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Deborah Mascalzoni *Editor*

Ethics, Law and Governance of Biobanking

National, European and International Approaches

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Contents

Ethics Law and Governance of Biobanking: A Very Complex Normative Puzzle

Deborah Mascalzoni

The Food and Drug Administration in the US recently granted premarket clearance for a DNA sequencing platform with increased diagnostic power. Francis Collins et al. stated in an editorial in the New England Journal of Medicine that this approval may open the door "for the development and use of innumerable new genome-based tests" (Collins et al. 2013). Collins et al. called the approval "a landmark move that will finally open the way to realize the promise of personalized medicine" (Collins et al. 2013).

We are moving into a world where whole-genome scanning of individual DNA samples will start to become routine in medical research and clinical practice; proposals for routine screening of genomic profiles have already appeared in the public policy arena. The borders between medical research and clinical practice are to a certain extent blurring, so that research sequencing platforms are starting to gain clinical validity and clinical practice is beginning to rely more immediately and more closely on research results.

Biobank research and genomic information are reshaping our notions of health and medicine and offering the promise of more tailored medical treatment. The cost effectiveness of these treatments and of pharmacogenomics in general are part of this conversation, but it has been claimed that the way forward relies on bio-specimen research.

In Europe, the investments in research infrastructure and the linkages between existing biobanks and biomedical projects are extensively supported by public funding. The EU Seventh Framework funding programme invested heavily in the

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creation of network infrastructures and working consortia in order to facilitate the genomics movement on a large scale, and the research and innovation programme Horizon 2020 seems to be following the same philosophy.

The rapid pace of technology development in genome sequencing has an impact on how we think about biobank-based research regulation and health regulation. Thus, for example, the advances in bioinformatics and the augmented power of computing technologies together with the availability of widespread access to different network facilities have completely reshaped our notion of informational risk, leading to the conclusion that the very idea of anonymity in research may be a fairy tale.

How should these developments impact the current regulatory approaches, which rely heavily on anonymity and confidentiality in research? In the European parliament, the fear that the increased computer processing power associated with Web 2.0 internet technologies could impact individual privacy interests led to the proposal for a General Data Protection Regulation (GDPR) in January 2013, which initially suggested very strict rules for research. This proposal was severely criticised by patient associations, and there were widespread comments from scientists, scholars and professional associations who feared its possible impact on research.

While the first impression is that regulations follow scientific development, in fact, there are very complex dynamics in the co-production of bio-objects and regulatory approaches. Just as regulations impact research, research impacts regulation and governance approaches. Bottom-up approaches and self-regulation are constantly informing scientific practice. In a highly complex relationship, social values, existing rules, health expectations and science each play a role in reshaping the regulatory context.

The existing wealth of regulations on local, regional, national and international levels creates a complex picture that must be deciphered in order to conduct research. Binding legal rules need to be acknowledged together with ethical requirements and non-binding professional guidelines that sometimes overlap and diverge.

This book outlines the current developing situation with respect to biobanking regulations. The very definition of what constitutes a biobank is not unequivocal. Barbara Parodi explains the differences in the lexicon. She has explored the main literature in the field to provide a glossary that will help to map the complexity of the existing reality. It appears that the terms biorepository, biological resource centre and biobank can refer to very different structured collections of biological samples and associated data. They can include human tissues, animal tissues, cells, bacterial cultures and even environmental samples. These terms are often confused and sometimes misplaced in the literature. The associated regulations pertain to the kind of materials collected and the possible uses of those materials. Therefore human tissues collected for clinical use will be associated with a different legal and ethical framework than animal cell lines collected for research purposes. Relevant aspects such as proprietary rights, patenting, etc. will therefore have a very different basis. Barbara Parodi looks at how the various biobanks and

bioresources can be established within academic, medical or research institutions, pharmaceutical/biotechnology companies and stand-alone organisations.

The category in which the bioresource is filed has serious implications for the regulatory framework that should be applied (clinical regulation, research) and for access to funding, etc. A clear distinction among biobanks used for research, diagnostic or therapeutic purposes is not always easy to obtain (e.g. cord blood stem cells, typically collected for therapeutic purposes, can be used for research, and tumour tissue samples can become the basis for tumour vaccines). Laboratories involved in cell therapy and tissue engineering clinical trials (cell factories) also handle biobank samples for clinical use. The legislation, ethical and social issues, and handling of the biological specimens are remarkably different for these different types of biobanks. Some authors differentiate research biobanks into four types: clinical case/control biobanks, based on biological specimens from patients with specific diseases and from non-diseased controls (e.g. pathology archives); longitudinal population-based biobanks, which follow a segment of the population over a long period (e.g. the Estonian and UK biobanks); population-isolated biobanks, with a homogeneous genetic collection based on a specific environment and population (e.g. the Icelandic biobank); and twin registries, with samples from monozygotic and dizygotic twins (e.g. the Genome EU twin and the Swedish Twin registries). However, in some specific contexts, classification goes even further, with up to six types of biobanks. Accurate definition and categorisation of the types of biobank are an important step in developing appropriate regulations.

Mariachiara Tallacchini looks at the standard response to the blurring notions of property rights and individual autonomy with respect to biological materials in two different legal systems (the EU and the US). She discusses the development of the legal interpretation of issues as they are raised by scientific advances and are responded to socially. According to her analysis, within the complex world developed around the biobanking of human biological materials and information, the US and Europe have adopted strikingly different strategies. The US has focused on the notion of individual property rights and Europe has focused on individual autonomy—mostly interpreted as the right to privacy. The US has dealt with the question of bodily property by negating the uncertain "proprietary interest" of private citizens to their bodies. Proprietary rights have been translated into more consolidated intellectual property rights and, to justify the acquisition of control by research and market structures, terminology describing the "donation" of one's own tissues has been introduced. In Europe, the general approach instead went in the direction of removing corporeity by restricting the discourse to within the limits of the dignity of individual autonomy—according to which the body is "priceless". Tallacchini shows that these categories are opaque and unbelievable and that, in fact, the negation of the marketability of the body went hand-in-hand with the institutionalization of a European tissue market.

The consequences of both these perspectives are very important and, in both cases, undesirable: the proprietary language diverts us from more socially responsible considerations of the human tissues as public interest or public good and, from the other perspective, privacy has become more of a constructed "myth" than

a perceived need and, Tallacchini suggests, a screen to protect the interests of the market rather than individual positions. Privacy can become an obstacle and an undesired and paternalistic form of protection, while simultaneously hiding important shared interests for individuals such as the quest for better healthcare. The most negative effects of the proprietary legal framework include the precariousness of many collections of materials, the monopolies on certain types of tissue, and the creation of force-based relationships between nonprofit research institutions and pharma industry. However, in the author's words, "the most serious and evident consequence concerns the net gap between research and therapy—exactly where it emerges clearly that the two areas are intimately connected and that the law should promote integration." In fact, we are witnessing the development of dual artificial divergent regulations for the use of human tissues in research and the clinical field that have serious consequences for the politics of research, leading to the creation of restrictive regimes that do not reflect citizens' views. In fact, citizens tend to be less concerned with the privacy or individual property rights of materials, and more concerned with the shared goals of research. The need for a shared collective civic dimension that can be believed and trusted could lead to the possibility of requalifying the use of human tissue. In the last chapter, Claudio Corradetti further explores empirical methods of achieving socially justified grounds for research.

Naomi Hawkins discusses one of the most controversial concepts to be debated in the field of biobank regulation: intellectual property (IP) in biobanks. The concept of property overlaps with the notion of privacy in many respects and Mariachiara Tallacchini and Matteo Macilotti analyse the implications of IP from a legal-philosophical perspective and a constitutional perspective, respectively. However, Hawkins discusses the regulation of IP in the new research infrastructure that is represented by biobanks. The purpose of biobanks is to allow ground-breaking research in genomics, in the hope that this research will ultimately benefit patients. Is it possible and desirable to develop IP policies which aim to maximise patient benefit?

The IP debate in the context of biomedicine and genomics is highly emotional and contradictory. IP is considered by some to be an incentive for innovation and the development of new treatments for disease. Others think that IP rights are blocking innovation and preventing legitimate academic and scientific research, to the detriment of the patients. In Hawkins' analysis, the justifications for granting IP rights are the recognition of an author's natural rights over the products of their creativity and the consequentialist consideration that IP rights induce desirable activities. The patent system in genomic research is most commonly justified on the basis that it provides inventors with an incentive to invest or is considered an incentive to disclose information to the public which would otherwise remain secret. On the basis of this second justification, IP rights fulfil a socially useful purpose. A biobank is a research infrastructure to be used by others for research purposes that may lead to the development of useful innovations. Various key issues are discussed: Can a biobank be the subject of IP? Can research done on the biobank samples be the subject of IP? How can a biobank manage its IP policy to shape the translational outcomes which arise from research?

Matteo Macilotti et al. look closely at how the interplay between current European and national regulations has impacted on the field of genomics in Italy. Special attention is given to the role of the current privacy regulations and how they have led to a highly complex picture that researchers must take into account.

From a comparative perspective, the Italian regulatory approach differs from that found elsewhere in Europe, especially with regard to the UK and Spain (see the chapter by Casado da Rocha). The need to identify a clear relationship between different legal sources (soft law provisions and hard law provisions) becomes especially relevant where the impact of new technologies requires a coordinated approach to ethical and legal issues about informed consent, confidentiality, individual identity, discrimination, self-determination, the secondary use of samples and data, the return of results to the subject, and data sharing.

The limits put in place by regulatory frameworks in clinical research are quite strict but genomics poses new challenges for the protection of research subjects. The traditional conflict between freedom of research for scientists and the interests of the patient is challenged by the introduction of broader models of consent, by the possibility of considering biological materials to be the property of the researchers, and by the creation of national criminal DNA databases. Industry also plays a role in shaping these dynamics, with the result that biobanking is often regarded as a commercial enterprise. Thus, the need to rebalance the relationships among patients/donors, clinicians and researchers becomes compelling.

The multifaceted reality of biobanking in Italy, together with the existence of multiple international and supranational regulations, and the absence, in Italy, of a specific statutory law, highlight the need to specifically define the regulatory framework in this field of biolaw. Abroad, an approach centring on top-down regulation and a "softer" strategy based on traditional instruments and ethical principles is emerging, while in Italy the matter has not yet been directly tackled.

Roberto Lattanzi's chapter offers insight into the basic reasoning behind privacy rules and their impact on research, as well as examining the common ground from which the regulatory bodies could better direct the discussion towards an approach focused on research. The current debate in the European Parliament about the data protection directive may have a severe impact on how biobank research will be performed in the next few years. Lattanzi addresses crucial concerns about privacy regulation and the theoretical reasoning behind it. The first important issue discussed here is the assessment of data protection principles in relation to research. Are data protection principles suitable for regulating the relationships between techno-science and law in the framework of genetic research, and especially with regard to biomaterials? Or does the belief that personal data protection legislation is an obstacle to scientific research have some grounds? Is the data protection regulation framework focusing enough on the collections of biological samples and biobanks? An assessment of these basic questions is a necessary preliminary consideration to be put forward for any further development of rules to be applied to research. In the European debate and in the following ruling, the importance of the biological samples is reduced to their informational dimension. This is why regulations on biomaterials are considered to be related to

data protection regulations. However, the nature of genetic research in biobanks that provide an infrastructure for future projects poses problems if we try to apply the current rules. The open timeframe and the open-ended nature of this kind of endeavour are not easily reconciled with the legal requirements for informed consent. If biobanks constitute modern "infomediaries" then other strategies, not necessarily on the legal level, should be developed to allow research to flourish in a more specific space designed especially for it.

Jane Reichel and Anna Sara Lind offer an overview of the development of the current EU regulations on personal data. The political pathway to the final approval is complex and the content of the regulations as they stand could severely impact research and biobanking.

Jane Kaye follows up on the problem of privacy and underpins the tension between the need to protect privacy and the need for extensive data sharing. Biobank-based research requires wide access to specimens and specific health-related and lifestyle data. Only large collaborative efforts on an international level can achieve the numbers required for statistical significance. Research efforts are becoming more global, and the challenges posed by international data sharing are especially difficult. While biobank research has definitely moved in the direction of globalised data sharing, governance mechanisms that are needed to support this at the meta-level are still under development. The move to global data sharing has been facilitated by several initiatives, which have supported large international collaborative projects and helped with the development of open access policies. The current policy and regulation framework was shaped around the notion of single exchanges that can be controlled by single actors. The changes we are facing in data-sharing practices challenge some of the basic principles of protection of research participants and the current research governance frameworks. One of the key challenges is to define how to protect the privacy of individuals while enabling the sharing of data and samples through global networks. Jane Kaye's review outlines the issues involved in privacy protection. She describes the trends that have transformed genomics research practice and facilitated data sharing and explains how current data sharing challenges current ethical principles and overview mechanisms for medical research. Current approaches to informed consent and governance systems are obsolete in responding to the challenge of globally based research, although technology and the sociology of science offer some alternatives as a way forward. Jane Kaye's chapter presents some of the new initiatives being developed to facilitate data sharing and enable sustainable genomics research with an interesting focus on new forms of patient-centric approaches such as dynamic consent mechanisms.

Jennifer Viberg in her chapter reviews the arguments for and against disclosure proposed in the academic debate regarding the return of incidental findings. If a whole genome scan can return clinically valid findings (incidental or not), under which system should this procedure be regulated: clinical or research? The requirement to return incidental findings to the participants is an increasingly important issue that is currently under wide discussion. Statements from important professional associations and scholars have attempted to assess this novel issue,

which does not yet seem to have a solution. The return of incidental findings has been the interesting focus of many tentative bottom-up self-regulatory approaches in biobanking. The very definition of an incidental finding is in some ways problematic and the policies associated with it are highly variable. The question being asked is: how should an incidental finding be handled ethically and responsibly in genome-wide association studies and disease-specific genetic research? Until recently, the conversation has neglected a distinction that should be kept at the forefront of the discussion, especially concerning genetic biobank research: the distinction between an incidentally discovered disease and an incidentally discovered increased genetic risk for disease of unclear predictive value. Unlike the case with monogenic disease testing, little is known of the best way to handle complex risk information associated with multifactorial disorders. For complex risk information, many factors come into play and different outcomes are achieved for different individuals. The value of being informed about an incidentally discovered genetic risk is therefore much more difficult to assess. In the current debate and in the proposed policies, this important distinction is missing and therefore many of the arguments fail to address the more complex kinds of incidental findings that increasingly arise in biobank research. Further research should be conducted before the discussion can be considered conclusive and lead to regulations.

The chapter by Ruth Chadwick and Heather Stange focuses on the need for harmonisation of regulations in the field of biobanking. Population-wide biobank research is of potentially very great importance for future healthcare. To maximise its effectiveness, however, and achieve sufficient statistical power, extensive international collaboration is required. The existence of a very differentiated regulatory corpus among countries should not stop science from pursuing its important goals.

Harmonisation in science is not a novelty. In the field of international collaboration, data cannot be compared between different biobanks without the harmonisation of different ways of collecting and storing those data. This does not mean standardising the way they are collected, because that would invalidate existing collections. When we turn to ethics, there may also be barriers if the legal requirements lead to gaps in the various national legislative frameworks. This is, for instance, the case if we consider the object of informed consent and the actual consent requirements. To a certain extent this is addressed by harmonisation of the law, the regulations and the governance, for example in the EU context. A fundamental question remains, however, as to what would count as a standard in ethics, or whether harmonisation is the concept of choice. Chadwick's suggestion is that ethics should be understood as different voices singing the same text to different vocal lines in a choir. None of them is more correct than the others, and harmonisation in ethics is best understood as a process, and not as an end point. Standard rules can be produced, for example in ethical guidelines, but the process of harmonisation in relation to these texts is completely different, and we may end up with diverse applications of these common rules in different realities. How much variation in the interpretation of commonly accepted guidelines is acceptable is the next important question to be addressed.

Emmanuelle Rial Sebbag and Anne Cambon Thomsen report on the attempt to provide coordinated international guidance to the biobanking world by the Ethical,

Legal and Societal Implications (ELSI) work package of the Biobanking and Biomolecular Resources Research Infrastructure at the European level (BBMRI.eu). The preparatory phase for the ELSI BBMRI project was specifically aimed at developing an ethical and legal platform assessing key issues relating to biobank networks and at providing models and tools to address them. Developing an infrastructure "properly embedded into European ethical, legal and societal frameworks" requires specific preparation on the ELSI, with respect to both operational questions that deal with the immediate feasibility of the endeavour and more fundamental questions. The group worked extensively in an international and multidisciplinary coordinated fashion in order to produce an assessment of existing regulatory frameworks and to finalise proposals of new approaches and methodologies. The general objective of the ELSI work package was to design an agreed, harmonised and implementable ethical, legal and social framework for the establishment of a European biobanking and biomolecular infrastructure and to propose corresponding strategies and scenarios as a basis for the operational concept and contractual agreements. The specific objectives were: to manage and oversee ethical and corresponding legal aspects in practice within the BBMRI preparatory phase; to develop an online platform on legal aspects for uploading and validating existing legal documents in use by BBMRI members and partners; to work out the concept of harmonisation as compared to standardisation with regard to ethics, and to present practical mechanisms to achieve this in the context of the BBMRI; to provide mechanisms for the BBMRI to interact openly and transparently with the European citizenry and for assessing the debate regarding such an infrastructure in the population and among the relevant stakeholders in the different countries; to define, describe and demonstrate an integrated conceptual and operational model for ELSI approaches in the BBMRI; and to prepare proposals for training in the domain of ELSI relevant to the BBMRI in Europe.

Jane Reichel closely analyses the new research governance tool developed within the EU, the European Research Infrastructure Consortium (ERIC), focusing on one specific research infrastructure: the BBMRI.eu. The BBMRI has 54 members and more than 225 associated organisations (largely biobanks) from over 30 countries, making it one of the largest research infrastructure projects in Europe. The BBMRI-ERIC was instituted in Graz, Austria, in 2013. The aim of this section is to analyse how a certain field of administrative law can be regulated in an integrated or composite administrative legal way, where the division of competence is not always clear and where governance strategies may be used instead of binding regulatory acts as in ethical codes.

Can the governance framework of European biomedical research be facilitated by the introduction of the BBMRI-ERIC? Individually, the Member States cannot provide sufficient resources to compete on the global market any longer, either economically or in terms of competence, especially with the US and the far eastern countries. On the other hand, the competence within the EU in the field of research and innovation is limited. The enactment of a regulation establishing a research infrastructure is therefore one way to find a solution for a common problem: enabling researchers from the EU to collaborate with third-state researchers

on a long-term basis. Within the ERIC, research projects can be run under a common legal order which regulates issues such as taxes, public procurement of technical equipment and their operation, employment arrangements and so forth. Legal regulations connected to the research itself will, however, remain in the hands of the state in which the research is conducted.

David Winickoff's chapter looks at the deep interplay between scientific development and regulation. The example reported refers to the history of the first National Biobank Law in Europe: the Health Sector Database Act (HSDA). The Icelandic law and the story of the collaboration between DeCODE and the Icelandic government is a very instructive case study that is discussed in this chapter by David Winickoff. DeCODE Genetics was one of the first entrepreneurial experiments in public-private partnership for biobanking-based research: the company helped transform medical and genealogical information into a new type of commodity. However, the story of the HSD and the HSDA constitutes in itself a genomics-governance experiment. The Icelandic case formed the backdrop against which much of the current debate on ethical and legal issues around biobanking has been shaped and legal provisions have been developed. David Winickoff effectively reconstructs the story of the co-production of the HSD, of the public debate and of the approval of the HSDA. The attention on the HSD also fostered a lively, highly controversial debate around the development of global norms governing the relationships among citizens, medical information, markets and the state. By scientific standards, the company is widely successful with important publications in major journals. However, the business model of deCODE began to be shaky before the Icelandic economy imploded. Desperate for more immediate revenue streams, the company launched "deCODEme" in November 2007, and became one of a handful of private companies offering customers a personal view of their genetic code and an analysis of certain traits, disease markers and drug sensitivities. Clearly, deCODE's biobank had become a "private asset", despite starting as a unique blend of public and private. Iceland became the first place in which concepts of individual consent and genetic privacy were reframed in relation to the new biobanking-based research world. There was no pre-existing answer to how the traditional ethical principles should be applied in genomics research. The process of constructing a new norm was not linear and was definitively shaped by the different forces involved in the debate. As an indicator of this interplay of forces, Winickoff mentions the WMA Declaration on Ethical Considerations Regarding Health Databases that was published in 2002. It remains important to narrate the story of Iceland's national HSD project, for it retains important meanings for large-scale biobanks today.

On an international level, biobanking facilities are set up every day, and are becoming part of the requirements for good clinical practice in certain clinical areas such as cancer. Corinna Porteri and Aimee Keis discuss two very important case studies of biobank regulations, one in Italy and the other in Estonia.

Aimee Keis' chapter presents a case in which institutions follow the development of science. She presents the development of the Estonian Genome Center, which started as the Estonian Genome Project (EGP). The EGP was one of the

first examples of public-private partnership on a national basis. The private company EGeen LTD had a twenty-five-year licence to use the anonymised data of the Estonian national biobank. After a considerable and highly controversial debate, the contract with the private company was terminated and new rules were developed for the Estonian Genome Center, taking into account the public debate and internationally recognised rules. The creation of the Estonian Genome Center in 2001 was an innovative event in the foundation of large-scale population-based biobanks that are trusted by the public. Discussions between politicians, ethicists, the public and scientists created a situation of distress. Public awareness about genetic research was minimal not only in Estonia. After the failure of the EGP, negotiations began with the Government of Estonia, aimed at providing continued funding. One condition was incorporating the Estonian Genome Project into the University of Tartu. Regaining trust was a tough goal that was pursued on multiple levels. Now, the Estonian Biobank has developed effective legislation and a strict ethical framework that ensures the sustainability of the Estonian Genome Center at a societal level.

The case presented by Porteri explores the construction of a policy model for a biobank in the field of neuropsychiatric disorders set up in an Italian institute for research and care. Gaps in regulations pertaining to the collection and storage of biological materials in a biobank made the writing of local guidelines essential from an ethical point of view. Nevertheless, until very recently, the drawing-up of local guidelines for the collection, use and storage of biological materials in a biobank has been an exception in Italy. The aim of Porteri's chapter is to present a concrete experience of self-regulation of the ethical aspects related to the constitution and management of a biobank for research purposes.

Antonio Casado Da Rocha presents how the Spanish law on biobanks impacts ethical issues. Biomedicine is now "big science", and as such it has a permanent need to legitimise itself in order to obtain social, political and economic support. Research is very demanding on society not only in terms of public recognition and funding, but also for the substantial request of cooperation and trust from the research participants. While biomedical research and its contributions to human health are positively valued in Spain, as they are elsewhere in Europe, the governance of biobanks raises many issues at a global level. Informed consent is probably the most studied controversy in the theory and practice of biobanks, and the debate is far from being resolved. In this chapter, the theoretical question of how to promote the autonomy of participants in accordance with research ethics requirements is read in the context of the Spanish biobank law. The 2007 Spanish law on biobanks enabled a move towards a middle way between broad consent and informed consent. Individuals can give explicit consent for the use of their samples for one kind of research project and then consent to further unspecified uses of the samples in projects that are related to the original aim. Research ethics committees should provide an overview mechanism to this further use: we are facing the implementation of a "governance-by-committee" approach which is still under scrutiny. According to Casado Da Rocha, this may develop into a slippery slope whereby the requirement for consent progressively erodes away. A different

notion of autonomy is required in order to face that risk. We need to go beyond the reductionist reading of respect for autonomy as a single-act consent procedure. In an extended view of autonomy, the role of public consultation and the media in the popular understanding of biobanks may play a major role in reshaping policies and regulation frameworks.

Claudio Corradetti and Gillian Bartlett's chapter, in agreement with Mariachiara Tallacchini's, goes further, identifying public participation as the way to render scientific governance accountable. The process of controlling and setting the agenda for health policies has rarely been established in accordance with publicly shared priorities. Experts have served their narrow perspectives and prioritisation, and regulation has rarely taken into account the complexities involved.

An assessment grounded in public understanding has been blocked by prejudices preventing the involvement of public sectors of society in the decision-making processes. The blocking notion with respect to "scientific truth", whereby scientific research is capable of providing a form of truth that is "exempted" from competing arguments, is a misplaced reconstruction of how science should proceed. The proposed governance involves an ongoing relational model grounded in the social legitimisation of science which relies on a *structural* continuum between scientific truth and its public accountability.

The immediate implications of such a frame of socially agreed practices within the domains of genomics and pharmacogenomics can be summarised in three major areas: 1. the establishment of mechanisms of cooperation and trust between science and society; 2. increased transparency in decision making; and 3. the legitimisation of policy guidelines for scientific enquiry.

The process of participation for obtaining legitimate policies and regulations leads to public accountability and introduces the concept of public reasons into the construction of the policies themselves. The deliberative model proposed in Canada in the case study reported was specifically aimed at developing policy guidelines to be possibly adopted by health state agencies and governments in general.

Linus Johnsson et al. analyse the effect of improper and excessive ethical regulation in biobank research. Research ethics produce *normative* outputs on what ought to be done. Results of this normative reasoning constitute the framework for extra-legal regulatory systems. The trend to translate ethics into steering documents, overseeing bodies, and formal procedures has created an overflow of ethical guidelines and professional ethical codes to guide research. In their chapter, Linus Johnsson et al. argue that ethics reviews and guidelines are insufficient to ensure morally responsible research and in some circumstances may constitute more of a hindrance than a help. The initial assumption of many of the ethical guidelines is associated with a paradigm of *institutionalised distrust* based on past atrocities, and this should not be the basis for a model unless the proposal is intended as a necessary or efficient means of preventing future atrocities. The chapter also carefully considers the limitations of ethics review and guidelines: "with regard to ethics review, requirements of consistency invite rigidity; lack of reliable indicators of a project's moral soundness may lead to idiosyncratic decisions; and the fact

that committees depend on the moral agency of investigators is often overlooked. Strict adherence to guidelines is also no guarantee that moral responsibilities have been discharged. In fact, if guidelines are used as standards against which performance is measured, responsible conduct will occasionally be punished and blind rule-following praised." Old and new issues contribute to creating a complex puzzle, and new trends raise a number of challenges for obtaining consent, protecting participant privacy concerns and maintaining public trust. Exclusively relying on formal normative approaches and neglecting the moral competence of researchers is neither effective nor desirable in the long run.

Analysis of the chapters in this book allows a conclusion to be drawn: there is tension between the need for the transparency and trust demanded by society and the solutions that have been developed to date.

In fact, we are witnessing the development of dual, artificially divergent regulations on the use of human tissues in research and in the clinical field that will have serious consequences for the politics of research, leading to the creation of restrictive regimes that do not always reflect citizens' views and that also impact the gap between research and therapy. Citizens appear to be concerned more with the shared goals of research than with privacy or individual property rights. A shared civic dimension that is believed and trusted could lead to better shared policy directions in which it is possible to requalify the use of human tissues. Thus, for instance, IP policies need to account for the tension between the need for incentives for innovation and the development of innovative new treatments for disease, and the fears of society that the results will be to the detriment of patients.

The need for scientifically informed regulations should lead to flexible, differentiated approaches reflecting differing degrees of sensitivity to be applied to different kinds of data in accordance with their possible impact on a person's life. Diagnostic data about Huntington's disease has to be treated with greater caution than susceptibility data about obesity, although the question of who decides the level of sensitivity may be another issue. Even a simple epidemiological study may carry a discriminatory power if associated with a defined population, as is the case for genetic screening (McNally et al. 2004).

Some theoretical limits to the very conception of the rules may constitute a barrier. In the western legal tradition, the subject of rights has always been associated with the individual, as is the case for bioethical inquiries in genomics. The current proposal on the EU Data Protection regulation provides an example of an unbalanced normative approach that could seriously affect biobanking research by emphasising the individual auto-determination right as absolute (Mascalzoni et al. 2013, 2014). In the European debate, the biological sample is reduced to its informational dimension and is therefore considered to be a matter for data protection regulations.

The emphasis on personal autonomy here misses a very central point in biobanking-based research. In biobanking-based research, the focus is never on a single individual, although the people involved are valuable as participants, especially if they are taken as a group and not just as single individuals. Genome-wide research relies on large numbers with shared characteristics and, in biobank

research, the subjects involved are seen as a whole, either as a community sharing some characteristics, or as a closer, more extended family, where any given individual is genetically related to others. Only large collaborative efforts on an international level can achieve the numbers required for statistical significance and research efforts are now moving towards a worldwide dimension, although the challenges posed by international data sharing are especially difficult to deal with. The current policy and regulation framework was shaped around the notion of single exchanges that could be controlled by single representatives. The changes we are facing in data-sharing practices challenge some of the basic principles of protection of research participants, and the current research governance frameworks. Exploring the possibility of a balance between individual and common rights may result in new horizons in the development of shared goals and policies.

The traditional conflict between freedom of research for scientists and the interests of the patient is challenged by the introduction of broader models of consent, by the possibility of considering biological materials the property of the researchers, and by the creation of national criminal DNA databases. Industry also plays a role in that biobanking can be regarded as a commercial enterprise. There is thus a compelling need to reshape the balance in the relationships among patients/donors, clinicians and researchers. Current approaches to informed consent and current governance systems have proved to be obsolete in facing the challenges of a rapidly evolving landscape that involves globally based research. Moreover, the rapidly developing techniques of next generation sequencing will soon require more extensive strategies and tools in order to allow ongoing research—as in the case of unexpected/incidental findings.

The need to develop common strategies on a regulatory level led to the development of European endeavours such as the BBMRI-ERIC. Establishing regulations for research infrastructures is a response to the need for common pathways for facing the challenges posed by the complex regulatory world of biobanking in order to enable researchers to collaborate on a long-term basis. One thing that appears to be limiting expert-driven frameworks from informing regulation is the lack of goals that are shared with communities.

The theoretical question of how to promote the autonomy of participants in scientific research in accordance with research ethics requirements while at the same time promoting research found a middle ground in a Spanish law that served as a model for others. However, the implementation of a "governance-by-committee" approach is not unproblematic and is still under scrutiny; it may constitute a slippery slope whereby the requirement for consent progressively erodes away. A different notion of autonomy is required in order to face that risk. Moreover, as highlighted by Johansson, an ethical overview is not always effective. Requirements for consistency can invite rigidity and a lack of reliable indicators of a project's moral standing may lead to idiosyncratic decisions. The composition of ethical boards varies greatly among countries and the regulation of a proper review process may require stakeholder involvement in order to identify a good strategy.

Although this ethical/legal overview may not be the final solution for regulating science, random deregulation and oversimplification may also be detrimental.

The risk is a general loss of trust between science and society. Stakeholders and civil engagement may help in framing policies that meet the needs of both sides by avoiding both the lack of legitimation of scientific enquiry and the lack of transparency. Deliberation and participatory approaches are aimed precisely at introducing criteria for democratic legitimation in research and producing relevant epistemic results for policy orientation. On the one hand, they can help make explicit those reasoned concerns and mistrusts that come from society, while also disentangling those prejudices that prevent cooperation; and on the other, they can help raise public awareness on the relevance of research genetics and its potential contributions. Trust appears to be seen as at least instrumentally essential for the implementation of biobanks, because participation is a direct consequence of it. From an ethical point of view, however, this trust should be founded upon values and should not be merely instrumental. In a democracy, trust and consent are not granted forever without ever being questioned. Therefore, for example, if we ask participants to show broader trust in research by providing broad consent, we should balance this request by providing tools that ensure this trust is well deserved. Advances in information technology may well help in building a research-participant communication framework that is not a major burden for research. Understanding engagement and consent as a multiple level issue—individual and social—may also return a super-individual dimension and promote wider social understanding.

Finally, deliberation could provide the agenda and the general orientation for public policies aiming to bridge the gap between science and society that could constitute a theoretical basis for regulation on both ethical and legal levels. This may be the approach to face the current challenge on regulation: balancing commercial private interests with patients interests.

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Biobanks: A Definition

Barbara Parodi

The terms biorepository, Biological resource centre (BRC), biobank refer to structured collections of biological samples and associated data, stored for the purposes of present and future research. Both biorepositories (ISBER 2001) and BRCs (OECD 2007) can include tissues from humans, animals, cell and bacterial cultures, and even environmental samples (see below the OECD definition of BRCs), while a biobank typically handles human biospecimens—such as tissue, blood, urine—and information pertaining to the donors: demography and lifestyle, history of present illness, treatment and clinical outcomes.

1 Types of Biobanks

Biobanks can be established within academic medical or research institutions, pharmaceutical/biotechnology companies or as stand-alone organizations. A clear distinction among research, diagnostic and therapeutic biobanks is not always easy (i.e. cord blood stem cells, typically collected for therapeutic purposes, can be used for research, and tumor tissue samples can become the basis of tumor vaccines). Laboratories involved in cell therapy and tissue engineering clinical trials (cell factories) also handle biobanks for clinical use. However, legislation, ethical and social issues, handling of the biological specimens are remarkably different for these different types of biobanks.

Gottweis and Zatloukal (2007) differentiate between four types of research biobanks: clinical case/control based on biological specimens from patients

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with specific diseases and from non-diseased controls (e.g. pathology archives); longitudinal population based biobanks that follow a portion of the population over a large period of time (e.g. Estonian and UK Biobank); population isolate biobanks with a homogenous genetic and environmental setup of the population represented (e.g. the Icelandic Biobank); twin registries with samples from monozygotic and dizygotic twins (e.g. the GenomEUtwin and the Swedish Twin registry).

Rebulla et al. (2007) take the classification even further and differentiate between six types of biobanks: leftover tissue biobanks collected during clinical pathology diagnostic procedures; population biobanks; twin biobanks; disease biobanks form patients suffering from a specific condition; organ biobanks; nonhuman biobanks (e.g. Primate Brain Bank).

A more general distinction within the research biobank domain can be made between population based prospective biobanks (focused on the study of the development of common, complex diseases over time, and mainly based on blood/nucleic acids collection) and biobanks of tissue samples and clinical data (also referred to as disease oriented or clinical biobanks, mainly based on tissue sample collection). This classification has been used by the pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), which has set two work packages on biobanks, WP2—population-based biobanks and WP3—disease-oriented biobanks.

2 Population Based Biobanks for Genetic Research

Genetic studies based on biobanking are becoming increasingly common as researchers recognize the need for large amounts of samples to identify the genetic basis of susceptibility to common complex diseases. Large scale population biobanking projects link genetic data with information on health status, lifestyle and environmental factors. Population biobanks have recently been defined by OECD as "collections of biological material and the associated data and information stored in an organized system for a population or a large subset of a population" (OECD 2006).

Another definition of population biobank has been given by the Council of Europe:

> a collection of biological materials that has the following characteristics: the collection has a population basis; it is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects; it contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; iv. it receives and supplies materials in an organised manner (Council Of Europe 2006).

In the international context, the Public Population Project in Genomics (P^3G), a not-for-profitinternational consortium (Knoppers et al. 2008), plays an important role for population based genetic research, through open-access research tools

for effective collaboration between biobanks, enabling the international research community to share expertise and resources and facilitate knowledge transfer for the health of populations. The 28 charter members of P^3G, international, national or regional not-for-profit organizations, are conducting, or will be conducting large population genomics projects such as biobanks or large-scale cohort studies (N > 10,000 samples).

In Europe, the diversity of populations is a beneficial feature for genetic research, and centralized population-based biobanks have been established in a number of European countries, as Europe's national health care systems have facilitated collection of clinical samples and produced highly reliable health care records.

Biobanks collecting samples from twins are also part in the domain of population biobanks. Twin cohorts and Twin Registries provide a unique competitive advantage for investigations of the role of genetics and environment or life style in the etiology of common diseases. The international GenomEUtwin project[1] (Genome-wide analyses of European twin and population cohorts to identify genes predisposing to common diseases), a collaboration between Twin Registries in the Netherlands, Denmark, Norway, Sweden, Finland, Italy, UK and Australia, aims at identifying genetic variants associated with common diseases by pooling epidemiological and phenotype information from over 600,000 twin pairs, and genotype data from an ascertained fraction of those.

To overcome fragmentation, the most prominent European population biobanks are collaborating within the work package 2 of BBMRI, aimed at providing a strategy to solve the legal, governance and financial challenges involved in the Europe-wide cataloguing and storage of the vast amount of information collected in large epidemiological sample collections and population cohorts. The effort involves epidemiologists, biobankers, clinicians, experts in different fields of laboratory medicine, molecular geneticists and experts in high-throughput 'omics' technologies, with the goal of establishing an European infrastructure for collection, storage, annotation, validation and dissemination of the diverse data collected.

3 Disease-Oriented Biobanks

Disease-oriented biobanks (which may also be referred to as clinical biobanks) are placed at the interface between clinical practice and research. They collect biological samples from patients, aiming at discovery and validation of genetic and non-genetic risk factors of diseases. They are usually established in hospitals and research institutes, and multi-centre collections can raise from clinical trials and genetic studies. Two domains of clinical biobanks can be distinguished: tissue banks and rare disease biobanks.

[1] http://www.genomeutwin.org.

3.1 Tissue Banks

Tissue banking is a strategic activity for research and innovation in biomedicine in a clinical context, essential for the procurement of high quality samples for translational research. Well annotated and pathologically reviewed case-series (either based on specimens collected and processed in the course of clinical diagnostic activities or in specific tissue collection protocols) are required for identifying biomarkers and molecular targets for therapy, establishing their prevalence and formulating hypotheses on their biological and medical significance in ex vivo analyses. Validation of a potential biomarker requires applying ex vivo analyses within study designs with adequate epidemiological and statistical power; these studies may be constructed using retrospective or prospective collections. Finally, translating biomarkers into clinical practice requires applying them to large series of specimens collected using standard operating clinical protocols.

Tissue banking implies informing patients and obtaining the proper consent, data acquisition, tissue procurement, annotation, preservation, storage, cataloguing, managing of access, processing and distribution. It requires expertise in pathology, cryobiology, quality management, legal/ethical aspects, project management, administration and networking.

Specialized pathology expertise is required to identify and define the nature and origin of the tissues to be kept in the biobank. Pathologists make decisions on what should be biobanked, making sure that the requirements of clinical diagnosis and the optimal preservation of biological products are both respected. Pathology archives represent a special type of tissue repository, that may support tissue banking. The primary role of these archives is to document diagnosis and to support later diagnostic analyses, but they can play a role in research as well.

3.2 Rare Disease Biobanks

Rare (orphan) diseases are defined as low prevalence diseases, affecting less than one citizen in 2,000. Rare disease biobanks (also referred to as genetic biobanks) have been recognized as important tools for research and treatment. Biological samples from rare diseases (blood, tissues, cell lines, DNA) are precious, because of their rarity and diversity. This emphasises the need of transnational collaboration, quality control of the samples, training and education of scientists using the biomaterials. Quality of biomaterials and associated information rather than their quantity is critical in rare disease biobanking: small collections or even individual samples may be extremely precious for research, and have direct relevance for patients' health. Most rare disease biobanks work through the active participation of patients and patient organizations, and share benefits with them.

Orphanet, the European portal for rare diseases and orphan drugs, has developed a comprehensive disease coding system and a database listing more than 100 rare disease biobanks in Europe. EuroBioBank is a European network of

rare disease biobanks with a focus on neuromuscular disorders. In Italy, Telethon has in place a national plan for rare disease biobanking that assures high quality standards through regular assessments.

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A Participatory Space Beyond the "Autonomy Versus Property" Dichotomy

Mariachiara Tallacchini

1 Introduction

In response to the various questions that have arisen around the biobanking of human biological materials (HBMs) and information, two strategies have been adopted in the US and in Europe; these are distinguished by their respective focus on two main legal concepts: individual property rights and individual autonomy—or the right to privacy.

The US addressed the question of proprietary interests in the human body explicitly and directly. In fact, the US justice system has always explicitly defined the question in terms of property, removing privacy from the equation essentially as a way to "avert the danger" of the proprietary issue. The tendency has always been to negate the uncertain "proprietary interests" associated with the bodies of private citizens, and to use the much stronger and more consolidated "proprietary rights", meaning intellectual property; or else to justify the acquisition of control over the HBMs by research and market structures through a presumption of donation and subsequent abandonment of human tissues by the sources of those tissues. In Europe, the approach went instead in the direction of removing the corporeity of HBMs, seeing them instead as symbolically representing the most secure limits of human dignity, according to which the body is "priceless." The opaqueness and unworkability of this is made clear by the fact that negation of the marketability of the body went hand in hand with the institutionalisation of the European tissue market.

There are two inconvenient principles inherent in these two perspectives. The first is the reduction of the means of control of HBMs to one proprietary, operative

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model, where all powers are allocated to the owner-subject and the object in itself lacks any ultimate value, be it individual or even social. This model has demonstrable limits which can be seen, for example, if it is applied to the environment, which has several affinities with the theme of tissues. The second principle concerns the misleading prevalence of language of individual autonomy, when the actual values in question instead reflect public space, collective dimensions, and a sense of scientific citizenship—which are taken as recognition of the rights of citizens to participate, even if it is epistemic, in public decisions.

In fact, in both cases, the conversation is affected by tensions and reciprocal diffidence between the scientific and political institutions, with market operators on one side and citizens on the other, as seen in the theoretical and practical investigation of what is private and what is public.

In many ways, privacy has become more a constructed "myth" than a perceived need, a screen to protect the interests of the market more than those of the individual. Privacy can, in fact, be transformed into an obstacle, an undesired and paternalistic protective barrier, while showing one's face and name can, in some circumstances, be important for individuals.

The undue impoverishment, or even removal, of the potential of proprietary language in the name of bodily dignity also prevents the exploration of forms of non-unilateral management of HBMs, thus at the same time preventing better legitimacy and enduring stability for existing initiatives and the formation of new initiatives in this sector.

This situation is producing numerous negative effects including, for example, the development of a situation where the safety of many collections of materials is uncertain, and the establishment of monopolies on certain types of tissue, and of relationships of force and subordination between nonprofit research institutions and pharmaceutical firms.

However, the most serious and evident consequence concerns the gap between research and therapy—at a point where the two areas are clearly intimately connected and where the law should be promoting integration.

This gap partly depends on the established uncertainties around the uses of research but also depends, more than anything, on the artificial separation that exists between therapeutic use and research, a situation that particularly manifests itself in Europe, in the irrevocability of donating tissues for therapeutic use and the revocable nature of donating tissues for research. The most interesting intersection between these points of view comes from approaching the subject from the overall picture of donated tissues—for therapy and research. This perspective, which redefines the problem of the use of tissues in much more extensive terms, permits the identification of common foundations and points of escape from the judicial qualifications and tissue policies.

While the desire to involve citizens in scientific research projects is actually increasing (Malone et al. 2002; O'Doherty and Burgess 2009), it is also becoming more clear that the citizens themselves are approaching the subject with more solidarity than expected. The establishment and those working with theory are, in fact, perhaps not as concerned with privacy issues or the "individualistic-possessive"

property approach with respect to HBMs (as a source of wealth), but are more concerned with the meaning and goals of research (Wynne et al. 2007).

Until now, lawmakers and policymakers have struggled to reach a shared collective civic view that is believed and trusted; and ethics, with its presumed "redeeming" representative-participatory role, has so far further undermined the possibility of reaching this goal (Tallacchini 2009). There is a need for one or maybe more public groups to make a space within which to requalify the use of human tissue from a social point of view.

2 Human Biological Materials (HBMs): An Established Puzzle

The decisions affecting the uses of cells and tissues came about in stages, as problems were encountered on the way. One of the first questions concerned the separation and/or overlap between the materials and the information they contained; a second theme was that of informed consent for secondary uses of HBMs; a third problematic area was related to the procedures of ensuring anonymity, which was seen as a possible solution to the secondary use problem.

The principles and rules that govern the dissemination of the physical cells and tissues and all the informative data that accompany them were developed in order to protect material goods. When information (personal, family, clinical, biological and genetic) is gathered, the main objective is the protection of the privacy of personal data and the right to privacy; however, when cells and tissues are obtained, the determining factors involve the need to maintain the principles of freedom and solidarity on the part of the person conferring the biological material and the need for security in its use.

In any case, the two sectors were soon united by similar needs, such as the need for informed consent, guardianship of any confidential information, and agreement on the operative powers of the involved parties in access to the materials and information. However, despite the recognition of a need for agreement on the treatment of HBMs and the information relative to them (EGE 1998) and the general recognition of the impossibility of isolating these two questions, the relative disciplines remained separate for a long time and essentially remain separate now.

Although the relationship between biological materials and sensitive information is now being clarified, other problems remain confused. Many experts in the sector recognise that the areas encompassing consent, the treatment of information, confidentiality, the exchange of materials and data, and the sharing of derivative benefits from biological samples are still surrounded by uncertainty (Cambon-Thomsen et al. 2007; Hansson 2005) in both Europe and the US (Andrews 2006; Charo 2006; Rao 2007; Glantz et al. 2008).

The main issue concerns the consent for so-called "secondary uses" of HBMs, meaning cells and tissues that are originally collected for diagnostic or therapeutic reasons and are subsequently used in research that was not predicted at the time

of harvesting. The unpredictability of these subsequent uses has made the rules governing the consent that a donor or patient is asked to provide regarding the materials ambiguous.

The main problem of obtaining informed consent for secondary use is related to the difficulty of obtaining that consent with the passage of time, a particular problem for material banks and existing data, or for research that could not have been hypothesised when consent was given.

The debate involves the form, either explicit or implicit, of the consent, as much as its content, specific or generic.

The expansive literature that has developed on the theme has gone from elaborating reasons and solutions to offering models that range from restricted consent, through a partially restricted, reasonably wide consent, to blanket forms of consent (Harrison 2002; Tutton et al. 2004; Wright Clayton 2005; Lipworth et al. 2006; MRC 2006; Da Rocha and Seoane 2008; Porteri and Borry 2008; Salvaterra et al. 2008; Zika et al. 2008; Hofmann 2009).

In the US, there is still a tendency to use specific or multi-layered forms of consent for secondary use (NBAC 1999; Greely 1999, 2007; Caulfield 2007) and the Code of Federal Regulations (45 CFR 46.116) is employed to prevent the use of forms offering "blanket consent" (DHHS 2004).[1] In Europe, although the established groups remain cautious and specific (COE 2006), more and more theoretical voices are suggesting open, general consent forms (Cambon-Thomsen et al. 2007; Hansson 2005).

In this divided context, the process of ensuring the anonymity of biological samples (that is, the prevention of referring information to an individual subject) has been the most used techno-juridical resource, and is also the most fascinating process from a legal philosophy perspective (Tallacchini 2005). In fact, the procedures of anonymisation have had a double effect: operatively, they were used to limit the necessity for reiteration of consent, and symbolically and rhetorically, they represented the strategy of maintaining a public climate of trust and reassurance.

The de-identification of the subject—who is made anonymous—from the samples and anonymised data was thus simultaneously and implicitly associated with the loss by that individual of interest in the materials and the information they contained (Lowrance 2002).

This then resulted in the development of the idea that the donor was renouncing all forms of control of these materials, and desired to abandon them. This in turn allowed the operators of the market to acquire biological materials as *res nullius*

[1] DHHS (2004): "No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence." 45 CFR 46.116. *Examples of exculpatory language* By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances; I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items".

(nobody's property) (Tallacchini 2005). In this way, a subtle but clear connection is established between the identification of a subject and the power to control biological materials.[2]

3 Legal Strategies: The Myth of Privacy and the Denied Body

Although there are many elements that have entered the historical regulation of biobanks, the fundamental question concerns the operative relationship between the person who is giving up their own biological materials and the HBMs themselves. The configuration of that relationship is vital for establishing the legal destiny of HBMs.

The modalities of informed consent, the extension of possible future use, and the anonymisation of materials are ancillary to the nature of this relationship.

The fact that the entire picture is normally presented in the inverse order—where a broad consent is given in the primary form, and the sense of the material belonging to the body is removed (thus also removing the problem of corporeity)—is a reflection of the ideology that the US judge James Boyle called "informational" reduction of the body (Boyle 1996). According to Boyle, in fact, the neocolonisation operated by science, market and law has resulted in the body being progressively de-materialised and then reconstructed in terms of information. In this paradigm of information that involves, aside from the body, other relevant social goods such as many products of technological innovation, there is a "tendency to economically and conceptually separate the informational message from the means of support (cells, discs, etc.) and to progressively devalue the means of support (literally, to reduce marginal cost) in relation to the message transmitted" (Boyle 1996, 7).

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[2] At the end of the 1990s the National Bioethics Advisory Committee (NBAC 1999), which was the first permanent ethics committee in the United States, was the first to clarify that only the samples that were originally unidentified remain that way once destined for research, while all samples identified at the moment they were taken, even if they were subsequently coded oranonymised, still maintain a certain level of re-identifiability. The NBAC thus unequivocably established that all identifiable materials and information are connected to a subject—and therefore must be treated according to the principles of research on subjects—and that only those that are totally anonymous from the start are pure data objects.

Section 45 of the Code of Federal Regulations (CFR, at 46.102(f)) from the 2004 guidelines of the US Department of Health and Human Services (DHHS) further reinforced the point, affirming that "to gain private identifiable information or biological samples identifiable for research purposes integrates the extremes of research on human subjects" (DHHS 2004).

The most recent proposals for standardisation of practices, for example that of the International Conference for Harmonisation between the United States, Europe and Japan (ICH 2007), have introduced a distinction between *single coded* and *double coded* samples—to be inserted between the definitions of *coded* and *unlinked*—in which codified materials are recodified and the two codes are then linked by a third code. The codes are entrusted to different subjects and, in order to re-identify the individual, it is necessary to possess all the codes.

This dematerialisation of the body, i.e. its reduction to "bodily information," has had many outcomes (Tallacchini 2009). In particular, these involve: information that is connected to informed consent, which in turn affects the autonomy between receiving information and deferring desire; the anonymisation of HBMs, with the resultant canceling of personal and identifying bodily information, which deprives it of subjective guardianship; and the biological and isolated, purified genetic information that, when extracted from raw corporeality, constitutes the real basis of biotechnical patentable inventions. In all cases, information dominates the means that drive it and lives its own life: scientifically, economically, and judicially.

Thus, the law pertaining to the body and the related information in part did not allow individual control of biological materials, allocating those powers to the market of science (Gold 1996; Andrews and Nelkin 2001). However, in a certain sense, the materiality of the body has re-emerged through the legislative and judicial history, making today's picture less convincing as a whole.

4 The US Framework: Privacy v. Property, and the Abandoned Gift

In the US, where the problems associated with the subsequent use of human tissues were first encountered and where, consequently, the first explicit rules were composed, strangely privacy was not primarily addressed by the law. Reference to privacy continued to appear in judicial records pertaining to tissues, but without any particular associated problems. This fitted with the common American practice of removing all obstacles to the proprietary discussion (as in the Moore case[20]). As noted earlier, the same procedures of anonymisation, ostensibly aiming to protect privacy, were explicitly thought of as a form of (inside-out) "judicial transubstantiation", or the conversion of subjects into objective data, freed from the original subject and therefore liberally appropriable.

Thus, the proprietary discussion is at the centre of the whole debate, taking the form of continual attempts to redefine the many proprietary concepts, material and intellectual, strong or attenuated, composed of rights or interests, that have been evoked and inserted into the game of controlling human tissues.

As mentioned previously, the event that summarised the initial judicial framework of biological materials that are reused for research and commercial purposes occurred in the US (Office of Technology Assessment; OTA 1987). This was Moore v. Regents of the University of California, which dealt with personal and patrimonial property rights with respect to biological human materials.[3] In 1990, the California Supreme Court made a very important conceptual distinction between privacy and property with respect to secondary use of HBMs.

[3] Moore v. Regents of University of California, Cal. App. 2 Dist. 1988; Regents of University of California v. Moore 51 Cal. 3d 1990.

The famous statement that it is not necessary "to force the round pegs of 'privacy' and 'dignity' into the square hole of 'property' in order to protect the patient" resulted in the double destiny of HBMs, where they were ambiguously perceived in terms of autonomy, of an implicit will on the part of the donor to abandon them (*res derelictae*), and of *res nullius*, and potential intellectual property rights, on the part of the receiver.

By explicit admission of the Court, the acceptance of the dual roles of tissues as both private and property was entirely the result of the necessity to avoid possible resentment from the pharmaceutical industry, which would not allow its access to "necessary raw materials" to be limited.

These opportune judicial pronouncements were predisposed during the Moore case by the OTA; the scientific-technological consultants for the United States Congress. In a 1987 document, the OTA observed that HBMs could be adequately seen as *res derelictae* and also as *res nullius*, proposing a weird analogy between biological materials detached from the human body and the literally huntable wild fowl: "It could be argued the patient and his tissues stand in a relationship similar to that between a landowner and wild animals on his land. …Not having exercised dominion or control over the tissues, the patient's rights therein would be like those of a landowner who had made no attempt to capture wild animals passing over his land" (OTA 1987, 82).

The National Bioethics Advisory Commission then observed that "the biological materials are available not to anyone, but in general are restricted to those who have legitimate research interests in their use and presumably possess the capability to perform sophisticated scientific studies that can reveal biological information about the samples or even health-related information about the persons from whom they came" (NBAC 1999, 59).

The arguments favouring the theory of abandoning tissues and the social (and implicit commercial) utility of research uses are theoretically reinforced by patenting, which sanctified the proprietary, immaterial nature of rights to the biological materials. If there is no true property right to raw materials, an immaterial property right can exist for the engineering work that is applied to them, and this can be made out to be factually and legally distinct from mere cellular material.

After these initial discussions, the issue of the availability of HBMs has been constantly debated in the US through several major court decisions.

In 2003, the Greenberg v. Miami Children's Hospital Research Institute case (264 F. Supp. 2d 1064 S.D. Fla. 2003) dealt with the donation of samples for the study of Canavan disease by Greenberg to Dr. Reuben Matalon, a researcher at Miami Children's Hospital. The Court argued that the relationship between researcher and tissue donor is not comparable to the doctor-patient relationship. In particular, the researchers are not subject to the same financial obligations, even those concerning the communication of possible economic interests. Once they had acquired a patent on the Canavan gene, Miami Children's Hospital became the undisputed owner of the materials involved in the invention of the test for Canavan disease developed by Matalon.

The Greenberg and Moore cases thus depicted researchers as legitimate judicial figures who were morally confident and entrepreneurial, but the Greenberg case

also highlighted the missing information on the economic aspects of the donation, representing a recognised violation of Moore's rights. However, the Florida Court was in accordance with the California Supreme Court in indicating the judicial existence of a right to property in the patent.

Thus, in both the Moore and Greenberg cases, the patent allows biological materials from non-appropriable "natural" entities to have artifact status, and therefore to have an actual, recognised judicial right to be property.

With regard to the question of abandoning the tissues, the Court in the Greenberg case introduced another factor regarding the free availability of biological materials to the industry by stating that the limited property right on tissues "evaporates" when these are donated to a third party.

In 2006, another case, Washington University v. Catalona (437 F. Supp. 2d 985 E.D. Missouri 2006), dealt with a similar situation. The controversy here concerned the destiny of biological materials stocked in a biobank in their natural state, where it was not possible to invoke the patent which was the source of property rights.

In this case, the Court of Appeal of Missouri found that the prostate samples received by Dr. William Catalona from his patients while he was working at Washington University that he and his patients wanted to transfer to Northwestern University of Chicago belonged to Washington University; and the US Supreme Court declined the case in 2007 (US Supreme Court 2007). Washington University, according to the court, had received the HBMs through an "unconditional donation".

Opinions on the Catalona case were strongly divided in the US; authors like Lori Andrews would have liked the case to be decided in favour of Catalona and his patients, while Glantz and Annas approved of the outcome. In fact, throughout the US justice system, arguments favouring the market and innovation were prevalent; only a few courts adopted a different attitude.

Apart from the disagreement on how to allocate biological materials as property to private parties or industry, there is wide convergence in the American literature on accepting "proprietary interests" for tissues, and on the belief that clear recognition must be found.

Lori Andrews, who was in favour of individual rights to HBMs, pointed out the existence of previous judicial findings, although these were unusual, that on many occasions had affirmed proprietary interests on the part of the person who gave up the tissue (Andrews 2006).[4] The patient's intentions, the aim of the donations and the conviction that the patient conserved power over their own tissues were decisive elements in the configuration of the "proprietary interests" of citizens who donated their tissues for beneficial aims.

[4] Lori Andrews cites on this matter: *York v. Jones, 717 F. Supp. 421, 426 (E.D. Va. 1989)*, where "proprietary interest" was recognised for a couple for their own pre-embryos, thus limiting the powers of the clinic where the pre-embryos were deposited; *Hecht v. Superior Court of Los Angeles County, 16 Cal. App. 4th 836, 850 (Cal. Ct. App. 1993)*, which recognised the inheritants' ownership of the seminal liquid of the deceased; and *Whaley v. County of Tuscola, 58 F. 3d 1111 (6th Cir. 1991)*, relative to the proprietary interests of a relative to the body of the deceased.

Meanwhile, Glantz et al. (2008), even as they applauded the Court's decision, requested legislative affirmation of property rights on HBMs in favour of research institutions. The current situation would actually leave human tissues in a judicial no-man's land, and research requires the stability of a uniform judicial opinion.

In this perspective, Glantz and Annas pushed further, confronting the question of the analogy between "research on human subjects" and "research on human materials." This analogy, according to which the right to revoke consent should have equal worth in experimentation on subjects and materials, would be misleading and inadequate, deriving from a hurried assimilation of the two legal paradigms. The question is still largely undiscussed, but it is becoming a point of convergence for dissatisfaction with the status quo, and has raised some interesting perspectives.

Is the analogy between research on subjects and research on materials correct and adequate, or does it represent the somewhat hurried result of previous events in the field of human experimentation? Glantz and Annas have stated that the two themes are now radically different and have provided a conceptual clarification that definitively separates their destinies. However, when the discussion attempts to resolve the objective materiality of bodily tissues in subjective terms, it is dominated by the European approach.

5 The European Framework: Heteronymous Autonomy and the Destruction of the Donated Body

In Europe, the disposal of HBMs was discussed almost solely in terms of the two "mantras" of the principle of autonomy and the prohibition of gaining profit from the body and its parts. This was to a certain extent the result of the complex and unresolved economic-political paradox in which the European Union (EU) was debating the harmonisation of the original idea of markets along with subjective political views, with a resultant split identity for the consumer-citizen (Tallacchini 2007, 2009).

In the face of the new prospective uses for human tissue, the EU (formerly European Communities, EC) and the Council of Europe (COE) intervened; the EU provided a framework for dealing with cells and tissues donated for therapeutic use, and the COE provided policy regarding materials conferred for research. Although the literature on human tissues rarely discusses these two areas together, this more extensive look at the European framework is useful in order to comprehend some of the presuppositions causing the divergences in the regulations.

6 The EU Institutions

The EC/EU institutions separated tissues donated for therapeutic use from those donated for research although, to begin with, the orientation seemed to lean toward unity of perspective. In 1998, the European Group for Ethics (EGE) at the

European Commission, recognising the urgency of regulation for tissues, defined as a "moral imperative", made no distinction between the types of donation or among diagnostic, therapeutic or research uses (even when there were commercial implications), and included the essential elements of informed consent, which was seen as revocable.[5]

The EGE was, in fact, concerned with establishing a solid connection between the individual act of freely contributing tissues and the public trust dimension in relation to potential public benefits derived from the donation, for both therapeutic and research uses. This meant creating a shared policy on tissue for both groups. The EGE was well aware of the substantial difference between organ donation and cell and tissue donation; while organs are used in their natural state, cells and tissues are the basis for developing many "therapeutic products", which are usually patentable and are always destined for the market.

Because of their potential destination in the market, their divided experimental character, and for safety and storage reasons, research use of cells/tissues has more in common with therapeutic use of cells/tissues than with therapeutic use of organs/tissues.

However, this unity of direction was less apparent in the legislative process, where a notable distance between therapy and research was seen. This was reflected, for example, in decisions made by ethics committees. Directive 2001/20/EC on best practice in medicine is termed only with respect to clinical experimentation, thus leaving secondary use without ethical control. Moreover, the (then) attitude of the COE in the area of human rights and biomedicine did not make it easy for the EU to intervene directly in the area of research.

In 2004, Directive 2004/23/EC, which dealt with the donation, supply and warehousing of all tissues (with the exclusion of organs and blood) and cells, was approved (Law 191; 2007). This directive introduced the principle of donation of human tissues, proposing an explicit "European philosophy" of donation, with the aim of defining quality laws and security for HBMs destined for human applications, but foreseeing that some research could also include their use.

The Directive was completed in 2007 from Regulation 1394/2007/EC.[6] which aimed to improve the methods of centralised authorisation in the marketing of all "products" derived from tissues and cells (cellular and genetic therapies and products of tissue engineering), which were defined as advanced therapy medicinal

[5] EGE (1998, 8): "The information provided to the donor should concern:
- the procurement arrangements, in particular concerning the free nature of the donation, and the extent of its anonymity.
- possible tissue storage time and conditions, and conditions of registration of data in databases, in conformity with requirements of private life protection and medical confidentiality.
- foreseeable use of the tissues (diagnostic, allograft or autograft, pharmaceutical products, research, production of cellular lines for various uses, etc.). The donor may at any time withdraw her/his consent".

[6] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

products (ATMPs). In addition, the two documents constructed and accurately separated the free sphere of tissue donation by European citizens and the reality of the European tissue market: European donors were asked to freely provide biological materials for pharmaceutical purposes out of a sense of solidarity, therefore consenting to the production of new therapeutic products to put on the market, which they were then able to purchase.

In addition, the EU legislation had to cross the threshold of proprietary language applied to the body when it came to defining who owned the tissues donated by European citizens that were to become the base materials for the production of ATMPs (Regulation 1394/2007).

The question of proprietary systems addressing the HBMs and the necessary legislative harmonisation was explicitly addressed during the consultative process that preceded the approval of the Regulation. The comments received on the draft of the regulation (DG Enterprise 2004) established that it should clarify the methods of appropriation of tissues.[7]

The Regulation did not, in fact, clarify this point, limiting itself to requiring, at least in principle, that "cells or human tissues contained in medicines for advanced therapies should come from voluntary and free donation" (Art. 15). Nonetheless, although the full question of ownership was avoided, it was clear that materials that were to be used for producing ATMPs would become the property of those who were to use them for research and experimentation and subsequently put them on the market.

Thus, it can be seen that the language of and need for proprietary stability were not foreign to the community legislators, but that they nonetheless reduced proprietary language or even made it disappear, while at the same time promoting the research/marketing system. It is obvious that the legislation around ATMPs was not framed in terms of gratuitousness as was the case for organs or blood, but was instead framed in terms of commercial pharmaceutical products.

However, moving on from the problematic aspects of this "European tissue market", it should be emphasised that Directive 23/2004 excluded the possibility of revoking a donation, in order to give stability to the economy of tissue products. The donor must be reassured regarding the confidentiality of the present and future use of the information, but cannot take back what has been contributed.

Further, in policy regarding ATMPs, the same rights to privacy, even when named and guaranteed, do not appear as stringent as in the case of research. The Directive foresees that tissues and information are completely traceable—from the donor to the product to the recipient (Art. 8); and the Regulation on ATMPs describes total traceability of tissues (Art. 15). Traceability of tissues and the anonymity of the donor and recipient then coexist in different "public spaces"; donor/recipient citizens are anonymous within the group, but are able to be traced by institutions and industries involved in warehousing and using the biological materials.

[7] DG Enterprise (2004, 6): "Ownership of the cells and tissues after donation: as legislation differs from one Member State to another, it is recommended that the regulation should provide clarity on this issue".

7 The Council of Europe

Almost in parallel with the work of community institutions, the human rights branch of the COE approved a Recommendation in 2006 (Rec 4; 2006) that dealt with research on HBMs with respect to attributing power to the patient-citizen and guarding his rights regarding possible scientific research uses of the HBMs.

The premise behind the Recommendation, following a widespread tendency (UNESCO 2008), was that research on HBMs is completely comparable to research on human beings. "Biomedical research", the Report on the Recommendation explicitly observes (CDBI 2005), "can be carried out not only on human subjects, but also on materials of human origin." From this came the extension of requirements for consent in biomedical research, including in the treatment of HBMs.

The Recommendation strongly requested explicit (and detailed) consent for the use of HBMs in research and indicated different forms for de-identifying materials. Furthermore, it recognised the same right that subjects involved in a clinical trial have to abandon the study at any time for the person donating tissues for research, adding the right to request the destruction or anonymisation of the materials.[8] Donors, therefore, have the power to destroy the donation when their materials are identified.

It is not totally clear, although the point is further discussed in the explanatory report of the recommendation (CDBI 2005), whether destruction and anonymisation of the materials are considered totally equivalent options, or whether the donor or the institution has the right to choose which of these options they wanted.

Instead, the discipline of donation was fractured, which resulted in donations being revocable or irrevocable depending on the different goals in play.

Those commenting on these decisions at the time either did not mention or did not discuss the separation of research and therapeutic use and the two different destinies of tissue donations, taking that division as an "unarguable normative fact" (Cambon-Thomsen et al. 2007); instead, they paid attention solely to the possibility of extending informed consent in order to amplify the manoeuvring space of the research institutions, a consequence which seemed to spring directly from the reinterpretation of autonomy in terms of solidarity. In fact, this autonomy has little to do with solidarity, and the concept seems to have had the outcome of mere acceptance of heteronymous sources of normative structure (laws and

[8] Rec(2006)4, Article 15—Right to change the scope of, or to withdraw, consent or authorisation—"(…) When identifiable biological materials are stored for research purposes only, the person who has withdrawn consent should have the right to have, in the manner foreseen by national law, the materials either destroyed or rendered unlinked anonymised". And the Explanatory Report states at 73: "The individual has the right to withdraw from the research and the right to destruction of his/her biological materials and data. In the case where a person withdraws and the research has already generated findings, these findings ought to be rendered unlinked and anonymised, unless they have already been published or it is otherwise impossible to withdraw them from the research".

regulations),[9] or even acceptance of the private goals of research or industrial entities. Nonetheless, while homage to federal laws does not lack an ethical foundation, since the laws were created according to accepted criteria of legitimacy, acceptance of the idea of "autonomy in solidarity" does not in itself guarantee the existence of legitimacy.

This vision (which was particularly endorsed by Hansson (2007, 2009), according to whom informed consent implied total acceptance that the decision-making power was now in the hands of the recipient of the HBMs) re-proposes traditional medical paternalism, by using the language of autonomy, and projects it into the area of research; in addition, it also includes the potential risk of decreased financial duties, as seen in the Greenberg case.

Therefore, the question becomes: does it still make sense, or is it misleading, to maintain the language of autonomy where values and the associated necessary guarantees are part of the judicial-political sphere, with regard to socially shared aims, investments in health, transparency, and the democratic functioning of institutions?

It is difficult to resist the impression that when autonomy was redescribed this way in heteronymous terms, it allowed the rapid (but opaque) attainment of possibilities that should instead have been reached through federal guarantees of human rights.

The COE left the citizen with very little empowerment, and "ethically" strained the decisions/recommendations to purify them from any reference to ownership of HBMs, leaving the "proprietary discourse" to reappear immediately just under the surface; this can be seen in the European judicial pronouncements on the theme of patents. The courts declared themselves to be lawful in granting patents on biological and genetic materials; in fact, they constantly repudiated counterclaims founded on the absence of informed consent for use of the materials.

One of the most famous cases on the subject is the Myriad case. Myriad Genetics holds the patent for diagnostic tests for breast and ovarian cancer linked to the mutation of the BRCA1 gene, and many research institutes, doctors' associations and patients tried to oppose the granting of this patent in the name of the serious effects (for clinics and research) produced by a monopoly.

In its 2007 decision on BRCA1 (European Patent Office, EPO 2007), the Board of Appeal of the EPO rejected as irrelevant the argument that Myriad would never have obtained consent to use the biological materials concerned in the patent,

[9] Hansson (2009, 9): "Making autonomous decisions in accordance with the Kantian tradition thus involves taking into account the well-being of others through a judgment of how one's own decisions affect other people's ability to act in a morally responsible way and to attain their own goals. Autonomy in the Kantian tradition is inherently social, with the implication that the working out of legal protections for self-determination and privacy in association with biobank research must simultaneously do justice to both the research subject's independence and to this individual's dependence on others for fulfilling mutual interests such as new biomedical knowledge and new treatment opportunities".

specifying not only that consent was not a requirement for patentability (neither according to the Convention of Munich nor according to the European directive on biotechnological inventions 1998/44/EC) but also that the same Court of Justice of the (then) European Communities had judged it misplaced to even raise such fundamental questions on human integrity in the context of patents.

8 Beyond Consent and Property: The Participatory Turn

As Rao (2007, 380) and others have observed, the proprietary paradigm is so powerful that it has been accepted more or less implicitly in the appropriation of HBMs, even where it has been formally rejected or avoided.

Human tissue is basically owned and treated as property, and the continued controversies on the subject only demonstrate more clearly the necessity to move towards forms of different judicial arrangements than informed consent (Glantz et al. 2008). Consent for research use becomes more and more "unconsciously figurative consent".

The most frightening aspect of the power of the proprietary paradigm is that the economic dimension, more than the possible relationships between a subject and an object, is susceptible to multiple readings. The use of the expression "proprietary interests", which is present in both the literature and judicial statements, appears to be an attempt to overcome the exclusive semantics of autonomy and generalised use of informed consent, while at the same time softening the acceptance of the notion of property.

Several proprietary models have been explored and tested in the history of legal systems. Some concepts deal with diminished proprietary relationships, in which the relationships and socially shared dimensions of the object limit the operative powers of the subject. In these models, individual duties and powers are combined in a different way to account for different values and guardianship levels of the object for third parties and posterity, relative to its overall destiny.

It is interesting to remember that "proprietary interactions" have been discussed in "environmental rights philosophy" (and also in environmental protection discussions). Far from involving unilateral visions of dominion and control, these proprietary interactions were more about administrational relationship, stewardship and partnership between subjects and goods, aimed at common uses, both present and future, since these uses are not arbitrarily available in the case of environmental goods, the donated good of environmental value and the collectivity interested in its conservation (Edelman and Hermitte 1988). These minority visions of property correspond, moreover, to historically "losing" visions of relationships between human beings and the environment in the Western world, as a result of past attitudes to administration and conservation of nature.

According to Rao (2007), the idea that property involves stewardship, or care-taking, can also be applied to the body. This concept is not new; it was, for example, spoken of by the seventeenth century philosopher John Locke.

According to Rao, one can speak of proprietary rights with respect to the body, making the body "dormant property", but with the concept described in terms of stewardship.

In this perspective, curiously, the right to withdrawal of consent and the connected right to request destruction of HBMs as suggested in the European framework, neither negates the proprietary paradigm nor represents the version describing individual ownership, as affirmed in human rights models in civil law between the 1700s and 1800s.

In fact, the French judge Rèmond-Gouilloud, in an essay on the environmental crisis, interpreted the expression of property rights according to article 544 of the Napoleonic Code of 1804 as consisting not of the power to destroy the object but of "the right to destroy" (Rémond-Gouilloud 1989).

The possibility of losing the uses, utility and shared or sharable benefits of HBMs that have been previously donated, through the "desire to destroy", is reminiscent of the destruction of the environment, which Garrett Hardin called the "tragedy of common goods" (Hardin 1968).

If the idea of consent cannot be separated from the most radical proprietary logic, beyond the limits previously highlighted, the problem is no longer that of avoiding appropriation, but is rather that of exploring the least extreme and most "flexible" dimensions of proprietary interactions.

In addition to the civil sphere knowing of these alternative proprietary models, these alternatives were in fact often practised in common law, in particular in environmental law and inheritance law.

In general, these are the institutes that deal with both obligatory rights and real rights, and that aim, through recourse to fiduciary ideas, to protect public or collective interests. Property is described in terms of modules used for specific purposes or for sharing, and the objective is to increase the value of and conserve the goods in question.

In the theoretical and judicial conversation in the US, two specific hypotheses were framed in order to define tissues: donation agreements and charitable trusts.

In the first hypothesis, donation agreements, the donor is bound to a specific, stable outcome, leaving it open for the act to take an absolute or conditional form. For unconditional donations, there are no restrictions on the use of HBMs, while for conditional donations, the donation may be subject to limits on the destination of or wealth resulting from the donation. In the literature, this model was supported by Glantz et al. (2008), who outlined a formal procedure for donation and a solution to the proliferation of judicial controversies about HBMs and the interpretive fragmentation by the Courts. In the opinion of these authors, the analogies used when discussing the material components of the body—birds of passage in a field, buried treasure, but also the gathering of books or software programs—are simply inadequate for the specific aims of biobanks.

In charitable trusts, the "proprietary interests" associated with tissues are transferred to a custodian or trustee who, together with the proprietary powers, also carries the fiduciary duties of responding to certain predetermined uses of the goods in favour of any third parties (the public, or current and future patients).

The recipient has duties of transparency in the care of the received goods, and the donor retains a consultative role and controls these same activities (Winickoff and Winickoff 2003).

All these attempts are moving toward what Gottweis and Lauss have called a "participatory turn" in the governance of biobanking (Gottweis and Lauss 2010). "There is a need for new strategies to regulate the relationships between individual citizens, society and biobanks, and to find new solutions for dealing with the core issues of consent, privacy, ownership, access and benefit sharing in the linking of society, citizens and biobanks. …Participatory arrangements that are responsive to the views of patients and 'lay people', and also operate on a transnational level, will be key to such novel arrangements" (Gottweis and Lauss 2010, 187).

In 'The Immortal Life of Henrietta Lacks' (Skloots 2010), Rebecca Skloots tolds a story in which poetry and civic sense seem to merge. It is the story of Henrietta Lacks, an African American woman who died of cervical cancer in the early 1950s. The cell line derived from Ms Lacks' tissues, patented as HeLa, became the first successful cell line, used globally for diagnostic tests and genetic research.

It is not clear if Ms Lacks ever knew of the extraordinary potential of her cells. Her family was uninformed for years after she died. However, Skloots says, her cells became immortal, and now her story has restored her dignity, previously hidden by an anonymity that cancelled, with her name, the importance of memories.

"We must not see any person as an abstraction", reminds Skoots, quoting Elie Wiesel.

This case occurred in the empty space of social and legal unconsciousness. Contemporary awareness may help to fill this gap, by building a shared space where individuals and their social utility are not divided but can meet.

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Intellectual Property and Biobanks

Naomi Hawkins

1 Introduction

Biobanks are a new form of research infrastructure, which enable exciting new ways of conducting research, made possible by advances in genomic sciences. The purpose of biobanks is to allow groundbreaking research in genomics, in the hope that this research will ultimately benefit patients. In this chapter, it is argued that, having regard to this purpose, biobanks should develop IP policies which aim to maximise patient benefit.

Any consideration of intellectual property (IP) rights in the context of biomedicine, and genomics more specifically, arouses strong feelings. On the one side, there are those who laud IP as incentivising innovation and leading to the development of innovative new treatments for disease. In contrast, others claim that IP rights cause blocks to innovation and prevent legitimate academic and scientific research, to the detriment of patients.

The justifications for the grant of IP rights over intangible property tend to fall into one of two general categories. The first is related to natural right to the products of labour; for example, copyright is frequently justified as recognition of an author's natural rights over the products of their creative endeavour (Drahos 1999). The other major justification is instrumental; that IP induces or encourages desirable activities (Machlup and Penrose 1950). The patent system is most commonly justified on the basis that it provides inventors with an incentive to invest in the research and development of new products, or an incentive to disclose technical information to the public which would otherwise remain secret.[1] Under this

[1] *Asahi Kasei Kogyo*, [1991] RPC 485, 523.

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second justification, IP rights are not solely about benefit for individuals; instead, they serve the purpose of providing a sufficient reward for creators of IP, in order that they develop innovations which have a socially useful purpose. In the biomedical sciences, the incentives tend to be provided by patents, although copyright may also play a role.

Although there have been many considerations of IP in biomedicine, IP in the context of biobanks is less discussed, perhaps largely because biobanks are a relatively new type of research infrastructure, and translational outcomes are still on the horizon. A biobank is a research infrastructure or resource, which is built up from many individual parts, to be used for research. It is therefore intended, and likely, that a biobank will be used by others to develop useful innovations.

There two key issues which will be considered in the following chapter. The first key issue is that of the subsistence of IP rights: can a biobank be the subject of IP, and how may research done on the biobank be the subject of IP? The second key issue is the question of how a biobank may manage its IP policy to shape the translational outcomes which arise from research.

2 What IP Arises from a Biobank?

The first relevant question to consider in relation to IP and biobanks is the ways in which IP might arise. Below, I consider the question of whether there is IP in the biobank itself, and if so, what purpose it might serve. Secondly, I consider the more important question of the IP that arises in innovations developed through research on the biobank.[2]

It is worth noting at this point that information per se cannot be owned.[3] As a result, an individual genetic profile in a biobank is not the subject of IP rights.

2.1 Is the Biobank Itself IP?

A biobank is a compilation of information. IP rights can arise in compilations in two areas; through copyright, and the database right.

A biobank may be the subject of copyright protection as a database (Harris and Rosenfield 2005). Under UK copyright law, a database is protected as a literary work.[4] A database is defined very broadly as a collection of independent works,

[2] This chapter is a consideration of IP rights, and I therefore do not consider the question of any property rights in the physical samples.

[3] *Douglas v Hello! Ltd* (*No 3*), [2005] EWCA 595, [119], *OBG Ltd and another v Allan and others*, [2007] UKHL 21, [275], *Boardman v Phipps*, [1967] 2 AC 46, 127 per Lord Upjohn, *Oxford v Moss*, (1979) 68 Cr App R 183, Hardcastle (2007, 12).

[4] *Copyright, Designs and Patents Act 1988* (*UK*), s3(1)(d).

data or other materials which are arranged in a systematic or methodical way, and which are individually accessible by electronic or other means.[5] The database will only be protected if it is the author's own intellectual creation, by reason of the selection or arrangement of the contents of the database.[6] It seems reasonable that the far from routine skill and knowledge required to select the appropriate participants for a biobank, and then arrange the material within the biobank, would satisfy this requirement.

Copyright in a literary work arises automatically, without application or registration, and subsists for the life of the author plus 70 years. When the database is created in the course of employment by an employee, provided there is no agreement to the contrary, the copyright will vest in the employer.[7] Copyright provides for a number of exclusive rights which vest in the owner, such as the right of reproduction and the right of distribution. Infringement occurs if the defendant carries out an activity which falls within the copyright owner's substantial control, the defendant's work was derived from the copyright work and the act was carried out in relation to a substantial part of the original work.[8] In the case of a biobank, copying of a substantial part of the database without the authorisation of the copyright holder would amount to infringement.

The second type of IP right that may arise in a biobank is the database right. This is a sui generis right which was introduced in Europe to protect the work involved in creating a database. The database right is a property right that subsists in a 'database' which is defined as a collection of independent works, data or other materials that are arranged in a systematic or methodical way, and are individually accessible by electronic or other means.[9] The right arises if there has been a substantial investment of financial, human or technical resources, and the investment may be substantial in terms of quality, quantity or a combination of both. The creation of a biobank would quite clearly satisfy these requirements. The database right vests in the maker of a database. The maker is the person who takes the initiative in obtaining, verifying or presenting the contents of a database, and who assumes the risk of investing in that obtaining, verification or presentation. In the case of biobanks, it is likely that there would be joint making, as the responsibilities for these actions would be split among a number of parties such as funders who take financial responsibility and multiple institutions such as universities and hospitals. Where an employee makes a database in the course of employment, the employer is regarded as the maker of the database.[10]

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[5] Ibid., s3A.

[6] Ibid., s3A(2).

[7] Establishing ownership may be more complicated if the biobank is being developed by various people who are employed by different institutions. In such cases, the ownership of the copyright in the biobank should be provided for by contract.

[8] *Copyright, Designs and Patents Act 1988* (*UK*), s16(3).

[9] *The Copyright and Rights in Databases Regulations 1997* (*UK*), r12.

[10] Ibid., s14(2).

The database right is infringed where a person, without the consent of the owner of the right, extracts or re-utilizes all of, or a substantial part of, the contents of the database. The fact that material is only transferred to another medium after critical examination does not preclude a finding of extraction.[11] 'Substantial' means substantial in terms of quantity or quality or a combination of both, and this is assessed by reference to the investment in the creation of the database and the prejudice caused to that investment by the act of extracting or re-utilising that part.[12] It is arguable that the unauthorised use of the database for the purposes of research would be an infringement of the database right. The remedies which are provided for infringement of the database right are the same as for copyright in the UK. Copyright and the database right may coexist.

IP might also arise in other aspects of a biobank. For example, software, manuals or standard operating procedures all could be the subject of copyright. These aspects of the biobank could therefore be protected from unauthorised copying, and could also be licensed commercially, or placed in the public domain.

These IP rights are likely to be relevant in the following ways. Firstly, the holder of copyright, or a database right can prevent unauthorised copying. Therefore, if there is unauthorised access and copying of the biobank information, copyright may provide a basis to prevent further copying or use of the information or recover damages for the unauthorised copying. It is worth noting that an unauthorised use that harms an individual participant, for example theft of data on an individual, is unlikely to constitute copying or extraction of a substantial part so in such a case neither copyright nor the database right would provide a remedy. Secondly, IP is often regarded as useful for the raising of funds; investors are said to be reluctant to deal with a party that does not hold IP. Therefore, a biobank may be in a stronger bargaining position with a potential investor if it can point to specific IP rights in the biobank. The final area in which the ownership of the copyright or the database right in the biobank is likely to be significant is in the case of the bankruptcy, dissolution or other ending of the biobank (Vorhaus and Moore 2009). In such a case, the IP is an asset, which can be sold or otherwise transferred.

Despite these three functions, the significance of the subsistence of IP in the biobank itself is not high. Biobanks exist in order to provide access to their information to researchers, not to protect it from being copied. Provided that the security of the biobank is good, and access is provided under the terms of a well drafted contract, copyright protection is only likely to be of use in rare cases when there is some sort of unauthorised access. Should there be any problems with a researcher who has gained access under a contract, the contract is likely to provide a much better scheme for relief than copyright law.

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[11] *Directmedia Publishing Gmbh v Albert-Ludwigs-Universität Freiburg* (*Case C-304/07*), [2009] 1 CMLR 7.

[12] *The British Horseracing Board Ltd and Others v William Hill Organization Ltd* (*Case C-203/02*), [2005] 1 CMLR 15, [69].

2.2 Can IP Arise from Research Done on the Biobank?

When research gives rise to an innovation, then that invention could potentially be patentable. A patent is a limited monopoly that is granted in return for the disclosure of technical information. In contrast to copyright and the database right, patents are only granted after the applicant satisfies the requirements of registration.

In order for an innovation to be patentable, it must satisfy a number of criteria. Patents are available for inventions in the form of products, such as chemicals or useful objects, and also processes, or methods. The invention must be novel, that is, not previously made available to the public anywhere in the world, prior to the date of filing.[13] It must be non-obvious, or inventive.[14] It must also be susceptible of industrial application, or useful in some way; inventions which have a clear role in treating disease are susceptible of industrial application.[15] Genetic inventions, such as the isolation of a gene encoding for a particular protein, where the physiological role of that protein is unknown, which are 'useless for any known purpose' do not fulfil this requirement.[16]

Inventions in patents must also be sufficiently described, in order to enable that invention to be performed. The applicant must disclose the invention in a manner that is clear and complete enough for it to be performed without undue burden by the person skilled in the art using his or her common general knowledge to supplement the information contained in the specification.[17] This requirement reflects the general principle that a patent monopoly is only awarded provided that the inventor makes the invention available to the public.

In Europe, patents are only available for inventions, and not for discoveries.[18] Patents reward a technical contribution, and not the mere discovery of an existing law of nature. A distinction is drawn between naturally occurring substances and the products and processes which result from the human effort involved in isolating those substances from their natural environment. The case law is clear that not only the process for isolation, but also the product per se, where it is new in the absolute sense of having no previously recognized existence, are both patentable.[19] In relation to biotechnological inventions, the limits of the prohibition on the

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[13] *European Patent Convention 1973*, Art 54, *Synthon BV v Smithkline Beecham Plc* (*No 2*), [2005] UKHL 59, [2006] RPC 10.

[14] *European Patent Convention 1973*, Art 56, *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28.

[15] *Hematopoietic receptor/Zymogenetics* (*T898/05*), [8].

[16] *Eli Lilly v Human Genome Sciences Inc* [2010] EWCA Civ 33, *Eli Lilly and Co v Human Genome Sciences Inc*, [2008] EWHC 1903 (Pat), [2008] RPC 29, *Chiron Corporation v Murex Diagnostics*, [1996] RPC 535, 607.

[17] *European Patent Convention 1973*, Art 83, *Eli Lilly and Co v Human Genome Sciences Inc*, [2008] EWHC 1903 (Pat), [2008] RPC 29, [239].

[18] *European Patent Convention 1973*, Art 52, *CFPH LLC's Application*, [2005] EWHC 1589 Pat, [2006] RPC 5, *Genentech Inc's Patent*, [1989] RPC 147.

[19] *Howard Florey/Relaxin*, [1995] EPOR 541, [5.1].

patenting of discoveries are further elaborated by the terms of the Biotechnology Directive,[20] which provides in art 5(1) that 'the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions'. Article 5(2) provides, however, that '[a]n element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element'. However, patents may be awarded in relation to the technical manifestation of a discovery. In this way, a genetic diagnostic test which is the technical embodiment of the discovery of the relationship between a gene and a disease is patentable, while the mere relationship between the gene and the disease, in the abstract, is not.

2.3 Ownership

Ownership of a patent is key, as the patent owner is able to exploit and control the use of the patent, make decisions about the assignment, licensing and mortgage of the patent and sue for infringement.[21] The first owner of a patent is usually the person who is entitled to grant. In most cases, this will be the inventor(s) of the patent.[22] There are two cases where an employer is entitled to grant of the patent. The first of these is where inventions are made by employees during the course of normal and specifically assigned duties, where the invention was made in circumstances where an invention might reasonably have been expected to arise from the carrying-out of those duties.[23] The second case is where an employee's position and status within an organisation is such that they will be taken to be under a 'special obligation to further the interests of the employer's undertaking'.[24] In the case of biomedical inventions, in the vast majority of cases, the employer will own the patent in question, as in most of these cases, employees are employed to invent.

In relation to inventions which are created by parties who have accessed a biobank, the patent is likely to be owned by the employer of the inventor. In the absence of an agreement with the inventor, the biobank itself will not be an inventor, nor will it have any entitlement to the patent. A biobank could however, as a term of the access agreement, provide that it was entitled to own any patent arising from the biobank information.

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[20] *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions* [*1998*] *OJ L213/13*, (6 July 1998).

[21] Ownership of inventions is dealt with as a matter of national law, not under the *European Patent Convention 1973* and therefore provisions referred to in the following sections are from the *Patents Act 1977* (*UK*).

[22] *Patents Act 1977* (*UK*), s7(2)(a).

[23] Ibid., s39(1)(a).

[24] Ibid., s 39(2).

The way in which the law allocates ownership of inventions prioritises certain types of contribution over others. It is extremely unlikely that participants would provide the inventive contribution required to be recognised as inventors under English law.[25] The supply of crucial starting materials, in this case the genetic material necessary to conduct the study, is not sufficient to establish an inventive contribution sufficient to be an inventor on the patent.[26] Thus, the 'inventive' contribution to a patent is deemed to be the most important, and the contribution of material which is necessary to the invention, but which is considered to be routine, is not allocated any benefit. This may be contested as unfair, or unreasonable. Indeed, many commentators in this field consider that traditional IP models do not adequately or appropriately recognise the contribution of participants in genomic research (Dickenson 2008, p. 531; Merz et al. 2002).

Although the legal allocation of ownership of a patent may fail to appropriately recognise the role of participants in a study, it is also arguable that participant ownership of patents on inventions arising from biobanks is inappropriate. Whilst participants in a particular biobank may contribute to the development of an innovation, modern genomics research relies on the contribution of many thousands of participants, in many studies (Wang et al. 2005). For example, genomics research could not proceed without the HapMap data, but there is no call to allocate IP ownership rights to every person who participated in any genomics research which was utilised in developing a particular innovation, because to so would be practically unworkable. Moreover, there is no way of recognising group rights as a matter of law, and such group ownership is likely to be impracticable because of a lack of common viewpoint among biobank participants.

Some of the concerns about ownership rights stem from concerns about exploitation, and unfairness of big business profiting from inventions derived from participant samples, without any return to participants (Dickenson 2008; Merz et al. 2002). However, other concerns are related to the need to ensure fair access to useful innovations derived from that research (Forsberg et al. 2009). The concerns about fair access apply equally to all in society, not only those who participate in a particular biobank, and individual benefits should not be excessively focused on, at the expense of solidarity and altruism (Hawkins et al. 2009).

The concerns for appropriate recognition, reward and access for participants and wider society will not be adequately addressed by ownership of IP alone, but ownership of IP is not the only means by which these concerns may be addressed. In the absence of IP ownership, biobanks may nonetheless exercise some control over the patenting and exploitation of inventions derived from the biobank through contractual means, discussed below.

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[25] *Rhone-Poulenc Rorer International Holdings v Yeda Research and Development Co Ltd*, [2007] UKHL 42; [2007] All ER (D) 373.

[26] Bently and Sherman (2009, 531). Citing *Moore v Regents of the University of California*, 793 P2d 479 (Cal. 1990).

2.4 Why Patent?

Patents exist in order to incentivise innovation. The patent system draws a distinction between basic science and inventions. Basic science and discoveries are not patentable, and are freely available for all to use without restriction. In contrast, patents are available for technically useful inventions, and monopolies are awarded for limited periods in relation to these inventions, to incentivise innovation. In the biotechnology and genomics arena, the distinction between what is basic science, which should be freely available to all to use without restriction, and what is industrial science, which may require incentives to development, is not as clear as in other fields. Many commentators have raised concerns about the potential for the patent system to force a market dynamic on a system of scientific research with which it does not naturally fit (Hope 2008; Piper and Gold 2008; Rai 1999). Scientific research, particularly in the field of biomedicine, proceeds according to an academic model, with its own complicated system of social norms. Part of this system relies on the free flow of information and open communication within the scientific community (Eisenberg 1987). There are three aspects to this freedom: free flow of conclusions from research, both informally and through publication; free flow of data; and sharing of materials. The traditional method of dissemination of academic research results is through formal publications in academic journals, and conference presentations. There is also more informal sharing with academic contacts and collegiate discussion. The data on which conclusions are based has also traditionally been shared at the point of publication. In genetics and genomics research, data sharing has become more formalized, with agreements for the release of sequence data prior to publication during the course of the Human Genome Project. Funders and other powerful interests, including some drug companies and famous scientists, have been instrumental in pushing forward open access and data sharing regimes in genomics (Kaye et al. 2009). This extends the norms of free information flows that are traditional in academia.

The patent system, and a view of science tied into property rights and the market, does not fit well with these scientific norms. The patent system reflects an implicit social contract, which balances private and public interests. Private interests are served through the grant of a limited monopoly right, which provides the incentive for further invention, investment in research and development (Machlup and Penrose 1950). The public interest is served through the development of innovative products and through disclosure of technical knowledge (Van Overwalle 2007, p. 19). This balance depends on the underlying assumption that innovation will not occur, or will occur less efficiently, in the absence of the patent rights.

Traditionally, IP protection has not been available for basic research discoveries (Eisenberg 1987). This is because the legally defined limits on patentable subject matter and requirements for patentability have usually excluded basic scientific discoveries from patent protection. However, in the field of biotechnology, and particularly genetics and genomics, the distinction between basic and applied

research has been much more difficult to maintain. In reality, much research in genetics is patentable. However, as the field develops, patent offices and courts will become more adept at drawing this distinction at an appropriate level, and there is some evidence that this is already occurring.[27]

At the same time, patents are an important incentive in biomedical research. They guarantee a return on investment in the research and development that is necessary to take a product to market. They ensure that free-riders cannot enter the market before the patent holder has an opportunity to recoup the investment. Our current models of biomedical innovation rely on commercial involvement in order to get a biomedical product to market. The purpose of universities and the public sector is not to bring products to market, and the involvement of industry is necessary in this field. When there is industry involvement, there is the need for appropriate patents.

Patents are more important for some types of innovation than for others. For pharmaceutical products for example, there is generally accepted economic evidence that patents are necessary (Bessen and Meurer 2008). For other types of innovation, patents may be less necessary; for diagnostics there is less evidence of the need for patents (SACGHS 2010, p. 32). When an invention relates to something that there is an intention to widely distribute, with no view to making a profit, then it is likely that a patent would be inappropriate. For example, a charitable organisation that develops a new technique for vaccine preparation for the developing world may opt to make the technology available in the public domain, so that it can be freely used by many different parties. In such a situation, the transaction costs of licensing the invention to many parties are high, and given the purpose of the development, unwarranted.

3 Managing IP that Arises from a Biobank

A discussion of IP which considers only the question of what IP rights subsist considers only part of the picture. IP rights are not an end in themselves; instead, they are a means to an end. The exploitation of IP should be considered by reference to the purpose for which biobanks exist. Biobanks are developed as a resource, which can be used by many researchers in order to enable genomics research. These researchers are expected to carry out research with the biobank material or information, with a view to increasing the sum of human knowledge about genomics. It is not unreasonable to view the overall purpose of biobanks as being to enable the development of translational outcomes which are intended to benefit patients. Indeed, many biobanks have such an explicit aim.[28] This purpose of furthering the

[27] *Eli Lilly and Co v Human Genome Sciences Inc*, [2008] EWHC 1903 (Pat), [2008] RPC 29, *Eli Lilly v Human Genome Sciences Inc* [2010] EWCA Civ 33.

[28] See for example UK Biobank, "UK Biobank—Improving the health of future generations," http://www.ukbiobank.ac.uk/.

public good is particularly pertinent given that many biobanks are developed partly or entirely with public funding. Moreover, many participants view their contribution to a biobank as contributing to research which will benefit patients in the future (Kettis-Lindblad et al. 2005).

If the purpose of biobanks is to enable translational outcomes, then the question arises as to the best means for this to happen. In reality, a biobank is likely to be somewhat removed from whatever biomedical innovation results, unless the biobank itself carries out a programme of research, which is not something that many biobanks in fact do. Instead, the party that accesses the biobank and develops an innovation directly is the party that is most in control. It is likely that this party will obtain the patent and may then engage in commercialisation, through a spin-out or alternatively license or assign the patent to a larger company. In this process, the patent is key; it provides the necessary basis on which commercial parties deal.

However, biobanks need not be completely removed from this process of translation and commercialisation. Patents for innovation are only a tool, and ownership of IP, whilst important, is only one aspect of the range of legal regimes which is relevant to the control of how an innovation is developed. Biobanks can have recourse to contractual mechanisms to set up a model for the exploitation of IP that suits their underlying ethos.

3.1 How Can IP Be Managed to Achieve an Objective?

IP is not intrinsically good or bad; instead, it is a tool which can be used to serve various purposes. It is true that patents may be used to extract monopoly profits, but they may also be used in different ways to ensure than an invention is made available to those who need it. It is important that biobanks recognise that IP has a role in biomedical innovations. Policies which treat IP as intrinsically negative, and as a result try to constrain or discourage patenting in all circumstances may result in a block to development, because there is no protection for investment.

There are many different ways that biobanks may manage the translational research process using IP and contractual mechanisms. Biobanks should develop a policy which is appropriate to their aims and ethos, and which will best allow translational outcomes. Biobanks should determine their priorities for development. They may wish to prioritise access for patients of a particular disease group, or they may have particular concerns for access in developing countries for example.

A biobank could, as a term of the access agreement, provide that the biobank is entitled to ownership of any patents which arise from research on the biobank material. There are three reasons why this may be inappropriate. Firstly, biobanks do not have the time or expertise to manage a large patent portfolio. Secondly, unless all biobanks provide for similar ownership terms, researchers are likely where possible to preferentially access other biobanks with more favourable terms.

Finally, funders, universities and hospitals are all parties who have legitimate claims to ownership of inventions, and to gain the agreement of these parties to such a restrictive term is likely to be difficult. Moreover, commercial parties seeking access to a biobank are extremely unlikely to cede ownership of patents in this way. However, as already noted, ownership of IP is only one means of achieving an objective. Contractual obligations may be highly effective in achieving a desired outcome.

Policies which achieve the aims of maximising both innovation and access are difficult to devise. It is difficult to determine a hard and fast policy; flexibility is key in this area. Policies can nonetheless be effective, even in the absence of absolute obligations, in encouraging changes in practices and the development of community norms.

An additional complicating factor in devising these policies is the widespread sharing of data across many biobanks that routinely occurs in genomics research (Kaye et al. 2009). Harmonization in biobanking is difficult enough, taking into account the different requirements of different jurisdictions, without adding complicated IP policies into the mix.

Despite these difficulties, there are some key areas where biobanks can look to the policies which have already been developed with a view to maximising patient benefit. The first area where a great deal of work has been done is in licensing models which look to maximise public benefit. For example the Association of University Technology Managers in the USA developed principles on licensing in the public interest (CIT et al. 2007). The NIH and the OECD encourage non-exclusive licensing of genetic inventions where possible (NIH 2005; OECD 2006). Biobanks could require as a condition of access that licenses to patented inventions developed from the biobank would be granted on certain terms, such as royalty free licenses for research use. Practical suggestions for licensing models which ensure access for those in developing countries have been proposed by Stevens and colleagues (Stevens and Effort 2008).

Biobanks could also investigate the possibility of developing patent pools for inventions developed from their resource (Van Overwalle et al. 2006; Verbeure et al. 2006; Van Overwalle 2009). This may be particularly relevant where there are many patents held by many different parties which are all necessary in order to develop an innovation, such as a diagnostic test.

Biobanking involves new models and ways of doing research. The legal means which biobanks use to ensure that the fruits of that research are widely available can be similarly innovative.

4 Conclusions and Recommendations

The purpose for which biobanks have been created should be kept central to any consideration of IP rights. Biobanks should have a policy on IP rights which emphasises their underlying commitment to maximising access to innovations

developed from the biobank. It is acknowledged that it this goal is difficult to attain; there is a fine balance between incentivising innovation, so that products are developed, and ensuring that any products are available to as many people as possible at a reasonable price. Neither lack of incentive to invest in development, nor extremely high prices are desirable.

It is important that biobanks recognise that IP rights play an important role in biomedical innovation. IP policies which suggest that no IP should arise from biobank research are neither realistic, nor effective. Important innovations which are denied IP protection will not necessarily be available to more people; instead, it may simply be the case that no industrial partner can be found to develop the innovation to market. This is not to say that biobanks should encourage patenting in all cases. Patents are a useful tool in the appropriate case, but are not suitable on early stage or upstream innovations.

These IP policies developed by biobanks should be clear and straightforward. In addition, there should be arrangements for review of the policies at appropriate intervals. In a field that is moving as rapidly as genomics, it will be important that policies on IP are reviewed as translational outcomes become routine. Regard should be had as to whether the policies put in place are effectively achieving their objectives.

Finally, it is essential that biobanks are upfront and clear in their communications with participants about the role of IP rights in the biobank. Most consent forms include provisions which inform participants that they will not benefit financially from participation in the biobank and such clauses seem appropriate (Hawkins et al. 2009). Many participants seem content to participate in a biobank from an attitude of altruism. They do not expect any direct benefit for themselves, but they do expect that some benefit will arise in the future for patients. At the same time, participants express concern about commercial involvement in biomedical research, and want to know about the potential for commercial profit (Haddow et al. 2007). Biobanks should be upfront about the ways in which they foresee this benefit arising, and the means through which they will ensure maximum access. Indeed, a clear and strategic policy about IP, which addresses the way the biobank intends to manage IP to ensure that translational outcomes and access to them are maximised, seems likely to help build the relationship of trust which is necessary for the effective functioning of a biobank.

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Consent, Privacy and Property in the Italian Biobanks Regulation: A Hybrid Model Within EU?

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1 Introduction

The discussion about genetic information and about the related possibility of storing DNA samples and associated data into an organised database has, in Italy, only recently developed and for sure it did not outline all the core problems and possible questions to be answered yet. The stage of finding solutions seems to be, therefore, quite far away by now.

Anyway, the advent of DNA analysis and the improvement of techniques which allow a protracted conservation of biological samples and the capacity of simultaneously processing a lot of information, gave also Italian researchers the possibility of pushing their work even further. In this specific field of scientific research, public support for better medical diagnosis and treatments has to be balanced with anxieties and concerns: when DNA samples and genetic information are collected and

It has to be pinpointed that, even within a general context of co-elaboration, agreement and sharing of the contents and opinions expressed within this text, the first paragraph has to be ascribed to Marta Tomasi (Ph.D. candidate, Department of Legal Sciences, University of Trento), the second one to Simone Penasa (Ph.D., Fellow researcher in Comparative Public Law, Department of Legal Sciences, University of Trento) and the third one to Matteo Macilotti (Ph.D., Fellow researcher in Comparative Private Law, Department of Legal Sciences, University of Trento).

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subsequently used, ethical and legal issues about informed consent, confidentiality, individual identity, discrimination, self determination, secondary use of samples and data, return of results and data sharing have to be faced. Quick and often overwhelming scientific developments have, therefore, to be dealt with and to be properly regulated.

In general, scientific research is usually assisted by a variety of precautions and limits which, even if not absolute, are sufficient to assure the research subject's interests to be protected and guaranteed. The traditional conflict between patients' interests and scientists' freedom of research is, in relation to biobanks, made even stronger by the elaboration of broader models of consent, by the possibility of considering biological materials property of the researchers or of the institutions,[1] by the creation of national criminal DNA databases and, finally, by the intervention of private companies.[2] As it has been observed: «DNA banking is quickly changing from an academic research activity to a governmental and commercial enterprise conducted by DNA brokers» (Roche and Annas 2006).

These are the main reasons of the need of reshaping the ordinary balance in the relationship among patients/donors, clinicians and researchers: this should be done both with legally binding measures or with softer regulations provided, for example, by advisory bodies, ethical review boards or professional organisations (Cambon-Thomsen et al. 2007).

While in many countries small collections of samples in academic or hospital settings are often side by side with large-scale national repositories, the Italian situation is characterized by a huge number of unofficial collections, frequently made up of previously collected materials and left-over samples from medical care, which obviously give rise to critical disputes about consent requirement.

The existence of multiple international and supranational documents dealing with research biobanking and the absence, in Italy, of a specific statutory law highlight the necessity of defining the regulatory framework of this field of biolaw. It is important to be stressed how, abroad, requests for a down regulation and for a "softer" strategy based on traditional instruments and ethical principles are showing up, while, in Italy, the matter had not been directly approached yet.[3]

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[1] Consider the great interest arisen by *Moore v. Regents of the University of California*, 793 P.2d 479 (Cal. 1990).

[2] The Icelandic experience had to face similar matters because of the decision of conceding to a private company, *DeCode Genetics*, the exclusive use of the data collected in the national population biobank.

[3] On the contrary, within the field of criminal law, the Italian Parliament recently approved a law (Statute n. 85, 2009, in the Official Journal of the Italian Republic n. 160, 13 July 2009) which, authorising the ratification of the so called Prüm Convention (Convention between the Kingdom of Belgium, the Federal Republic of Germany, the Kingdom of Spain, the French Republic, the Grand Duchy of Luxembourg, the Kingdom of the Netherlands and the Republic of Austria on the stepping up of cross-border cooperation, particularly in combating terrorism, cross-border crime and illegal migration), instituted a national DNA database in order ease criminals' identification.

The first paragraph of this brief analysis aims at outlining the regulatory framework of biobanks' governance in Italy, which comprehension is essential for any further consideration. The second paragraph focuses on the legal consequences of the multidimensional nature of genetic information, with special regard to its legal object (sample regulation and data protection), the involved subjects ("source" subject and the so called co-subjects) and the normative instruments of regulation (legislative and not legislative sources). The last part is dedicated to the analysis of the issues related to property of human tissues starting from the consideration of their bi-dimensional nature (molecular aggregates and sources of personal data).

2 Legal Italian Framework

In many cases, the lack of a specific statutory regulation about biobanks implies that their discipline springs out of the combination and the coexistence of a variety of disparate rules aiming at the protection of different interests and addressing the topic from different viewpoints. Thus, in Italy, different sets of rules having reference to different layers have to be taken into account: on the one hand, biological samples should be considered in their material dimension and rules about, for example, storing and patents become relevant. One the other hand, these rules are to be necessarily balanced and harmonised with those protecting the "informational" dimension, made up of genetic data. At the same time also indications about best practices for researchers have to be involved in this process of shaping a regulatory framework.

Therefore, postponing to next paragraphs some reflections about the relationship between the material and the informational dimension, it is by now important to underline that different guidelines, coming from different bodies and characterised by different levels of binding strength (hard law and soft law. For a definition of soft law see Senden 2005), have to be considered and combined in order to understand the Italian discipline of biobanking for research purposes.

2.1 The International Level: Between Hard and Soft Law

First of all, at the international level, general principles can be found in two documents adopted by UNESCO, respectively in 1997 and in 2003. The first article of the "Universal Declaration on the Human Genome and Human Rights" highlights the relevance of this topic affirming that the «human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity». This first provision has to be read together with the fundamental role played by scientific research in our society, recognised by article 12, (b): «(f)reedom of research, which is necessary for the progress of knowledge, is part of freedom of thought.

The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole». In any case, research purposes should not prevail on «rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people» (art. 6).

These provisions, generically related with genetic data treatment, have to be highly regarded even when dealing with matters of management and organisation of biobanks.

Similar provisions, together with the requirement of a «prior, free, informed and express consent» in order to lawfully collect, use and store genetic data and biological samples (art. 8), can be found as well in the text of the "International Declaration on Human Genetic Data".[4]

More recently, similar contents can be found in the text of the Recommendation on Human Genetic Research Databases, approved by the Organisation for Economic Cooperation and Development[5] in 2009.

On the contrary, binding relevance should be ascribed to the "Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine" (Ovideo Convention). This Convention of the Council of Europe aims at the protection of dignity and identity of all human beings and at a full respect of rights and fundamental freedoms with regard to the application of biology and medicine. It sets, therefore, some limits within which scientific research can fairly develop: these borders are represented by respect of relevant professional obligations and standards (art. 4), the principle of free and informed consent (art. 5), respect for private life (art. 10) and a specific clause against genetic discriminations (art. 11). Even if not explicitly, the Convention addresses biobanks in requiring for the storing and use of biological tissues[6] written consent and proper information of the donor.

The main problem about this document is that Italy did not complete the procedure necessary for the ratification of an international treaty. Italy subscribed the Convention and the Parliament adopted a statute for the authorisation to its ratification, but that law was never delivered to the Council of Europe: this means that the so called Oviedo Convention can not be considered properly binding within the Italian legal system (Penasa 2007)[7]. Following the opinion of the Court of Cassation, anyway, even if the provisions of the Convention should bend in front

[4] Adopted by UNESCO on 16 October 2003.

[5] In this document OECD defines itself as a «forum where the governments of 30 democracies work together to address the economic, social and environmental challenges of globalisation». The Organisation «provides a setting where governments can compare policy experiences, seek answers to common problems, identify good practice and work to co-ordinate domestic and international policies».

[6] Art. 22 of the Convention refers to parts of a human body removed during an intervention.

[7] Also according to the Council of Europe's website, Italy appears among the countries which signed the Convention, but not among those which completely ratified it (http://www.coe.int/t/dg3/healthbioethic/source/INF(2009)3%20état.%20sign%20ratif%20réserves.doc).

of the existence of contrasting national rules, nonetheless they must be used in order to choose the interpretation of internal norms which is the closest to that expressed by the text of the Convention.[8]

It is also important to take into consideration the additional Protocol concerning Biomedical Research, adopted in Strasbourg on January 25, 2005. The main question about the usefulness of the rules in it contained, beyond procedural considerations, is that this Protocol expressly limits its field of application to the «range of research activities in the health field involving interventions on human beings» (art. 2.1.). Parts separate from the human body seems therefore to be excluded. Thus, even if general principles informing scientific research have to be highly regarded, it is quite evident that broad statements such as that contained in art. 3 about the primacy of human being[9] should be reconsidered and rebalanced, bearing in mind the different object of the research.

Even more restrictive is the 4th additional protocol to the Convention concerning Genetic Testing for Health Purposes,[10] which explicitly excludes from its field of application genetic tests carried out for research purposes (art. 2.b.).

In the European context, the Committee of Ministers of the Council of Europe gave some guidelines with the Recommendation R(2006)4.[11] This document, strictly applicable to the topic we're dealing with,[12] beyond setting rules about consent, non discrimination, prohibition of financial gain, common to other instruments,divides «unlinked anonymised materials»[13] from «linked anonymised materials»[14] and from «materials».[15] This kind of detailed classification is very difficult to be applied in Italy where, as we will underline, normative provisions barely distinguish the informational dimension from the material one.

With specific regard to the "informational" dimension, rules set by the "Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data"[16] of the Council of Europe have to be taken into account.

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[8] Case n. 21748/2007, paragraph 7.2.

[9] Article 3—Primacy of the human being: «(t)he interests and welfare of the human being participating in research shall prevail over the sole interest of society or science».

[10] This Protocol was signed in Strasbourg on 27 November 2008.

[11] Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin, adopted on March 15, 2006.

[12] Art. 2.1.1. «This recommendation applies to the full range of research activities in the health field involving the removal of biological materials of human origin to be stored for research use».

[13] Art. 3.ii. «Non-identifiable biological materials (…) are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned».

[14] These are biological materials which, alone or in combination with associated data, allow the identification of the persons concerned through the use of the code, but users of the biological materials do not have access to the code, which is under the control of a third party (art. 3).

[15] In this case identification is possible through the use of a code, which is available to the users of the biological materials (art. 3).

[16] Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, adopted in Strasbourg on 28 January 1981.

2.2 The European Union Context: Indirect Relevance of EU Directives

The need for a unified framework which ensures high standards of quality and safety in the testing, processing and storing of tissues and cells within the European community is at the base of two directives, one by the European Parliament and Council and the other by the Commission. The first one, of 2004,[17] aims at «standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells»,[18] while the latter[19] is aimed at the implementation of the former, with regard to certain technical requirements. Problems similar to those underlined talking about the additional Protocol to the Oviedo Convention arise: the first directive clarifies that it «tissues and cells intended for human applications»[20] and does not apply to «research using human tissues and cells, such as when used for purposes other than application to the human body».[21] It is hence clear that only a few biobanks are established for the pursuit of such purposes.[22]

It is worth noticing, also to emphasise the Italian attitude towards these matters, that while the first directive, that of 2004, was implemented within the Italian legal system with the adoption of legislative decree n. 191/2007, Italy failed to acknowledge the second one and was condemned on November 12th, 2009 by the European Court of Justice.[23] The directive was finally implemented in 2010 with the legislative decree n. 16.

The regulation and organisation of biobanks should also consider Directive 98/44/EC on the legal protection of biotechnological inventions which provides that national patent law remain the essential basis for the legal protection of biotechnological inventions and that States shall, if necessary, adjust their national regulation to take account of the provisions of the Directive.[24]

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[17] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, Official Journal of the European Union L 102, 4 April 2004, 48–58.

[18] Excluding blood and blood products (other than haematopoietic progenitor cells) and human organs, as well as organs, tissues, or cells of animal origin (point 8 of the preamble).

[19] Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, Official Journal of the European Union L 38, 9 February 2006, 40–52.

[20] Point 10 of the preamble.

[21] Point 11 of the preamble. The ratio of this limitation is quite clear: strict and specific procedures are set in order to guarantee a good quality of the samples which will be used on human body.

[22] Such as biobanks of stemcells or umbilical-cord (blood) (point 7 of the preamble).

[23] C-12/09 Commission of the European Communities v. Italian Republic.

[24] Point 8 of the preamble and art. 1.

2.3 The National Level: Legislator's Apathy and Other Sources' Intervention

Turning to the national level, relevant but non binding guidelines were given by two governmental advisory bodies.

The National Committee for Biosafety, Biotechnologies and Life Sciences (Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita)[25] intervened in 2006 with a document containing useful information for the creation and acknowledgment of biobanks. Paragraph 2.3.1. is specifically dedicated to genetic biobanks which are considered to be different from the others (tissue biobanks) because of the necessity of maintaining a link among the sample and family and clinical information in order to guarantee the possibility of creating a complete genetic profile and of obtaining essential follow up results. Rules about the protection of personal data are therefore indispensable. With specific regard to consent, it has to cover all the steps of collection, storing and use of the sample.

In 2008 a second document was adopted in which, after a global reconnaissance of the general problem, the analysis of the Italian situation and a comparison with other realities, the Committee strongly endorses an intervention of the legislator on these matters.

A couple of months after the publication of the former document, the Italian Committee on Bioethics (Comitato Nazionale per la Bioetica)[26] delivered and opinion about that document and about the Recommendation of the Council of Europe.[27] This document highlights the *fil rouge* which connects the additional Protocol to the Oviedo Convention on biomedical research, the Recommendation of the Council of Europe and the Italian guidelines given by the other Committee. The National Bioethics Committee substantially agrees with the principles and rules outlined by the Council of Europe and by the Committee on Biosafety and Biotechnologies with regard to consent, right to access, information, non discrimination and gratuity, underlining the necessity for a precise regulation, even if recognising the impossibility of setting too strict rules.

In the absence of a statutory law addressing to research biobanks, attention has to be focused, generally speaking, on genetic data treatment. Considering properly binding provisions, in Italy, the general discipline of personal data is contained into a single code,[28] which specifically attributes to an independent administrative authority,[29] which aims at the protection of fundamental rights and freedoms and at guaranteeing

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[25] The Committee is a consultative body instituted by the Presidency of Council of Ministers with art. 43 of the statutory law n. 142 of 2002.

[26] Created by the President of the Council of Ministers on 28 March 1990.

[27] Recommendation Rec(2006)4, see Footnote 11.

[28] Legislative decree n.196, 30 June 2003, *Codice in materia di protezione dei dati personali*, in the Official Journal of the Italian Republic n. 174, 29 July 2003.

[29] This body, called Garante per la Protezione dei Dati Personali, was created with art. 30 of the statute n. 675 of 1996, in the Official Journal of the Italian Republic n. 5, 8 January 1997.

the respect of human dignity in the treatment of personal data, the task of regulating that particular category of sensitive data, made up of genetic information.

Following this legislative indication of 2003, in 2007 the privacy Authority released a General Authorisation for the Treatment of Genetic Data (which effects have been extended until the end of 2010).

First of all a consideration has to be made about the peculiar administrative nature of this document: such a kind of choice should reflect the need for down regulation cited above but, considering the stage of discussion about these topics in Italy, it turns out to be quite peculiar into a legal system where the legislator often intervenes with really strict provisions about biolaw.[30]

Moreover, with regard to the contents' profile, it has to be stressed that the same rules are set both for the biological samples and for related information, with no kind of distinction. More precisely, the text considers the two entities as separate elements and gives singular definitions, but this distinction is never recalled in the following provisions and biosamples are scarcely ever recalled. This monistic approach is possibly to be regarded as an outcome of the inactivity of the legislator and of the subsequent subsidiary role played by the Authority. On these aspects further considerations will follow in the next paragraph.

The analysis of the first provisions of this Authorisation immediately outlines that scientific and statistic research, if aiming at the protection of public health, are considered to be lawful purposes to be pursued through the treatment of genetic information. Compelling, in this case, is the principle which requires the consent of the "donor" (paragraph 3 c).

Another general rule is that identifiable data should be used only if anonymised data are not feasible for the pursued aim (paragraph 3).

If genetic information or biological samples are contained into a genetic database, they should be coded and the donor will be recognised only if necessary (paragraph 4.3.)[31] in order to avoid risks and abuses.

Moreover, according to paragraph 4.2., scientific research and statistics have to be realised through the elaboration of a detailed project, which helps in the identification of the aims pursued and in which rules about data treatment will be outlined, in order to make the provisions of the privacy Code and of the Authorisation concrete.

Trace of the monistic approach, which unifies the material and the informational dimension, can be also found in the extension of some requirements originally set by the provisions of the Code of privacy for the treatment of genetic profiles, also to biological samples (paragraph 4.2. or 4.3.).

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[30] Consider, for example, statutory law n. 40/2004, concerning human assisted reproduction. This law was modified by an intervention of the Constitutional Court (judgment n. 151/2009), which somehow tried to loosen the strictness of some rules and to re-establish the borders of the legislator's latitude. A restrictive legislative approach will be chosen, as well, with regard to end of life decisions whether the bill about advanced directives, currently under discussion at the Parliament, should be approved.

[31] This is the problem of follow up information, which repeatedly proved to be a fundamental element for the fulfilment of the research projects.

A further profile which heavily affects the discipline of biobanks is that of consent process: the 2007 Authorisation openly embraces a quite narrow conception of consent procedures. In establishing the content of the information that must be given to the donor/patient, which draws the borders of the consent, paragraph 5 requires an analytic and detailed description of all the pursued finalities and the possibility for the subject of limiting the use of its samples and data, excluding some purposes. This kind of individual and restrictive approach has to be compared with frequent voices abroad, claiming for an opener view, embracing also third subjects' interests,[32] and for the adoption of a broad consent based model (Otlowski 2009; Hansson et al. 2006). In Italy, anonymisation seems to be the only mean possible to overcome the strict rule of consent and it needs to be applied to both samples and data.

This reconnaissance of the regulatory framework of biobanks in Italy clearly outlines the difficulty of singling out the concrete provisions which affect and orientate the discipline of this topic. Moreover, it is quite clear that biological samples often find themselves floating into a vacuum between rules about scientific research on human being and rules set for the protection of the informational dimension of genetic data.

3 Italian Biobanks Regulation. Issues at Stake

One of the main features of genetic data is their *complexity*. This complexity is due to its multidimensional nature (Jiménez 2006), which calls for new protection mechanisms which go to integrate traditional "property based" means. Biobanks regulation is deeply related and conditioned—oriented—by the special nature of genetic information. The multidimensional nature of the latter finds an equivalent in the former, which is characterised by a heterogeneous structure and nature, depending from its concrete content. The *summa divisio* between genetic data and biological samples emerges in all its normative conditioning power of the biobanks regulation. It clearly testifies the separation between the samples' *source* and the persons potentially *affected* by the genetic data treatment. The multidimensional nature of genetic data involves also biobanks regulation. From this perspective, it is possible to isolate three different levels of complexity within biobanks regulation.

3.1 The Legal Object from Biological Dispositions to Genetic Rules

According to international legal sources and national regulations (Gibbons 2007), it seems to emerge a trend toward a normative distinction between tissue regulation and data protection, in order to guarantee the effectiveness of legal regulation and the

[32] On these matters see infra.

harmonisation within the EU legal framework (see Data Protection Working Party—article 29, Directive 45/96/CE). This distinction may represent a shared ground in order to achieve «a common understanding of the different issues relating to the processing of genetic data» (Document on "Genetic Data", by the Data protection Working Party, 2004). The need for a harmonic distinction derives directly from the special nature of genetic information, which represents a further derivation of genetic data treatment (the so-called "genetic knowledge"). This special nature derives from the singularity of genetic information ("genetic rules"), compared with the classical personal/sensitive data, due to its double nature which expresses an intrinsically relational construction which does not characterise the "biological provision" (human tissue).

The Italian model can be defined as a "hybrid-integrated model". Apparently, the distinctive approach finds a concrete application within the Italian legal system, coherently with the need for a harmonious distinction between data protection and tissue regulation. On the one hand, there is a set of systematic rules specifically dedicated to genetic data, deriving from both legislative—the Code of privacy, art. 90[33]—but also administrative-secondary sources, such as the cited General Authorisation for the Genetic Data Treatment provided by the Italian Authority for Personal Data Protection (2007). On the contrary, with regard to the tissue regulation, it has been chosen a "sectional" regulative approach, according to which it has been regulated specific kinds of biological samples for specific aims of utilisation[34] but a coherent legal intervention is lacking in the field of samples collection, storage and utilisation for research purposes.[35]

The General Authorisation of 2007 partially covers this regulative vacuum, combining data and samples regulation within the same general principles and operative means. It seems that tissue regulation is attracted by and dissolved into the data protection, as if a double relation inspires the regulatory structure, which influences the same legal relevance of the former one: a chronological precedence of biological sample, in reason of its nature of source of genetic information; a functional subordination, revealing the exploitable character of biological samples compared to data protection (Macilotti et al. 2008).

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[33] Section 90 (Processing of Genetic Data and Bone Marrow Donors) states that «Processing of genetic data, regardless of the entity processing them, shall be allowed exclusively in the cases provided for in ad hoc authorisations granted by the Garante, after having consulted with the Minister for Health who shall seek, to that end, the opinion of the Higher Health Care Council. The authorisation referred to in paragraph 1 shall also specify the additional items of information that should be contained in the information notice pursuant to Section 13, with particular regard to the purposes sought and the results to be achieved also in connection with the unexpected information that may be made known on account of the processing as well as with the data subject's right to object to the processing on legitimate grounds».

[34] Such as organs for transplant, blood and its products for transfusion, embryos and gametes for reproductive purposes and Haematopoietic stem cells derived from cord blood for therapeutic purposes.

[35] It is relevant to stress that the Directive 2004/23/CE on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells does not cover research using human tissues and cells, such as when used for purposes other than application to the human body, e.g. in vitro research or in animal models.

The Authorisation of 2007 expressly identifies a normative ground for this methodological option, even though it derives from a soft law source. The document on "Genetic Data" provided by the Data protection Working Party in 2004 recommends that, in prescribing genetic data protection measures, it is essential to take into account and regulate also biological samples' status, because of their attitude to become sources of personal data.

Recently, the trend toward this regulative distinction has been put in doubt. It has been debated «whether continuing to regulate data and tissue separately—particularly for biobanks—is the most sensible or desirable approach» (Gibbons 2009), arguing that a «bifurcated situation» in regulating data protection and human tissues is not fully satisfactory «due to inconsistent legal standards, duplication, cost, confusion, and discordance with biobanking practice and professionals' own understandings» (Gibbons 2009). Significantly, the Authorisation defines both genetic data («the data which, independently from its typology, is related to person's genotypic constitution or to genetic characters transmissible within a blood-related group») and biological sample («any biological sample which contains genotypic information characterising an individual») because of both constitute the Authorisation object without providing a differentiated regulation.

This approach may potentially engender a state of legal uncertainty and a lack of regulative efficacy. This is not due to an overlap between legal issues (data protection and tissue regulation) which can be regulated differently, but to an "a-systematic approach" to tissues' regulation. Within the main, even though not legislative, source in this ambit—the Authorisation of 2007—the principles related to tissue regulation emerge in an apparently "intermittent" and subsidiary way compared to data protection. It is formally absent with regard to the aims of the treatment, exclusively dedicated to genetic data, but it re-appears in the sections entitled to «and safety procedures» (point 4), «counselling and consent process» (points 5 and 6) «data and tissues preservation and circulation» (points 8 and 9).

The need for a new normative framework exclusively dedicated to biobanks for research purposes has been stressed also by the National Committee for the Biosafety, the Biotechnology and the Life Sciences, in the above cited Document of 2008. In this Document, which goes to integrate—even if it lacks of legal binding power—the biobanks regulation, the Committee declares that a legislative act is essential also for the biobanks for research purposes, in order to clarify primarily that biological samples have to be preserved and utilised exclusively for the common good of the community.

3.2 The Involved (Co?) Subjects. The Necessary Relation Between The (Health) Purposes and the (Informed) Consent Process

The need for a consistent distinction between tissue regulation and data protection derives also from the special nature of genetic information, within which it has to be drawn a distinction between the «source»-subject, from whom biological

material is derived, and other subjects («co-subjects») (Hondius 1997) directly involved in genetic data treatment since they belong to the same biological family. With regard to the former one (source-subject), it is identifiable a mono-dimensional legal approach, because of a concentration in the same person of the need for his/her right protection (individual ownership of the biological samples); the latter (co-subjects) have a multi-dimensional approach, due to the plurality of subjects potentially involved in the genetic data treatment (genetic data co-holders) (Liao 2009).

Is a new, legally relevant, social group emerging, as the international level seems to suggest?[36] Does the Italian regulatory framework take into account this new level of normative criticism?

We face the inadequacy of traditional concept of "third subjects" with regard to the shared nature of genetic information: an intermediate legal category, constituted by all individuals sharing the same genetic line, to which a hybrid legal protection seems to be recognised (Santosuosso 2002).[37] Even stressing the potential ambiguity of the attribution of legal relevance to a group of people, it is at the same time remarkable how the emerging relation of interests among individuals belonging to the same genetic line is legally relevant, although exclusively at the "individual" level more than a "communitarian" one. From an "Italian centred" perspective, more than a direct reference to the constitutional status and protection of the family guaranteed by art. 29 of Italian Constitution,[38] it is more proper to refer to the "social group" recognised by art. 2 of the Italian Constitution[39] as means of development of individuals personality, in which the fundamental rights (right to health but also right to identity and privacy) have to be protected (Weisbrot 2009). In order to harmonise and defuse the risk of a clash of individual rights, it seems to be advisable to change the perspective, moving from a forbidden to a controlled circulation, through an ex post (later on) control power on the genetic information (Pardolesi 2003). We may refer to an informational self-determination right intended as a right

[36] The Document on "Genetic Data" of the Data protection Working Party clarifies that this biological group «does not include family members such as one's spouse or foster children, whereas it also consists of entities outside the family circle—whether in law or factually—such as gamete donors or the woman who, at the time of childbirth, did not recognise her child and requested that her particulars should not be disclosed—this right being supported in certain legal systems». Furthermore, Recommendation R (97) 5 of the Council of Europe defines genetic data as «all data of whatever type concerning the hereditary characteristics of an individual or concerning the pattern of inheritance of such characteristics within a related group of individuals».

[37] It is also possible to make reference to the Explanatory Memorandum of Recommendation R (97) 5 of Council of Europe, in which it is specified how «The drafters agreed to accord an intermediate status to members of the data subject's genetic line so as to distinguish them from third parties in the strict sense of the term and to grant them a hybrid legal protection».

[38] Article 29 declares that «The Republic recognises the rights of the family as a natural society founded on matrimony».

[39] «The Republic recognises and guarantees the inviolable rights of the person, as an individual and in the social groups where human personality is expressed. The Republic expects that the fundamental duties of political, economic and social solidarity be fulfilled» (art. 2).

to maintain the control on his/her own information, through a re-thinking of the traditional mechanisms by evolving from a static (prohibition of collection) to a dynamic and procedural protection (control over its disclosure).

How does the Italian legal system react to this new issue? It is advisable to make again reference to the Authorisation of 2007. The approach seems schizophrenic.

On the one hand, among the admitted purposes of genetic data treatment it is included the health protection not only of the source subject but also of third subjects belonging to the same genetic line, peculiarly with regard to genetic pathologies and genetic identity protection. In this case, the treatment is allowed with exclusive regard to genetic data already collected and if it is essential for guaranteeing an aware reproductive choice or it is justified by the availability of therapeutic or preventive means (point 3, letter b). The legal relevance of thirds' health right is therefore appreciated, at the time of individuation of genetic data treatment purposes. This normative asset derives from the balancing between the source subject's right to privacy and the right to health of other persons potentially interested, due to a sharing of the same genetic line, in having access to genetic information already collected. It represents a formalisation of a principle expressed by the Authority's case law, according to which the access to health (and genetic) data may be justified by the need to protect the psycho-physical wellbeing of a third person, which allows a reasonable sacrifice of the right to privacy of the source subject.[40]

It is also relevant to stress how the General Authorisation, in enumerating the admitted purposes (point 3), makes reference exclusively to genetic data, without doing any reference to biological sample access. This lack is anyway filled in by the section dedicated to data communication and diffusion, in which it is clearly said that biological samples can be placed at disposal to third persons (without specifying who has to be intended as «third persons», whether exclusively other research groups or also other subjects, as the persons belonging to the same genetic line) only in order to guarantee the pursuit of the admitted purposes. Indirectly, this rule seems to open to a broad interpretation of the admitted purposes, in the sense of comprehending also samples' treatment, even if a "sample specific" set of rules should be more advisable, considering the data and samples different structure (mono-dimensional and property based the former and multidimensional and personalities based the latter one).

The pluralistic structure of data treatment seems to be appreciated by the regulation, through a teleological link between data treatment, samples dissemination and health protection. But this normative appreciation of biological links among individuals, rising out in the field of treatment admitted purposes, disappears in the counselling (informative) and consent process. No reference is made to the possibility that genetic information may eventually affect also third persons belonging to the same genetic line within the informative process, which is a crucial step into

[40] Authority, Decision 24.5.1999.

the consent process. A discontinuity between purposes regulation and consent process emerges, undermining the whole normative structure in terms of rights effective protection: the relevance recognized to thirds' health right within the admitted purposes does not find an equivalent within the consent process, which has to be considered incomplete from this perspective. On the contrary, it may be recommendable that «any new legal instrument would have to address the familial nature of genetic information» (Kaye 2006).

This normative choice is hardly compatible with international standards. The Fourth Protocol to the Convention oh Human Rights and Biomedicine concerning Genetic Testing for Health Purposes clearly declares that the person shall be provided with a prior appropriate information on the purpose and nature of test, as well as the implications of this results (indirect reference ex art. 8) and that when the result of a genetic test can be relevant to the health of other family members, the person tested shall be informed (direct reference, art. 18). Also the Joint Group composed by the National Bioethics Committee and the Biosafety, the Biotechnology and the Life Sciences National Committee has stressed in 2009 that at the international level the eventual consequences for the donor or for his/her family members of the genetic analysis' results constitutes an essential element of the informative process.[41]

According to a broad interpretation and in order to individuate some general principle related to this issue, it may be possible to read the faculty of limiting biological samples diffusion and the eventual utilisation for further aims in the sense of admitting the chance to exclude the "co-subjects" from having access to genetic information. This interpretation seems to be corroborated by the principle according to which the research results, whether they entail a concrete and direct therapeutic interest for persons belonging to the same genetic line, may be communicated exclusively by request and conditioned to the express consent of the interested person (source subject).

Another suitable source in order to achieve some general applicable rule is the Italian Professional Ethic Code (2006). This act, although not legally binding, has been recognised by the Italian Constitutional Court, together with the Bodies entitled to guarantee its enforcement, as a normative means which takes part in protecting individual rights of persons involved in therapeutic but also research activities (case n. 282/2002). Article 12 clearly provides that personal data disclosure is allowed also whether the patient withholds his/her consent in case of emergency in order to protect life or health of third subjects.

The Italian regulatory approach puts itself into a line of discontinuity at the comparative level.

The Human Tissue Act (UK) assigns to the Human Tissue Authority a derogation power from the general rule of donor's consent, in all those cases in which «it is desirable in the interest of another person that the material be used for the

[41] See the Document on "*Raccolta di campioni biologici a scopo di ricerca: consenso informato*" (Biological samples collection for research purposes: informed consent), February 26, 2009, p. 8.

purpose of obtaining scientific or medical information about the donor» , even thought only when it is not reasonably possible to trace the person from whose body the material has come (Section 7) (Lucassen and Kaye 2006).

Also the Spanish legal order provides for a systematic and differentiated model, which is grounded on a distinct, even if coordinated in the same legal means (Title IV of Law 16/2007 on Biomedical Research), regulation for genetic data/information and biological samples (Seoane Rodríguez and Casado da Rocha 2008; Romeo Casabona 2008). On the one hand—data regulation—article 49 (Right to information and right not to know) provides that whether the genetic information derived from genetic analysis are necessary to avoid serious damage to the health of the biological family, the affected persons or their legally authorised representative may be informed, limiting the communication exclusively to the data necessary for these ends. At the same time, with regard to the duties of confidentiality, article 51 provides—as general rule to be complied with by the personnel—that the disclosure of personal genetic data to third parties (without any express reference to the genetic family) is only permitted with the express written consent of the person to whom such duty relates. With specific regard to genetic analysis involving several members of a family, the results shall be filed and individually communicated to each one of them.

On the other hand—tissue regulation, to which is dedicated a specific Chapter of the Law—the "source subject" or the family may use the samples for health reasons, when required, provided that these are available and have not been anonymised (art. 58). This allowed utilisation finds, differently from the Italian legal system, a pertinent reference within the informative-consent process. Article 59, among the prior information to the use of biological samples to be provided with, includes also a warning about the possibility that the information obtained could have implications for the person's family members and their right, where appropriate, to convey that information to them (letter j).

The Spanish approach, also considering a common constitutional ground, may represent a useful model to be adopted by the Italian regulation. It expresses, at the formal level, the principle according to which it is advisable, even if in the same legislative act, to provide separate and specific sets of norms for genetic data protection and biological samples regulation, with the biobanks regulation representing a sort of intermediate-harmonisation level. At the substantial level, this systematic organisation within the Act turns into a perspective and modular structure in which regulation follows the specific nature and structure of its object, personal genetic data (articles 49 and 51) and biological samples (article 59).

3.3 The Normative Means. The Need for a Physiological Relation Between Legislative and not Legislative Sources

It is discussed the need for a distinction between an exclusively legislative intervention and a regulatory one, that provides normative means (e.g. administrative regulations or authorisations) in a subsidiary and complementary function (McLean 2009).

These means seems to be able to guarantee the efficacy of regulative mechanisms, due to its adaptability to the on-going scientific development, and the effectiveness of all involved subjects' protection. A "not exclusively legislative" approach may also increase the incorporation of mechanisms which facilitate timely adaptation to changing circumstances (Stranger and Kaye 2009), such as the temporal limitation of the instrument's legal efficacy or the inclusion of an "updating clause" which force the regulators to adapt normative contents to the scientific progress.

Within the EU legal context, the Italian model seems to be exceptional. This "*exceptionalism*" is due to the nature of the normative means utilised for regulating genetic data treatment. As said before, it is characterised by an integration between a very limited legislative intervention specifically dedicated to genetic data treatment (article 90 of the Italian Code of Privacy) and a genetic data specific oriented administrative act (the General Authorisation for Genetic Data Treatment), to which the Legislator has substantially delegated the systematic regulation of the issue. Compared with other national experiences, the balancing between the law and the administrative intervention in regulating genetic data treatment seems to be more overlooked toward the latter one in Italy than in Spain (Law on Biomedical Research, n. 14/2007) or in the United Kingdom (Human Tissue Act, 2004). As said before, this tendency represents an exception also within the same Italian legal system with regard to health law, in which traditionally (human assisted reproduction, end of life decisions) the legislative source constitutes the exclusive regulative means, concretely impermeable to expertise influence (not directly referred to the Italian legislation, see Caulfield et al. 2004).

This normative choice entails pros and cons. On the one hand, the Authorisation contains a "due date clause", according to which its temporal efficacy is predetermined, in order to allow/foster «its integration or modification also in connection with fast development of research and technologies applied to genetics and the evolution of scientific knowledge». It may also guarantee the involvement of expertise and of the persons directly affected, according to a settled jurisprudence of Italian Constitutional Court which has strongly recognised the essential relevance of scientific bodies in regulating scientific activity within the legislative making process (see decision n. 185/1998 and 282/2002). In this judgement the Court has explicitly stated a mutual relationship between legislative power and scientific expertise, which must be integrated into a shared decision making process characterised by both a heteronymous (legislative) and an autonomous (expertise) intervention. According to the Court, technical-scientific bodies must develop an essential relevance within the medical field—both in therapeutic and experimental activity—because their opinions are invested of a "binding normative efficacy", representing an *extra-legem* regulatory means with a scientifically bound content excluded from the chance to be challenged before the Constitutional Court (Penasa, 2008).[42] From this perspective, it may be appropri-

[42] In the decision n. 188/2000, the Court makes reference to a "*reserved competence*" of the technical-scientific bodies in determining the technical content of therapeutic activity (in the specific case, the list of tumorous diseases admitted to a free selling of the drugs), stressing at the same

ate to provide—together with the "sunset" and the "updating" clauses—a public consultative mechanism, through which individuals but also interested groups or associations should be involved into the decision making process, as the Italian Authority has provided for regulating the patients' electronic health record[43] and the on-line examination records.[44]

On the other hand, this exceptional approach centred on not legislative instruments seems to hide a legislative inactivity, developing not a physiological integration between different normative sources, but de facto a pathological relation in which the Authority makes up for the lack of Legislator in regulating the issue. This approach reveals its pathological nature more with regard to biological samples and biobanks regulation than to genetic data protection, in which the integration among regulative means seems to find a proportionate balance (legislative decree providing general principles integrated by a more flexible and adaptable instrument as the Authorisation).

As stressed above, biobanks for research purposes lack for a specific regulation, both at the legislative and regulatory level, being necessary to gather some general principles from genetic data regulation in a subsidiary and supply (replacing) way. A systematic and organic intervention is still missing, going to decrease the certainty of the regulation and therefore the level of persons' rights protection and researchers' freedom, that are not able to individuate the appropriate rules to apply to their research activity.

On the contrary, the European Directive on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells for medical and therapeutic purposes has been implemented. It has been approved, starting from 2002, a succession of Executive's Orders (on behalf of health Ministry), providing "*Urgent measures with regard to umbilical stem cells*".[45] In November 2009 two Executive's Decrees

Footnote 42 (continued)

time the liability corresponding to these bodies. In the decision n. 282/2002 the Court has declared that a legislative intervention on the merit of therapeutic choices related to their pertinence cannot derive from evaluations based exclusively on the mere political discretion of the legislator, but the legislator must provide for the elaboration of opinions (advice) based on the check of the level of the acquired scientific knowledge and experimental evidence, by means of scientific—national and international—institutions, considering the "*crucial relevance*" which has to be recognized to the technical-scientific bodies. In any case, according to the Court, the legislative intervention must be the *result* of this kind of (previous, within legislative process) check.

[43] **Guidelines on the Electronic Health Record and the Health File,** ***as*** *published in* Official Journal of the Italian Republic *n. 178, 3 August 2009.*

[44] **Guidelines on Online Examination Records,** *published in* Official Journal of the Italian Republic *n. 288, 11 December 2009.*

[45] There is also a set of "*Guidelines for the collection, handling and clinical utilization of Haematopoietic Stem Sells*" contained into an Agreement between Italian Government (on behalf of Health Ministry) and the Italian Regions and Autonomous Provinces (2003). The Guidelines provide for "qualitative and operational standards, in coherence with the international ones, related to the structures which carry out the taking of, preservation, processing and transplant of Haematopoietic Stem Cells deriving from homologous or hallogenic donor or from the umbilical cord donation".

have been approved. The first one concerns the preservation of umbilical cord stem cells for homologous-dedicated utilisation. The second one, providing for the «establishment of a national net of biobank for the umbilical cord blood' preservation»,[46] which is oriented to cord blood collection, preservation and distribution for haematopoietic transplant and which goes to integrate the "*Guidelines for the collection, handling and clinical utilization of Haematopoietic Stem Sells*" contained into an Agreement between Italian Government (on behalf of Health Ministry) and the Italian Regions and Autonomous Provinces (2003)».[47]

4 The Property of Human Tissues Stored in Research Biobanks

The definition of the legal status of the human biological materials has always been a hotly contested issue (Rao 2007). This issue is even more pressing in the context of current biomedical research, in which the demand of human tissues is constantly rising. In fact, they represent an irreplaceable source of biological and genetic data, useful for implementing new genetic tests, therapies and medicines.

In this context, which is strictly linked to the definition of the legal status of human tissues, we assisted to the explosion of the debate about the ownership of biological samples and their commercialisation (Alta Charo 2006). If, in the past, this debate had only theoretical consequences, today it implies a lot of practical effects. Indeed, recognising property rights on biological samples means to determine which subject can perform scientific research, to what extent and with which limits. More in general, the assignment of property rights requires to deal with the existing relationship among science, society and market.

The balance among these three elements is not neutral but it depends on the particular ethical position that we presuppose (Brownsword 2009). Although, in some cases, the ethical positions are hidden by the legal technicality, they represent the guide in the allocation of property rights. Consequently, when we cope with the issue of property rights on human biological materials we have to take into consideration these "ethical presuppositions" (Tallacchini 2009).

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[46] It has set up the Italian Cord Blood Network (ITCBN), to which it assigns—among other functions—the function of promoting «donation and preservation of umbilical cord blood and the achievement of a number of blood unities able to satisfy national requirements» (art. 2, paragraph 1, letter d); promoting «studies and researches regarding cord blood procurement, preservation and processing in order to achieve an higher quality and safety level» (letter f); promoting «in cooperation with interested voluntary organizations, projects oriented to present solidarity donation of umbilical cord blood to the population, especially to the mothers-donors» (letter h).

[47] The Guidelines provide «qualitative and operational standards, in coherence with the international ones, related to the structures which carry out the taking of, preservation, processing and transplant of Haematopoietic Stem Cells deriving from homologous or hallogenic donor or from the umbilical cord donation».

Moreover, as it will be clarified in the next pages, the reflection about ownership of human biological materials is deeply influenced by their own legal nature (Björkman and Hansson 2006). Today, they are not to be considered only as aggregates of molecules, but they primarily represent a source of personal, health and biological data. Therefore, it is possible to consider the relationship with human tissue from two distinct viewpoints: the first one is the relationship with the data and the second one is the relationship with the materials (Macilotti 2008). The pivotal point is to consider how these two dimensions are related.

4.1 The Legal Status of Human Biological Materials

Once removed from the body, human tissues are to be considered as autonomous and independent entities, given that researches and interventions led on them do not directly compromise the health of the human body from which they were separated. Consequently, we can't use the statute of human body in order to define the legal status of human tissues and we can not automatically export the norms that ruled the human body with regard to human tissues (Rodotà 2006).

That being stated, we have to consider that historically, when the informational capacity of the human genome was still unknown, human tissues were considered as an aggregate of molecules. Therefore the law focused on the material nature of tissues. For this reason, the scholarship never doubted that the relationship between the donor and the removed tissues should be based on ownership rights. Tissues were viewed as a common "*res*", object of appropriation such as a pen or a book.

Scientific knowledge revolutionised this perspective, demonstrating the huge informational capacity contained within the tissues. With the development of genetics studies and research technologies, biological materials started to be considered as a valuable source of medical and genetic data, contributing to the progress of medical sciences. These data contain useful information about the patient such as health, biological identity and the predisposition to specific diseases. From simple aggregates of molecules, tissues are coming to be considered as data sources.

The "informational dimension", anyway, has different features from the "material dimension". Human tissues and human body share the same information, also after separation from the body. Indeed, tissues contain the genetic pool of the body they have been removed from. Therefore, from an informational point of view, the separation of human tissues from human body does not imply the complete autonomy of the biological materials from the original body.

This feature is relevant, given that in the European continental legal systems the relationship between the person and his/her personal information is not inscribed inside the category of "property rights", but in the category of "personality rights".

From a descriptive point of view the double relationship between individuals and tissues and between individuals and information related to the samples can be considered as a "belonging relationship". Property should be considered as a

border aspect of the more general concept known as "belonging". In the property relationship, the owner and the owned object are two separate entities. The highest level of "belonging" exists when there is a correspondence between owner and owned object. This is also the case of the "personality rights" which are not distinguished from the individual who owns the rights, but are parts of his/her identity. For instance, dignity is not an external good from the person, but it is part of the person and it is inextricably linked to it.

The law considers personality rights as external objects to one's identity. But this is only a rhetoric *fictio*, useful for applying the legal structure of "subjective rights", shaped on the property rights' structure, which implies the presence of an owner and an owned object (Zatti 2007).

Biological samples entertain therefore two types of relationships with human body. They entertain a material relationship, which is based on property rights and an informational one, based on personality rights.

This distinction can be found also at the economical level. Biological sample is a good that entirely expires within a certain time. Personal data (related to the tissues), "survive" even if the relative tissues are consumed. The material dimension is rival in consumption and easily excludable while the informational dimension is non-rival a hardly excludable to the use of third persons.

The informed consent of the donor for processing personal data does not imply any real property right for the researcher. It simply implies a right to use these data within the limits established by the rules about personal data protection. The consent of the donor does not imply the property right of the donor on material, but an individual right to protect his own privacy.

The common law systems are not familiar with the category of "personality rights" as recognised in civil law legal orders, but the distinction between the material dimension and the informational dimension of human tissues is represented through the distinction between property and privacy. Many parallels may be drawn between the right of privacy and the prevailing understanding of property. As noted by Rao (2000) «privacy, like property, encompasses the right to exclude others from protected space and the corollary right to exercise control within one's own territory (…). The core of both "privacy" and "property" involves the same abstract right: the right to exclude unwanted interference by third parties». Despite the connections and structural similarities, also in the common law systems there are some significant differences between privacy and property. Thus, property protects the owner's autonomy over what is owned, whereas privacy safeguards an inviolable corporeal identity. While human tissues can be manipulated, alienated, transformed on the market, just like property, privacy bundles together all interests in the body within a single person. As a result, bodily privacy is inalienable and unassailable (Rao 2000).

The bi-dimensional nature characterising human tissues, both considered as molecular aggregates and as sources of genetic data, represents the main problem in the definition of the relationship between individuals and removed tissues. The pivotal point is to establish if these two dimensions can or can not be ruled by the same legal rules.

4.2 The Two Dimensions of Human Biological Materials

What is the relationship between the material dimension and the informational one? From a legal point of view, is it possible to split the material dimension of human tissues from the informational dimension?

The answer to these questions depends on the possibility for these two dimensions of circulating separately or on the possibility of creating a space of autonomy for these dimensions. If they are inextricably interconnected, it would be necessary to identify a common regulation able to protect both the dimensions.

Continental Europe and the United States chose different strategies. The United States' courts (i.e. Moore v. Regents of the University of California, Greenberg v. Miami Children's Hospital Research Institute and in the recent case Washington University v. William J. Catalona) placed the relationship with human tissues, within the sphere of the property rights. The need to protect the market of science has led the courts to consider the property rights of researchers on the human tissues preeminent than the personal rights of the patient on the human biological materials.

This approach has the merit of emphasising the public interest in the progress of human biotechnology, but it does not adequately protect the rights and the interests of the single person.

The European legislators adopted a different strategy. In Europe emphasis has been shifted from the physical dimension to the informational one. Patients' privacy right prevails over the property interests of the researchers and the biotechnology market. In Italy, for instance, according the above cited General Authorisation of the Privacy Authority, tissues have to be destroyed whenever the consent of the donor concerning data processing for medical research is revoked. The destruction of the human samples is ruled by an authority protecting personality rights and that confirms the absorption of the legal protection of individual biological samples within the personality rights' protection system. The biological sample becomes a physical support containing data. This "de-materialisation" makes legal personality protection essential in terms of rights to privacy and self-determination. In this context there is no space for property rights.

Anyway, it is restrictive to consider the relationship with the tissues only in the personality rights' protection system. Indeed, it would mean to associate the material dimension to a discipline about the informational dimension and, therefore, to consider tissues as mere informational entities which work as physical supports. The right to privacy protects the individual, but it does not take into consideration the public interests in the use of human samples. The individual has the exclusive control of his tissues, although he does not have the possibility to reap the benefits provided by tissues removed from his body. Researchers, in contrast to patients, have the possibility of extracting useful information from tissues, and have the technical know-how to obtain valuable data, that are fundamental for the scientific progress.

Therefore, it is necessary to create a regulatory framework able to protect all interests deriving from the use of the human tissues: the interests of the involved person, the biotechnology market interests, as well as the public interest. It is necessary to build a public space where to protect the rights of people involved

but, at the same time, where to allow samples to be freely used by researchers (Tallacchini 2009).

4.3 The Double Nature of Informational Dimension and the Biobank

The attraction of the regulation of human tissues under the "personality rights" depends on personal data deriving from human tissues. As said before, in the material dimension, human tissues are simple aggregates of molecules.

In order to be considered as "personal", data have to refer to a specific individual. Clearly, if data could not specifically identify one individual, there would be no longer danger of damaging a human being or injuring his/her personal identity.

These features suggest the existence of a double level in the informational dimension structure. There are data which identify an individual and data which simply describe the mere physical-chemical characteristics of the biological sample, without identifying any specific human being.

The first level includes personal data, which allow the identification of a specific individual. If these data are deleted, the sample is considered as "non-identifiable" and from a legal point of view, the material dimension of the sample shall now prevail on the informational and personal one. The destruction of data implies, therefore, that the sample is considered both as an informational and as an autonomous entity. But after the data deletion, the subject is no longer identifiable. Consequently, the follow up data relating to the patient's clinical evolution will not be available any more. It is therefore important to find a way of maintaining both dimensions without renouncing to one of them.

In order to preserve all dimensions, one potential solution could be to single out a third autonomous entity. This entity should be a third party, other than patients and researchers, a sort of trustee (Winickoff and Winickoff 2003). Its aim should be to assure the respect of the right to privacy of the patients in order to allow science to deal with both "material samples" and non-personal data.

Personal data management through suitable technical measures should be the main duty of this third entity, which might therefore ensure to be the only responsible for the connection of informational data (first dimension) to the respective biological samples. These measures could manage successfully the updating of the follow up information. In that way, samples could circulate remaining anonymous and it would be possible to update the follow up data.

4.4 Biobanks' Role

The role of an autonomous entity of that sort could be easily played by biobanks. Thanks to them science could benefit of non-identifiable biological samples delivering updated medical information (second level information). Clearly, if they are

a third party, people carrying out the storage and checking biobank's activities are supposed to be other than people carrying out researches on the samples.

There is another important consequence. Thanks to the institution of biobanks, samples acquire their "materiality" back and the focus shifts again to the property relationship between individuals and tissues. Who should be the owner of the human tissue stored in the biobank?

The Italian and the EC legislations give no answers to this question. In order to find an answer it is necessary to balance the interests and the values involved in the allocation of property rights on human tissues.

The first hypothesis is to assign the property rights to donors. Donors are not able to extract from them any useful information and this allocation could be inefficient. Moreover, assigning property rights of biological materials to donors would cause deleterious effects on the integrity of biobanks and consequently could produce disastrous consequences for medical research. The patient, indeed, as owner of the tissue, has at any time the right to ask for the destruction of the sample, reducing therefore the possibility for researchers of carrying out long term comparative studies on stable tissue collections.

According to a second hypothesis it would be possible to allocate property rights to researchers. On the one hand researchers are able to extract useful information from tissues, while on the other one they also have an adequate know-how useful for interpreting the meaning of data.

In this allocation there are also some critical aspects. The recognition of fully property rights to researchers could lead to confusion between the controller and the controlled one, due to a lack of separation of the material dimension from the informational dimension.

Moreover, a research entity owning tissues could impede the use of biological material to external researchers and their potential would be consequently severely reduced. Rivalries could also raise between different research entities for the ownership of biological materials. Additionally, given the importance covered by the study of human tissues in biomedical science, it is easy to imagine that the availability of biobanks might become an essential precondition in order to obtain useful research funding.

That precondition would most probably be the main cause of trouble between different research institutions, which would also limit and damage medical research development.

These considerations suggest that an alternative model should be created in order to fulfil the contradictions generated by the dual nature of biomaterials: they should be considered under the economic category of "commons". Once their use has been granted from the donor, they would neither belong to researchers, nor to donors, but they would become property of the entire community and the biobank could be the custodian of the materials, in favour of the community.

The institution of autonomous entities for managing human tissues could be an efficient strategy. Independent biobanks subjected to public control would represent an effective solution because it would allow them to protect patients' personal data and, at the same time, to proportionally and democratically distribute biological materials in order to ensure scientific research development (Winickoff and Neumann 2005).

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Data Protection Principles and Research in the Biobanks Age

Roberto Lattanzi

1 Time for Rethinking and Looking Forward

Are the principles of data protection suitable for regulating the relationships between techno-science and the law for the specific area of genetic research, particularly with respect to collections of biological samples—often referred to as biobanks? Or is it true, as is widely believed in medical and scientific circles, that personal data protection legislation, or at least its implementation,[1] is an obstacle to medical and scientific research, and in particular to genetic research?

Furthermore, what has personal data protection legislation, which is mainly focused on personal information, to do with the legal status of biobanks?[2]

The article builds on the speech presented at the International Meeting on "*Rethinking autonomy in the research biobanks age*", Università degli Studi, Milan, 17–18 December 2009. The author would like to thank Mr. Antonio Caselli for translating the text. Opinions and views expressed are the author's only.

[1] The insufficient clarity of these disciplines (even when explained by the general clauses) and the absence of guidelines (or of case law) are often seen as obstacles by the operators, who may not have specific legal competency: see Kollhosser (1995, 463): "Die vorhandenen Unklarheiten und Unsichereiten über die rechtlichen Grenzen des Datenschutzes können somit faktisch zu einer Behinderung der medizinischen Forschung führen".

[2] It is not necessary to define the meaning of the term "*biobank*" here: in this article it is sufficient to use a wide definition meaning the collection of biological samples and related information that are destined (originally or subsequently, regarding the moment of the collection) for genetic research. For more on the necessity for quality standards related to *tissue banking,* see the report of the Expert Group on Pathology, BBMRI WP3 expert meeting on Pathology, 17–18 December 2008, Munich.

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Beginning with these questions, although they may seem to trivialise the import of the actual issues to be faced, allows us to discuss the legal status of medical and scientific research in the age of biobanks by looking at the interactions with personal data protection legislation and also, perhaps more importantly, allows us to assess whether it is necessary (or considered appropriate) to introduce new legislation or to amend the existing rules in the European scenario.[3]

It could be said that an assessment of this sort is not an end in itself, as such an assessment will actually be instrumental in deciding which steps will be taken, and the decisions by policy- and rule-makers must not be postponed further, particularly given the wealth of literature available on the topic.

The many reasons for this urgency may be summarised as follows. The technical and scientific advancements in the genetics sector are obvious to all, and expectations are increasing that descriptions of the causes and identification of the treatments for serious diseases that affect large proportions of the population (such as cancer or degenerative diseases[4]) and other less common diseases that are the result of genetic defects will soon be available, for the benefit of both current and future generations; information technology, and particularly bioinformatics, is constantly improving and healthcare systems are increasingly affected by this improved technology—well beyond their computerisation—and both of these factors are bound to result in a repository of information with increasingly high-quality, cost-effective features that can be (re)used for research purposes[5]; large biobanks are being set up in many countries (for example, Iceland,[6] England and Estonia), and existing collections of biological samples are being sorted and stored, while research projects and scientific networks are increasingly being

[3] It will therefore, first of all, be necessary to check the areas in which there is already substantial consensus regarding the existing rules (or good practices) and to take note of the areas where there are still uncertainties or divergences.

[4] See Council of the European Union (2009), which allowed the possibility to "share, where appropriate, existing research studies and infrastructures or develop new ones in areas such as coordinated registries, biobanks for blood samples and tissues or the development of animal models for the study of these diseases" [preceded by the European Parliament resolution of 12 November 2009 on Joint Programming of research to combat neurodegenerative diseases, in particular Alzheimer's disease, and the Commission proposal of 22 July 2009 for a Council Recommendation on measures to combat neurodegenerative diseases, in particular Alzheimer's, through joint programming of research activities (COM(2009)0379)].

[5] For example, the progressive introduction in all western countries of *electronic health records*: "Electronic patient records hold great value for research purposes, prescribing practice, pharmacovigilance and public health. Linking genomic data to electronic patient records offers additional benefits for patient care and for research. […] We recommend the establishment of a new Institute of Biomedical Informatics to address the challenges of handling the linking of medical and genetic information in order to maximize the value of these two unique sources of information" (House of Lords Science and Technology Committee 2009, 51). See also for more references: Lattanzi (2008, 21).

[6] For a detailed description of the Icelandic Health Sector Database see Arnardóttir et al. (1999). For an outline of the issues raised in Iceland, see the decision of the Icelandic Supreme Court in *Guðmundsdóttir v. Iceland*, No. 151/2003 (November 27, 2003), which has been widely reported outside the national context from which it originated (see the Comment published in 118 *Harv. L. Rev.* 810 (2004); v. altresì Gertz (2004, 241). See also the article concerning an instance of bankruptcy filed in relation to the US-based deCode Genetics Inc. by Wade (2009).

restructured in multi-tier terms (regional, national, continental, inter-continental)[7]; and, finally, there are major business interests, both public and private, and investments involved in developing this sector.[8]

If these points do not sufficiently explain the importance of the issue, one only needs to browse the many documents issued over a very short period by national bio-ethics committees[9] which indicate the need for development of clear, harmonised rules, at least at a European level, for all the stakeholders in the area. Data protection authorities themselves have not remained passive in the face of the developments related to the processing of genetic data; they are actually contributing to the debate on biobanks, both at a national level[10] and via the Article 29 Working Party,[11] within their respective spheres of competence.

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[7] Knoppers et al. (2007). See also: Promoting Harmonisation of Epidemiological Biobanks in Europe (PHOEBE), www.phoebe-eu.org; Biobanks for health in Norway, www.fhi.no; CARTaGENE, www.cartagene.qc.ca; GenomEUtwin, www.genomeutwin.org; Public Population Projects in Genomics (P3G), www.p3gconsortium.org; P3G Observatory, www.p3gobservatory.org; Public Health Genomics (PHGEN), www.phgen.nrw.de; The German National Genome Research Network, http://www.ngfn.de; UK Biobank, www.ukbiobank.ac.uk; Molecular Phenotyping to Accelerate Genomic Epidemiology (MolPAGE), molpage.org; European Network of Genomic and Genetic Epidemiology (ENGAGE), www.euengage.org/science.html; Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), www.biobanks.eu/contact.html; and Genome-Based Research and Population Health International Network (GRaPH-Int), http://www.graphint.org.

[8] See House of Lords Science and Technology Committee (2009), *passim*; OECD (2009). Previously: OECD (2006).

[9] For a useful survey, see Matthiessen and Pitkänen (2004). However, papers and official documents on this issuehave recently multiplied, as explained in the text: see Comité de Bioética de Cataluña (2004); Nationaler Ethikrat (2004); Irish Council for Bioethics (2005); Académie Suisse des Sciences Médicales (ASSM) (2006a, b). In Italy see: Comitato Nazionale per la Bioetica (2006); Comitato Nazionale di Bioetica e Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita (2009). In Austria see: Bioethikkommission beim Bundeskanzleramt (2007); in Greece see: National Bioethics Commission. *Recommendation on banks of biological material of human origin (biobanks) In Biomedical research.* See also CCNE (2003); Nationaler Ethikrat—CCNE (2003).

[10] The general authorisation issued on the 22 February 2007 by the Garante per la protezione dei dati personali (in www.garanteprivacy.it, doc. *web* n. 1395420; prorogated with later decisions on 19 December 2008, doc. *web* n. 1582871, and 22 December 2009, doc. *web* n. 1683067), which represents the regulation of the subject in the Italian legal system, is notable although it is an exception in the European landscape. See also: Unabhängiges Landeszentrum für Datenschutz Schleswig-Holstein, Datenschutzrechtliches Gutachten, *Datentreuhänderschaft in der Biobank-Forschung—bdc\Audit (Biobank Data Custodianship/Audit Methodology and Criteria) Methoden, Kriterien un Handlungsempfehlungen für die datenschutzrechtliche Auditierung der Datentreuhänderschaft in der Biobank-Forschung, Schlussbericht*, Kiel, 30 April 2009.

[11] See Article 29 Data Protection Working Party, *Opinion 6/2000 on the Genome Issue*, Adopted on 13 July 2000; and Art. 29 WP, *Working Document on Genetic Data*, WP 91, adopted on 17 March 2004. For an initial reaction to the use of biobanks in research, see the statement adopted at the 20th Data Protection Commissioner's Conference, 16–18 September 1998, 20th International Conference on Data Protection in Santiago de Compostela, Spain, which discusses the Icelandic centralised electronic database containing health records and other related information, including genetic data.

2 Biological Samples and Personal Information: Two Worlds Apart?

The question remains of whether personal data protection legislation, and subsequently the independent supervisory authorities that are required in Member States to check on the lawfulness of personal data processing, has anything to do with biobanks that are used (or are intended to be used) for research purposes and, if so, the extent to which this is so.

One could argue that biobanks should fall within the scope of the rules applying to "*res*" (i.e. property) rather than "*personae*" (i.e. individuals), in which case this whole issue would be tackled from the standpoint of property rights rather than personal rights. This is the approach followed in common law countries, and indeed is the approach adopted by the US legal system, in which there are no general data protection laws, so that the protection of individuals relies only on theoretical models based on property rights, if applicable, which can be reconciled more easily with market logic.

The point is that the use of biological samples (and/or the genetic material extracted from them) for research purposes does not immediately imply consideration of their "material" nature along with the potential gain associated with the use and/or processing of those samples, because it is the "informational" dimension that is the focus of attention. In other words, it is the information extracted from biological samples that matters in the research context, rather than the sample as such; the sample plays the ancillary role of conveying the information it contains, which can only be disclosed if the sample is analysed appropriately.

If this were not the case, it would be hard to understand why the regulatory framework applying to the use of biological samples for genetic research is modelled closely on personal rights rather than property rights. Even if it is assumed that "ownership" of the biological sample is not vested in the individual from whom the sample was taken (as is the case, for instance, with the so-called "donation" of biological samples), the use of any information extracted from the biological sample is regulated in Europe according to personal data protection principles, if that information can be related to an identifiable and/or identified individual.

Thus, if the biological sample is only relevant to research insofar as it is a "container" and a "carrier" of (genetic) information,[12] the regulations applying to its preservation and circulation cannot be significantly removed from data protection principles—it is no

[12] On this assumption, some data protection authorities have compared biological samples to personal data and have therefore applied the same principles (e.g. the Danish authority, as referred to by Petersen 2004). While this is not the case in the "Garante per la protezione dei dati personali" with respect to the right of access exercised by a descendant to acquire the stored biological sample in a hospital (see Decision 21 June 2007, doc. *web* n. 1433975), this has not prevented the Garante from applying the principles contained in data protection law to rules regulating the conservation of biological samples (in addition to those regulating the processing of genetic data) in the *General Authorisation for the Processing of Genetic Data* mentioned in Footnote 10. See also (in Belgium): Louveaux and Moreau (1996).

mere chance that the term "*bioinformationelle Selbstbestimmungsrecht*"[13] was created in the literature to mirror the well-known *informationelle Selbstbestimmungsrecht*, as recognised by the German *Bundesverfassungsgericht* in 1983.[14]

This interpretation was endorsed more or less explicitly by the Data Protection Act (DPA) and, after being put forward by some scholars,[15] was recently upheld by the European Court of Human Rights in the case of *S. and Marper v. UK*.[16]

3 Fundamental Rights of Individuals and Protection of Research: A Conflict Past Reconciliation, or a Necessary Bond?

Having clarified that personal data protection principles are applicable not only to the personal information (including genetic information) that is used for research purposes, but also to the biological samples such information is (or can be) extracted from, one should tackle the first question—i.e. whether the protection of fundamental rights of individuals should override all other rights, including the right to scientific research, by way of a sort of "tyranny of values", given that this protection is at the core of our legal systems including, unquestionably, the EU system. Articles 7 and 8 of the EU Charter of Fundamental Rights have been incorporated into the Lisbon Treaty, which came into force recently.[17]

This stance, which has never actually been endorsed by DPAs, should be regarded as inadmissible. The recognition that the right to the protection of personal data is a fundamental right does not leave room for merely individualistic and/or radicalised views. In Italy, it has been authoritatively stated that fundamental rights, "being values that are recognised and safeguarded by the Constitution, … are always limited by their very nature—including those rights that are mentioned in the Constitution without any reference, not even in general terms, to their

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[13] Halasz (2004), passim.

[14] BVerfG, 15 December 1983, in *BVerfGE*, 65, 1; also in *NJW*, 1984, 419.

[15] See the wide-ranging discussion on this point in Beyleveld and Taylor (2007).

[16] ECHR, *S. and Marper v. the UK*, 4 December 2008 (30562/04 and 30566/04), point 68 states that "all three categories of the personal information retained by the authorities in the present cases, namely fingerprints, DNA profiles and *cellular samples, constitute personal data within the meaning of the Data Protection Convention as they relate to identified or identifiable individuals*", and that "given the nature and the amount of personal information contained in *cellular samples*, *their retention* per se *must be regarded as interfering with the right to respect for the private lives of the individuals concerned*" (point 73) (my italics).

[17] On the process of so-called "costituzionalizzazione della persona", see Rodotà (2007, 208 ss). See also the Communication of 28 May 2002 from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions (2002). Similar attention was also given to the topic in the action plan prepared by the Council and the European Commission for the Feira European Council (2000, 17 e 24).

limitations (e.g. the freedom of art and science: see Article 33 of Italy's Constitution). If two rights are in conflict, or a personal right is in conflict with a public interest protected by the Constitution, a balanced analysis should be carried out (being the so-called balancing of interests) in order to determine which right is to prevail, based on the specific circumstances, or else how those rights can be mutually reconciled".[18]

Furthermore, it should be pointed out that the opposite stance should also be rejected; i.e. that the world of medical and scientific research should be left free to decide on the applicable rules.

One should rather follow the approach based on praktische Konkordanz,[19] or practical co-operation, as recently highlighted by Beyleveld. In this manner, one could not only use interpretation standards applied to the principles that are enshrined in constitutional charters, but also remain true to the belief that it will only be possible to foster public trust in research and ensure that research activities can continue to be carried out[20] by ensuring respect for the fundamental values of individuals at the highest level.[21]

4 The Principles Underlying the Regulation of Biobanks

Before moving on to more detailed considerations, it should be clarified that the regulations that have been (or are about to be) introduced concerning the use of biobanks for medical and scientific research have been derived from multiple sources. On the one hand, they are related to personal data protection principles, as already pointed out, and to professional secrecy rules (especially in the healthcare sector) while, on the other hand, they are associated with the regulations applying to clinical drug trials[22] which are modelled to a large extent on the rules developed at an international level. The latter is especially true for the supervision by ethics committees of biobanks and, generally speaking, of the use of biological samples

[18] Mengoni (1998); on the necessity for balance between liberties and fundamental rights, provided for in the Constitution see Barbera (1975, 75 e 91).

[19] See Morr (2005), Antonow (2006) and Söns (2008).

[20] Reference should be made in this connection to the activities of the EC-funded project "*Privacy in Research Ethics and Law*" (PRIVIREAL), as reported by Beyleveld et al. (2004a, b, 2005).

[21] See also Hustinx (2009): "potential benefits can only be enjoyed in practice, if we are successful in ensuring a strong trust in healthcare systems, and a strong protection of health data and patient data in general. 'Trust' is a keyword in healthcare".

[22] For the limits of a mechanical extension to the rules laid down in the clinical trial sector and the different context of research that does not involve intervention on the person, see Lattanzi (2005)

for research purposes, as well as for the requirement that the proband's informed consent be obtained prior to using his/her data and samples for research purposes.[23]

However, it should also be pointed out that there is an ever increasing *corpus* of legislation that, though starting from the aforementioned principles, is attempting to particularise those principles by introducing regulations that deal specifically with research activities based on the use of biobanks; accordingly, this research sector is taking on features that differ from traditional clinical drug trials.[24] This is shown quite clearly by the adoption of the Council of Europe's Recommendation R(2006)4 on research on biological materials of human origin. Similarly, with respect to domestic legislation, specific laws have been enacted (and subsequently amended) in Norway, whereas the so-called *loi bioètique* is being revised in France specifically to keep the provisions on observational studies separate from those applying to clinical tests.

Therefore, one cannot rule out that law-making efforts in this area will be made at a Community level as well, especially given the increasing amount of research involving biobanks from several Member States; in fact, the shared principles introduced by the legislation enacted domestically to transpose directive 2001/10 cannot be applied to this sector.[25]

However, this is a topic best addressed by switching from general principles to specific rules so as to prevent obstacles from arising in the day-to-day research practice, despite the existence of such shared principles.

5 Supranational Data Protection Regulations and Scientific Research

Before embarking on a search for the peculiarities of genetic research and biobanks, it may be helpful to recall that Directive 95/46, which is an *omnibus* regulation, does not provide detailed guidance in this respect. This has left a broad manoeuvring space for national lawmakers as to the regulations applying to the research sector; indeed, Article 8(4) of the Directive allows for additional deviations from the prohibition against processing sensitive data, on condition that

[23] This remains one of the more controversial topics: see Weir and Horton (1995, vol. 17(4), 1 and vol. 17(5), p. 1).

[24] Except for some critical aspects of the data protection laws, in particular with regard to the (presumed) anonymity of the participants in clinical trials: see the guidelines issued by Garante per la protezione dei dati personali (2008).

[25] I have pointed out the inappropriateness of the *Guidance* adopted on the basis of art. 8, directive 2001/20 (with regard to biological samples): see Lattanz (2005, p 124)

"appropriate safeguards" are taken and that there are "substantial public interest reasons".

Nor are clear-cut guidelines available in supranational instruments; the general rule prohibiting the processing of sensitive data as per Article 6 of the Strasbourg Convention of 28 January 1981 actually allows the use of such data for research purposes, providing Member States adopt "suitable safeguards".

In Europe, national lawmakers can therefore exercise wide-ranging discretion in setting out, via standard legislation, the mechanisms for striking a satisfactory (albeit difficult) balance between the conflicting values at stake. Based on an initial analysis, as mentioned previously, all such values would appear to deserve to be implemented in full, as all of them can be considered to be important among those that are recognised and protected by our legal systems. They include the freedom of science and the task of fostering scientific research and development, and more specifically medical research, as well as the community's interest in establishing the causes of disease, which ultimately corresponds to the right to health as an interest vested in the community at large. On the other hand, they also include protecting personal rights and human dignity, in particular with regard to the right to data protection and informational self-determination.

Nonetheless, it should also be considered that personal data protection principles can be placed under serious strain by the requirements of genetic research and the new investigational methods applied in this research.[26] Some of the critical points in this respect are outlined below.

6 Compatibility Between Genetic Research and General Data Protection Principles

6.1 The Purpose Specification Principle

Given that there are no provisions specifically addressing scientific research, and in particular genetic research, in Directive 95/46, it is necessary to assess whether general data protection principles are compatible with the requirements typically applying to genetic research—which in principle, subject to different regulations, is carried out on the assumption of having obtained the participants' informed consent.

To that end, it is appropriate to start from the purpose specification principle, which is the focus of all data protection regulations. Article 6(1), letter (b), of

[26] It is, in fact, fundamentally important to investigate the lawfulness of the processing of personal data by researchers. On this issue, a greater interaction between the world of research and the data protection authorities is necessary, with a view to the possibility of developing (within the existing legal framework) codes of conduct that can contain guidelines while keeping pace with the changing methodologies of research in a flexible manner.

Directive 95/46 provides that personal data may be processed for "specific" and "explicit" purposes; having achieved the (lawful) purpose for which personal data is processed, one must—in principle—either erase or anonymise the data in question. Therefore, any processing operation concerning personal data is basically temporary in nature, as it should be terminated as soon as the relevant purpose has been achieved.

If this regulatory concept is applied to genetic research, there are some initial compatibility issues. Genetic research is characterised, more than other types of medical and scientific research, as an "open-ended process". That is to say, to quote the Italian wording, "you know where you are starting from, but you do not know where you will end". It is difficult to be sufficiently specific about the purpose(s) for which the data subject's "informed consent" is to be obtained. There is actually the risk of specifying boundaries that are either too broad ("for purposes of genetic research") or too narrow ("for the purpose of studying a specific genetic disease").

Major concerns have been raised by researchers about any provision requiring them to recontact data subjects in order to obtain their consent for a "new" area of genetic research using the information and biological samples collected previously. This is alleged to be difficult to put into practice, to entail additional costs, or to be downright impossible.

In short, the personal data and biological samples used for genetic research, which are liable to be used repeatedly within the framework of a basically endless cycle, risk challenging the concept whereby any processing operation concerning personal data should be temporary in nature; moreover, they can undermine the foundations of the so-called right to anonymity.

6.2 The Relevance Principle

However, the purpose specification principle (along with the related "informed consent" principle) is not the only principle that is challenged. Similar considerations apply to the relevance principle (Article 6(1), letter (c) of Directive 95/46/EC). There is no need to outline the detailed features of genetic research here; it is necessary only to stress that this type of research makes use of a considerable amount of personal data from the most diverse sources (genetic, genealogical, medical, and behavioural) plus information on habits and life-styles concerning both the data subject and their relatives. Genetic researchers also avail themselves of biological samples, which can be kept for an indefinite length of time.

It is difficult to differentiate "adequate, relevant, and not excessive data" from those that are not so (or may not become so in future), although one has to do this with sensitive data in this sector—which should be subject to stricter relevance criteria. In fact, genetic research "exposes" a person's most intimate details, and the research requires such "exposure" in order to be truly effective.

6.3 Genetic Research and Data Anonymisation

Another feature, which is also relevant to other types of medical and scientific research, involves the difficulties associated with anonymising data and/or biological samples. These are related not only (or not so much) to the circumstance that the data may be used repeatedly, but above all to the requirement that links between the various items of relevant information may need to be re-established in order to scientifically validate research findings or for longitudinal studies. It was not by chance that when the Icelandic legislation enacted the "deCode Project" the most debated issue was that of how to anonymise—or rather, encode—the personal data.

This is a very sensitive issue, partly because it is likely to be compounded by concerns arising from transborder data flow into countries in which genetic research has reached a highly advanced stage, although the existence of adequate protection levels for personal data is doubtful, in particular in the USA.

7 From Principles to Rules

These considerations, which deal with issues that are also referred to in the Working Document on Genetic Data released by the Article 29 Working Party,[27] allow an initial, tentative conclusion to be drawn.

The highly sensitive nature of the issues under discussion is illustrated by the amount and quality of the information that is processed, and the potentially unlimited period during which this information can be stored and disclosed worldwide. Far from justifying the appropriateness of dismissing the importance of personal data protection principles, these circumstances confirm that compliance with such principles is a precondition for society to trust research.

The flexibility that is a feature of personal data protection principles can prevent, from a conceptual standpoint, irremediable conflicts with the freedom to carry out scientific research. However, this requires certain legislative safeguards to be in place—there are requirements for a ban on using personal information and biological samples for purposes other than research; for the imposition of professional secrecy constraints on researchers (as is the case for physicians)[28]; and for an obligation for researchers to comply with technical and organisational guidelines in their work.

Although the relationship between the regulatory framework applying to personal data protection and genetic research is already tense, consideration should still be given to the desirability (in the lawmaker's view) of introducing sector-specific regulations. Indeed, an ad hoc regulatory framework that addresses the

[27] WP91, adopted on 17 March 2004.

[28] See Simites (2007).

peculiarities of genetic research is currently being developed at a national level. Such a framework is generally focused on the data subject's consent to the use of his/her personal data for genetic research activities and clearly provides for a ban on any use of the data (and biological samples) for purposes other than medical and scientific research. Strict encoding (double encoding procedures may be even better, depending on the nature of the research) and encryption mechanisms for the personal data (and biological samples) in question are envisaged, which will mean the involvement of a competent data protection authority.

This is actually the approach already followed by the legal systems where large-scale genetic research activities were first implemented—in particular, the Icelandic and Estonian legislation systems.[29] While the law policies and regulatory solutions devised in these legal systems may not all be equally satisfactory, there is a need for separate regulations in connection with large-scale genetic research and now also in connection with smaller biobanks.[30]

It is hoped that this process will not result in widening the gaps between national laws, at least in Europe, as this would make it considerably more difficult to carry out cross-border studies.

However, the letter of the law is not enough. Appropriately worded principles, using regulations that have been adjusted to suit the different sectors involved, must be put into practice. This raises a whole set of questions regarding the supervisory mechanisms available both inside the entities performing genetic research and externally, with particular regard to data protection authorities and ethics committees. Mechanisms for co-ordinating all these entities should be devised, while still keeping the respective functions separate.

In the current situation, the availability of clear-cut regulatory provisions in this highly sensitive sector is very much desirable from the standpoint of the data protection authorities.

8 Final Remarks: The Issue of the Proband's Informed Consent

One of the important issues regarding the conditions under which an individual may participate in genetic research performed with the help of biobanks that has yet to be solved involves how detailed the information provided should be in order for the person's informed consent to be valid. Informed consent is required both in connection with clinical drug trials and in personal data protection legislation.

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[29] However, see also, in Latvia: *Human Genome Research Law.*

[30] In Belgium, see the 19 December 2008 *Loi relative à l'obtention et à l'utilisation de matériel corporel humain destiné à des applications médicales humaines ou à des fins de recherche scientifique*; in Norway, see the 20 June 2008 Act no. 44, *Act on medical and health research* (with substantial amendments to the *Act Relating To Biobanks* of 2003); in Sweden, see the *Biobanks in Medical Care Act* (2002:297).

There are still major gaps to be bridged in the legislation that is being developed at a European level.[31] While some legal systems have accepted "broad consent" (this would appear to be the case with the UK biobank experience[32]), other lawmakers have considered it unnecessary to obtain the data subjects' express consent and have accepted an "opt-out right" (see the Estonian experience).

In most legal systems, a compromise solution is appearing whereby it is allegedly unnecessary to re-contact the data subject so as to obtain his/her consent if the new research is related (more or less directly) to and/or is not substantially different from the research for which consent was originally obtained.

While the merits of this issue may be debatable, it can be stated that if differing approaches were used by Member States, a "competitive disadvantage" could result for those researchers who happened to work under more restrictive (or more protective) conditions. It is also evident that any significant differences between national regulations could represent an obstacle to the conduct of research involving different legal systems.[33] Thus, a shared solution should be developed in this respect.

Needless to say, the broader the scope of the authorisation to use data and biological samples for research purposes, the tougher the institutional controls will have to be on the mechanisms deployed for specific research. This will apply in the first place to ethics committees, which will have to be equipped with the required resources and professional skills. The various stakeholders will also have to be involved to a greater degree in both the research activities and the running of biobanks, so as to ensure that these activities are as transparent as possible. The English experience was built on the unfortunate Icelandic experience[34]; governance of the "UK biobank" is guided not only by the Ethics and Governance Framework (EGF) but also by the Ethics and Governance Council (EGC).

If biobanks are to be the modern "infomediaries" in the field of genetic research, "broad consent" could enjoy greater acceptability, on condition that it is balanced with greater transparency in the way that research activities are conducted (without new bureaucratic measures). In this context, the role of

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[31] For similar difficulties in the American literature, see Andrews (2005): "If people's samples are entered into a biobank or research is undertaken on samples already in a biobank, the biobank should assure that participation by sources is informed and voluntary. A general blanket consent to all future research should not be considered sufficient to meet the standards of informed consent. People whose tissue samples are solicited or used should be given adequate information upon which to base their decision, including whether the use of their present or past tissue samples will lead to patents—and, if so, it should be disclosed that such patents can lead to higher cost diagnostics and treatments. Patient tissue sources should be told that perhaps other researchers would allow them to participate in a joint venture governing the use of their tissue".

[32] In this sense, see Macilotti (2009); see also Caulfield and Kaye (2009).

[33] See Kaye (2006).

[34] For critical considerations of the Icelandic case, see Helgason and Gibbons (2008); critical remarks on the opting-out principle adopted in Iceland have also been formulated by Roscam Abbing (1999).

information technology and particularly of the internet and e-mail, which act as low cost vehicles for information exchange for the participants in biobanks ("donors"), should not be neglected. Donors could use these media to express their interest in being contacted, for example, in the case of scientific discoveries that directly interest them. More general information made available (e.g. in annual reports), such as that relating to the biobank's use of biological samples, could be made available through the web. The same communication channels could be used in relation to possible future uses of biological samples (and personal information), therefore enabling the "donors" to revoke (or partially revoke regarding some specific studies) their previous consent.

These initiatives (and others) will relieve the impasse currently affecting the research world, ensuring both the ongoing participation of the "donors" in the process involving their information and biological samples, and the transparent "governance" of the biobanks.

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The New General Data Protection Regulation—Where Are We Are and Where Might We Be Heading?

Jane Reichel and Anna-Sara Lind

1 Introduction

The current EU Directive on Data Protection,[1] has been described as the most far reaching Data Protection regime in the world (Svantesson 2013). Still, the ongoing work within the EU to enact a new General Data Protection Regulation seems to be heading towards an even stricter regime.[2] Medical researchers in biobanking and epidemiology have had quite a fright on behalf of the proposal, especially the amendments suggested by rapporteur Albrecht of the European Parliament's LIBE Committee in December 2012,[3] that to a large extent were accepted by the

[1] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

[2] Commission proposal for a Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), COM (2012) 11 final.

[3] Draft report on the 17 of December 2012 on the proposal for a regulation of the European Parliament and of the Council on the protection of individual with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), Committee on Civil Liberties, Justice and Home Affairs, Rapporteur: Jan Philipp Albrecht.

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Committee in a October 2013[4] and the European Parliament in its first reading of the proposal in March 2014.[5] In this short overview, the status of the legislative procedures will be addressed, a comment on the consequences of changing the legal form from a directive to a regulation, as well as a brief description of the content of the General Data Protection Regulation relevant to research on health data.

2 The Legislative Process as It Stands in the Spring 2014

The legislative procedure for enacting the General Data Protection Regulation is the ordinary legislative procedure in Article 289.1 and 294 Treaty of the Functioning of the European Union, TFEU. It is a co-decision procedure where the European Parliament and the Council decide jointly on the adoption of a legal act, upon the initiative of the Commission.[6] If the European Parliament and the Council agrees on the same text at the first reading, the proposed act is enacted. In other case, the procedure continues with a second and possibly even a third reading, before which a conciliation committee is convened with members from the Council and the Parliament. The Commission continues to be involved throughout the procedure. First, the any amendments made by the Parliament or the Council must be accepted by the Commission, otherwise the Council can only enact the proposal unanimously, whereas otherwise a qualified majority is sufficient (Article 293.1 TFEU). Secondly, as long as the Council has not acted, the Commission may amend or even withdraw its proposal itself at any stage, if the developments are not in accordance with the interests of the Commission (Article 293.2 TFEU).

The process of enacting the General Data Protection Regulation coincides with the elections to the European Parliament in May 2014, and with the appointment of a new Commission later in the same year. This means that there now is a new European Parliament, which will not necessarily find itself bound by the views of the previous parliament. The position of the European Parliament taken on March 12, 2014, in the first reading, might thus be reassessed in later readings. However, the new Parliament can also decide not to start from scratch, but build on the work

[4] Report on the 22 of November 2013 on the proposal for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) Committee on Civil Liberties, Justice and Home Affairs (A7-0402/2013).

[5] European Parliament legislative resolution of 12 March 2014 on the proposal for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) (COM(2012)0011—C7-0025/2012–2012/0011(COD)).

[6] The relationship between the institutions in the EU legislative procedures are further discussed in the Chapter EU Governance for Research and Ethics in Biobanks in this book, Sect. 3.1. For an accessible overview of the legislative procedures of the EU, see the website of the European Parliament, http://www.europarl.europa.eu/aboutparliament/en/0081f4b3c7/Law-making-procedures-in-detail.html.

already done. The next step in the procedures at this point is the first reading of the Council, expected to be held in the summer of 2014. If the Council does not accept the amendments of the Parliament, negotiations between the Parliament and the Council can start. As mentioned above, the procedures can continue into a second and even a third reading. The ambition of the EU legislators is still said to be to adopt the text before the end of the year 2014,[7] but there are no guarantees that this timetable can be upheld. Further, according to the original proposal, the regulation shall apply from two years after it has entered into force (Article 90), allowing the Member States some time to make necessary adjustments to national law.

3 Change of Form: From Directive to Regulation

One of the more notable changes from the current situation is the fact that the proposed piece of legislation takes the form of a regulation and not as today, a directive. A regulation is a coherent form of legislation, which is binding in its entirety and directly applicable in all Member States. Directives are, on the other hand, merely binding as to the result to be achieved, but leaves to the Member States the choice of form and methods (Article 288 TFEU). A directive is thus a legislative form carried out in two steps, one European and one national, normally allowing some room for the Member States to adjust the legislation to national conditions, in form and to larger or lesser extent, in regards to content of the legislative act.

However, even for a directive the Data Protection Directive gives the Member States quite a large room for choosing different legislative solutions. As will discussed further below, in regards to several basic conditions for processing personal data, the Directive allows Member States to derogate from the main rules as long as "appropriate safeguards" are in place. For example regarding the requirements for purpose limitation, laid down in Article 6 of the Directive, 6.1.b states that reuse of personal data for historical, statistical or scientific purposes is not to be considered as incompatible with the original purpose, provided that Member States provide "appropriate safeguards". The same wording is used in relation to the possibility to store data for a longer period of time for historical, statistical or scientific use (Article 6.1.e). Member States have chosen to implement these rules in different ways, leading to substantial differences between the national implementation of legislation.[8] The proposed General Data Protection Regulation, in being a regulation, leaves much less flexibility to the Member States to choose their own

[7] See regarding the European Council, Conclusions of the 24/25 OCTOBER 2013, CO EUR 13 CONCL 7, para 8, regarding European Parliament, information on the webpage http://www.europarl.europa.eu/news/en/news-room/content/20130502BKG07917/html/QA-on-EU-data-protection-reform, the Commission, Press release Data Protection Day 2014: Full Speed on EU Data Protection Reform European Commission—MEMO/14/60 27/01/2014.

[8] The question is discussed further in the Chapter EU Governance for Research and Ethics in Biobanks, Sect. 5.2, in this book.

solutions. However, there are also in the proposed Regulation areas where the Member States are given possibilities to make national legislative choices, for example regarding balancing data privacy against the right to freedom of expression in Article 80.1 of the proposal, and in regards to processing personal data concerning health without consent, Article 81.2a, as will be discussed further in the following section.

4 Rules on Processing on Health Data

The proposal for a new regulation builds to a large extent on the same structure as the Data Protection Directive, with general provisions setting requirements for the processing of personal data (Articles 5 and 6), a general prohibition on processing sensitive data such as health data (Article 9.1) and possibilities to make exceptions (Articles 9.2, 81 and 83). As noted above, the General Data Protection Regulation includes stricter rules on processing of data than the current Data Protection Directive. There are especially three areas that can be identified as problematic for research on health data; the possibility to process health data without (re-)consent, the possibility to re-use health data for other purposes than they were collected for and the possibility to store data for longer periods of time.

The possibilities of exceptions from the requirement of an informed consent in the General Data Protection Regulation are not as general as in the Data Protection Directive. Today, the Directive states that for reasons of "substantial public interest" Member States may allow processing of sensitive data, if suitable safeguards are provided for (Article 8 Data Protection Directive). This opens for Member States to allow scrutiny of ethic review boards to replace the (re-)consent of the data subject, where appropriate. The General Data Protection Regulation contains further provisions. In the original proposal of the Commission, processing of health data for research purposes was regulated in the general provisions on research in Article 83.[9] According to this article, personal data could be processed for scientific purposes under two conditions; first, processing is only allowed if the scientific purposes could not be otherwise fulfilled by processing non-identifiable data, secondly, that identification of the data subject and that data on identified or identifiable persons are kept separately from the other information as long as these purposes can be fulfilled in this manner. In the original proposal, the Commission was to be mandated to enact further requirements through delegated legislation (Article 83.3).

The amendments laid down by the European Parliament added further requirements for processing personal health data in research, included in Article 81. The possibilities to make an exception from the consent criterion is found in Article 81.2a, where it is stated that the Member States may *provide for exceptions to the requirement of consent for research, but* only if the research in question is of "high public interest". The data should be anonymized or, if anonymisation is

[9] Article 81 in the original proposal refers to Article 83.

not possible, pseudonymised under the highest technical security standards. It is underlined that all necessary measures should be taken in order to prevent unwarranted re-identification of the data subjects. A further limitation is, however, to be found in Article 81.3 where it is stated that it is the Commission that decides what is to be considered "high public interest". Also, the demands put forth in Article 83 should be met (Article 81.2).

Also regarding the issue of new or broad purposes the proposed General Data Protection Regulation, taking into account the amendments of the Parliament, introduces stricter rules. It is a general requirement that data should be collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. Whereas the Data Protection Directive states that further processing of data for historical, statistical or scientific purposes is not be considered as incompatible provided that Member States provide appropriate safeguards (Article 6.1.b), no such general exception is included in the General Data Protection Regulation. According to Article 81.1b of the proposed Regulation there is a possibility, in cases where consent is demanded, to collect data for several similar purposes, if the data is "medical data exclusively for public health purposes of scientific research". This would mean that as long as the purpose of the research is public health, personal data can be gathered for several purposes. "Public health" should be interpreted broadly (compare paragraph 123 in the Preamble to the General Data Protection Regulation). The rule is, however, not that easy to interpret and it is important to follow what will happen in this regard.

As set out above, Article 81.2a gives the Member States a certain margin to make exceptions from the general demand on consent. This indicates that when the research in question has a new purpose, it does not mean that processing the data would be unlawful. Also Article 81.1(c) is of relevance in this context. The Article states that sensitive personal data concerning health, which has been collected in the public interest, cannot be used for *other* purposes without consent. Research, however, does not seem to be included in the group of excluded purposes that is enumerated in paragraph 123 of the original Preamble to the Article, as examples of such *other* purposes. This sentence was however taken out in the amendments laid down by the Parliament. The interpretation of the provision is thus somewhat unclear, but it may be readily accepted that it is stricter that the current Article 6.1.b Data Protection Directive.

Lastly, regarding the possibility to store health data for longer period of times, also here General Data Protection Regulation sets out further requirements. In this regard, the Data Protection Directive confers to the Member States the possibility to allow long term storage of data for historical, statistical or scientific use, as long as appropriate safeguards are in place. It follows from Article 83 a that research can be conducted on information from archives, according to rules that are to be decided by the Member States. These national rules should be decided in accordance with the Regulation's general standards, such as consent and presumably its applicable exceptions. A clear rule is not included in the proposal for a regulation, but the Parliament has deleted a suggested paragraph 40 in the Preamble that admitted personal data could be handled for a new purpose in research, as long as that new purpose was compatible with the first (initial) purpose.

To conclude, we can notice a major difference between the present Directive and the proposed Regulation. In the current regime with the Data Protection Directive, the regulatory competence in governing data protection is divided between the EU and the Member States in so far as that the EU sets out the general requirements and then allows the Member States to depart from them, provided that "appropriate safeguards" are in place. In the proposed General Data Protection Regulation the allocation of the regulatory competence has to a large extent shifted to the EU. The rules in the General Data Protection Regulation are in themselves more detailed and the Commission is in several areas to be given competences to enact delegated and implemented acts. Further, even when the Member States are given the possibility to allow for exceptions at the national level, the Commission may restrict the scope of application of the exceptions by defining key concepts, such as with exceptions from informed consent within the area health data, and the concept of "high public interest" in Article 81.2a. On the positive side, it may be beneficial to cross-border bio-medical research if the legal landscape of European data protection becomes less scattered. This would allow researchers in different Member States to adhere to one set of rules instead of today when EU data protection rules have been implemented quite differently in the different states. On the other hand, this will hardly be helpful if the rules themselves are so strict that they in practice render bio-medical research on health data unmanageable. Even if the general tendency clearly is to restrict the use of health data in general, it is worth pointing out that as the legislative process stands today, several key factors regarding the level of strictness in regards to use of health data for research purposes are yet undecided.

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The Tension Between Data Sharing and the Protection of Privacy in Genomics Research

Jane Kaye

1 Introduction

With the costs of sequencing technology falling rapidly, we are moving to a position where whole-genome scanning of individual DNA samples will start to become routine in medical research and clinical medicine. This is also a critical point in time for the building of infrastructure and the linkage of existing biobanks and bioclinical projects. These plans are starting to be operationalized to enable the sharing of data and samples in a systematic way on a large scale. However, the meta-level governance mechanisms that are needed to support this are still in development. The move to global data sharing has been facilitated by funding bodies on both sides of the Atlantic, which have supported large international collaborative projects and developed open access policies to encourage wide-scale data sharing. In combination, these trends challenge some of the basic principles of protection of research participants and the current governance frameworks for research. One of the key challenges is determining how to protect the privacy of participants while enabling the sharing of data and samples through global research networks. To provide some understanding of the concerns raised by data sharing, this review outlines the issues involved in privacy protection as well as the current trends that have transformed genomics research practice and facilitated

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data sharing. It describes how data sharing tests current ethical principles and oversight mechanisms for medical research. In conclusion, it discusses ways forward and some of the new initiatives being developed to facilitate data sharing and enable sustainable genomics research.

2 The Nature of Privacy

The protection of individual privacy is enshrined in legal instruments of all liberal democracies and is a benchmark of civil society. Although privacy is not an absolute right, interference must be justified in the public interest and/or according to law. An example of how the courts in the United Kingdom regard privacy is from Lord Justice Laws of the Court of Appeal:

> Subject to [certain] qualifications … an individual's personal autonomy makes him – should make him – master of all those facts about his own identity, such as his name, health, sexuality, ethnicity, his own image … and also of the "zone of interaction" … between himself and others. He is the presumed owner of these aspects of his own self; his control of them can only be loosened, abrogated, if the State shows an objective justification for doing so. (Wood 2009 at §21)

Individual expectations of privacy are context specific, and so can vary depending upon the individual and the circumstances. Within research, the expectations and norms associated with different kinds of research can lead to variation in the practices that apply. Privacy consists of four interrelated dimensions, which come into play in different ways depending upon the context: physical privacy, informational privacy, decisional privacy, and proprietary privacy (Laurie et al. 2010). In the case of genomics research, any or all of these dimensions may be activated depending upon the context. Within genomics research, some of the privacy risks have been identified "as analysis efforts aimed at exposing individual research participants' information, including revealing disease status, predicted future likelihood or past presence of other traits, or attempts to link another DNA result with a participant, for example, to determine presence or absence in a research cohort, ancestry, and relatedness (e.g., paternity/nonpaternity)" (Johnson et al. 2011). To safeguard against such harms, protections must be established to prevent discrimination against participants and ensure that their medical and personal information is not disclosed to third parties—such as their family or community members, employers, or insurance companies—against their wishes (Gitter 2011). This is because the character of DNA means that sequence information has implications for other biologically related family members, and "the fact that children carry half the genetic information of their parents implies that a decision to reveal one's genetic information today has repercussions for generations to come" (Johnson et al. 2011). These concerns have led to considerable debate within the genomics community as to how best to protect participants' and their biological relatives' privacy while still allowing research to proceed.

3 Trends Within Science

Over the past 10 years, there have been significant changes in the way that genomics research is carried out that have implications for privacy protection. These changes are part of a longer term evolution in scientific practice that has been occurring over a number of decades. Genomics research is now increasingly dependent upon the sharing of data and samples through global collaborative research networks. This widespread data sharing and the building of global research networks are possible only because of technological advances, considerable investment in infrastructure and international consortia, and the implementation of open access policies by funding bodies. Achieving research goals and priorities at an international level would not have occurred at the same scale and speed without the advances in bioinformatics and computing technology, which in turn have led to changes in scientific practice and the way that research is carried out. The relatively recent introduction of next-generation whole-genome sequencing technology adds another layer of complexity to this situation.

4 New Models

The way that genomics research is carried out today, based on the principles of open access and sharing, has its origins in the Human Genome Project, which commenced in 1990 and was completed in 2001. This project arked the beginning of a new way of doing genomics research, as it relied on the collaboration of many scientists, institutions, and funders from around the world (Colins et al. 2003). It marked a transition from a "cottage industry" approach based on bespoke laboratories to high-throughput sequencing involving teams of multidisciplinary experts (Watson 1990). The possibility of the human genome being patented by a private company, Celera, helped to confirm and develop the principle that such knowledge should be freely available to all (Nature 2001; Marris 2005). Using the Human Genome Project approach, a number of data-generating projects have been initiated through joint efforts by national funders, including the Encyclopedia of DNA Elements (ENCODE; http://www.genome.gov/10005107), the Human Epigenome Project (http://www.epigenome.org), the International HapMap Project (http://www.hapmap.org), and, more recently, the 1,000 Genomes Project (http://www.1000genomes.org). These have provided unrestricted access to sequence reference libraries via the Internet. Such resources allow new types of scientific questions to be asked, as "vast numbers of polymorphisms can be studied simultaneously, rather than focusing attention on a small number of genes," and "very many more individuals can be genotyped in a single study" (Day 2009). Such data sets have been presented as the "drivers of progress in biomedical research," and therefore open access policies have stated that they should be "made immediately available for free and unrestricted use by the scientific community to engage in the full range

of opportunities for creative science" (Marris 2005). The role of such projects in advancing science has been seen as testimony to the success of open access policies. However, there have been concerns expressed about the privacy risks that placing individuals' sequence data on the Web may have for research participants (Wood 2009 at §21).

In addition to sequence reference libraries, repositories have been established to centrally organize the storage and sharing of data derived from genome-wide association studies (GWAS) (GAIN 2007). These studies compare the genomes of healthy controls with those of people who exhibit a disease or a specific trait in order to identify the genetic variants associated with that disease or trait (Kaye et al. 2009). To obtain the sample sizes needed to do this, researchers have developed new models of collaboration and data sharing. Examples of these projects are the Wellcome Trust Case Control Consortium (Wellcome Trust 2007) in the United Kingdom, the European Genome-Phenome Archive (http://www.ebi.ac.uk/ega), and the National Institutes of Health's Database of Genotypes and Phenotypes (dbGaP; http://www.ncbi.nlm.nih.gov/gap) in the United States. The aim of these platforms is to maximize the public benefits that can be realized from data sharing (Gibbs 2005), and new methodologies and approaches have had to be developed to handle the vast amounts of data created (Pop and Salzberg 2008). Data must also be deposited within a specific period of time and must meet certain standards of quality. This requirement also includes statements about the nature of the study, which are intended to standardize models for performing studies and reporting results (Little et al. 2009). Such pooling of data ensures that the validity of results can be confirmed in replication studies before they are relied upon, providing a further reason for sharing data (Ioannidis et al. 2008). Unlike access to sequence reference libraries, access to these data sets is provided through a managed access system that requires researchers to establish their credentials and then be approved by a data access committee. There is concern that this managed access model is not as effective for sharing data as Web-based sequence reference data sets, which receive many more hits.

5 Infrastructure Development

In the field of biobanking there has been considerable investment in new population biobanks and cohort studies. One of the research rationales behind the establishment of these resources is to develop information that can help elucidate the fine associations between the genotypes and phenotypes that influence the etiology of common diseases. The need for diverse, well-characterized, large sample groups, both for investigative purposes and for use as controls (Burton et al. 2009), has led to an increased emphasis on cooperation at both the national and international levels (Hattersley and McCarthy 2005). A number of groups have been funded to develop the tools to standardize and harmonize collection and management procedures in order to facilitate wide-scale data

and sample sharing, including the Public Population Project in Genomics (P3G; http://www.p3gconsortium.org) and the International Society for Biological and Environmental Repositories (ISBER; http://www.isber.org). Over the past two years there has also been investment in infrastructure to facilitate the linkage and greater use of existing clinical collections of samples, including the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) (Viertler and Zatloukal 2008) and Biobank Standardisation and Harmonisation for Research Excellence (BioSHaRE; http://www.p3g.org/bioshare) projects in Europe and the Electronic Medical Records and Genomics (eMERGE) Network in the United States (McCarty et al. 2011). The aim of this investment is to provide resources that networks of interdisciplinary teams and consortia located around the globe can use to answer a number of research questions. Large international consortia within Europe and the United States have been funded, as have international collaborations on a grand scale such as the International Cancer Genome Consortium (http://www.icgc.org).

This new emphasis on the linkage of existing biobanks through a common infrastructure requires macro-level, international governance structures and processes to allow the secondary research use of existing information and samples. This raises significant questions about the oversight of global research activity and the best ways to safeguard researcher access to information while protecting the privacy of individuals. Many of the secondary research purposes such infrastructure will make possible were not anticipated at the time when consent was obtained for the collection of the data or samples. The arguments for using existing research collections for secondary research purposes are twofold: First, recruitment to large studies is expensive and time-consuming, and second, larger sample sizes are likely to accelerate research results. Reusing, integrating, and comparing collections will result in an efficient and effective use of funding. However, appropriate governance systems and procedures to link and network new and existing collections at this macro level are still being developed.

6 Open Access Policies

The arguments for the efficient use of resources funded by the public purse also underpin many of the recent open access policies that have been developed by the leading funders of genomics research within the United States, the United Kingdom, and Canada. These policies started with the sequence data [the Bermuda Principles in 1996 (HUGO 1996) and the Fort Lauderdale Agreement in 2003 (Wellcome Trust 2003)] and have now been applied to other forms of data [the Toronto International Data Release Workshop recommendations in 2009 (Birney et al. 2009), the Amsterdam Principles in 2008 (Rodriguez et al. 2009), and the Wellcome Trust joint statement by funders of health research (Wellcome Trust 2010)]. In addition, there are a number of policies for data sharing by the Organisation for Economic Cooperation and Development (OECD) (OECD 2007).

All of these policies have statements requiring the protection of individual privacy and in some cases the dignity of communities while at the same time encouraging wide-scale data sharing for public benefit.

Although these policies are still in their infancy, we are starting to see their impact on the planning, execution, and oversight of genomics research and on the way results are disseminated. The question now is how to share data rather than whether data should be shared at all (Kaye et al. 2009). These policies have created a climate in which data sharing is becoming more the norm—not just for large sequencing projects but for many different types of studies. However, there is still evidence to suggest that researchers are reluctant to share data (Piwowar 2011). Open access principles have also come into conflict with privacy concerns. In 2008, aggregate genetic data placed on the Web by researchers for GWAS use had to be withdrawn once it was realized that individual participants could be distinguished from the openly shared data (Homer et al. 2008). These problems of identifiability and disclosure risks are likely to become more frequent as increasingly diverse sources of data are linked (Heeney et al. 2011; P3G et al. 2009).

7 Technological Advances

Advances in information technology and genome sequencing technology have enabled significant changes in the ways that science is carried out and have provided a means to share data on a wide scale. Digital information can be deposited on the Web or in a cloud and then shared with colleagues and other third parties. Once DNA is sequenced from a sample and transformed into a digital form of AGTC base pairs, it can be used for many different purposes and analyzed by different researchers using different methodologies and approaches. The current challenges include issues of data storage, the quality of sequencing data, and the accuracy of genome assembly (Butler 2010) as well as how best to manage and interpret large data sets of sequence information (Mardis 2011). The advances in next-generation sequencing technology have resulted in far richer and more detailed sequence information at a lower cost. Whereas it is estimated that the Human Genome Project cost US$2.7 billion (NHGRI 2010), in 2009 the company Complete Genomics announced that it could sequence an individual genome for US$5,000 (Aldhous 2009). It is anticipated that these costs will continue to fall and that sequencing will no longer be a bespoke activity but will become a routine part of clinical care. As sequencing becomes cheaper, the use of whole-genome sequencing will become the norm in medical research and bring with it a number of new issues.

The challenges that this presents led Mardis and Lunshof (2009) to write that "the established framework of ethical, legal and social issues (ELSI) in genomics has been shaken to its foundations by something as simple as the emergence of personal genomes." Tabor et al. (2011) note that: whereas conventional technological approaches might generate data on hundreds of thousands, or even millions

of polymorphisms, the overwhelming majority of these variants are located in noncoding regions and likely not of functional significance themselves. In contrast, both exome sequencing (ES) and whole-genome sequencing (WGS) provide information on virtually all functional, protein-coding variants in the genome for each individual participant. This includes most variants known to influence risk of human diseases and traits. These technologies increase the possibility of identifying serious treatable conditions and generating other incidental findings (Wolf et al. 2008) and have created a heated debate as to whether there is an obligation to report research findings to participants and, if so, how this should be done. This reporting raises a number of ethical issues, such as how to develop management pathways and privacy safeguards, and questions of whether secondary and tertiary researchers also have an obligation to report back findings. New models of reciprocal participation in research that also provide individual-level information have been developed by companies such as 23andMe, where participants are treated as customers rather than "health information altruists" and are given access to genomic information (Kohane and Altman 2005). Further research is needed to establish whether such new models of participation are truly reciprocal, whether they could have wider application, and how management pathways for feedback could be developed (Van Ness 2008).

8 The Effect on Scientific Practice

In combination, these trends have had a marked effect on the scientific agenda and the conduct of genomics research. Research is now carried out by interdisciplinary teams of specialists brought together in flexible research collaborations that can process and analyze large amounts of information and large numbers of samples. The collection of information and samples is still carried out by individual researchers, but the model of large interdisciplinary collaborations means that existing collections can be brought together and reused for new purposes. This is possible only because technological advances make it easy to share and distribute data through global networks. Open access policies are changing the way that data are generated and distributed and are enabling new ways to mine data. Increasingly, there is now a distinction between data generators and data users. Data sets are no longer the sole creation or in the control of one individual or institution, but must be made available to the whole research community. For GWAS, this has been achieved through a new managed access model with formal application processes and access determined by data access committees in consultation with collectors, rather than decided by the principal investigator alone.

These changes in the way that science is conducted mean that the "secondary users of the data are far removed from the researchers who carried out the collection of the samples and data, as well as from the research participants" (Kaye et al. 2009). Data sharing has the potential to sever the ties between the researcher responsible for participant enrollment and the individual participants in an original

study. The onward sharing of data raises questions about who is accountable not only to research ethics committees approving new research but also to the research participants for the secondary uses of data in other studies. These advances also challenge our legal and ethical frameworks as data-sharing practices give a new twist to the old questions of informed consent, protection of privacy, and governance of medical research. These trends have had a significant effect on the principles that underpin research and the basis of research participation.

9 Protections for Research Participants

The main purpose of the current research governance system is to protect participants' interests and ensure that research is carried out ethically. It does not have a mandate to consider the broader ethical issues associated with data sharing, such as equitable access to biorepositories for researchers. A number of procedures, practices, and oversight bodies have been established that are designed to protect research participants. Common to all jurisdictions are the requirements that consent must be obtained before the research commences (although there are a number of exceptions to this basic principle), that an individual has a right of withdrawal, and that there must be some review of the research proposal by an appropriate committee, such as an institutional review board (in the United States) or a research ethics committee (within Europe and elsewhere). These protections derive from the Nuremberg Trial principles (NMT 1949, pp. 181–82), which were intended to protect individual research participants from physical harm rather than informational harm. They were not designed for use in global networks where information and samples flow through international research collaborations; rather, they were developed for a time when research was oriented toward one principal investigator, leading one research project, based within one country, located at one point in time—the "one researcher, one project, one jurisdiction" model (Kaye 2011). As a result, they are focused at the beginning of the research process, and oversight is largely reliant on expert committees.

The nature of whole-genome sequence data and the potential for global data sharing also brings into question the social contract that underpins research participation and the governance mechanisms that have been built around it. The basis for medical research participation has traditionally been an appeal to altruism (Hallowell et al. 2010), solidarity (Knoppers and Joly 2007), and/or the gift model (Busby 2004; Tutton 2002), depending upon the nature of the study (Kohane and Altman 2005). The degree of participant involvement in the research process has varied depending upon the type of study—for example, whether it is clinically based with direct patient contact or epidemiological and concerned with population trends. In some cases, participants have had a passive role as providers of samples, information, and interesting case examples of disease. In other types of research, such as research on HIV/AIDS, participants have been more actively involved in defining the research agenda (Kahn et al. 1998). In all cases,

good practice has required that in return for being altruistic, participants' personal, identifiable information should remain confidential and, if possible, be rendered anonymous. This has also been the basis for not having to obtain explicit consent for new research in cases where this may be difficult and when the risks to individuals are perceived to be low. Research procedures and practices have been established on the basis of this implicit social contract. The traditional workhorses of medical research governance—informed consent, withdrawal, anonymization, and oversight mechanisms—are tested by the new developments in genomics research practice caused by wide-scale data and sample sharing.

10 Informed Consent

Informed consent has been used to respect individuals and to enable research participants to exercise their autonomy in medical research and make decisions about privacy risks. The requirements for informed consent have been enshrined in a number of ethical documents, one example being the Declaration of Helsinki (WMA 2008). With wide-scale data sharing, it is impossible to fulfill the conditions of traditional informed consent as outlined in many ethical and legal documents (Boddington et al. 2011). Participants cannot be informed of all future uses of their information and samples over many years at the time of collection, nor can they be given an assessment of all the potential privacy risks of participation in the research (Beskow et al. 2001). Broad consent has become a practical solution to this problem for biobanks, but this is still contentious within the bioethics literature (Caulfield and Kaye 2009) as research participants are giving a broad consent at the beginning of the research process for the use of their sequence and data for many years. There is some doubt as to whether this enables individuals to fully exercise their autonomy, as they cannot choose whether to be involved in specific research projects using different biorepositories, determine what kind of research they participate in, or properly assess the privacy risks of involvement (Boddington et al. 2011). The focus on individuals and informed consent can also eclipse legitimate family and group privacy concerns, which may differ from those of individuals.

At the present time, consent forms are the only means by which the wishes of research participants can be obtained and recorded. This occurs at the beginning of the research process, when potential participants are presented with an agreement that they cannot negotiate (but can refuse to sign) and that, in the case of biobanks, has to hold for a considerable amount of time. Another limitation of the one-off informed consent form is that researchers must anticipate all eventualities to make the consent future-proof and avoid costly and time consuming recontact processes. This means that if data-sharing plans are described—which quite often is not the case—it is usually done in very broad terms (Beskow et al. 2001). This raises questions as to how informed participants actually are (Pearce and Smith 2011) and whether they are really in a position to assess the privacy

risks of research involvement. Currently, efficient and cost-effective mechanisms by which to go back to individuals for new consent for secondary research are not commonplace. Effectively, broad consent is "consent for governance" by others, as judgments about appropriate uses of data and samples often fall to researchers, advisory boards, or research ethics committees, who must make decisions on behalf of research participants (Kaye 2009). In response to these shortcomings, other models have been proposed such as tiered consent (Haga and Beskow 2008; Wolf and Lo 2004), authorization instead of informed consent (Arnason 2004), and "open consent" (Lunshof et al. 2008). New forms of governance models, such as patient interfaces that give individuals greater control over their information (J. Kaye, E. Whitely, S. Creese, D. Lund and K. Hughes, manuscript in preparation), are in development, and "adaptive governance" mechanisms that give voice to group concerns rather than just those of individuals have also been proposed to address some of the deficiencies of the individual consent model (O'Doherty et al. 2011; Winickoff and Winickoff 2003).

11 Withdrawal

The other foundational principle of medical research ethics is the right of withdrawal, which is the notion that a research participant can discontinue his or her participation in research at any time (Gertz 2008). This also applies to the data and samples that an individual may have given consent to use in research, and is one of the key ways by which an individual can enact decisional privacy. However, in the case of international data sharing this is extremely difficult, if not impossible, to achieve when data and samples are shared widely. Computer data sets containing personal information must be continually archived, and it is difficult to claw back minute segments of sequence spread over a global network when they are used in multiple research projects (Zika et al. 2008). The various deidentification and aggregation methods that have been put in place to protect privacy may also make it difficult to trace and remove individual derived data (Cambon-Thomsen 2004; NIH 2007). As we move increasingly toward networks and infrastructure research, it becomes impossible to withdraw completely from research—instead, it is only possible to prohibit the entry of new information and samples into the system. Therefore, the mechanisms that have been put in place to protect the privacy of data may actually make it very difficult to allow participants to withdraw and be forgotten. In addition to the practical difficulties, there are also economic and public-good arguments for disallowing absolute withdrawal. Arguments have been made in the biobanking field that complete withdrawal could lead to the wastage of resources invested in biorepositories and that, by withdrawing, "a person not only withdraws from one project, but from an indefinite number of future projects, including possibly some (many) that the person might want to participate in" Holm (2011).

12 Protecting Privacy

Part of the social contract in research is keeping information confidential as a way of respecting individual privacy. Best practice has involved the use of information technology mechanisms such as firewalls, encryption, passwords, and security compliance as well as the restriction of access to raw data that could directly identify an individual. Current research practice requires the deidentification of samples through the removal of personal identifiers when they are shared with other researchers. However, the uniquely identifiable nature of human genetic information means that with increased data sharing, it is very difficult to guarantee absolute confidentiality for research participants or their genetically related family members (McGuire et al. 2008a), especially if this involves only the removal of personal identifiers. Exome sequencing reveals rare alleles, including those that are of clinical or personal utility, which increases the risk of identity disclosure as well as breaches of confidentiality or privacy (Tabor et al. 2011). In 2008, Homer et al. (2008) demonstrated that it is possible to reidentify individuals who had been genotyped and even those in pooled mixtures of DNA, provided a reference sample is available. Once a person is reidentified, there is the potential for further personal information to be revealed about the formerly anonymous source. The standard protections, such as encryption, that have been used to anonymize or deidentify sequence information are challenged with new sequencing technology that produces richer and more detailed information on individuals (Greenbaum et al. 2011).

A key issue in current research practice for the sharing of genomic data is whether an individual can be "distinguished" from sequence data or whether it is possible to actually "identify" who the individual is Malin et al. (2010) have argued that "genomic sequence data, for instance, and possibly other laboratory and molecular expression data, are often highly distinguishing" but that this is "insufficient to claim that the corresponding individual's privacy will actually be compromised"; to breach privacy, as these sequence data must be matched with data of a named individual, there must be a mechanism to relate the deidentified and identified resources. This assumes that the individual's privacy interest is extinguished if information and data are rendered nonidentifiable or anonymous. However, individuals may still have a concern about how their data might be used in research, even if the data is rendered anonymous. The difficulty here is developing a workable model that allows individuals to control the use of their information but also enables research to proceed. Current research practice rests on the premise that being able to identify an individual would constitute a breach of privacy because of the potential harms that could result, whereas just being able to distinguish someone from a number of sequences does not. As Tabor et al. (2011) note, "inferring the identity of a study participant could facilitate linking them to other genetic or phenotypic data that might be stigmatizing or discriminatory, regardless of whether or not they have a disease or carry a disease-causing variant." Once sequence information is linked to other data sets that contain

identifiable information, the potential for privacy breaches increases. The difficulty is that this can be contrary to the research endeavor, which can require linkage for innovation. There is the danger that privacy protections may become so elaborate that they start to limit what can be done with the data in research terms (Anderson and Edwards 2010).

The increasing availability of publicly available data sets on the Internet and sequence data outside the controlled cocoon of research also raises a number of concerns about potential privacy risks. Whereas genomic information used to be obtainable only through research sequencing laboratories, people can now obtain access to their own genome through direct-to-consumer companies (Lumley and Rice 2010) as well as ancestor-tracing companies. Examples of the use of publicly available information to identify individuals are becoming more common, such as the case of the boy who tracked down his sperm donor father using an ancestor-tracing company Motluk (2005) and Gitschier's (2009) use of publicly available data sets on the Mormon population to identify individuals. This is possible because relatively small numbers of single-nucleotide polymorphisms (SNPs) can identify an individual. If someone has access to individual genetic data and performs matches to public SNP data, a small set of SNPs could lead to successful matching and identification of the individual (Nyholt et al. 2009). Therefore, the development of networks must include appropriate controls both to protect individual information when data are shared within the research community and to ensure that this information is protected from those outside. The traditional focus of privacy protection in research on consent and anonymization cannot address the concerns raised by data sharing and whole-genome sequences. Owing to the extensive nature of information available on the Internet, privacy risks must be assessed in this broader context, not only within the narrow confines of one project or the activities of the research community in isolation (Heeney et al. 2011).

13 Oversight of Research

A number of interrelated mechanisms are involved in the governance of research, which can vary depending upon the jurisdiction (Kaye et al. 2012b). However, in most countries the key gatekeepers are the institutional review boards or research ethics committees. These bodies have the authority to determine whether research will proceed, yet they have limited enforcement powers, and decision making can vary between regions and countries. In the current governance system, these committees, largely run by medical professional peers, are the bodies that are increasingly being asked to stand in the shoes of research participants as part of "consent for governance." The authority of these bodies is national, yet in the context of increasingly global research, such bodies adjudicate on the complex issues associated with international data sharing and privacy. National oversight bodies do not always have the authority, scope, or expertise to assess the privacy risks associated with global data sharing or to ensure compliance with their decisions.

For research using stored samples and/or data, this system is largely dependent upon researchers going back to oversight bodies for additional approvals for new research and to ensure that all ethical requirements are met. Research participants themselves are not always asked to make a decision on privacy risks associated with new research using stored samples and/or data, as such deliberations are usually made by researchers or by oversight bodies. When data are shared publicly on the Web, they become freely available, and no additional oversight is provided for new research using these shared data. This has often been regarded as legitimate because the new research falls within the scope of the original consent or because there have been mechanisms that effectively render data deidentifiable or anonymous. As sequencing technology improves and data are shared more widely, whether this current form of governance is desirable and whether these conditions for approval of new research can be fulfilled are brought into question.

Concerns about the ethical sharing of GWAS data and the implications for privacy have led to the development of managed access mechanisms to protect sequence data generated through research. These require researchers to establish their credentials and sign a number of contracts that outline their obligations and the approved use of the data. Special data access committees have been established for GWAS projects in addition to the normal research ethics committees. Although these committees provide accountable access oversight for specific projects, they do not provide a simple solution for researchers who may want to access multiple data sets, as they must obtain a new approval from each project they wish to access. If at some point there were a proposal to integrate the different GWAS projects, then this policy may need rethinking. These bodies replicate the model of expert committees and the use of paper forms that characterize institutional review boards and research ethics committees.

These special data access committees develop a new tier of oversight in addition to research ethics committee approval, but there is some doubt as to whether they are the right model to enable effective supranational data sharing. For example, such bodies do not have effective mechanisms to monitor data use by secondary or tertiary researchers once information has been obtained from a managed access repository. Regarding cases where results are then reposted on the Web, Johnson et al. (2011) opine, “Once results are posted publicly, they cannot be deemed safe even if posted results are eventually retracted, since backups may have been created. … [C]ontrolled access models have decreased the overall risk for results misuse across studies, but the examples of reposting uncovered illustrate that controlled access is not fool-proof.” They go on to say that there needs to be clearer guidance regarding appropriate disclosure of derived data when data are accessed through managed access repositories.

These factors in combination raise questions as to whether the current protection for the privacy of research participants is suitable in the case of genomics and data sharing. The scientific agenda requires the long-term participation and commitment of research participants. But, at the same time, it is difficult to guarantee anonymity for participants, provide information to satisfy the requirements of informed consent, and ensure complete withdrawal from research when requested.

Research participants are being asked, on the basis of altruism and solidarity, to involve themselves in research projects that could potentially expose them and their families to privacy risks (Winickoff 2007). Current mechanisms to protect privacy are increasingly tested by the comprehensiveness of the data that can be assembled from different sources for research purposes. At the same time, oversight systems are not equipped for global data sharing and the possible breaches of privacy that may arise, and yet these are the bodies that are being asked to stand in the shoes of research participants. However, it is widely accepted that there can be research benefits if sequence as well as phenotypic data are shared, as this is considered a good use of public resources. For the future of genomics research, we need to develop a sustainable and coherent governance framework that addresses these concerns.

14 Ways Forward

To move forward, we need to improve the current governance systems for research so that they are responsive to individual privacy concerns but can also be effective at a global level. These systems must be anchored and informed by individual and local contexts but also able to be enacted at a global level. The current system of governance based on paper forms and expert committees is derived from a "one researcher, one project, one jurisdiction" model that is not effective for global networks. We need to move to a system of e-governance that can complement these existing governance systems, with a greater reliance on the use of technology to ensure compliance with ethical and legal requirements. This requires the development of e-governance systems that are designed according to ethical, legal, and social norms—or "ELSI by design"—to ensure that participants' privacy is protected and public trust is maintained. Sustainability can be achieved only by building partnerships between all stakeholders in research, developing appropriate global governance structures, and enhancing translational research approaches.

15 Building Partnerships with Research Participants

Sustainable data sharing requires long-term commitment and wide-scale support from the public to maintain the high participation levels necessary for infrastructure initiatives as well as to guarantee the heavy investment of resources by publicly funded bodies. The recent Havasupai case (Dalton 2004) and the HeLa case (Skloot 2010) demonstrate that a lack of transparency and respect for individual wishes can have a detrimental effect on trust (Hudson 2011); to ensure the sustainability of genomics research, we need to move to a situation where participants, rather than being passive providers of information, have the opportunity to become more active partners in the research process. This will require a change in practice

and attitude for some and the development of new forms of governance to enable such participation. These new governance structures must address the concerns of participants while at the same time ensuring effective data sharing that allows the translation of new knowledge into the clinic and promotes public trust in genomics research.

Recent research on the views of data sharing participants from the United States suggests that plans for data sharing must be clearly explained to participants and that the main concern of participants is that they wish to be asked for their consent for involvement in data sharing. One study found that "90 % of survey respondents, all of whom had consented to sharing with dbGaP, reported that it was important that researchers had asked for their consent"; alternatives to consent, or informing people after data had been deposited for sharing, were viewed as unacceptable by many respondents (Ludman et al. 2010). This was confirmed in another study that found that participants would feel deceived or angry if they found out that their data were shared without their knowledge or consent—a finding that "is noteworthy because it demonstrates the high value research participants place simultaneously on the benefits of health research and on personal autonomy" (McGuire et al. 2008b). Research with the eMERGE participants, however, "suggests that, although most are willing to share their data, there is a strong desire for some data-use limitations" (McGuire et al. 2011). As noted by Tabor et al. (2011), "these studies suggest that in any genetic studies that require broad genetic data sharing in dbGaP that researchers should consider the trust relationship with participants and mechanisms for providing transparency about how genetic data are being shared, and for what purposes they are being used." As a way of addressing these concerns, a number of participant-centric interfaces (PCIs) have been developed that place patients and research participants at the center of decision making by enabling them to give consent for the use of their samples and personal information for research over time and to be active partners in the research process (Kaye et al. 2012a). Examples of PCIs in research are 23andWe (United States; http://www.23andme.com/research), Cooperative Health Research in South Tyrol (CHRIS) (Italy; http://www.eurac.edu/en/research/institutes/geneticmedicine/chrisstudy) CuraRata/String of Pearls Initiative (Netherlands; http://www.curarata.nl/uk/3/patients), Ensuring Consent and Revocation (EnCoRe)/Oxford Radcliffe Biobank (United Kingdom; http://www.encoreproject.info), Genomera (United States; http://www.genomera.com/about), Genomes Unzipped (United Kingdom; http://www.genomesunzipped.org), Indivo personally controlled health records (United States; http://www.indivohealth.org/research), PatientsLikeMe (United States; http://www.patientslikeme.com), Private Access (United States; http://www.privateaccess.info), and TuAnalyze (United States; http://www.tudiabetes.org/forum/topics/tuanalyze-ishere). An example of a PCI approach to consent that supports individual privacy preferences is the EnCoRe IT interface developed for the Oxford Radcliffe Biobank in the United Kingdom (J. Kaye, E. Whitely, S. Creese, D. Lund and K. Hughes, manuscript in preparation). It has a "dynamic" rather than "informed" consent model, which enables consent to be obtained when needed, in real time, as part of a bidirectional, ongoing, interactive process between patients

and researchers as well as other health care professionals. This interface enables individuals to change their mind and preferences over time, to have their choices revoked where appropriate, to track and audit any changes made, and to choose when and how they are contacted. The use of "sticky policies" enables individual preferences to be tracked as information and samples move through localities over time. Using PCIs ensures that research is compliant with the legal requirements for data and privacy protection, as consent for the use of identifiable information is a general requirement in all jurisdictions. By acting with consent, researchers can code data out of respect for individuals, not because it is difficult to obtain their consent. This reduces the resources and time that have to be put into anonymization strategies that are not necessarily beneficial for research. In addition, such interfaces expedite the research process by allowing easy recontact with participants for involvement in further studies, cutting down on referrals to research ethics committees. This technology has the potential to encourage new forms of engagement with the public by fostering new kinds of partnerships with research participants. PCIs have been used to develop new ways of carrying out research (e.g., 23andWe, PatientsLikeMe, and TuAnalyze) and to provide the basis for personalized medicine. A PCI approach means that other bodies no longer stand in the shoes of participants and that the local context can influence how data are continually used by researchers. Through these mechanisms, the importance of research priorities can be explained so that the balance between individual decision making and the research agenda can be more nuanced. PCI approaches can also complement other governance mechanisms that support participant involvement, such as representation on key oversight bodies. Trinidad et al. (2011) suggest that innovation is needed in the consent and notification procedures for data repositories and other data-sharing resources, but also propose that there need to be "transparent, accountable oversight processes that include community representation; and … opportunities for study participants to provide input on decisions concerning the stewardship of their data, e.g., dialogue between researchers and participants, ongoing community consultation, deliberative processes, or reconsenting a representative sample of participants." Adaptive governance models have been proposed for biobanking, as they put in place representative governance systems that can be responsive to changing conditions and allow for the consideration of community concerns by participant representatives (O'Doherty et al. 2011).

16 Conclusion

Our current governance system for research does not allow participants to have any further control of their data once they have signed a consent form. Recent empirical studies focused on data sharing in research suggest that this is contrary to what research participants want. The development of IT interfaces for research participants has the potential to enable individuals to be more informed about the research uses of their data and to give consent for secondary uses to protect their

privacy interests by exercising their autonomy and decision-making capacities. Such systems are designed to complement the existing governance structures of research ethics committees and the mechanisms used to safeguard the confidentiality of information. They must also be constructed as part of a broader system of new e-governance tools that incorporates biobank and researcher IDs as well as mechanisms to enable statistical analysis without compromising privacy, such as the Sage bioinformatics platform (http://www.sagebase.org). Moving to such participant-centric systems will enable individuals to know how their data are used and enhance public trust and knowledge of the research process. It could also increase the transparency and accountability of the research governance system as data sharing and the use of next-generation sequencing technology become more widespread. The choice is whether to continue to invest resources in attempts to anonymize information—which is impossible and so will always carry a risk of privacy breaches—or to consider new ways of engaging with research participants that could include e-governance mechanisms. To do so respects the dignity of participants and protects fundamental human rights, and is also a hallmark of civil society.

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Incidental Findings: The Time Is not yet Ripe for a Policy for Biobanks

Jennifer Viberg, Mats G. Hansson, Sophie Langenskiöld and Pär Segerdahl

1 Introduction

A much discussed problem associated with biobank research is the return to participants of incidental findings (Ifs): 'a finding concerning an individual research participant that has a potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study' (Wolf et al. 2008a). How should such information be handled ethically responsibly in genome-wide association studies and disease-specific genetic research?

In this paper we argue that the discussion up until now has neglected a distinction that should be held in the forefront of the discussion, especially concerning genetic biobank research: the distinction between an incidentally discovered *disease* and an incidentally discovered increased genetic *risk* for disease of unclear predictive value. Biobank research and rapidly increasing studies in genomics,

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proteomics, and nutrigenomics continue to identify many genes and biomarkers associated with risk of disease. Genetic testing for monogenic disorders are well established in health services, but little is yet known of the best way to handle complex risk information associated with multifactorial disorders in which the predictive importance of individual elements—genetic, epigenetic, or environmental—will differ for different individuals. The value of being informed about an incidentally discovered genetic risk (be it inherited or caused by a virus) is therefore much more difficult to ascertain than that for an incidentally discovered pathogenic condition revealed, for example, in a brain imaging study.

The aim of this paper is to exhibit the absence of a distinction between disease and complex genetic risk for disease in the discussion, and to show how the arguments therefore fail to address the more complex kinds of incidental findings that increasingly arise in biobank research. Further research should be conducted before the arguments can be considered conclusive.

Disease risks can be discovered also in imaging studies, of course, a blood vessel with thin walls can imply an increased risk for stroke. Our focus in this paper, however, is on genetic biobank research, where IFs increasingly concern multifactorial risks for disease having both genetic and environmental dimensions, which we believe introduce complications that so far have not been addressed.

2 Synopsis of the Argumentative Field

We will not conduct a complete literature review of the arguments that have been used in ethical discussions of IFs in biobank research, but will only chart the most important kinds of arguments that have been used to discuss the subject, in order to show how the distinction mentioned above is downplayed or neglected.

2.1 Arguments for Disclosure

2.1.1 Disclosure Is Beneficent for Individuals

A common normative statement in the discussion is that disclosure should be an option for participants because it will maximize their benefit and minimize harm if participants receive timely risk information. Under this argument, conditions have been formulated in which IFs are likely to impart benefit to the participant and therefore should be disclosed. If the genetic information reveals significant risk of a condition likely to be life-threatening, can be used to avoid or to ameliorate a condition likely to be grave, or can be used in reproductive decision-making, the information is held to be beneficent and appropriate for return (Wolf et al. 2008a, 2012). It has been emphasized that incidental findings are beneficent and should be returned if they are analytically valid, clinically significant, and actionable (Knoppers et al. 2012).

2.1.2 Disclosure Promotes Autonomy

The principle of respect for persons, or respect for autonomy, is used as a premise in another argument for disclosure. If people get important information in time, they can change their lives and therefore be more autonomous; by knowing, individuals can take control over their lives and direct it as they wish. Respect for persons includes respect for participants' self-determination and therefore also for their need to have information relevant to their health and well-being, and thus motivates disclosure (Wolf et al. 2008b). In a similar vein, it is argued that if results have clear clinical use, or are relevant to life decisions, there is an obligation based on respect for persons to disclose them. Furthermore, it is argued that it would be paternalistic to protect participants from potential anxiety instead of letting them know what is known about them (Affleck 2009).

2.1.3 Reciprocity Requires Disclosure

Reciprocity between researchers and participants can be maintained by giving participants something in return for the participants' donation, in this case individual research results. It has been emphasized that participants' contribution to research cannot be assumed to be purely altruistic with no expectations of some personal gain, including knowledge, in return (Quaid et al. 2004). This argument holds that people deserve something in return for their contribution to an enterprise or to society (Wolf et al. 2008b). It may also be argued that research would benefit from disclosing individual research results to participants; because offering something in return might motivate participation, the offering of individual findings could be useful in recruiting and retaining research participants (Murphy et al. 2008). Reciprocity may also promote trust between researchers and research participants (Knoppers et al. 2012).

2.1.4 Return of IFs Accords with Participants' Wishes

Empirical surveys show that many people want to receive individual results (Meulenkamp et al. 2010; Murphy et al. 2008). People do not consider their contribution as a gift, but participate in research with the expectation of getting something in return (Gaskell et al. 2011). Another study of public preferences suggests that people want to receive individual research results and that they believe that researchers have a duty to inform participants about mutations in their genes. This wish to receive individual results is typically motivated by the potential of such information to be used to improve health through changing health-related behaviours, getting treatment, or preventing disease. Some informants in this survey maintained that findings about them actually belong to them as a matter of ownership (Bollinger et al. 2012).

2.2 Arguments Against Disclosure

2.2.1 Practical Issues Make Disclosure Unfeasible

It is sometimes claimed that it would be too time-consuming and costly to contact research participants, and that disclosure would therefore inhibit important research (Bledsoe et al. 2012a). It has also been argued that variability in biobanks and practical implementation issues (biobanks vary in scale, biobank projects take a variety of forms, samples may be drawn from healthy participants or from those with disease) make it difficult to have a 'one-size-fits-all' approach to disclosing individual results. Moreover, the return of individual results to participants requires that biobanks retain links to identifying information, which implies the risk of breaching confidentiality. The issue of who should be responsible for re-contacting participants, whose samples may be involved in many projects over a long period of time, is also unresolved (Bledsoe et al. 2012b).

Another argument posits that if participants have a right to know about IFs, they must also have a corresponding right not to know (Kaye et al. 2010). If participants have the right to choose whether or not to know, this option should therefore be prominent on the consent form (Ravitsky and Wilfond 2006). This brings up further practical issues about how informed choices can be made about disclosing IFs, since by definition not even the researchers know what kinds of IFs may be found.

Another practical argument against disclosure is that it is virtually impossible to identify such findings in much biobank research. Cho, for example, mentions that it can be difficult to distinguish IFs from other findings in genetic and genomic research because the research question can be very open-ended and descriptive (Cho 2008). Virtually nothing (or everything) is 'incidental' because the research question rather is like an imperative to find complex patterns, the components of which may not be known at the outset.

2.2.2 Disclosure Can Harm Participants

Disclosure of IFs can be harmful to participants if it is not valid or if no treatment can be offered. If participants cannot or do not know how to respond to IFs, they may suffer anxiety (Forsberg et al. 2009; Hens et al. 2011). Returning findings can have negative consequences for both biobanks and participants. Procedures must be in place to ensure that the analysed sample is actually from the person it is believed to be from. Participants can be harmed by receiving risk information that does not apply to them. Such safety demands are lower in exploratory biobank studies than in biobanks used for clinical trials. Their results are therefore less trustworthy on an individual level. Participants also risk being harmed by being informed about and acting on IFs whose quality, accuracy, clinical utility, or even origin is uncertain (Bledsoe et al. 2012b). Ensuring the same quality in explorative studies as is required for clinical trials may arguably be too expensive for the biobank systems.

It is further important to consider that giving participants information about IFs blurs the distinction between research and health care, a confusion that resembles the therapeutic misconception (Forsberg et al. 2009; Solberg and Steinsbekk 2012). The therapeutic misconception is held by individuals who believe that they receive care when they function as research participants.

Randomization and other aspects of the scientific method, however, prohibit the application of personal care (Appelbaum et al. 1987). The therapeutic misconception is traditionally discussed in connection with clinical trials. When IFs in biobank research are seen as a basis for decisions about treatment, however, this can create expectations among those who donate samples that resemble the therapeutic misconception. Receiving their results back may encourage participants to assume that the research was carried out for their own personal benefit. If participants are encouraged to expect individual results, they may think of their research participation as akin to receiving some form of care and they may expect treatment for risks or conditions suggested by their results. If, however, they do not receive further information and they are not recontacted, they will tend to assume that all is well, which could be also harmful rather than helpful.

A further aspect of biobank research that can cause harm if Ifs are returned is that samples can be used in several studies. It can be disturbing and irrelevant for participant to receive a call, many years later after the donation of the DNA sample, of potentially health important information. People might not know that research still is ongoing. They may even have forgotten that they donated a sample, since donation is not as concrete and memorable as undergoing functional magnetic resonance imaging or computed tomography (Clayton 2008).

2.2.3 The Relationship Does not Create a Duty

Another concern is that researchers do not have the same close and individual relationship to the participants as doctors have to their patients, and are not trained in the counselling skills necessary to returning individual results properly (Bledsoe et al. 2012b). This is more than a merely practical difficulty. If there is no doctor-patient relationship between researcher and participants, there is also no duty of disclosure (Forsberg et al. 2009; Ravitsky and Wilfond 2006; Solberg and Steinsbekk 2012).

2.2.4 Disclosure Can Harm Research and Prevent Research from Doing Good

Another line of argument against the disclosure of IFs focuses on the need to distinguish between research and care (Meltzer 2006). Unlike the therapeutic misconception mentioned above, this argument focuses not on the participants' perceptions, but on the concern that if research begins to be organized

similar to healthcare, it will harm the aims of research. The biomedical principles of beneficence and nonmaleficence (do good and do not harm) may be misapplied if the distinction between research and care is neglected. Doing good in healthcare and doing good in research have different meanings, and the different contexts produce different rights and duties. It is argued that the beneficence sought in research must be understood on the collective level and not on the individual level. Returning IFs to individual participants would be seeking to do good in an individualized fashion that is inappropriate for research. And because participants contribute to research, not to healthcare, it would be wrong not to maximize beneficence on the collective level appropriate to research (Forsberg et al. 2009; Fryer-Edwards and Fullerton 2006; Solberg and Steinsbekk 2012). There is, moreover, a risk that disclosure of 'preliminary results from ongoing epidemiological studies may jeopardize the scientific validity of the study due to changes in behavior or selective dropouts' (Forsberg et al. 2009).

The clinical ethos, then, cannot be transferred directly to the research setting because research has a purpose different to that of care (Forsberg et al. 2009; Solberg and Steinsbekk 2012). Forsberg et al. (2009) point out the similarity between donating money to the Red Cross and donating a sample to biobank research. From the donor's point of view, the moral duty of the Red Cross is to ensure that the donation leads to as much of the intended good as possible, and not to inform individual donors about the results of the donation (Forsberg et al. 2009).

3 Suggested Policies Do not Address the Complexity of Genetic Risk Information

As shown, the main arguments for disclosure focus on the possibility that disclosure can be beneficent to participants' health if the information is validated, has clinical utility, and is actionable. Disclosure can also promote autonomy, support reciprocity, and satisfy participants. The arguments against disclosure of IFs are that it is not practically feasible, it can be harmful to participants, and there is no relationship between researcher and participant that creates such a duty. Disclosure can also harm research.

The arguments for disclosure depend very much on the hypothetical possibility that knowing genetic risk information might be beneficent for participants. In brief, if the information is valid and useful, participants who want to know should be informed. Here are some examples of how this is expressed:

> If results can enhance treatment and care, there is an ethical imperative to offer feedback (Affleck 2009).

> IFs with confirmed clinical utility where there is the possibility of treatment or prevention should be disclosed, with exceptions (Christenhusz et al. 2012).

Knoppers et al. as mentioned before, argued that IFs should be returned if they reveal material risks that have:

1. analytical validity;
2. clinical significance; and
3. actionability (Knoppers et al. 2012).

If results can enhance treatment; if they concern a material risk; if they have clinical utility; if they are life-saving—then they should be disclosed. It may seem that no one could object to these proposals, since they condition disclosure to what clearly would be beneficial for the participant. But we intend to show that these properties are less self-evident in the case of multifactorial risk information.

The prevalence of provisos in the argumentation shows up in an unexpected way in a systematic review of arguments by Christenhusz et al. (2012). According to this review, 'the strongest reason in favor of disclosure of an IF is its confirmed clinical utility and the possibility of treatment or prevention.' The problem is that this is hardly an argument for disclosure of genetic risk information of unclear predictive value, although it is an oft-repeated prerequisite for the disclosure of genetic information.

4 Idealized Conditions for the Application of Ethical Principles

Why are there so many provisos in the arguments for disclosure of IFs in biobank research? We believe these conditions reveal a tendency to conflate genetic risk information with the kind of IFs that are more characteristic of imaging studies, for example, in which the IF may be a tumour—information that obviously should be communicated to the participant.

'Comparison to IFs in imaging studies is instructive,' Wolf et al. (2008a) write, but in our view the analogy can introduce problems. Disease risks can of course be discovered also in imaging studies (such as a blood vessel with thin walls implying an increased risk of stroke), and it seems that the provisos work to handle such cases. Very few would deny that those types of IFs, likely to occur with some frequency in imaging studies, should be returned. Relevant ethical principles are applicable and support disclosure. But do the conditions of analytical validity, clinical significance, and actionability imply the same straightforward beneficence to the disclosure of complex genetic risk information of unclear predictive value? One could easily be led to think so if one believes that genetic risk information reveals possible futures. In this view, although an actual tumour (or a fragile blood vessel) would not be discovered in biobank research, the possibility of a tumour developing in the future might be discovered and the possible tumour treated before it began. But can genetic information about cancer risk really be understood to reveal "possible" tumours that can be treated before they "actually" develop?

In another discussion, about informed consent and informational privacy, Manson and O'Neil (2007) point out that 'possessing genetic information is not like possessing a crystal ball, and future facts are not "contained" within DNA'. If they are right, the discussion we surveyed in this article builds on a questionable analogy. Between genes and multifactorial diseases like diabetes, cardiovascular disease, and dementia there are complex processes involving both genes and environment. The disease depends not only on deviation in several, rather than single, genes but also on interaction with environmental factors such as diet, exercise, and smoking. The information given to participants will be an expression of a risk that is dependent on not only on various environmental factors, but also on the penetrance of the disease (i.e., how likely it is that a particular genetic defect will be expressed and actually lead to symptoms). The meaning of the risk information also depends on the level of accuracy of the analytical test, as described before.

Actionability, then, has a different meaning when applied to genetic risks of unproven predictive value risks rather than to an accidentally discovered tumour, a fragile blood vessel, or a genetic risk associated with dominating genes with high penetrance. By downplaying such differences, these conditions are idealized as if inherently beneficial, regardless of whether we are discussing diseases and easily identifiable conditions implying immediate risk, or complex and multifactorial disease risks. On closer examination, then, these conditions are not as realistic as they first appear, but seem to be posited to mirror the requirements for applying the principles. They do not provide sufficient friction for the real-life application of the principles and cannot be used to decide whether it would actually be beneficial to a participant to know the genetic risk information under discussion.

What determines the actual medical case history of a human life, if Manson and O'Neil (2007) are right, is a tremendously complex and variable interaction between genes and environment. This complexity is not reflected in the mantra of analytical validity, clinical significance, and actionability. There is therefore a need to move beyond this verbally constructed façade of beneficence and explore how genetic risk information can be perceived and evaluated in reality. Would people really want to receive genetic risk information of unproven predictive value?

5 Empirical Surveys Need to Take the Complexity of Genetic Risk Information into Account

A reason for disclosure emphasized also in discussions that take objections seriously is that 'empirical studies confirm that participants prefer to have genetic results returned to them, at least when the results are actionable and accurate' (Bredenoord et al. 2011). The problem that we want to address, however, is that the simplistic provisos reappear in these studies (and are repeated in arguments using these studies in favour of disclosure) (Beskow and Dean 2008; Beskow and Smolek 2009; Bollinger et al. 2012; Murphy et al. 2008). The results of studies with such a design are predictable. If you ask people whether they would want

information about an IF if the finding meets the conditions *x, y,* and *z,* and *x, y,* and *z* make the finding sound beneficial to know, then they will probably answer in the affirmative. If we are right, however, genetic risk information has a complexity that makes it difficult to assess accuracy and actionability. For this reason, it is interesting to note that informants tend to change their attitude to individual genetic findings when they are informed about the actual nature of such findings in typical biobank research. A quantitative survey showed that patients, who can be assumed to know more about the complexity of multifactorial diseases, were slightly less strong in their preference for receiving individual research results and their opinions about the researchers' duty to inform than were a representative sample of the general (Dutch) population (Meulenkamp et al. 2010).

This suggests that the methods of conducting empirical studies need to be changed and highlight the complexity of genetic risk information in the questions posed. Instead of asking potential participants whether they would want health relevant genetic information, to which they could hardly say no, they should be asked questions based on realistic presentations of risk information and what it means.

Survey data may be helpful in formulating research hypotheses on which preferences should guide policy-making. However, surveys are not causal in nature. They can only show correlations of preferences. Moreover, they do not capture the trade-offs that respondents might make when facing complex decisions, e.g., would they want to receive IFs if the risk were of unproven predictive value, had low penetrance, and would not result in symptoms until after perhaps another 30 years? Therefore, new methods are needed to capture what kinds of risk information participants truly prefer to receive, and their relative importance for participants.

6 Conclusion

IFs in genetic research, in genome-wide association studies as well as in disease-specific studies, need to be explored differently, both theoretically and empirically. Theoretically, the discussion needs to address the actual nature of genetic risk information and the complexity of the modern understanding of genetics. Arguments for disclosure should not rely on repeating beneficial-sounding provisos that do not reflect this complexity. New empirical studies need to be designed in which genetic risk of unproven predictive value is described to informants, and not as a revelation of future conditions that can be treated before they are manifest. Informants' responses to offers of genetic risk information are relevant only if they understand what that information really is and how it differs from information about disease or immediate disease risk that can be obtained from imaging studies or other tests.

This article is not meant as another argument against the disclosure of IFs in biobank research. Rather, our point is that existing arguments and empirical evidence fail to address some of the most relevant properties of the IFs under

discussion, namely unproven predictive value. Perhaps when this complexity and uncertainty is taken into account in the future discussions, theoretically as well as in empirical studies, support for a policy of returning such findings can still be found. However, we are not there yet.

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Biobanking Across Borders: The Challenges of Harmonisation

A Short Comment

Ruth Chadwick and Heather Strange

1 Introduction

The development of national initiatives in biobanking in countries such as Iceland, Estonia, and the UK, has given rise to a great deal of social, legal and ethical discussion over the past decade and more. It is the possibilities of exchange at the international level, however, that have now moved centre stage. They have led, first to arguments for the desirability of exchange of samples and data, and second to issues about standardisation and harmonisation to make this possible.

The argument for exchange goes as follows. Population wide biobank research is of potentially very great importance for future health care—for example, by finding out the genetic basis underlying the variation influencing our susceptibilities to common diseases and to adverse drug responses. To maximise its effectiveness, however, and achieve sufficient statistical power, collaboration between different initiatives is required.

There are, however, obvious hurdles to collaboration. If data cannot be compared between different biobanks, because information is collected in a different way, then comparison may not be possible. In order to exchange information readily, something analogous to the USB stick is required—a standard which facilitates the exchange of data.

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When we turn to ethics, there may also be barriers to meaningful collaboration—for example, if completely different norms operate in different contexts about what people have consented to, it may not be possible to compare results from one context to another. To a certain extent this is addressed by harmonisation in law, regulation and governance, for example in the EU context. There are ethical issues outside the remit of law, however, hence the search for ethical standards. There is a question, however, over what would count as a standard in ethics, or whether harmonisation is the concept of choice: is there an ethical equivalent of the USB stick?

In 2009 we published an article on harmonisation and standardisation (Chadwick and Strange 2009), which based our argument on a musical analogy, taking our inspiration from the following entry in the Oxford Companion to Music:

> It seems natural and right that music which is … harmonious, should be highly regarded in civilised societies … there is a clear correspondence between the concept of society as a mutually supportive commonwealth, and those manifestations of concert and theatre music which attract the collective approbation 'civilized'. Collective performance, as in singing the same text to different but interdependent vocal lines, can be regarded as the musical correlate of civilised democracy (Whittall 2002).

It was this idea of different voices singing the same text to different vocal lines that seemed to us to hold an important insight—that harmonisation in ethics is best understood as a process, and not as an end point. Standards, or 'texts' can be produced, for example in ethical guidelines, but the process of harmonisation in relation to these texts is something different. There may be, and indeed is, variation in interpretation of guidelines (which may of course occur in relation to law too, but we are not addressing that here)—the important question is, what is the acceptable scope for variation in relation to the text?

That there must be some limits to variation is clear: although in ethics agreement is not readily to be found on some issues, morality has a certain core. This gives a clue as to a potential response to possible criticism of the musical analogy, namely how one deals with those who are completely out of tune, or tone deaf. This raises deeper issues relating to the problem of the failure to accept moral reasoning at all: the individual who can see no answer to the 'Why should I be moral?' question, as opposed to disagreement on particular issues, and we will not attempt to deal with that in this short article—it is a problem for 'end point' views as well as our process approach.

When we turn to the 'text', or standard, in this context a standard is a rule established to have action-guiding force. Busch (2013) has pointed out that an important (ethical) dimension here is who has the power to set standards? If we look at another context the issues of power become obvious: in pictures of meetings between international leaders, for example, we can see that despite the different cultural backgrounds of the participants, a common standard of dress has been adopted: the western business suit. What does this say about the power to set standards? Where one leader adopts a different style of dress, it really stands out—a statement is being made. In some contexts, where power lies to set standards may not be traceable: in ethics in general, and in the context of biological and biomolecular resources in particular, however, transparency may be assumed to be a prerequisite.

In the 2009 article we proceeded to identify three potential *areas* for standard setting in dealing with cross-border flow of data and materials: consent, feedback and privacy. We argued that the stronger the interests being protected, the more likely it was that a common standard would be required. Likewise, room for different voices, variation, in relation to the standard, or text, would depend on the strength of those interests (how close they are to the 'core' of morality). From considering these three cases, we argued: that the strongest argument for a common standard existed in relation to informed consent (that is, an argument for *some* common standard, not necessarily for any particular form of informed consent); there was room for variation in relation to feedback, and as regards privacy, the whole area needed a rethink (Lunshof et al. 2008).

In order to demonstrate the issues of standardisation and harmonisation, we will use a case study of a European project which produced 'texts' in the sense that we are speaking of standards. It is important to make it clear that we are not presupposing a sense of harmonisation as it is used within debates about harmonisation across the EU, e.g. by the use of Directives. When, for example, it is said that a particular area is 'harmonised' across the EU, that suggests an end point view. We are speaking about the extent to which harmonisation is possible in the context of ethics, and what it might mean, and our view is that it is a process. The case study, however, suggests that there may be insights here for both regulatory and ethical considerations.

2 Case Study: The EUCoop Project

The 'Legal basis of EU-wide collaborations between biomaterial banks' or BMB-EUCoop project[1] aimed to examine, starting from the German perspective, many of the legal and ethical challenges which are faced by international biobanking collaborations. In order to help us examine the way in which diverse legal and ethical frameworks involved in the governance of international biobanking collaborations interact, and to allow us to highlight specific areas of concern relating to the process of ethical and legal harmonisation, we will now examine a paper (Goebel et al. 2009) which details some empirical results of this study, and looks specifically at the legal and ethical consequences of European biobanking collaborations. The number of countries involved here was limited (The UK, Netherlands, Austria and Switzerland are examined from the German perspective). It is explicitly acknowledged that, whilst it would be highly beneficial, a comprehensive comparative analysis of all international biobanking practices and standards would be highly demanding, although such a comparison has since been attempted (Zika et al. 2010).

[1] Legal basis of EU-wide biobanking cooperation (BMB-EUCoop) project http://www.tmf-ev.de/EnglishSite/Topics/Biobankingandmolecularmedicine/V01002BMBEUCoopEN.aspx.

The paper firstly summarises the main objectives and results of the BMB-EUCoop project, which was set up primarily to address three major questions:

1. To what extent do foreign laws affect the property rights, personal rights and the right of informational self-determination of German biobanking donors?
2. To what extent does the transfer of biomaterials and data to foreign partners affect the property rights and the rights of commercial exploitation of German biobanks?
3. How can the positions of German biobanks and their donors be protected against the risks identified under 1 and 2, and how can such protection be enforced in practice, if so required?

The issues here are partly legal and partly ethical, and it is not always easy to make a strict dichotomy between ethics and law. Nevertheless the case provides an interesting point of departure for our interest in examining some of the issues at stake in standardisation and harmonisation in ethics. Several areas of potential conflict between the legal and ethical practices of different states were identified by the project as requiring explicit examination, these included: human and personal rights, property rights, medical professional regulations, commercialization and intellectual property rights, supranational and international rights, benefit sharing, criminal law and prosecution, and data and privacy protection.

In relation to the degree to which both ethical and legal standardisation had been established, the study reveals varying results across the different areas of inquiry. In relation to both the personality and property rights of donors a good degree of legal and ethical convergence seemed to be present in the cases studied here. Similar requirements for protection of personality rights were identified in all five legal systems and the legal situation relating to property rights was found to be almost identical. Whilst some minor differences in regulatory frameworks were found, it was suggested that any potentially negative consequences of divergent regulations could be remedied by appropriate stipulations in contractual agreements between parties in different states. This implied that there exists an implicit dependence upon ongoing negotiation: here, we may suggest, is a practical example of the use of ongoing and open-ended dialogue between stakeholders, which may function in a way that closely mirrors our vision of harmonisation as a process. Other areas of inquiry suggested that a fairly high level of standardisation was present: in relation to criminal law it was found that the legal frameworks across all five countries were fairly similar (complexities in the technical functioning of national and international criminal and depositive law were, however, seen to present particular obstacles) and the statutory requirement of physician confidentiality also applied to all research on human biomaterial in all of the countries covered by the study.

More problematic seem to be those areas in which standardisation may be present, but a significant degree of divergence in implementation is present. EU-wide standards have been outlined for the governance of the patenting of biomaterials under the EU Biopatenting Directive[2]; it was found, however, that significant

[2] EU Biopatenting Directive (Directive 98/44EC) http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=31998L0044&model=guichett.

differences exist between national approaches to the process of implementation. Similarly, in relation to data and privacy protection, a high degree of legal standardisation across different national jurisdictions had been achieved, as a result of there having been a robust process resulting in the form of the implementation of the EU Data Protection Directive which governs this area of practice.[3] It was explicitly acknowledged, however, that inconsistencies in legal practice existed between different states, and that different levels of administrative stringency and efficiency in one country threatened to undermine standards. It is in areas such as these that the need for continuous, open dialogue between all stakeholders must be highlighted.

Certain areas of inquiry seemed to be lacking any significant degree of either standardisation or harmonisation: considerable differences were found to exist between different national medical professional regulations applicable to the international transfer of biomaterials (concerning storage, documentation and the requirement to inform donors of relevant research results). It was also found that international regulations governing biobanking practice often failed to provide clear-cut differences between normative and ethical regulations, or between 'soft' (not legally binding) law and nationally enforceable 'hard' law. This was seen to be particularly relevant to the issue of benefit-sharing: it was found that in this case, although most regulations are part of soft law and therefore not legally binding, researchers may still be subject to morally binding ethical obligations. The problems associated with this lack of basic standardisation tend to be negotiated by producing explicit contractual agreements which aim to protect the interests of internationally operating biobanks and their donors: this is a complex and challenging process that is likely to have significant practical effect on all collaborations. It could be suggested that, in order to facilitate efficient and successful collaboration, international regulatory and governing agencies ought to work together produce comprehensive guidelines: full harmonisation may be too great a challenge to strive for here, but the provision of robust standards would at the very least provide basic guidance, and could function as a platform for ongoing discussion and debate.

The paper concludes that the best way to address the problematic issues which arise as biobanks from countries with substantially different legal and ethical systems collaborate, is to ensure that detailed contractual agreements which cover the obligations and entitlements of all parties are made. This requires a process of ongoing negotiation between a diverse range of stakeholders which is somewhat akin to that which is endorsed by the approach we endorsed in the 2009, paper, of dialogue between a multiplicity of voices. In a practical effort to help alleviate some of the problems found to be associated with a lack of standardisation and/or harmonisation in European Biobanking, the BMB-EUCoop project produced a series of generic texts which were designed to address the issues outlines above and protect the interests of German biobanks and their donors: these included

[3] EU Data Protection Directive (Directive 95/46/EC) http://ec.europa.eu/justice_home/fsj/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf.

information for potential donors, consent forms and a contract for collaboration between German biobanks and international partners. These texts were explicitly designed so that they could be adapted to individual situations with minimal effort. This provides us with a practical example of how a flexible, contextual approach to the resolution of problems can be utilised in order to help facilitate ethical and legal harmonisation: the awareness of the potential diversity of research settings and stakeholder interests, and willingness to pay attention to particular contexts that is evident here suggests that the reasoning behind this project very much parallels the 'variation in dialogue' approach. In order to successfully begin this process of harmonisation, however, the setting of appropriate standards can be key: as the paper points out, if existing legal and ethical discrepancies were to be resolved by changes in national and international law, the functioning of international biobanking collaborations would immediately become less problematic. There needs to be a theme, or a text, in relation to which variation can take place. With appropriate standardisation successful cooperation between international projects is greatly facilitated, and the ongoing process of aiming towards harmonisation can begin.

3 Conclusion

The examination of this case study confirms our earlier view that harmonisation in ethics should be seen not as an end point, but as an ongoing process in relation to a text. The question of how much variation in relation to a text is permissible, becomes central. It also, however, is suggestive that this may be a useful insight in thinking about harmonisation in regulation too, especially with reference to variation in implementation.

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Governing Biobanks Through a European Infrastructure

Ethical, Legal and Social Implications

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1 Introduction

In the framework of the 2007 call to support the preparatory phase of the European biobank infrastructures, the European Commission funded a specific project aiming to prepare a pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) for biomedical and biological research in Europe and worldwide (Yuille et al. 2008). This infrastructure, which was to be built on new and existing national networks, resources and technologies, would be specifically complemented by innovative components and would be properly embedded into European ethical, legal and societal frameworks.

The project had four main objectives:

- to benefit European health-care, medical research and, ultimately, the health of the citizens in the European Union (EU);
- to create a sustainable legal and financial conceptual framework for a pan-European biobank infrastructure;
- to increase scientific excellence and the efficacy of European research in the life sciences, especially in biomedical research; and
- to expand and secure the competitiveness of European research and the industry in a global context, especially in the field of medicine and biology.

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The infrastructure was to include samples from patients and healthy persons, representing different European populations (with links to epidemiological and healthcare information), molecular genomics resources, and biocomputational tools to optimally resource for exploit this global biomedical research.

The key components of the BBMRI included comprehensive collections of biological samples from different (sub-)populations in Europe, of which some could be linked to continuously updated data on the health status, lifestyle and environmental exposure of the sample donors. Other kinds of biobanks and biomolecular tools were also envisioned in addition to longitudinal, population-based biobanks; patient-based collections, tumour banks, and molecular reagents, for example, were to be well characterised. These different categories of resources and their variants were addressed in three work packages (WP2, 3, 4).

This could only be achieved by the federated network of centres that had been established in most, if not all, European Member States.

Therefore, the format of the BBMRI was to follow a distributed hub structure in which the hubs coordinate the activities, including the collection, exchange and analysis of samples and data for the main domains. The biobanks, biomolecular resources and technology centres that are members of the BBMRI were each to be associated with a specific domain hub. Furthermore, a variety of public and private institutions[1] (e.g., universities, hospitals, companies) were to provide biological samples, data, technologies or services, with the possibility of being associated with certain BBMRI members. This structure provides great flexibility, allowing new participants to be connected at any time, and can be easily adapted to the emerging needs of biomedical research.

The preparatory phase for the BBMRI project has focused on technical, governance, and financial issues in WP5 (information technology), WP7 (financial aspects) and WP1 (coordination and governance), and has developed the ethical, legal and social implications (ELSI) platform in order to identify key issues relating to the networks used by biobanks, to provide schema and tools, and to trigger a stakeholder forum with various inputs.

Developing an infrastructure that is “properly embedded into European ethical, legal and societal frameworks” requires specific preparation, both on operational questions that deal with the immediate feasibility of the endeavour and on more fundamental questions. This preparation was intended to help the understanding of how these issues could impact on the organisation of the future BBMRI, and the public’s perception of the BBMRI and their engagement with it. Both aspects had to be addressed first in the preparatory phase, by means of coordination activities; WP6 was in charge of this task. The respective groups worked in two directions: (1) rapid operationality based on existing frameworks, resulting in practical tools, and (2) preparatory steps for the long-term, solid foundation of the ELSI of the BBMRI, resulting in background papers, proposals and some level of piloting of approaches and methodologies.

[1] During the preparatory phase, the participants in the BBMRI were private and public institutions; during the implementation phase of the BBMRI-ERIC, the partners will be States.

This section presents the work done by the BBMRI ELSI group to highlight the key challenges in building such an infrastructure and to evaluate the results for improving the translation from research activities to clinical or health system application.

The general objective of the ELSI working group was to design an agreed, harmonised and implementable ethical, legal and social framework for the establishment of a biobanking and biomolecular European infrastructure and to propose corresponding strategies and scenarios as a basis for the operational concept and contractual agreements.

The specific objectives were to manage and to oversee the ethical and corresponding legal aspects in practice in the BBMRI preparatory phase; to develop an online platform on the legal aspects of uploading and validating existing legal documents in use by BBMRI members and partners; to work out the concept of harmonising, as compared to standardising, the ethics and to present practical mechanisms for achieving this in the context of the BBMRI; to provide mechanisms for the BBMRI to interact openly and transparently with the European citizenry and the means for assessing the debate regarding such an infrastructure in the population and among the relevant stakeholders in the different countries; to define, describe and demonstrate an integrated conceptual and operational model for the ELSI of the BBMRI; and to prepare proposals for training in the domain of ELSI relevant to the BBMRI in Europe.

The competencies and experience represented by the four partners of this working party have allowed access to a large network of experts in each of the main domains and disciplines involved (ethics and bioethics, law, and social sciences); this core group has interacted frequently and in a dynamic way with a group of about 20 experts from 17 countries covering these three domains.

The core group has produced background documents, in particular in the fields of ethics (1) and public consultations (2), templates, and methodological considerations for each of the specific questions requiring an answer before the BBMRI can be launched; these documents are being used to assess the existing situation and to identify gaps through expert consultation, and are systematically communicated to the other functional bodies of the BBMRI preparatory phase for comments and integration. For legal aspects, a bottom-up approach has been set up through an on-line wiki-platform, a web-based tool providing administrative information to researchers who want to exchange samples across borders, and a proposal to trace and assess the uses of bio-collections (3). Based on this previous work, we are now ready to set up governance rules for the implementation of the European biobanks infrastructure (4).

2 Harmonisation

Among the topics to be addressed when constructing a network of entities across borders, in this case a network of biobanks, the harmonisation of the related ethics is particularly complex. The issue is: on the one hand, ethics is seen as a cultural

aspect of the Member States, which could induce strong differences between them about the way to address life sciences; on the other hand, in view of the globalisation of research and the subsequent increased collaboration between teams, research ethics should not be seen as hampering scientific collaboration. This paradox has been addressed through Ruth Chadwicks' paper (Chadwick and Strange 2009), in which she identifies various processes and the corresponding ethical theories, as follows:

The harmonisation of a process is a consistent, universal, global system based on concepts and/or principles. Is this possible and/or desirable in ethics?

The standardisation of a process is less burdensome, as standards are often established without requiring full-blown harmonisation.

Standardisation alone, whilst practical, is probably not sufficient in this instance.

These processes rely on conceptual theories (Fleischacker 1999) that can be summarised through the following models.

The Necessary Conditions model: this is a philosophical approach used to identify cross-cultural ethical features and to produce abstract, descriptive principles. The success of this model is limited because of cultural bias.

The Human Rights model: this is a political/legal approach which can be functional but minimal. Its abstract nature fails to account for a multitude of perspectives, and it is more akin to standardisation.

The Cultural Dialogue approach: this requires comprehensive, continual, intercultural discussion and aims to discover parallel norms and to produce a concrete, global ethic.

As a result, it has been suggested that what is commonly intended in the context of the BBMRI by the term 'harmonisation' of ethics, namely common values, might better be regarded as the establishment of common standards. However, that is not sufficient. Agreement on the ethical credentials of the initiative itself is a prerequisite. Beyond that, harmonisation is indeed necessary, but not as an end point, rather as an ongoing process—the interplay of different voices in relation to the 'text' of the standards in question. The voices in question must also include the voices that are heard less often.

To illustrate this conceptual approach, a survey was conducted as part of WP6 among national ethics committees (NECs) and other official bodies across the member and partner countries of the BBMRI to obtain their opinions on biobanks. The aim of this analysis was to highlight the similarities and differences regarding ethical questions on biobanks. Twenty-five countries have been studied.[2] The report consists of an overview and analyses of the current opinions of national ethics committees or the opinions adopted by public authorities (e.g. the Ministry of Research) or professional societies among the BBMRI partners and members. In order to identify the relevant texts regarding ethical views, our research encompassed the following categories: formal and national bodies (opinions issued by

[2] Austria, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Malta, Norway, Spain, Sweden, The Netherlands, United Kingdom, Australia, Cyprus, Greece, Faroe Islands, Poland, Portugal, Romania, Saudi Arabia, Slovenia, and Turkey.

NECs), more specific institutional advice (public institutes or universities) and advice from legal and ethical experts when no texts were available or accessible. With regard to the extent and diversity of the ethical issues dealt with in these diverse opinions, and considering the goal of the BBMRI, we focused on and addressed specific relevant ethical issues.

Studying these diverse opinions highlighted important ethical issues which weren't necessarily identified as such in the first attempt to list the aspects to be explored and compared. For example, the question of further use of biological matter needed to be treated separately, and not as belonging within the category of informed consent.

The following six ethical issues were finally derived:

1. Definitions of biobanks and their scope of application
2. Informed consent
3. Confidentiality
4. Exchanges between centres
5. Public or private sectors
6. Further use

These issues have been discussed in comparison to the concept of standardisation to propose recommendations for implementing them in the context of the BBMRI.

Analysis of the results showed that all the participant NECs thought that biobanks and biomolecular resources raised ethical issues. Two attitudes can be pinpointed in analysing the spirit of these opinions.

For some NECs, ethics was seen as a governance tool. Opinions were built on general ethical values and the objective of these NECs was to enlighten the researcher on the ethical issues that should be taken into account in the biobank research field.

Other NECs insisted on specific procedures to be respected by researchers and provided guidelines in order to outline a code of conduct for professionals; for these NECs, ethics was seen as a standardising tool.

In the light of this observation, we analysed the six selected issues more deeply and found that the meaning of the ethical requirements in these issues varied from one country to another; for example,[3] regarding the definition of a biobank and adequate informed consent.

2.1 Definition and Scope of Biobanks

- In France, Finland, Greece, Sweden, United Kingdom, The Netherlands and Saudi Arabia, biobanks are defined in fairly broad terms, i.e. in terms of medical research, diagnosis and therapy, public health research, or population genetics.

[3] These two points are examined in detail here as examples; in the final report, the analysis has been done on all six issues.

- In Austria, Germany and Portugal, biobanks are defined in terms solely related to medical research.
- In Cyprus, Estonia, Greece, Ireland, Norway and Spain, biobanks are defined in terms of diagnostic, therapeutic or research purposes, medical research, national biobanks, or any banks of biological material.

2.2 Informed Consent

The various types of qualified consent that were found can be summarised as follows:

- Wide consent: Germany, United Kingdom
- Appropriate consent: Cyprus, Estonia, France, Austria
- Specific consent: Finland, Greece, Ireland, Sweden
- Choice between restricted or wider consent: Iceland

The Human Genetic Commission in the United Kingdom proposed a specific procedure: general consent can be used only in the case of subsequent anonymisation, and specific consent is required where there is no anonymisation. In Saudi Arabia, consent is required, but the level of consent is still controversial: a paternalistic approach requires implicit consent and a "rights" based approach requires explicit consent.

To improve collaboration within the BBMRI, we recommend that a broad definition of biobanks, covering collections of samples and personal data, be adopted to fit with the spirit of the majority of the opinions of the countries investigated and also that the following points should appear in the definition of informed consent:

- The existence of a withdrawal procedure that is linked to the extent of the confidentiality.[4]
- The mention of further use of the biological matter or data (which could appear in the initial consent form or in a re-consent form).
- Provisions regarding vulnerable or deceased donors.
- Provisions regarding the use of residue from medical interventions, such as samples obtained during medical procedures when an additional quantity is not required for diagnostic purposes but can be used for research purposes.
- The right of feedback (each country can determine whether this is of benefit, and whether it will be a general or personal result to be returned to the participants).

[4] The withdrawal procedure cannot apply to research biobanking in the same way that it applies to clinical research. For biobanking activities, the withdrawal procedure is connected to the level of identification between samples and data. If data are totally anonymised, the withdrawal is not possible, and this information has to be clearly indicated in the information sheet. It is also impossible to withdraw when complex procedures of coding are in place.

3 Public Consultations

In order to address the question of "what corresponds to the BBMRI as a European infrastructure on the societal level?" and in the absence of a "European society" the BBMRI concentrated in the preparatory phase on various "European public groups", and discussed possible strategies for the BBMRI to interact with these groups. The basic assumption was that it was important for the BBMRI to interact openly and transparently with the European citizenry. Any other strategy would have been conceived as against the assembled wisdom of science and society studies conducted in Europe during recent decades. The Stakeholder Forum and other relevant BBMRI groups were coordinated under the leadership of H. Gottweis. This group used previous publications such as identification of the relevant points to consider (Avard 2009), their impact on governance issues (Gottweis and Petersen 2008), and various surveys in different countries (Hoyer et al. 2004; Kettis-Lindblad et al. 2007a, b; Pardo et al. 2002 and recently Tupasela et al. 2010) to prepare the basis of a European-level survey. Because most of the existing data in this domain were derived from the populations of the United Kingdom (UK Biobank 2008), the United States and Northern Europe, a more diverse focus had to be worked out. In addition, almost nothing is currently known about the relationships between biobank projects, their increasingly transnational ramifications, and public perception of the trans-nationalisation of biobank research. The approach for Europe was therefore based on the following:

1. A pilot study was to be carried out in two countries (Austria and The Netherlands) using focus groups (Hennink 2007) in different public areas. The focus groups (8–12 people in group discussion, recorded and analysed) explored the topic of biobanks: how biobanks were perceived by the group or panel, how they were evaluated with respect to their purpose, which issues of concern and risk arose, and what benefits were perceived. Based on this pilot study, two further steps emerged.
2. Specific questions for a quantitative study in the framework of a Eurobarometer survey were proposed; this study took place in 2010. The Eurobarometer is a series of surveys that have been carried out regularly on behalf of the European Commission since 1973. It produces reports of public opinions on certain issues relating to the EU across the Member States. The 2010 Eurobarometer for Life Sciences and Biotechnology 73.1 contains eight questions on biobanks. The results were released in November 2010 and were summarised as follows in the report from the European Commission[5]: "While approximately one in three Europeans have heard about biobanks before, nearly one in two Europeans say they would definitely or probably participate in one, with

[5] http://ec.europa.eu/research/science-society/document_library/pdf_06/europeans-biotechnology-in-2010_en.pdf.

Scandinavian countries showing the most enthusiasm. People do not seem to have particular worries about providing certain types of information to biobanks: blood samples, tissue samples, genetic profiles, medical records and lifestyle data elicit similar levels of concern. However, amongst those similar levels there are some nuances. In twelve countries, providing one's medical records provokes the most worry, and in ten countries it is the genetic profile that is most worrying. Asked about who should be responsible for protecting the public interest with regard to biobanks, we find a split between those countries opting for self-regulation (by medical doctors, researchers and public institutions such as universities or hospitals) and those opting for external regulation (by ethics committees, national governments, international organisations and national data protection authorities). Broadly speaking, respondents in those countries which show higher levels of support for biobanks tend to favour external regulation more than self-regulation. In those countries where biobanks are unfamiliar, self regulation is a more popular way of guarding the public interest. On the issue of consent, almost seven in ten Europeans opt for specific consent—permission sought for every new piece of research; one in five for broad consent, and one in sixteen for unrestricted consent. However, of those more likely to participate in the biobank, some four in ten opt for either unrestricted or broad consent."

3. A refined script and methodology of analyses for further focus groups was to be set up in several countries (Germany, Greece, United Kingdom, Finland, and France, in addition to Austria and The Netherlands). Only the "general public" have so far been analysed. This work will be pursued further, but the preliminary analyses already underline the importance of trust, the preference for narrow consent in general, and the preoccupation frequently encountered regarding privacy and data protection. Although people generally seem to accept this as the way that science is going, there is a general desire for regulation and a focus on governance issues.

This part of the WP6 work in the BBMRI preparatory phase is seen to be an essential element of the information that will be key to the future pan-European BBMRI.

4 Tools

Among the general objectives of the ELSI work was the aim to develop practical tools that would be useful for researchers to improve both their information and their collaboration. Subsequently, we developed and improved two web-based tools. The first aims at helping in the exchange of human samples across borders (the human sample exchange regulation navigator, hSERN; see Rial-Sebbag et al. 2009a) and the second aims at delivering legal information concerning biobanks in general and reference templates for useful documents (Wiki Legal Platform; see Bovenberg 2007).

4.1 The Human Sample Exchange Regulation Navigator (HSERN)

The uses for human tissue or cell samples in genetic research have widened with the development of new methodologies, and the exchange of these tissues across country or state borders has raised new ethical/legal questions. Currently most research projects involve teams from various countries (within and outside of Europe) and the exchange of samples is encouraged. However, the legal requirements attached to the practicalities of this exchange often cause problems for the researchers. A solution to these problems was first considered in terms of a European network on Asthma.[6] As the law cannot be seen to obstruct the sharing of samples, a web-based tool (hSERN) for delivering valid administrative information to researchers wanting to exchange human samples across borders was constructed in collaboration with computer scientists and lawyers. hSERN[7] provides a practical approach to relevant issues on the regulatory aspects of exchanging human biological samples across borders, for different countries.[8] This tool permits users to obtain information on both theoretical and practical legal aspects with respect to the exchange of human biological samples for research purposes.

4.2 The WIKI Legal Platform

The WIKI Legal platform was proposed and is led by lawyer J. Bovenberg in response to the need to properly embed the pan-European BBMRI into the European legal framework. "The objective of this platform is to serve as a dynamic, online, grass roots platform for sharing, discussing, validating and issuing authoritative and reliable legal forms and standards to aid the BBMRI community in navigating the legal pathways that govern its pan-European, cross-border, multi-jurisdictional infrastructure and operations. The platform is to unearth any existing knowledge, expertise and templates currently in use by (prospective) BBMRI members and partners.[9]" The following topics have been documented to date:

- The European legal framework
- Templates for European research (the Standard Personal Data Processing Security Agreement, the Material Transfer Policy and Agreement, the Data Access Policy and Agreement)

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[6] GA^{2}LEN (Global Allergy and Asthma European Network) project, EU-FOOD-CT-2004-506378.

[7] www.hsern.eu/.

[8] Eleven countries are currently, or are planned to be, described: Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, Switzerland, The Netherlands, United Kingdom.

[9] http://www.legalpathways.eu/.

- Templates for national research (for the following countries: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden, United Kingdom)
- Templates for collaborative research with non-EU countries.

4.3 Bioresource Impact Factor (BRIF)

In collaboration with another EU-funded project (GEN2PHEN, contract no. 200754),[10] work has begun on incentives to motivate all users of biobanks to share their resources (Cambon-Thomsen 2003). One of these incentives is the possibility for the work of organising and sharing the bioresources to be better recognised, biobanks being one of the most prominent users of such resources. This can partly be achieved through quantitative measurement of the actual use and impact on scientific knowledge of the resources via a new index: a bioresources impact factor (Kauffmann and Cambon-Thomsen 2008). An online discussion and working group has been set up with the following brief: to conduct a community consultation, to decide on a unique identifier for the bioresources, to organise a way of automatically tracking the citation of these bioresources in publications, and to define the parameters of this index. This work will eventually culminate in setting up a complete study.

In conclusion, work on the different levels of the ELSI and development of tools in collaboration across disciplines and across countries has allowed the establishment of initial operational aspects of the BBMRI.

5 Prospective Governance

The BBMRI will be implemented within a few months of writing this chapter. The passage from the preparatory phase to the operational phase involved the study of various governance policies so as to propose a sustainable ELSI approach for the BBMRI European Research Infrastructure Consortium (ERIC). This transition has been helped by the adoption of a new legal status for infrastructures in Europe through a Council Regulation[11] on the community legal framework for the ERIC.

The various models of governance developed by the BBMRI partners were used to propose criteria to assist in building up the future European infrastructure of biobanks.

[10] http://www.gen2phen.org/general-information.

[11] EC No 723/2009 of 25 June 2009, OJ L 206, 8.8.2009, p. 1.

5.1 Influences of Governance

The main specification for a European infrastructure is that biobanks from different countries, and therefore from different jurisdictions, be linked together. This implies the need for a set of legal rules and ethical principles which could vary from one country to another but which also fit in a supra-national framework (e.g. a European framework or an international framework).

Thus two levels of influence are required for construction of an infrastructure (Wallace et al. 2008):

- External governance, which is seen as the rules that "must be fulfilled by the biobanks". Wallace et al. (2008) identified five categories of external governance: legislation and regulations; socio-cultural norms; funders' requirements; scientific peer review (of the biobank); and ethics and privacy review (of the biobank).
- Internal governance can be defined as the internal processes put in place by the biobanks. This principally concerns: data access; sample and data storage/laboratory practices; ethics advisory/oversight (of the biobank); scientific advisory/oversight (of the biobank); and public engagement.

5.2 "Context-Based" Governance

In order for governance to be sustainable, the societal context in which biobanks develop their activities must be taken into account.

Firstly, biobanks must be identified as such among the available research tools. This means that it is necessary to develop a globally accepted legal definition of "what a biobank is". Several definitions have already been adopted in nationally binding instruments and in standardisation documents. We propose a basic definition that also identifies future participants in the BBMRI-ERIC: "Biobanks are infrastructures designed to store, organise, use and provide human biological samples and associated data for research projects".[12]

Secondly, the ethical principles at stake have to be defined and analysed prospectively in order to ensure acceptance of the project. In this perspective, particular attention has to be given to informed consent, secondary use, withdrawal of material/data, public engagement, etc. We propose the inclusion of three core ethical principles—autonomy, dignity and respect—in order to ensure some level of donor control over their materials/information. From an ethical point of view, the goal of the future BBMRI-ERIC infrastructure will be to propose strong, agreed principles to the BBMRI community. These principles should be discussed or modified by the community "in action", which presupposes the existence of consultation mechanisms for biobanks under the central coordination of BBMRI (Chadwick and Strange 2009).

[12] Research is one of the fields covered by the definition, which can also be applied to therapeutic-use or judicial biobanks.

5.3 From Biomedical Research to Research Bio Banking

During the preparatory phase, we identified some legal analogies between biomedical research (protection of the whole body, its elements and the person herself) and the uses of human biological elements. We demonstrated that this situation can stall research using human biological materials, as the existing legal rules for biomedical research cannot be applied ipso facto to biobanking research. As a consequence, when research is conducted with body elements, particular attention should be addressed to the type of regulation to be applied, the informed consent content and form, and the policies of the ethics committees.

On the specific point of informed consent, and in order to improve biobanking research, we propose a shift from a traditional approach based on legal protection of the participants, to more pro-active participation, where consent is seen as part of a larger process of individual involvement (Rial-Sebbag et al. 2009b).

If biobanks challenge the "post-genomic age" (Gottweis and Lauss 2010), the European infrastructure will raise issues not only involving scientific areas, but more than likely also involving public acceptance, sustainability and communication.

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EU Governance for Research and Ethics in Biobanks

Jane Reichel

1 Introduction

In this paper the new governance tool for research developed within the EU, the European Research Infrastructure Consortium, ERIC, will be studied. One specific research infrastructure is put in focus, the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI.eu), a pan-european research infrastructure financed by the EU, the Member States and associated countries involved.[1] The aim of BBMRI is to use human biological samples including associated medical data, and biomolecular research tools to unravel the interplay of genetic and environmental factors causing diseases and impact on their outcome, identification of new targets for therapy and reduction of attrition in drug discovery and development. The BBMRI will build on existing sample collections, resources, technologies, and expertise, which will be specifically complemented with innovative components. As of today, BBMRI has 54 members and more than 225 associated organizations (largely biobanks) from over 30 countries, making it

[1] The research for this paper is a part of BBMRI.se, the Swedish part of the project financed by the Swedish Research Council. The financer had no influence on the design and content of this article. I am mostly appreciative and thankful to my colleagues within BBMRI.se for their many insightful comments during my work with this paper, Jan-Eric Litton, BBMRI-ERIC and Karolinska Institute, Mats G. Hansson, Deborah Mascalzoni and Joanna Stjernschantz Forsberg, Center for research and bioethics, Uppsala University and Anna-Sara Lind, Faculty of law and Center for research and bioethics, Uppsala University.

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one of the largest research infrastructure projects in Europe.[2] In November 2013 BBMRI-ERIC was instituted, with its seat in Graz, Austria (Reichel et al. 2014).[3]

The aim of the paper is however wider than merely studying the BBMRI-ERIC in itself. The aim is to analyse how a certain field of administrative law can be regulated in an integrated or composite administrative legal order, where the division of competence is not always clear and where governance strategies may be used instead of binding regulatory acts. Furthermore, biobanking is a complex policy area that involves the application of several individual rights of donors and patients, as well as the interest from the public to facilitate medical research. In this paper these issues will be referred to as *bioethics.* The question thus is who governs European biomedical research and the bioethics to be applied to the research. Can these issues be resolved or at least facilitated by the introduction of a BBMRI-ERIC?

The reason why the question of European research infrastructures has arisen can be attributed to the globalisation and europeanisation of research in general, as well as the technical developments of research equipment. On their own the Member States cannot provide sufficient resources any longer, neither economically nor in terms of competence, to compete on the global market, especially with the USA and the Far East. On the other hand, the competence within the EU in the field of research and innovation is limited. The enactment of a regulation establishing research infrastructures is therefore a way to find common solutions for common problems, enabling researchers from the EU, together with third state researchers, to collaborate on a long term basis.[4] Within the ERIC, research projects can be run under a common legal order, regulating issues such as taxes, public procurement of technical equipment and the operation thereof, employment arrangements and so forth. Legal regimes connected to the research itself will however remain in the hands of the state where the research is conducted.

The paper is divided into three parts. Starting in Sects. 2 and 3, a background is given to the constitutional setting of EU administration and its connection to and cooperation with the administration in the Member States. The second part consists of Sects. 4 and 5, where the regulatory and governance-related difficulties of biomedical research will be explored, focusing on the legal sources of

[2] http://bbmri.eu/. In Article 2a of the Council regulation (EC) No. 723/2009 of 25 June 2009 on the Community legal framework for a European Research Infrastructure Consortium (ERIC), "research infrastructure" is defined as facilities, resources and related services that are used by the scientific community to conduct top-level research in their respective fields and covers major scientific equipment or sets of instruments; knowledge-based resources such as collections, archives or structures for scientific information; enabling Information and Communications Technology-based infrastructures such as Grid, computing, software and communication, or any other entity of a unique nature essential to achieve excellence in research.

[3] See further the Statutes for the Biobanking and Biomolecular Resources Research Infrastructure European Research Infrastructure (BBMRI-ERIC), available at http://bbmri-eric.eu/.

[4] Council regulation (EC) No. 723/2009 of 25 June 2009 on the Community legal framework for a European Research Infrastructure Consortium (ERIC).

fundamental rights and the administrative organisation enforcing them, in order to properly appreciate the complexity of this specific field of law. In the last part, Sect. 6, focus is directed to the BBMRI-ERIC.

2 Basic Principles of Division of Powers Between the EU and the Member States and Its Importance for the Development of an Integrated Administration

The starting point for implementing EU law within the Member States has generally been that this is a matter for Member States to resolve independently from the EU.[5] The doctrine of division of powers between the EU and the Member States is sometimes referred to as *executive federalism*, i.e. the EU decides and the Member States implement.[6] The legal basis for this can be found in the Treaties, Article 5.2 Treaty of the European Union (TEU) and the principle of conferral of powers, stating that the EU can only take action in areas where the Member States have transferred competence to the EU. The Article is to be read in conjunction with Article 6g Treaty on the Functioning of the European Union (TFEU), introduced by the Lisbon Treaty, which states that EU competence in the field of administrative cooperation is limited to carry out actions to support, coordinate or supplement the actions of the Member States. Articles 4.3 TEU and 291 TFEU stress that Member States shall take all measures of national law necessary to implement legally binding Union acts, and that the Commission may adopt implementing legislation only in cases where uniform conditions for implementation are necessary. From this it seems to follow that the main responsibility for the implementation of EU law at national level rests securely on the Member States and their respective constitutional orders.

2.1 From Direct or Indirect to the Shared Administration of EU Law

The implementation of EU law has however not been left to the Member States to take care of entirely separate from the EU. Article 197.1 TFEU, where EU competence under Article 6g TFEU is specified, also pronounces that the effective

[5] The principle of the institutional autonomy of the Member States was introduced in Case 51-54/71 *International Fruit Company* v. *Produktschap voor groenten en fruit* [1971] ECR, p. 1107, Para. 4, and the principle of procedural autonomy in Case 33/76 *Rewe-Zentralfinanz* v. *Landwirtschaftskammer für das Saarland* [1976] ECR, p. 1989, Para. 5. See also Reichel (2013a).

[6] Hofmann et al. (2011, p. 259).

implementation of EU law by the Member States, which is essential for the proper functioning of the Union, shall be regarded as a matter of common interest. It is up to Member States to implement EU law, but it is a matter of common interests that—and not seldom how—it is done. If we instead consider the issue from a more practical perspective, the implementation of EU law is usually divided into three parts, direct, indirect or shared administration. EU institutions themselves thus provide direct administration, particularly the Commission, indirect administration is when the implementation is taken care of by the Member States, while the shared administration is carried out by the Member States in cooperation with EU institutions and agencies.[7] Nowadays EU law is mainly implemented through various forms of shared administration, with national administrative organs working closely with EU institutions and agencies.[8]

Another relevant factor is that the EU's own administration has grown significantly, through the establishment of over 30 independent European agencies. The EU authorities have different characteristics, but most of them, the so-called regulatory agencies, have the overall task of promoting the implementation of EU law in different ways.[9] The regulatory agencies may provide technical or scientific advice to the Commission and the Member States, be responsible for operational activities or create networks between administrations. They may also collaborate with private organisations and undertakings.

There have been efforts within the EU, not least by the Commission, to establish better balanced governance for the EU agencies, which has been surprisingly difficult. In 2012 a joint statement of the European Parliament, the Council and the Commission was adopted, as well as a follow-up road map, in which a common approach was presented to improve the consistency, effectiveness, accountability and transparency in the work of the EU authorities.[10]

2.2 Regulating Administrative Issues on Substantive Legal Basis—or Vice Versa

Although the EU has no independent competence to regulate the internal institutional or procedural organisation of the Member States, there are now a vast number of EU legislative acts containing such rules. The explanation lies in a broad interpretation of the articles providing the EU with a legal basis to adopt rules in

[7] Ibid. and Harlow (Harlow 2011, p. 443).

[8] Chiti (EUI Working paper Law No. 2005/10, 2005, p. 7).

[9] Communication from the Commission to the European Parliament and the Council of 11 March 2008.

[10] Joint Statement and Common Approach (Parliament, Council and Commission) and Roadmap on the follow-up to the Common Approach on EU decentralised agencies, both published on the Commission webpage. http://europa.eu/agencies/regulatory_agencies_bodies/.

substantive policy areas. Within the EU food policy, for example, the EU has adopted a regulation with common rules for monitoring the implementation of EU food regulations.[11] In the preamble it is stated that the Member States should enforce the feed and food law, animal health and animal welfare rules and monitor and verify that the relevant requirements thereof are fulfilled, and that it is therefore appropriate to establish a harmonised framework of general rules for the organisation of food controls.[12] The legal basis for the regulation is found in three articles on substantive policy areas, the present Article 43 TFEU on agricultural policy, Article 114 TFEU on internal market and Article 168 TFEU on public health. Further examples can be found in a number of horizontal legislative acts within the internal market, which contains instructions and minimum rules for the competent authorities of Member States to handle administrative matters regarding free movement of citizens, goods or services, as well as instructions on how the competent authorities in the Member States should cooperate, etc.[13]

Within the area of research and innovation, which is especially relevant for this paper, the conditions are almost the opposite. The EU catalogue of competencies, article 4.4 Para. 3, TFEU, states that the EU has limited competence to act in this area:

> In the areas of research, technological development and space, the Union shall have competence to carry out activities, in particular to define and implement programs; however, the exercise of that competence shall not result in Member States being prevented from exercising theirs.

The Union may "carry out activities", which is not the same as enacting binding legal tools. Further, the principle of preemption, which otherwise applies when the EU has exercised its competence in areas where competence is shared with the Member States (Article 2.2 TFEU), does not apply here. Any action taken by the EU does not prevent the Member States to act themselves.

According to Article 179 TFEU, the EU shall have the objective of strengthening its scientific and technological bases by achieving a European research area, characterised by the free circulation of researchers, technological development and space. Articles 180–181 TFEU set out what action the EU may take, mainly complementary and coordinated action. According to Article 187 TFEU,

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[11] Regulation (EC) No. 882/2004 of the European Parliament and of the Council of 29 April 2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules.

[12] Paragraphs 6 and 7 of the preamble.

[13] For example, Directive 2004/38/EC of the European Parliament and the Council of 29 April 2004 on the right of citizens of the Union and their family members to move and reside freely within the territory of the Member States; Directive 2006/123/EC of the European Parliament and the Council of 12 December 2006 on services in the internal market; Regulation (EC) No. 764/2008 of the European Parliament and the Council of 9 July 2008 laying down procedures related to the application of certain national technical rules to products lawfully marketed in another Member State; and Directive 2005/36 EC of the European Parliament and the Council of 7 September 2005 on the recognition of professional qualifications, among others.

however, the EU may "set up joint undertakings or any other structure necessary for the efficient execution of Union research, technological development and demonstration." It is under this legal basis that the EU has enacted the above-mentioned regulation establishing the European consortium for research infrastructures, the ERIC consortium, discussed further in Sect. 6.

3 From Community Method and Judicial Activism to Governance in a Composite European Administration

The constitutional framework of the EU legislative process is based on certain conditions that affect which legal acts are available and their interrelated hierarchies. Two aspects are covered here, the Community method applied in the EU's legislative process and the Meroni doctrine regarding the limitations on delegation of legislative powers within the EU. In addition, reconnection will be made to the principle of conferral, discussed above. These factors have paved the way for the increased importance of the composite administration, that is, to fill the vacuum caused by constitutional rules setting up constraints on a development that is otherwise considered desirable.[14]

3.1 The Community Method

The first aspect refers to the specific characteristics that the EU has in comparison to other international organisations, namely its capacity to adopt legal acts that bind the Member States and their citizens directly.[15] The treaties have established procedures to be used for various forms of legislation, attributing specific roles to EU institutions in the process. The original legislative model is usually denoted Community Method.[16] A basic idea of the method is that the central EU institutions listed in Article 13 TEU are to represent specific interests within the Union. By regulating the functioning of the different institutions in the legislative process, these interests may be balanced against each other. It is thus not a question of separation of powers in the traditional sense, where three branches of the state, the legislature, the executive, and the judiciary, are divided in order to balance each other. The basis of the Community Method may rather be seen as a division of interests, in order for them to balance against each other.

[14] For an example from the food area, see Randall (2006, p. 411).

[15] Case 26/62 *Van Gend en Loos* v. *Nederlandse Administraie der Belastingen* [1963] ECR, English special edition, p. 1.

[16] Wiberg (2013, p. 238).

The legislative power rests with the Council that represents the interest of the Member States, together with the European Parliament that represents the interest of the citizens of the Union. The legislative initiative can however only be taken by the Commission, which represents the interests of the Union as a whole, being completely independent of the Member States. The Court of Justice of the European Union and the European Court of Auditors are given the task of control: to ensure that the law is observed and to examine Union accounts.[17] The institutional balance is thus of central importance in EU constitutional order, as well as the right for the institutions and the Member States' right to initiate a judicial review of all the legal acts adopted.[18]

Even though the European Community, the EC, was replaced and succeeded by the Union in the Lisbon Treaty (Article 1 TEU), the Community Method has actually increased in importance, since it is now only the common foreign and security policy that is still dealt with according to traditional international decision making procedures (title V of the TEU). For a new act to be adopted in the EU, it is generally required that the Commission submits a proposal that a sufficient majority in the European Parliament and the Council can accept.[19]

3.2 The Meroni Doctrine

The second aspect of the EU's constitutional order that can be identified as relevant, the restrictive approach to delegation of legislative power, can also be seen as a way to uphold institutional balance in the EU's legislative procedure. According to the classical Meroni doctrine, there are only limited possibilities to derogate from the distribution of powers which the Treaties have set out. Delegation is only possible if the delegated powers are clearly defined, the exercise of the delegated powers is under the control of the delegating institution on the basis of specific and objective criteria and that the delegation does not include discretionary powers that allow a margin of appreciation.[20] As seen

[17] van Gerven (2005, p. 14), Temple Lang (2006, p. 134) and Commission White paper on European Governance, COM (2001) 428 final, p. 9.

[18] In a famous case, C-70/88 *Parliament* v. *Council (Chernobyl)* [1990] ECR I-2041, the Court of Justice of the European Union found that the European Parliament should have a right of standing before the court and to initiate an action for annulment regarding a legislative act, despite the fact that the Treaty at that time did not provide for such a right. The Court stated that "it is the Court's duty to ensure that the provisions of the Treaties concerning the institutional balance are fully applied and to see to it that the Parliament's prerogatives, like those of the other institutions, cannot be breached without it having available a legal remedy", Para. 25.

[19] Some exceptions to the Commission's exclusive right of initiative are set out in Article 76 TEUF, regarding cooperation on criminal matters and police cooperation.

[20] The doctrine was established in a case from 1958, Case 9/56 *Meroni* v. *High Authority* [1958] ECR, English special edition, p. 133. See also Bergström (2005, p. 48).

above, in recent years a large number of EU agencies have been established. This development has taken place without any further mechanisms for delegation being introduced in the Treaties. The tasks of the EU agencies vary, but some are equipped with the authority to make decisions in individual matters,[21] and others can play a role in the EU legislative process in the form of expert bodies giving advice.[22]

An interesting example of the latter category is the three EU agencies in the financial sector, established in 2011,[23] which play a significant role in their respective areas, both in connection to the Commission's adoption of delegated legislation relating to technical standards and the issuing of non-binding guidelines and recommendation to the competent authorities of the Member States. According to Article 10 of the respective regulations, the authorities are to draft technical standards for submission to the Commission and the Commission may not derogate from or modify the draft, without first consulting the Authority. In Article 16 the authorities are conferred a competence to adopt guidelines and recommendations "with a view to establishing consistent, efficient and effective supervisory practices within the ESFS, and to ensuring the common, uniform and consistent application of Union law". The same article also states that the competent authorities of the Member States "shall make every effort to comply" with these guidelines and recommendations, which they must confirm to the EU authority. If the competent authority does not intend to follow the guidelines or recommendations, the reasons for this should be expressly stated. The guidelines and recommendations are not formally binding legal acts in a formal sense, but in practice they are not far from it. Hofmann has in the light of these developments found in general that the gap between the constitutional regulation and the reality of the emerging European administration is increasing.[24]

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[21] For example OHIM, the Office for Harmonisation in the Internal Market; Council Regulation (EC) 207/2009 on the Community trade mark; and ECHA, the European Chemicals Agency; European Parliament and Council Regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

[22] For example EFSA, the European Food Safety Authority; and the European Parliament and Council Regulation (EC) No. 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.

[23] Regulation (EU) No. 1093/2010 of the European Parliament and of the Council of 24 November 2010 establishing a European Supervisory Authority (European Banking Authority); regulation (EU) No. 109472010 of the European Parliament and of the Council of 24 November 2010 establishing a European Supervisory Authority (European Insurance and Occupational Pensions Authority); and regulation (EU) No. 1095/2010 of the European Parliament and of the Council of 24 November 2010 establishing a European Supervisory Authority (European Securities and Markets Authority).

[24] Hofmann (2009, p. 502).

3.3 The Principle of Conferral and Alternative Forms of Regulation

Besides the two aspects described above, a further aspect may be emphasized, namely the above-mentioned principle of conferral. The principle is relevant both for explaining why the EU cannot take general measures to regulate the national implementation of EU law, but also why certain policies generally fall outside the competence of the EU, or why the EU only has limited competence. Examples of the latter category are the EU's employment policy, which will be mentioned only briefly, and the EU's research and innovation policies.[25]

The EU has no competence to take legally binding action in employment, but may under Article 5.2 TFEU adopt measures to coordinate Member States policies, "in particular by defining guidelines". Traditionally, the open method of coordination, OMC, has been used in this area, whereby national policies can be coordinated without competence formally having been transferred to the EU.[26] The approach is to identify and define common objectives, after which the Member States adopt individual programs for achievement. By making use of benchmarking and comparative studies, the programs are evaluated. The process is intended to function decentralised, with the EU, Member States, regional and local levels as well as the social partners and civil society actively involved, using variable forms of partnership.[27]

With regard to EU policies for research and innovation, the EU has merely competence to take complementary and coordinated actions vis-à-vis national policies (Sect. 2.2). Even so, Ruffert and Steinecke maintain that the EU acts as a supranational organisation in the international field of research.[28] This can be explained by the organisational regimes and soft law mechanisms that the EU can utilise within the European research area. In the 2020 strategy, the EU has defined several steps to achieve a sustainable economy and growth in Europe.[29] One part of the strategy is directed to research and innovation. The EU has introduced several agencies, programs and instrument to facilitate research. One of them is the European Strategy Forum on Research Infrastructures, EFRSI, a Commission instrument to support a coherent and strategic policy for research infrastructures in Europe.[30] The ESFRI identifies and describes the scientific needs for research

[25] Another area where the EU does not have competence but has found ways to cooperate is the area of e-governance, Reichel (2010, p. 67).

[26] Radaelli (2003, p. 14).

[27] Lisbon European Council 23–24 March 2000, Conclusions of Presidency, Para. 38.

[28] Ruffert and Steinecke (2011, p. 65).

[29] Communication from the Commission, Europe 2020 A strategy for smart, sustainable and inclusive growth, COM (2010) 2020 final.

[30] http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri. See further Beijer (2012).

infrastructures within the EU in the near future through roadmaps.[31] Within the ESFRI, the national competent authorities in the research area are represented and the needs identified at the EU level will also influence the priorities made at the national level. For example, in the Swedish equivalent to the ESFRI road map, the Research Council guide to infrastructures 2012, it is stated that the ESFRI road map has been used as an important basis.[32] The Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) was one of the first projects to enter the European Research Infrastructure's preparatory phase of the ESFRI roadmap, funded by the Commission.[33] BBMRI.eu today has 54 members, with more than 225 associated organisations (largely biobanks) from over 30 countries. The Swedish Research Council funds the Swedish part of the project, BBMRI.se.

3.4 Towards a Composite but Fragmented European Administration?

The growing cooperation between European and national administrative bodies in various forms has come to be regarded as an administrative organisation in itself, known as an integral or composite administration.[34] An important difference between this composite European administration and national administration is that the composite administration is not organised under one coherent political structure. Neither the EU nor the Member States can by themselves steer or control the European composite administration as a whole. Instead, the composite administration is a part of all 29 constitutional orders at the same time, the EU and the 28 Member States.[35] A specific feature of the composite administration is its fragmented structure; the organisation and inter-relationships between its constituent bodies vary from one policy area to another.[36] This heterogeneous administrative model, with its indistinct boundaries between the European and national, as well as between the private[37] and the public, may in itself open the doors for the use of alternative regulatory methods, using soft governance tools rather distinct legal rules. One of the main driving forces behind the development of a composite

[31] Three roadmaps have been published so far: The European Roadmap for Research Infrastructures 2006, and two updated versions in 2008 and 2010. They are published on the Commission's webpage. http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri.

[32] Vetenskapsrådets guide till infrastrukturen (2012, p. 3).

[33] ESFRI Roadmap for Research Infrastructures, Update 2008, and BBMRI.eu.

[34] Schmidt-Aßmann (2011).

[35] Reichel (2010) (note 25 supra) p. 213.

[36] Hofmann et al. (2011) (note 5 supra) p. 908 ff.

[37] This aspect has not been addressed in this paper, but it is an important feature of the European composite administration and governance structures. See further Wiberg (2013) (note 16 supra) p. 235.

administration is its ability to solve common European problems that are out of reach for the individual entities, the EU and the Member States.[38] By coordinating European and national policies and infrastructures, a more efficient outcome of policies may be attained. On the other hand, the ability to steer and control the heterogeneous administration may prove more difficult, since it is not directed by one coherent policymaker. With this further follows a risk of fragmentation, since different policy areas develop rather independently of each other. What this implies for the area of medical research and bioethics will be discussed in Sect. 6.

4 Sources and Administrative Regimes Applicable to Global Biobanking

Within bioethics, there are some basic notions that have been recognized more or less on a global scale. In connection with the Nuremberg trials after World War II, a public code for medical research was formulated for the first time. Childress and Beauchamp have identified four basic moral principles; respect for autonomy, non-maleficence, beneficence, and justice.[39] The first principle, autonomy, is central for the study undertaken here. The right of autonomy includes a right to decide for oneself how issues regarding one's health and body should be dealt with. The respect for autonomy therefore underpins other legal principles and rules, such as the right of individuals to have information regarding their health being treated with confidentiality, and an obligation for professionals within medical care and research to obtain informed consent before handling either data or biological samples from the individual.[40] Ruffert and Steinecke have described the requirement of informed consent as one of the two legal notions within bioethics that have found 'overall' acceptance.[41]

From the perspective of medical research on biobanks, informed consent can from a legal perspective be divided into three dimensions or parts: the sample donor must give his or her consent to the storing of the actual sample in a biobank, processing personal data extracted from the sample or otherwise collected, and participating in the research itself.[42] These basic principles have been laid down in

[38] Hofmann and Türk (2007, p. 262).

[39] Beauchamp and Childress (2012, Chaps. 4–7).

[40] *Op. cit.* pp. 104, 117.

[41] Ruffert and Steinecke (2011) (note 28 supra) p. 94. The other notion referred to is the prohibition of the reproduction of human beings.

[42] For example from Swedish law, the three dimensions of the informed consent are regulated by three different acts, the Biobanks in Medical Care Act (lag [2002:297] om biobanker i hälso- och sjukvården m.m.), the Personal Data Act (personuppgiftslag [1998:204]) and the Act concerning the Ethical Review of Research Involving Humans (lag [2003:460] om etikprövning av forskning som avser människor).

international, regional and national law, which will be discussed briefly from a fundamental right perspective (Sect. 4.1) and from an administrative law perspective (Sect. 4.2). After this, the issues will be discussed from a public benefit perspective, i.e. the more collective oriented rights to health and the interest of freedom of science (Sect. 4.3). In Sect. 4.4, a presentation of the prevailing administrative organisation with research ethics committees will be given.

4.1 Fundamental Rights in International Law and European Law

As set out above, the notion that individuals have the right to decide if and how parts or samples of their body are to be used in medical research is strong in the International Community.[43] International law at the global level does not provide for any binding legal rules regarding the above-mentioned three parts of informed consent, only soft law.[44] A central document is the UNESCO Universal Declaration on Bioethics and Human Rights, where Article 6 states that the right of autonomy of every person to decide on participation in research, for example by donating samples, should be protected, and Article 9, concerns the protection of the privacy of the persons concerned and the confidentiality of personal information. Furthermore, the OECD Guidelines for Human Biobanks and Genetic Research set out the protection of participants' privacy and the confidentiality of data as a founding principle in section 1.D, and informed consent as the main rule, in section 4.B.

At the European level there are some binding legal acts. The Council of Europe has adopted two acts containing general provisions on rights to privacy, health and dignity, namely the European Convention for the Protection of Human Rights and Fundamental Freedoms from 1950 and the Social Charter from 1961. In 1997 the Council of Europe adopted the Convention on Human Rights and Biomedicine, with more specific requirements for informed consent (Articles 5–9) and the right to privacy and to information (Article 10). The Council of Europe has further enacted a Convention in 1981 for the Protection of Individuals with regard to Automatic Processing of Personal Data, based on which the EU Data Protection Directive[45] is modeled (see Sect. 4.2.1).

The EU Charter of Fundamental Rights, which is binding since entering into force of the Lisbon Treaty 2009, contains several relevant articles. Article 3 states

[43] This topic is covered in depth by Anna-Sara Lind in this anthology and will therefore be handled more briefly here.

[44] Rynning (2009, p. 303). See further Reichel (2013b).

[45] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

the right of each individual to integrity within the fields of medicine and biology, which is respected by obtaining informed consent, and Article 8 grants the right to the protection of personal data.

4.2 International Administrative Regulation

Under the level of fundamental rights, there are hardly any international or European sources containing binding administrative rules concerning cross-border biobanking directly.[46] EU law contains secondary legislation that may be applied in connection to biobanking (4.2.1). Instead, the main source consists of soft law (4.2.2).

4.2.1 Secondary EU Law

Within the EU, there is some secondary legislation that applies to biobanking, at least indirectly. This is due to the lack of any specific legal basis conferring competence to the EU to regulate ethical issues. As seen above, Article 168 TFEU contains a legal basis for the EU in the field of public health, but the competence is limited in several ways and does not confer any basis for enacting rules on ethical issues directly.[47] Furthermore, it has proven difficult for the Member States to reach workable agreements on issues that affect ethical and moral issues, as shown by, for example, the so-called moral clause in the Biopatent Directive,[48] and the legal framework concerning genetically modified organisms, GMOs.[49]

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[46] Rynning (2009) (note 44 supra) p. 301.

[47] See, for example, Amended Proposal for a Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells COM (2003) 340 final, p. 4, where the Commission rejects certain proposals from the European Parliaments on ethical issues, on the grounds that Article 168 TFEU (at the time, Article 152 EC) does not give the EU competence in that field. See further H. Busby (2008, p. 820).

[48] Article 6 of the Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions. The Directive has been the object for an extensive legal debate, see for example several contributions in Plomer and Torremans (2009), as well as judicial proceedings before the Court of Justice of the European Union (CJEU), C-377/98 *Netherlands* v. *European Parliament and Council* [2001] ECR I-7079, and more recently, Case C-34/10 *Oliver Brüstle* v. *Greenpeace e.V.* [2011] ECR, not yet reported.

[49] For example, Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms. Also this directive has been the subject of academic debate, see for example Krisch (2006), 256 ff.; as well as judicial proceedings C-165/08 *Commission* v. *Poland* [2009] ECR I-6843.

EU law does however contain two secondary legislative acts relevant to the area of bioethics, if not directly regulating it, the Data Protection Directive[50] and the above-mentioned Biopatent Directive.[51] The Data Protection Directive, currently undergoing revision,[52] has the dual aim to protect the free flow of personal data between Member States at the same time as upholding a high level of protection for the privacy of data subjects. Since the transfer of samples in international medical research normally also includes the transfer of personal data, the Data Protection Directive in reality is highly relevant. The impact of the Directive will be discussed further below (Sect. 5.1.2). Other regulatory measures also affect the area indirectly, such as the decision on the seventh Frame Work Programs for research, which states that all research shall be carried out in compliance with fundamental ethical principles.[53] According to the preamble of the decision, the opinions of the European Group on Ethics on Sciences and New Technologies (EGE) will be taken into account.[54]

4.2.2 Soft Law

The main source for administrative practices in the area of ethics in international biobanking is soft law, from international organisations as well as NGOs. One reason may be that this is a sensitive area for many states, which makes it difficult to develop common binding rules. On the other hand, in the area of science, the use of self-regulation and soft law is widespread. Ruffert and Steinecke have stated that 'what is pertinent in the field of science is the prominence of standards generated by private or at least hybrid actors: networks of scientific institutions, professional bodies or other non-state actors'.[55]

At the international level, there exists an abundance of documents of different sorts in the area of bioethics. Apart from the human rights acts mentioned above (Sect. 3.1), the WHO has also issued a 'Guideline for obtaining informed consent for the procurement and use of human tissues, cells and fluids in research'. In collaboration with CIOMS,[56] the WHO has further issued two guidelines,

[50] Directive 95/46/EC (note 45 supra).

[51] Rynning (2009) (note 44 supra).

[52] Commission proposal for a Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), COM (2012) 11 final. See also chapter The New General Data Protection Regulation—Where Are We Are and Where Might We Be Heading? in this book.

[53] Decision 1982/2006 concerning the Seventh Framework Program of the European Community for research, technological development and demonstration activities (2007–2013) [2006] OJ L412/1. See further Busby (2008) (note 47 supra) p. 833.

[54] Paragraph 33 of the preamble to the decision. See further Plomer (2008, p. 847).

[55] Ruffert and Steinecke (2011) (note 28 supra) p. 115.

[56] Council for International Organizations of Medical Science.

International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002, and International Ethical Guidelines for Epidemiological Studies, 2008. The Council of Europe has issued an additional protocol and an explanatory memorandum to the protocol to the above-mentioned convention on biomedicine,[57] as well as recommendations that may be relevant to biobanking.[58] Also the World Medical Association (WMA), an independent confederation of free professional associations for physicians, has enacted several different declarations,[59] where the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, is the most important one.[60]

At the EU level, there are two advisory groups under the Commission adopting opinions relevant for bioethics, the above-mentioned EGE and Article 29 Data Protection Working Party.[61] The latter advisory group is connected to the Data Protection Directive, and specialises in questions regarding personal data protection.

4.3 The Public Benefit Perspective

Also, fundamental rights other than autonomy rights may be relevant in the field of biobanking for medical research purposes, namely those rights and interests that may exist on a collective level usually referred to as public benefit or public good. The right to the enjoyment of the highest attainable standard of physical and mental health was first articulated in the 1946 Constitution of the World Health Organization (WHO), and the right to health is also included in the United Nations Universal Declaration of Human Rights from 1948 (Article 25) and in the United Nations International Covenant on Economic, Social and Cultural Rights from

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[57] Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 2005, and Council of Europe Committee of Ministers, Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research.

[58] For example Recommendation on research on biological materials of human origin, adopted by the Committee of Ministers of the Council of Europe, and Recommendation No. R(99)4 of the Committee of Ministers to member States on principles concerning the legal protection of incapable adults.

[59] WMA Declaration on the Rights of the Patient (1981), WMA Statement on Patient Advocacy and Confidentiality (2003), WMA Declaration on Ethical Consideration Regarding Health Databases (2002), WMA Statement Concerning the Relationship Between Physicians and Commercial Enterprises (2004) and WMA Statement on Genetics and Medicine (2005).

[60] See further www.wma.net.

[61] See, for example, Article 29 Data Protection Working Party, Working Document on Genetic Data, 12178/03/EN, 2004 and EGE Opinion no. 15 on Ethical Aspects of Human Stem Cell Research and Use. In the proposed General Data Protection Regulation, Supra note 52, the Article 29 Data Protection Working Party Group is suggested to be replaced by new European Data Protection Board (EDPB), Infra note 103.

1966 (Article 12). In Europe, the right to health is protected in the Council of Europe Social Charter (Article 11), and in an equivalent manner, the EU Charter of Fundamental rights (Articles 34 and 35).[62]

Furthermore, the researchers themselves can also benefit from some protection, since the freedom of science is also protected in several international treaties. The 1948 Universal Declaration on Human Rights includes a right to share scientific advancements and benefits (Article 27), which is not exactly directed to the researches themselves. The International Covenant on Economic, Social and Cultural Rights contains an obligation on the Contracting States to "respect the freedom indispensable for scientific research and creative activity", Article 15.3. The EU Charter of fundamental rights declares, in Article 13, that the arts and scientific research shall be free of constraint. Framed like this, the freedom of science is hardly an individual right for the researchers to rely on, but nevertheless a recognition of the importance and value of science.[63]

4.4 Administrative Organization of Ethics Review

As a general point of departure, research ethics committees at the national level carry out the assessment of ethical issues in relation to medical research on biobanks. All of the above-mentioned guidelines and recommendations require the involvement of ethics committees in some form.[64] In the OECD guidelines on human biobanks and genetic research databases (HBGRD) the use of an independent research ethics committee is considered as one of the main prerequisites of best practices[65]:

The establishment, governance, management, operation, access to, and use of the HBGRD and its protocols and processes for research activities, should be approved or reviewed, as applicable, by an independent research ethics committee.

Ruffert and Steinecke maintain that these types of committees exist in almost all countries.[66] The approval by a research ethics committee might, according to

[62] Lind (2009, part III; 2011, pp. 67–76).

[63] Ruffert and Steinecke (2011) (note 28 supra) p. 31.

[64] See, for example, the CIOMS/WHO International Ethical Guidelines for Epidemiological Studies, guideline 2; International Ethical Guidelines for Biomedical Research Involving Human Subjects, p. 24; Article 9 of the Council of Europe Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg; Articles 15, 25 and 29 of the WMA Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

[65] Paragraph 1.2 of the guidelines.

[66] Ruffert and Steinecke (2011) (note 28 supra) p. 98.

national law, be required both when collecting samples for a specific research project, or when re-using old samples already stored in a biobank. Standardised forms are usually used when obtaining the consent of sample donors. These are usually drafted by the researchers themselves, after models are made available by associations,[67] the biobanks themselves,[68] or, as discussed above, provided by groups of researchers.[69]

The assessment of the committees may, on many occasions, include the balancing of interests between the individual rights involved and the possible benefits for the public, since the review of whether the aim of the research can motivate the use of possibly privacy sensitive issues, i.e. human biological material and personal data is central to the committees' task. The research ethics committees can be considered as being well-equipped for this task, since the committee can provide a far broader range of perspectives upon issues under consideration because membership of ethics committees are typically drawn from different disciplines.[70] On the other hand, which will be discussed further below (Sect. 5.2), it may be questioned whether the research ethics committees at the national level are so well-equipped to assess medical research on biobanking conducted cross border, on a global scale.

5 Applying the Law to Global Biobanking

Bioethicist Stjernschantz Forsberg has argued that the two perspectives presented in Sect. 4, individual rights on the one hand, and public benefit on the other, need not be viewed as contradictory, but can be interpreted as coexisting.[71] This view can be taken as a point of departure for the following analysis. The question discussed here is how a regulatory or governance strategy can be construed in order to attain a properly balanced coexistence. In the following section, the regulatory landscape will be discussed in connection to rules on conflict of law, in order to identify what actor may take decisions on global biobanking, and in what circumstances (Sect. 5.1). After this, the difficulties connected to the application of ethical and legal principles to large scale research biobanks will be analysed (Sect. 5.2).

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[67] See, for example, in Sweden, the National Biobank Council, consisting of representations from regional municipalities (health care principal), universities and pharmaceutical industries, provides various model forms on its website: www.biobanksverige.se.

[68] See, for example, the UK biobank's website: www.ukbiobank.ac.uk.

[69] See Sect. 3.3 regarding BBMRI.eu, www.legalpathways.eu.

[70] McHale (2011, p. 236).

[71] Stjernschantz Forsberg (2012, pp. 56, 67).

5.1 Administrative Conflicts of Law

When administrative matters move beyond the state, there are basically two methods for deciding on what rules should apply. Either a common understanding of what rules to be applied can be developed, so that administrative actors apply the same or similar rules, or administrative actors stick to their own rules and develop meta-rules for when to apply what set of rules. As stated by Ruffert and Steinekke, referring to an example suitable for this article[72]:

> The execution of a bio-ethically doubtful research project by a multinational research institution could be governed either by the bio-ethical rules of an international organisation or by conflicting rules of different States (the State where the institution is seated, where the project is mainly performed, where the researchers originate from…)

The two methods do not exclude each other, but may interact in an intricate manner. What makes global biobanking difficult is that the same solution does not necessarily apply to all three dimensions of the informed consent condition described above, in relation to handling the biological material, the data connected to it and to the participation in research. Within a procedure only involving research on Swedish sample donors/data subjects, all three parts can be reviewed by a research ethics committee in one single application. In a global context, the situation is quite different. A national research ethics committee cannot enact legally binding decisions addressing legal subjects abroad directly. At a global level, the three parts are handled separately. In the following, the legal situations will be analysed using Swedish law as an example, but with references to an international context.

5.1.1 Cross Border Consent to Handle Biological Material

As seen above, there are no internationally applicable administrative rules regulating issues of transferring samples, and certainly no rules on the control of the use of the samples in the receiving country in practice. Regarding the transfer of the biological material itself, there are, as seen above, no globally applicable administrative rules. Generally, all the requirements for informed consent must be fulfilled in accordance with the law of the land where the sample is collected.[73] This means that one and the same research project collecting samples from several states may need to seek approval from committees in every state. When a sample is to be sent from one state to another, a specific approval from a research committee may also be needed, even though it might not be necessary to obtain new consent from the donor. The transfer must usually be preceded by entering into an agreement between the sender and receiver, a material transfer agreement (MTA). All the conditions for handling the samples are regulated in the MTA, specific

[72] Ruffert and Steinecke (2011) (note 28 supra) p. 20. See also Reichel (2013b) (note 44 supra).

[73] See for a description of Swedish law, www.biobanksverige.se.

restrictions regarding the given consent, etc. Standardised forms for MTAs are often made available by the same actors providing forms for informed consent (above Sect. 4.3).

5.1.2 Cross Border Consent to Process Personal Data

Within the EU, the transfer of personal data is regulated by the Data Protection Directive.[74] The directive allows sensitive personal data, for example, data concerning a person's health, to be transferred between Member States under the same conditions as within one Member State. This usually means that the data subject has to give its informed consent, but the Directive leaves some room for the Member States to allow exceptions, for example, if an ethical review board gives its approval.[75] The possibility to transfer personal data outside the EU is governed by the principle of mutual recognition in different forms. A transfer to a third country is only permissible if the country in question ensures an adequate level of protection, where the administrative regime of the receiving state can be understood as giving an equal protection to that of the sending state.[76] The Commission has been assigned the task of entering into negotiations with third countries and may also find that a country ensures an adequate level of protection in the meaning of the Directive.[77] In this case, personal data may be transferred to these countries on the same conditions as within the EU. The Commission has further concluded so-called Safe Harbor agreements with the USA, allowing transfer of data to entities within the states that adhere to the principles laid down in the agreement.[78] If none of these options are available, the Commission has further enacted standard contractual clauses, containing the necessary set of information for allowing the transfer of personal data outside the EU.[79] As stated in the preamble to the decision, the use of the standard contractual agreements is voluntary as the clauses are only one of several possibilities under the Data Protection Directive.[80] However, since there are today a number of competing,

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[74] Directive 95/46/EC (note 45 supra).

[75] See Article 8 Data Protection Directive.

[76] See Article 25.1 Data Protection Directive.

[77] See Article 25.5–6 Data Protection Directive. The equivalent rules in the proposed General Data Protection Regulation, supra note 52, can be found in Article 40–45.

[78] Commission decision C (2000) 2441 pursuant to Directive 95/46/EC of the European Parliament and of the Council on the adequacy of the protection provided by the Safe Harbor Privacy. Principles and related Frequently Asked Questions issued by the US Department of Commerce.

[79] Commission Decision 2004/915/EC of 27 December 2004 amending Decision 2001/497/EC with regard to the introduction of an alternative set of standard contractual clauses for the transfer of personal data to third countries, OJ L 385, pp. 74–84.

[80] Paragraph 3.

and to some extent divergent standard contractual clauses available,[81] the Commission further maintains that data exporters must stick to one set of standard at the time; it should not be allowed to amend these sets or totally or partially merge them in any manner.

5.1.3 Cross Border Consent to Participate in Research

In contrast to informed consent for using biological material or processing personal data, the applicable law for informed consent to research is the law of the country where the research is conducted, no matter where the sample or data has been collected. The consent does not follow a researcher pursuing cross border research when he or she goes abroad. An approval from the Swedish research ethics committee is thus only valid within the Swedish territory.[82]

To conclude, in an international research group each researcher will thus be governed by the law applicable at their own research institute, while the law governing the samples and the data connected to it will follow the sample, albeit in slightly different ways. All in all, this means that there may be quite a large number of national administrative rules applicable to one and the same research project. Many borderline cases can be identified, where the law is unclear. Even with the best of intentions, it might be a great challenge to abide by the law.

5.2 The Application of Ethical and Legal Principles to Global Research Biobanks—An Inventory of Problematic Issues

Which specific problems do the administrative regulatory regimes of international biobanking encounter? Three problematic issues can be identified.

First, even if medical research on biobanks today is to a large extent conducted cross-borders, the legal situation is still predominantly national. Kaye has referred to the conceptual underpinnings of current research governance structures as being based on the "one researcher, one project, one jurisdiction" model. She maintains that the nationally based governance bodies in the field of biobanking do not have

[81] The Commission refers to clauses adopted by the International Chamber of Commerce (ICC), Japan Business Council in Europe (JBCE), European Information and Communications Technology Association (EICTA), EU Committee of the American Chamber of Commerce in Belgium (Amcham), Confederation of British Industry (CBI), International Communication Round Table (ICRT) and the Federation of European Direct Marketing Associations (FEDMA), footnote 3.

[82] Section 5 of Ethical Review of Research Involving Humans Ethics Review Board Act (2003:460).

the legal powers or expertise to adjudicate on the complex issues, such as privacy and disclosure risks that are raised by cross-border data sharing.[83] Even in the area of processing of personal data within the EU, which is governed under the same Data Protection Directive, there are substantial differences between the national implementation of legislation. As stated by an expert group under the Commission, with Kaye as rapporteur, the inconsistencies between domestic laws are a direct result of the fact that the Data Protection Directive allows for a margin of appreciation in implementation by Member States, but also because its provisions are highly general in their scope[84]:

> While this flexibility can be beneficial allowing Member States to determine the way that the Directive is implemented in a national internal system, this is highly problematic for ongoing (and future) biomedical research on biobanks. The degree of national regulation makes it difficult to provide an updated, detailed and complete overview of the (sometimes complex) legal framework in force in all jurisdictions across Europe. This can have a significant effect on the ability of scientists to collaborate and plan international initiatives.

On the other hand, the medical researchers in biobanking and epidemiology have had quite a fright on behalf of the proposal for a new EU Regulation,[85] especially the amendments put forward by the European Parliament.[86] A more coherent legal framework would be beneficial to the biobanking Community, but hardly to the price of significantly stricter rules.[87] The issue will be discussed further in Sect. 6.2.

Second, and related to the first, biobanking on the global scale is to a large extent governed by legal tools of low hierarchical value, overlapping and sometimes contradictory soft law.[88] The combination of practical need and lack of political will and/or legislative competence within the global regime seems to have paved the way for soft law. Another prominent feature of biobanking, nationally as well as internationally, is the importance of standardised forms for collecting consent from sample donors and entering into agreements for sending biological samples and personal data. In many cases, the actual protection of the

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[83] Kaye (2011, p. 377).

[84] Report of the Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research, p. 40.

[85] COM (2012) 11 final (note 52 supra).

[86] European Parliament legislative resolution of 12 March 2014 on the proposal for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) [COM (2012)0011–C7-0025/2012–2012/0011(COD)]. See also chapter The New General Data Protection Regulation—Where Are We Are and Where Might We Be Heading? in this book.

[87] Several actions have been undertaken by stakeholders in the biobanking community, for example, a statement from EUORDIS, an organisation for rare deceases in Europe. http://download.eurordis.org/documents/pdf/DataProtectionStatement22Feb2013.pdf. See also Mascalzoni et al. (2013).

[88] Eriksson et al. (2008).

privacy of sample donors in practice boils down to the drafting of a form, where the information of the current as well as possible future research project is set out for the sample donor to consider. These forms are normally reviewed by research ethics committees and, to some extent, research funding institutions, within the administrative procedure at state or regional levels.

Summarising the problematic factors in the second area, the legal tools available in international biobanking are of low hierarchical legal value, there is a widespread use of standardised forms drafted by low-level administrative or hybrid private-public organs, which are, at least when involving transferring samples and data outside the EU, monitored by agreements between researchers and/or versions of the principle of mutual recognition, with very diffuse mechanisms invoked to control what happens to the sample in practice. From a national point of view, this seem to be a rather strange way of regulating issues involving several fundamental rights, namely the right to autonomy and privacy of the sample donor/data subject, the right to health for patients, and—at least indirectly—the scientific freedom. Fundamental rights, and especially the limitation of such rights, have traditionally been found to be best regulated by democratically elected parliaments, allowing the sensitive balancing of contradictory interests, the protection of privacy and the interest in medical research, to be performed by an organ directly accountable to the people. Furthermore, in the areas of bioethics and biobanking, nationally as well as internationally, the role of courts is limited. The implementation of the administrative rules is carried out by research committees,[89] usually with limited or no right to appeal to the regular court system. Thus, the traditional mechanisms of political and judicial control to a large extent are unavailable. Today there is a lively discussion in legal doctrine on how to develop mechanisms of participation and deliberation in regulatory procedures beyond the nation state, but there still seems to be a long way to go before such procedures are in place.[90]

The third problematic area is concerned with the functionality of biobanks in themselves, not only at a global level. Biobanking in itself has difficulties fitting into current legal regimes on autonomy and privacy. O'Doherty et al. has argued that biobanking regulations face several failures; privacy cannot be upheld in longitudinal data collection as this would undermine the scientific value of the biobanks, by hindering the use of the same sample on different medical research projects over time. And furthermore, individuals' consent to participate in biobanks cannot be fully informed because the very nature of biobanks is to collect samples for future research uses that may not yet be formulated.[91] In Sweden,

[89] The statement of Kaye, cited above, may be reiterated that the nationally based governance bodies in the field of biobanking do not have the legal powers or expertise to adjudicate on complex issues, such as privacy and disclosure risks that are raised by cross-border data sharing. Kaye (2011) (note 83 supra) p. 377.

[90] See further Reichel (2013b) (note 44 supra).

[91] O'Doherty et al. (2011, p. 367) and Hansson et al. (2006).

one of the largest research projects funded by the Swedish Research Council, LifeGene, was stopped by the Swedish Data Inspection Board in December 2011, due to this very reason.[92]

The way forward suggested by O'Doherty et al. is to focus on innovative governance and engagement strategies so as not to be held captive by a "contractual interpretation of informed consent documents".[93] These authors include representativeness, accountability, transparency, reflective practice and sustainability as necessary conditions for trustworthy biobank governance.[94] Within the EU, the above-mentioned expert group under the Commission has also recently published a report focusing on governance strategies for biobanks.[95] One of these governance strategies is the BBMRI-ERIC, that will be discussed in the following, last section.

6 BBMRI-ERIC—An Effective Governance Tool for European and Global Biobanking?

As seen in Sect. 2.2, Article 187 TFEU allows the EU to set up international organisations for researchers, in the form of ERICs. These consortia are neither EU authorities, nor a part of the Member States, but have their own international organisation, established by a decision of the Commission at the request of one Member States and two other countries that are either Member States or associated countries.[96] Through the consortia the Member States can jointly fund and operate research facilities, in addition to what each Member State is able to do itself. So far, three consortia have been established, Common Language Resources and Technology Infrastructure (CLARIN ERIC) and the Survey of Health, Ageing and Retirement in Europe (SHARE ERIC) and that one of interest here, an infrastructure for biobanks, Biobanking and Biomolecular Research Infrastructure (BBMRI ERIC).

The question raised here is how these ERICconsortia are to be understood. In what way can an ERIC facilitate the complex legal environment for biobanking in Europe and beyond? Before going into this question more specifically (Sect. 6.2), the functions and procedures of the ERIC will be presented (Sect. 6.1).

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92 Swedish Data Inspection Board decision December 16, 2011, dnr 766-2011.

93 O'Doherty et al. (2011) (note 91 supra) p. 369.

94 Ibid.

95 Biobanks for Europe (2012).

96 Article 9.2 ERIC Regulation. Associated country is defined as a third country which is party to an international agreement with the Union, under the terms or on the basis of which it makes a financial contribution to all or part of the Union research, technological development and demonstration programmes, article 2c. The status of associated countries was strengthened through amendments enacted in the ERIC Regulation in 2013.

6.1 ERIC Consortia: Functions and Procedures

As seen already in the introduction, the objectives for introducing the ERIC was to facilitate long term European research projects by enabling them to function under a common legal framework. In the preamble to the ERIC regulation, the importance of having common rules for governing establishment, financing and operation of European infrastructures in order to compete with the Union's global partners is underlined.[97] However, as will be outlined in Sect. 6.1.1, there are only a limited number of the activities of an ERIC that are governed by the common rules, whereas the actual research conducted within the ERIC will remain under the law of the country where the activities take place. In Sect. 6.1.2, the setting up of an ERIC will be presented. In both cases, BBMRI-ERIC will be used as an example.

6.1.1 Legal Capacities and Structures of the ERIC

Even though an ERIC is set up through a decision of the Commission, it is not an EU organ, but an independent international organisation. According to Article 7 of the ERIC regulation, an ERIC shall have legal personality and shall, in each Member State, have the most extensive legal capacity accorded to legal entities under the law of that Member State. It has its own budget and is liable for its own debts (Articles 13 and 14 of the ERIC regulation). The connection between the ERIC and EU is however strong. It is the Commission which takes the decision to establish the ERIC (Article 6) and the Commission must approve of amendments of core parts of the statutes of the ERIC (Article 11). As seen above, it is not only Member States of the EU which can become members of the ERIC, associated countries, other third countries as well as intergovernmental organisations (Article 9.1) can also become members. However, the Member States or associated countries shall hold jointly the majority of the voting rights in the assembly of members, the organ of the ERIC with full decision-making power (Article 9.3 and 12).

The ERIC must further report to the Commission and to the relevant public authorities, presumably the competent authorities in the Member States, on a yearly basis (Article 17.1). The Commission thus supervises the ERICs, not merely on grounds of financial issues, but also on the substantive work of the ERIC. According to Article 17.3–5, the Commission may on the suspicion of a serious breach of the ERIC regulation, the decisions adopted on the basis thereof or other applicable law, first request explanations from the ERIC and/or its members, then, if the Commission concludes that an ERIC actually is in serious breach of the above-mentioned legal sources, first suggest remedial actions and then, as a final resort, repeal the decision establishing the ERIC.

[97] Para. 5 of the preamble to Council regulation (EC) No. 723/2009 (note 3 supra).

This supervision does however not exclude the regular supervision on parts of the Member States where the research is actually conducted. The ERIC is thus not only governed by EU law. According to article 15 of the ERIC regulation, the setting-up and internal functioning of an ERIC shall be governed by EU law, in particular the ERIC regulation, and the decisions taken by the Commission to establish the ERIC or amend its statutes, by the law of the State where the ERIC has its statutory seat and lastly, by the statutes of the ERIC and their implementing rules. The law applicable to the activities carried out by the ERIC will in the first hand be the law of the country where the ERIC has its seat. Regulations regarding the hiring of staff, tax issues, buying and running equipment, etc. will be governed by this legal system.

An ERIC can however be either single-sited, or distributed, meaning that the ERIC will have activities in more than one state. For example, the BBMRI-ERIC has its seat in Graz, Austria, but the biobanks will be distributed to the different national nodes coordinating the national biobanks.[98] According to Article 3 of its statutes, the aim of BBMRI-ERIC is to facilitate the access to resources as well as facilities and to support high quality biomolecular and medical research. In order to accomplish this, the BBMRI-ERIC is to conduct *common services*, one common biobanking and resource service, providing procedures and standards for different types of population-based, clinical-oriented biobanks and biomolecular resources, one common information technology (IT) service, coordinating and implementing the interoperability of the existing and new biological databases of biobanks, and lastly a unit providing services within ethical, legal and societal issues that supports and supervises ethical and legal compliance within the activities of the ERIC. The law of that country where the activity is actually conducted will govern these common services. This issue is not clearly laid down in the ERIC regulation itself, but in Para. 21 of the preamble, it is stated that if the ERIC has a place of operation in another state, the law of that latter state should apply in respect of specific matters defined by the statutes of the ERIC.

The biobanks connected to the BBMRI-ERIC as well as the common services will therefore continue to be governed by a multitude of different national regulatory regimes, as described in Sect. 5. The current difficulties with consent orders and ethics reviews for each participating state will thus not be altered or facilitated by the introduction of an ERIC.

6.1.2 Preconditions for Being Established as an ERIC

The main reason for the EU introducing the ERICs as a part of the research and innovation policies was, as seen, to strengthen conditions for conducting world class research within the EU. Accordingly, in order for a research project to be

[98] See Articles 1.9 and 3 of the Statutes for the Biobanking and Biomolecular Resources Research Infrastructure European Research Infrastructure (BBMRI-ERIC).

established as an ERIC, there is a need to demonstrate that the research conducted within the project is of the highest quality, a center of excellence. In Para. 9 of the preamble to the ERIC regulation, the following is stated:

> Research infrastructures should help to safeguard the scientific excellence of Community research and the competitiveness of the Community's economy, as based on medium-term to long-term forecasts, through the efficient support of European research activities. To achieve this they should be effectively open to the European research community at large in accordance with the rules established in their statutes and should have the aim of enhancing European scientific capabilities beyond the current state of the art and should thereby contribute to the development of the European Research Area.

According to article 5 of the ERIC regulation, the Commission is to assess the application of an interested entity, including obtaining the views of independent experts in particular in the field of the intended activities of the ERIC.

Furthermore, the researcher who wishes to establish an ERIC also has to convince their respective Member States to apply for an ERIC on their behalf. As set out above, according to Article 9 of the ERIC regulation, it is the Member State, or associated state as the case may be, that is the member of the ERIC, not the actual research group or institute. It may be presumed that a Member States applying for membership in an ERIC considers the research important and may thus be willing to support it on a long term basis. As will be discussed further in the next section, this condition may in itself be valuable for the research project.

6.2 BBMRI-ERIC as a Way Forward?

Could a focus on governance regimes in the form of an ERIC be a way forward for European biobanking? If the main object was to address the problematic areas depicted in Sect. 5.2, the answer would probably be negative. The three problematic areas identified here, the fact that medical research to a large extent is regulated from a national perspective, not very adapted to the cross-border realities of the researcher, that the legal tools available at the international or even European level often are of low hierarchical value, in the form of overlapping and sometimes contradictory soft law, with a widespread use of standardised forms drafted by low-level administrative or hybrid private-public organs and agreements between researchers the principle, and lastly that biobanking in itself has difficulties in fitting into current legal regimes on autonomy and privacy, due to the very aim of research biobanks to provide biological material and health data for medical research projects over time. None of these issues are addressed by the ERIC regulation, which instead has as its point of departure not to change any of the legal regimes applicable to the actual research conducted within the ERIC and therefore does not give its participants any leeway to choose which law applies to their project.

What may then be achieved by establishing an ERIC? No hard law solutions, but perhaps soft ones, governance tools enabling the participants to navigate better

in the complex European composite administration with its unclear boundaries and competence divide. First, the aim of the ERIC in itself should be to facilitate European research and through the long term work of the project itself, some solution may occur. The BBMRI-ERIC has, as seen, common services to facilitate and develop both IT and legal and ethical solutions suitable for the research field. A part of BBMRI.eu intends to build a so-called WIKI platform where legal texts relevant to BBMRI are collected. According to its webpage, the mission of the platform is to properly embed BBMRI into the European legal framework[99]:

> The objective of this platform is to serve as a dynamic, online, grass roots platform for sharing, discussing, validating and issuing authoritative and reliable legal forms and standards to aid the BBMRI community in navigating the legal pathways that govern its pan European, cross border, multi-jurisdictional infrastructure and operations. The platform is to unearth any existing knowledge, expertise and templates currently in use by (prospective) BBMRI Members and Partners.

The text and information on the platform does of course not have a recognized legal status, despite the statement that the platform will provide authoritative and reliable legal forms and standards. However, in an area where common binding international are few, but soft law is plenty, standard-setting activities among a large group of researchers may in the long run have some normative effect.[100] The BBMRI-ERIC could further the work in a more structured manner, resulting in a bottom-up approach to rulemaking in the area of bioethics.

Secondly, the ERIC may in itself be an effective platform for influencing EU policies and a channel for communication between the ERIC and the relevant stakeholders within the European Research Area. As presented in the section above, the establishment of an ERIC can in itself be seen as a recognition of the excellence of the research conducted within the project, to which the Member States, at least hopefully, have made a long term commitment to support. As seen above, all the ERICs are to report to the Commission and to the relevant public authorities on a yearly basis. Since the ERIC regulation also established that the Commission should be assisted by a Comitology committee, in the form of a management committee (Article 20), this means that all Member States, not only the ones that are members of the ERIC, will be in direct contact with the ERIC. This might in itself be a good opportunity to explain and promote the research and perhaps also shed some light on problems connected to the research area. It might also improve the possibilities for receiving further and continued research funding from the different programmes run by the EU.

Whether these soft governance mechanisms will in the long run enhance the possibilities of developing a legitimate and transparent regime for European biobanking may be questioned.[101] A traditional point of view might be that an area

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[99] http://www.legalpathways.eu/index.php?option=com_joomlawiki (7.4.2013).

[100] Compare Ruffert and Steinecke (2011) (note 28 supra) p. 115.

[101] Reichel (2013b) (note 44 supra).

such as medical research on human biological samples, including the adjudication of several fundamental rights and important public interests, would be better regulated by involving classical actors such as democratically elected parliaments and independent courts. As long as this road is not available to any individual national parliament, neither to the EU legislator, due to lack of competence and perhaps also lack of common political will, soft governance mechanisms are what are available at the moment. The raison d'être of the European composite administration, its flexible problem solving capacities, will enable at least some level of foreseeability for the parties involved.

There are however also further issues which cannot be addressed very easily within policy areas driven by soft governance tools. As pointed out in Sect. 3.4, in the absence of the unifying functions of a government, the European composite administration, not to speak of global administrative regimes, risks dealing with one topic at the time with very little attention being paid to common interest, or even conflicting interests, with neighboring policy areas. The balancing of different interests within bioethics, as those discussed above (Sect. 5) regarding individual rights on the one hand, and public benefit on the other will be more difficult to carry out.

The question is thus how different aspects of bioethics are handled within the EU. Will the BBMRI-ERIC provide channels also to other parts of the EU political arena, such as the growing area of privacy issues? An illustrative example is the handling of the LifeGene matter in Sweden, mentioned above (Sect. 5.2). The Swedish Data Protection Board decided to stop the largest research project ever funded in Sweden, since the board found that the data subjects, who had on a voluntary basis given their health data to the research project, could not be sufficiently informed regarding the aims for the processing of the data, in order for them to give an informed consent. This is, as seen, a problem for long term infrastructures that collect samples and health data in order to use for future, not yet defined projects. The fact that LifeGene intended to use the BBMRI.se infrastructure for its samples, and thus was a part of the same area of research that ESFRI and the Swedish Research Council have been eager to support did not seem to carry any weight.

Another example from the same policy area is the current redrafting of the Data Protection Directive, which is proposed to be enacted in the form of a Regulation.[102] As discussed is more thoroughly in the chapter The New General Data Protection Regulation—Where Are We Are and Where Might We Be Heading? of this book, the proposal introduces a stricter regime for processing personal data, including what seems to be a more limited exemption for research with health data without informed consent. However, even without these apparent restrictions on possibilities to conduct medical research on health data, there are new and innovative mechanisms in the governance structure that may also prove to

[102] COM (2012) 11 final (note 52 supra). See also chapter The New General Data Protection Regulation—Where Are We Are and Where Might We Be Heading? in this book.

be challenging for the biobanking community and BBMRI-ERIC, however less obvious. The proposed regulation introduces an administrative structure where national supervisory authorities, with the assistance from the Commission and a new European Data Protection Board (EDPB),[103] will be given an independent role in the enforcement of the data protection policy area (Reichel and Lind 2014, 30–32). In Article 53 of the proposal, the national supervisory authorities are to be given investigative power to obtain all necessary information from the entities handling personal data, i.e. the controller and the processor, as well as access to the premises, as well as authority to engage in legal proceedings. In order to guarantee a consistent application throughout the Union, several steps are taken to ensure that the supervisory bodies will cooperate. There is a specific duty to give each other mutual assistance and engage in joint investigative tasks, joint enforcement measures and other joint operations (Articles 55 and 56). Furthermore, now a consistency mechanism has been introduced, where the supervisory authorities may raise unresolved issues to the Commission which, after hearing the EDPD, may issue an opinion on the matter.

All together, the administrative structure established to uphold privacy issues is strong, which is underlined by the fact that the supervisory authorities act with complete independence in exercising the duties and powers entrusted to it (Article 47 of the proposal). That is, also independent from their national government and parliament. This tendency, to tie national authorities close to the Commission in order to safeguard an effective and loyal cooperation, has by Egeberg been referred to as 'agency capture'.[104] In the heterogeneous and fragmented European composite administration, where different policy areas have developed administrative structure quite independently from each other, there is an obvious risk of fragmentation also affecting how the content of the regulatory regimes is interpreted and further developed. What may be a bit worrying from the point of view of the biobanking community is if the constructive balancing between individual rights and public benefit advocated by Stjernschantz Forsberg will be difficult to achieve in an administrative structure all devoted to one of the two sides. The question is whether this administrative structure for privacy issues will be open to communicate also with other organs, representing other standpoints. Will the channels of communication provided by the BBMRI-ERIC be able to reach the proposed administrative structure around data protection and privacy?

One possible way forward could be to further the responsibilities of the Commission to take an overarching role in the European composite administration, in order to achieve the unifying functions of a government. It may however be questionable if this is suitable. In general, it would lead to a federalization of the composite administration that would hardly be legitimate, accountable or even efficient, taking into account the broad spectrum of policy areas and the

[103] Replacing the current Article 29 Data Protection Working Party, Para. 110 of the Preamble to the proposed regulation.

[104] Egeberg (2006, p. 14).

manifold potential conflicts of interest. Especially within the area of research, given the limited competence of the EU, this solution does not seem possible. Another way could be to promote transparency, participation and deliberation, or with an administrative term a right to be heard, in combination with a right to an efficient judicial review in individual matters. The strong administrative structure for privacy issues must be open for constructive dialogues with representatives within the civil—and public[105]—society in a structured and transparent manner. This route has been followed by the European Court of Justice in other areas of the European composite administration where balancing of conflicting interests must be handled, especially the classic internal market area.[106] Within legal doctrine it has further been argued that these principles could be used as vehicles in the process of legitimating governance beyond the state,[107] or at least in order to assess the legitimacy of global administrative regimes.[108] In the ongoing work of redrafting the EU legislation these issues should be considered closely.

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[105] The divide between public and private is not easily upheld in the European composite administration, as in global administrative regimes all together. Even though BBMRI-ERIC consists of Member States, it is far from obvious that their interest will be taken into account automatically by other parts of the Member States or the composite administration.

[106] For example, Case C-205/99 *Analir* v. *Administración General del Estado* [2001] ECR I-1271; Case C-63/94 criminal proceeding against *Sanz de Lera* [1995] I-4821; Case C-24/00 *Commission* v. *France* [2004], ECR p. 1277; Case C-438/02 *criminal proceeding against Hanner* [2005] ECR I-4551; and Case C-341/05 *Laval un Partneri* v. *Svenska Byggnadsarbetareförbundet* [2007] I-11767.

[107] von Bogdandy (2012). See also Mendes (2011).

[108] Kingsbury et al. (2005).

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A Bold Experiment: Iceland's Genomic Venture

David Winickoff

1 Introduction

In 2008, like an overheated nuclear reactor, Iceland's banking sector melted down. After investors pulled money out of Iceland *en masse*, the Icelandic government took control over the last and largest of the country's three major banks and shut down the stock exchange. On October 9, 2008, the *New York Times* reported that "Iceland's financial system collapsed," with a University of Iceland professor stating for the record that "Iceland is bankrupt… The Icelandic *krona* is history." A fact-finding team from the International Monetary Fund had been in Iceland all week and had enacted an emergency financing system, expediting loans to the country (Pfanner 2008). Reykjavik, where two-thirds of Iceland's 300,000 people live, had been the center of one of the world's fastest economic booms. It was now the site of one of its greatest crashes. But out of the ashes grew hope: on November 20, 2008, Iceland received international backing in the form of a $2.1 billion loan by the International Monetary Fund and an important guarantee by a group of Scandinavian countries (Jolly 2008).

Like the Icelandic economy, deCODE Genetics Inc.—the progenitor of modern genomic biobanks and a touchstone for other major population genomics initiatives around the world—has emerged from bankruptcy. Built on technological advances in the late 1990s and a bold entrepreneurial vision, the company helped transform medical and genealogical information into a new type of commodity. Their scientific and social innovations—or more precisely, the controversies they

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have spawned—also helped precipitate the development of global norms governing the relations between citizens, medical information, markets, and the state.

By scientific standards, the company is widely regarded as a success: deCODE has reported many markers for diseases such as diabetes, heart disease, and cancer, and has published widely in top journals such as *Nature* and *Science* (Kaiser 2009). However, by the time the Icelandic economy imploded, deCODE Genetics already had long-standing financial problems. The business model proved to be shaky: genetic variants are often quite rare, and account for very little variation, reducing their utility as drug targets or genetic tests. As anthropologist Mike Fortun has argued, deCODE's value has always been—similar to the biotech industry as a whole—highly speculative and predicated on promises (Fortun 2008).[1] Desperate for more immediate revenue streams, the company launched "deCODEme" in November 2007, becoming one of a handful of private companies offering customers a personal view of their genetic code and an analysis of certain traits, diseases markers and drug sensitivities. Like its competitor and predecessor in the personal genomics business, "23andMe" of California, "deCODEme" claims to provide insights into disease variants and geographical origins.

Despite these strategic turns and with mounting liquidity problems, deCODE Genetics filed for bankruptcy on November 17, 2009. But just as the Icelandic banks found financial angels a year previously, so did the company. On January 21, 2010, deCODE emerged from financial limbo when two U.S.-based venture capital companies took over the company. DeCODE stated that would it continue conducting genetics research and gene-based diagnostics, but that it would cease efforts to develop drugs from its discoveries. Earl Collier—an attorney and previously vice president of Genzyme and a member of deCODE's board of directors—would be its new CEO. The company's previous CEO and notorious co-founder, Dr. Kari Stefansson, would be the new head of research.

Until the company was acquired, there was wide speculation as to what would happen to the biobank itself. One company official said the company had been "talking to a whole range of present and potential customers and partners from pharma to biotech to government and academic groups" (Fortun 2008). Clearly, deCODE's biobank had become a "private asset," but the venture had started as a unique blending of public and private: through an enabling statute and commercial license, deCODE would gain access to national health records for collection, storage and research; in exchange, the country would get a national electronic health record system, and the allure of a biotechnology sector that might retain Icelandic scientists. In the process, the legislation would try to create a new kind of public-private biotech company. DeCODE continues to find genetic factors, and lives on as a commercial enterprise, but this bold public-private experiment was a failure. It remains important to narrate the life and death of Iceland's so-called National Health Sector Database (HSD) project, for it retains important meanings for large-scale biobanks today.

[1] This book is an important in-depth look at deCODE with an anthropological lens (Fortun 2008).

2 Iceland's Health Sector Database Act

In December 1998, the Iceland Parliament passed the Act on a Health Sector Database (HSD Act) by a vote of 37–20, with 6 abstentions. The Act set out a new regime for the control of citizen health information in a modern democracy. Such information was at once declared a "national resource" to be controlled by the state, and allocated to private industry for inclusion into a commercial genomic database of national scope. The Act immediately took on international significance and has been written about widely by journalists and scholars alike.

The core of the Health Sector Database Act (HSD Act) was the authorization of the database's creation and operation in Iceland by the private sector licensee, with a reversion of the computerized health data to the state after the license term.[2] The license to operate the database could be granted for a renewable term of no more than 12 years and had to meet the requirements of Iceland's Data Protection Commission, which had been created by a previously enacted privacy law. DeCODE Genetics secured the license to create and operate the HSD in 2000, but this was a *fait accompli* from Bill's earliest days. Notes from the Bill state that the idea for the database initiated with deCODE and Kari Stefansson, and the company reportedly drafted the first version of the bill as early as the summer of 1997.[3] DeCODE's plans to link the health data with genetic and genealogical information were widely known, although the Act itself said nothing about biological samples or DNA, and did not mention genealogical records.

The Act authorized the licensee to use the data for profit, but it provided for the protection of privacy in a number of ways. First, the licensee could not grant direct access to the database or information it contained to third parties. Second, it would have to process the information itself in ways that could not be linked to identifiable individuals. The Act provided that the licensee may be civilly liable for negligent disclosure of information and authorized other penalties, including fines, imprisonment, and possible revocation of the license for violations, by the licensee or others, of the Act, the license, or government regulations under the Act.

The HSD Act's most controversial provision authorized the transfer of all medical record data to the licensee for commercial development without the express consent of individuals, invoking a rule of "presumed consent." Further, information of the deceased would be automatically be included, despite the potential privacy interests of relatives and individuals. Icelanders had 6 months after the passage of the act to opt-out of the database unconditionally, a provision that had

[2] Act on a Health Sector Database no. 139/1998 (Passed by Parliament at 123rd session, 1998–1999). Art. 1, http://ministryofhealth.is/laws-and-regulations/nr/659#allt.

[3] A Bill on a Health Sector Database was first submitted to the Althing in March 1998, and debated at several sessions. There was immediately strong opposition to the bill from large sections of the clinical and biomedical research communities in Iceland, which led to the Bill's withdrawal. A second draft of the bill was introduced in late June 1998, with a number of changes. This version was the one that was enacted in December 1998.

only been added to the Act after the initial version drew significant criticism for its lack of informed consent. The new version also specified a more rigorous encryption architecture for the health information, and provided for lower fees for non-commercial access to the database.

A small and vocal percentage of Icelandic civil society objected, and strenuously. The Icelandic Medical Association publicly opposed both iterations of the HSD Bill for what it saw as its ethical short comings: the failure to protect the rights of research subjects to have informed consent, the lack of a mechanisms for subjects to withdraw from the database once they are entered in, and the monopolistic aspects of the license.[4] Furthermore, a small network of physicians, scientists, human rights activists, intellectuals, and patient activists formed a group in opposition to the HSD ACT called Mannvernd. Mannvernd's English subtitle was the Association of Icelanders for Ethics in Science and Medicine. The Icelandic word *mannvernd* means "human protection," and this captures the organizing idea of the group, namely that the "Health Sector Database Act infringes on human rights, personal privacy, and on accepted medical, scientific and commercial standards."[5]

Despite the development of a network of scientists and doctors organized into opposition to the HSD Act, the law was passed as noted above in December 1998. By claiming the authority to transfer to a commercial entity the medical information of all Icelandic citizens, the government imposed a new regime of control of Icelandic medical records. One important legal effect was to sever the ability of doctors to prevent their health institutions from handing over patient medical data without their authorization. The directors of health institutions would be empowered to negotiate all transfer of information, without review by any independent ethics committees, the normal ethical requirement for accessing medical records for research. At the same time, the government claimed the power to provide access to the medical information, and indeed to license it for commercial use: because the state paid for the medical care giving rise to the data, the state may control and "exploit" that data for the benefit of Iceland. Rhetorically, the Act both denies that medical data can be owned, but this language is mere formalism: access, use, and control are nothing but the traditional components of property.[6]

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[4] Tómas Zoëga. 1999. Interview by Paul Wouters. Science Channel, Netherlands. Transcript on file with author. Zoëga was Chair of the Ethical Council of the Icelandic Medical Association at the time. In response to the Icelandic Medical Association's opposition to the Bill in the summer of 1998, David Oddsson remarked that "privacy standards were so lax in Icelandic health institutions that it was hypocritical of the IMA to oppose the HSD Bill on the grounds that it threatened the doctor-patient confidentiality." See Skúli Sigurdsson, "Yin-Yang Genetics, or the HSD deCODE Controversy," *New Genetics and Society* 20, no. 2 (2001), 103–117.

[5] Mannvernd, "about Mannvernd," www.mannvernd.is/english/. Accessed Spring 2006. Website currently inactive.

[6] The Notes to the Bill state that "[d]ue to the nature of the data and their origin [Icelandic health records] cannot be subject to ownership in the usual sense. Institutions, companies or individuals cannot therefore own the data [because t]hey exist primarily due to the treatment of patients." Bill on a Health Sector Database (Submitted to Parliament at 123rd session, 1998–1999). On file with author.

In effect, the state reduces the complex web of legal interests around the medical data by cutting off the doctors, and asserts the power to license, a property interest (Winickoff 2003).

By December 1998, the critics had been effectively neutralized by the passage of the HSD Act. The path was paved for deCODE's exclusive commercial access to the trove of medical data on all Icelanders, and the essential conditions for construction of the Health Sector Database had been established. But we have yet to explain how such a political stroke was accomplished.

3 The Birth of the Health Sector Database

The passage of the Health Sector Database Act, was a watershed event as much for the fields of genomic research, venture capital, and bioethics as it was for Icelandic society: in one unprecedented stroke, a national parliament had authorized the transfer of citizen medical information to a private corporation for commercial exploitation and development, and without the a priori permission of individual citizens. Here we explore how such a coup for Stefansson, CEO of deCODE, could only be achieved through the effective enrollment of Iceland's natural and social history in its business plan.[7] With a national heritage in tow, the business narrative would in turn have to persuade American venture capitalists and their scientific advisors, a majority of Icelandic MPs, and the public itself that their interests necessarily lay in the passage of the Health Sector Database Act. The effectiveness of Stefansson's pitch lay in its versatile ability to address the most pressing problems of these key constituencies.

3.1 Enrolling Iceland's Natural and Social History

Stefansson's genomic vision of Iceland was predicated upon a single compelling theory, namely that Iceland was likely to be a very valuable place to hunt for genetic factors of common human diseases. This hypothesis was supported by a set of foundational claims about Iceland's natural and social history. First and foremost was the idea that Icelanders were a genetically homogeneous people because of their historic isolation. In a 1995 business plan, and in language that would be echoed throughout the debates about the HSD Act, Stefansson wrote,

> Iceland is a small island in the North Atlantic which was inhabited between the years 870 and 930 AD, mostly by Norwegian entrepreneurs and Irish slaves. The year 1000 AD [sic], the population was around 70,000 but around the year 1410 AD the Plague had reduced it down to approximately 30,000. The population had again grown to about 70,000 when

[7] The tale of the passage of the Health Sector Database Act has been told many times, but seldom well. For important exceptions (Rose 2001; Sigurdsson 2001, 2003; Fortun 1999).

> at 1700 AD Hekla, the most powerful volcano in the history of Europe, spew lava and ash all over Iceland which led to a famine that reduced the population again down to approximately 30,000. Today, the population of Iceland is 270,000 and they are almost all derived from the original settlers or 30,000 of their descendants who lived in the country around the year 1410 AD and another 30,000 who lived in the country around the year 1710 AD. Therefore, the Icelanders are genetically a homogeneous people and they display a strong founder effect; by following genetic markers it is possible to trace a common origin of a large proportion of them (Stefansson 1994).

This was not a simple claim of genetic homogeneity, but one embedded in a colorful natural history of the Icelandic genome replete with plagues, volcanic eruptions, and famines. Stefansson draws a powerful connection between the founder effect[8] that helps make Iceland attractive for gene hunting, and the founders themselves. Although the "facts" of Icelandic homogeneity would become contested within the pages of top science journals as the HSD controversy developed,[9] the idea of homogeneity played powerfully both inside and outside Iceland.

Second was the existence in Iceland of intricate and detailed genealogical records. In its early business plans, Stefansson touted the existence of a lineage database for 100 % of Icelanders back to 1910 and 85 % of Icelanders back to 1800, and explained how this would make it "relatively easy to determine relationships between participants or subjects in genetics studies done in Iceland."[10] A third foundational claim was the existence of high quality medical records dating back to the beginning of the Icelandic national health service in 1920, many of which were "centralized and accessible." Hence, the business plan explained, "it is relatively easy to find a match between genotypes of Icelanders and whatever genetic traits are reflected in their diseases or health."

As Stefansson and company representatives would explain over and over again to Icelanders, foreigners, and investors alike, these factors gave Iceland an advantage for discovering new genetic factors for disease. If all three resources—Icelanders DNA, genealogies, and the phenotypic data—could be linked together, it would create a uniquely powerful tool for conducting genetic linkage studies as well as allelic association studies. This tripartite and integrated database was the technological bore that would locate genetic diamonds in the rough. The scientific logic was simple: with fewer variations in alleles because of genetic homogeneity, it would in theory be easier to identify candidate genetic variations that

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[8] Defined by Ernst Mayr in 1963 to be the genetic effect of establishing a new population by a small number of individuals, carrying only a small fraction of the original population's genetic variation and whereby the new population may be distinctively different, both genetically and phenotypically, to the parent population from which it is derived.

[9] The ways in which the company's factual claims about Iceland's genetic homogeneity came under attack will have to be saved for another article. While Stefansson used such claims to naturalize his business narrative, some Icelandic geneticists later attacked these claims as factually incorrect, both in public talks and scientific studies (Árnason et al. 2000; Árnason 2003; Abbott 2003). DeCODE's scientists countered with more of their own studies (Helgason et al. 2003).

[10] deCODE Business Plan, 8. These records already existed due to what one Icelandic anthropologist has described as an Icelandic "fascination" with genealogical trees and family histories that is "extreme" (Pálsson 2002).

were associated with disease. And the idea of folding health data, genetic data, and the genealogical information—compiled through generations of Icelanders—into a single resource was as culturally compelling to venture capitalists as it was to Icelanders. It was a powerful symbol of Iceland itself.

3.2 Enrolling Venture Capitalists

The mid-1990s were boom years for venture capital, and biotech investors and their scientific advisors were looking for big ideas that would solve big problems. One of the big scientific and political problems facing genetics in the mid-90s involved how to translate the massive amount of new genetic code being generated by the public human genome projects into discoveries and therapies. Gene hunting was turning out to be harder than anticipated: it proved to be difficult to identify specific genetic variants that caused common diseases, thus shifting the understanding of disease to polygenic and epigenetic models of causation. Some argued that in order to sort out more complex mechanisms, larger populations of people manifesting both health and illness would need to be sequenced, studied, and compared. Taking a "population" approach to genomics would not have been imaginable even a few years previously, as doing such studies at the desired scales required recent advances in DNA sequencing and information technology that gave birth the nascent field of "bioinformatics."[11]

What was needed were promising populations of research subjects upon which these new tools could be turned. As Stefansson put it in his business plan, "it is a commonly held view that the next big steps in the genetics of human diseases will be taken by those who have access to the most suitable populations rather than by those who ask questions, or develop new technologies." Stefansson was correct that major powerhouses of human genetics, both in academia and in industry, were searching for the appropriate populations on which to apply these new tools and that Icelanders would be appealing. A now famous letter to Stefansson dated 26 May 1995, Kevin J. Kinsella, the President and CEO of Sequana Therapeutics and already involved in the gene hunting business,[12] adopted Stefansson's naturalized account of Iceland's genomic potential:

> As we discussed, Iceland is perhaps the ideal genetic laboratory since there has been virtually no immigration, … it is of manageable size (200,000+ inhabitants), is an island expected to have many founder effects, has high quality national healthcare – from which we can expect excellent disease diagnosis, has formidable genealogies and the population is Caucasian – of most interest to pharmaceutical companies.[13]

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[11] These technologies included PCR and high-through-put sequencing (Rabinow 1996).

[12] Sequana Therapeutics at that time was a young biotechnology company with a strong venture component. It merged with Arris in 1997 to form AXYS Pharmaceuticals, which in turn was acquired by Celera Genomics.

[13] On file with author. Also quoted in Greely (2000).

Stefansson managed to raise roughly $12 million in U.S. venture capital in an initial round, and on this strength, another $25 million from Icelandic institutional investors.[14] In 1996, *Red Herring*, a prominent U.S. technology business magazine, declared Stefansson one of their "entrepreneurs of the year," (Rose 2001) and deCODE became a Delaware corporation. Stefansson's ability to raise this seed money indicates that the biotech venture firms and their scientific advisors were convinced that Iceland's population was potentially a unique resource for untangling the complex genetic factors of disease, and for addressing the new problems for translation emerging from the American-led human genome project.

Presenting Iceland as a promising solution to the problem of finding a population was perhaps enough to achieve a first round of major venture funding, but that raised another problem that would have to be solved before large institution investors came on board: the problem of *enclosure*.[15] In short, even if the Icelandic population—with its comparative homogeneity, its genealogies, and its health records—presented a promising opportunity to find disease factors when they are all thrown together, how could these common resources be packaged in such a way as to attract investment? What would give deCODE an advantage over some other highly capitalized biotech firm in order to engage in this gene-hunting venture?

Stefansson realized that some sort of exclusive privatization agreement with Iceland's health ministry and government authorities would an indispensable piece of any business plan—for therein lay deCODE's particular competitive advantage. Just exactly what that arrangement would look like became clear when the firm reportedly faxed the first draft of the Health Sector Database Act to Iceland's Ministry of Health in 1997[16]: the authorization of the Icelandic government granting an *exclusive* licensee the power to create and operate a database containing health record information of all Icelandic citizens for commercial biomedical research and the now famous regime of "presumed consent." Other companies would have to work through individual informed consent, a much more time consuming process that would yield fewer participants. This ingenious proposal was not a direct act of enclosure, as the medical records in paper form would still be freely available to other researchers. But the Health Sector Database Act amounted to an indirect act of enclosure—a regulatory subsidy that would cost the nation nothing out-of-pocket, yet confer deCODE unique terms of access to a newly imagined commons.

In Fall 1997, the draft of the Bill on a Health Sector Database had not been made public, but Iceland's Prime Minister, David Oddsson was already publicly declaring his support for deCODE's plans to build a genotypic-phenotypic-genealogical

[14] DeCODE Genetics, "Public Corporate Summary Sheet" (2000). On file with author. The original U.S. venture firms to commit included Advent International, Alta Partners, Atlas Venture, Arch Partners, Falcon Technologies, Medical Science Partners, and Polaris Venture Partners.

[15] For a useful account of the enclosure movement in its historically land-oriented form and in its recent expansion into informational realms, see Boyle (2003).

[16] This information is contained in Gudni Jóhannesson's treatment of the deCODE history in Icelandic (Jóhannesson 1999).

database, even in the face of traditional ethical restraints (Rose 2001). In February 1998, deCODE struck a deal with Hoffman-LaRoche, then the fourth largest pharmaceutical company in existence, for rights to discoveries derived from their existing work. David Oddsson reportedly "passed the pen" between the two companies for their meeting in Reykjavik. This deal was worth a reported $200 million in benchmark payments over 5 years, and gave deCODE and Stefansson national celebrity status and global recognition.[17] But it remained to convince the Icelandic Parliament, and the Icelandic public, that granting access and use rights to deCODE on an exclusive and "presumed consent" basis was a good idea. As we will see, enrolling U.S. venture capital and global pharmaceutical giants went a long way towards this challenge.

3.3 Enrolling Politicians and the Public

Commentaries regarding the passage of the HSD Act have espoused different theories as to why the majority Independence Party carried it through the *Althing*, and why the Iceland people seemed to go along. DeCODE was better able to control the public discourse through a US-style publicity campaign in which critics were out-muscled and out-maneuvered, and passage reflected the confluence of strong lobbying by deCODE, a strong parliamentary majority, and party discipline.[18] But to read the passage of the Act merely as a case of special interest politics would miss something crucial. Specifically, it would miss the important ways in which deCODE's rhetoric addressed the central political problem of Iceland as it looked towards the 21st century. This was the pressing problem of survival itself: how could such a remote island society best leverage its natural and social resources in order to remain a viable sovereign nation in the global order?

Icelandic society has sought independence throughout its long history. Whether it has been the Norwegian or Danish monarchy, raiding Vikings, or the modern behemoths of the European Union and the United States, Iceland has struggled

[17] Benchmark payments are of course conditional upon achieving those benchmarks, although this $200 million was often spoken of as if it were hard cash.

[18] Anthropologists Gísli Pálsson and Paul Rabinow consider the 9-month debate leading up to the passage of the Act to be a model in terms of democratic engagement and deliberation (Pálsson and Rabinow 1999, 2001). Other commentators have been deeply critical of this position (Sigurdsson 2001). See also Michael Fortun, "Open Reading Frames: The Genome and the Media" stating that "the vast majority of those hundreds of media accounts that are cited as evidence of a democratic debate in Iceland were little more than dressed-up deCODE press releases issued on a regular basis, passing on messages about jobs for Icelanders, predictions of wealth in the national coffers, and pieties about how Iceland would contribute to the improvement of world health and the universal progress of biomedical research" (Fortun 2001). Reprinted in *After the Fact*, the publication of the Institute for Science and Interdisciplinary Studies (Summer 2001) and by the Council for Responsible Genetics, http://www.gene-watch.org/genewatch/articles/14-6fortun.html.

with foreign political determination.[19] The HSD Act passed because deCODE's theory spoke boldly to the nation's deepest aspirations and fears about survival and independence in the global economy. For some years, fishing has provided 70 % of export earnings and employed 4 % of the work force and the Icelandic economy remains vulnerable to declining fish stocks as well as to fluctuations in world prices for its major exports: fish and fish products, aluminum, and ferrosilicon. But since the mid-1990s, Iceland had started a concerted campaign to develop new economic sectors such as information technology, financial services, and tourism. Biotechnology was emblematic of the sort of knowledge-based industry that Iceland's Independence Party viewed as a solution, and deCODE was poised to launch this sector. And for its part, the Progressive Party in Iceland, which controlled the Health ministry and was part of the majority coalition, was more than willing to be led by this vision, perhaps convinced that this was a cheap way to computerize Iceland's health system.

Politicians could also make the argument that helping build a strong deCODE would stem the tide of brain drain that many feared was weakening the island nation. Stefansson had created his commercial laboratory near Reykjavík by November 1997 to be operated under deCODE's Iceland subsidiary, Íslensk Erfðagreining (IE), and in a short amount of time the company had spent more on research than the Icelandic Government's entire annual research budget, roughly $65 million. The consequences of "brain drain" are not only economic, of course, but also social: families find themselves pulled apart. The idea of the tri-partite genomic database—weaving together as it does individuals and families, past and present, into a single entity—presented a potent symbol of collective strength. The theme of solidarity, through the idea that deCODE could help keep families together, was invoked to outweigh abstract notions about the autonomy, patient-doctor confidentiality, and the erosion of scientific integrity.

The HSD Act's critics had trouble effectively countering the economic, political and cultural strength of the deCODE-Independence Party alliance. Pétur Hauksson, a psychiatrist and human rights advocate, led Mannvernd in its efforts to criticize the project in the public sphere when the Icelandic Minister of Health, Ingibjörg Pálmadóttir introduced the first version of the Bill to the *Althing*. For Hauksson, the Bill was illegal both under Iceland's right to privacy[20] as well as under the Helsinki Declaration and the Nuremberg Code, international human rights norms that lay out the need for informed consent in human subjects research. He and others saw how a healthy majority in Icelandic society may be under-valuing the need for privacy and control of medical information because

[19] The most famous novel of Icelandic Nobel Laureate Haldór Laxness, *Independent People*, deals with this theme, linking one farmer's struggles to remain financially independent to questions of national character and collective independence. See Einar Árnason and Frank Wells, "Iceland and deCODE: A Critique," in *Encyclopedia of the Human Genome* (who mention Iceland's "fear of engulfment" (Árnason and Wells 2003).

[20] Icelandic Constitution, Article 71 ("everyone has the right to respect for his private and family life and his home"), http://government.is/constitution.

they lacked their own sensitive medical histories of sickness and/or mental illness: it was these sensitive members of society that constitutional rules of privacy and autonomy were meant to protect vis-à-vis majoritarian decision-making. Although some individual doctors broke rank to support the Bill, the leaders of the Icelandic Medical Association agreed with Mannvernd, giving the opposition a boost from a highly respected national professional association. But, deCODE was simply able to build a larger network of supporters in Parliament and Icelandic society than Mannvernd, largely because of its demonstrated ability to raise investment capital, and the power of its economic promises.

But not only so. DeCODE's successful appropriation of cultural tropes and resources reimagined Iceland, while constructing a future for it. In political debates and interviews, Stefansson could invoke the historic struggles of the Icelandic people with a brutal physical environment, and give these common histories new meaning and new value. These same hardships now made the Icelandic genome a valuable commodity in the global economy. What might seem to outsiders as a peculiar practice, the tracing of genealogical connections through countless generations, now became a lynch-pin of a cutting-edge biomedical technology. A common set of Icelandic founders had passed their genetic markers down through the generations, producing a key element in a new collective history of Iceland. But just as importantly, the database's narrative of aggregation and social linkage provided a powerful cultural symbol of an integrated, independent, and modern people.

4 The Death of the Health Sector Database

> In light of the development of our business since the Agreement was entered into, the lack of the required agreement with the [National University Hospital] and the fact that the Icelandic Data Protection Authority has not issued the required security certification, we do not expect to operate the IHD [i.e., the combined database] under the terms of the Agreement.[21] (deCODE Genetics in its SEC financial disclosure statement for the fiscal year ending December 31, 2003)

By June 2003, roughly 20,000 Icelanders or 6.67 % of the population had opted out of the Health Sector Database. While this was taken as a signal of general discontent by Mannvernd, it is unlikely that this fact would have shaken the company. The rate of opting out dropped sharply after deCODE received the Health Sector Database operating license in the summer of 2000, which was shortly before the company launched a successful initial public offering on NASDAQ. Nevertheless, little over 3 years later, deCODE disclosed to its public investors that it had no expectation of ever constructing or operating either the Health Sector Database or the tri-partite "minable" database containing

[21] United States Securities and Exchange Commission, Form 10-K, fiscal year ended December 31, 2003, 49.

health, genealogical and genetic data. Although the company publicly blamed the National University Hospital and the Data Protection Commission, the failure to reach deals with these institutions were only the proximate cause of the failed Health Sector Database. The national database failed to materialize because the Act triggered an international normative controversy and could not, ultimately, satisfy an emerging consensus within and without Iceland about the norms that should govern the new population genomic research. This in turn caused crucial members of deCODE's assemblage to drop out of the network required to produce the database.

4.1 The Critics' Network Expands Internationally

While the network of critics of the Health Sector Database Bill had been insufficiently strong to sway the Independence Party-Progressive Party majority or galvanize the Icelandic public against the Bill, the passage of the HSD Act helped trigger a small explosion of international scrutiny and criticism. An early salvo came in a *New York Times* op-ed by the eminent population geneticist at Harvard, Richard Lewontin, who provocatively declared that Iceland had just transformed "its entire population into a captive biomedical commodity" (Lewontin 1999). As major news outlets covered the story of the law, a volley of criticism came in the form of letters to the editor and op-ed pieces, many of them from Icelandic expatriates (Andersen 1999). By April 1999, leadership of the Icelandic Medical Association had taken the case of the HSD Act to the World Medical Association (WMA) and at a meeting in Chile, the WMA declared that it stood "fully behind the position taken by the Icelandic Medical Association in opposing the Icelandic Healthcare Database legislation recently passed by the Icelandic Parliament." The WMA governing council underscored "the need to protect the integrity of patient data and to have open access to all scientific data, and urged "all national medical associations and governments to ensure that science is furthered by continued research that in no way breaches medical ethics and patient confidentiality" (WMA 1999).

By the summer of 1999, claims and counterclaims by company officials and HSD Act critics filled the opinion pages of the elite international science magazines (Andersen and Árnason 1999; Gulcher and Stefansson 1999; Chadwick 1999, 2000). The network of critics had become international, and the debate became distinctively normative: were there existing standards of informed consent that applied to this type of research? Did the act really commodify the bodies of Icelanders in an ethically problematic way, and was the ethos of sharing health data in biomedical research under attack? During this period, both sides of the debate would have to attempt to master the intricacies both of existing international rules and of information encryption architectures. And although the debate began to play out at a high level of technicality, at stake was the very reformulation of sovereign power, individual rights in personal medical information, and the claims of patient-doctor confidentiality.

4.2 Normative Ambiguity and the Proliferation of Debate

Although those on both sides of the debate tried to claim traditional bioethical norms to support their positions, a few years of hindsight have made one thing obvious: the information-driven population genomics paradigm envisioned by deCODE was a new sort of research that did not fall comfortably within pre-existing bioethical norms of informed consent or pre-existing legal rules on the protection of personal data. A high profile exchange in the *New England Journal of Medicine* from summer 2000 between the top deCODE officers and George Annas, an internationally-known professor of bioethics and law from Boston University, illustrates the terms of the emerging international debate. Stefansson and Jeffrey Gulcher, then the Chief Scientific Officer of deCODE, argued forcefully that "presumed consent" with the opt-out provision was justified and legitimate in Iceland for three main reasons. First, they argued that an exogenously imposed notion of individual consent should not trump the democratic will of a sovereign nation: the passage of the Act after "vigorous debate in Icelandic society" indicated the "community consent" to the opt-out compromise. In essence, they argued from a position of cultural specificity rather than universality with respect to this sort of project, stating that "norms may vary from one society to another and may change with time," and that democratic will should rule.[22] Second, they argued that in fact, "presumed consent is the standard used in research on health care data that is produced in the process of delivering medical service," adding that "it is not certain that we would have health care as we know it today if explicit consent had been a prerequisite for the use of medical data." Third, they argued that privacy concerns could be managed effectively through information encryption technologies rather than the use of individual rights as prophylaxis. Here Gulcher and Stefansson argued that since the social identification numbers from the medical records would be encrypted by the Icelandic Data Protection Commission, which received its charge under the Iceland's Privacy Law, the information would actually be more protected than it was in non-encrypted paper form, sitting in files within health institutions.

George Annas, a strong advocate of the special sensitivity of genetic information and proponent of genetic privacy in the United States, acknowledged that "research on data from medical records that cannot be linked to individual patients has often been considered an exception" to the "general rule" of informed consent for all human subjects research. In this sense, he admits that the project does not break, at least in a flagrant way, existing bioethical norms. However, he also stated that the "commercial nature of the data bank and its for-profit agenda" militated for the requirement of explicit informed consent in this case. Thus, Annas seemed to stake out a more moderate position than Mannvernd and the Icelandic Medical Association with respect to the pre-existing requirements of informed consent for

[22] It is interesting to note that this idea of cultural context and democratic will was adopted by a pair of cultural anthropologists studying the controversy, one from the University of Iceland, the other from University of California at Berkeley. See note 16.

the use of health records from the medical record. His position was predicated on the assumption that the information banked in the database would be "unlinkable" back to the medical record. Since the Health Sector Database Act seemed to authorize the use only of "non personally-identifiable health data" by the licensee, this was a fair assumption.

Mannvernd and the Icelandic Medical Association were operating under a different assumption, one derived from plans for data protection publicly released by the government in the legislative appendix to the Act. The IMA commissioned Ross Anderson, a Lecturer in the Cambridge University Computer Laboratory, to analyze the proposed design for the database. Anderson concluded that as a matter of logic, deCODE and the Data Protection Commission would be using a system of coded identifiers that necessarily allowed linkage: if the planned database was to be updated on an ongoing basis Linkage had to be preserved (Anderson 1999). This longitudinal updating of the database was one of the key features touted by the company, for in this way the database could track disease progression and differential response to pharmaceuticals over time. Furthermore, Anderson emphasized an inherent limitation of de-identified databases, namely that many patients could be identified by partial information of their circumstances, especially for a database that will contain comparatively few individuals and also links genealogical records. If the information turned out to be linkable without an unreasonable amount of effort, then existing international informed consent standards would seem to apply.

Ross Anderson's opinion came in the context of politicized debates over technical aspects of both the proposed encryption technology and the proper legal standard governing the use of "non-identifiable personal information." In a series of law articles written at the time, legal experts came to different opinions on the question of the HSD Act's legality, in part because there was ambiguity with respect to three issues: first, what was the proper standard of de-identification required under the HSD ACT? Second, what was the standard of de-identification of personal data required to avoid needing a priori consent under European data protection laws? Third, did the encryption architecture proposed by deCODE meet both of these standards? There was reasonable disagreement among knowledgeable jurists within and without Iceland on all three of these issues.[23] The Health Sector Database Act was based on the premise that all data would be made "non personally-identifiable," which usually means coded but linked to identifiers. But, the Notes to the Bill evince an assumption that all banked data would lack a coding "key," and would therefore effectively be "anonymous."[24] Furthermore, legal experts could disagree as to whether the proper criterion of non-identifiability under the European law was anonymity, which seemed to require the complete absence of any possibility of

[23] For an overview of the thorny legal questions and conventions involved, see Arnardóttir et al. (1999), Abbing and Roscam (1999).

[24] The proposed encryption architecture was contained in Appendix VI of the Bill on a Health Sector Database, and had been prepared by an Icelandic information technology company, Stiki hf. See Arnodóttir, "The Icelandic Health Sector Database," 332, n. 73.

direct or indirect linkage, or merely "reasonableness"—under which data would be considered "non-identifiable" if identification required an "unreasonable amount of time and manpower."[25] In this context, Ross Anderson's expert assessment was important because he denied that the proposed architecture could possibly satisfy even the lesser "reasonableness" interpretation of non-identifiability.

Soon after deCODE received the operating license in 2000, relations began to become tense between the company and the Icelandic Data Protection Commission (DPC). The DPC was responsible for overseeing rights of privacy and data protection in Iceland, and under the terms of the Regulations promulgated under the HSD Act was in charge of setting the technology, security and organizational terms under which the database would be constructed and used by deCODE.[26] By 2002, the company was struggling with the data protection requirements that the DPC was imposing, stating in its annual SEC filing that these requirements were proving to be "expensive and time-consuming and may delay the development of the Icelandic Health Sector Database and the deCODE Combined Data Processing system or make such development more expensive than anticipated." One important area of disagreement lay in how deCODE's customers would access the data. DeCODE's business plans called for the marketing of access to the Health Sector Database by pharmaceutical and biotechnology firms directly over the internet. The DPC refused to authorize the release of data for this purpose, on the grounds that the proposed web-based searching tool would insufficiently protect the identities of the data sources: they predicted that the system would allow users to deduce the identities of individuals through data linkage to genealogies, and through non-coded demographic information.[27] This was precisely the concern raised by IMA and Ross Anderson years before, but now it was threatening to stall the implementation of the HSD Act indefinitely.

4.3 A Shifting Business Paradigm

The company's failure to bring the Data Protection Commission and the IMA leadership into line certainly was an impediment to constructing the database, but by 2002 the company might have been looking for a way out of its obligations under the HSD license. In 2000, deCODE had described itself as a "genomics and health informatics company" for which the Health Sector Database would be a central selling point for investors. By 2002, deCODE had repackaged itself. Although the database and bioinformational services side of its business were still

[25] This standard comes from *Recommendation R (97) 5 on the Protection of Medical Data*, pursuant to the 1981 *Council of Europe Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data*.

[26] Icelandic Government Regulation on a Health Sector Database, Article 30.

[27] DPC personnel, in discussion with the author, Reykjavik, July 2003.

discussed in its annual report, deCODE's more traditional family-linkage studies had been scientifically productive, yielding a number of potential new genetic factors involved in peripheral arterial occlusive disease (PAOD), schizophrenia, and stroke. DeCODE had some cash on hand, and looked to acquire smaller biotech companies that were selling at discount amidst the technology flop. In early 2002, the company acquired MediChem Life Sciences, Emerald BioStructures, and Encode—companies that provided fee-for-service work in the drug discovery process including running clinical trials—as part of a shift in strategy to capture more of the upstream value from these research efforts. By 2002, deCODE described itself as a diversified "biopharmaceutical company" with greater vertical integration in the drug discovery chain, in which the future potential of the operating the Health Sector Database was a smaller part.

The somewhat vague conception of how the national database itself would actually generate revenue must have seemed much less attractive to biotech investors after the dot-com bubble burst. Many biotech companies with large and speculative research investments, floated on hype and speculation, had folded or been acquired by larger pharmaceutical companies as debt accumulated and revenue failed to materialize. At some point, deCODE must have realized that its core research efforts should focus on its traditional family linkage studies that were still yielding some results, rather than on building an expensive database with only speculative value.

Furthermore, deCODE had found a way to amass large amounts of health information and samples by traditional methods, methods that did not require building the HSD architecture for Iceland. By the time the company filed for 2002, it was still touting the advantages of gene hunting in Iceland, but a remarkable shift had taken place: instead of speaking about the national three-part database whose centerpiece was the Health Sector Database license, deCODE explained that in addition to assembling the computerized genealogical database, it had assembled a large set of "genotypic and detailed medical data from more than 90,000 volunteers, one of the world's highest-throughput genotyping facilities, and statistical algorithms and software systems … developed for storing this data and mining it for correlations between genetic variation and disease." Rather than trying to rely on health institutions to transfer the medical data, the company explained that "all genetic and medical data being used in the company's gene research has been obtained under the strictest standards of informed consent" and that "approximately 95 % of all those who are asked to take part in our genetic studies agree to do so."[28] These filings from 2002 illustrate an important reason why the company could declare its willingness to abandon hopes of building the Health Sector Database: the company was compiling a large trove of medical information, but only through the more tedious and piecemeal process of getting individual consent.

[28] United States Securities and Exchange Commission, Form 10-K, fiscal year ended December 31, 2002, 7.

4.4 The Icelandic Supreme Court

The Health Sector Database and its regime of presumed consent may have received its death knell on November 27, 2003, the day the Icelandic Supreme Court rendered judgment in the case of *Gudmundsdóttir versus Iceland*.[29] The case concerned a young woman who wrote a February 2000 letter to the Icelandic Health Ministry requesting that the information contained in her father's medical records, and any genealogical or genetic data on him that might exist, not be transferred to the Health Sector Database. The Medical Director of Health had obtained a legal consultation by government lawyers, and based on this opinion denied her request: the HSD Act text was silent on this issue, but the Notes on the Bill had stated that it was not the legislative intent to allow children to opt-out their deceased parents.[30] Gudmundsdóttir initiated legal proceedings in April 2001, claiming that she had a personal interest in preventing the transfer of data from her father's medical records to the Database "as it is possible to infer, from the data, information relating her father's hereditary characteristics which could also apply to herself." The Icelandic District Court ruled that the medical information included in the database was not personally identifiable and that Gudmundsdóttir lacked standing to challenge the inclusion of her father's information in the database.

The Icelandic Supreme Court reversed on the standing issue, granting that she had a personal privacy interest in her father's medical data. But the court went much further. Noting that Icelandic medical records were required by law to contain extensive information on people's health, their medical treatment, lifestyles, social circumstances, employment, and family, the court held that "[i]t is unequivocal that the provisions of Paragraph 1 of Article 71 of the Constitution"—the provision that "everyone shall enjoy freedom from interference with privacy, home, and family life"[31]—apply to information of this kind and … "guarantee protection of privacy in this respect." Although the court agreed with the District Court's conclusion that the "one-way encryption discussed in" the HSD ACT "could be carried out so securely as to render it virtually impossible to read the encrypted information," the Act made no indication "as to what information from medical records must be encrypted in this manner prior to transfer." The annex to the operating license "impl[ied] that only the identity number of the patient will be encrypted in the database and that the name, both of the patient and his family, together with the precise address will be omitted." However, the "vague limits" set by the provisions of the Health Sector Database Act inadequately provided for the protection of Gudmundsdóttir's constitutional right to privacy, and so her right to opt-out her deceased father's health information was affirmed.

Less than 4 months later, deCODE Genetics Inc. filed its annual report for 2003, in which it stated it did not plan to operate the Health Sector Database under the terms

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29 *Gudmundsdóttir v. the State of Iceland*, No. 151/2003 (Nov. 27, 2003) (Ice.).

30 Ibid. at Sect. I.

31 Icelandic Constitution, Article 71, http://government.is/constitution.

of the Health Sector Database Act and the license. Effectively, the national database to be constructed through presumed consent and transfer of health information was a dead letter. The demise of the database was certainly precipitated by the recalcitrance of the National University Hospital, the IMA, and the failure of the company to reach agreement with the Data Protection Authority. The company's diminishing estimation of the national database's business value was also a likely factor.

Nevertheless, the construction of the HSD under the terms of the Act was ultimately undone by the emergence of consensus, in both local and external institutions, that a priori consent of patients should be indispensable for engaging in this type of research in all but the rarest exceptions. These were not simply technical disputes, but cut to the core of the relations among individuals, clinical health institutions, markets, and the state. As I will explore briefly in the next section, the normative development around genomics that occurred through the Iceland case constituted an important innovation in its own right: for these developments have laid the groundwork for genomics programs across the globe.

5 Legacy and Implications of the HSD Controversy

The history of the Icelandic Health Sector Database has shaped the technological, political and normative terrain of all large-scale genomics initiatives today, not just Iceland's. The extent to which the Icelandic HSD controversy reached distant shores, and activated international commentaries that in turn fed back into national and international bioethical debates, demonstrates how the Icelandic Health Sector Database became an experimental site not only for genomics, but for genomic governance as well. In this sense, both these new genome projects and their governing norms are an important piece of the Icelandic Health Sector Database's legacy; further, Iceland provides an important window on the process of innovation in the life sciences, illustrating the ways in which technological, normative, and politico-economic changes occur within a mutually dependent system.

5.1 Multiple Innovations of Global Significance

Many genomic projects, national in scope, have been drawn up in explicit attempt to follow Iceland's lead (Kaiser 2002). For instance, the CARTaGENE project in Canada plans to sample 1 % of all Quebec citizens between the ages of 25 and 74 to represent "the entirety of the population" for a study of "the genetic contribution to the health and illness of the entire Quebec population."[32] In 2000, the Parliament of Estonia passed an Act to "regulate the establishment and maintenance of a Gene Bank, to organize the genetic research necessary therefore, to ensure the voluntary nature of

[32] See CARTaGENE website, http://www.cartagene.qc.ca/.

gene donation and the confidentiality of the identity of gene donors." In 2002, the United Kingdom, the Medical Research Council, the Wellcome Trust (a private charitable organization) and the Department of Health funded the creation of "UK Biobank," a longitudinal prospective population genomics study to involve roughly 500,000 adults aged 45–69 from the general population of the United Kingdom.

If other countries looked explicitly to Icelandic genomics as a model for state-supported life science, they also held out the Health Sector Database Act as a negative example of how to handle consent and other ethical and legal aspects of state-sponsored genomics. As other countries sought to enter the population genomics game in various configurations, at least one aspect was constant: Iceland's Health Sector Database Act was invoked as a bad model for handling consent, and the norm of informed consent was described in more or less detail. But this is only part of the important constructive role the HSD played in producing the normative conditions in which genomics operates today. As policy consultants for UK Biobank observed in 1999, "much of the recent international discussion of the issues raised by the use of biological sample collections has been stimulated by developments in Iceland …" (Martin and Kaye 1999). Indeed, the Iceland debates became an important channel through which the stakes of individual consent and patient-doctor confidentiality were clarified and reframed in relation to issues that were new to the world of biomedical research.

The novel contexts presented by population genomics included the linkage of different forms of personal information, exclusive commercial licensing of data and databases, encryption architectures, and propriety claims of the state over medical information. There was no pre-existing answer to question of how the traditional principle of informed consent should adapted to the genomics context, even though parties to the Icelandic Health Sector Database dispute claimed otherwise. Rather, they would have to emerge through legalistic interpretation, technological specification, and active negotiation and deliberation between disparate groups at different scales of governance.

It is clear that this process of norm construction and development was non linear, and that interaction through social networks at national and international levels operated as a dynamic system. Before the regime of presumed consent had been rejected within Iceland itself, it had helped precipitate an emerging global consensus that the "technological fix" of a thick encryption architectures would not replace affirmative consent from individuals prior to their enrollment in these population genomics projects. As an indicator of the development spurred by the HSD ACT, the World Medical Association promulgated a "Declaration on Ethical Considerations Regarding Health Databases" that attempted to codify these emergent norms in 2002.[33] These emergent norms of personal control of medical information fed back

[33] In this Declaration, the WMA affirmed as its first principle that "the right to privacy entitles people to exercise control over the use and disclosure of information about them as individuals," and that "[t]he privacy of a patient's personal health information is secured by the physician's duty of confidentiality." Further, it was affirmed that as a general rule, "patient's consent is needed if the inclusion of their information on a database involves disclosure to a third party or would permit access by people other than those involved in the patients' care".

into the Iceland, and likely helped persuade the Data Protection Commission as well as the Icelandic Supreme Court that Iceland's presumed consent regime was incompatible with the operation of the national database as originally conceived. But in the process, the Icelandic Supreme Court took up the mantle of innovation. Its recognition of the collateral privacy rights of Gudmundsdóttir in the health data of her father was a bold legal innovation that has reverberated abroad.[34] For these reasons, one could be completely justified in the view that the Iceland HSD case has a globally important *normative* legacy, as much as a *technological* one.

5.2 Biotechnology, Nationhood and Global Order

There persists a tendency to suppose in hindsight that technological development occurs on a linear path and according to a trajectory determined more by material factors and some uniform notion of human ingenuity than through its social conditions. Sociologists of science and technology have for some time been arguing that technological change cannot be seen in isolation from the social forces that shape it, whether they be economic, normative, psychological etc. (Winner 1986; Bijker and Law 1992; Sclove 1995). This work tends to suggest that the precise form that technology takes in the world is contingent on the kinds of social work that go into it. The story of the life and death of the Health Sector Database illustrates this latter description of the innovation process. The same powerful narrative that helped persuade the Independence Party to support the Health Sector Database Act had already drawn a network of venture capitalists into its fold. As Stefansson realized, establishing the exclusivity which the Act seemed to provide allowed the company to attract international attention and more investors. Without national sponsorship of the project, it is doubtful that Stefansson would have been able to raise the large amounts of speculative capital necessary to set up his laboratories in the suburbs of Reykjavik.

The significant normative and political impediments to implementing the national database shaped genomic technology in Iceland as much as the passage of the Act. The fact that many doctors refused to relinquish control of the data for ethical reasons, and that the Data Protection Commission ended up taking a stricter view on encryption than anticipated, forced the company to focus on its more traditional familial linkage approach, rather than the non-hypothesis driven shot-gun correlation approach associated with the tri-partite database. This strategy has become the most fruitful research path for deCODE scientifically, and the expensive construction of a national-level database with the greater degree

[34] As an example of the rulings international reach, the *Harvard Law Review* featured an extended case note on the case heralding the fact the "Gudmundsdottir Court appears to be the first to recognize that someone other than the source of genetic information—the proband—has a legally cognizable privacy interest in the proband's information." Recent Cases, *Harvard Law Review* 118 (2004), 810–817.

of de-identification demanded by the Act would have set the company on an alternative, and arguably less promising, trajectory.

But there is a deeper story that Iceland tells about the interpenetration of science, technology and society, one that is relevant to the politics of the nation state in an era of globalization. The story of the life and death of the Health Sector Database manifests the extent to which science and technology have become, or are at least widely seen to be, *constitutive* of modern nationhood itself. For the Independence Party, the HSD Act was part of a larger strategy for nation-building and maintaining national independence in the face of a global economy and global politics that threatening to engulf Iceland. Indeed, the debates between proponents and opponents of the Health Sector Database Act were arguing not only over technicalities of encryption architectures and European Data Protection law, but also over different visions of the nation itself.

Proponents were drawn to the ways in which the Health Sector Database promised to reinvent the nation by drawing together powerful and existing cultural resources (common histories, cultural practices like genealogy, traditions of science, fierce independence) and transposing them into a new key. In order to underwrite future economic growth and survival, a bold new reconfiguration of state-science-market would need to be born in Iceland—only through this alchemy could Icelandic genes be transformed into the next natural resource for Iceland. The Act, with its regime of presumed consent, exclusivity and privatization, were a simultaneous means of creating the new resources and maximizing its extraction value to Iceland.

For its critics, the Health Sector Database Act represented a critical departure from the codes of modern science and modern democracy, the very principles that made Iceland a strong and modern nation. Adherence to these codes accounted for the impressive standing Iceland already enjoyed at the international level as viable modern democracy, one capable of producing top scientific researchers and an enviable health care system. As a general matter, critics within the medical and scientific establishment in Iceland looked to an idealized ethos of science as a model for the Icelandic polity. The traditional scientific ideals of skepticism, disinterestedness, shared property, and universalism created optimal conditions for preserving individual freedom and organizing collective action.[35] For the members of Mannvernd, most of whom were scientists and physicians, the Health Sector Database Act signaled the state-sanctioned departure from these ideals, for the plan dangerously embraced a naive scientific hype, commercial dominance, and the privatization of common cultural and scientific resources. Many critics saw an erosion of Icelandic democratic order embodied in an attack on scientific order,

[35] These idealized norms were classically formulated by the sociologist Robert K. Merton in his essay "The Normative Structure of Science" (Merton 1973). For the classic statement of the thesis that "science" is a model polity, see Michael Polanyi, "The Republic of Science" (Polanyi 1962). For excellent modern treatments on the constitutive role of science in modern democratic order, see Yaron Ezrahi, *The Descent of Icarus: Science and the Transformation of Contemporary Democracy* (Ezrahi 1990).

corruption of the state within the corruption of science. For some, science and state were being reconfigured in such a way that threatened to destabilize the social and political order that underpinned Iceland's claims as a Western liberal democracy, and which helped knit Iceland into the fabric of global political culture.

Whereas one vision argued that what the nation needed was to take bold collective action to provide the optimal economic and regulatory conditions for one biotechnology company to take root, the other vision saw ethical, social and political costs of leveraging Icelandic biotechnology in this way. This side perhaps saw that the route to modern Iceland, and even to genome nation, were not one, but many; and that the Health Sector Database Act sacrificed too much with regard to individual rights and the existing ethos of science and medicine in Iceland.

The fact that these two visions for Iceland clashed so starkly should not overshadow what they had in common: for both proponents and opponents, science and technology were both symbolic and practical resources for the production of the polity. This powerful insight animates political struggles in many other nations as they look to the frontiers of the life sciences, both scientific and ethical, as opportunities and vehicles for nation-building. Stem cells in South Korea and the creation of "Biopolis" in Singapore are just two other examples. The Icelandic Health Sector Database controversy certainly prefigures these emerging cases. It also underscores how smaller nations and their innovations, not just those of the major powers, can and do become critical sites for the formation of global order.

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The Estonian Genome Center, University of Tartu

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1 Introduction

The Estonian Genome Center, University of Tartu (EGCUT) was incorporated as a research and development institution at the University of Tartu, Estonia, on the first of April 2007.

Until November 2009, the EGCUT was known as the Estonian Genome Project. This name was changed because the EGCUT is not only a data storage facility but is also a research institution, which collaborates closely with the Institute of Molecular Biology and Biotechnology at the University of Tartu.

The EGCUT is a large-scale, population-based biobank. The idea of establishing a national gene bank was proposed by Professor Andres Metspalu with two purposes in mind: to identify disease-causing genes by comparing genotypes within a group of patients with a certain disease, and to set up a healthcare database that would give Estonians access to their own data, so that they could benefit from personalised medicine in the future. The systematic collection of data and blood samples has resulted in a database which enables the discovery of new information about genes that cause and influence common diseases. This knowledge helps to improve individualised treatment and determine the risk of developing certain diseases in the future.

The gene bank database includes phenotype and genotype data from the Estonian population that are used to conduct scientific research and genetic and health studies in order to find the genes that cause and influence common diseases.

The data are collected by general practitioners and data collectors in participant recruitment offices. In the data collection procedure, a tissue sample is collected and a questionnaire about the participant's genealogy, lifestyle and health is filled out.

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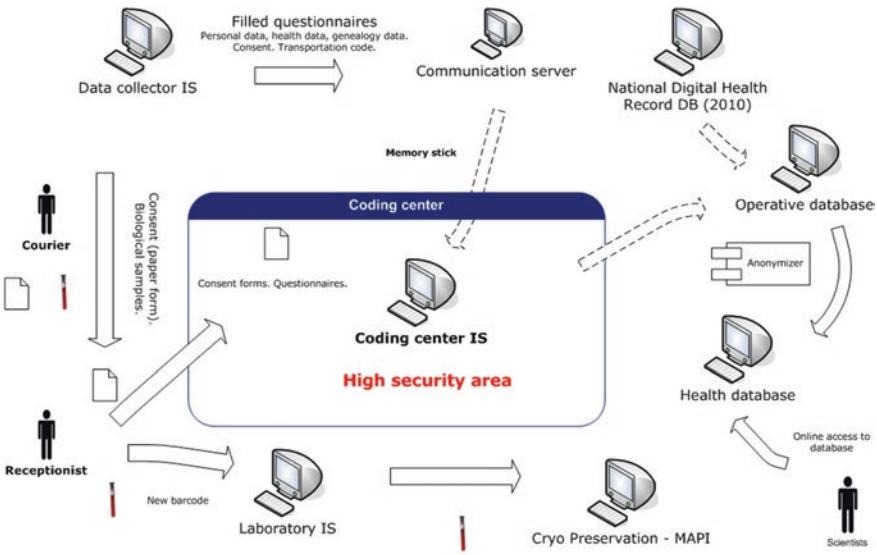

Scheme 1 Data and sample collection at the Estonian Genome Center, University of Tartu

To ensure the participants' confidentiality, the EGCUT has a double-coding system—the first code is a temporary transportation code assigned by the data collector, after which the personal data are separated from the other data and the transportation code is replaced with a unique code by EGCUT employees.

The monitoring and quality system (MQS) of the EGCUT was set up to verify that:

1. The rights of gene donors are protected.
2. The data presented in questionnaires are exact, complete and verifiable on the basis of the initial data.
3. All procedures are performed in accordance with the law and other regulation acts.

The MQS checks that the data in the EGCUT database are in accordance with the initial data in medical records and other databases (Scheme 1).

2 The Structure of Governance at the EGCUT

The EGCUT is registered in a database of research and development organisations at the Ministry of Education and Research of Estonia.

The director of the EGCUT is elected to office for a five-year period by the University government, and the seven to nine members of the supervisory board are appointed for 5 years by the rector of the University of Tartu. These members comprise the director, and representatives from the Faculty of Science and Technology and the Faculty of Medicine plus others as required by the EGCUT director. The EGCUT director is the chairman of the supervisory board.

The EGCUT also has an international steering committee, whose five members meet once a year to assess the development plan and its progress.

The quality management system certificate ISO 9001:2008, which regulates all standard operating procedures (SOPs) performed by the EGCUT and authorised processors and data collectors, has been in place since 2003.

3 Historical Overview: From Private to Public

The original project was presented to the public and politicians in 1999 after the Estonian Government reached an agreement that the planning of the project could begin. The Estonian Genome Project Foundation was developed by the Government of the Republic of Estonia in 2001. The first data were collected in a pilot project in October 2002. From 2001 to 2004, the project was a public-private partnership. The private investor funded the project through the company EGeen Ltd, which had a twenty-five-year licence to use the anonymous data in the biobank.

By the end of 2004, the database contained a little more than 10,000 tissue samples and phenotype data entries.

In 2003, conflict arose in the Estonian Genome Project. The vision for the gene bank's activities differed between the investors and the public sector. The private sector wanted to concentrate more on specific disease groups but the public sector wanted to continue the creation of a population-based biobank. In November 2004, the licensing and financing contract with private investors and with the company EGeen was terminated. The activity of the Genome Project stopped for a few years, as extended negotiations between scientists (under the leadership of Professor Metspalu) and politicians endeavoured to find a way to finance it, to continue data collection, and to achieve the goals developed in 2001.

This discussion ended in 2006 when the Government of Estonia approved a budget to cover these costs (to begin in 2007), and the project was incorporated into the University of Tartu. Active data collection was then restored and, by the end of 2009, the EGCUT database included more than 41,000 tissue samples and phenotypes. Initially, funding was obtained from the Estonian Government through three ministries: the Ministry of Social Affairs, the Ministry of Education and Research, and the Ministry of Economic Affairs and Communications. However, now that the active data collection phase is complete, the activity of the EGCUT is financed by the Ministry of Social Affairs alone. The EGCUT is now a publicly funded biobank.

4 Legal Framework: The Human Genes Research Act and Other Regulatory Activity of the EGCUT

The activities of the EGCUT are required to be based on internationally acceptable norms of ethics and good practice in order to protect the rights of participants and guarantee the success of the project by avoiding fragmentation of societal solidarity and ensuring public acceptability and respectability. The data collected by the

EGCUT will be useful for a very long time and can be used repeatedly, since there is no expiry date for its use. As the developments and opportunities of genetic research are unpredictable, it was seen necessary to regulate the process of data collection for the genetic database.

Legal regulations were prepared by an international workgroup under the leadership of Bartha-Maria Knoppers. The Human Genes Research Act (HGRA) was founded on two international regulations dealing with genetic research: UNESCO's Universal Declaration on the Human Genome and Human Rights (1997) and the Council of Europe's Convention on Human Rights and Biomedicine (1997). The HGRA was prepared in 1999 and was passed by the Parliament of Estonia on December 13, 2000.

According to the HGRA and the Data Protection Act, the chief processor of data for the EGC is the University of Tartu and the data also belong to the University of Tartu (HGRA Chap. 3 article §15).

The HGRA was passed because it ensures the confidentiality and privacy of each participant. The main goals of the HGRA were to regulate the maintenance of the EGCUT, to organise the necessary genetic research, and to protect people from misuse of their genetic data and discrimination based on the interpretation of the structure of their DNA and any genetic risks arising from that.

The main provisions of the HGRA were to describe:

1. the conditions for processing tissue samples, descriptions of DNA, descriptions of the state of health and genealogies in the gene bank;
2. the rights and obligations of gene donors, the chief processor and other authorised processors of the gene bank, and of genetic researchers, in relation to tissue samples, descriptions of DNA, descriptions of the state of health and genealogies;
3. the conditions for the establishment and maintenance of the gene bank;
4. the restrictions on the use of tissue samples, descriptions of DNA, descriptions of the state of health and genealogies collected by the gene bank; and
5. the conditions for genetic research in relation to the gene bank and the organisation of its supervision.

The HGRA stipulates how to ensure the autonomy, confidentiality and privacy of the participants. In particular, the process of data collection should be performed only after obtaining informed consent from the donor. Partial or conditional consent are not valid.

Respect for the autonomy of the individual is described in chapter Biobanks: A Definition of the HGRA. Firstly, the confidentiality of the identity of the gene donor is protected by double-coding the data, and only the gene donor has the right to disclose his or her identity. The fact of whether a person is or is not a gene donor remains classified. It is also prohibited to influence a person's decision to become a gene donor, including threatening the person with negative consequences, promising material benefits or providing subjective information. Gene donors have the right to request the destruction of their materials and to withdraw their consent to be a gene donor.

The gene donors have the right to know or not to know their genetic data results. They also have the right to personally access their data stored in the EGCUT, but they do not have the right to access their genealogies. The last clause prevents the disclosure of sensitive information, for instance information about paternity.

One issue that has caused much debate and argument is the promise of providing feedback to the gene donor—participants have the right to obtain genetic consultation from the EGCUT about their personal data, and they also have the opportunity to obtain their genetic data and to learn about their risk of developing diseases. However, the participants may not benefit from the project directly, although benefit could arise from the development of medicines or techniques available to society.

The HGRA prohibits the discrimination of gene donors by employers or insurance companies on the basis of the structure of the person's DNA and the potential genetic risks resulting from this, and also prohibits discrimination of individuals on the basis of their being a gene donor or not. The EGCUT does not collaborate with judicial authorities or forensic structures. Nor can the EGCUT be used for surveillance.

The HGRA stipulates criminal conviction if there is coercion to become a gene donor, if secret and confidential information is disclosed, if discrimination occurs, or if illegal human genetic research is conducted.

The HGRA also allows people who are not capable of giving informed consent to become gene donors if they have legal representatives. This issue initially caused some dispute between scientists and ethicists because of the question of allowing children between the ages of 7 and 17 years to donate tissue samples and health-record data to the EGCUT. Based on international conventions, for example the Council for International Organisations of Medical Sciences and the World Medical Association Declaration of Helsinki, it has now been agreed that children cannot be included in the EGCUT databases.

The HGRA is the over-riding law for regulating the activity of the EGCUT. As far as other legislations are concerned, the procedures of the EGCUT should follow the Data Protection Act and the Public Information Act.

The EGCUT data collection and database rights are registered by the Data Protection Agency and the EGCUT consequently has the right to process personal and sensitive data.

5 Informed Consent and Privacy Protection

Participation in the gene bank process and donation of biological material and data is a voluntary process.

The participants are required to sign the Gene Donor Consent Form (GDCF), which provides written informed consent for the clinical information collected about the donor to be used for scientific purposes. Consent is obtained from the donor at the preliminary meeting, where relevant information and explanations are offered and voluntary participation in the EGCUT project is confirmed. The GDCF contains eleven points itemising the gene donor's basics rights. The GDCF newsletter, which is provided with the consent form, explains the procedure in detail and helps the donor to understand the aspects related to the EGCUT better.

Essentially, the GDCF obtains broad consent (also known as open or blanket consent). The form was developed in accordance with the HGRA and was confirmed by decree of the Minister of Social Affairs in 2001, at which time it set a precedent. Discussion on the best way of obtaining fully informed consent relating to biobanks is currently widespread in many countries. While full notification of individuals is problematic because no-one can predict the future of human genetic research, the future public benefits of gene research could be significant.

According to the HGRA, individuals should be fully informed about the following issues: the purpose of the establishment and the activities of the EGCUT; that becoming a gene donor is a voluntary process and that discrimination is prohibited; that the gene donor is not able to demand a fee for providing the EGCUT with data and allowing the use of that data for research, transferring the rights of ownership to the University of Tartu; that they have the right to access their own results (except for genealogy); how data are decoded and how they may be contacted later; and that they have the right to withdraw consent and to request the destruction of their data and biological material.

The GDCF notifies the participants that the anonymous data could be given out from the EGCUT to groups conducting genetic research and that the EGCUT has the right to link the data to other databases to obtain information on the state of health of the participants.

After signing the GDCF, the person gives permission for tissue samples (venous blood) to be taken and fills in the health state questionnaire. The completed genealogy information, personal data and tissue samples are then coded by the EGCUT and used for genetic research.

The participant should also receive information about foreseeable harm and risks before their consent. In order to minimise these risks, the EGCUT subscribes to the chapter in the HGRA that describes the prohibition of discrimination among participants, obtaining informed consent, and keeping personalised information secret.

The data that are collected by the EGCUT are personalised. In order to protect the privacy of the participants, the EGCUT uses a double-coding system and stores the coded biological material separately from the phenotypes and personalised information. The GDCFs containing identifiable data and the phenotype database are stored in a special room in the Coding Centre. Only a few employees of the EGCUT have access to this centre.

Researchers can receive data for genetic research in coded form only.

If a gene donor withdraws their consent and requests the destruction of the biological material and data, the EGCUT is obliged to follow a strict protocol, confirmed by decree of the Minister of Social Affairs.

6 Using Data Collected by the EGCUT

The HGRA states that the EGCUT may be used only for scientific research, research into and treatment of illnesses of gene donors, public health research, and statistical purposes.

The data stored in the EGCUT belong to the University of Tartu, which is the chief administrator of the EGC. The data can be given out for scientific research only in coded form. Applications for using the data can be submitted by scientists from the Republic of Estonia and by foreign researchers as well. The chief administrator of the EGC has the right to charge a fee for using the data.

Before the data are released, the scientific projects must be approved by the ethics committee. From 2002 to 2004, the activities of the Estonian Genome Project Foundation were assessed by its own ethics committee. The role of this committee was to counsel the supervisory board on ethical questions. However, the question of independence was raised and the ethicality of the procedures and scientific projects of the EGCUT are now assessed by the Ethics Committee on Human Research of the University of Tartu, which is an independent, multidisciplinary body with members from various fields of life.

After the research project has been approved by the ethics committee, it must then be approved by the Scientific Advisory Board of the EGCUT before the contract is signed. This board, which comprises four members appointed by the Supervisory Board of the EGCUT, evaluates the scientific validity of the research to be conducted with the EGCUT data.

The procedure for issuing data has been laid out by decree of the Minister of Social Affairs. A material transfer agreement protocol, which reflects points of conduct between the EGCUT and the third party and establishes that the results are to be returned to the EGCUT, is also required.

When tissue samples are sent abroad for scientific research, the EGCUT is required by law to apply for permission from the Government of Estonia. This requirement could be seen as being too protective since the University of Tartu collaborates only with generally acknowledged scientists and, as described above, the projects are already required to pass through several stages of evaluation before they are approved. However, most countries also have regulations regarding genetic research and international rules are well accepted.

The EGCUT has applied to the Parliament of Estonia to change this paragraph. It is suggested that a reasonable solution would be for the Council of the University of Tartu to have the right to give permission for sending tissue samples abroad, since this would make the data issuing procedures more flexible.

7 Conclusions

The creation of the Estonian Genome Project in 2001 was an innovative event in the foundation of large-scale, population-based biobanks. During its first three years of activity, the project succeeded in gaining the trust of the public. However, subsequent discussions among politicians, ethicists, the public and scientists were vigorous and occasionally heated. It was particularly difficult for trust to be established between society and the geneticists. One of the difficulties was the minimal public awareness about genetic research in Estonia, as in many other countries. After the withdrawal of funding for the Estonian Genome Project Foundation

and the subsequent failure of the Genome Project itself in 2004, many published articles criticised the business model used, for which funding mostly came from the foreign private sector.

When negotiations with the Government of Estonia resulted in continued funding and re-establishment of the Estonian Genome Project, one condition was that the project was to be incorporated into the University of Tartu.

Starting data collection again after a three-year break was extremely difficult. The EGC had lost the trust not only of society but of the general practitioners as well. A large number of general practitioners ceased to collect data for the biobank. The EGCUT had to establish another data collection network through participant recruitment offices.

Two years into the second period of data collection, in 2009, public awareness and trust in the EGCUT was higher than it had been over the previous eight years.

Despite all the obstacles, by 2009 the EGCUT had collected sufficient data to move to the next phase—use of the data for genetic and epidemiological research while continuing to update the database. In that year, the EGCUT was involved in almost 30 international scientific projects.

Although it has not been a smooth process, establishment of an Estonian biobank has now been achieved. Both private and public models of governance were used in the process, and good legislation and a strict ethical framework now assure the sustainability of the EGCUT as a publicly funded, large-scale, population-based biobank (Dierickx and Borry 2009; Gottweiss and Petersen 2008; Lunshof et al. 2008).

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Management of the Ethical Aspects of a Local Mental Diseases Biobank for Research Purposes: The Italian Experience

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1 Introduction

Recent developments in genetics have furthered large-scale genetic research efforts as well as the creation of large biological banks at international, national and local levels.

The scientific value of biobanks is evident, in that the possibility of using a large number of biological samples will increase genetic knowledge and allow future studies on the same samples to be planned, which is not currently conceivable. The constitution of biobanks is of necessity based on human values; in fact, it is hoped that the progress of biomedical science and practice—which essentially depends on research involving human biological materials—can contribute to fighting diseases and improving the quality of human lives (Porteri and Borry 2008).

Nevertheless, the creation and management of biological banks raise profound ethical and legal issues concerning informed consent, confidentiality, the ownership of biological materials (and related information), access to the biobank, commercial interests and discriminatory use of the research results (Godard et al. 2002).

Sensitivity to the ethics of the issues raised by the creation and management of biobanks and by biological research in general has greatly increased in recent years, but regulations concerning the storage of human biological materials and genetic data are still evolving in most European countries; there are many variations in the definitions, scope and purposes of guidelines and legal instruments (Zika et al. 2008).

The need for a regulatory system for biobanks is clear, as is demonstrated by the efforts of committees and societies dealing with research on biological materials in different countries. In Italy, this is exemplified by the documents

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and guidelines of the National Bioethics Committee (Comitato Nazionale per la Bioetica—CNB), the National Committee for Biosafety, Biotechnology and Sciences of Life (Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita—CNBBSV), the Italian Society of Human Genetics (Società Italiana di Genetica Umana—SIGU) and the Telethon Foundation (Fondazione Telethon) (SIGU 2003; CNBB 2006; CNB 2006, 2009).

Gaps in the regulations pertaining to the collection and storage of biological materials in a biobank, at least in the European context, made the writing of local guidelines essential from an ethical point of view.

However, until very recently, the elaboration of local guidelines for obtaining, using and storing biological materials in a biobank has been an exception in Italy, as in all the European countries.

The aim of this chapter is to present a concrete experience of regulation of the ethical aspects related to the constitution and management of a biobank for research purposes in the field of neuropsychiatric disorders, as set up in an Italian institute for research and care.

2 The Fatebenefratelli Biobank

The Scientific Institute San Giovanni di Dio Fatebenefratelli is a Scientific Institute for Research and Care (IRCCS) of national relevance. Its mission involves translational research (from bench to bedside) in the rehabilitation of patients with dementia or other psychiatric disorders.

A genetic and biological sample bank has been set up in the Institute. The collected biological material consists of DNA, RNA, plasma, serum, liquor and fibroblast (skin cell culture) samples.

Up to 2,500 samples have been collected in the field of neurodegenerative disorders: these come from donors affected by different forms of dementia, mainly Alzheimer's disease. In the psychiatric field, the bank has collected 1,800 samples from donors affected by schizophrenia, depression, bipolar disorder and personality disorders. Six hundred samples come from subjects suffering from both dementia and behavioural disorders. Healthy controls have contributed almost 1,500 samples to the biobank.

The collected biological materials are used to identify genetic and/or biological patterns which could help in the early, differential diagnosis of neuropsychiatric disorders and in the discovery of novel and more precise treatment options, as well as in the assessment of genetic mutations and susceptibility genes that could be associated with the development of neuropsychiatric disorders. The peripheral tissues (plasma, serum, blood, RNA and fibroblasts) that are collected are employed in transcriptomic, proteomic and biochemical studies for the identification of biomarkers and in vitro models used for the personalisation of pharmacological and nonpharmacological therapies in patients with mental disorders.

From an ethical point of view, the biobank is regulated by the ethical code for the use of biological materials for research or experimental purposes, as elaborated by the ethics committee of the Institute (CEIOC; 21 March 2002).

3 The Ethical Code for the Use of Biological Material Elaborated by the Ethics Committee (CEIOC)

The first draft of the ethical code for the use of biological material for research purposes was developed by an interdisciplinary working group that included members of the ethics committee as well as researchers from the Institute. The code was then discussed and approved in plenary meetings of the ethics committee. The interdisciplinary nature of the body developing the code guaranteed that both ethical and scientific issues were taken into consideration.

The development in 2002 of a written ethical code for the use of biological materials should be recognised as a sign of sensitivity to the ethical issues raised by the creation and management of biobanks for research purposes. However, discussions are still in progress at national, European and international levels regarding the legal and ethical regulation of biobanks, and attention continues to grow on the matter from all the actors involved. Revision of the ethical code to take the current discussions into consideration along with the 8 years of experience gained by enforcement of the code is therefore foreseen.

As a general rule, the ethical code needs to be linked with informed consent in order to make the subjects fully aware of the ways in which their biological materials might be used. In addition, the code is published on both the Fetebenefratelli Institute website and the CEIOC page on the National Monitoring Centre for Clinical Trials website (CEIOC 2002) in order to inform external sponsors (profit and not-for-profit) of research projects about the rules governing the use of biological materials taken from patients referred to the Fatebenefratelli Institute.

The ethical code addresses a number of important issues concerning the use of biological materials and the creation and management of a biobank, namely: the acquisition of informed consent for obtaining, using and storing biological materials; the confidentiality of the data; the prohibition of financial gain; the independent revision of research protocols by the ethics committee; the rules for the transfer of biological materials to other laboratories; and the rules relating to any future cutbacks in the biobank.

In our view, the two most notable points in the CEIOC ethical code are those regulating the subjects' informed consent and the transfer of biological materials to external laboratories.

3.1 Informed Consent for the Collection, Use and Storage of Biological Materials

The ethical code regards the maintenance of a strong link between the use of biological materials and the subject's consent as the most important ethical issue in the collection, storage and use of biological materials for research purposes.

The relevant article provides a choice of possibilities for the donor. A form with three options can be used when the subjects are asked to take part in research, to make the possibilities clear.

The first option is for the subject to consent to take part in a single well planned research project. As is evident, the ethical issues related to the use of biological materials for a single research project are quite different from those related to the storage of biological materials in a biobank. In the latter case, the main ethical issue is that this form of consent, by definition, will not include description of the specific, defined research projects that the data may be used for in future. However, for a single, well planned research study using biological materials, the requirements for the consent form are similar to those in other clinical research fields.

The second option is for the subject to consent to the storage of the biological materials in the biobank of the Institute, with the proviso that the donor will be asked for further consent for the use of those materials in future research projects.

The third option is for the subject to consent to the storage of the biological materials in the biobank and the use of those materials for other research projects within the same field of investigation.

In some instances, the research project has not been fully planned or defined, and in this case the ethical code states that the subject can be asked to consent to the storage of the biological materials in the biobank and the use of those materials in future research projects within a well defined and explained field of investigation.

The stance of the ethical code on informed consent is ethically relevant in that it regards the donor as the main actor in the biological research enterprise. The code states that the person concerned should be well informed on the essential elements of the current and foreseeable future uses of his/her biological materials, and that he/she should have the right to choose to participate in the research project, as well as in the creation of the biobank. Moreover, he/she should have the possibility to place limitations on the otherwise potentially unlimited use of the materials.

3.2 The Transfer of Biological Materials to External Laboratories

The clear, transparent statement in the rules about the transfer of biological materials to external laboratories is an important point in the CEIOC ethical code. The relevant articles outline the conditions under which the biological materials can be transferred to external national or international laboratories.

Firstly, the biological materials are required to be used by the external laboratories according to the ethical code elaborated by CEIOC. This means that the person in charge of the research on the biological materials in the external institution and the person authorised to act on behalf of the institution where the research activity will be carried out need to provide written documentation in which they pledge to operate according to the ethical code and within the limits authorised by CEIOC.

Secondly, the transfer of the biological materials and every research investigation for which these materials will be used need to be approved by CEIOC; this involves receipt of complete documentation and information regarding the research project(s).

Finally, all of the biological materials remaining at the end of the research activity must be returned to the institute that sent them.

This obligation to act under the rules stated in the CEIOC ethical code has resulted in only very few of the external laboratories renouncing the planned research activities on biological materials taken from patients whose data were in the Fatebenefratelli Institute.

The development of strict rules for the transfer of biological materials to external laboratories has the clear aim of assuring the donors that their biological materials will be used by external researchers only under the same conditions which regulate the use of biological materials in the Fatebenefratelli biobank. However, the ethical imperative to promote access and to exchange information also needs to be remembered; the full benefits of the research for which the subjects give their samples will in fact be realised through maximising collaborative, high quality research (ESHG 2003). This means that a balance should be found between the imperative to improve large scale research and the need for control of the biological materials by the institution that first collected them.

3.3 The Participation of Subjects Affected by Neuropsychiatric Disorders in Research on Biological Materials

The ethical code elaborated by CEIOC applies both to the Fatebenefratelli Institute and to other hospitals dealing with a number of pathologies other than neuropsychiatric disorders. For this reason, a specific section regarding the peculiarity of patients with neuropsychiatric disorders was not included in the ethical code. Nevertheless, the article regarding informed consent mentions the case of people who are asked to take part in research projects and in the constitution of a biobank but who lack the capacity to consent.

Informed consent is clearly the most problematic issue when dealing with the participation in research projects of persons suffering from dementia or other psychiatric disorders.

It is necessary first to emphasise that a diagnosis of dementia or a psychiatric disorder does not mean in itself that the subject is not able to understand informed consent; clinical experience and empirical studies show that a number of patients with Alzheimer's disease (Dunn et al. 2006), schizophrenia or depression are in fact able to understand and appreciate the concepts involved, and to express a valid choice when asked to take part in a research project. It is therefore important to evaluate the patient's specific competence when obtaining informed consent, avoiding the risk of equating individual competence with the diagnosis assigned to that individual. When assessing competence, the physician can evaluate the patient informally or, particularly when the patient's competence is questionable, can use specific tools for the evaluation. The use of these tools for assessing the patients' understanding and competence may, in fact, show respect and help to promote the

patients' autonomy even if they are able to express their informed consent, while also offering them protection when they are unable to give their consent. The fact that genetic research, biobank activities and future studies on biological materials are particularly complicated should be kept in mind while explaining the research activities and assessing the patients' competence; explanations should be kept as simple as possible and should only deal with the essential elements of the research.

The CEIOC ethical code states that if a person lacks the capacity to consent, biological materials can only be taken when it is "absolutely indispensable"—that is, when the research is of high value and cannot be carried out by only enrolling people fully capable of giving consent—as long as informed consent is given by the patient's representative. If there is any "disagreement of the person concerned or of his/her relatives", the material may not be collected.

The aim of this statement is both to protect subjects who might not have full decision-making capacity from undue exploitation, and to allow research to occur in fields of investigation, such as those related to dementia and psychiatric disorders, where concerns regarding the acquisition of fully valid consent should not prevent the participation of the patients in research or their benefiting from the progress of science.

The model of informed consent in use in the Fatebenefratelli Institute for research enrolling patients suffering from dementia, who might not be fully able to understand and express consent, includes space for the signature of the caregiver family member in addition to that of the patient. In particular, the caregiver must state that he/she attended the information process, in conformity with the patient's wish, and that he/she agrees with the wishes expressed by the patient.

The involvement of the patient's caregiver in the process of informed consent can be regarded as a way of protecting patients with poor understanding and decisional capacity who have no appointed legal guardian or support administrator who can give consent on their behalf according to Italian law. The involvement of a family member who has spent time and shared experiences with the patient in the past and who also has a close current relationship with the patient, has the particular value of allowing the patient's wishes and previous values and beliefs to be respected (Porteri et al. 2009).

4 Conclusions

This chapter presents a summary of the experience of regulating the ethical aspects related to the creation and management of a biobank for research purposes set up in a scientific institute for research and care in the field of dementia and psychiatric disorders in Italy. In particular, the rules related to informed consent and to the transfer of biological materials to external laboratories are discussed.

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Biobank Governance in Spain: From the Autonomy of Research Ethics Committees to the Autonomy of Lay People

Antonio Casado da Rocha

> Ethical inquiry does not typically address how the social and cultural milieu in which genomic information circulates shapes people's understanding of that information, nor how values and beliefs inhere in the language we use, the stories we tell, the images and visual technologies that are a part of our daily lives. We rarely notice those devices, but they structure our most basic thoughts. Nor do most such discussions address how the language, narratives, and images emerging from research in the genome sciences influence the way we imagine our bodies, our selves, and our social responsibilities. (Wald and Clayton 2007, ix)

1 Introduction

According to *Time Magazine*, biobanks are one of the "10 ideas changing the world right now" (Park 2009), nothing less. Collecting biological material for research is not a novel thing, but developments in genomics have renewed interest in establishing new biobanks, as well as increasing access to existing collections. This is changing the way research is being done in the biomedical sciences, and also the way it is governed by society. In this sense, "governance" is the set of processes, norms and institutions affecting the way people direct, administer or control something; in the context of biobanks, governance relies more on soft law guidelines and the organic growth of international collaborative tools than on government or state action.

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Biomedicine is now "big science", and as such it has a permanent need to legitimate itself in order to obtain social, political, and economic support. Society needs research, but research needs a lot from society: not only recognition and funding, but also cooperation and trust from the subjects, sick or healthy, who are willing to take part in a study or clinical trial, or to donate a sample to a biobank. While biomedical research and its contributions to human health is positively valued in Spain, as elsewhere in Europe, the governance of biobanks raises many issues at the global level. The main ones—or at least those most discussed in the recent literature—include informed consent, benefit sharing, privacy and access, and the nature and role of the governing bodies. The main focus of this chapter will be consent, because it is probably the most studied controversy in the theory and practice of biobanks. There is a building consensus in the literature, yet the debate is far from being resolved. Here I will privilege the perspective of the lay participant (patient or donor) more than that of the policymaker or the researcher. My concern is how to promote the autonomy of participants, in tune with the traditional requirements of research ethics, in the new context of biobanks as exemplified in the Spanish case.

Spain has recently enacted (2007) a law on biobanks which demonstrates a move towards a flexible, middle way between broad consent and informed consent. This law allows for the possibility that individuals might give explicit consent for the use of their samples for one kind of research project and then consent to further unspecified uses of the samples in projects that are related to the original research project, whether by the same team or another. It is up to a Research Ethics Committee (REC) supervising the biobank to make the decision on the unspecified research on the donor's behalf. This is, I think, a "governance-by-committee" approach which is still being developed; as it provides a new regime for biobanking, it is important to test its success and determine whether this model might be suitable for other countries.

There is a lot of discussion and bibliography on the ethical, legal and social issues (ELSI) of biobanks. In this chapter I will describe only a few selected features of the present situation in Europe, but will analyze with more detail the law for biobanks being implemented in Spain. Because there are already many exceptions to the traditional requirements in this law, I have concerns that it might prove to be a slippery slope whereby the requirement for consent progressively erodes away. In order to prevent this, a more comprehensive concept of autonomy is needed, one that does not reduce respect for autonomy to single-act consent procedures. In the last pages, I will briefly comment on this matter, emphasizing the role of public consultation and the media in the popular understanding of biobanks.

2 The Present Situation

Although many governance structures established for biobanks aim to ensure that research is carried out in an ethically correct way, most governance systems in place do not involve research participants in decision-making (Stranger and

Kaye 2009, 3). Spain is no exception; the involvement of lay participants is seen by experts as something that is desirable but hard to put into practice, and at the present moment this absence of social and patient participation in the RECs is perceived as a problem (Nicolás and Romeo 2009, 124).

Still, biobanks are flourishing across the world in response to the demands of research, business, and policy. And even when they do so largely ahead of adequate regulatory frameworks, transcending national borders and pushing the boundaries between public and private enterprise models, they are also pioneering new forms of governance and embracing the need for public engagement. The Icelandic deCODE case—widely discussed since the end of the 1990s—showed the need for public engagement in the early phases of establishing a biobank. As Mark Stranger and Jane Kaye put it,

> Public engagement should not be considered as simply a necessary step on the way to establishing a biobank—a box to be ticked and move on—rather it is essential that it becomes an integral part of the overall governance structure of the biobank. This is especially the case given the rapidly evolving nature of the science and research environment and the fluid societies in which they operate. (Stranger and Kaye 2009, 11–12)

Biobanks are changing quickly. There is a powerful global trend towards standardization of procedures, so that biobanks can coordinate the sharing of practices and samples. For instance, in Europe the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) aims to secure access to biological resources required for health-related research and development intended to improve the prevention, diagnosis and treatment of disease.[1]

By the end of 2010, the BBMRI expects to have a prototype system working with the most advanced biobanks which pose the fewest difficulties, and adding others as they are ready. Still, the BBMRI reckons that a major bottleneck lies in harmonising the widely different ethical and legal requirements of each of the thirty member states. Education about and attitudes towards biomedical research differ between countries, as do interpretations of EU legislation such as the Data Protection Directive.[2]

Specific questions about the public perceptions towards biobanking have been included in the Eurobarometer survey which is conducted by the European Commission to monitor social and political attitudes; the results are also forthcoming in 2010, but five years ago, when asked about the principles of governance that should guide scientific research, some fifty-nine percent of Europeans opted for "scientific delegation", that is, a form of decision-making based primarily on the advice of experts about the risks and benefits involved (Gaskell et al. 2006, 43). This is, I believe, one of the reasons the governance of biobanks has initially relied on RECs made up by experts on the field; the involvement of lay participants, if it comes to happen, will come at a later stage. As we will see now, this is at least what has happened in the governance-by-committee model implemented in Spain.

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[1] www.bbmri.eu.

[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:HTML.

3 Biobanking in Spain

When the BBMRI completed a review in 2009 of more than 300 major biobanks, it included four full participants and fourteen other associated members from Spain. One of the former is the National DNA Bank, located at the University of Salamanca and run by Dr. A. Orfao,[3] which is also the only Spanish charter member of the Public Population Project in Genomics (P^3G).

Biotechnology in Spain is concentrated in the human health sector, and biomedical research has undergone significant growth in the last decades. It has also received social and political support. According to the Eurobarometer, Spain has scored the highest index of optimism for biotechnology across the EU between 1991 and 2005 (Gaskell et al. 2006, 13).

Public control over biomedical research in Spain depends on a cluster of governance bodies and laws, in a sort of complex "normative archipelago" or "regulatory space".[4] There is a general consensus about the basic principles and declarations that should guide this activity, but the laws and institutions in charge of their implementation are many and diverse, depending on a host of factors, and reflecting the political power sharing practices between the central government and the autonomous communities, which is a main feature of contemporary Spain (Nicolás and Romeo 2009, 71).[5]

Accordingly, biomedical data in Spain are not subjected to a unique, specific piece of legislation. The collection and use of personal data and health care information (including genetic data), as well as informed consent procedures, are regulated by a cluster of legal instruments—such as the Organic Law 15/1999 on the Protection of Personal Data; the Law 41/2002 on Patients' Freedom, Rights and Duties on Information and Clinical Documentation; and the European Convention on Human Rights and Biomedicine (1997), which provides a more general framework.

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[3] www.bancoadn.org.

[4] The same could be said of other European countries. For instance, Kaye and Gibbons (2008) describe the very limited role played by a small number of formal regulatory actors related to biobanking in some way, and the greater role played by many informal stakeholders. The latter actively compete for power and dominance, producing guidelines and other recommendation documents (which frequently overlap and are mutually inconsistent), setting standards, commissioning research, educating professionals, etc.

[5] Health care in Spain is managed by the autonomous communities, and therefore the governance of biomedical research is not centralized in a single agency. For instance, the Basque Biobank for Research (O + Ehun) is a resource to manage human samples originated in the Basque hospitals that can support a diverse range of research intended to improve the prevention, diagnosis and treatment of illness. One of its branches is the Basque DNA Biobank, managed by the Basque Foundation for Health Innovation and Research (www.bioef.org), an agency depending on the Basque Government which seeks to provide a framework for communication and cooperation between the various sectors involved in health research, development and innovation in the autonomous community of the Basque Country.

However, a new law enacted in 2007 and still in process of implementation has significantly changed the legal landscape all over Spain. A summary of its effect upon biobanking follows (Casado and Etxeberria 2009).

4 The Law on Biomedical Research

One of the most novel aspects of the *Ley de Investigación Biomédica* 14/2007 concerns the creation, in a specific chapter, of a regime for the regulation of biobanks within the wider framework of biomedical research. Structured in eight main sections or "Titles", the law devotes the fifth of these to the regulation of human biological samples, their storage and use in medical diagnosis and research, and Chapter IV in this Title V contains specific rules regarding biobanks.[6]

The Law 14/2007 defines a biobank in article 3 as "a non-profit institution, public or private, storing a collection of biological samples for purposes of biomedical diagnosis or research, conceived of as a technical unit with common criteria of quality, organization and purpose." In the Preamble, the text that gives guidance on the spirit behind the legislation, it says that the intention of the law is to be focused on the donor's consent and the information needed in order to secure it. The law is described as an effort towards a "flexible, middle way" in between open (or generic) and specific (or traditional) types of consent. Articles 58–62 regulate how samples are to be obtained, preserved, used and transferred, and the issue of the regulation of genuine informed consent appears again.

According to the law, the initial act of consent might include consenting to further, related but unspecified uses of the samples. The law allows that specific act of consent to include consenting to the use of data and samples in other research projects, "related to the one initially proposed", by the same team or another one (art 60.2). The "degree of relationship" between the two projects remains unspecified and open to interpretation by the relevant body, which is usually the REC supervising the biobank.

The notion of "project relatedness" is undefined in the legislation, and to date there has been no case law on this point. There seem to be at least two ways of understanding "project relatedness", taking either a wide or a strict interpretation. In a strict sense, individual research projects are related when they represent "lines of enquiry" pursued by the same team, with the core theory and the body of previous research changing only slightly from study to study, and much of the prior work being reused in each new line of research. In a wide interpretation, taking into account the speed of scientific development in the area of genetics and the vast spectrum of potential research hypotheses that may arise and be addressed by biobanks, there will be a range of possible uses and no easy way to predict what the range will be.

[6] An unofficial English translation of the law is to be found at: http://www.catedraderechoygenomahumano.es/images/novedades/SpanishLawonBiomedicalResearch.pdf.

Eventually, RECs will have to decide about this issue of "project relatedness" and will have to produce appropriate guidelines and criteria. However, as of 2008 there were 136 Research Ethics Committees, working mostly in the assessment of clinical trials, and some of them will have to act as review boards associated with biobanks. There is a Coordinator Centre (known as CC-CEIC) that is supposed to act as a contact point for further information on the network of RECs in Spain. But there is also a general feeling that the CC-CEIC has not done properly its job, failing to provide guidelines for all the other RECs (Nicolás and Romeo 2009, 124).

Given this precedent, a large variation in results is to be expected. If the requirement of project relatedness is generally understood in the wide, more inclusive sense, what the Spanish law puts in place would virtually be a single-act, open-consent, non-commercial model, with opting-out and other procedural safeguards. However, much still needs to be decided, and we will have to wait for the decisions of the RECs and the courts as the law evolves and is put into practice. As of January 2010, there is not a national body that will produce guidelines for all the other RECs. Still, the draft of a forthcoming Law on Science, which is expected to be passed soon, includes an article creating a Spanish Research Ethics Committee whose mission will be the production of recommendations, guidelines, and reports about these matters.

5 Possibilities of Consent in the New Spanish Law

Informed consent is probably the most studied and controversial issue in the literature on the ELSI of biobanks. Some researchers feel that the vast array of guidelines set up to control the way samples are collected and used in biobanks could create confusion and thus hamper science. Arguments in favour of harmonizing the terminology about anonymity and allowing general consent have been presented, and the new Spanish legislation follows such attempts closely.

As is well known, as a result of the Declaration of Helsinki, informed consent requires that individuals be given information about the research. However this is often impossible to do at the time data and samples are collected, since biobanks are designed to be used by many researchers and for many projects well into the future (they are "open goal" in the sense that the goals of biobank research may change over time according to initial results obtained and the development of new technologies with which to use the resources). The result is that informed consent remains in most declarations at the global level the standard ethical requirement for medical research, but at the same time the new circumstances of biobanks are thought by many to be sufficiently different to require a different ethical and legal standard, more in tune with their "open goal" nature, and flexible enough to cope with the changing demands of research.

The new Spanish model also uses a "flexible, middle way" approach to the regulation of the samples already collected and stored in existing biobanks. According to the Law on Biomedical Research, consent can be obtained upon the collection of the sample, or at a subsequent time (art 60.1). In the Preamble it is explained that the law had to make provisions concerning "biological samples obtained for any purpose before the passing of this law, so as to make possible their use for research, while at the same time protecting the donors' interests" (IV). In addition, some of the "Dispositions" (that is, practical enforceable provisions placed outside specific articles at the end of the legal text) are of particular relevance to the governance of biobanks. As we will see presently, the Second Transitory Disposition concerns what is to be done with samples stored before the passing of this law, and the Third Final Disposition empowers the Government to regulate the transfer of samples abroad.

The Second Transitory Disposition of the law lays out the situations in which existing samples may be used for biomedical research. This is when the donor has consented; they have been anonymized; the process of obtaining consent entails an "unreasonable effort" (this key concept is defined in art 3.i as "a disproportionate amount of time, work or other expenses"); or when the donor is dead or cannot be located. The use of the samples for all of these situations only requires the approval of a REC, which will examine whether the following conditions are met: (*a*) the research is of general interest; (*b*) lack of data would make research impossible or less effective; (*c*) there is not an explicit objection to it; and (*d*) the confidentiality of personal data is guaranteed.

These exemptions from the principle of informed consent are far wider for samples collected and stored after the passage of this law. The general rule is that informed consent must be obtained before a sample is collected; however, the law provides a number of exceptions. If obtaining consent for the new use was not feasible or entailed an "unreasonable effort", the requirement of consent may be waived. It does not matter what purpose the sample was originally collected for, and it need not be anonymized (that is, the donor's identity can eventually be traced). Exceptionally, says the law, use of the samples requires only the approval by a REC, which will take into account whether above conditions *a–d* are met, and whether (*e*) research will be carried out by the same institution that initially obtained the sample (art 58.2). In addition, once the sample is stored, the law allows its use in other biomedical research projects with no restriction other than those established by the scientific and ethics committees of the biobank, which will grant permission provided that the projects are of a scientific nature, and the request of samples includes information about the ends of the research and declares that they are not to be used for any other purpose (art 69). This gives quite a broad margin to the sharing of samples between biobanks.

The import and export of human biological material to and from other countries is an issue that is not covered directly in the Law on Biomedical Research. There is a Third Final Disposition in which it grants the Government "power to dictate as many dispositions as necessary to develop and execute" this act, in order

to "establish the internal, inter- and extra-community regulations on exchange and circulation of biological material of human origin for research". At the time of writing this chapter (January 2010), no law or decree has been enacted to that purpose. One of the leading research institutions in Spain, the Health Institute Carlos III (Madrid), prepared a draft for disposition in late 2007, but this draft is still being rewritten after receiving feedback from several stakeholders and Ministries. The creation of the Ministry for Science and Innovation which followed the elections in 2008 added to this delay.

In conclusion, approval by a REC is generally compulsory in order to obtain, transfer and use biobank samples, especially when samples from deceased persons are involved, or when samples are to be used in research unrelated to that for which the sample was obtained (art 62). In this sense, despite what the lawmaker says about informed consent being the general rule, the law makes it possible to talk about a "consent waiver" model, in which most decisions concerning permission to use already collected samples are to be taken by a REC acting as an overseeing third party.

Putting much of the decision making in the hands of the committees associated with each biobank suggests that new RECs will be needed or existing ones will need their capabilities greatly expanded. Specific guidelines will also have to be developed so that they can properly perform all the functions assigned to them by the Law on Biomedical Research.

6 From Consent to Autonomy

The Council for International Organizations of Medical Science, in its revised *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, declares that informed consent "protects the individual's freedom of choice and respects the individual's autonomy" (CIOMS 2002, Commentary to Guideline 4). This still represents the standard doctrine at the level of global declarations. However, there are three points that critically affect this position and seem to undermine the relationship between individual autonomy and informed consent, as it has been traditionally understood:

1. Despite the differences in existing biobanks and their governance structures, it is widely acknowledged that the only opportunity for the participant to make an active choice is when his or her informed consent is requested, usually by simply signing a form (Mascalzoni et al. 2009, 9).
2. There is a global trend, of which the Spanish scenario described above is just an example, moving from the traditional requirements of informed consent towards new models more favorable to genomic research. This movement might entail a decreasing degree of autonomy for the individual in decision making associated with biobanks (Casado and Seoane 2008; Mascalzoni et al. 2009, 6).

3. Compelling arguments suggest that placing the emphasis just on personal autonomy misses that in genomics research the focus is never on a single individual as such (Mascalzoni et al. 2009, 7).[7] Therefore, the autonomy to be protected is not only the isolated individual's, but also that of the whole group or community involved.

Several ways out of this problem have been attempted. The concern that broad consent undermines individual autonomy (shared by Kaye et al. 2009, 334) has been successfully addressed by Mascalzoni et al. (2009) in their proposal of a model for rethinking consent in an open-time/open-goal framework suitable to genomics research. According to their analysis, the autonomy of participants is not undermined when consent goes in the direction of "a participated governance mechanism, a circular open process of communication which the Informed Consent sheet signature is just one instance of" (Mascalzoni et al. 2009, 2). As I see it, the idea is to expand consent both in time (informing also the participants while the research project unfolds) and in space (informing also the participant's family).

Another way out lies in re-conceptualizing autonomy. If individual autonomy requires decisions to be based on full information, we have a problem, because of the "open goal" nature of biobanks discussed above, and therefore at the time consent to provide a sample is requested it will be impossible to adequately inform subjects about the research to be done with it. According to some authors, however, full information is not required for autonomous consent as long as individuals understand the broad nature of what is proposed and understand that they do not have all the details of what is involved. Of course, the latter situation demands a greater level of trust in the individuals and institutions concerned (Kaye et al. 2009, 334), and this is not always possible to achieve. In addition, others are doubtful that one can autonomously consent to something and, at the same time, understand that one does not know what one is exactly consenting to. In a "substantive" (as opposed to a merely "formal") concept of autonomy, the consenters cannot consent to lose control of their involvement with a research project and still be deemed autonomous.

Both approaches also share the intuition that there is more to autonomy than the ability or right to opt in/out by means of a signature. Autonomy involves decision making, but also something else: ongoing participation and active empowerment of patients, tissue donors, and all other subjects participating in research. As much as we need a comprehensive theory of patient autonomy for health care (Casado 2009), we need also a comprehensive account of the role played by autonomy in research ethics.

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[7] "The present discussion about ethical aspects of biobanking is dominated by the conventional and individual-centered moral categories of medical ethics and bioethics. Especially in this context of biobanking, however, focusing always on individual rights and protections […] will undermine individual rights and interests in ways that benefit some organized interests" (Brand 2007, 232).

7 What is Missing?

In light of the above considerations, what are the problems facing a governance-by-committee approach such as the one being implemented in Spain? If, as we have just seen, there is a building agreement that both research and ethics requires an open-time/open-goal framework such as the one described by Mascalzoni et al., participants should be informed beyond the initial acts of consent to donate their samples. Informed consent is a process, not a document; the signed form is just a piece of evidence that the process is taking place. Given the central role that RECs assume in the governance-by-committee approach, it is up to them to take measures so that this information process is implemented in genomic research.

Unfortunately, one of the problems identified in the most comprehensive review to date of the Spanish governance of biomedical research, coordinated by Nicolás and Romeo, is precisely that RECs in Spain do not contemplate taking into account the viewpoint of participants in any biomedical study, including those of the "source subjects" donating samples to a biobank. These authors recognize that the consideration of the subjects' views is one of the aims of RECs, but also that this is not currently in practice, and that it will be difficult to achieve in the future. They also propose that patients should be asked about their views during the research project (Nicolás and Romeo 2009, 124; 133), but I am afraid something else is missing. What about informing and consulting the public *before* they are recruited in a research study, or before the establishment of a biobank?

The link between donor participation, public trust and public consultation has been widely recognized (Stranger and Kaye 2009, 3), but in Spain there has been significantly less public consultation about biobanking than in other countries such as the UK. And, crucially, not only the participation of subjects or patients depends on the information they have prior to their recruitment. The better informed they were, the more autonomous their decision to take part in a research study or store a sample in a biobank would be. In other words, not only do we need a better governance model, we also need to improve public understanding of genomic science.

We cannot dispense with the benefits of using RECs. Their independence and moral authority are valuable assets wherever they happen to exist. However, these committees consist of volunteer professionals and lay people, who may or may not have the training necessary to understand the privacy concerns associated with sharing samples in a biobanking network such as the ones implemented in Spain and Europe. Their decisions are not uniform and can vary between regions in countries and between countries. Therefore RECs would have to develop "a system of uniform, transparent and accountable decision-making that was recognized across Europe" (Kaye 2009, 210).

In other words, what is really lacking in Spain might be the kind of public involvement that is already happening in other countries like Canada. It is true that these pan-European technical aspects of biobank decision making pose significant challenges to generating meaningful discussions among a lay group of

participants. However, models for deliberative public engagement on biobanks have already been presented (Winickoff 2009, 61), making it possible to envision "partnership governance" for biobanks, moving from an emphasis on benefit sharing to an emphasis on power-sharing practices.

8 Biobanks and the Scientific Culture of Lay People

This is a time where applied ethics is being institutionalized, both at the local and global level, where governance is seen as a soft regulative tool with tangible normative effects. The creation of RECs has brought forth an increased self-consciousness of the task ahead in the field of applied ethics, and a more intense and open dialogue between science and society in Europe (Tallacchini 2009, 281–2). I believe that, in order for this dialogue to continue, RECs must inform lay-people participants by using the culture that is proper to them. And this culture is increasingly a global one, in which literary and audiovisual narratives unfold in a multiplicity of hybrid genres.[8]

Very little is known about the way biobanks are portrayed in popular culture. Hofmann et al. (2006) have studied the role of rhetorical devices such as analogies, which are pervasive in popular media such as film and television. They argue that analogies tend to have a figurative function, bringing in something new and different to the standard ELSI analysis of biobanking. Indeed, a review of the literature suggests that the perceptions of lay people are heavily influenced by the ways in which popular media characterizes risk topics such as biobanks (Longstaff and Secko 2010, 3).[9]

While popular culture as a tool to enhance public understanding of science might be a double-edged sword, with a potential for confusion as large as that for instruction, the seductive power it holds over the population is not to be dismissed. Biobanks are beginning to appear in TV shows about science.[10] In addition, nowadays novels and films have become important tools for bioethicists, as they offer scenarios in which to dramatize possible implications of discoveries and policies, as well as ethical dilemmas. Moreover, their literary and visual analysis might uncover the "vocabulary that inflects public understanding of science. Such insight

[8] I have discussed this issue in my bioethics blog (in Spanish): http://www.dilemata.net/index.php/Bioetica-para-legos/cinetica-el-papel-de-la-divulgacion-filosofica-en-la-promocion-de-la-autonomia.html.

[9] In Canada, Holly Longstaff and David Secko organized a deliberative public engagement event that sought to narrow deficits of democracy related to the governance of biobanks. The participants of the event were asked to continue viewing popular media reports (i.e., TV, newspaper, radio) of the deliberation topic before the event and were encouraged to research and discuss the controversial concept of biobanking with friends and family.

[10] See for instance http://www.pbs.org/kcet/wiredscience/video/210-biobanking.html.

can elucidate how the information produced by scientific research emerges within and in turn shapes the assumptions and classifications that structure social existence." However, even though research in genomics and its attendant over inflated expectations has saturated mainstream culture, few members of the literary or artistic branches of the humanities have gained a voice in the ELSI of biobanks (Wald and Clayton 2007, viii; x-xi).[11]

9 Conclusion

The creation and management of biobanks is surrounded by confusion; some of it comes from the diversity of definitions and guidelines present in transnational research, while some also comes from the attempt to apply old ethics to new problems. One of the most discussed issues has to do with informed consent, and how to prevent it from becoming a merely legal step with no effect upon the respect and protection of the autonomy of participants.

The problem of informing about future research makes this problem more difficult to solve in the context of biobanking. The new legal situation in Spain is representative of an attempt to balance protection and flexibility, and of a trend affecting other countries which, in recent efforts towards harmonization in the international scene, are implementing governance mechanisms, REC self-regulation and more flexible approaches in informed consent policies. The result is a model of governance where RECs have a considerable margin of autonomy to work.

Enacted in July 2007, the Law on Biomedical Research (*Ley de Investigación Biomédica*, also known as Law 14/2007) includes a specific and novel regime for biobanks. This new law relies heavily on decision making by RECs. How this will work is currently unclear, as key concepts in the legislation are not yet defined. Such ambiguity makes room for many possible outcomes, and the new law might eventually set in place something unlike the traditional demand of informed consent.

To succeed, this movement from the traditional requirements of informed consent towards a governance-by-committee model will need recommendations and new RECs to take on the role of making decisions on behalf of participants in the short term. However, it will also need to find a way to inform the general population; in this task, the intersection of the ELSI in biobanking and popular culture studies is a territory worth exploring in future work, both in Spain and elsewhere.

[11] One exception would be the www.literatureandgenetics.org web site, which was produced as part of an interdisciplinary, multi-institutional project to study literature, film, and biotechnology from 2003–2006, funded by the ELSI program of the National Human Genome Research Institute (USA). Another one comes from the UK: Stemistry, a creative writing and sci-art project for people interested in stem cell research and associated ethical issues (www.stemistry.com). But neither of them deals specifically with biobanks.

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Public Deliberation and the Role of Stakeholders as a New Frontier in the Governance of Science: The British Columbia Biobank Deliberation and the DePGx Project

Claudio Corradetti and Gillian Bartlett

1 Introduction: Deliberation a New Frame of Decision Making in Genomics

With the ever rapid development of scientific and technological research in the 19th century, the power growth of scientific institutions and their specific influence have expanded incredibly due to the results they have achieved in several research areas. Due to the enormous occurrence of scientific discoveries in everyday life, state allocation of public funding has been consequently devoted to the promotion of certain promising patterns of research. The process of control and the setting of the agenda for health policies though has only rarely been established in accordance to shared priorities of public concern. Too often, indeed, governments have subordinated resource allocations to "health technicians" who, in their turn, have prioritized only one narrow perspective over the complexities involved. So far,

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therefore, the public management of scientific research has been kept isolated from a multiperspective assessment grounded in public understanding. It is believed that the widespread prejudice preventing the involvement of public sectors of society into the decision making processes, consists in an old-fashioned idea of "scientific truth" as "correspondence" which can only provide a form of self-legitimization to science itself. The view according to which scientific research is capable of providing a form of truth "exempted" from competing arguments is not only a naïve view of science, but it is also a misplaced reconstruction of how science proceeds. Indeed, scientific explanatory accuracy of physical phenomena proceeds through an assessment of contrasting empirical counter-evidences in the light of what Popper has presented as the principle of "falsifiability". The question being referred to here is very complex and indeed, it cannot be adequately addressed at this time. For the present purposes, it suffices to say that Popper's central tenet for scientific statements claims that systems of statements—namely scientific theories—can be are particularly relevant at suchdefined as scientifically relevant only if they can be falsified on the basis of empirical counter-evidences. This point helps us introduce the reasons in support of a more articulated scheme of what counts as truth in science, as well as to advance a more articulated model on why different stakeholders should be involved in the process of scientific decision-making. The question can be put as following: as scientific truth per se is characterized by competing theories exhibiting a falsifiability status and gaining credibility in accordance to their explicatory force, then, as for the responsibility of which public health policies should be reasonably pursued, different actors must be allowed in order to provide their distinctive perspective. The type of argument proposed makes reference to a sort of transliterated model of scientific truth into the public domain. In other words, a polyarchical model for the governance of science through social legitimization which relies on a *structural* continuum between scientific truth and its public accountancy is defended here. Since one possible objection is that there is here a conflation between the epistemic and the moral domain, it is important to stress only the structural overlapping and not the substantive one. The implied thesis is that there are interesting—and yet only formal—elements of similarity between scientific truth and public truth, and that the way in which they are connected provides an indication on how they must be understood.[1]

With this in mind, it is now possible to turn to what are the immediate implications of a frame of socially agreed practices within the domain of genomics and of pharmacogenomics. Three points are particularly relevant at such regard: (1) the establishment of mechanisms of cooperation and trust between science and society (2) the increase of transparency in decision making (3) the legitimization of policy guidelines for scientific enquiry.

[1] For a more detailed account of this point see Habermas (2003) on a unified sense of validity to be adopted for both the empirical-epistemic (descriptive) and the evaluative approach to the world.

As far as the first point is concerned, it is crucial to stress that a coordinated and integrated approach to science and society activates, in its turn, institutional and interpretive mechanisms of co-dependence between scientific governing bodies, public governmental bodies, groups of interest and the citizenship. Furthermore, as far as the second point is concerned, the channeling into public discussion *fora* of alternative views allows for an organic construction of complex critical arguments that clarify the terms of cooperation for each actor as well as its distinctive contribution. The critical mass resulting from the encroachment of confronting perspectives provokes an institutional setting oriented to a progressive clarification of the reasons leading to the prioritization of a certain health research objective over another. Transparency in decision making is thus achieved on the basis of a convergence of different epistemic frameworks of understanding that force to the institutionalization of institutional and non-institutional channels of discussion in order to achieve "order" within potentially conflicting perspectives/interests. Finally, the third point is concerned with the process of legitimization of public policies due to a *democratic* and fully transparent process of decision making. In modern democracies, to obtain legitimate policies, means to be publicly accountable and to be able to defend those public reasons that have contributed to certain health policies. The deliberative model here proposed is specifically aimed at obtaining, as an outcome, a certain amount of policy guidelines to be possibly adopted by health state agencies and governments in general.

Let us turn now to the dynamics activated by the process of deliberation. The idea here is that of a limited number of people holding differentiated epistemic backgrounds and gathering under the supervision of a deliberative coordinator. Discussion is conducted on set of predefined questions whose method of selection is based upon an in-depth consideration by the analysis of widely shared *ethical* concerns bearing *public* relevance. The detection of relevant topics to discuss will spring from the analysis of experts' roundtables, consultation with stakeholders and from the evaluation of the research level achieved in pharmacogenomics. What characterizes the type of discussion conducted in deliberative polls is the search for an *unanimous agreement* on deliberative outcomes. The general orientation of the participants towards a common objective is precisely what differentiates deliberative polls from other sorts of discussion groups. Whereas in the latter there is no need to be oriented towards a common agreed result, in the former, all the discussion is conducted by keeping in mind a *reasonable* outcome to be shared by each in view of a shareable outcome. At this stage, one might wonder why should there be a specific attention to deliberation as a form of ethical assessment of publicly relevant health issues. The answer to this question lies in the added value that deliberation bears in comparison to other forms of ethical assessment, as well as the functions it plays. First of all, deliberation exhibits an *epistemic function*, that is, it provides a privileged tool for the exchange of different reasons and the improvement of the quality of the arguments grounding certain outcomes; secondly, by raising the ethical issues involved, deliberation provides a democratic legitimization to pharmacogenetics (as is the example in this case). This is due to the dynamics of its same functioning, that is, to its capacity to be all-inclusive of several perspectives, as

well as to be capable of providing a qualitative improvement of the complexities of the rationales involved. Finally, the democratic legitimization of scientific research through deliberation, would allow for both an *internal* and an *external* structuring of research policies on the basis of the organizing activities conducted by research institutes and local and national authorities. The functions just introduced apply *generally* and *unconditionally* to all deliberative activities, granting certain properties to the outcomes involved.

In the next paragraph, a comparative overview of some crucial qualitative methodological tools will be provided. This will be followed by the evaluation of two already completed deliberative projects on genomics, one of which is the result of the mutual collaboration between the authors (DePGX project). The exigency of providing an alternative deliberative framework relies on the maximization of the epistemological result one wishes to achieve. As it will be made clear at the end of the paper, the proposal advanced here wishes to be mostly inclusive of the epistemological variety of the actors involved as well as to bring close unity to such variety in an homogeneous and coherent deliberative outcome.

2 Comparing Qualitative Tools for Stakeholders' Involvement into the Management of Science: Focus Groups, Opinion Polls, Citizen Juries and Deliberative Polls

When addressing the issue of scientific governance, it is possible to describe a distinctive number of methods aimed at providing, at different levels, a qualitative assessment of perceptions, attitudes, informed opinions and arguments that stakeholders have in regard to medical research through the analysis of words, text or data that can be observed but not necessarily measured. In general, the objective of qualitative methods is to obtain a complete, detailed description. This differs from quantitative research, where the aim is to classify features, count them and construct statistical models in an attempt to explain what is observed and usually focuses on collecting numerical data that can be measured. Within the realm of qualitative research, the most commonly used tools are generally known by such terms as focus groups, opinion polls, citizen juries and deliberation. We will provide a brief description of these tools in order to provide a comparison for deliberation, which will be addressed in more depth.

Such methods, when compared, represent an ascending degree of complexity with differing modes of ethical rationalization for scientific decision-making. Overall, the tools all fall within the general characteristics of qualitative research. This latter includes a broad spectrum of investigative instruments mostly, but not exclusively, based upon interviews which take into account the quality of the results obtained rather than the quantity of the information collected. For certain theoretical frameworks of qualitative research, the common tool is often a form of interview. Interviews can either be structured, semi-structured or in-depth.

Structured interviews are characterized by set responses such as "yes" or "no" to a previously determined set of questions, whereas semi-structured interviews contain structured questions as well as open ended questions where the participants answer the questions using their own words instead of selecting from a set of responses. Finally, in-depth interviews, ask only a very few questions with the aim of evoking a more detailed answer. All such forms involve an interviewer/interviewed relationship that can be very significant for the results obtained.

In contrast, focus groups, citizen juries and deliberative polls minimize this factor. They nevertheless have other constraints or limitations, such as the necessity for representativeness manifested respectively by opinion polls (which have to be indicative of what the majority thinks of an issue) and focus groups (which *can* but *do not have to* serve this scope). Furthermore, while focus groups represent a collective enterprise, sometimes made of two divergent groups *exchanging* information, but not necessarily oriented to achieve a *commonly shared outcome* (as in the "two-way focus group" where there is a reciprocal check on outcomes and interactions but not a merge of opinions between the groups), citizens juries share with deliberative polls the orientation towards shared recommendations to be given through public hearings. In addition, in citizen juries the criterion of selecting participants does not have necessarily to reflect a specific target group. Selected people are randomly chosen in view of representing the public at large.

This is also appropriate for deliberative polls, where the core part of the process of rationalization through conversational exchange lies in the diversity of the reasons put forth in the public arena of discussion, and not in the representational function exhibited by participants. This point helps to understand, in a more appropriate way, that in deliberative experiments, differences in participants' background (such as race, religion, age etc.) should be secondary in respect to the anticipated outcome. In other words, the method prevents assumptions created by the participants' divergent backgrounds from implicitly influencing the outcome of the discussion by requiring participants to explicitly state their arguments and come to a mutual understanding or agreement. Additionally, whereas in some forms of qualitative research such as in certain variants of focus groups, the facilitator not only can influence the participants, but has to do so (as in the "dueling moderator focus group" where two moderators purposely engage in two opposite sides of the discussion), in deliberative polls facilitators are *prohibited* from doing so.

As mentioned previously, it is important to distinguish between forms of pure communication, such as interviews or focus groups, from those requiring an intentional or *deliberate* involvement of the participants. On the one hand, the former methods serve a specific functional aim of permitting a de facto condition of the perception of the participants for what is ethically relevant in genetic investigation, whereas deliberative tools are instead oriented to the production of an a perception that is not preconceived but originates from the participants. In these latter cases, an evaluation of contrasting ethical perspectives is sought, so that through discussion a more refined perspective on the ethical problems at stake is obtained. Demographic diversity has been thus conceived in view of

such epistemic differentiation, that is, as a classificatory tool for the selection of a diversified ethical approach to the issues at stake.

A critical investigation of the typical results and of the dynamics of deliberation will be explored using the example of biobanking, by considering first the British of Columbia Biobank Deliberation and then the DePGx Project.

3 The Role of Deliberation in the Management of Biobanking: Insights from the British Columbia Biobank Deliberation

The British Columbia Biobank Deliberation represents the first and, so far, the most advanced experiment in biobanking deliberation aimed at involving stakeholders not simply for purposes of consultation, but also as active participants in the design of the policies regulating biobanks.

The most distinctive point of public deliberation is that to move beyond "the mere collection of data about public perceptions and instead lead to informed deliberative input in biobank governance" (Avard et al. 2009, p. 12). For this deliberative polling experiment, 34 people were contacted, from which 27 agreed to participate, 23 registered for the first session and 21 people completed the second weekend session. The criteria of selection were based upon the 2001 Canadian Census and specifically upon a characterization of diversity based on ethnicity, religion, sex and employment. As a result, participants were selected randomly while maintaining a minimum of 2 for each of five different geographical regions. The sample was not aimed at being statistically representative of the province of British Columbia, but at including a differentiated sample of backgrounds and with various levels of knowledge or experience with the subject matter. Whereas in deliberation, diversity of age, background etc. is granted in order to ensure epistemic variety, in the final report of the British Columbia deliberative experiment M. Burgess and K. O'Doherty, assert with a certain approximation, that "[…] since the event could not be politically representative of the provincial population, recruitment should aim for diversity while minimizing selection biases to design the most deliberative and representative event on a 'small' scale and with a 'limited' budget" (Burgess and O'Doherty 2007, p. 4). This statement is quite misleading since it confuses the reason for selecting epistemically diversified people with the impossibility of *representing* the provincial population. Based on the deliberative methods, there is no such rationale included in the deliberative principles and strategies. Indeed, as already stated, there is no *representational goal* to be achieved, but rather an "epistemic clash" among different ethical points of view. From this it follows that the selection of a diversified epistemic background is a precise choice to be made on methodological basis, and not instead a "second best" option to be considered whenever a satisfactory territorial representation cannot be achieved.

Going back to the methods used for the project, it is important to notice that before deliberations themselves took place, participants received general presentations of the problems at stake by researchers supporting the biobanking programme. Participants were also given a booklet entitled "Biobanking in British Columbia: a Deliberative Public Consultation". In this booklet, five possible scenarios were described in order to stimulate reflection upon the following topics: collection of biospecimen; initial contact between biobank and donor/introduction to the patient; linking samples to personal identifying information; consent; and finally, governance of biobanks and associated data. Each scenario included an explanatory note and definitions of the terms adopted. For instance, for the governance of biobanks, it was noted that the regulation of biobanks was relevant for the maintenance of a relationship of trust with the stakeholders. In addition, it was claimed that there are several kinds of regulations and codes of ethics, as well as directives aimed at governing the biobanks with a reference made to an accompanying booklet on "Regulating Biobanks". A specific mention was devoted to the role of Research Ethics Boards (REBs), which were said to be responsible for the supervision of research concerning humans. On the section concerned with "Other important information/considerations", the legal and ethical responsibility of REBs for biobanks was noted completing the available information for answering five questions connected to three hypothetical scenarios. These scenarios principally focused on the outcome of standard operating procedures leading to possible (mis)-uses of anonymized samples. One point to consider is the choice of "scenarios" in order to facilitate or frame deliberative consultation. A criticism can be made that these scenarios may have resulted in an arbitrary restriction of potential topics for discussion thereby frustrating the creativity of the deliberative process. In addition, for an unbiased outcome in deliberation, a strict criterion of information provision must respect the general principle of impartiality in information. Given this, the scenarios may have presented too much research-oriented information to participants.

A further mechanism of information disbursement and involvement of the public has been conceived with the set-up of a website. The website was set up in order to facilitate on-line discussions in between the first and the second meeting. This allowed for an in-depth reflection of the problems at stake that have in their turn provoked a more informed discussion level during the actual deliberation. Once again, it must be noted that the role of information communication is crucial for a free and unbiased deliberative confrontation.

Evaluation of deliberative discussions included both quantitative and qualitative measures based on pre- and post surveys, analysis of transcripts, follow-up with telephone interviews etc. Qualitative methods were combined to quantitative ones. In such cases participants were asked to provide an evaluation ranging from $+5/-5$ for value and policy statements. Overall agreement was manifested on the following points: (1) general support for biobanks (2) standardization of procedures (3) independence of governance from funding resources. Qualitative

analysis of the discussion polls, though, is quite interesting in regard to the issues of persistent disagreement at stake, as well as to the degree of such disagreement. As a matter of fact, while deliberation is oriented to produce the maximum of convergence among participants, whenever overlapping of ideas cannot be realized, then persistent disagreement has to be recognized.

Some persistent disagreements centered on the degree of privacy protection granted by biobanking operations. While some participants considered that there was no need for a high level of privacy protection (due to a too high involvement of the government), others on the contrary argued for an high level of protection of privacy. Reasons in favor of a higher standard of protection were connected to difficulties in obtaining insurance coverage or even employment in case of diseases. Additionally, disagreement was manifested in regard to the members sitting in the Research Ethics Board (REB) governing biobanks. In particular disagreement concerned whether community involvement is a required feature and worthy of being represented. Also, disagreements concerned whether REB representatives should be either elected or appointed. Another set of disagreements concerned whether individual consent should override group consent or not, or also whether a blanket consent should be allowed or not.

Persistent disagreements are important because they inform us as to what are the most crucial ethical difficulties requiring extra reflection in order to be resolved. They are indicative of the limits of our ethical resources presently at our disposal by pointing to the necessity of additional reflection on possible solutions. Such extra reflection can be considered as a prompt for further deliberation and refinement of arguments. As a matter of fact, ethical stalemates rather than representing an endpoint of reflection are indicative of those social ruptures needing to be bridged. One relevant aspect of deliberation, according to the critical perspective presented here, consists in the added value it provides when applied in an *iterative* way. Deliberative iterations allow for a smooth resolution of ethical clashes, due to a refinement and to a *boot-strap* of argumentative strategies. An important feature to be added to deliberative processes as part of the ethical-scientific assessment consists in the consideration of such an *iterative* element of discourse replication in view of an improved (ethical)-outcomes. This means that deliberative processes should not be applied as a one-off process but, on the contrary, as a recursive resource of ethical evaluation to be iterated across time.

One final difficulty with deliberative outcomes is the one concerned with the translation into public policies. One strategy which has been adopted for the biobank design at the W. Maurice Young Centre for Applied Ethics, University of Columbia, has consisted in differentiating between "analytical outputs and deliberative outputs" when analyzing qualitative data (O'Doherty and Burgess 2009). Such differentiation consists in recognizing the following characteristics as belonging to deliberative and to analytical outputs respectively:

1. *Deliberative outputs* are based on explicit outputs of participants; reflect actual language expressions; do not require too much of an analytical analysis nor technical categories by the analyst; should be expressively endorsed by participants.

2. *Analytical outputs* are subordinated to principles of scientific analysis, rather than participants' ratification; consider participants' affirmations as contingent statements based upon their socio-cultural discursive contexts; they are drawn from several sources of data (videos, recordings, field notes etc.).

In deliberative outcomes it is certainly more difficult to detect a policy indication since there is not a clearly predefined question to be answered. This means that it is important for the researcher to reconstruct a feasible and practically realizable indication of the deliberative will. In order to achieve this goal, O'Doherty and Burgess (2009) suggested that operations for policy translation are operationalized *before* actual deliberations are realized.

4 DePGx Project: Assessing Ethical Implications of Pharmacogenomics in Primary Care Through Deliberative Consultation

We will now move to the presentation of a most recent deliberative experiment which we have completed. The DePGx Project (Deliberative Pharmacogenomics) is funded by the Canadian Institutes of Health Research as a joint cooperation between the Department of Family Medicine at McGill University in Montreal, Quebec and the Institute of Genetic Medicine of the European Academy, Bolzano, Italy. The goal has been that of elucidating different views on those ethical issues arising from pharmacogenomics research. The project has implemented a set of deliberative polls, whose output will provide government agencies the basis for the construction of publicly agreed health policies. In what follows, the results of the project will be presented as well as the rationale of the deliberative polls.

First of all, one of the main advantages of introducing deliberative tools within the assessment and the management of scientific research, is that deliberative outcomes provide "the public" (citizens, stakeholders, experts, institutional representatives) with critically agreed perspectives on how to proceed in research (Avard et al. 2009). The advantage consists in the added value that deliberation guarantees to the rationalization of the issues involved, as well as to the decisions of public policy that should be adopted. Why does deliberation represents a vantage point in respect to alternative decision-making solutions?

The reason is that deliberative outcomes are not aimed at representing those "personal interests" of the participating parties, rather, they are oriented to the assessment of what should represent the "common good". Nevertheless, such goal is achieved *through* the public assessment of partial and, very often, conflicting interests, so that a common outcome is the result of numerous interest-mediations in view of a common benefit.

If this represents the general goal of any deliberative process, then, the specific architecture of each deliberative system might vary in accordance to different parameters. For example, in recent participatory and deliberative experiments

on biobanking such as CARTaGENE (Godard et al. 2007), the British Columbia Biobank (O'Doherty and Burgess 2009) or the United Kingdom Biobank, various definitions were adopted on what counts as "the public". Such definitional differences are reflected in the types of parameters adopted in selecting the participants (such as their professions, age, skills and cultural-religious backgrounds). One point to be observed, though, is that in contrast to socio-political experiments that utilize qualitative interviews or focus groups, where a representative sample of the society is to be provided, deliberative polls have as a primary function of delivering a sound outcome which expects to be superior to partial points of view. This means that the perspective advanced by deliberation is not aimed at being representative of the diversity of social reality, but rather at overcoming partial perspectives.

Deliberation, through its dynamics, is particularly suitable for overcoming idiosyncratic perspectives and for achieving an insight on the common reasonable agreement. This can be reached through different means and, in the case of the DePGx Project, it has been pursued through the following strategy. First of all participants were selected on the basis of the epistemic differences of their knowledge. The criterion of epistemic difference has been considered as the crucial factor, above other traditional criteria such as gender, age, race, for the construction of the polls. Accordingly, participants have been grouped first in view of a "variability within similarity" of their epistemic backgrounds and then representatives of each poll have been mingled in a final deliberative poll. More specifically, participants were grouped around three polls representing respectively: general practitioners, lay-people, stakeholders (policy makers and interest groups). The deliberative activity was conducted in two phases, a first and a second round. As far as the first round was concerned, the idea was that of provoking a "critical clash" among the different epistemological narratives within the same deliberative groups themselves. From each deliberative poll precise outcome was expected, that is, a deliberative result upon which each group participant would have finally agreed upon. From each group, a sample of representatives were selected in order to take part in the second and final phase of the deliberative activity.

The second stage of deliberation, in its turn, was aimed at provoking the same "critical clash" by increasing the level of specificity of the argument produced for or against certain specific identified issues. These issues were submitted for consideration to the participants by the coordinator on the basis of the analysis of the outcomes of the first-round polls. For the second stage, a mixed deliberative poll including the representatives of all previous polls was arranged and a final deliberative outcome was obtained. Due to the peculiar methodological properties adopted, namely the epistemically differentiation of participants, the outcomes produced by deliberation have produced new findings and opened new roads for understanding the ethical concerns in pharmacogenomics. Indeed, it is from the disagreement of the participants that new and fair solutions have been sought both during the first and the second stage of deliberation.

5 Questions for Deliberation in the DePGx Project: Ethical Relevance of Pharmacogenomics in Primary Care

On the basis of what has been claimed so far, it is important now to clarify why deliberation is relevant for the assessment of those ethical issues arising from pharmacogenomic research. The DePGx project was conceived in order to provide two frames of discussion focusing respectively (1) on basic ethical concerns raised by pharmacogenomics and (2) on the ethical implications raised by primary care pharmacogenomic interactions, as for instance a possible rethinking of informed consent forms. For the first point, participants were provided with two sets of basic issues to be assessed. The first provided a brief scenario where personalized medicine was presented as developing in view of specific population/race/territorial diseases emergencies and genetic reactions. The foreseeable consequence suggested was that those groups showing a lower genetic capacity for reaction to certain sets of medical treatments would be excluded from personalized medical treatment and pharmaceutical research. This point has been considered as raising a serious ethical threat from ethically unchecked policy for pharmacogenomic research and drug development. Connected to this point, the issue regarding the terms of individual interest maximization in respect to the group was mentioned. This crosscutting issue intersects the above-mentioned macro topic since it involves resource investments into specific diseases affecting a small number of people against the totality, as well as the interest of corporate groups, such as insurance or pharmaceutical companies coming into possession of personal data.

The assessment of these points is directly relevant, then, for the understanding of which public policies should be pursued. All considered, the questions answered dealt with the risk-benefit assessment, their ethical implications and the actual promise of pharmacogenomic research. One of the most discussed points was whether there are enough convincing reasons to invest future research attempts into the pharmacogenomic sector, and on which specific grounds should public authorities invest into this sector. The evaluation of such points has been considered to explicate what is to be the public policy function that deliberative activities target, that is, the added advantage that a plurality of discussing actors would provide to the ethical assessment of pharmacogenomic research.

For the second area of application, the project wished to highlight possible ethical issues within the domain of informed consent. The question to be answered by participants regarded whether, in accordance to the existing state and international parameters on informed consent, whether personalized medicine may possibly worsen the condition of privacy or data protection. Indeed, even if health risks in taking part into genetic testing are excluded from consideration, the range and number of problems involved in such an analysis are wide and reflect all the usual security measures of anonymization of data involved into an ordinary system of

privacy protection as well as sensitivity of the health information revealed. Below are reported the specific questions that were provided to participants:

First Framework of Relevance: Basic Ethical Issues Raised by Pharmacogenomic Research

1. Consider a scenario where personalized medicine is developed in view of specific population/race/territorial diseases emergencies and genetic reactions. The consequence is that those groups showing a lower genetic capacity for reaction to certain sets of medical treatments will be excluded from personalized medical treatment and pharmaceutical research. *Connected issues*: Within which terms can one maximize the interest of the individual against that of the group? i.e. through resource investment into a specific disease affecting a smaller number of people against another affecting more and so on.
2. All considered (risk-benefit assessment, ethical implications, the actual promise of pharmacogenomic research etc.), are there enough convincing reasons to invest future research attempts into pharmacogenomic sector? On which specific grounds would you suggest public authorities to invest into this sector?

Second Framework of Relevance: Ethical Issues Raised by Pharmacogenomic Application in a Family Physician-Patient Relation

1. What sorts of problems would you see in the actual informed consent procedures when applied to the doctor-patient relation for pharmacogenomic testing? According to the actual parameters/rules of your country, would the development of pharmacogenomic testing worsen the condition of privacy and protection of personal data?

The ethical rationale which has prompted the above-mentioned areas of discussion was based upon a certain number of ethical concerns that personalized medicine, as part of genomic testing and research, has raised. Accordingly, in as far as the first area of discussion is concerned, it was thought that pharmacogenomics would possibly raise the following issues:

Possible Issues I

Equality Principle that equal dignity requires equal access to medical treatments. Pharmacogenomics can challenge this due to a different genetic, individual and population, response to a drug.

Patient Stratification along socioeconomic, ethnic, and racial lines. At the group level one would obtain so-called “orphan population”: (1) either because their genotype raises difficulties in developing drugs, or (2) because their genotype includes too small a number of people to be economically attractive; at the individual level one would obtain: (1) exclusion from medical trials due to economic reasons, and (2) racial discrimination.

Risk distribution as a consequence of patient stratification, some groups’ genotype might be excluded from trial and yet be prescribed this same tested drug. Risk would be therefore unevenly distributed along the genotypic spectrum.

Possible Advantages

Utilitarians would see pharmacogenomics as a possible instrument for reducing costs of hospitalization in view of a higher drug efficiency and safety.

For the second area of ethical relevance, it was considered that informed consent might require some further specifications. In particular it has been thought that:

Possible Issues II

Informed Consent

Pharmacogenomics highlights all the well known issues of informed consent. Patients should be informed on the purpose of the study, results, and what information they want to know or not to know once the study is finished. Also, in as far as the relation of the family physician and the patient is concerned, patients should be aware of the possible disease interconnections that a genomic test might suggest.

Finally, the fourth and final deliberative poll included the participation on a voluntary basis of some of the participants of the previous groups. Participants gathered together in order to discuss the institutional and the legal or quasi-legal chartering based on ethical implications of pharmacogenomics. Questions covered the following areas:

Pharmacogenomics and the new Frame of Institutional Cooperation between the Public and the Private Sector.

Pharmacogenomics will obtain public acceptance and legitimization only if a strict agreement is enacted between the government (and in particular provincial health care bodies) and the pharmaceutical companies operating within the provinces. In your opinion, which areas should be restructured or emphasized for these agreements? How or which needs do you think should be improved?

Example:

Generally, do you think that the adversarial position between the public interest and the private interest should be reviewed in order to achieve new forms of agreement?

More specifically, do you think that in the light of a new era of drug production based upon very sensitive information (genome), there will be the need of new public institutions incorporating also the perspectives of the private sector?

A Proposal of a Charter on Ethics and Pharmacogenomics

As a consequence of a new institutional or quasi-institutional setting proceeding from the suggested framework for pharmacogenomic research, which ethical and governing principles would you list in a hypothetical charter on ethics and pharmacogenomics as a morally binding document?

Besides the proposed questions, participants suggested a certain number of new ethical problems to be considered in the case of pharmacogenomic research. The results of the deliberative polling sessions are presented in the subsequent sections.

6 Analyzing the Results of the Deliberative Polls: "*E Pluribus Unum*". Providing Policy Guidelines to Government and Public Health Agencies

In the previous sections, an overall presentation of the dynamics and the methodology of the project was provided, as well as of the areas of ethical relevance that were considered as important for debate. In this final paragraph a discussion of the results achieved in each of the polls will be presented, both for the first and of the second stage. This will allow us to summarize at the end what general outcomes have been achieved in order to make a recommendation to public healthcare bodies.

Before starting the presentation of the results, it is important to articulate the selection criteria for recruitment of participants. Patients were recruited on the basis of the circulation of an electronic information notice through the network of patients associations affiliated to McGill University Family Care Department and the McGill University Hospital Centre. As far as the recruitment of family physicians is concerned, the invitation was circulated through the associations of family physicians in Montreal. Stakeholders were identified through an earlier workshop that involved interested parties for genomic research in primary care.

6.1 Textual Analysis of Stakeholders' Deliberations

Stakeholders, first of all, focussed on the fact that pharmacogenomics, besides certain possible negative and discriminatory effects, can further the study and the understanding of treatment for rare diseases. The tendency, as in the USA for instance, is that of creating special categories for such diseases. A distinction has been suggested separating between the relevance of rare diseases and the rarity, not fully corresponding, of genotypes. It was thought that it is rather in the latter sense that ethical issues may arise due to possible low profits that such groups would provide.

Positive trends in interpreting the role that pharmacogenomics can play internationally were discussed based on research conducted in developing countries. Examples were given of pharmacogenomics research that are currently conducted in third world countries due to the premise that a great amount of money may be saved by avoiding non-effective treatments. Although it was felt that there is serious problem if pharmacogenomics are considered only in the context of a cost-benefit pharmaceutical-driven perspective.

Participants reached a general understanding and agreement on the fact that a cost-benefit analysis cannot be taken as the only perspective in order to measure the advantages or the disadvantages of pharmacogenomics. Furthermore, none believed that pharmacogenomics provides a complete "solution" to many of the issues with prescription medication. Pharmacogenomics has been rather perceived

as a method that should be "integrated" to supplement the already existing best practice strategies to optimize patient treatment.

The discussion then switched to the Canadian scenario, both at the national and provincial level. The general understanding was that certain evidence was needed to convince politicians to place more money in pharmacogenomics research given that there is currently at least three drugs that have been resubmitted to the FDA for approval and that are based on pharmacogenomics segmentation. One of the current problems is that, in Canada, at present, there is no official national agency looking at the clinical validity of pharmacogenomic tests and that both tests and drugs based upon pharmacogenomic testing are not available in the national health system or provincial formularies.

Since most of the pharmacogenomic tests do not go the federal route to get approved and therefore they are not reimbursed at the provincial level, it follows that they are not recognized and that family physicians do not use them. In Ontario, though, a backdoor solution has been provided. The solution consists in treating pharmacogenomics tests as foreign medical tests, so that such tests are now conducted in the USA on behalf of the Ontario patients. At present there is no reimbursement for pharmacogenomic testing and care done in Canada by the national health system, but if this ever does occur, then pharmaceutical companies will have to write a brochure to support the tests and comply with general regulations.

A final point touched upon the need or opportunity of enacting a Non-Discriminatory Genetic Act in order to protect genetic information from insurance companies and employers. While there are ways to obtain personal health information through family history tools, genetic information has been perceived as extremely sensitive and therefore in need of higher protection. While a general agreement was reached in considering genetic information on a par with normal medical information that might be contained in a chart; no general agreement was reached on the utility of legal acts in regulating the field or protecting this information. Indeed, some participants thought that Acts will then prevent future modifications, blocking the process of updating policies as scientific/genetic research improves. The suggestion made by some, has rather been that of activating common policies and best practice agreements to protect the information and the patients.

6.2 Textual Analysis of Patients' Deliberation

The discussion immediately addressed the costs of pharmacogenomics research, as well as the role that the federal government should play within the entire process. This topic dominated most of the discussion. Some of the ideas that were proposed concerned the fact that the government should be allowed to buy at a convenient price the required drugs in order to avoid patient discrimination and pharmaceutical speculations. The health system in Canada is public, and while this provides

several advantages, it currently runs into several difficulties due to burdensome costs. Indeed, reservations were expressed in case research on pharmacogenomics would cut into the provision of services in other relevant sectors. Since genome testing is perceived as not being "the only solution" for treating diseases, then it was felt that a cautious approach should be adopted. At present, it was considered that pharmacogenomics would increase the amount of public expenditure in health, and this seems to be unrealistic due to the contingent economic situation. Nevertheless, in the long run, pharmacogenomics promises to reduce health costs even if this is not the case yet.

One point of convergence consisted of thinking that as soon as the genomic test becomes cheaper, then we should certainly utilize them in practice. Yet, in such a future scenario, some further ethical issues may arise such as those regarding the privacy of genomic information. While this does not represent a new problem, its relevance and seriousness is perceived as higher than before. One participant expressed forcefully the idea that the more information that can be provided about an individual, the better treatment they may receive therefore highly supported genomic testing. All together, the participants expressed a diversified range of perceptions ranging from the most sceptical to the most persuaded. While the discussion addressed mainly the cost/benefit problem, a crucial turning point in the debate was the switch into a hypothetical scenario where costs were considered to not be relevant. This generated an in-depth discussion on the ethical implications of pharmacogenomics. However, one line of reasoning pointed out the fact that since in Quebec there is a severe shortage of family physicians, the development of pharmacogenomics will not be much help since there are large portions of populations do not have the opportunity of accessing the primary health care system anyhow.

As a result of the deliberation, common consensus has been expressed on the following points: at present there are not sufficient reasons and evidences for investing money on pharmacogenomics research. Nevertheless, it is believed that if no investment is made in this field, then we will never know what advantages can be obtained. Participants all agreed therefore that money can be invested in genomic research only upon the condition that the government would be involved in regulating costs possibly by restricting the profit margin on drugs patented by the pharmaceutical companies. Also, a general agreement was expressed on the constraining role that the government should play towards pharmaceutical companies in order to not let them manipulate genomic research and consequently the health care system, with only a profit motivation.

6.3 Textual Analysis of Family Physicians

Family physicians focussed mainly on the ethical concerns raised by a scenario characterized by a lack of medical care. Indeed, racial implications connected to profiling were not perceived as a new issue to the current medical practice, even if

the potential for pharmacogenomic testing to worsen this scenario has been considered. Participants established an interesting point of interconnection between racial implications and pharmacogenomics by focussing on the case of a lack of medical care as a consequence of a genetic profiling. The point they addressed was the following: how should family physicians behave in the case a genetic screening would tell that the person screened will not be able to respond to the currently available drugs? This was considered to have very serious ethical implications. One physician said: "Suppose you have 2 or 3 quite effective drugs, and then you do a test to someone in order to know if the person would respond…I would be very anxious in saying to someone 'sorry there are no medications for you', I'd rather not do the test at all."

This hypothesis produced conflicting feelings in the perception of pharmacogenomics. Indeed, it was considered that if, in the first instance, personalized medicine produced many positive feelings, the possibility for a physician to have to tell someone: "sorry there are no drugs that will work for you", caused many negative feelings. At the same time, the case was made in more positive way that there were advantages in avoiding giving someone something that will not be beneficial and effective at all, that is, something that will have only side effects.

One further problem taken into consideration and being extensively connected with this issue were people's expectations. Indeed, if you have to tell somebody "sorry this will not work because of you genetic profile", then you will have to enter into an extensive conversation where you will have to explain why this would not work. Also, the physician will have to answer to a series of patients' questions or concerns such as "well…but this drug has worked in the case of my friend". What was considered as fundamentally important was the relevance of a large public information campaign in order to cope with people's expectations. This touches upon a further aspect that was also debated, that of the perceived effects of a genetic test in accordance to the result it might provide. Indeed, it has been said that it must be considered the possible effects on depression arising from not being able to provide an effective drug as a consequence of the test. A general agreement by the participants has been expressed on the fact that pharmacogenomics promises to reduce the "poisoning" and the side-effects of general drugs used nowadays, but a concern has been expressed on the timing in obtaining the profiling results as well as on the necessity of an alternative system of management between all the interested sectors (family physicians, hospital laboratories etc.).

A second issue, which was briefly discussed, concerned informed consent. It was felt that personalised medicine does not seem to raise special issues that are not yet part of the current practices for informed consent (i.e. the same issue would be there renal function which does not require informed consent). In general, there was a general agreement for investing money for research in this sector, and the basic reason which was expressed concerns the fact that in the long run this will help save money by avoiding hospitalizations by producing effective drugs. At the same time, though, a certain scepticism was expressed for the approach that would

present pharmacogenomics as "the only" possible solution for health care, as well as in the possibility that it can divert funds from other relevant areas such as oncology research.

Overall, general support was expressed for pharmacogenomics. Nevertheless, the worry that this information may eventually be related to genetic disease prediction was mentioned. It was hypothesized that in as far as pharmacogenomics is supposed to present as an extension of the family history, then, no specific ethical problem would arise. The worry, as mentioned before, was perceived more as relying in the "mechanical" procedure that all this new approach would imply as well as in the privacy of the data that should be granted and in the delay in providing answers to patients. Finally, a concern was expressed in the role that pharmaceutical companies will play within this process. A totally unanimous agreement has been expressed in keeping pharmaceutical companies outside the process of genetic profiling in order to guarantee as much as possible independency and privacy of data. Even if it is easy to foresee that pharmaceutical companies would offer to pay the genetic screening, which currently runs from hundreds to thousands of dollars, a general understanding was reached in considering that money for screening can be progressively taken from the cutting off of the costs of hospitalization as well as in the progressive reduction of the costs of the tests.

6.4 Textual Analysis of the Final Polling Session with Representatives of All Groups

In the fourth polling sessions, participants tried to propose practical solutions to the ethical concerns arising from the previous sessions. Nevertheless, before addressing in a more specific way the two questions submitted, participants spent time in discussing the problem of patenting, either as test patenting, or as gene patenting etc. as well as the more general issue of intellectual property rights. The discussion turned then to the question of who should regulate the process of pharmacogenomic research and drugs commercialisation. Some thought at the beginning that medical physicians should be given a stronger role in health policy, even if after discussion all converged on giving higher representation and power to patients. It has been claimed that patients' psycho-social insights have to be taken more seriously within ethical committee and governing bodies and that they should be give a higher decision-making role. With only one exception, participants finally agreed on the fact that there is no need of a yet another regulatory agency, but that the already existing ones should be reformed in accordance to the above mentioned indications of patient representation and empowerment. A participant confirmed that Genome Quebec is actually thinking of including patients representatives within its body and that this issue is becoming more pressing. Nevertheless, perplexities were advanced on who is going to select patient representatives, since a wide range

of perspectives should be taken into account. The proposal has been made of including a high range of patient participants within governing bodies with the aim of restricting then the possibility of voting only to a limited number.

As second suggestion focussing more on the regulatory scope, addressed the issue of providing health bodies with a more extensive powers to regulate what pharmaceutical companies can and cannot do with samples. While aware of the significance of several existing policy statements, participants agreed *unanimously* in the draft of a charter document on the ethical principles guiding pharmacogenomic research and clinical treatment. The charter should be a national one, and be a reference document for the ethical approval of research projects and so on. The charter should provide a sense of a standard to lower level policy enactments at the provincial, city, and hospital level.

7 Outcomes of DePGx Deliberative Polling

From the above mentioned deliberative findings, a picture emerges where pharmacogenomic research is seen as a very promising field of investment for the reduction of costs of hospitalization, as well as of for the production of more efficient drugs. Nevertheless, the promise of a paradigm shift in medical and pharmaceutical research is perceived by all involved groups as determining a wide range of ethical concerns in need of a regulatory enterprise. The proposal of a national charter on pharmacogenomic research has been thought, therefore, to be the most appropriate initial step to be taken before future investments by the government and private companies are made. In the light of such indication, it is therefore our hope that governmental bodies will take all the appropriate steps in order to facilitate the promulgation of a charter on pharmacogenomic research.

8 Conclusion

This essay has shown that there is a wide variety of qualitative outcomes and instruments connected to the governance of science. In particular, the specificity of deliberative tools for the qualitative analysis of biobank's ethical issues was addressed and some further improvements were proposed based on the British Columbia Biobank Deliberation. Insights form the deliberative polling DPGx provided a viable outcome that will help promote a publicly relevant policy and research program for pharmacogenomics research. It is hoped that such mechanisms of choice rationalization within medical research will increase in the near future and that more and more research institutes will be willing to make their research publicly accountable to the public at large.

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Making Researchers Moral

Why Trustworthiness Requires More Than Ethics Guidelines and Review

Linus Johnsson, Stefan Eriksson, Gert Helgesson and Mats G. Hansson

1 Prescript

In this paper we discuss how the individual researcher's moral responsibility for her work relates to research ethics as an extra-legal regulatory framework. Though we address biomedical research in general rather than biobank research specifically, much of what is said here is equally relevant in both contexts. First, informed consent, here as elsewhere, is taken to be morally required, and many authors hold high expectations regarding its leveraging power. In contrast, public awareness of biobank research is rather low, and people tend to be more concerned about matters that informed consent procedures rarely address, such as the

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actual goals of research and how benefits are to be shared. Second, much of what is going on behind the scenes in biobank research obviously falls outside the scope of ethics review, perhaps more so than in traditional biomedical research. Ethical reflection on one's research must therefore be an ongoing process rather than a one-shot affair. Lastly, legal and ethical documents governing biobank research continue to proliferate at an alarming rate, highlighting the need for a discussion on how researchers are supposed to orient themselves in an ever-changing and confusing ethico-legal landscape. The link between this paper and biobank research is elaborated in greater detail in Linus Johnsson's thesis, available on the Uppsala University website.

2 Introduction

Research ethics, unlike the natural sciences, produces *normative* output—in essence, statements on what ought to be done. Still an academic discipline, it has thus quite naturally come to double as the framework for extra-legal regulatory systems, much like jurisprudence is the foundation of legal regulation. It is tempting to assume that to be effective in guiding action, ethics must be formalised in the same manner, through steering documents, overseeing bodies, and formal procedures.

Today, the number of ethical guidelines and professional ethical codes intended to guide research is increasing at a tremendous pace (Eriksson et al. 2008). We also expect more of them: The Declaration of Helsinki, for instance, has gone from modestly declaring itself "only a guide" (World Medical Association 1964) to forcefully asserting that "No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration." (World Medical Association 2008) General principles have partly given way to enumerations of concrete rules, for instance with regard to what pieces of information should be disclosed to research participants. In some contexts, ethics review has increasingly become a matter of scrutinising informed consent forms (Edwards et al. 2011; Coleman and Bouesseau 2008; Hoeyer et al. 2005a).

In this paper we argue that ethics review and guidelines are insufficient to ensure morally responsible research. In some circumstances, regulatory research ethics can be more of a hindrance than a help. We begin by describing the paradigm of *institutionalised distrust* that currently informs it. Next, we argue that past atrocities cannot be drawn upon to back claims that research must be more strictly regulated unless what is proposed is a necessary or efficient means to prevent future ones. We thereafter consider the main limitations of ethics review and guidelines. With regard to ethics review, requirements of consistency invites rigidity; lack of reliable indicators of a project's moral soundness may lead to idiosyncratic decisions; and the fact that committees depend on the moral agency of investigators is often overlooked. Strict adherence to guidelines is also no

guarantee that moral responsibilities have been discharged. In fact, if guidelines are used as standards against which performance is measured, responsible conduct will occasionally be punished and blind rule-following praised.

In the next-to-last section, we identify some particular risks with the current system. First, ethics review that focuses strongly on some ethical aspects of research risks diverting attention from other morally significant issues. Second, guidelines with a low level of abstraction—that is, those orienting towards rules rather than principles—encourage a checklist-like approach to ethics that makes individual moral deliberation appear redundant, eventually leading to heteronomy of action. Third, when rules contradict (which they often do), they fail to provide guidance to researchers, and may even alienate them. The irresponsible conduct that follows tends to precipitate tighter regulation, thus perpetuating the vicious circle. Consequently, though substandard behaviour in the short term is indeed worrying, the moral competence of researchers in the long term should be cause for even greater concern.

3 Institutionalised Distrust

Social scientists have described the drive toward tighter regulation and systems of oversight as an expression of the ambivalence and insecurity that pervades postmodern society (Miller and Boulton 2007). People, it is argued, can no longer rely on social norms to govern the actions of others; to dare cooperate, they must look for other guarantees. Where developing a personal relationship with the other is not feasible, one must then either find a trusted person to vouch for the other, or fall back on formal structures such as laws, rules and contracts—backed, of course, by appropriate mechanisms of sanction.

To the degree that this picture accurately describes the societies we live in, biomedical research is in trouble. If trust depends on social norms, the researcher will—to most people at least—count as an unknown other who should not be trusted. In some contexts, health care personnel with whom potential research subjects are more familiar can act as "proxies" or guarantors (Johnsson et al. 2012), but this is not always a viable option. It could be argued that if researchers are either insufficiently trusted or insufficiently trustworthy, we ought to at least make their actions more predictable so that public support of biomedical research may continue. This normative position forms the essence of the paradigm known as *institutionalised distrust* (Sztompka 1998; Hall 2005). This paper focuses on two of its mechanisms: *oversight* and *formal rules*. By giving an overseeing body—in our case, research ethics committees (RECs)—the task of distrusting researchers, the public will not have to; they can go on cooperating, confident that the necessary control systems are in place. But to ensure effective oversight and maintain the legitimacy of the overseeing body, we also need clear rules or performance standards against which deviations can be spotted. Guidelines, once intended to provide guidance, are today designed with this regulatory need in mind.

Institutionalised distrust resembles distrust between people in that it implies taking precautions, doing checkups, and developing contingency plans in order to minimise risk. But it rests on instrumental rather than empirical standards of justification: Whereas distrust between people is warranted by evidence of untrustworthiness, institutionalised distrust is rational insofar as it is likely to make the research enterprise more trusted and—perhaps—more trustworthy. This must be borne in mind whenever past experiences are used to back future policies.

4 The Problem to the Solution

If the Nuremberg Code is the foundation of bioethics, the Nazi atrocities that preceded it serve as the precautionary tale. But what moral does it tell? It is commonly claimed that it teaches us the necessity of *informed consent* (Goldworth 1999). As we already know that informed consent is important, we may fail to notice the tenacity of this claim. Granted, involuntary participation is impossible insofar as the ideal of informed consent is in fact realised. But it does not follow that merely *requiring* that informed consent be obtained would have been effective. A legal requirement of voluntariness was in place already in 1931, but did little difference to the victims (Hoeyer 2008). Arguably, no amount of research regulation will protect minorities in a totalitarian state, let alone one embracing Nazi ideology.

Now consider a more recent large-scale transgression of human rights, the Tuskegee syphilis study. The subjects—exclusively African-Americans—were led to believe that they were receiving treatment. This was a lie: Despite the risks of untreated syphilis being repeatedly proven throughout the study and penicillin being readily available, they never got any. Through carefully placed letters to other physicians in the vicinity, the investigators even prevented the subjects from being treated elsewhere. Tragically, the Department of Health, Education and Welfare concluded in its Final Report that where the investigators had failed was in *obtaining informed consent* from their research subjects (Brandt 1978). Ignored or overlooked was the fact that even before the age of informed consent, what transpired would have counted not as morally problematic, but as obviously racist and evil.

Another lesson ostensibly taught by these examples is that researchers are unreliable unless watched. But we must not forget that the Nazi atrocities, though invented by individuals, were perfectly in line with contemporary public policy. Would an REC, had there been one, have condemned these experiments, or applauded them? As for the Tuskegee case, there *was* oversight. A committee at the Communicable Disease Center (now the Centers for Disease Control and Prevention) decided in 1969 that the study was to be continued—casting some doubt on the "mad scientist" account. Only when details of the study were leaked in 1972 was the project forced to a halt (Brandt 1978). In other words, it took a whistleblower—an individual—to end what the authorities let pass.

By virtue of their bestiality, the Nazi and Tuskegee cases remain persuasive even when badly told. But this is also what makes them miss the mark with regard to research regulation and oversight. The simple fact that some people are capable of murder does not make it reasonable to view every passer-by as a potential murderer. Similarly, atrocities committed in the name of research provide us with no good reason to distrust researchers across the board. What they do point out is what happens when abuse and exploitation is condoned or even encouraged by the society. As with other major crimes, state-sanctioned or not, the solution is hardly to be found in better monitoring.

A better chosen example to illustrate the need for research regulation would be one that points out *genuine and justified uncertainty* regarding researchers' behaviour. It has been observed, for instance, that researchers occasionally impose more than reasonable risks on research subjects (Savulescu 2002). The question is: Should this count as a reason to monitor them even more closely, or to question the efficacy of such measures in cultivating trustworthiness?

5 Limitations of Ethics Review

Independent review by RECs has been argued to serve a key role for maintaining public trust in biomedical research (Hansson 2005). Its success in this regard may depend on how it is presented. It has been noted in other contexts that abundant use of corrective measures breeds further distrust, presumably by implying that there is much to correct (Koski 2007). For similar reasons, other authors have argued that institutionalised distrust should remain "in the shadows, as a distant protective framework for spontaneous trustful actions." (Sztompka 1998) What ethics review does for the *trustworthiness* of research is a different, and for our purposes more important, issue. Ideally, it will help prevent badly designed or otherwise morally problematic research from being carried out. But here, too, are some important limitations to consider.

5.1 Rigidity

The legitimacy of RECs as extra-legal regulatory bodies hinges on their ability to reach rationally justifiable verdicts. This implies, first, a degree of consistency over time and, second, that inconsistencies that do arise can be reasonably attributed to moral progress. Guidelines rarely provide answers clear-cut enough to stave off the threat of indeterminism. For this reason, RECs have been found to rely more on local precedents than on theoretical frameworks (Stark 2012, 165). Through their "institutional memory", RECs are able to embody norms and carry them over to future generations of researchers. But institutional memory can also become a burden that impedes progress. Demands of consistency makes it

impossible to improve one's standards without calling past decisions into question. RECs also become less likely to critique societal norms, which undermines their position as moral authorities (if not as regulatory bodies). For instance, in a society infused with racist ideology, one could hardly trust an REC to reject a Tuskegee-like project. More generally, we cannot trust RECs to react to wrongs that common morality does not conceive of as such, or to abandon principles that no longer protect important values.

5.2 Idiosyncrasy

A main task of RECs is to weigh benefits and risks of proposed projects. The metaphor of *weighing* lends a flavour of objectivity to the procedure, as if it actually involved a set of scales. In reality, reaching consensus is very much an organic process. No matter how competent its members, an REC is not always ideally positioned to evaluate the scientific merits of research projects, especially when they deviate from the paradigm (Fistein and Quilligan 2011). It is tempting therefore to distinguish between "ethical" and "technical" issues, where the former but not the latter would be the responsibility of RECs (McGuinness 2008). But since badly designed research is by definition unethical, this position is difficult to justify.

Worse, arguments passed during REC meetings may not always draw on observations that are rationally related to what they are supposed to assess. In an American study of IRBs (institutional review boards), references to embodied, firsthand knowledge—sometimes even personal life experiences—often turned out to be more persuasive than scientific facts, perhaps because they were harder to challenge directly (Stark 2012, 37). With the independency from research institutions that has become the norm in many countries, RECs usually lack personal knowledge of the applicants and so are unable to keep an extra eye on potential troublemakers (Kerrison and Pollock 2005). Though this was arguably never their responsibility, the fact remains that at least some RECs regard judging the character of the researcher a crucial task. Some come to resort to surrogate measures such as her spelling abilities (Stark 2012, 15–18). It is reasonable to suspect that the diversity in how RECs judge projects—which poses a great problem for researchers—reflects such idiosyncrasies rather than, as is often claimed, local community values (Klitzman and Appelbaum 2012).

5.3 Dependency

A final limitation of RECs consists in the fact that their trustworthiness depends on that of researchers. This is so for several reasons. First, researchers are not merely the objects of evaluation; especially when new areas of research are

broached, their suggestions are sometimes elevated to local precedents (Stark 2012, 49–50). Second, RECs commonly draw at least some of their members from the research community. Third, as RECs are usually not required to ensure that the research protocol is actually followed—which would in any case be prohibitively time-consuming—they will not be able to prevent harmful research unless researchers can be trusted to do what they have proposed to do and nothing else. Fourth, even the most diligent of RECs will sometimes fail to identify risks associated with a proposed project. When both the researcher and the REC fall short in this respect, people might be harmed (Savulescu 2002). In addition, the time and effort that some RECs put into "wordsmithing" informed consent documents (Klitzman and Appelbaum 2012) may leave them little time for such double-checking. The responsibility ever resides with the researchers.

It has been observed in other contexts that in hierarchies of overseers and subjects, distrust tends to propagate upwards (O'Neill 2002, 130–133). The present case seems to be no different: Already voices are heard asking how RECs are to be monitored (Coleman and Bouesseau 2008). If one assumes the moral integrity of researchers to be compromised, such anxiety is understandable. Nevertheless, in the face of the problems we have pointed out, second-order monitoring would be largely unhelpful.

6 More Guidelines are Needed?

Just like ethics review formalises ethical deliberation, guidelines formalise its principles. They are crucial to, but do not imply, institutionalised distrust. To the contrary, there are at least three conceivable normative positions on what they are supposed to achieve. The first two, it turns out, are untenable, while the third requires us to rethink how guidelines are to be written.

6.1 Steering

The first normative position is based on a perceived need for accountability, and thus for steering documents. To preclude corruption, it conceives of a division of labour between legislators, arbitrators (RECs) and subjects (researchers). Just like an engineer fine-tunes the workings of intricate machinery, the rule-maker works with constraints and springs, trying to devise rules that cover any contingency and incentives persuasive enough to ensure compliance. To the degree that the rules require interpretation, RECs have the final say. But the *optimal* document will be one containing nothing but propositions the truth value of which different evaluators will consistently agree on, regardless of their domain knowledge; in other words, a checklist. Guidelines have moved some way toward this ideal. Several items in recent revisions of the Declaration of Helsinki—for instance, those listing

the required contents of research protocols and informed consent forms—lend themselves to box-ticking (World Medical Association 2008).

As tools for minimizing harms resulting from human forgetfulness, checklists have proved immensely useful where mistakes may cause disasters. Successful examples are seen in aviation and some areas of health care (Hales and Pronovost 2006; Haynes et al. 2009). On the downside, checklists may cause "checklist fatigue" and be perceived by doctors as "a limitation to their clinical judgment and autonomous decision making" (Hales and Pronovost 2006). At least some professionals, we believe, will be genuinely concerned about complex decisions being oversimplified rather than simply disgruntled over their loss of authority. Similarly, use of ethics checklists during hospital ward rounds (Sokol 2009) may "reinforce the image of ethics as the application of ready-made concepts and rules" (Eriksson 2010), which is not how it ought to be carried out—or so many ethicists would argue.

Using checklists not only as reminders but to judge performance presents an even more fundamental problem. Any departure from standard procedure—regardless of whether it was in fact the best course of action—will count as an error unless those who judge see fit to grant an exception (and are authorised to do so). In other words, we risk punishing responsible conduct and praising blind rule-following. This problem is not unique to checklists; it pertains to any formal standard against which performance is assessed or judged. Provided that rule-following is not the only value at stake, any rule will occasionally be inapplicable or need to be applied differently than anticipated. In such cases, individual professionals—in our case, researchers—will be morally obligated to break rather than follow protocol. Of course, since they will also bear the consequences, we can expect many to become compliant rather than moral.

6.2 Education

The second normative position, unlike the first, presumes that researchers are motivated to act morally. However, it also presumes that they lack the requisite skills, and conceives of guidelines as the remedy. In practice, researchers familiar with guidelines may well be in minority (Eastwood et al. 1996). They may not be all that different from health care professionals, who are often unfamiliar with codes, have negative attitudes to the growing volume of codes, believe that they have little practical value, seldom use them, and much prefer to rely on previous experience and peers' opinions when making moral judgements (Höglund et al. 2010). One might be inclined to dismiss such attitudes as misplaced scepticism, in itself indicating a need for education. But since the inference makes sense only if we think of guidelines as the "golden standards" of ethical conduct, this would be question-begging.

We should instead ask: Assuming that there is indeed a "moral deficit", will guidelines be helpful in remedying it? Regrettably, they will not. With hundreds

of guidelines applicable to a single research project, going by the book is already nigh impossible. And even if researchers were to read them all, guidelines would offer no panacea. They cannot just be "followed"; deciding which rule should be applied to a particular situation requires judgment—presumably, *moral* judgment (Eriksson et al. 2007). One must then ask what kind of judgment they are intended to support in the first place.

Lastly, if guidelines could actually educate, we should expect more widely recognised and more consistently structured documents—national legislation, for instance—to be at least as crucial to moral conduct. But few of us have more than passing familiarity with the letter of the law, yet most lead mainly lawful and morally responsible lives. Guidelines, just like laws, seem better suited to *express* the current state of morality than to actually educate it.

6.3 Inspiration

Which leads us to the third possibility: that guidelines are to advise or inspire researchers, or serve as "rallying points"—as was the intention of the original Declaration of Helsinki. In practice, prevalent contradictions and ambiguities both within and between documents as well as their sheer volume proves a major hindrance to many researchers. Efforts to make guidelines more specific and thus more easily applicable have only aggravated this problem. Principles and values can be weighed against each other; but how does one weigh a concrete rule, such as one specifying a piece of information to be provided in an informed consent form, against other ethical concerns? Here at least, guidelines fail to give proper guidance (Eriksson et al. 2008). There is also the problem of legibility: All too often, guidelines are infused by increasingly technical language that makes them more or less opaque to all but legal experts.

To truly inspire, guidelines need a much higher level of abstraction than is the case today. On the other hand, they might then lose legitimacy among researchers who have come to expect clear-cut directives. Practical problems aside, it is worth noting that a system resting on documents with a high level of abstraction implies optimism regarding the capacities of individual researchers, and thus is fundamentally different from one that embraces institutionalised distrust.

7 What We Risk

More numerous and more detailed guidelines, more oversight and more severe punishment of deviants may be less effective than one would think. Still, one might argue that less effective is better than nothing. Such measures may at least, the argument goes, convey the gravity of the matter and make researchers aware of moral issues that they would otherwise have overlooked or ignored. Unfortunately,

however, they also entail risks against which such potential benefits must be weighed. They all have in common that they pertain to researchers' moral competence, and thus to the ability of future generations to handle unexpected moral problems, such as those that arise during the course of a project. As the Tuskegee case has taught us, this threat is not to be taken lightly.

7.1 Blinkering

Among the topics discussed in contemporary bioethics, informed consent has received most attention by far (Hoeyer 2008). Though there is significant disagreement on what we can hope to achieve through informed consent (Hoeyer 2003; Ducournau and Strand 2009; Dixon-Woods et al. 2007; Manson and O'Neill 2007), there seems to be some agreement that not all ethical concerns are covered by it. For instance, while people might be able to protect their *individual* interests by refusing to participate in research, doing so does not help them voice any concerns they might have about the *societal* effects of a particular project (O'Doherty et al. 2011). This is not just a marginal issue. At least in Sweden, what matters most to people may not be that they are informed of all details of a study, but that its results are readily applicable, that its benefits are justly distributed, and that commercial interests do not determine the research outlook (Hoeyer et al. 2005b). These matters are both largely opaque to research participants and unlikely to influence REC decisions.

Nevertheless, informed consent seems to all but dominate the review process. According to one study, informed consent was the most frequent cause for discussion between researchers and RECs (Edwards et al. 2011). Some RECs spend much time on the wording of informed consent documents because such issues seem particularly susceptible to objective resolution (Coleman and Bouesseau 2008) or because they find that there is little else about a project that they can control (Hoeyer et al. 2005a). In qualitative research, the requirements imposed by ethics review have been claimed to distract researchers from more pressing moral problems (Bosk and de Vries 2004). In short, bureaucratic procedures entail a risk that important but less "manageable" moral matters are left unaddressed.

7.2 Heteronomy

One of the many contributions of 18th century philosopher Immanuel Kant was his idea that to act morally is to act out of the moral duties prescribed by practical reason. This process, commonly referred to as self-legislation, is guided by formal principles that preclude any arbitrariness. Kant did not claim that we ought to do without laws or regulations, only that they can never provide sufficient moral reasons for acting. Whenever we act for any other reason than out of duty, we do not,

says Kant, act morally. This pertains even to actions that are lawful, bring about good consequences, and do not violate any moral duties: Unless the maxim of action is chosen *because* it is one's duty, one does not act morally, but only *legally*.

Two hundred-odd years later, Kant's idea of self-legislation—a kind of moral authorship—remains convincing. In contrast, the division of labour between legislators, arbitrators and subjects that we see in research ethics is a pragmatic move less about doing ethics than about restricting the range of problems that can be discussed on each level. Some researchers are happy with this because it allows them to concentrate on their research while remaining confident that ethical matters are taken care of by others (Wainwright et al. 2006). On the other hand, to judge from ethics review applications, many researchers fail to recognise moral problems in their projects because they view them solely through a legalistic perspective (Hoff 2003). Standardised procedures and ready-made checklists may be to blame, as they provide researchers with neither reason nor opportunity to practice their moral skills.

Of course, barring legal imperatives, morality could still lose out to naïveté or complacency. Which one of complacency and legalism is the worst vice remains an open question; it comes down, we suspect, to long-term consequences. But whereas naiveté can be cured simply by pointing out whatever moral problem has gone unnoticed, researchers suffering from legalism can be expected to continue to ignore them, comfortable with the fact that formal requirements have been met. This makes them particularly ill prepared to handle unexpected moral problems.

7.3 Alienation

With an increasing number of documents to follow and no clear guidance to how they relate to each other, researchers will increasingly find themselves subjected to contradicting requirements (Eriksson et al. 2008). Unless they learn to ignore some of them, they will fail to resolve moral problems. For instance, many biobank researchers think that reconsent must be sought when samples are to be used for new purposes, but many of them also claim that doing so would be practically impossible (Edwards et al. 2011). In a single system of norms, this conflict would be resolved by concluding either that previously obtained samples ought not to be reused or that reconsent cannot be a universal requirement. That the contradiction remains suggests that many researchers struggle with inconsistent sets of norms.

Further, there have been disconcerting reports of researchers experiencing more harmful than beneficial effects of ethics review, mostly related to excessive delay of projects (Edwards et al. 2011). Others see review as a merely symbolic activity (Fistein and Quilligan 2011). Ethnographic researchers in particular have complained that their research is often misunderstood and rejected by RECs for nonsensical reasons, while the real moral dilemmas encountered on the field cannot possibly be predicted let alone fitted into an application (Bosk and de Vries

2004). Some researchers have begun to delegate the task of filling out the review application (Kerrison and Pollock 2005). This is in line with experiences from health care, where regulatory approaches to ensuring moral conduct tend to foster "don't get caught" attitudes (Mills and Spencer 2001). As these examples point out, it is quite possible to acknowledge and even adhere to ethical demands while simultaneously *alienating* oneself from them. Since ethics and morality thrive on involved argument and debate, this is a development that neither researchers nor academic research ethics can afford.

8 Trustworthiness Through Individual Responsibility

Institutionalised distrust and its implementation through concrete and well-defined rules, systems of oversight, and clear incentive structures may bring benefits: increased short-time compliance, reassurance to the public, and protection against governmental infringement of the autonomy of research. Its limitations notwithstanding, worthwhile alternatives may seem to be lacking. As we know that research quality suffers from researchers' breaking of rules, must we not take steps to ensure better compliance? To be sure, if ethical conduct implied rule-following, anything less than perfect compliance would be unacceptable. But as we have argued in this paper, responsible conduct often runs obliquely to compliance with rules, and even where they intersect, institutionalised distrust may backfire, undermining rather than supporting morality. We do not hereby claim that any kind of regulation is counterproductive; after all, most of us do not habitually break laws. But for most of us, abiding by the law is unproblematic since we have already acquired certain moral standards at an early age. Many minor offences—speeding, for instance—are committed not because people are unfamiliar with the law, but because certain laws lack legitimacy in the eyes of the public. We can expect much the same in research ethics: Unless a norm is sufficiently internalised, enforcing it will be less effective than it could be.

How are we to ensure that the appropriate norms are internalised? An interesting point has been made by Martinson et al. (2005) about the possible causes of scientific misconduct. The authors conclude that the very abundance of misconduct counts against the predominant view of it as the province of occasional bad apples. They suggest, instead, that explanations be sought in the pressure that comes from fierce competition and burdensome regulations. Though this may not be the whole story, it seems to be in line with concerns expressed by other authors that financial rewards and promise of personal advancement may compromise research integrity (Koski 2007) and that the culture of secrecy that so often prevails in scientific institutions may increase the likelihood of both inadvertent errors and fraud (Wicherts 2011). Together, these findings point out *abundance of incentives* and *shortage of norms* as a particularly unfortunate pair. Tighter regulation may be a bad choice of remedy precisely because it adds yet another layer of incentives without—we suspect—making researchers more likely to internalise

the norms in question. If our assumption is correct, regulation will succeed in directing action appropriately only insofar as the rules are designed *just right.* Moreover, equating ethics with rule-following risks undermining moral agency in the long run since researchers do not get to practice their moral skills. Therefore, once reasonably effective measures—sound cultural and social norms, legislation that prohibits abuse, and independent review—are in place to counter worst-case scenarios, cures to more prevalent maladies must be sought elsewhere.

8.1 Play to the Strength of RECs

Many RECs have, through training and tradition, acquired a great deal of ethical and scientific competence. Though we can hardly do without them, there may be much to gain from rethinking their role in a way that plays more to their strengths. First and foremost, RECs should be required to rationally justify their decisions. At least in Sweden, this is not standard practice with regard to approved projects. Not only would such a practice be crucial to quality assurance; it would also offer an opportunity to educate those researchers that take ethics seriously but lack experience, and serve to reinforce the legitimacy of the review process. Face-to-face meetings—though time-consuming—are preferable since they also allow REC members to become familiar with the applicants and their capacities for ethical decision-making (Hedgecoe 2012). This would aid the risk-benefit analysis, potentially reducing the number of idiosyncratic decision. Such meetings also encourage a more dynamic and nuanced ethical discourse, effectively countering rigidity. Ideally, after approval, the REC should remain available to researchers as an advisory body with whom the researchers may discuss ethical concerns that have arisen during the course of the project. In such a system, the dependency of RECs on the moral agency of researchers need no longer be considered a deficiency.

8.2 Use Guidelines Judiciously

We have argued that using guidelines as regulatory tools is a move away from the discursive nature of ethics, and so risks inhibiting rather than supporting the moral agency of researchers. If ethical guidelines are to actually inspire researchers to make better decisions, they must have a sufficiently high level of abstraction to give room for deliberation. They must never be allowed to degenerate into checklists. It can even be doubted whether guidelines can ever afford to list specific requirements, since this inevitably changes the way the document is conceived of and applied. The Declaration of Helsinki is just one of many examples where the authors might have taken the wrong turn towards legalism. If worst comes to worst, moral deliberation is reduced to box-ticking. Of course, specific rules—or

even laws—may be inevitable where there is a considerable risk of harm. But as we have pointed out, the risks we run by under-regulating research must always be weighed against the potential damage done by over-regulating it. This should be possible to avoid if we, instead of seeing guidelines as standards against which research conduct should be tried and measured, regard them as statements in the ongoing debate on proper research conduct.

The sheer volume of ethical guidelines out there is a problem in itself. In general, we believe that sticking to a few generally aimed documents the legitimacy of which is widely accepted is much preferable to developing specific guidelines, even though the former may leave some issues underdetermined. When specific guidelines cannot be avoided, their relationships with other documents that pertain to the same field must be explicitly stated rather than ignored. Researchers should not be left in the dark as to how conflicts between different documents are intended to be resolved.

8.3 Nurture Individual Moral Competence

We have argued that neglecting the moral competence of researchers paves the way for disaster. It has been long known to social scientists doing field work (Anspach and Mizrachi 2006), but should be recognised by biomedical researchers as well, that researchers must be prepared to handle unexpected ethical problems that they alone are in a position to handle. To this end, developing deliberative skills is arguably more important than learning the ins and outs of ethics guidelines (Eriksson et al. 2008). Ethical reflection must be a process that continues naturally throughout any research project (Halavais 2011). Efforts on the part of researchers to cultivate their skills should be coupled with greater trust from RECs (Miller and Boulton 2007).

8.4 Peer Review and Openness in Research Institutions

Given that cultural, economical or organisational factors may be crucial to researchers' prospects of acting morally, it is imperative to nurture openness within research institutions. One possibility is to complement ethics review with professional self-regulation through peer review (Murphy and Dingwall 2007). Such a system does not necessarily have to be formalised: Encouraging researchers to systematically having a trusted peer comment on study design and double-checking their data might suffice. The benefits of such an approach are most readily apparent with regard to ensuring proper scientific conduct, but it is reasonable to expect openness to stimulate ethical discourse not just on proper handling of data but on a wide variety of issues.

Researchers must also take care not to restrict their interaction with the outside world to publications in scientific journals. By communicating with the public through lay media and with colleagues through, for instance, hospital- or institution-based lectures and seminars, researchers could find much-needed opportunities to practice voicing ethical concerns about their research as well as justifying it to others.

9 Conclusion

Moral conduct—in research or otherwise—implies moral discretion and competence. We have argued in this paper that research ethics cannot be a matter of bioethicists drawing up documents and procedures which are then applied by the professionals. Ethics must, if it is to remain a practice of its own rather than developing into a branch of jurisprudence, be practiced through discourse. For this reason we need ethics review to be an arena for researchers to discuss their research, receive advice, and practice their ethics skills, and guidelines to be generally applicable, value-based and inspirational rather than specific, rule-based and regulative.

Whatever doubts we may have about the moral competence of researchers, in the long run it will be crucial to morally acceptable research. Though institutionalised distrust may still have its place in the regulation of biomedical research, much is to be gained by reworking ethics review and ethical guidelines to meet another end: supporting researchers in taking individual responsibility for their research.

10 Postscript

Current trends in biobank research regulation make it evident that we are busy building a system that has no hope of ever becoming foolproof, although its growing complexity has made it increasingly opaque. Yet we are reluctant to abandon ship. Piecemeal approaches—in particular, the plugging of perceived gaps in statutory law by means of ethics guidelines—do not contribute to the internalisation of moral norms, but serve instead to aggravate the confusion. The position defended in this paper implies that biobank researchers have a nonconferrable moral responsibility for judging their work in the context of larger societal trends and informed by shared norms and values. Efforts to secure the “autonomy” of donors do not exhaust the range of ethical questions that ought to be asked. A researcher might ask, for instance, in what way his or her research contributes to equitable health care. Ethics guidelines should aim to inspire such ethical reflection rather than to promote simple rule-following.

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