adequate information on the epidemiology and prevalence of rare diseases is a necessary basis for efficient action. This type of information is also essential when deciding whether an orphan drugs designation is appropriate. The key element for improving diagnosis and care in the field of rare diseases is to provide and disseminate accurate information in a format adapted to the needs of professionals and affected persons. Since 2000, the Orphanet database [26], with the support of the Health Programme and the Framework Programmes for Research, has been providing information about over 5,000 diseases in six languages. It provides a comprehensive encyclopaedia of rare diseases; a directory of professional services in 35 countries; a directory of European centres of expertise; a database of orphan drugs providing information on their stage of development and availability in EU countries; and a range of other services for specific categories of stakeholders, including a facility to retrieve diagnoses through symptoms and signs and a library of recommendations for emergency situations. Orphanet has already established a searchable database of clinical symptoms and provides a valuable resource which constitutes the European and world reference for the identification and epidemiological description of rare diseases. Funding for Orphanet should be confirmed with additional resources to allow the dictionary of rare diseases to be translated into all EU languages and provided in print version to make it accessible across all Member States. A Joint Action is scheduled in the Work Plan for the Implementation of the Health Programme for the year 2010.

The establishment of a dynamic inventory of rare diseases will contribute to tackling one of the main causes of neglect of rare diseases, namely ignorance of which diseases are rare. There is a need for an accurate inventory of rare diseases, regularly updated and classified by medical specialty, prevalence, mechanism and aetiology, to maximise awareness and provide documentary support to research and data storage in general. This European inventory of rare diseases could also inform and influence health-care spending and planning. It would therefore need to be agreed by Member State Governments, and health, care authorities and be made available to appropriate professionals. The forthcoming EU Committee of Experts on Rare

Diseases could be responsible for establishing this inventory. Consideration should be given to Orphanet's fundamental role in developing and hosting this inventory.

This support for a more EU oriented information framework does not make support for existing (or future) specific disease information networks any less essential. Exchanging information via existing European information networks, promoting better classification of particular diseases, developing strategies and mechanisms for exchanging information between stakeholders, defining relevant health indicators, developing comparable epidemiological data at EU level, supporting exchanges of best practices and developing measures for patient groups are all major priorities. Such projects make a key contribution to our overall understanding of rare diseases (e.g. EUROCAT for congenital anomalies [16], ENERCA for rare anaemia disorders [12], Rare Bleeding Disorders Database [30], EuroWilson [20], etc.). Ongoing EU projects have already proven their relevance. This type of project should be supported at both Member State and EU levels.

An excellent example of a type of project that the European Union can support in the field of rare diseases is EUROCAT (Surveillance of Congenital Anomalies in Europe). EUROCAT provides essential epidemiological information on congenital anomalies in Europe based on a common dataset with common coding as specified in the EUROCAT Guide and the EUROCAT Data Management Programme (EDMP) used by member registries for data input/import, validation and annual transmission to the Central Registry. They act as information and resource centres for the population, health professionals and managers regarding clusters or exposures or risk factors of concern. They provide a readily available collaborative network and infrastructure for research into the causes and prevention of congenital anomalies and the treatment and care of affected children, and survey policies and practices with regard to periconceptional folic acid supplementation.

Electronic services developed by Orphanet and by other EU funded projects, are a clear demonstration of how e-technologies can contribute to putting patients in contact with other patients, to sharing databases between research groups, to collecting data for clinical research, to registering patients willing to participate in clinical research, and to submitting cases to experts which improve the quality of diagnoses and treatment. The development of e-Health in the field of RD using on-line and electronic tools could be very efficient and should be a strong part of the EU strategy on RD. They can save life of persons with RD in emergency situations. The European Commission should provide financial support for this activity through the Public Health Programme and the FP and MS.

25.8 Improving Registries on Rare Diseases

Registries and databases constitute key instruments to develop clinical research in the field of RD. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research. Registries of

patients treated with orphan drugs are particularly relevant as they allow gathering the evidence on the effectiveness of the treatment and on its possible side effects, knowing that marketing authorisation is usually granted at a time when evidence is still limited although already convincing. Collaborative efforts to establish data collection and maintain them should be supported, providing that these resources are accessible upon agreed rules. Many research and public health networks financially supported by DG RTD and by DG SANCO have put in place such shared infrastructures, which proved to be efficient tools to improve knowledge and organise clinical trials.

At the last count by Orphanet [28], and excluding cancer registries, there were 244 rare disease registries and 8 rare disease cohort registries in Europe, and the number is growing. From this there are 34 registries having a EU dimension from which 16 (47%) are financed by the EU Programmes. Only a handful is funded by industry; most are operated by academics and clinicians, or by patients' organisations. The value to research, and ultimately to patients, of a well designed and well run registry is beyond question. Yet many face issues relating to funding and sustainability. A workshop organised by EPPOSI (European Platform for Patient's Organisations, Science and Industry [29] identified several potential policy actions which governments and the European Commission can take to improve the always precarious funding situation. In particular, the workshop concluded that a working group needs to be established to look into providing, for example, customisable downloadable software for registries. Much more attention should be paid when setting up registries to data exchange, and, to the establishment generally of common data standards.

Networks of biobanks are also of great interest. A specialised network, such as EuroBioBank [14], an FP5-supported project, represents an invaluable European resource which requires long term funding and EU based approach in order to be fully developed and its use optimised. This type of initiative should be supported at MS and EU level and long-term funding should be made available for these infrastructures, providing that their utility is established. A specific need in Rare Disease biobanking is to allow collection and storage of material from patients with very RD, even in the absence of an on-going research protocol.

An EU Project has been selected by the FP7 in order to prepare for the construction of a pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) [1] for biomedical and biological research in Europe and worldwide, building on existing infrastructures, resources and technologies, specifically complemented with innovative components and properly embedded into European ethical, legal and societal frameworks. Main objectives are: To benefit European health-care, medical research, and, ultimately, the health of the citizens of the European Union. To have a sustainable legal and financial conceptual framework for a pan-European Biobank infrastructure., to increase scientific excellence and efficacy of European research in the life sciences, especially in biomedical research., and to expand and secure competitiveness of European research and industry in a global context, especially in the field of medicine and biology.

25.9 Community Action in the Rare Diseases Field

Community action in the Rare Diseases field is clearly justified by a combination of the subsidiarity principle ("The Union does not take action (except in the areas which fall within its exclusive competence) unless it is more effective than action taken at national, regional or local level") and Article 152, which is the legal basis for EU action in the area of Public Health. The EU has no mandate for the organisation of health care in Member States.

In order to integrate all the necessary initiatives that have to be taken at national and/or regional levels, Member States are invited by the Council Recommendation on a action in the field of rare diseases adopted the 9th June 2009 to establish national or regional action plans or strategies for Rare Diseases before 2013 in order to implement the actions suggested in the Commission Communication and the Council Recommendation. European guidelines for the elaboration of action plans for RD might be useful. In this sense a project EUROPLAN (European Project for Rare Diseases National Plans Development) [11] has been selected for funding in 2007 in the Public Health Programme. The project will ensure that common policy guidelines are shared everywhere in Europe and will contribute to the development of national programme for Rare Diseases within Member States linking national efforts with a common strategy at European level. EUROPLAN defines a rare diseases plan as "A national plan/strategy (NP/NS) can be defined as the sum of integrated and comprehensive health policy actions for RD to be developed and implemented at national level. As such a NP/NS should have well specified objectives and actions to be supported by a budget, implemented within a time frame, evaluated with specific indicators". Only a limited number of Member States have adopted or will soon adopt a National Plan/Strategy or launch relevant initiatives. While only France has established a comprehensive action plan (2005–2008) [25] and will launch the Second Plan in 2010, Bulgaria for the period 2009–2013 [21] and Greece for the period 2008–2012 [22], other Member States have adopted national strategies not explicitly supported by a budget (Portugal [23], Spain [24]) or national policies in a certain number of areas which can be translated in the form of a plan or strategy very soon (Italy, Sweden, Denmark, United Kingdom, The Netherlands, Czech Republic, Romania, Luxembourg). The development of health indicators is needed to monitor the situation of affected persons in the EU and its evolution. Compilation of existing sources of data should be encouraged, especially those already funded at EU level.

25.10 Neonatal Screening

Another key element of the Commission Communication (point 5.8) and in the Council Recommendation (point 17 d) is the statement that neonatal screening for phenylketonuria and congenital hypothyroidism is current practice in Europe and proved highly efficient in preventing disabilities in affected children. As

technology evolves, many tests can now be performed for a wide range of rare diseases, especially metabolic disorders and genetic conditions in general. The Council Recommendation refers also to the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences, as a privileged area of cooperation between the Member States. This is the aim of a call for tender launched in July 2009 by the European Commission. The output should be an extensive report on the practices of NBS (Newborn Screening) for rare disorders implemented in all the Member States including number of centres, estimation of the number of infants screened and the number of disorders included in the NBS as well as reasons for the selection of these disorders. A possible Council Recommendation on NBS for some rare disorders could be submitted to discussion with Member States around 2011.

25.11 Preprimary Prevention and Genetic Testing

Primary preventive measures should be adopted when possible. There are very few rare diseases for which a primary prevention is possible. Environmental factors are important in the causation of a wider range of rare congenital malformations, as well as childhood cancers. What is needed to prevent these Rare Diseases is special targeting of the preconception period and pregnancy in public health measures aimed at major health determinants – nutrition, obesity, alcohol, smoking, recreational drugs and environmental pollution. Vaccination against diseases such as rubella (for prevention of congenital rubella syndrome) must take into account the consequences of migration between countries with different vaccination policies. In addition, attention must be paid to women before conception and in early pregnancy in the management of chronic diseases such as diabetes, epilepsy and infertility. Among the possible interventions is raising folic acid intake of women before the time they conceived as to prevent neural tube defects (e.g. spina bifida) and other malformations. Many studies provide evidence that adequate folic acid intake, during the peri-conceptional period, can prevent more than half of the neural tube defects [15]. Action in this field should be the topic for a debate at EU level aiming to determine for which RD primary preventive measures may be successful.

In relation to availability and accessibility of accurate diagnostic tests, including genetic tests, it's a fact that many RD can now be diagnosed using a biological test which is often a genetic test. These tests are major elements of an appropriate patient's management as they allow an early diagnosis, sometimes a familial cascade screening or a prenatal test. Given the large number of tests and the need to design and validate a specific set of diagnostic assays for each, no single country can be self-sufficient in the provision of testing and in an efficient external quality assessment of the provided tests. This results in exchange of patient material and testing across national borders. Transborder flow is clearly a mechanism that will fill a significant gap in the availability of tests for RD. There is a need to enable and facilitate this exchange through clearly stated, transparent, EU agreed standards

and procedures. There is a need for bridging regulatory differences among countries in confidentiality practices, reimbursement, sample transport and storage and certification of laboratories. Laboratories should be encouraged to participate in proficiency testing, with special attention to result in reporting. Provision of pre- and post-test genetic counselling should be ensured. This requires support at the appropriate level (depending on the number of tests per year) to reference laboratories. Different stakeholders (the European Commission, the Council of Europe and in particular the OECD) have put efforts in the quality assurance policy of laboratories in the past two years. There is a well established EU-wide quality framework for clinical pathology testing for rare diseases and cooperation between centres of excellence, but this is currently on a voluntary basis. Childhood cancers are increasingly being broken down into ever rarer subgroups according to their molecular biology. Some of these molecular tests are already used for risk stratification and determining treatment intensity; sometimes the clinical impact can be the difference between treatments can be as great as no further treatment versus high dose therapy with stem cell rescue. There is therefore clearly a need to ensure uniform standards and procedures in such molecular testing and to facilitate quality assurance schemes with sample exchange and the development of national reference laboratories.

EuroGentest [17] and the EMQN (European Molecular Genetics Quality Network) have had so far an important role in Europe to try to promote and harmonize quality testing and counselling in rare genetic diseases. The sustainability of the EuroGentest quality lab network should be supported by the EU. Evaluation systems of individual tests such as the ones in place in UK, in German and in France should benefit, when possible, to the whole EU through EuroGentest. The Patient Leaflets developed also by EuroGentest (and accessible through its website) are an example of general information materials (mostly about services) already available in many European languages. The EC should continue supporting these efforts and ensure the long-term sustainability of EuroGentest.

25.12 Patient Organisations

Patient organisations play an active and instrumental role in determining rare diseases research policies and projects. Due to the large number of rare diseases, there are over 1,700 patients' organisations in Europe. Many of them are organised into national alliances of rare diseases, and/or affiliated to EU disease-specific umbrella organisations, such as the European Organisation for Rare Diseases (Eurordis) [18]. Eurordis gathers organisations in 33 countries, permitting a direct dialogue between the European Commission, other stakeholders and the patient community of rare diseases. Patient organisations have proven to be invaluable partners, at the Member States and EU level, to increase the visibility of rare diseases, to gather and disseminate the information required for defining a public policy on rare diseases, to improve access to quality information on rare diseases and orphan drugs, to organise

workshops at European and national level, as well as to produce guidelines and pedagogical documents.

These specific initiatives described above (orphan drugs, codification, European Reference Networks, registries, National Plans, research on rare diseases) aims to improve the chance for patients to get appropriate care and information on rare diseases and to reverse the current situation of uncertainty and invisibility for people suffering from a rare disease. Health professionals and public health authorities have insufficient knowledge of the majority of rare diseases. This lack of knowledge underlies diagnostic error – a great source of suffering for patients and their families – and delayed care provision, which can sometimes be prejudicial. Proposals are still being developed, but are currently structured around ten specific objectives and actions in the Commission Communication and in the Council Recommendation on an action in the field of rare diseases:

1. To improve information, identification and knowledge on rare diseases
2. To improve prevention, diagnosis and care of patients with Rare Diseases
3. To develop national/regional centres of reference and establish EU reference networks
4. To help ensure equal access to all EU patients to orphan drugs and compassionate use
5. To help to develop specialised and adapted social services for rare diseases patients
6. To accelerate research and developments in the field of Rare Diseases and Orphan Drugs in order to strength at European level the limited and scattered expertise on rare diseases.
7. To empower patients with Rare Diseases at individual and collective level
8. To support implementation of National Plans for Rare Diseases
9. To develop international cooperation on rare diseases
10. To coordinate relevant policies and initiatives at EU level

25.13 Committee of Experts on Rare Diseases

The Commission Communication and the Council Recommendation will require an intensive work of implementation involving all the stakeholders. In this sense a Committee of Experts on Rare Diseases where Member States, Patient's organisations, industry, research and public health projects on rare diseases and other interested parties has been created by a Commission Decision of 30 November 2009 establishing a European Union Committee of Experts on Rare Diseases [8]. This Committee will assist the Commission in formulating and implementing the Community's activities in the field of rare diseases, and shall foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved as well as to assist the Commission in the monitoring, evaluating and disseminating the results of measures taken at Community and national level in

the field of rare diseases, contribute to the implementation of Community actions in the field, in particular by analysing the results and suggesting improvements to the measures taken and deliver opinions, recommendations or submit reports to the Commission either at the latter's request or on its own initiative.

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Chapter 26
National Plans and Strategies on Rare Diseases in Europe

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Abstract This analysis of national plans and strategies on RD in Europe shows that a few countries have already set up national plans. Existing national plans show a good consistency, but also a quite different stage of progress, depending on start date as well as on resource allocation. Several other EU countries have launched actions on RD, often with a considerable strategic effort; however, such initiatives are yet not integrated in a consistent national strategy taking into account the EC recommendations. The project EUROPLAN represents a major initiative to support the development of a shared strategy on RD at EU and Member State level; critical steps include the comparative evaluation of existing plans and actions, identification of gaps and achievements, the development of consensus indicators, as well as the integration of successful national achievements within the EU strategy.

Keywords Indicators · Public health · EUROPLAN · Orphan drugs · Advocacy

26.1 National Plans

Implementing a strategic planning approach to rare diseases (RD) is a high-level priority for countries, clearly defined in the EU Council Recommendation on action in the field of rare diseases, adopted on 9th June 2009 [3]. For the current paper, we define a national plan for rare diseases as an official strategic public health document, accepted by the government, containing specific priorities, actions, timetable for implementation and own budget. By the end of 2009, several European countries have already accepted (Bulgaria, Greece, Portugal, Spain) and even realized (France) their national plans on rare diseases (Table 26.1) [1]. Strategic planners could draw from the experience that has been accumulated so far and could save a lot of precious time and efforts in the long process leading to a success [17].

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Table 26.1 Short summary of the available national plans on rare diseases

National plan	Bulgaria	France	Greece	Portugal	Spain
Governmental approval date	27 Nov 2008	20 Nov 2004	N/A	12 Nov 2008	3 June 2009
Main priorities	9	10	6	7	7
Timetable	2009–2013	2004–2008	2008–2012	2008–2015	2010–
Budget	≈ 11.3 M €	≈ 108.5 M €	≈ 27.7 M €	N/A	N/A

France takes the lead as the first country in the world that has developed a National plan for RD. The National Rare Diseases Plan 2004–2008 as part of the 9 August 2004 Law relating to public health policy, is seen as the instrument to develop, reinforce and bring coherence to the different initiatives undertaken and ongoing in France [11]. Its aim is "to ensure equity in the access to diagnosis, to treatment and to provision of care" for people suffering from a rare disease through ten strategic priorities:

1. Increase knowledge of the epidemiology of rare diseases
2. Recognize the specificity of rare diseases
3. Develop information for patients, health professionals and the general public concerning rare diseases
4. Train professionals to better identify them
5. Organize screening and access to diagnostic tests
6. Improve access to treatment and the quality of healthcare provision for patients
7. Continue efforts in favor of orphan drugs
8. Respond to the specific needs of accompaniment of people suffering from rare diseases and develop support for patients' associations
9. Promote research and innovation on RD , notably for treatments
10. Develop national and European partnerships in the domain of RD

Each of these priorities consists of specific actions and the total budget has been estimated to 108,460,000 Euros.

Accordingly to the French National Plan, "labelled centres of reference" have been established. These centres, made up of multidisciplinary teams, have the following missions:

- to facilitate diagnosis and define a strategy of therapeutic and psychological care and of social accompaniment;
- to define and circulate care protocols, in association with the National union of national health insurance funds (*Haute Autorité de Santé* and the *Union Nationale des Caisses d'Assurance Maladie* (UNCAM);
- to coordinate research and participate in epidemiological surveillance, in association with the *Institut de Veille Sanitaire* (InVS);

- to participate in training and information initiatives for health professionals, patients and their families, in association with the *Institut National de Prévention et d'Education pour la Santé* (INPES);
- to manage and coordinate the networks of health and socio-medical care providers
- to be the main interlocutors for the ministries and patients associations.

In 2009, the French plan underwent a thorough evaluation by an independent committee [13]. The results from this evaluation will serve to analyze the benefits from implemented activities and project a new plan, expected to start in 2010 or 2011 at latest.

Bulgaria is an example for a small country with economy in transition, however with a substantial work and activities in the area of RD policy and organization done in a very short time [18, 19]. On 27th of November 2008, the Bulgarian Council of Ministers approved officially the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009–2013). Its main aim is to create an adequate institutional framework and mechanisms for the provision of timely prevention, diagnostics, optimal treatment and rehabilitation of patients with rare diseases (genetic, congenital malformation, and nonhereditary disease). The plan consists of 9 priorities:

1. Provision of epidemiological data on rare diseases in Bulgaria by the establishment of a National Register.
2. Improvement of the prevention of rare diseases with genetic origin by extension of the screening programs.
3. Improvement of the prevention and diagnostics of rare diseases with genetic origin by the introduction of new genetic tests, decentralization of laboratory activities and facilitated access to genetic counseling.
4. Integrated approach to the implementation of prevention, diagnostics, treatment, and social integration of patients with rare diseases and their families.
5. Increase of the physicians' professional qualification in the field of early diagnosis and prevention of rare diseases.
6. Research on the necessity, opportunity, and criteria for the establishment of a reference center for rare diseases on a functional principle in Bulgaria.
7. Organization of a national public awareness campaign on the problems of rare diseases and their prevention.
8. Support and collaboration with non-governmental organizations and the associations of patients with rare diseases.
9. Close collaboration with other EU member-countries working to achieve the purpose of the program and with the Rare Disease Task Force at DG SANCO, EC.

Similar to the French plan, each priority consists of several actions. The total budget of the plan is about 22.1M BGN (approximately 11.3 million euros).

The Greek National Plan on Rare Diseases contains 6 main priorities with a total budget of 27,703,834 Euros, as follows [1]:

1. Early Diagnosis
    1.1. To adopt a legislative framework for mass screening
    1.2. To improve the availability and the accessibility of diagnostic tests and genetic counselling
2. Medical Treatment
    2.1. To establish national standards and specialized centres for rare diseases
    2.2. To improve the availability of orphan medicinal products
3. Prevention
    3.1. To respond of the specific need of patients with rare diseases and their families
    3.2. To recognise and evaluate the economic costs of rare diseases
4. Research
    4.1. To create national database for rare diseases
    4.2. To promote research on rare diseases
5. Education
    5.1. To improve information and knowledge of patients and their families
    5.2. To improve the professional qualification and knowledge of medical specialists
6. Partnership and co-operation strategies
    6.1. To create national rare diseases platform and actively participate in European rare diseases activities

Portugal announced its national plan on rare diseases with the general aim to define the needs of patients with RD and their families as a national health priority and improve the quality and equity of healthcare services for them. It contains 7 priorities [1]:

1. To create a national network of reference centres for RD
2. To improve the access of patients with RD to adequate healthcare
3. To improve the mechanisms of integrative management of RD
4. To respond the need of people with RD
5. To improve knowledge and domestic research on rare diseases
6. To promote innovation and accessibility to orphan drugs
7. To ensure the cooperation in the framework of the European Union and the Community of Portuguese-speaking Countries (CPLP)

The budget for the plan, which has a pilot (till 2010) and implementation phases, has not been preliminary defined.

Spain launched officially its national plan on 20 October 2009. It targets medical professionals and patients with the general aim for improvement of the health and quality of life of people with rare diseases [1]. The Spanish plan has not specified a timetable for implementation of activates and budget. It has defined 7 main priorities:

1. Information on Rare Diseases
    1.1. Information on rare diseases and available resources
    1.2. Health registers
    1.3. Coding and classification of RD
2. Prevention and Early Detection
    2.1. Prevention
    2.2. Early Detection
3. Healthcare
4. Therapies
    4.1. Orphan medicinal products, adjuvants and health products
    4.2. Advanced therapies
    4.3. Rehabilitation
5. Integrated Health and Social Care
6. Research
7. Training

All these examples of national plans, though adopted before June 2009, enlist most of the guidelines and directions of the EU Council Recommendation on action in the field of rare diseases (Table 26.2).

Table 26.2 Conformity of existing national plans on rare diseases with the EU Council Recommendation

Priorities of the Council Recommendation of on an action in the field of rare diseases		Countries with existing RD national plans				
		Bulgaria	France	Greece	Spain	Portugal
I. Plans and strategies in the field of rare diseases	(1) Establish and implement plans or strategies for rare diseases	X	X	X	X	X
II. Adequate definition, codification and inventorying of rare diseases	(2) Use a RD common definition of no more than 5 per 10,000 persons.	X	X	X	X	X

Table 26.2 (continued)

Priorities of the Council Recommendation of on an action in the field of rare diseases		Countries with existing RD national plans				
		Bulgaria	France	Greece	Spain	Portugal
	(3) Adequate coding, trace and recognition in the national healthcare and reimbursement systems		X		X	
	(4) Easily accessible and dynamic inventory of rare diseases	X	X	X	X	X
	(5) Specific disease information networks, registries and databases	X	X	X	X	X
III. Research on rare diseases	(6) Identify ongoing research and research resources in the national and Community frameworks	X	X	X	X	X
	(7) Needs and priorities for basic, clinical, translational and social research and promote interdisciplinary cooperative approaches	X	X	X	X	X
	(8) Foster the participation of national researchers in research projects	X	X	X	X	X
	(9) Fostering research in the field of rare diseases.	X	X	X	X	X
	(10) Research cooperation with third countries		X		X	X
IV. Centres of expertise and European reference networks for rare diseases	(11) Identify appropriate centres of expertise	X	X	X	X	X

Table 26.2 (continued)

Priorities of the Council Recommendation of on an action in the field of rare diseases		Countries with existing RD national plans				
		Bulgaria	France	Greece	Spain	Portugal
	(12) Participation of centres of expertise in European reference networks	X	X	X	X	X
	(13) Organise healthcare pathways for patients	X	X	X	X	X
	(14) Use of information and communication technologies	X	X	X	X	
	(15) Diffusion and mobility of expertise and knowledge		X		X	
	(16) Centres of expertise, based on a multidisciplinary approach to care	X	X	X	X	
V. Gathering the expertise on rare diseases at European level	(17) Gather national expertise and support the pooling of that expertise with EU	X	X	X	X	X
VI. Empowerment of patient organisations	(18) Consult patients and facilitate access to updated information	X	X	X	X	X
	(19) Promote the activities performed by patient organisations	X	X	X	X	X
VII. Sustainability	(20) Ensure the long-term sustainability of infrastructures	X	X	X		

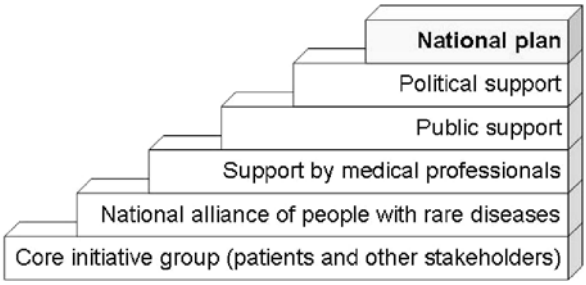

Fig. 26.1 Roadmap to national plans development and approval

The benefits of having a national plan on rare diseases are enormous. On one hand, the document officially recognizes and acknowledges rare diseases as a public health priority [12]. On the other, it expresses the long term governmental intentions for specific measures regarding people with rare diseases and other stakeholders in the country. Summarizing the experience of countries with national plans on rare diseases, important conclusions and recommendations can be derived. The roadmap to a successful national plan development starts by a small core group, usually consisted of patients and medical professionals, directly occupied with their treatment and follow up (Fig. 26.1). The next step is to attract and join the efforts with bigger patient organizations (e.g. neuromuscular disorders, cystic fibrosis, lysosomal storage diseases, thalassemia, hemophilia etc.) which are more experienced in public awareness and political lobbying [10]. The active participation of medial professionals is essential [17]. Specialist in clinical genetics, hematology, neurology and public health tend to be most active. The next step is to raise public awareness and sympathy on rare disease issues by all possible means – newspaper articles, press-conferences, TV interviews, case stories etc. This support is essential prerequisite for accumulating enough political support, necessary for governmental action and budget allocation. Putting accent on EU recommendations, international comparison and especially competition with neighboring countries increases the chances for successful political lobbying. This stepwise bottom-up model is proved to be effective in most of the countries with national plans in Europe – France, Bulgaria and Spain. National plans of Portugal and Greece have been developed top-down, e.g. mainly as a governmental initiative.

26.2 Other Initiatives in Countries Where No National Plans Have Been Adopted

Besides Bulgaria, France, Greece, Portugal and Spain, where a number of measures have been adopted by means of national plans, a few other Countries support rare disease patients with a range of measures. A full description of the different arrangements in each European Country is out of the scope of this short chapter. Therefore a selection of information on well developed actions or on expected developments

is presented, as resulting from a survey carried out by the EUROPLAN project (see the paragraph on this project).

26.2.1 Belgium

No mandatory plans/strategies have been established so far. However, a comprehensive national plan regarding RD and OD which will target all priority areas is in preparation. Moreover, a number of mandatory measures and actions, have been developed, including: a national infrastructure, laws and procedure to regulate orphan drug national registration and reimbursement; nationally recognized centres for subsets of RD that work under conventions with the National Reimbursement Institute; some national registries, such as the cystic fibrosis registry. Many elements of the plan for cancer and the plan for chronic diseases may be of benefit for a subset of RD patients. There is also a Special Solidarity Fund that can be used for patients for which costs are not covered by the health system. Non-binding initiatives are also developed in hospitals genetic centres aimed to help RD patients and their families.

26.2.2 Czech Republic

A Czech National Strategy for Rare Diseases is under preparation by the Ministry of Health and will comprise all the aspects indicated in the EU Recommendation. Planned measures are being prepared at a horizontal level, but with a specific focus on establishment of specific measures for the more common rare diseases where Centre based approach is more economical (e.g cystic fibrosis, group of metabolic disorders etc). Thus far, the health care system covers all treatments related to rare diseases, preferably at specialised centres. There are specialised centres where treatment with orphan drugs is reimbursed.

26.2.3 Denmark

The health legislation is not specially aimed at RD, but is a general legislation aimed at ensuring the most efficient and highest quality hospital care. However, the Danish National Board of Health published a special report on RD in 2001 with recommendations on RD in general and on 14 specific RD to be cared for at two highly specialised centres for RD. In June 2009 public regional hospital departments and private hospitals of the 36 medical specialities have applied to receive the designation as specialized regional centres or highly specialized national centres for different rare diseases. This designation lasts for 3 years. Finally, some clinical guidelines have also been prepared for some rare diseases.

26.2.4 Germany

Federal Ministry of Health establishes the legal framework conditions, by means of the Social Code V, mainly in the form of federal laws. In this process, it regulates primarily the reimbursement of costs, the provision of services, as well as quality assurance in the health care system. The Federal Laender, or more specifically their individual ministries, are responsible for hospital planning. There have been several modifications in the last years concerning the health care and reimbursement mechanisms in special competence centres for patients with RDs (Social Code V §116b, §120, §119, §87). The Federal Ministry of Health just published the final report of the study entitled "Measures to improve the health situation of persons with rare diseases in Germany", which looks into the situation of persons suffering from rare diseases in the German health care system; the identification of areas for action to improve the situation of affected persons; and the development of solution scenarios while taking into account developments at EU level. The Federal Ministry of Health is now going to promote an action with the participation of all institutional actors and other key organizations to discuss and implement the relevant measures following the results of the mentioned Report.

26.2.5 Italy

Although there is no specific national plan on RDs, Italy has adopted a number of measures for the care of rare diseases [15, 16]. The three year National Health Plans, which are intended as directions for actions to be followed in the entire country, have been indicating since 1998 that rare diseases are among the priorities for the health care system. The framework of current measures related to rare diseases and the associated disabilities is the following. A national network of Centres has been established in 2001 for rare disease prevention, diagnosis, treatment and surveillance, which is instrumental also for the application of cost exemptions for related health service provisions. With reference to surveillance, it has included the provision for the establishment of a national registry of rare diseases at the National Centre for Rare Diseases of the National Institute for Health (Istituto Superiore di Sanità, ISS), connected to regional registries and to qualified Centres designated by the Regional authorities. The National Centre for Rare Diseases has been established, at the ISS, with the mission of carrying out research and public health actiovities finalized to prevention, treatment (orphan drugs and others) and surveillance of RDs (www.iss.it/cnmr). A list of rare diseases has also been established, including 284 single and 47 groups of rare diseases, to facilitate referral of suspected patients to the appropriate diagnostic Centre, and to waive costs for diagnostic tests when a rare disease is suspected. The list of rare diseases can be updated based on the progression of scientific and technological knowledge, the epidemiology of diseases and diagnostic and therapeutic pathways.

A number of general provisions to facilitate access to drugs in special situations have been issued, which are of particular advantage for RD patients. These

provisions allow, altogether, at no costs for the patient but under different conditions: the use of drugs marketed abroad; the use of drugs not authorized but subject to clinical trial; and the off-label use of drugs; and the use of a drug, which is not authorized but is subject to phase II or III clinical trials. Moreover, to support costs of treatment of patients with rare diseases, a fund has been established financed with a small share of the budget allocated by the pharma industry to advertise drugs. Patients suffering from disabilities associated with RDs are eligible for assistance, including not only compensation for reduced working ability, but also integration at work, on the basis of the current general regulations for civil inability. Indeed, the applicable regulations encompass also the permanent functional impairments resulting from physical and/or psychical and sensory illnesses. For those patients younger than 18 and older than 65, it also covers permanent difficulties related to performing tasks and activities typical of their age. Research on rare diseases and their therapies have been funded with specific research programmes by the Ministry of Health, the National Institute for Health and the Italian Drug Agency. Finally, the decision-making process at national level regarding measures for rare diseases takes into account the patients' opinion, although it is not binding [20].

26.2.6 The Netherlands

Since April 2001 the Minister of Health, Welfare and Sport (VWS) has appointed the Steering Committee Orphan Drugs (http://www.weesgeneesmiddelen.nl/?lang_id=2) in The Netherlands. The committee is an independent organisation and consists of eleven members and two observers. The members are representatives of umbrella organisations for patients and for pharmaceutical companies, physicians and a hospital pharmacist, scientists, a representative of the Dutch medicine evaluation board and a representative of the Dutch health insurances board and health insurance companies. The steering committee has the mission to encourage the development of orphan drugs and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases. The Ministry of VWS has made available an annual budget of maximal Euro 450,000 for the committee. The secretariat is situated at the research organisation ZonMw in The Hague.

The committee organised an invitational conference in November 2001 to discuss with fifty dedicated participants the main problems concerning development and orphan drugs and care for patients with a rare disease. Subsequently, the committee finalised its plans and introduced them at a symposium in January 2002. New updated action plans were written in 2004 and 2008.

The plans of the steering committee can be summarised in four themes: (1) the committee *collects information* on rare diseases and orphan drugs in The Netherlands and functions as an information centre, also on the internet; (2) the committee will develop a *new research programme on rare diseases* and will give more publicity to the European funding programmes; (3) The committee will investigate the existing models for diagnosis and treatment of rare diseases in The Netherlands

and abroad and will encourage those care models that function well; (4) furthermore, the committee wants to stimulate registration of patients with a rare disease.

More recent activities of the committee include:

(a) to stimulate and follow-up the preliminary phases for the development of a national plan on RD;
(b) to identifiy expertise centres in the country;
(c) policy making activities about reimbursement of orphan drugs;
(d) to create awareness in the general population (articles, media);
(e) coordination of several rare diseases projects and workpackages (national and international, like E-RARE and EUROPLAN). In fact, the Steering Committee Orphan Drugs encourages international collaboration.

26.3 The EU Commitment on Rare Diseases

Cooperation among Member States and support to their action in order to ensure a high level of health protection has become matter of Community-level action after the Treaty of the European Union [9], signed in Maastricht on 7 February 1992. A clearer and wider Community mandate in the area of public health was established with the Amsterdam Treaty (1997) [8]. Therefore, the focus on rare diseases is relatively new in the framework of the European Union competence, as distinguished from the national competences.

Since then, the European Commission has developed a number of actions in the area of rare diseases [2, 3, 7]. The first approach was fostering the cooperation among institutions and organizations in different Member States by funding projects for public health action on rare diseases. Three generations of Community action programmes [4–6], starting since 1999 have prioritised (a) improving knowledge and facilitating access to information about these diseases; (b) networks, which centralise information on as many rare diseases as possible to improve information, monitoring and surveillance; (c) the exchange of information via existing European information networks on rare diseases, and the development of strategies and mechanisms for information exchange and co-ordination at EU level to encourage continuity of work and trans-national co-operation. Moreover, as a result of the open method of coordination assisted by the European Commission in the area of public health, the health authorities of the Member States, within the activities of the working group “Cross-border healthcare purchasing and provision” of the High Level Group on Health Services and Medical Care, decided to prioritise the establishment of European networks of centres of expertise for the health care of rare diseases [14].

Recently, the European Commission prepared an acceleration and quality change to the Community action with the presentation to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions its Communication on “Rare Diseases: Europe’s Challenges”

(COMM(2008) 679) [2]. This Communication sets out a Community strategy with three main aims: improving recognition and visibility of rare diseases; promoting the implementation of national plans for rare diseases in the Member States; and strengthening European cooperation for rare diseases diagnosis, care and research.

Following the Commission Communication, the EU Council adopted, on 9 June 2009, the Council Recommendation for an Action in the Field of Rare Diseases [3], which foresees the adoption of national plans and strategies for rare diseases within 2013, and establishes the lines for the cooperation and coordination among Member States to better utilize national resources and expertise in this field and reduce inequalities in the accessibility to high quality care. In this way, the Recommendation provides an integrated ground which exploits better the outcomes of the Framework Programmes for Research and Technological Development and the specific regulatory framework already in place for "orphan" designated medical products.

In more detail, the EU Council Recommendation [3], besides indicating the establishment of national plans or strategies as a means to improve the coordination and coherence of national, regional and local initiatives addressing rare diseases and cooperation between research centres, urges the EU Member States for: the adoption of an appropriate classification and coding, shared among all EU Member States, in order to improve the recognition of rare diseases in the national health system; the participation of qualified Centres of expertise in European Reference Networks to facilitate the exchange of information and the movement of experts among Member States; establishment of financial tools and governance systems for the inventorying and coordination of projects and resources dedicated to RD research at national, Community and international levels; facilitate Community initiatives for the definition and sharing of best practices for diagnosis and care, adequate education and training for health professionals, and population screening, as well as sharing national reports for the assessment of orphan drug added value. The involvement of patient representatives in the development of policies and in activities targeted to patient empowerment is also promoted by the Recommendation.

The European Commission established an EU Committee of Experts on Rare Diseases, where representatives of the health authorities of all the EU Member States, patients associations, the industry, and other experts will participate. It is expected that the Committee will give further moment to the implementation of the EU Council Recommendation, providing a permanent seat for regular discussion and coordination of actions among Member States.

For more details, see the EU Commission web site: http://ec.europa.eu/health/ph_threats/non_com/rare_diseases_en.htm.

26.4 The EUROPLAN Project

Despite the progress made over the last years in the field of rare disease (RD) a comprehensive and evidence-based approach is still missing in many EU MS leading to an incomplete and often inadequate framework to address rare diseases.

In this contest in 2008 the European Commission (DG SANCO) funded the project entitled European Project for Rare Diseases National Plans Development (EUROPLAN) which is coordinated by the National Centre for Rare Diseases of the National Institute for Health (Istituto Superiore di Sanità, Roma, Italy). Following an inclusive process, up to now, EUROPLAN involves 30 partners, including all 27 EU countries, USA, Turkey and EURORDIS (www.europlanproject.eu).

The general aim of EUROPLAN is to contribute to ensure access to prevention, diagnosis, treatment and care for patients with RD through the production and dissemination of data and recommendations for developing plans or strategies for RD. This is important because at the present stage still a comprehensive, strategic and evidence-based approach is missing in several EU MS leading to an incomplete and therefore often inadequate framework to address RD.

EUROPLAN aims at developing:

(a) recommendations on how to define a national/regional plan or a strategy for RD; they will include either examples of actions already taken by countries to address RD as well as technical information on the different steps to develop a plan/strategy on RD.
Fifteen national consultations organized by EURORDIS will be held in 15 MS during 2010 to assess the transferability of such recommendations to different settings and countries. The final version of the document will be launched in an EU workshop which will be held in Rome (Italy) in spring 2011 and after widely disseminated.
(b) a list of indicators for the monitoring and implementation of national/regional plans or strategies.

Namely, the specific aims of EUROPLAN are:

- Describe EU Member States initiatives on RD
- Elaborate recommendations for the development of RD strategic plan
- Identify indicators to monitor and implement national/regional plans or strategies
- Discuss the recommendations and present the EU Commission Communication on Rare Diseases during Fifteen national consultations organized by EURORDIS will be held in 15 MS during 2010

The whole project aims at providing information on the different steps to develop a plan or strategy for RD in order to create a culture of planning for RD. The recommendations support the integration of public health strategies on RD throughout Europe, contributing to reducing inequalities in healthcare services for EU citizens with RD and their families.

Most important, EUROPLAN aims at identifying and describing examples of actions taken by MS in order to share information, models and data on effective strategies to address RD. The recommendations include also a critical analysis of the functioning of the current activities in key areas of intervention for RD (institutional framework; provision of care; surveillance system; support to patients

organisation); thus, EUROPLAN recommendations will serve as a guidance manual to support EU MS in the development of national plans for RD. In this context, the recommendations will also serve as an advocacy instrument at policy level.

EUROPLAN aims at capitalising the existing efforts and experiences by

(a) actively searching the collaboration and link with current and new EU projects in the field of public health policy on RD, as well as
(b) avoiding duplication of activities and strengthening possible synergies among RD community.

In this context, active collaboration with and involvement of the European structures dealing with RD is a EUROPLAN priority, which will be ensured by the participation of the coordinator to the new EC Committee on RD. In addition to the link with EU projects, it is worth mentioning the collaboration with the Office for RD (NIH-USA), that will enrich the discussion by providing additional insights from a well experienced Country.

In addition, if the EU Commission Communication on RD will ensure that common policy guidelines are shared everywhere in Europe, EUROPLAN will contribute to the development of national plans or strategies for RD within EU MS linking national efforts with a common strategy at European level.

26.5 Conclusions

This analysis of national plans and strategies on RD in Europe shows that a few countries have already set up national plans. A bottom-up development, starting from core medical groups with strong interaction with patient organizations, is an effective strategy to grow a national plan on RD; alternatively, national plans may also start as governmental initiatives. Comparative assessment of the objectives of existing national plans show a good consistency as well as only minor discrepancies with the EU Council recommendation on RD. On the other hand, the plans are at a quite different stage of progress, depending on start date, but also on financial, organizational as well as human resources that are devoted by each Member State. Last but not least, consensus indicators have to be defined in order to monitor the implementation of plans.

Several EU countries that do not have a national plan, have nevertheless established national initiatives on RD, often with a considerable strategic effort. Such initiatives, include targeted policies, establishment of national centres, networking, national and international research programmes, as well as policies towards citizens with RD. Some initiatives have a major bearing at national level and may represent interesting models; on the other hand, there are obvious limitations, due to the lack of integration in a consistent national strategy taking into account the EC recommendations. Therefore, a two-way interaction is to be foreseen: more countries should devote efforts and resources to develop consistent national strategies,

whereas successful outcomes of pilot actions should be capitalized to target and further implement strategies at national and EU level.

The project EUROPLAN represents a major initiative to support the development of a consistent and effective strategy on RD; critical steps include the comparative evaluation of existing plans and actions, identification of gaps and achievements as well as the development of consensus indicators.

Thus, EUROPLAN will promote the integration of diverse efforts on RD by the member States within the EU strategy.

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Chapter 27
Ethical Aspects on Rare Diseases

Luis A. Barrera and Gilberto Cely Galindo

Abstract In this chapter we discuss several of the most relevant subjects related to ethics on Rare Diseases. Some general aspects are discussed such as the socio-psychological problems that confront the patients and their families that finally lead to marginalization and exclusion of patients affected by these diseases from the health programs, even in wealthy countries. Then we address problems related to diagnosis and some ethical aspects of newborn screening, prenatal, pre-implantation diagnosis and reference centers, as well as some conditions that should be met by the persons and institutions performing such tasks. Alternatives of solutions for the most critical situations are proposed. Subsequently the orphan drugs subject is discussed not only from the availability point of view, prizes, industrial practices, and purchasing power in developed and developing societies. The research related to rare disease in children and other especially vulnerable conditions, the need for informed consent, review boards or ethics comities, confidentiality of the information, biobanks and pharmacogenetics are discussed.

Keywords Rare diseases · Orphan drugs · Bioethics · Research · Diagnosis

27.1 Ethical Aspects on Rare Diseases

Research on the human genome and the resulting applications open up vast prospects for progress in improving the health of individuals and of humankind as a whole, but emphasizing that such research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics [32].

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27.2 Bioethics on Orphan Diseases

27.2.1 Introduction

The orphan diseases comprise the rare diseases and the neglected diseases. The rare diseases by definition are those of which the prevalence is 1/2,000 or less. They are estimated as 7,000 to 8,000 of which the majority are of genetic origin. The other may be transmissible, parasitic etc. The so-called RD is characterized for being severe, chronic, progressive, and therefore they constitute a threat to survival. The RD cause severe disabilities in the bio- psycho- spiritual- social development for the affected individual. According to EURORDIS [34] "Rare diseases patients face a lack of access to correct diagnosis, lack of information and public awareness, lack of scientific knowledge and expertise, lack of research, lack of therapeutic development, lack of appropriate healthcare, high cost for most of few existing drugs, inequalities in access to treatment and care, and lack of specialised social services".

Neglected diseases are around 20, and among these are: chagas, filiariasis, toxoplasmosis, dengue, oncocercosis, and leishmaniasis. The neglected diseases usually occur in societies with poor sanitation systems and very low capacity to purchase medicines.

For the rare diseases there is good knowledge on only about 1,200 of these. It is especially noteworthy that in many of the international congresses and in the international conferences on rare diseases, one of the concerns is the poor knowledge regarding these diseases among general practitioners and pediatricians and other health professionals involved in their diagnosis and treatment.

Diagnosing is very slow and in some cases it may take close to twenty years. It is estimated that on average it takes between 4 and 6 years in the developed countries. In the underdeveloped it takes longer and most of these diseases have not been diagnosed.

The lack of diagnosis causes the patients and their family, among others, the following problems.

Guiltcomplex. One of the usual occurrences with a non-diagnosed genetic disease is the husband blaming the wife for the transmission of the disease and vice versa. It is noteworthy that in the cases of recessive disease in which both parents are carriers, the diagnosis many times serves to help to rebuild the marital life.

The other characteristic of the non- diagnosed disease is the feeling of self- guilt. Often when a couple comes in search of diagnosis for a son, the mother and father separately try to talk privately with the health professional to ask whether the disease of the child is due to the consumption of alcohol, venereal disease that one of the parents has had sometime during his or her life, intake of medicines or some other completely unrelated causes. In many cases the diagnosis as a recessive disease is a relief for both parents, who have been thinking that he or she is the only one to blame for the disease of the child, without any reason.

Given the fact that most of the rare diseases are invalidating, in a couple that has a son affected by a rare disease, only one member of the family can work, because the other one has to stay at home to assist the child in his or her needs and all

the daily demands originated by his or her health condition. Therefore, the income is usually lower than for a common couple, which is an additional problem to the high expenses brought about by the medical care of the patient. It is therefore not uncommon that one of the parents, usually the father, abandons the home, leaving the partner with the whole responsibility for the disabled child.

For the invalidating disease that is life-threatening, which is the case in many of the severe diseases, the parents do no delegate the care of their child to a third person, like friends, babysitters, or even health care personnel, because of the fear that those persons would not take appropriate care of the child in a crisis. Many of these parents usually do not have any social life, they isolate themselves from their friends or in some other cases their friends segregate them, because the parents usually prefer to stay home and take care of the disabled son or daughter, instead of socializing.

In the case of genetic diseases or non-diagnosed diseases, the siblings of the patients may have a hard time trying to get married, because of the fear of the suitors of having children with the disease like the one that runs in the family. In many cases the family gets socially discriminated for fear that they transmit a disease that is not transmissible, such as some skin diseases that may give the impression of being contagious. Likewise the physical appearance of patients with genetic diseases may produce discomfort, pity or other feelings that many people prefer to avoid All of this points towards the necessity to establish the diagnosis, the type of inheritance, the risks and the opportunities for these patients and their social inclusion.

Rare and neglected diseases are orphans in the sense that the industry has no interest in the production and marketing of appropriate drugs, because for the rare diseases there is not enough number of patients, even worldwide, to make the manufacturing and marketing attractive. Regarding the neglected diseases the frequency may be high in some countries, but are diseases associated to poverty, and the affected individuals usually have a very low capacity to buy medicines.

The rare diseases are excluded from the health systems, because these are organized to take care of the most prevalent conditions, disregarding the fact that by themselves the rare diseases are not frequent, but together they affect between 6 to 8% of the general population, and therefore should be seen as a public health problem. Lack of knowledge about them is one of the reasons that they are considered as a non-priority by the governments in underdeveloped countries faced with meager resources to attend the human health necessities of their fellow citizens. At the same time, the private philanthropic institutions dedicated to provide social services for these patients and their families are very few, and the pharmaceutical industry in general is not interested in research and development of new drugs for these diseases.

Animal species in which the nervous system is highly developed have built a moral sensibility in favor of the most vulnerable members of their species. This is the starting point for the social construction of single and collective moral values to watch over and help those unable to overcome their limitations by themselves. Therefore the health protection of people with orphan and rare diseases in any country is an ethical imperative.

The health professionals that commit themselves to treat or study the individuals affected by rare and orphan diseases, and their families, are confronted with unavoidable ethical commitments, challenges and responsibilities that go beyond the sole somatic aspects and enter into the psychosocial jurisdiction of the person. This forces them to take into account and give due respect to the moral, spiritual and religious values of the patients and their relatives. Their actions are ruled by national and international regulation and ethical canons, such as CIOMS 2002 that articulate the research in human subjects with the psychological aspects related to medical basic sciences [6]. The ethics committees must take care that all the actions related to research screening programs, biobanks, and all aspects associated to the diagnosis of rare diseases go even beyond the best legislation to protect and help these people who may be classified among the most vulnerable members of the societies.

Even in rich countries these patients and their families have been ignored by the health systems, but as any other citizens they have the right to health coverage, diagnosis, treatment and social inclusion. There is then a moral and ethical obligation to provide solutions to the problems of these patients and their families [12].

27.2.2 Diagnosis

As has already being mentioned, the first big problem in the diagnosis of rare diseases is the lack of knowledge among health professionals with respect to such diseases. There is no excuse not to teach about these diseases in the health sciences schools. The clinical health professionals should be prepared to participate in the diagnosis and treatment of the common diseases as well as the rare diseases, or at least to have enough knowledge to give emergency care in the case of physicians. Not preparing the physicians, and other health specialists like nutritionists and laboratory personal at least for first tier diagnosis and management of these diseases, is the main reason for sub-diagnosis, non -justified complications, and most of the problems related to rare diseases. The lack of interest by many governments and legislators in these diseases derives from the lack of pressure from the scientific and medical societies who should represent the needs and interests of the patients. So, there is an ethical obligation of the health educators and professionals to learn and teach about rare diseases.

In many of the rare diseases the diagnosis needs special tests not commonly available. These may be genetic tests, biochemical tests, or molecular biology tests. Usually one test should be confirmed with another more exact one, until achieving absolute confidence that the diagnosis is correct, so as not to give wrong treatment that may harm the patient or deprive him of a correct diagnosis or treatment. Hence, the health systems have the obligation to make the diagnostic tests available for both: common and uncommon diseases, to the best of their abilities. It is clear than in some situations health systems in developing countries do not have the means to provide the diagnostic procedures and coverage available in advanced countries, but this does not excuse them from not having special programs for rare diseases, adequate and proportional to their resources. In this respect, it is appropriate to

remind that the best laboratory cannot replace the good clinical judgment of a doctor. It is also important to remember that people affected by rare diseases are among the most vulnerable members of the population, therefore there is a moral obligation to establish programs to give them support, relief and help [12, 23].

27.2.3 Genetic Screening

Genetic screening may be used to test embryos, fetus, newborns, in adults to detect carriers in selected families or groups, in populations for public health reasons, in employees for economical interests of the companies for which they work, by the government for forensic national safety, or eugenic purposes conflicting with ethics. Therefore genetic screenings have enormous beneficial aspects and potential risks [25, 26].

27.3 Newborn and Selected Screening

The advantages of a genetic screening are: It gives the possibility of a better outcome with an early treatment. It avoids unnecessary additional investigations. With some reservations it may give a good idea of the prognosis. It allows diagnosis to be used in coming pregnancies. It makes it possible to give genetic counseling, identification of affected siblings or other family members; it allows prenatal diagnosis in affected pregnancies and carrier detection.

A newborn screening program for a disease is recommended when the following conditions are met:

The disease constitutes an important health problem and a reliable diagnosis test should be used; there must be a favorable cost/ benefit ratio for the program; there should be a more precise test to confirm the diagnosis; there should be an effective treatment or at least a considerable improvement in the quality of life. Likewise, there should be a well-organized program for diagnosis, treatment and an interdisciplinary team to provide genetic counseling to the patient and the family. It is necessary to provide education to make an appropriate use of the sexual and reproductive rights and options. There should be a non-symptomatic period of the disease that may be identified by the tests. A policy to decide who should be considered as a patient must exist [26, 27].

Beyond the benefits for the individuals, a screening program may be useful for the following reasons.

Newborn screening gives the possibility of genetic diseases prevention, gives the possibility to establish program for treatment, or the improvement of the quality of life in diseases for which there is not an effective cure.

Screening helps to understand the clinical facts including diagnoses of the disease and possible available treatments, if any. In the genetic diseases it is useful also to know the mode of inheritance and the risk of recurrence in the relatives. It contributes to understand the available options to face the risk of recurrence. It helps to

make a responsible decision to deal with the risks, the family projects, the ethical and religious values and how to proceed according to all those aspects that face the individuals and the family, as a group.

Until a few years ago, neonatal screening was performed for less than 10 diseases. Today it is performed for close to 40 diseases in most states in the USA and in many countries of Europe, and *now* also in some Latin American countries. Commercial companies are working hard to extend these programs everywhere. Without recognizing the importance they may bring for diagnosis of rare diseases a word of caution is important in order to avoid unnecessary or ineffective programs. Emphasis should be made that in no case a screening program is justified unless there is a well organized plan for the treatment, it is subsidized or affordable by everybody and there are well planned means to confirm and follow up the positive cases and provide counseling to the patient and the family.

With the advancement of chips capable of examining thousands of genes in the same assay and other diagnostic tests, in the near future it will be possible to screen for thousands of conditions. Some of these have effective treatments, some do not, some have very bad prognosis, some benign prognosis. For some of these the prognosis may be reasonably calculated, for some is not known, and it is not predictable in many others. It is clear that a positive test may lead to discrimination or refusal by the insurance companies, high premium for admission, exclusions from care of the preexisting conditions, and possible misuse of the information gathered by the insurances such as sharing that information with employers [13]. In any case, it is important to remind that social discrimination and exclusion are problems that people suffering rare diseases have to face in everyday life and that one of the moral society duties must be working in order to abolish these situations. Non-massive but selective tests may be used to screen for carriers of diseases more prevalent in some geographical areas or in ethnic groups in which some diseases are more frequent. For example, Tay Sach disease is more prevalent in the Ashkenazy Jewish population, sickle cell disease in malaria regions, etc [29].

In the Ashkenazy Jewish communities' premarital exams are available to find out if the members of the future couple are carriers of this recessive disease, for which a condition to transmit the disease to a child is that both parents must carry a copy of the defective gene. The chances to transmit the disease are also enhanced by inbreeding, which are quiet frequent in this and other ethnical groups. The biochemical tests for this disease are suggested by the rabbis to the future parents before making any decision about marriage. This preventive step has been adopted already for a few other severe diseases, and perhaps in the future it will be extended to several conditions in selected populations.

A question frequently asked is: "should genetic tests be accepted as condition for adoption?" In principle, adoption should be made in the interest of the child and not of the adopters. However, there are growing pressures for genetic tests before adoption. In practice this has been seen as a discrimination against the most vulnerable such as the people affected by rare diseases. But on the other hand one may pose the question: "should adopters be forced to adopt a handicapped child if they do not want or are not capable of ensuring a good life for the adoptee".

One of the risks associated with massive screening is the possibility that the data may be used for discrimination of the affected individuals for reasons associated with the nature of the disease, ethnicity, employment, political reasons and eugenics. Therefore a screening program must guarantee the confidentiality and privacy of the data and must give full guarantee that the samples would not be used without due authorization from the donor or the mentor.

In many cases, to help in the diagnosis of a family or other reasons, tests are performed on persons that would not consent to be tested otherwise. As such it is important to emphasize that in those cases the person has the right to refuse to know the outcome of the tests [13, 23, 30].

A very comprehensive document about the requisites for the establishment of newborn screening program was published by the Instituto de Salud Carlos III of Spain [2].

27.3.1 Prenatal Diagnoses

The prenatal tests may be divided into physical such as ultrasound, X-rays, that can be performed in uterus. They can be used to see gross malformations. They do have a certain margin of uncertainty and error and therefore they should be complemented with other tests such as alpha-fetoprotein, ACTH, HCG, for the assay of Down syndrome in uterus. However, the certainty in the best of the cases only reach close to 98%, and there is between 1 and 2% of death risk of death due to amniocentesis and 1–2% of risk of false positives and therefore of abortion. These figures of risk of death and abortion have been used as arguments against the prenatal testing.

The prenatal diagnosis has been seriously questioned on the grounds that it leads to abortion depriving the fetus of the right to be born. On the other hand the advocates of prenatal diagnosis argue that since most of the prenatal tests turn out to be normal, the procedure helps to avoid abortions driven by the fear of another severely affected child. Moreover there are many diseases for which there is effective treatment that started shortly after birth may help the individual to have a very good outcome. In any case, one of the ways counselor may help the family to make a well-informed decision is to put the parents in contact with a family who have successfully handled the disease, to exchange concerns, experiences and ways of handling the situations derived from the child's disease. The prenatal tests can be performed in chorionic villus in amniotic fluids or in cultured amniocytes. The chorionic assay has the advantage that in case of being found positive, the pregnancy may be interrupted with minimum risk for the mother. The possibility of abortion in experienced hands could be around 1%. There are few reports of amniotic brides associated to chorionic villous procedures, leading to interruption of development of limbs and legs. The use of cultured fibroblast may be more reliable and in some cases the amniotic fluid can be used without need of culture, shortening the procedures in about two weeks, but in those two cases in the eventuality of interruption of pregnancy is more risky for the mother than in chorionic villous. All this information should be given in detail to the parents early enough to make a rational decision

about the type of test they are going to ask for. These exams are not included in the insurance coverage in most developing countries and the question to be asked is if it is fair for the poor people not to have the option that rich people have [18].

Another aspect of prenatal diagnosis is that in many cases the false positive rates are high. However, there are ways to reduce the rate using the enzyme assay together with diagnostic images, magnetic resonance procedures, DNA tests, but in most cases we are not going to get 100% confidence, due to the probability of error that is inherent to any type of test [29].

On the other hand there have been some cases in which people born with some severe diseases are suing their parents or the physicians for not having performed the prenatal diagnosis and for letting them be born. The responsibility of the people performing prenatal diagnosing is extremely serious; therefore it should be made only by very specialized people with profound and strict sense of ethics and legal values.

27.3.2 Preimplantation Diagnosis

With the advance of molecular biology techniques, it is now possible to make diagnosis of diseases such as hemophilia and Tay Sachs and other severe diseases in one or more cells derived from an embryo created by in vitro fertilization (IVF), before pregnancy, to avoid implantation of embryos carrying a genetic defect.

With regard to preimplantation diagnosis there is some opposition on the grounds that the affected embryos would be disposed of and therefore for the believers that life commences with conception, any procedure aimed at destroying an embryo constitutes a killing of a human being. However legislation in many countries allows those procedures The decision has to be left to the parents after unbiased and professional counseling from the experts in reproduction. It is advisable that the preimplatations diagnosis should be restricted to serious diseases and it should not be used for sex discrimination. In no case preimplantation genetic diagnosis should be extended to include behavioural traits in the normal range, such as intelligence, sexual orientation and personality traits [21, 25, 30].

27.3.3 Reference Centers

The diagnosis of rare diseases is difficult, of very high responsibility and entails very specialized centers where there is a multidisciplinary and integral approach to diagnosis and treatment. But before that, there is a great need of well-trained general practitioners, pediatrician, neonatologists and child neurologists ready to refer the patients to such centers and to work as a team with specialists from other disciplines. A team requires, beside the physicians already mentioned, genetic counselors, nutritionists, biochemists, geneticists and social workers, very well trained and with enough laboratory support to give real solution to the parents.

Special consideration should be given to those diseases for which diagnosis is still not possible and which may be as high as 30–40% according to some specialists. Usually those families have gone from doctor to doctor and consider a specialized

center as the last resource and the hope to solve a complicated situation they have lived with for months or even many years. In those cases the frustration of not reaching a diagnosis may worsen an already complicated situation. Help to the family and the patient is the only thing that would give them some relief. These centers should accordingly have psychological and family counselors specialized in rare diseases problems.

The National Institutes of Health (NIH) of USA has established the Undiagnosed Diseases program with the following aims.

"To provide answers to patients with mysterious conditions that have long eluded diagnosis

To advance medical knowledge about rare and common diseases"

They are very clear in informing that there is no guarantee that they will reach a diagnosis, but that the program will yield valuable medical information that will be used to:

Help identifying previously unrecognized rare diseases. Suggest new ways to treat and prevent common illnesses, and determine promising options for continued medical research.

Perhaps, working as a network, with common and very well established protocols and without having to move the patients to USA, some of the developing countries could participate and contribute with cases that may help to elucidate the biochemical and DNA defects in the ultra rare diseases.

¿How should the diagnosis be given in the case of a severe and incapacitating disease? The diagnoses of a serious illness should not be announced to a patient or the family without previous preparation. It is not uncommon to listen to parents saying: I almost jumped out of the doctor's office window when the diagnosis of my child was given to me, it was so unexpected and we were so unprepared.

The diagnoses should be given by a team which should includes, besides the medical doctor, the psychologist that has prepared already the family, the best friends of the family, in religious families the spiritual advisor and, in the case of genetic diseases, the genetic counselor should be also present. After the diagnosis is given the family have to make decisions that may drastically change their way of living, they sometimes have to make big expenses, move to other cities, quit working etc. and for that, the advice of their best friends who know well the family situation, their fears, emotions, and beliefs may be fundamental. Moreover, the friends, who probably are more calmed and alert, may understand better the recommendations and help the family in the process of understanding the disease and making decisions [27].

The family should be explained extensively about the disease, not leaving any room for them to get through Internet or some other means, incomplete or wrong information they do not understand, or misunderstand, and that would most certainly lead them to wrong decisions. The health professional has the ethical and moral obligation to give accurate, updated and reliable information, so that the family may make the best possible decision. In most cases the family is so confused and shocked by the diagnosis they were given that they are not capable of listening or understanding the doctor's recommendation, so they should be informed in various sessions. In the case of rare diseases in which the physicians are so poorly trained in these aspects, especially in developing countries, this aspect is very difficult to solve

locally and there may be alternatives such as sending the patient and the family to specialized centers, trained to offer those services in the appropriate way and in the right circumstances [34].

27.3.4 Orphan Drugs and Treatments for Rare Diseases

It should be stated from the beginning that any medicine used for the treatment of rare diseases should comply strictly with the requisites of efficacy, safety and ideally lowest possible cost, because it will be used in highly vulnerable and underprotected persons. Orphan drugs are different from other type of drugs since the drugs used to treat common diseases usually have large markets and big margin of profits.

Some of the reasons given by the pharmaceutical industry to justify the sometimes very expensive costs of some orphan drugs are, the large time for the development and approval of a drug which usually takes between twelve and fifteen years. High costs of research and development that may amount up to 800 million dollars for a drug according to some calculation and 80 in average according to others. Whatever the situation may be, it is well known that the pharmaceutical industry that could or should produce these medicines is one of the most profitable worldwide. According to the Fortune 2009 ranking Bayer, Glaxo Smith Kline, and Roche, among others, in 2008 had very large profits, remarkable when compared with industries of much larger capital such as the oil and automobile industry [11].

One of the ideal expectations from pharma industry is that being in the health field some of those large profits could be devoted to alleviate the cost of drugs in the poor countries. However with some remarkable exceptions, this is not the situation and in many cases the prize of some medicines in non-developed countries are higher than in USA or Europe. However, countries like Brazil or India, by using the local legislation to protect the public health, have been able to negotiate so that that the cost of VIH drugs are only 25% of that in some other part of the world. This, and other similar examples, would mean that the combined effort between governments lowering taxes, and laboratories reducing their profits, would lead to lower costs of orphan drugs [19].

How do the industry manage to have such high prices in rich and poor countries? Some of the reasons that have been mentioned in several publications are the following:

It has been made public, very intense lobbying by some sectors of pharma industry, with the governments and legislators, to the point of financing election campaigns for persons prone to legislate or take government actions to give undue privileges to the industry, often against the patients benefits. These unethical practices have been used in the past and are still being used, but fortunately are being opposed with rigorous codes of ethics for the industry and the health professionals. It is also known that some companies spend an enormous amount of money in publicity, gifts and even masked stipends. The propaganda has been calculated to be up to 30% of the expenditure of the big companies, costs that are charged to the

product prizes and in the long run are paid by the patients. Many analysts claim that if all these expenditures are curtailed, the drug prizes could be lowered significantly in favor of the patients.

A special mention should be made of the scientific events devoted to rare diseases. The scientific meetings are the spreaders of the new knowledge and are essential to the medical practice. In developing countries where rare diseases are not on the list of priorities, the support from the government or other agencies is usually absent or very meager. The main source to finance these meetings comes from the industry. The industry sponsorship in most cases is very ethical and professional and the organizers of meetings may receive support from different companies, even competitors, without compromising the scientific independence and rather showing to the participants the different options and ways of judging the efficacy of the products, so that the health professional when prescribing a medicine is in a position of advising the patient about the best option, not only from the point of view of efficacy and safety, but also prize- wise. The contribution of the industry may be seen as one of the most plausible and best way to contribute to optimal medical practice. Therefore, it should be encouraged under strict rules of ethics, preferentially agreed upon and accepted internationally. This is maybe one of the subjects to be addressed by organizations like EURORDIS and ICORD.

The number of patients with rare diseases is low worldwide; therefore, the companies in charge of the commercialization should have the capacity to work worldwide. This in some way favors the monopolies which in its turn favor the possibilities to unilaterally set the prizes. Some of the therapies are quiet expensive because the technologies involved are still expensive (gene isolation, gene synthesis, identification of the appropriate cells for cloning, design and construction of vectors, protein synthesis and purification etc) as well as the costs involved in research and development [9, 12]. Some examples of the high cost technologies are enzyme replacement therapies, gene therapy, stem cells, but there are some others medicines based on small molecules that may be less expensive [15]. However, the same companies that develop research-intensive drugs of very high production costs, in many cases develop other therapies based on small molecules that could be marketed much cheaper, however having the monopoly of the two technologies, they are able to set the prizes for both.

The prize of drugs for rare diseases may varies widely, and some are very high cost drugs. In the case of these diseases in poor countries it should be kept in mind that what may be cheap for a rich person may be a large sum for a poor person. Since the low cost drugs for rare diseases do not interest the big pharma because of the low profitability, those that not require sophisticated knowledge and equipment in their manufacture, may be encouraged to be produced under strict scientific and good manufacturing practices, by small laboratories in developing countries, that may be interested in profits not as big as the large pharmaceutical companies.

The new therapies, such as transplants, enzyme replacement therapy and stem cells, are very expensive technologies because their development demands many years of research, the cost of production is usually high, and their production needs very good expertise and risk capital. However, many of those products were

developed by scientists working in research institutes funded with public money who afterwards migrated to the private sector to open, or work for, private companies and in many cases therefore the industry cannot reasonably justify the high prices they charge on the grounds of investment on research and development [15].

27.3.5 Research

For the rare diseases, as opposed to common diseases, there are only a few thousand patients worldwide and this makes it very difficult to gather enough number of participants for the clinical trials (Phase I, II and III,) required for the approval of any drug for human use. It is therefore necessary to recruit volunteers all over the world. Some commercial companies are conducting clinical trials in third world countries, because in some cases they have larger populations and therefore more affected individuals than the developed ones. It is also possible that these trials may be less expensive, it may be easier to get the research permissions because often the regulations are not as strict as in developed countries.

The difficulties in deciding when to approve or not a research protocol is exemplified by the placebo control trials. It is obvious that in such trials the subjects receiving placebo are excluded from receiving an effective therapy and the risk that their clinical condition may worsen is increased. For these and other reasons many ethicist think that the placebo control trials are only justified and acceptable when evaluating drugs for conditions for which there are no other effective treatment, and the risks are reasonable compared to the possible benefits for the subjects and the importance of the scientific knowledge. Placebo control trials are very important for the pharma industry because they provide additional information on efficacy and safety prerequisites for the approval of the drugs by FDA or other agencies, and there are legal incentives for this type of research for scientists, physicians and the institutions where they are conducted. In any case a review board or ethical committee should examine each protocol in order to ensure that the criteria of non-exposure of the subjects to unnecessary risks and a favorable risk/benefit ratio are observed in each protocol. This demands experienced people in the review boards, willing even to share the responsibilities the researchers and the institutions face, in cases of negligence claims either by the patients, the sponsors of the research or any other parties affected by the wrong design of a protocol.

To comply with the requirements established by international protocols the patients have to be fed well and kept under strict medical surveillance for several months, therefore in the absence of health coverage for these diseases, in many cases the families and the treating physicians decide to authorize participation of children in the studies as the only possible mean to get access to medical treatment and good nutritional help.

Conflict of interests between the pharmaceutical companies, the researchers, the institutions where the research is performed and the patient advocacy groups, may be avoided making it mandatory the approval of the research protocols by review boards or ethics committees. The researchers must declare any conflict of interest in

the proposals and the review boards should examine how they may affect the participants, the outcome and the credibility of the results. In order to avoid the conflicts of interest, the following aspects should be examined by the ethic committees when studying a clinical trial or research proposal, involving human subjects [6, 33].

a. All patients must be aware of the conflicts of interest, and this information must be included in the informed consent.
b. The financial interest of the researchers and the institution conducting the research must be informed to the ethics committee.
c. All funding sources should be reviewed by the ethics committee.
d. In any publications, including oral presentation, the conflict of interest of the researchers and the institutions conducting the research, should be disclosed.

27.3.6 Informed Consent

The purpose of informed consent is that, prior to a given authorization to be part of a clinical trial, a research project or a medical intervention, the individual understands the purpose, process, risks, benefits, and alternatives and makes a free, voluntary decision to participate or not in the project or grant permission for a medical intervention. It is not exaggerated to affirm that the way it has been used in many cases seems rather to be directed to protect the researcher from complains from the patients than to protect the subjects from risks of wrongdoing during research or medical procedures. Often informed consents are written in a very technical language, the researchers do not take enough time to explain to the research subjects the characteristics of the study, or they do not have the ability or preparation to convert into plain language the contents of the protocols. The informed consent is especially difficult for illiterates or communities with very low levels of education, as is the common case in developing countries. In indigenous communities there are language problems difficult to solve and sometimes the most capable translators are children being educated in languages different to their native one. Cultural and religious beliefs have to be respected, therefore, the persons handling the consent have the ethical obligation of writing and giving the instructions for the informed consent, in such a way that is understandable and acceptable to all the persons that will give the informed consent either by signing o with finger prints. The informed consent must include the obligations of the researcher or the institution conducting the study with the patients in case of failure or wrong doing. The researcher should not ask for a signature in an informed consent, before assuring that the participants have understood the purpose of the research, the pain, discomfort inconveniences to the individual or his family, the risks, benefits and possible contributions of the research to the community or to the society in large It is also important to state the way the donor and or the community may participate in the profits derived from any commercial use of blood, tissues or organs donated after surgical procedures.

The informed consent should be short, precise, and understandable by persons with low level of education in the health sciences, and should include the way the

researchers or clinicians would proceed in case of emergencies derived from the procedures [16, 20, 33].

27.3.7 Ethics Committees

The research proposals including the informed consent should be approved by the ethics committees, in which lay people and a permanent member, or invited person expert or at least well informed about rare diseases, should participate. The duties of the committee are not only approving the research proposal or the clinical trial, but to closely follow the execution of the different activities, especially in those projects that involve risk for the participants [22, 24].

Given the need of a considerable number of patients for clinical trials, that in the case of rare diseases often may not be met without the participation of patients from different countries there is a growing interest to conduct research on rare diseases in developing countries. This has raised a justified concern, because due to the lack of legislation and adequate education in many of these countries the ethical standards to carry out those studies may be more lax than in the developed world. Ethically it would be expected that the same standards for clinical trials should be used worldwide and that ethics committees would be in charge of supervising the compliance to those requirements. Consensus among FDA, EMEA to have common requirements and to reject any clinical trials that do not meet such standards, will provide a research guide in developing countries with the highest standards according to the available technologies. However, to have competent ethical committees, knowledgeable on rare diseases is very difficult, especially in countries with a low or recent tradition on research. Therefore, there is an urgent need in developing countries to prepare people with enough knowledge on rare diseases and ethics, to participate in a competent and responsible manner in the approval and follow-up of research projects on rare diseases [14].

27.3.8 Confidentiality of Information

With the progress in medicine genetic profiling is possible even in a single drop of blood, or in a single cell. In the newborn screening programs whole blood is being collected for newborn screening and is kept for future confirmations using more advanced techniques. The possibility arises that these samples may be used for purposes different from the ones they were collected for. Internationally it has been agreed that a sample belongs to the person it was taken from, and that it may only be used for the exam(s) authorized in the informed consent. There is a growing concern that such samples may be used for non-authorized uses, or that the information derived may be used without authorization by insurance companies, employers, for legal matters by the governments or for commercial purposes, as has already happened in many cases that were denounced when the discussion about human gene patents took place worldwide a few years ago.

27.3.9 Biobanks

Biobanks are organized to collect, store, process and distribute biological materials. The biobanks play very important roles in the development and confirmation of new diagnostic techniques, medicines, or therapies, especially in the case of rare diseases, where the number of patients is very limited worldwide. The biobanks are responsible and should guarantee the integrity of the samples and the confidentiality of the information, privacy of the donors and the use only for those purposes that have been authorized by the donor. The samples must be stored in optimal conditions so as to protect them from any kind of damage. Many questions may be asked in this respect. For example, may informed consent cover non specified future uses of the samples? How may the donors or their families or the communities be rewarded in the case of discoveries with commercial applications? Is the compensation agreed before collecting the samples? ¿May the samples be used for legal purposes without the donor's authorization? [10] ¿Could individual researchers organize biobanks or should these be exclusively organized by institutions that guarantee permanence, accountability, and capacity to guarantee the correct preservation of the samples? For how long should the samples be preserved? To what extent could samples be exchanged for research projects? Should all samples have duplicates in different locations in order to protect them from natural disasters? ¿Who is going to pay for the maintenance of the samples? Since Biobanks data is stored in computers ¿How are they going to be protected from hackering? [33]

In the past many samples were sent from developing to developed countries for diagnosing purposes. They were kept and used for research, sometimes without proper authorization, and these samples are still out of their countries of origin. ¿When and how are they going to be returned to the countries from where they were taken? ¿Who would supervise the process? ¿Should they be destroyed if there are no means of proper banking in the countries they belong to? Could an international agency take care of these samples to prevent them from being lost? [1].

27.3.10 Participation of Children in Research Projects

It is often said that children are not little adults, to emphasize that they are physiologically, psychologically and metabolically different and therefore research done in adults may not be extrapolated and need to be confirmed in children. Validating or performing new research in children, especially in the case of medicines and therapies that have been developed for adults, should be encouraged and supported. However, the use of children in research raises the questions about proper justification of the projects, assessment of benefit in relation to risk, ability to consent, compensation, and the appropriate selection of subjects [17]. Under no circumstances should the sole interest of society prevail over that of the child and prevention and treatments should benefit the disabled children and never lead to their exclusion or marginalization

There should be a clear commitment of researchers to protect the rights of the children and fully understanding of the duties of the adults who are tutors or foster parents, and are representing and controlling a human being that is at disadvantage not only for being a child but because is in a vulnerable condition due to a rare disease.

As a minimal guideline the following criteria should be used to allow the enrollment of children in rare disease research [3, 5, 7, 17, 18, 28, 31].

1. Research should not be done in children if the same can be done in adults.
2. All the protocols should be carefully evaluated and approved by an ethics committee who should verify the following aspects: that the benefit outweigh the discomfort, pain and other inconveniences for the patient and the family; that the trial has been appropriately designed and, includes an adequate sample to get meaningful results; that the community participated in the design; and that there are means to communicate the research findings to the participants.
3. The researchers should guarantee that the informed consent is real, in other words the patient or the guardian fully understand, the porpoises of the study, the risks, benefits, and are free to refuse to participate or to withdraw without any penalty [8].
4. Ethnic, religious and social values of the family should be respected
5. When the research involves ethnic communities permission should be obtained from the authorities.
6. The Child decision to participate or refuse a clinical trial should be considered and attended according to his mental age. Some researchers consider that a child 7–10 years of age is capable of understanding the information when properly presented in a plain language and could therefore sign the consent.
7. If appropriate compensation is legally permitted in the country, it may be given in medicines, health services and coverage of the expense generated by the participations in the trials, always respecting the social values of the communities and taking care that it does not constitute a means of undue pressure to participate and stay in a research study or clinical trial.
8. When research involves participants from developed and underdeveloped countries, there should be no differences in the research requirements in either one of the countries regarding informed consent, safety, selection of patients, guarantees to the patients, and health attention in case of accidents or wrongdoing .
9. Every precaution should be taken in order to avoid exploitation of children
10. Provisions should be made to ensure privacy of the subjects and confidentiality of the information and of how and when information that benefit the subjects or the community may be disclosed.

27.3.11 Pharmacogenetics

A response to a given medicine is determined by factors such as environment, diet, general health of the patient and also by the genetic constitution of the

person. Pharmacogenetics is the study of the beneficial or adverse effects of a drug depending on the genetic makeup of the different individuals. This new technology oriented to provide a "completely" safe medicine for each person will require genetic profiling of the individuals, and this in its turn entails new problems regarding confidentiality, privacy and property of the genetic information. Improving the safety and efficacy of medicines would be in principle of great value, not only to individual patients, but also to society. Some of the main concerns raised by pharamacogenetics are: ¿what impact is this going to have on medicine? ¿Is this going to increase costs substantially and make orphan drugs distribution even more unfair for the people from underprivileged societies?

It is important to respond to these legitimate concerns so that the benefits of pharmacogenetics may be achieved globally and potential problems minimized. It is also important, if pharmacogenomics is going to be taken seriously, to undertake studies all over the world to investigate the response of different ethnic groups to a given drug. Local authorities may in the future ask for those studies as a prerequisite for the marketing approval of a new drug, which may foster research in developing countries with the risks and benefits already discussed somewhere in this chapter [4].

Finally, pharmacogenetic tests should not be seen as a replacement for clinical judgment. It is an aid to be incorporated into clinical decision-making.

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Part VII
Patient Organizations Role

Chapter 28
Advocacy Groups and Their Role in Rare Diseases Research

Mary Dunkle, Wayne Pines, and Peter L. Saltonstall

Abstract One of the remarkable and unique aspects of the recent history of rare disease research has been the evolving role of patient advocacy groups and the collaborative partnership that exists among such groups and the scientists who study rare diseases, as well as the government officials charged with overseeing medical research and regulatory processes. This collaboration, which in many respects developed out of necessity on all sides, is unparalleled in other areas of medical research and product development. It has played a significant role over the past 30 years in the adoption of public policies, available research funding and other factors affecting the general climate for research on rare diseases. Specific areas of interest include the adoption of the *Orphan Drug Act* in the U.S. in 1983 and subsequent similar legislation elsewhere in the world; the relationship of patient advocacy groups with government research funding and regulatory entities; the role of patient advocacy groups in seeking to "de-risk" orphan product development through initiatives such as facilitating patient registries and disease natural histories; the role of advocacy groups in ensuring that patients have access to treatments; and the increasing globalization of patient advocacy initiatives.

Keywords Rare diseases · Patient advocacy groups · Orphan products · Orphan drug act · Social security

28.1 Introduction

When Abbey Meyers, the founder of the National Organization for Rare Disorders (NORD), tells the story of how orphan drug legislation was passed by the U.S. Congress in 1983, it crystallizes the role of advocacy groups in the rare disease/orphan medical product arena.

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Abbey is fond of describing herself as “a simple housewife from Connecticut with children who have a rare genetic disorder.” As she relates it, her first contact with the Food and Drug Administration (FDA) came in the late 1970s, when her oldest son was severely impacted by a rare disease. The Meyers family tried many medications to no avail.

Abbey tells the story best: “Finally he was put on an investigational drug, and it worked. But a few months later the manufacturer decided to stop development of the compound. I did not know at the time that the decision was based solely on economic – not medical – reasoning. The drug was being developed for a prevalent disease and it was not effective for that condition. The manufacturer didn’t care that it worked for my son’s disease because the market was too small to be sufficiently profitable. In other words, it was an ‘orphan drug’.

Abbey went on: “Since I had no answers as to why we couldn’t get the drug, I phoned the FDA. Eventually I spoke to a woman in the Neuropharmacology Division and asked why development of the drug was being stopped. In particular, I wanted to know if my son was in danger; for example, did FDA find out that it caused a serious side effect such as cancer and therefore ordered the sponsor to discontinue the clinical trials?”

The woman on the phone said, “I can’t talk to you until I speak to a Freedom of Information Officer, and she promised to call me back. A few hours later she did call me back”. She said, “I spoke to the Freedom of Information Officer, and he said I cannot talk to you.”

“Needless to say, I hung up the phone in disbelief. That phone conversation, however, was the very beginning of a battle that culminated in passage of the Orphan Drug Act of 1983. I spoke with numerous rare disease support groups who felt the orphan drug dilemma needed to be solved, and that coalition evolved into NORD, dedicated to the identification, treatment, and cure of rare diseases through programs of education, advocacy, research, and services for patients and families. Ultimately the American orphan drug program became the model for an international effort to alleviate rare disease.” (http://www.rarediseases.org/news/speeches/news/speeches/wiley_lecture_0405)

28.2 The Role of Patient Advocacy Groups

No story is better than Abbey’s in understanding the role of advocacy in the rare disease community. The advocates on behalf of the rare disease community – be they consumers or patients or health care professionals or government officials – are much like Abbey: people who are committed to advancing a better scientific understanding of and better treatments for patients with rare diseases. In today’s health care environment, controlled as it is by insurance plans, there also is a deep need to assure that patients have access to the treatments they need.

Because most of the organizations that represent patients with rare diseases are small, they banded together almost three decades ago to make their collective voices heard more persuasively than they could by themselves. NORD was formed to be

the umbrella group over the organizations that represent and advocate for patients with rare diseases, and has been, since 1983, the leading and most effective advocate on behalf of rare disease issues.

Other organizations address sub-segments of the concerns of the rare disease community. For example, the Genetic Alliance deals with the evolving use of the knowledge of genetics to understand better and treat rare diseases (http://www.geneticalliance.org). The Kakkis Everylife Foundation was formed to seek to improve the process that FDA uses to review new drugs. NORD, as the umbrella group representing the patient community, works with these organizations on common goals (http://www.kakkis.org).

NORD strives to focus public attention on the need for more funding for research, for access to treatments, and for fair and reasonable insurance and reimbursement options.

Since 1987, NORD has administered Patient Assistance Programs (PAPs) for uninsured (or underinsured) patients who are financially eligible. NORD provides drugs at no charge through its Medication Assistance Programs. Individuals who are uninsured and not eligible for any state or federal assistance, and insured people with a low annual prescription cap or no prescription drug plan, are eligible for assistance.

NORD is committed to offering financial support to patients with certain medical conditions who have prescription drug coverage but still cannot afford the out-of-pocket costs associated with their plans. NORD currently operates premium and co-payment funds for certain oncology, neurological, autoimmune, metabolic, and blood disorders. NORD's programs have set the standards for fairness, equity, and unbiased eligibility, and have gained respect from the patient communities, pharmaceutical companies, healthcare professionals, government officials, and the public. Participants have assurance that NORD protects their confidentiality.

In some cases patients and families must travel to distant research centers to participate in clinical trials. NORD provides travel and temporary housing assistance to alleviate financial and relocation stresses.

NORD is recognized as the pioneer of PAPs. For example, NORD is mentioned, by name, in the Settlement Agreement dated September 3, 1992, in the *Clozapine Antitrust Litigation* in which 23 states and the District of Columbia settled with Sandoz Pharmaceutical Corporation and Caremark Inc. The settlement provided that Sandoz, "through NORD," shall provide a rebate for patients taking Clozaril who are on Social Security Disability Income. This court-ordered program was one of the points of entry for NORD into providing patient assistance services.

28.3 Target Audiences

The essence of effective advocacy is to identify the issues that are of importance to the constituent community, and then to advocate policies and programs that address those issues. Within the rare disease environment, there are a number of entities that affect the health and welfare of patients. NORD focuses its attention and programs

on the audiences that have the influence and ability to advance the best interests of patients with rare diseases.

Among these entities are.

28.3.1 Capitol Hill

One of the major achievements of Abbey Meyers and the coalition that became NORD was advocacy on Capitol Hill for the Orphan Drug Act [1], which was passed in 1983. The Orphan Drug Act provided for a series of financial incentives to entice drug companies into developing treatments for small populations of patients. The main incentives are:

- Seven years of exclusivity for orphan drugs, during which time no other company is allowed to sell the same drug for the same disease;
- Research grants provided by the FDA to support pivotal clinical trials;
- A 50 percent tax credit on every dollar a company spends on clinical research;
- Written protocol assistance, meaning FDA offers to help with clinical research study design; and
- A waiver of FDA user fees for qualifying companies.

What is interesting about the underlying philosophy of this law is that it adopted an economic solution to a medical challenge. At the time this legislation was being developed, many rare disease support groups were raising money to fund research on their disease. The vast majority of these groups were small, without significant resources or influence. When a researcher did discover a new treatment, more often than not, no pharmaceutical company was willing to commercialize it. Drug companies generally felt that the cost of research and development for new treatments for small populations was not financially justified.

Working with the Congress, the rare disease community recognized that since the orphan drug problem was economic, it demanded an economic solution. If companies were afraid that they could not profit from developing and marketing an orphan drug, the rare disease community had to find a way to ensure that these products were worthy of development, and could be a wise investment. Fortunately, the Congress was able to reach a consensus on how to provide the economic incentives needed to encourage orphan drug development.

Originally, the law defined an orphan drug as a drug of limited commercial value, that is, a drug whose cost of research and development outweighed its potential for profit. The FDA struggled with that definition, and after two years concluded that the "limited commercial value" definition was unworkable. There was no way for a company to prove the drug would never make a profit. As a consequence, the law was amended in 1985 to define orphan drugs according to population size, using incidence and prevalence data. A drug for a disease affecting 200,000 or fewer people in the United States could obtain an orphan drug designation and the benefits that the law provides.

Why 200,000? At the time that the law was passed, in 1983, there were potential treatments for narcolepsy and multiple sclerosis that were not being developed, and the population size for patients with those diseases was estimated at 200,000. Today we know that the prevalence of narcolepsy is much lower, and the prevalence of multiple sclerosis is higher, but those were the estimates in 1985, and that is why the law defines a rare disease as one that affects 200,000 or fewer people in the U.S.

The law has in fact been successful. More than 200 drugs and biological products for rare diseases have been brought to market since the law was passed in 1983. In contrast, in the decade before 1983 fewer than ten products developed by industry came to market.

The role of the Congress in advancing the needs of patients with rare diseases did not end with the enactment of the Orphan Drugs Act. The rare disease advocacy community works closely with the Congress on an ongoing basis. Representatives from NORD testify before Congressional committees on a regular basis, making sure that the voice of the community is heard [3].

Among the issues that the rare disease advocacy community focuses on are assuring that there is adequate finding for FDA as well as the National Institutes of Health (NIH) and the Social Security Administration (SSA). All three have programs that directly affect the rare disease community. NORD was very instrumental, for example, in founding the Alliance for a Stronger FDA, an organization that seeks to educate the Congress on the need for FDA to be adequately funded.

The rare disease advocacy community also participates actively in advocating for policies that will advance access to and research into orphan drugs and devices. For example, NORD advocates for extended patent periods for orphan products, so as to provide manufacturers with an increased incentive to develop them. And NORD has been a leading advocate for the removal of lifetime caps from health insurance policies and for legislation to improve patient access to clinical trials.

28.3.2 Food and Drug Administration

FDA, of course, is the gatekeeper for all medical products, so it naturally is one of the key audiences for the rare disease advocacy community. The community wants to be sure that there are no barriers, real or perceived, at the FDA that would discourage orphan product development.

NORD and its member patient organizations have a positive relationship with the FDA. All of the directors of the Office of Orphan Products Development within FDA have been strong advocates for orphan product development and have worked closely with the patient community.

The role of the FDA in advancing the special concerns of patients with rare diseases dates at least back to the 1970s. In 1979, for example, an Interagency Task Force on Significant Drugs of Limited Commercial Value, which was chaired by the FDA's Marion Finkel, M.D., then Associate Director for New Drug Evaluation in the Bureau of Drugs, and later the first head of the FDA's Orphan Drug Office, issued a report calling on all segments of the health care industry to provide

assistance to patients with rare diseases and also encourage research. The task force urged immediate attention to the issues faced by the rare disease community as well as an effort to determine how to frame legislation. This task force and its report served as a precursor to effort just a few years later to enact the landmark Orphan Drugs Act of 1983. ("Significant Drugs of Limited Commercial Value," Report of Interagency Task Force to the Secretary of Health, Education and Welfare, June 29, 1979) [1].

FDA continues to play a leadership role in advocating for patients with rare diseases. NORD, as the advocate for the rare disease community, often serves as an interface between the FDA and the companies developing orphan products. For example, NORD helps companies understand the benefits of orphan product designation and how to apply for such designation. NORD communicates the needs of rare disease patients to both companies and the FDA, and provides a "neutral ground" for communication regarding orphan product development at its Corporate Council and other meetings. NORD's principal interests with the FDA are in expediting the review and approval of safe, effective orphan products, and assuring that an adequate supply of approved drugs is maintained.

A good example of how the advocacy process works with FDA occurred during the 1980s, when HIV infection was emerging. Most AIDS patients were dying of a rare type of pneumonia called *pneumosystis carinii*. Researchers discovered that *pneumosystis carinii* could be treated successfully with inhaled pentamidine. But pentamidine was an old antibiotic that had been developed to treat a condition called Rhodesian sleeping sickness, and the manufacturer had stopped making it several years before (mostly because sales to third-world countries were not profitable).

NORD and other patient advocacy organizations worked closely with industry and the FDA to ensure that a dependable supply of pentamidine could be developed. The multi-national company that owned pentamidine was willing to give up its rights. NORD helped line up a generic company that specialized in the manufacture of liquid drugs that was willing to copy the original drug and supply it to researchers for clinical trials. The generic company was able to copy pentamidine, and the clinical trials moved forward. Eventually a New Drug Application was submitted to the FDA and the drug became available.

NORD and the rare disease advocacy community work closely with the FDA on the FDA processes for reviewing applications and setting the standard for drug and device testing. For example, FDA has conducted a number of special podcasts for NORD member organizations to explain how its processes work. These podcasts are available on NORD's website, www.rarediseases.org.

In May 2009, NORD held a Summit meeting, Partners in Progress, in Washington, D.C., to identify its public policy priorities. Many of the issues raised were FDA-related. Among the goals were that NORD should work with FDA to establish greater certainty in the orphan product approval process, in particular with respect to clinical trial design and endpoints. For example, the Summit's blue-ribbon panel recommended that NORD should seek to develop valid natural histories for rare diseases that can be used to define clinical endpoints. "What is needed is a

new paradigm for orphan drug development. Greater certainty would encourage investment in, and the development of, products for rare diseases," the panel report said.

Another goal advocated by the panel was that NORD should identify needed changes in the FDA law, regulations, and policies to encourage and facilitate product approvals. "FDA is the gatekeeper for new products, but beyond that also sets the standard for clinical trials and product development. NORD should advocate for FDA to have the tools and policies needed to support orphan product development," the panel report said.

Another FDA-related goal is that NORD should develop systems that will enable greater patient access and participation in clinical trials of rare diseases. Recruitment to clinical trials for orphan drugs and medical devices often is an obstacle to timely clinical development.

One especially critical goal identified by the panel is that NORD should seek to assure reimbursement for off-label uses of drugs used to treat patients with rare diseases. The panel said: "The vast majority of patients with rare diseases have no FDA-approved medicines. When treatments are used, they often are medicines that are approved to treat common diseases but not rare diseases. Physicians are legally able to prescribe drugs for any patient who may, in their professional judgment, benefit from them, but reimbursement policies increasingly are denying payment for uses not specifically approved by the FDA. This means that patients with rare diseases may be denied reimbursement even when the accepted standard of care is to use a product that is not approved by the FDA for that specific use."

Looking to the future, the panel said that NORD should provide policy leadership as more personalized medicines are developed. "Medical advances increasingly are focused on medicines and treatments that will be designed for individual patients based on their genetic makeup. New policies will be established by the FDA and other health agencies that must take into account the special needs of patients with rare diseases," the panel said.

The rare disease advocacy community will continue to seek to work closely with the FDA on policy and process issues that affect orphan drug development and availability.

28.3.3 National Institutes of Health

As the entity within the U.S. federal government that conducts and financially sponsors medical research, the rare disease community works closely with the NIH to assure that medical advances will continue, and most particularly that rare diseases will receive the research attention and funding they deserve.

Advocacy plays a central role, for example, in the NIH's Rare Diseases Clinical Research Network (RDCRN), which funds research consortia. The research explores the natural history, epidemiology, diagnosis, and treatment of more than 95 rare diseases. Since its creation in 2003, the RDCRN has enrolled more than 5,000 patients in 37 clinical studies in rare diseases.

The RDCRN is unique in its approach to addressing rare diseases as a group. Previously, the NIH's institutes and centers funded research on individual rare diseases in their respective disease-type or organ domains. The RDCRN is the first program that aims to create a specialized infrastructure to support rare diseases research.

In announcing new grants in 2009, NIH said: "The direct involvement of patient advocacy groups in network operations, activities, and strategy is a major feature of the RDCRN. Each consortium in the network includes relevant patient advocacy groups in the consortium membership and activities. These patient advocacy group representatives serve as research partners within their own consortia. Collectively, the Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all patient advocacy organizations associated with the RDCRN. The CPAG participants meet frequently throughout the year via teleconference and face-to-face meetings. They participate in network-level discussions and meetings. The CPAG chairperson is a voting member of the RDCRN Steering Committee." (http://www.nih.gov/news/health/oct2009/od-05.htm)

NORD promotes awareness of the RDCRN through its website and publications, and a NORD representative participates in all CPAG teleconferences and face-to-face meetings.

The rare disease advocacy community also will play a central role in the NIH's newest initiative, Therapeutics for Rare and Neglected Diseases (TRND). Its objective is to form a drug development engine within NIH to help accelerate the development of new treatments. The NIH Office of Rare Diseases Research will oversee TRND, while TRND's laboratory operations will be administered by the National Human Genome Research Institute. The advocacy community, including NORD and the Genetic Alliance, is working with NIH on this important and innovative program, which promises to bring a trans-NIH approach to translational medicine.

As with FDA, NORD maintains a close relationship with NIH on behalf of the rare disease community and actively advocates for policies at NIH that will lead to greater support for research into rare diseases.

28.3.4 Social Security Administration

SSA oversees the disability program that helps support many patients with rare diseases. Many people seriously affected by rare diseases, some of which are severely debilitating and/or life-threatening, have been denied Social Security Disability insurance and have been forced to go through the lengthy and often expensive appeals process. This is because few rare diseases are included the SSA *Listing of Impairments*, nor are they included in the U.N's *International Classification of Diseases*. In many cases, initial denials of benefits are reversed following appeals but not before patients and their families have lost precious time and spent thousands of dollars on legal assistance.

Just one example is typical: Lymphangioleiomyomatosis (LAM) is a serious lung disease that tends to strike young people, almost always women, and is thought to be

related to hormones. It is not caused by smoking. A woman in her 40s told NORD that she received her diagnosis in December of 2005 and was told by her physician at Cleveland Clinic that she would no longer be able to work. She had previously worked as a clerk in retail stores.

The woman first applied for assistance in January of 2006, but a few months later received a denial letter which stated that she should still be able to do "sedentary" work. She hired a lawyer and appealed the decision. Again, she was denied. She hired a different lawyer and appealed again. This time, she was notified, in November 2007, that the denial had been reversed. By that time, she had lost her home and her car. She was getting food from a food bank, and relying on friends and people from her church for help with buying necessities, such as toothpaste. She had accumulated $3,500 in attorney fees that wouldn't have been necessary if her physician had been better able to make his voice heard earlier in the process.

Another problem with SSA disability judgments has been delays in securing approval for benefits. Patients with clear disabilities have had to wait literally for years to obtain the benefits to which they are entitled.

In October 2008, SSA announced its Compassionate Allowance Program which identified 50 serious and disabling diseases for which benefits would be paid on an expedited basis. NORD advocated that SSA adopt this program and the NORD Medical Advisory Committee worked with SSA and NIH to identify candidate diseases. NORD's role was recognized by SSA in the press release announcing the inauguration of the program. SSA expanded the program in February 2010.

The SSA Compassionate Allowance Program is an example of how government can work with the rare disease advocacy community to solve problems faced by patients, and how effective advocacy can lead to real, tangible benefits for patients.

28.3.5 Pharmaceutical/Biotech/Devices Industries

NORD has long recognized that drug and device development is performed by companies. While the NIH performs much of the basic research and funds clinical trials, and while the FDA serves as the gatekeeper for new products and sets national standards for safety and efficacy, it is the industries – the pharmaceutical, biotechnology and medical device industries – that develop and market new products, and that invest in the needed developmental process [2].

Thus NORD, on behalf of its member organizations, has developed a collaborative approach with the medical products industries. Many companies participate in NORD's Corporate Council, which provides opportunities for companies to work with NORD on issues of mutual interest. NORD also honors companies that develop orphan products at NORD's annual dinner in May in Washington, D.C.

Appropriate collaboration with companies is an important aspect of advocacy for the rare disease community. To the extent that patients with rare diseases can influence companies interested in developing new products for rare diseases, the medical advances can be enhanced still further. For example, patient organizations can work with companies on patient recruitment during clinical trials.

28.3.6 Healthcare Professionals

The patient advocacy community obviously must work with healthcare professionals – not only to assure that individual patients are accorded proper medical care, but also as part of the policy advocacy process. Healthcare professionals who specialize in one or more rare diseases have a special knowledge and understanding of the challenges faced by patients, and this perspective and knowledge brings an important perspective to policies affecting their patients.

On behalf of its member organizations, NORD has since its inception sought to maintain a close relationship with the healthcare community. NORD, for example, has a Medical Advisory Committee so that the views of healthcare professionals can be incorporated into the advocacy process. NORD also produces a unique database of medical information about rare diseases that can be accessed by patients and healthcare professionals alike.

Finally, NORD seeks to advance medical knowledge about rare diseases through its grant program that supports medical research. For example, in 2008 NORD grants made possible the study of five rare diseases: alveolar capillary dysplasia, APECED syndrome, olivopontocerebellar atrophy and related diseases, Tarlov cysts, and tyrosinemia. Four of these grants were the results of collaboration with disease-specific organizations.

28.4 Rare Disease Day

One important element in advancing the issues of concern to the rare disease community is public advocacy. In 2009, NORD created Rare Disease Day to call attention to rare diseases. In 2008 more than 220 organizations, agencies, and companies signed on as Rare Disease Day Partners to promote awareness of rare diseases as a public health issue. Rare Disease Day, commemorated on a world-wide basis, takes place on the last day of February – which means that once every four years, it occurs on February 29, truly a rare date.

28.5 International Advocacy

Rare diseases know no geographic borders, and so advocacy organizations on behalf of patients with rare diseases also function overseas. In Europe, the advocacy group that parallels what NORD does is called the European Organization for Rare Diseases or EURORDIS. In the European Union, a disease is considered rare if it affects fewer than one in 2,000 people. There are 30 million Europeans with rare diseases, the same number estimated to have a rare disease in the U.S.

In 2009 NORD and EURORDIS signed a Memorandum of Understanding to join forces on several key strategic initiatives on behalf of rare disease patients and their families. The intent is to increase global awareness, promote research and the development of new treatments, and provide advocacy for more compassionate public policies. As part of their strategic partnership, EURORDIS and NORD will:

- Co-organize an annual global Rare Disease Day
- Establish common positions on key advocacy priorities
- Play a pivotal role in the International Conferences for Rare Diseases and Orphan Drugs (ICORD) to help expand the rare disease movement
- Collaborate in the development of international web media and social networking information and communication services
- Implement an international mentoring project for rare disease patient organizations
- Coordinate more closely activities to enhance relations with the pharmaceutical and biotechnology industry

EURORDIS and NORD also collaborate on a joint public policy advocacy blog and shared online communities.

This collaboration among patient advocacy leaders mirrors similar actions on the government level. FDA and its counterpart in Europe, the European Medicines Agency (EMA), have in place a collaborative effort to ensure appropriate conduct of clinical trials. The two agencies have also adopted a common application for "orphan" products – products being developed as treatments for rare diseases.

28.6 Conclusion

Advocacy on behalf of patients with rare disease is an important element in seeking to assure that federal and worldwide policies address the concerns of these patients, and that policies recognize the unique challenges faced by patients with rare diseases. Effective advocacy means advancing policies with the appropriate target audience.

NORD seeks to work with all the influencers and with all segments that affect patients with rare diseases. NORD and other advocacy groups on behalf of the rare disease community share with patients their sense of urgency and their sense of purpose.

NORD's advocacy is entirely patient-centered. Underlying the advocacy by NORD and by the entire rare disease community is the belief that government and private sector policies should not stand in the way of assuring that research and product development advance without barriers, and that patients should have access to the treatments that may or will help them, and to the benefits to which they are entitled.

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