

COWDEN SYNDROME

A 3-in-1 Medical Reference

A Bibliography and Dictionary
for Physicians, Patients,
and Genome Researchers

TO INTERNET REFERENCES

COWDEN SYNDROME

A BIBLIOGRAPHY AND
DICTIONARY

FOR PHYSICIANS, PATIENTS,
AND GENOME RESEARCHERS



JAMES N. PARKER, M.D.
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The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on Cowden syndrome. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

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CHAPTER 1. INTRODUCTION

In March 2001, the National Institutes of Health issued the following warning: “The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading.”¹ Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with Cowden syndrome is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about Cowden syndrome, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to Cowden syndrome, from the essentials to the most advanced areas of research. Special attention has been paid to present the genetic basis and pattern of inheritance of Cowden syndrome. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on Cowden syndrome. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to Cowden syndrome, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

¹ From the NIH, National Cancer Institute (NCI): <http://www.cancer.gov/>.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. We hope these resources will prove useful to the widest possible audience seeking information on Cowden syndrome.

The Editors

CHAPTER 2. STUDIES ON COWDEN SYNDROME

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on Cowden syndrome. For those interested in basic information about Cowden syndrome, we begin with a condition summary published by the National Library of Medicine.

Genetics Home Reference

Genetics Home Reference (GHR) is the National Library of Medicine's Web site for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions. Here you can find a condition summary on Cowden syndrome that describes the major features of the condition, provides information about the condition's genetic basis, and explains its pattern of inheritance. In addition, a summary of the gene or chromosome related to Cowden syndrome is provided.²

The Genetics Home Reference has recently published the following summary for Cowden syndrome:

What Is Cowden Syndrome?³

Cowden syndrome is a rare disorder characterized by multiple noncancerous, tumor-like growths called hamartomas and an increased risk of developing certain cancers.

Almost everyone with Cowden syndrome develops hamartomas. These growths are most commonly found on the skin and mucous membranes (such as the lining of the mouth and nose), but can also occur in the intestinal tract and other parts of the body. Abnormal growths on the skin and mucous membranes typically appear by a person's late twenties.

² This section has been adapted from the National Library of Medicine: <http://ghr.nlm.nih.gov/>.

³ Adapted from the Genetics Home Reference of the National Library of Medicine: <http://ghr.nlm.nih.gov/condition=cowdensyndrome>.

People with Cowden syndrome have an increased risk of developing several types of cancer, including cancers of the breast, thyroid, and the lining of the uterus (the endometrium). Noncancerous breast and thyroid diseases are also common. Other signs and symptoms of Cowden syndrome can include an enlarged head (macrocephaly); a rare, noncancerous brain tumor called Lhermitte-Duclos disease; and mental retardation.

How Common Is Cowden Syndrome?

Researchers estimate that Cowden syndrome affects about 1 in 200,000 people; however, the exact prevalence of this condition is unknown because it can be difficult to diagnose.

What Genes Are Related to Cowden Syndrome?

Mutations in the **PTEN** (<http://ghr.nlm.nih.gov/gene=pten>) gene cause Cowden syndrome.

PTEN is a tumor suppressor gene, which means that it normally prevents cells from growing and dividing too rapidly or in an uncontrolled way. Mutations in the PTEN gene have been identified in about 85 percent of people with Cowden syndrome. These mutations, which affect all of the body's cells, prevent the PTEN protein from effectively regulating cell survival and division. Uncontrolled cell division can lead to the formation of hamartomas and cancerous tumors.

The cause of the remaining Cowden syndrome cases is unknown. Mutations in a region of DNA that regulates the activity of the PTEN gene may be responsible for some cases of this condition.

How Do People Inherit Cowden Syndrome?

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to increase the risk of developing noncancerous and cancerous tumors.

In some cases, an affected person inherits the mutation from one affected parent. Other cases may result from new mutations in the gene. These cases occur in people with no history of the disorder in their family.

Where Can I Find Additional Information about Cowden Syndrome?

You may find the following resources about Cowden syndrome helpful. These materials are written for the general public.

MedlinePlus - Health Information

- <http://www.nlm.nih.gov/medlineplus/cancer.html>

Educational Resources - Information Pages

- Madisons Foundation:
<http://www.madisonsfoundation.org/content/3/1/display.asp?did=537>
- Orphanet:
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=201
- University of Virginia Health System:
http://www.healthsystem.virginia.edu/uvahealth/adult_breast/cowden.cfm

Patient Support - for Patients and Families

- American Cancer Society:
<http://www.cancer.org>
- National Coalition for Cancer Survivorship:
<http://www.canceradvocacy.org>
- Resource list from the University of Kansas Medical Center:
<http://www.kumc.edu/gec/support/cancer.html>

Professional Resources

You may also be interested in these resources, which are designed for healthcare professionals and researchers.

- Gene Reviews - Clinical summary:
<http://www.genetests.org/query?dz=phts>
- Gene Tests - DNA tests ordered by healthcare professionals:
<http://www.genetests.org/query?testid=53766>
- PubMed - Recent literature:
<http://ghr.nlm.nih.gov/condition=cowdensyndrome/show/PubMed;jsessionid=16F137EDB29B3CD400578A78FEE0E07B>
- OMIM - Genetic disorder catalog:
<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=158350>

References

These sources were used to develop the Genetics Home Reference condition summary on Cowden syndrome.

- de Jong MM, Nolte IM, te Meerman GJ, van der Graaf WT, Oosterwijk JC, Kleibeuker JH, Schaapveld M, de Vries EG. Genes other than BRCA1 and BRCA2 involved in breast cancer susceptibility. J Med Genet. 2002 Apr;39(4):225-42. Review. PubMed citation
- Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000 Nov;37(11):828-30. No abstract available. PubMed citation
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- Kelly P. Hereditary breast cancer considering Cowden syndrome: a case study. *Cancer Nurs.* 2003 Oct;26(5):370-5. PubMed citation
- Pilarski R, Eng C. Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. *J Med Genet.* 2004 May;41(5):323-6. Review. No abstract available. PubMed citation
- Waite KA, Eng C. Protean PTEN: form and function. *Am J Hum Genet.* 2002 Apr;70(4):829-44. Review. PubMed citation
- Zhou XP, Waite KA, Pilarski R, Hampel H, Fernandez MJ, Bos C, Dasouki M, Feldman GL, Greenberg LA, Ivanovich J, Matloff E, Patterson A, Pierpont ME, Russo D, Nassif NT, Eng C. Germline PTEN promoter mutations and deletions in Cowden/Bannayan-Riley-Ruvalcaba syndrome result in aberrant PTEN protein and dysregulation of the phosphoinositol-3-kinase/Akt pathway. *Am J Hum Genet.* 2003 Aug;73(2):404-11. Epub 2003 Jul 03. PubMed citation

A summary of the gene related to Cowden syndrome is provided below:

What Is the Official Name of the PTEN Gene?⁴

The official name of this gene is “phosphatase and tensin homolog (mutated in multiple advanced cancers 1).”

PTEN is the gene's official symbol. The PTEN gene is also known by other names, listed below.

What Is the Normal Function of the PTEN Gene?

The PTEN gene acts as a tumor suppressor gene, which means that it helps regulate the cycle of cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. The PTEN gene provides instructions for making a protein that is found in almost all tissues in the body. This protein modifies other proteins and fats (lipids) by removing phosphate groups, which consist of three oxygen atoms and one phosphorus atom. Based on this activity, the PTEN protein is a type of enzyme called a phosphatase.

The PTEN enzyme acts as part of a chemical pathway that signals cells to stop dividing and triggers cells to self-destruct (undergo apoptosis) when necessary. These functions prevent uncontrolled cell growth that can lead to the formation of tumors. Evidence also suggests that the PTEN enzyme helps control cell movement (migration), the sticking (adhesion) of cells to surrounding tissues, and the formation of new blood vessels (angiogenesis).

⁴ Adapted from the Genetics Home Reference of the National Library of Medicine:
<http://ghr.nlm.nih.gov/gene=pten;jsessionid=16F137EDB29B3CD400578A78FEE0E07B>.

What Conditions Are Related to the PTEN Gene?

Cowden Syndrome - Caused by Mutations in the PTEN Gene

Researchers have identified more than 100 mutations in the PTEN gene that can cause Cowden syndrome. These mutations, which affect all of the body's cells, include changes in a small number of DNA building blocks (base pairs) and, in some cases, deletions of a large number of base pairs from the gene. PTEN mutations cause the gene to make a version of the PTEN enzyme that does not function properly or does not work at all. The defective enzyme is unable to restrain cell division or signal abnormal cells to die, which can lead to the development of noncancerous growths called hamartomas and cancerous tumors.

Other Disorders - Caused by Mutations in the PTEN Gene

Researchers have identified more than 100 mutations in the PTEN gene that can cause Cowden syndrome. These mutations, which affect all of the body's cells, include changes in a small number of DNA building blocks (base pairs) and, in some cases, deletions of a large number of base pairs from the gene. PTEN mutations cause the gene to make a version of the PTEN enzyme that does not function properly or does not work at all. The defective enzyme is unable to restrain cell division or signal abnormal cells to die, which can lead to the development of noncancerous growths called hamartomas and cancerous tumors.

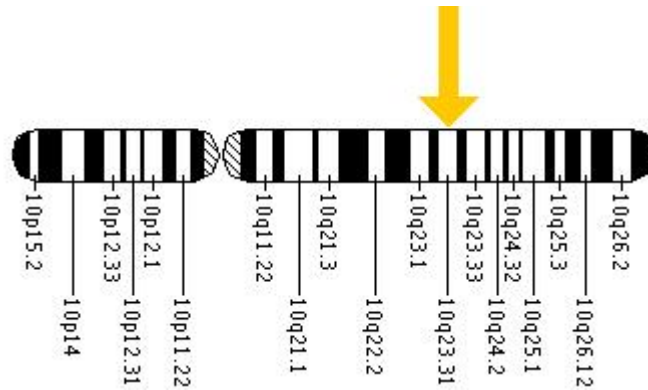
Other Cancers - Associated with the PTEN Gene

Mutations in the PTEN gene cause several other disorders that are characterized by the development of noncancerous tumor-like growths called hamartomas. These disorders include Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome. Together, the disorders caused by PTEN mutations are called PTEN hamartoma tumor syndromes (PHTS). The mutations responsible for these syndromes are present in all of the body's cells. Some of these mutations lead to a defective version of the PTEN enzyme that cannot perform its function as a tumor suppressor. Other mutations prevent the PTEN gene from producing any enzyme. Without the PTEN enzyme, cells can divide in an uncontrolled way and damaged cells continue to divide inappropriately, leading to the development of hamartomas.

Where Is the PTEN Gene Located?

Cytogenetic Location: 10q23.3

Molecular Location on chromosome 10: base pairs 89,613,174 to 89,716,381



The PTEN gene is located on the long (q) arm of chromosome 10 at position 23.3.

More precisely, the PTEN gene is located from base pair 89,613,174 to base pair 89,716,381 on chromosome 10.

References

These sources were used to develop the Genetics Home Reference gene summary on the PTEN gene.

- Chu EC, Tarnawski AS. PTEN regulatory functions in tumor suppression and cell biology. *Med Sci Monit.* 2004 Oct;10(10):RA235-41. Epub 2004 Sep 23. Review. PubMed citation
- Eng C. PTEN: one gene, many syndromes. *Hum Mutat.* 2003 Sep;22(3):183-98. Review. PubMed citation
- Gene Review: PTEN Hamartoma Tumor Syndrome (PHTS)
- Hamada K, Sasaki T, Koni PA, Natsui M, Kishimoto H, Sasaki J, Yajima N, Horie Y, Hasegawa G, Naito M, Miyazaki J, Suda T, Itoh H, Nakao K, Mak TW, Nakano T, Suzuki A. The PTEN/PI3K pathway governs normal vascular development and tumor angiogenesis. *Genes Dev.* 2005 Sep 1;19(17):2054-65. Epub 2005 Aug 17. PubMed citation
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- Sansal I, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. *J Clin Oncol.* 2004 Jul 15;22(14):2954-63. Review. PubMed citation
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- Zhou XP, Waite KA, Pilarski R, Hampel H, Fernandez MJ, Bos C, Dasouki M, Feldman GL, Greenberg LA, Ivanovich J, Matloff E, Patterson A, Pierpont ME, Russo D, Nassif NT, Eng C. Germline PTEN promoter mutations and deletions in Cowden/Bannayan-Riley-Ruvalcaba syndrome result in aberrant PTEN protein and dysregulation of the

phosphoinositol-3-kinase/ Akt pathway. Am J Hum Genet. 2003 Aug;73(2):404-11. Epub 2003 Jul 03. PubMed citation

Federally Funded Research on Cowden Syndrome

The U.S. Government supports a variety of research studies relating to Cowden syndrome. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.⁵

NTIS (National Technical Information Service)

The NTIS (www.ntis.gov), a service of the U.S. Department of Commerce, has published the following information on sponsored studies related to Cowden syndrome:

- **"Novel Phosphatase Gene on 10q23, MINPP, in Hereditary and Sporadic Breast Cancer. - Annual rept. 1 Aug 2000-31 Jul 2001,"** published in August 2001.

Sponsored by: Ohio State Univ., Columbus.

Written by: C. Eng.

Abstract: PTEN is a tumor suppressor gene on 10q23 and encodes a dual specificity phosphatase. One of the major substrates for PTEN is phosphatidylinositol (3,4,5) triphosphate in the PI3 kinase pathway. When PTEN is dysfunctional or absent, P-Akt is high and hence, anti-apoptotic. PTEN is a major susceptibility gene for **Cowden syndrome** (CS), a hereditary disorder with a high risk of breast and thyroid cancer, and appears to be involved in a broad range of tumors. In addition, germline PTEN mutations have been found in a developmental disorder, Bannayan-Riley-Ruvalcaba syndrome (BRR) as well. This is an autosomal dominant disorder characterised by macrocephaly, lipomatosis, hemangiomas and speckled penis. Previously not thought to be associated with cancer risk, BRR families and cases with germline PTEN mutations have recently been shown to be at risk for cancers and especially breast tumors. Between 10- 80% (mean 60%) of CS families and 60% of BRR individuals have germline PTEN mutations. Families that do not have germline PTEN mutations are not inconsistent with linkage to the 10q22-23 region. Thus, genes with related function to PTEN in the 10q21-q25 region are good candidate genes for PTEN mutation negative CS, BRR and related sporadic tumors, eg, those of the breast and thyroid. MINPPI lies no more than 1 Mb upstream of PTEN and encodes an inositol polyphosphate phosphatase. In Year 1 of this award, the PI has ascertained 14 unrelated CS probands, 22 BRR probands and 20 CS-like probands known not to harbor germline PTEN mutations. To date, they have not been found to carry germline MINPPI mutations. We found 4 malignant and 3 benign thyroid tumors to harbor deletion or intragenic mutation of MINPPI. More interestingly, IVS3+34T>A was found in about 15% of FA cases and normal controls but not in patients with FTC.

- **"Novel Phosphatase Gene on 10q23, MINPP, in Hereditary and Sporadic Breast Cancer. - Final rept. 1 Aug 2000-31 Jul 2003,"** published in August 2003.

Sponsored by: Ohio State Univ. Research Foundation, Columbus.

⁵ Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

Written by: C. Eng.

Abstract: PTEN is a tumor suppressor gene on 10q23 and encodes a dual specificity phosphatase. One of the major substrates for PTEN is phosphatidylinositol (3,4,5) triphosphate in the P13 kinase pathway. When PTEN is dysfunctional or absent, P-Akt is high and hence, anti-apoptotic. PTEN is a major susceptibility gene for **Cowden syndrome** (CS), a hereditary disorder with a high risk of breast and thyroid cancer, and appears to be involved in a broad range of tumors. In addition, germline PTEN mutations have been found in a developmental disorder, Bannayan-Riley-Ruvalcaba syndrome (ERR) as well. Previously not thought to be associated with cancer risk, ERR families and cases with germline PTEN mutations have recently been shown to be at risk for cancers and especially breast tumors. Between 10-80% (mean 60%) of CS families and 60% of ERR individuals have germline PTEN mutations. Families that do not have germline PTEN mutations are not inconsistent with linkage to the 10q22-23 region. Thus, genes with related function to PTEN in the 10q21-q25 region are good candidates genes for PTEN mutation negative CS, ERR and related sporadic tumors, eg, those of the breast and thyroid. MINPP1 lies no more than 1 Mb upstream of PTEN and encodes an inositol polyphosphate phosphatase. While we have found no intragenic germline MINPP1 mutation in CS and ERR, MINPP1 has been found to be co-deleted with PTEN in one case of ERR with prominent GI features. MINPP1 also appears to act as a low penetrance susceptibility gene for sporadic follicular thyroid neoplasia but not breast cancer. While no somatic intragenic MINPP1 mutations were found in whole breast cancers, co-deletion of PTEN and MINPP1 occur in 30-40% of sporadic breast carcinomas. More interestingly, these codeletions have been shown to occur in the stroma. Therefore, MINPP1 plays a comodulatory (non-traditional) role in hereditary and sporadic breast cancer.

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.⁶ The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with Cowden syndrome, simply go to the PubMed Web site at <http://www.ncbi.nlm.nih.gov/pubmed>. Type **Cowden syndrome** (or synonyms) into the search box, and click **Go**. The following is the type of output you can expect from PubMed for Cowden syndrome (hyperlinks lead to article summaries):

⁶ PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

- A case of Cowden's disease accompanied by prostatic cancer.**
 Author(s): Inagaki T, Ebisuno S.
 Source: British Journal of Urology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8705235&query_hl=18&itool=pubmed_docsum
- A family with lesions on the face, hands, and buccal mucosa. Cowden's disease.**
 Author(s): Steffen C, Milligan M, Duboise J.
 Source: Archives of Dermatology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8239708&query_hl=18&itool=pubmed_docsum
- Alimentary tract lesions in Cowden's disease.**
 Author(s): Taylor AJ, Dodds WJ, Stewart ET.
 Source: The British Journal of Radiology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2684322&query_hl=18&itool=pubmed_docsum
- Allelic imbalance, including deletion of PTEN/MMAC1, at the Cowden disease locus on 10q22-23, in hamartomas from patients with Cowden syndrome and germline PTEN mutation.**
 Author(s): Marsh DJ, Dahia PL, Coulon V, Zheng Z, Dorion-Bonnet F, Call KM, Little R, Lin AY, Eeles RA, Goldstein AM, Hodgson SV, Richardson AL, Robinson BG, Weber HC, Longy M, Eng C.
 Source: Genes, Chromosomes & Cancer.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9443042&query_hl=17&itool=pubmed_docsum
- An overlap of Cowden's disease and Bannayan-Riley-Ruvalcaba syndrome in the same family.**
 Author(s): Perriard J, Saurat JH, Harms M.
 Source: Journal of the American Academy of Dermatology.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10640930&query_hl=18&itool=pubmed_docsum
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APPENDICES

APPENDIX A. HELP ME UNDERSTAND GENETICS

Overview

This appendix presents basic information about genetics in clear language and provides links to online resources.⁷

The Basics: Genes and How They Work

This section gives you information on the basics of cells, DNA, genes, chromosomes, and proteins.

What Is a Cell?

Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. Cells also contain the body's hereditary material and can make copies of themselves.

Cells have many parts, each with a different function. Some of these parts, called organelles, are specialized structures that perform certain tasks within the cell. Human cells contain the following major parts, listed in alphabetical order:

- **Cytoplasm:** The cytoplasm is fluid inside the cell that surrounds the organelles.
- **Endoplasmic reticulum (ER):** This organelle helps process molecules created by the cell and transport them to their specific destinations either inside or outside the cell.
- **Golgi apparatus:** The golgi apparatus packages molecules processed by the endoplasmic reticulum to be transported out of the cell.
- **Lysosomes and peroxisomes:** These organelles are the recycling center of the cell. They digest foreign bacteria that invade the cell, rid the cell of toxic substances, and recycle worn-out cell components.

⁷ This appendix is an excerpt from the National Library of Medicine's handbook, *Help Me Understand Genetics*. For the full text of the *Help Me Understand Genetics* handbook, see <http://ghr.nlm.nih.gov/handbook>.

- **Mitochondria:** Mitochondria are complex organelles that convert energy from food into a form that the cell can use. They have their own genetic material, separate from the DNA in the nucleus, and can make copies of themselves.
- **Nucleus:** The nucleus serves as the cell's command center, sending directions to the cell to grow, mature, divide, or die. It also houses DNA (deoxyribonucleic acid), the cell's hereditary material. The nucleus is surrounded by a membrane called the nuclear envelope, which protects the DNA and separates the nucleus from the rest of the cell.
- **Plasma membrane:** The plasma membrane is the outer lining of the cell. It separates the cell from its environment and allows materials to enter and leave the cell.
- **Ribosomes:** Ribosomes are organelles that process the cell's genetic instructions to create proteins. These organelles can float freely in the cytoplasm or be connected to the endoplasmic reticulum.

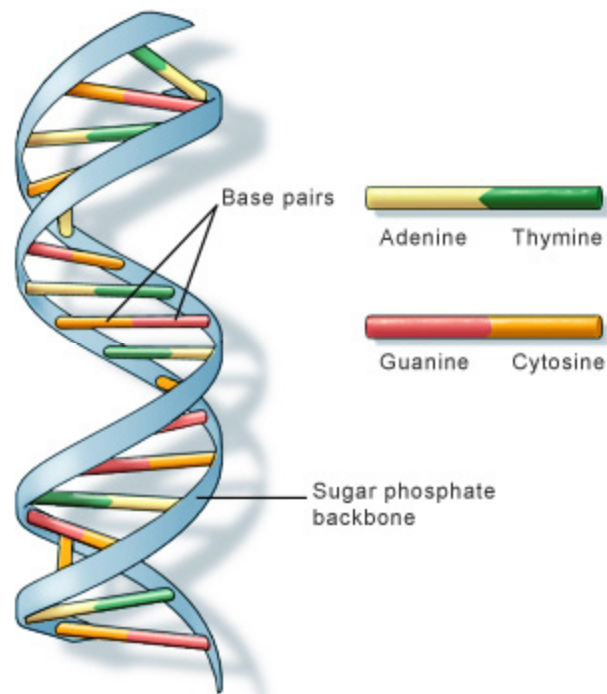
What Is DNA?

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA).

The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences.

DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base is also attached to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.

An important property of DNA is that it can replicate, or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell.



U.S. National Library of Medicine

DNA is a double helix formed by base pairs attached to a sugar-phosphate backbone.

What Is Mitochondrial DNA?

Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA or mtDNA.

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus (the cytoplasm).

Mitochondria produce energy through a process called oxidative phosphorylation. This process uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. A set of enzyme complexes, designated as complexes I-V, carry out oxidative phosphorylation within mitochondria.

In addition to energy production, mitochondria play a role in several other cellular activities. For example, mitochondria help regulate the self-destruction of cells (apoptosis). They are also necessary for the production of substances such as cholesterol and heme (a component of hemoglobin, the molecule that carries oxygen in the blood).

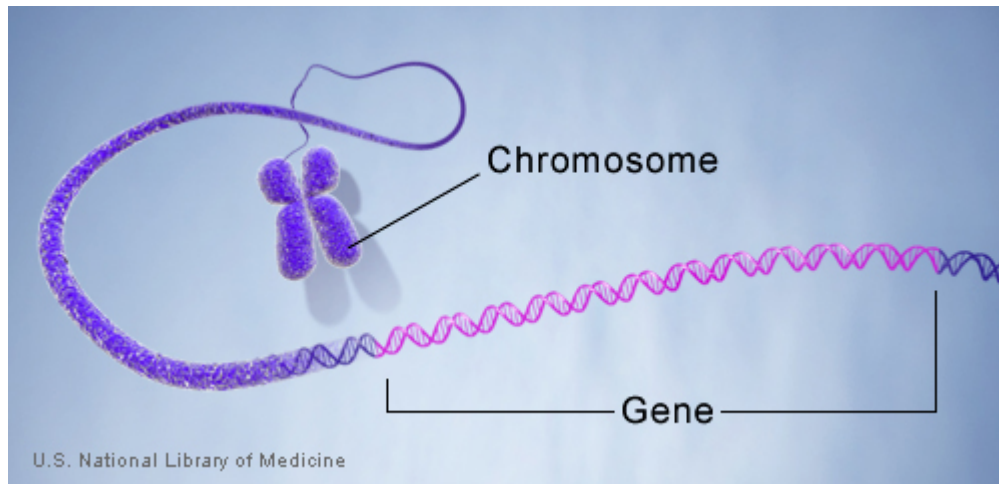
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), which are chemical cousins of

DNA. These types of RNA help assemble protein building blocks (amino acids) into functioning proteins.

What Is a Gene?

A gene is the basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 20,000 and 25,000 genes.

Every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1 percent of the total) are slightly different between people. Alleles are forms of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features.



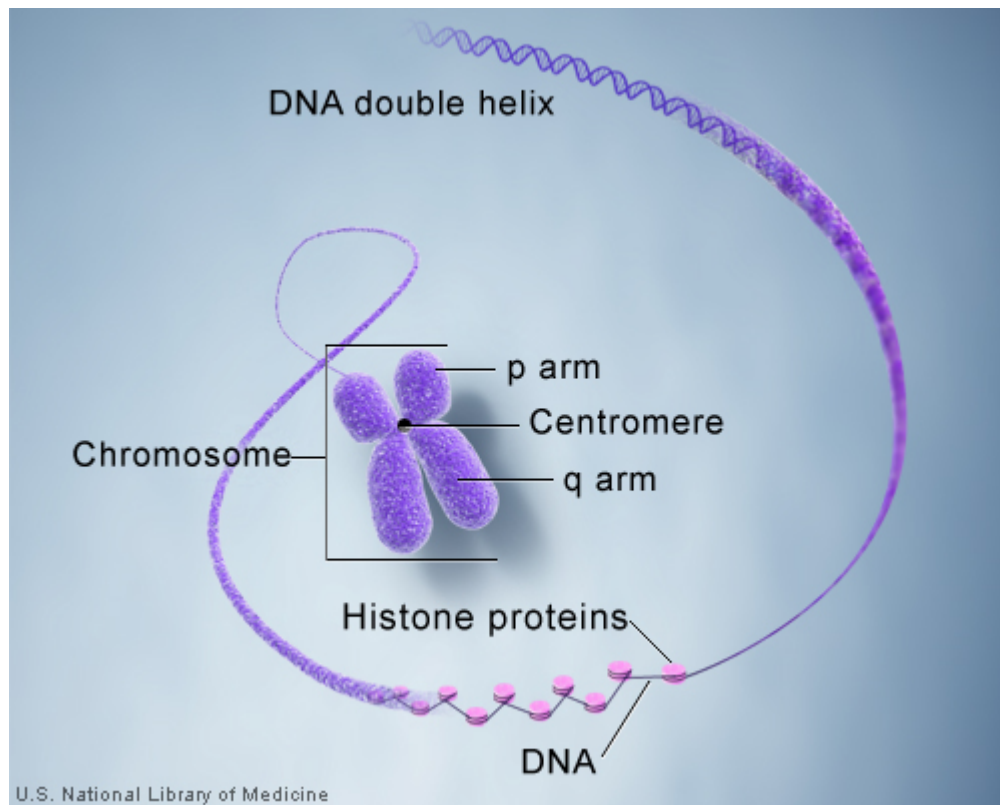
Genes are made up of DNA. Each chromosome contains many genes.

What Is a Chromosome?

In the nucleus of each cell, the DNA molecule is packaged into thread-like structures called chromosomes. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

Chromosomes are not visible in the cell's nucleus—not even under a microscope—when the cell is not dividing. However, the DNA that makes up chromosomes becomes more tightly packed during cell division and is then visible under a microscope. Most of what researchers know about chromosomes was learned by observing chromosomes during cell division.

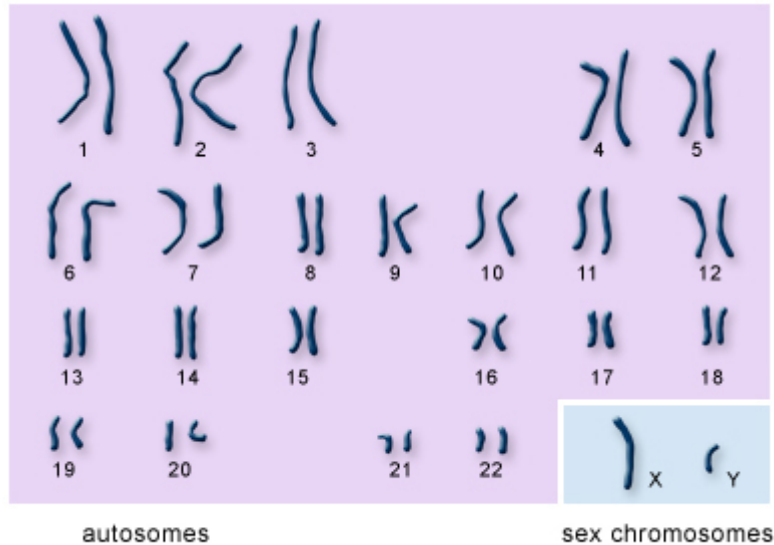
Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome its characteristic shape, and can be used to help describe the location of specific genes.



DNA and histone proteins are packaged into structures called chromosomes.

How Many Chromosomes Do People Have?

In humans, each cell normally contains 23 pairs of chromosomes, for a total of 46. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex chromosomes, differ between males and females. Females have two copies of the X chromosome, while males have one X and one Y chromosome.



U.S. National Library of Medicine

The 22 autosomes are numbered by size.

The other two chromosomes, X and Y, are the sex chromosomes.

This picture of the human chromosomes lined up in pairs is called a karyotype.

How Do Geneticists Indicate the Location of a Gene?

Geneticists use maps to describe the location of a particular gene on a chromosome. One type of map uses the cytogenetic location to describe a gene's position. The cytogenetic location is based on a distinctive pattern of bands created when chromosomes are stained with certain chemicals. Another type of map uses the molecular location, a precise description of a gene's position on a chromosome. The molecular location is based on the sequence of DNA building blocks (base pairs) that make up the chromosome.

Cytogenetic Location

Geneticists use a standardized way of describing a gene's cytogenetic location. In most cases, the location describes the position of a particular band on a stained chromosome:

17q12

It can also be written as a range of bands, if less is known about the exact location:

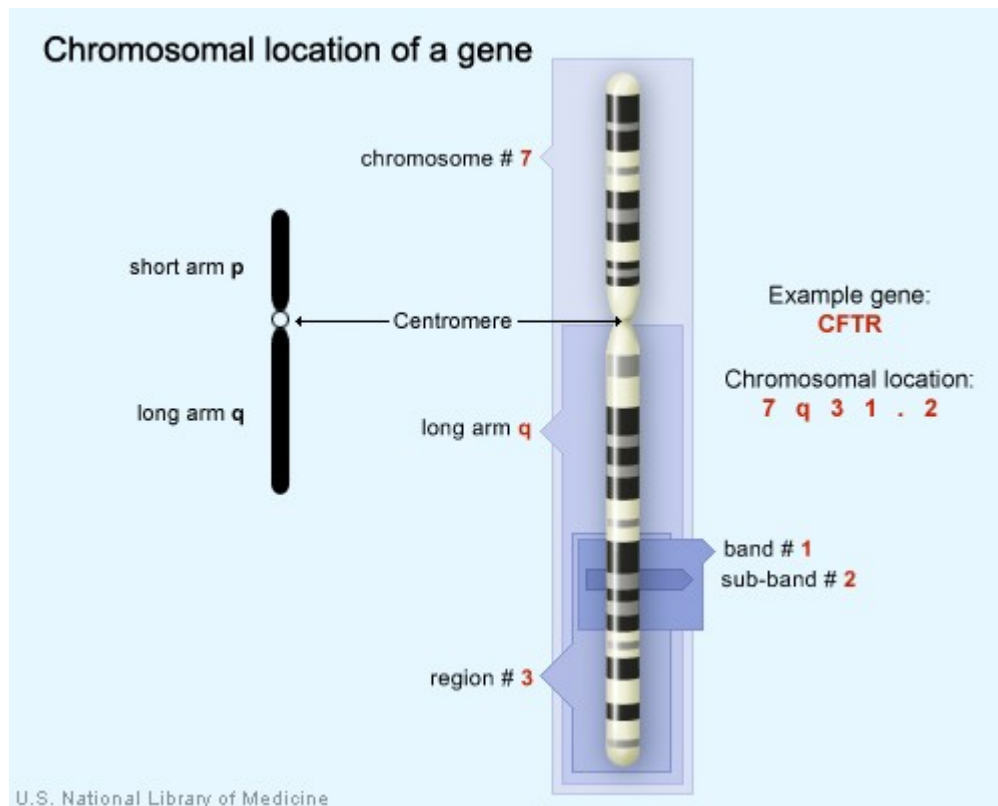
17q12-q21

The combination of numbers and letters provide a gene's "address" on a chromosome. This address is made up of several parts:

- The chromosome on which the gene can be found. The first number or letter used to describe a gene's location represents the chromosome. Chromosomes 1 through 22 (the autosomes) are designated by their chromosome number. The sex chromosomes are designated by X or Y.

- The arm of the chromosome. Each chromosome is divided into two sections (arms) based on the location of a narrowing (constriction) called the centromere. By convention, the shorter arm is called p, and the longer arm is called q. The chromosome arm is the second part of the gene's address. For example, 5q is the long arm of chromosome 5, and Xp is the short arm of the X chromosome.
- The position of the gene on the p or q arm. The position of a gene is based on a distinctive pattern of light and dark bands that appear when the chromosome is stained in a certain way. The position is usually designated by two digits (representing a region and a band), which are sometimes followed by a decimal point and one or more additional digits (representing sub-bands within a light or dark area). The number indicating the gene position increases with distance from the centromere. For example: 14q21 represents position 21 on the long arm of chromosome 14. 14q21 is closer to the centromere than 14q22.

Sometimes, the abbreviations "cen" or "ter" are also used to describe a gene's cytogenetic location. "Cen" indicates that the gene is very close to the centromere. For example, 16pcen refers to the short arm of chromosome 16 near the centromere. "Ter" stands for terminus, which indicates that the gene is very close to the end of the p or q arm. For example, 14qter refers to the tip of the long arm of chromosome 14. ("Tel" is also sometimes used to describe a gene's location. "Tel" stands for telomeres, which are at the ends of each chromosome. The abbreviations "tel" and "ter" refer to the same location.)



The CFTR gene is located on the long arm of chromosome 7 at position 7q31.2.

Molecular Location

The Human Genome Project, an international research effort completed in 2003, determined the sequence of base pairs for each human chromosome. This sequence information allows researchers to provide a more specific address than the cytogenetic location for many genes. A gene's molecular address pinpoints the location of that gene in terms of base pairs. For example, the molecular location of the APOE gene on chromosome 19 begins with base pair 50,100,901 and ends with base pair 50,104,488. This range describes the gene's precise position on chromosome 19 and indicates the size of the gene (3,588 base pairs). Knowing a gene's molecular location also allows researchers to determine exactly how far the gene is from other genes on the same chromosome.

Different groups of researchers often present slightly different values for a gene's molecular location. Researchers interpret the sequence of the human genome using a variety of methods, which can result in small differences in a gene's molecular address. For example, the National Center for Biotechnology Information (NCBI) identifies the molecular location of the APOE gene as base pair 50,100,901 to base pair 50,104,488 on chromosome 19. The Ensembl database identifies the location of this gene as base pair 50,100,879 to base pair 50,104,489 on chromosome 19. Neither of these addresses is incorrect; they represent different interpretations of the same data. For consistency, Genetics Home Reference presents data from NCBI for the molecular location of genes.

What Are Proteins and What Do They Do?

Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids that can be combined to make a protein. The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.

Examples of Protein Functions

Proteins can be described according to their large range of functions in the body, listed in alphabetical order:

Function	Description	Example
Antibody	Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.	Immunoglobulin G (IgG)
Enzyme	Enzymes carry out almost all of the thousands of chemical reactions that take place in cells. They also assist with the formation of new molecules by reading the genetic information stored in DNA.	Phenylalanine hydroxylase
Messenger	Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.	Growth hormone
Structural component	These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.	Actin
Transport/storage	These proteins bind and carry atoms and small molecules within cells and throughout the body.	Ferritin

How Does a Gene Make a Protein?

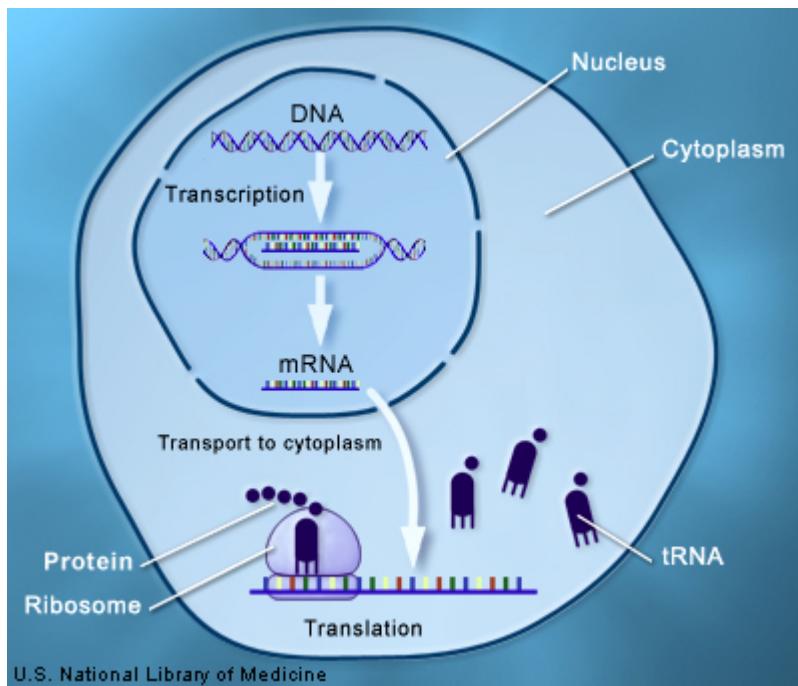
Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation. Together, transcription and translation are known as gene expression.

During the process of transcription, the information stored in a gene's DNA is transferred to a similar molecule called RNA (ribonucleic acid) in the cell nucleus. Both RNA and DNA are made up of a chain of nucleotide bases, but they have slightly different chemical properties. The type of RNA that contains the information for making a protein is called messenger RNA (mRNA) because it carries the information, or message, from the DNA out of the nucleus into the cytoplasm.

Translation, the second step in getting from a gene to a protein, takes place in the cytoplasm. The mRNA interacts with a specialized complex called a ribosome, which "reads" the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for

one particular amino acid. (Amino acids are the building blocks of proteins.) A type of RNA called transfer RNA (tRNA) assembles the protein, one amino acid at a time. Protein assembly continues until the ribosome encounters a “stop” codon (a sequence of three bases that does not code for an amino acid).

The flow of information from DNA to RNA to proteins is one of the fundamental principles of molecular biology. It is so important that it is sometimes called the “central dogma.”



Through the processes of transcription and translation, information from genes is used to make proteins.

Can Genes Be Turned On and Off in Cells?

Each cell expresses, or turns on, only a fraction of its genes. The rest of the genes are repressed, or turned off. The process of turning genes on and off is known as gene regulation. Gene regulation is an important part of normal development. Genes are turned on and off in different patterns during development to make a brain cell look and act different from a liver cell or a muscle cell, for example. Gene regulation also allows cells to react quickly to changes in their environments. Although we know that the regulation of genes is critical for life, this complex process is not yet fully understood.

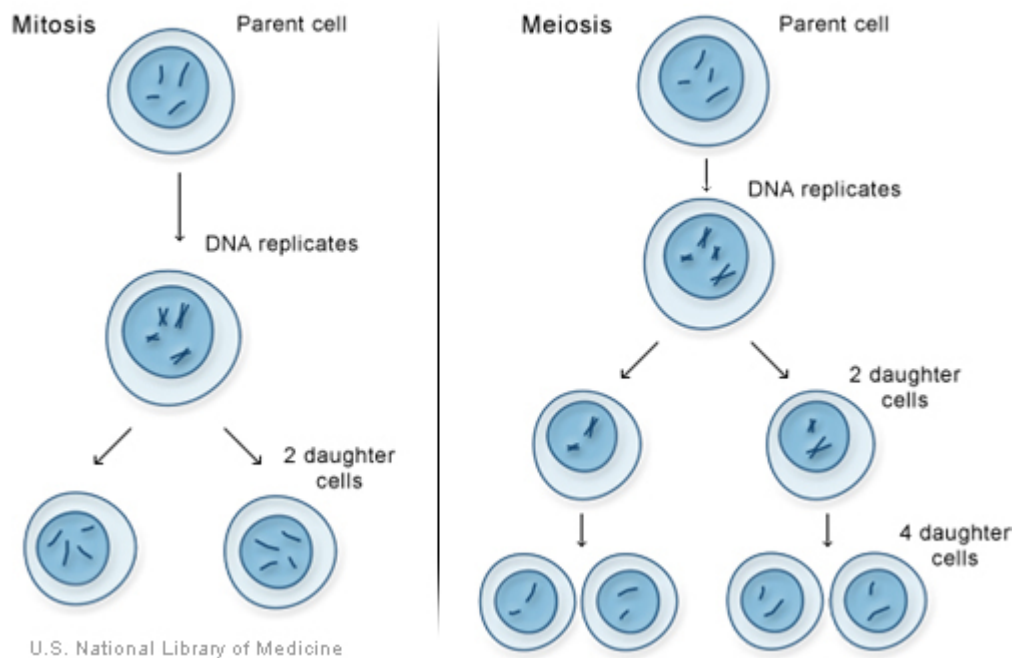
Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to regulatory regions of a gene and increase or decrease the level of transcription. By controlling the level of transcription, this process can determine the amount of protein product that is made by a gene at any given time.

How Do Cells Divide?

There are two types of cell division: mitosis and meiosis. Most of the time when people refer to “cell division,” they mean mitosis, the process of making new body cells. Meiosis is the type of cell division that creates egg and sperm cells.

Mitosis is a fundamental process for life. During mitosis, a cell duplicates all of its contents, including its chromosomes, and splits to form two identical daughter cells. Because this process is so critical, the steps of mitosis are carefully controlled by a number of genes. When mitosis is not regulated correctly, health problems such as cancer can result.

The other type of cell division, meiosis, ensures that humans have the same number of chromosomes in each generation. It is a two-step process that reduces the chromosome number by half—from 46 to 23—to form sperm and egg cells. When the sperm and egg cells unite at conception, each contributes 23 chromosomes so the resulting embryo will have the usual 46. Meiosis also allows genetic variation through a process of DNA shuffling while the cells are dividing.



Mitosis and meiosis, the two types of cell division.

How Do Genes Control the Growth and Division of Cells?

A variety of genes are involved in the control of cell growth and division. The cell cycle is the cell's way of replicating itself in an organized, step-by-step fashion. Tight regulation of this process ensures that a dividing cell's DNA is copied properly, any errors in the DNA are repaired, and each daughter cell receives a full set of chromosomes. The cycle has checkpoints (also called restriction points), which allow certain genes to check for mistakes and halt the cycle for repairs if something goes wrong.

If a cell has an error in its DNA that cannot be repaired, it may undergo programmed cell death (apoptosis). Apoptosis is a common process throughout life that helps the body get rid of cells it doesn't need. Cells that undergo apoptosis break apart and are recycled by a type of white blood cell called a macrophage. Apoptosis protects the body by removing genetically damaged cells that could lead to cancer, and it plays an important role in the development of the embryo and the maintenance of adult tissues.

Cancer results from a disruption of the normal regulation of the cell cycle. When the cycle proceeds without control, cells can divide without order and accumulate genetic defects that can lead to a cancerous tumor.

Genetic Mutations and Health

This section presents basic information about gene mutations, chromosomal changes, and conditions that run in families.⁸

What Is a Gene Mutation and How Do Mutations Occur?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Mutations range in size from a single DNA building block (DNA base) to a large segment of a chromosome.

Gene mutations occur in two ways: they can be inherited from a parent or acquired during a person's lifetime. Mutations that are passed from parent to child are called hereditary mutations or germline mutations (because they are present in the egg and sperm cells, which are also called germ cells). This type of mutation is present throughout a person's life in virtually every cell in the body.

Mutations that occur only in an egg or sperm cell, or those that occur just after fertilization, are called new (de novo) mutations. De novo mutations may explain genetic disorders in which an affected child has a mutation in every cell, but has no family history of the disorder.

Acquired (or somatic) mutations occur in the DNA of individual cells at some time during a person's life. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation.

Mutations may also occur in a single cell within an early embryo. As all the cells divide during growth and development, the individual will have some cells with the mutation and some cells without the genetic change. This situation is called mosaicism.

Some genetic changes are very rare; others are common in the population. Genetic changes that occur in more than 1 percent of the population are called polymorphisms. They are common enough to be considered a normal variation in the DNA. Polymorphisms are

⁸ This section has been adapted from the National Library of Medicine's handbook, *Help Me Understand Genetics*, which presents basic information about genetics in clear language and provides links to online resources: <http://ghr.nlm.nih.gov/handbook>.

responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders.

How Can Gene Mutations Affect Health and Development?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, it can disrupt normal development or cause a medical condition. A condition caused by mutations in one or more genes is called a genetic disorder.

In some cases, gene mutations are so severe that they prevent an embryo from surviving until birth. These changes occur in genes that are essential for development, and often disrupt the development of an embryo in its earliest stages. Because these mutations have very serious effects, they are incompatible with life.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has “the cystic fibrosis gene,” they are usually referring to a mutated version of the CFTR gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the CFTR gene.

Do All Gene Mutations Affect Health and Development?

No, only a small percentage of mutations cause genetic disorders—most have no impact on health or development. For example, some mutations alter a gene's DNA base sequence but do not change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed (makes a protein). Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an organism and its future generations better adapt to changes in their environment. For example, a beneficial mutation could result in a protein that protects the organism from a new strain of bacteria.

For More Information about DNA Repair and the Health Effects of Gene Mutations

- The University of Utah Genetic Science Learning Center provides information about genetic disorders that explains why some mutations cause disorders but others do not. (Refer to the questions in the far right column.)
See <http://learn.genetics.utah.edu/units/disorders/whataregd/>.

- Additional information about DNA repair is available from the NCBI Science Primer. In the chapter called “What Is A Cell?”, scroll down to the heading “DNA Repair Mechanisms.” See http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html.

What Kinds of Gene Mutations Are Possible?

The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:

- **Missense mutation:** This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.
- **Nonsense mutation:** A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.
- **Insertion:** An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.
- **Deletion:** A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).
- **Duplication:** A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.
- **Frameshift mutation:** This type of mutation occurs when the addition or loss of DNA bases changes a gene’s reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.
- **Repeat expansion:** Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

Can Changes in Chromosomes Affect Health and Development?

Changes that affect entire chromosomes or segments of chromosomes can cause problems with growth, development, and function of the body’s systems. These changes can affect many genes along the chromosome and alter the proteins made by those genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders.

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell. A change in the number of chromosomes leads to a chromosomal disorder. These changes can occur during the formation of reproductive cells (eggs and sperm) or in early fetal development. A gain or loss of chromosomes from the normal 46 is called aneuploidy.

The most common form of aneuploidy is trisomy, or the presence of an extra chromosome in each cell. “Tri-” is Greek for “three”; people with trisomy have three copies of a particular chromosome in each cell instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy – people with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

Monosomy, or the loss of one chromosome from each cell, is another kind of aneuploidy. “Mono-” is Greek for “one”; people with monosomy have one copy of a particular chromosome in each cell instead of the normal two copies. Turner syndrome is a condition caused by monosomy. Women with Turner syndrome are often missing one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Chromosomal disorders can also be caused by changes in chromosome structure. These changes are caused by the breakage and reunion of chromosome segments when an egg or sperm cell is formed or in early fetal development. Pieces of DNA can be rearranged within one chromosome, or transferred between two or more chromosomes. The effects of structural changes depend on their size and location. Many different structural changes are possible; some cause medical problems, while others may have no effect on a person’s health.

Many cancer cells also have changes in their chromosome number or structure. These changes most often occur in somatic cells (cells other than eggs and sperm) during a person’s lifetime.

Can Changes in Mitochondrial DNA Affect Health and Development?

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA (known as mitochondrial DNA or mtDNA). In some cases, inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body’s systems. These mutations disrupt the mitochondria’s ability to generate energy efficiently for the cell.

Conditions caused by mutations in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues that require a lot of energy (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA mutations vary widely, frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and abnormalities involving the eyes and vision.

Mitochondrial DNA is also prone to noninherited (somatic) mutations. Somatic mutations occur in the DNA of certain cells during a person’s lifetime, and typically are not passed to future generations. Because mitochondrial DNA has a limited ability to repair itself when it is damaged, these mutations tend to build up over time. A buildup of somatic mutations in mitochondrial DNA has been associated with some forms of cancer and an increased risk of certain age-related disorders such as heart disease, Alzheimer disease, and Parkinson disease. Additionally, research suggests that the progressive accumulation of these mutations over a person’s lifetime may play a role in the normal process of aging.

What Are Complex or Multifactorial Disorders?

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell anemia and cystic fibrosis, are caused by mutations in a single gene. The causes of many other disorders, however, are much more complex. Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause—they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Conditions caused by many contributing factors are called complex or multifactorial disorders.

Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. By 2010, however, researchers predict they will have found the major contributing genes for many common complex disorders.

What Information about a Genetic Condition Can Statistics Provide?

Statistical data can provide general information about how common a condition is, how many people have the condition, or how likely it is that a person will develop the condition. Statistics are not personalized, however—they offer estimates based on groups of people. By taking into account a person's family history, medical history, and other factors, a genetics professional can help interpret what statistics mean for a particular patient.

Common Statistical Terms

Some statistical terms are commonly used when describing genetic conditions and other disorders. These terms include:

Statistical Term	Description	Examples
<i>Incidence</i>	The incidence of a gene mutation or a genetic disorder is the number of people who are born with the mutation or disorder in a specified group per year. Incidence is often written in the form "1 in [a number]" or as a total number of live births.	About 1 in 200,000 people in the United States are born with syndrome A each year. An estimated 15,000 infants with syndrome B were born last year worldwide.

<i>Prevalence</i>	The prevalence of a gene mutation or a genetic disorder is the total number of people in a specified group at a given time who have the mutation or disorder. This term includes both newly diagnosed and pre-existing cases in people of any age. Prevalence is often written in the form “1 in [a number]” or as a total number of people who have a condition.	Approximately 1 in 100,000 people in the United States have syndrome A at the present time. About 100,000 children worldwide currently have syndrome B.
<i>Mortality</i>	Mortality is the number of deaths from a particular disorder occurring in a specified group per year. Mortality is usually expressed as a total number of deaths.	An estimated 12,000 people worldwide died from syndrome C in 2002.
<i>Lifetime risk</i>	Lifetime risk is the average risk of developing a particular disorder at some point during a lifetime. Lifetime risk is often written as a percentage or as “1 in [a number].” It is important to remember that the risk per year or per decade is much lower than the lifetime risk. In addition, other factors may increase or decrease a person’s risk as compared with the average.	Approximately 1 percent of people in the United States develop disorder D during their lifetimes. The lifetime risk of developing disorder D is 1 in 100.

Naming Genetic Conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a particular disorder are often the first to propose a name for the condition. Expert working groups may later revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately help researchers find new approaches to treatment.

Disorder names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency)
- One or more major signs or symptoms of the disorder (for example, sickle cell anemia)
- The parts of the body affected by the condition (for example, retinoblastoma)

- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome, which was named after Dr. Antoine Bernard-Jean Marfan)
- A geographic area (for example, familial Mediterranean fever, which occurs mainly in populations bordering the Mediterranean Sea)
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis, which is also called Lou Gehrig disease after a famous baseball player who had the condition).

Disorders named after a specific person or place are called eponyms. There is debate as to whether the possessive form (e.g., Alzheimer's disease) or the nonpossessive form (Alzheimer disease) of eponyms is preferred. As a rule, medical geneticists use the nonpossessive form, and this form may become the standard for doctors in all fields of medicine. Genetics Home Reference uses the nonpossessive form of eponyms.

Genetics Home Reference consults with experts in the field of medical genetics to provide the current, most accurate name for each disorder. Alternate names are included as synonyms.

Naming genes

The HUGO Gene Nomenclature Committee (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene. Some official gene names include additional information in parentheses, such as related genetic conditions, subtypes of a condition, or inheritance pattern. The HGNC is a non-profit organization funded by the U.K. Medical Research Council and the U.S. National Institutes of Health. The Committee has named more than 13,000 of the estimated 20,000 to 25,000 genes in the human genome.

During the research process, genes often acquire several alternate names and symbols. Different researchers investigating the same gene may each give the gene a different name, which can cause confusion. The HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. For specific information about how genes are named, refer to the HGNC's Guidelines for Human Gene Nomenclature.

Genetics Home Reference describes genes using the HGNC's official gene names and gene symbols. Genetics Home Reference frequently presents the symbol and name separated with a colon (for example, FGFR4: Fibroblast growth factor receptor 4).

Inheriting Genetic Conditions

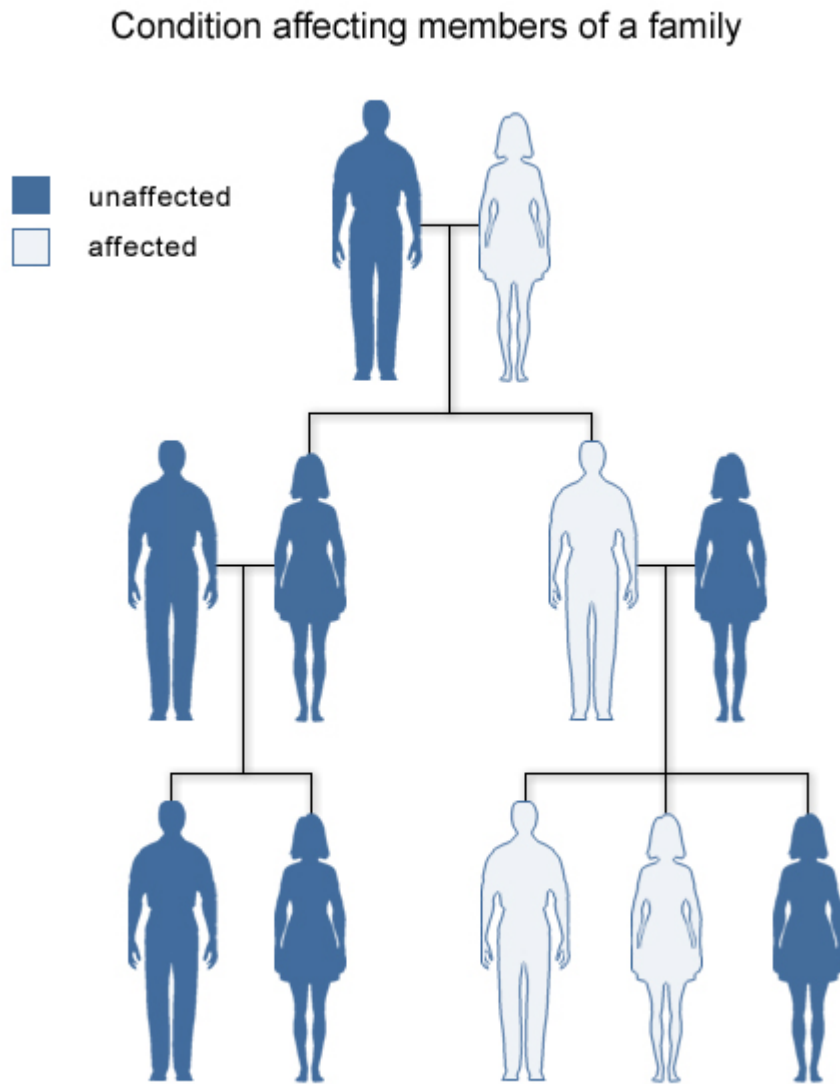
This section gives you information on inheritance patterns and understanding risk.

What Does It Mean If a Disorder Seems to Run in My Family?

A particular disorder might be described as "running in a family" if more than one person in the family has the condition. Some disorders that affect multiple family members are caused by gene mutations, which can be inherited (passed down from parent to child). Other conditions that appear to run in families are not inherited. Instead, environmental factors

such as dietary habits or a combination of genetic and environmental factors are responsible for these disorders.

It is not always easy to determine whether a condition in a family is inherited. A genetics professional can use a person's family history (a record of health information about a person's immediate and extended family) to help determine whether a disorder has a genetic component.



U.S. National Library of Medicine

Some disorders are seen in more than one generation of a family.

Why Is It Important to Know My Family Medical History?

A family medical history is a record of health information about a person and his or her close relatives. A complete record includes information from three generations of relatives,

including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and cousins.

Families have many factors in common, including their genes, environment, and lifestyle. Together, these factors can give clues to medical conditions that may run in a family. By noticing patterns of disorders among relatives, healthcare professionals can determine whether an individual, other family members, or future generations may be at an increased risk of developing a particular condition.

A family medical history can identify people with a higher-than-usual chance of having common disorders, such as heart disease, high blood pressure, stroke, certain cancers, and diabetes. These complex disorders are influenced by a combination of genetic factors, environmental conditions, and lifestyle choices. A family history also can provide information about the risk of rarer conditions caused by mutations in a single gene, such as cystic fibrosis and sickle cell anemia.

While a family medical history provides information about the risk of specific health concerns, having relatives with a medical condition does not mean that an individual will definitely develop that condition. On the other hand, a person with no family history of a disorder may still be at risk of developing that disorder.

Knowing one's family medical history allows a person to take steps to reduce his or her risk. For people at an increased risk of certain cancers, healthcare professionals may recommend more frequent screening (such as mammography or colonoscopy) starting at an earlier age. Healthcare providers may also encourage regular checkups or testing for people with a medical condition that runs in their family. Additionally, lifestyle changes such as adopting a healthier diet, getting regular exercise, and quitting smoking help many people lower their chances of developing heart disease and other common illnesses.

The easiest way to get information about family medical history is to talk to relatives about their health. Have they had any medical problems, and when did they occur? A family gathering could be a good time to discuss these issues. Additionally, obtaining medical records and other documents (such as obituaries and death certificates) can help complete a family medical history. It is important to keep this information up-to-date and to share it with a healthcare professional regularly.

What Are the Different Ways in which a Genetic Condition Can Be Inherited?

Some genetic conditions are caused by mutations in a single gene. These conditions are usually inherited in one of several straightforward patterns, depending on the gene involved:

Inheritance Pattern	Description	Examples
Autosomal dominant	One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent. Autosomal dominant disorders tend to occur in every generation of an affected family.	Huntington disease, neurofibromatosis type 1

Autosomal recessive	Two mutated copies of the gene are present in each cell when a person has an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers). Autosomal recessive disorders are typically not seen in every generation of an affected family.	cystic fibrosis, sickle cell anemia
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men and women. Families with an X-linked dominant disorder often have both affected males and affected females in each generation. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	fragile X syndrome
X-linked recessive	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men and women. Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	hemophilia, Fabry disease
Codominant	In codominant inheritance, two different versions (alleles) of a gene can be expressed, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic condition.	ABO blood group, alpha-1 antitrypsin deficiency
Mitochondrial	This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children. Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.	Leber hereditary optic neuropathy (LHON)

Many other disorders are caused by a combination of the effects of multiple genes or by interactions between genes and the environment. Such disorders are more difficult to analyze because their genetic causes are often unclear, and they do not follow the patterns of inheritance described above. Examples of conditions caused by multiple genes or gene/environment interactions include heart disease, diabetes, schizophrenia, and certain types of cancer. Disorders caused by changes in the number or structure of chromosomes do not follow the straightforward patterns of inheritance listed above. Other genetic factors can also influence how a disorder is inherited.

If a Genetic Disorder Runs in My Family, What Are the Chances That My Children Will Have the Condition?

When a genetic disorder is diagnosed in a family, family members often want to know the likelihood that they or their children will develop the condition. This can be difficult to predict in some cases because many factors influence a person's chances of developing a genetic condition. One important factor is how the condition is inherited. For example:

- **Autosomal dominant inheritance:** A person affected by an autosomal dominant disorder has a 50 percent chance of passing the mutated gene to each child. The chance that a child will not inherit the mutated gene is also 50 percent.
- **Autosomal recessive inheritance:** Two unaffected people who each carry one copy of the mutated gene for an autosomal recessive disorder (carriers) have a 25 percent chance with each pregnancy of having a child affected by the disorder. The chance with each pregnancy of having an unaffected child who is a carrier of the disorder is 50 percent, and the chance that a child will not have the disorder and will not be a carrier is 25 percent.
- **X-linked dominant inheritance:** The chance of passing on an X-linked dominant condition differs between men and women because men have one X chromosome and one Y chromosome, while women have two X chromosomes. A man passes on his Y chromosome to all of his sons and his X chromosome to all of his daughters. Therefore, the sons of a man with an X-linked dominant disorder will not be affected, but all of his daughters will inherit the condition. A woman passes on one or the other of her X chromosomes to each child. Therefore, a woman with an X-linked dominant disorder has a 50 percent chance of having an affected daughter or son with each pregnancy.
- **X-linked recessive inheritance:** Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder also differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. With each pregnancy, a woman who carries an X-linked recessive disorder has a 50 percent chance of having sons who are affected and a 50 percent chance of having daughters who carry one copy of the mutated gene.
- **Codominant inheritance:** In codominant inheritance, each parent contributes a different version of a particular gene, and both versions influence the resulting genetic trait. The chance of developing a genetic condition with codominant inheritance, and the characteristic features of that condition, depend on which versions of the gene are passed from parents to their child.
- **Mitochondrial inheritance:** Mitochondria, which are the energy-producing centers inside cells, each contain a small amount of DNA. Disorders with mitochondrial inheritance result from mutations in mitochondrial DNA. Although mitochondrial

disorders can affect both males and females, only females can pass mutations in mitochondrial DNA to their children. A woman with a disorder caused by changes in mitochondrial DNA will pass the mutation to all of her daughters and sons, but the children of a man with such a disorder will not inherit the mutation.

It is important to note that the chance of passing on a genetic condition applies equally to each pregnancy. For example, if a couple has a child with an autosomal recessive disorder, the chance of having another child with the disorder is still 25 percent (or 1 in 4). Having one child with a disorder does not “protect” future children from inheriting the condition. Conversely, having a child without the condition does not mean that future children will definitely be affected.

Although the chances of inheriting a genetic condition appear straightforward, factors such as a person’s family history and the results of genetic testing can sometimes modify those chances. In addition, some people with a disease-causing mutation never develop any health problems or may experience only mild symptoms of the disorder. If a disease that runs in a family does not have a clear-cut inheritance pattern, predicting the likelihood that a person will develop the condition can be particularly difficult.

Estimating the chance of developing or passing on a genetic disorder can be complex. Genetics professionals can help people understand these chances and help them make informed decisions about their health.

Factors that Influence the Effects of Particular Genetic Changes

Reduced penetrance and variable expressivity are factors that influence the effects of particular genetic changes. These factors usually affect disorders that have an autosomal dominant pattern of inheritance, although they are occasionally seen in disorders with an autosomal recessive inheritance pattern.

Reduced Penetrance

Penetrance refers to the proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder. If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance. Reduced penetrance often occurs with familial cancer syndromes. For example, many people with a mutation in the BRCA1 or BRCA2 gene will develop cancer during their lifetime, but some people will not. Doctors cannot predict which people with these mutations will develop cancer or when the tumors will develop.

Reduced penetrance probably results from a combination of genetic, environmental, and lifestyle factors, many of which are unknown. This phenomenon can make it challenging for genetics professionals to interpret a person’s family medical history and predict the risk of passing a genetic condition to future generations.

Variable Expressivity

Although some genetic disorders exhibit little variation, most have signs and symptoms that differ among affected individuals. Variable expressivity refers to the range of signs and

symptoms that can occur in different people with the same genetic condition. For example, the features of Marfan syndrome vary widely— some people have only mild symptoms (such as being tall and thin with long, slender fingers), while others also experience life-threatening complications involving the heart and blood vessels. Although the features are highly variable, most people with this disorder have a mutation in the same gene (FBN1).

As with reduced penetrance, variable expressivity is probably caused by a combination of genetic, environmental, and lifestyle factors, most of which have not been identified. If a genetic condition has highly variable signs and symptoms, it may be challenging to diagnose.

What Do Geneticists Mean by Anticipation?

The signs and symptoms of some genetic conditions tend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next. This phenomenon is called anticipation. Anticipation is most often seen with certain genetic disorders of the nervous system, such as Huntington disease, myotonic dystrophy, and fragile X syndrome.

Anticipation typically occurs with disorders that are caused by an unusual type of mutation called a trinucleotide repeat expansion. A trinucleotide repeat is a sequence of three DNA building blocks (nucleotides) that is repeated a number of times in a row. DNA segments with an abnormal number of these repeats are unstable and prone to errors during cell division. The number of repeats can change as the gene is passed from parent to child. If the number of repeats increases, it is known as a trinucleotide repeat expansion. In some cases, the trinucleotide repeat may expand until the gene stops functioning normally. This expansion causes the features of some disorders to become more severe with each successive generation.

Most genetic disorders have signs and symptoms that differ among affected individuals, including affected people in the same family. Not all of these differences can be explained by anticipation. A combination of genetic, environmental, and lifestyle factors is probably responsible for the variability, although many of these factors have not been identified. Researchers study multiple generations of affected family members and consider the genetic cause of a disorder before determining that it shows anticipation.

What Is Genomic Imprinting?

Genomic imprinting is a factor that influences how some genetic conditions are inherited.

People inherit two copies of their genes—one from their mother and one from their father. Usually both copies of each gene are active, or “turned on,” in cells. In some cases, however, only one of the two copies is normally turned on. Which copy is active depends on the parent of origin: some genes are normally active only when they are inherited from a person’s father; others are active only when inherited from a person’s mother. This phenomenon is known as genomic imprinting.

In genes that undergo genomic imprinting, the parent of origin is often marked, or “stamped,” on the gene during the formation of egg and sperm cells. This stamping process, called methylation, is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. These molecules identify which copy of a gene was inherited

from the mother and which was inherited from the father. The addition and removal of methyl groups can be used to control the activity of genes.

Only a small percentage of all human genes undergo genomic imprinting. Researchers are not yet certain why some genes are imprinted and others are not. They do know that imprinted genes tend to cluster together in the same regions of chromosomes. Two major clusters of imprinted genes have been identified in humans, one on the short (p) arm of chromosome 11 (at position 11p15) and another on the long (q) arm of chromosome 15 (in the region 15q11 to 15q13).

What Is Uniparental Disomy?

Uniparental disomy is a factor that influences how some genetic conditions are inherited.

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells or may happen in early fetal development.

In many cases, UPD likely has no effect on health or development. Because most genes are not imprinted, it doesn't matter if a person inherits both copies from one parent instead of one copy from each parent. In some cases, however, it does make a difference whether a gene is inherited from a person's mother or father. A person with UPD may lack any active copies of essential genes that undergo genomic imprinting. This loss of gene function can lead to delayed development, mental retardation, or other medical problems.

Several genetic disorders can result from UPD or a disruption of normal genomic imprinting. The most well-known conditions include Prader-Willi syndrome, which is characterized by uncontrolled eating and obesity, and Angelman syndrome, which causes mental retardation and impaired speech. Both of these disorders can be caused by UPD or other errors in imprinting involving genes on the long arm of chromosome 15. Other conditions, such as Beckwith-Wiedemann syndrome (a disorder characterized by accelerated growth and an increased risk of cancerous tumors), are associated with abnormalities of imprinted genes on the short arm of chromosome 11.

Are Chromosomal Disorders Inherited?

Although it is possible to inherit some types of chromosomal abnormalities, most chromosomal disorders (such as Down syndrome and Turner syndrome) are not passed from one generation to the next.

Some chromosomal conditions are caused by changes in the number of chromosomes. These changes are not inherited, but occur as random events during the formation of reproductive cells (eggs and sperm). An error in cell division called nondisjunction results in reproductive cells with an abnormal number of chromosomes. For example, a reproductive cell may accidentally gain or lose one copy of a chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra or missing chromosome in each of the body's cells.

Changes in chromosome structure can also cause chromosomal disorders. Some changes in chromosome structure can be inherited, while others occur as random accidents during the formation of reproductive cells or in early fetal development. Because the inheritance of these changes can be complex, people concerned about this type of chromosomal abnormality may want to talk with a genetics professional.

Some cancer cells also have changes in the number or structure of their chromosomes. Because these changes occur in somatic cells (cells other than eggs and sperm), they cannot be passed from one generation to the next.

Why Are Some Genetic Conditions More Common in Particular Ethnic Groups?

Some genetic disorders are more likely to occur among people who trace their ancestry to a particular geographic area. People in an ethnic group often share certain versions of their genes, which have been passed down from common ancestors. If one of these shared genes contains a disease-causing mutation, a particular genetic disorder may be more frequently seen in the group.

Examples of genetic conditions that are more common in particular ethnic groups are sickle cell anemia, which is more common in people of African, African-American, or Mediterranean heritage; and Tay-Sachs disease, which is more likely to occur among people of Ashkenazi (eastern and central European) Jewish or French Canadian ancestry. It is important to note, however, that these disorders can occur in any ethnic group.

Genetic Consultation

This section presents information on finding and visiting a genetic counselor or other genetics professional.

What Is a Genetic Consultation?

A genetic consultation is a health service that provides information and support to people who have, or may be at risk for, genetic disorders. During a consultation, a genetics professional meets with an individual or family to discuss genetic risks or to diagnose, confirm, or rule out a genetic condition.

Genetics professionals include medical geneticists (doctors who specialize in genetics) and genetic counselors (certified healthcare workers with experience in medical genetics and counseling). Other healthcare professionals such as nurses, psychologists, and social workers trained in genetics can also provide genetic consultations.

Consultations usually take place in a doctor's office, hospital, genetics center, or other type of medical center. These meetings are most often in-person visits with individuals or families, but they are occasionally conducted in a group or over the telephone.

Why Might Someone Have a Genetic Consultation?

Individuals or families who are concerned about an inherited condition may benefit from a genetic consultation. The reasons that a person might be referred to a genetic counselor, medical geneticist, or other genetics professional include:

- A personal or family history of a genetic condition, birth defect, chromosomal disorder, or hereditary cancer.
- Two or more pregnancy losses (miscarriages), a stillbirth, or a baby who died.
- A child with a known inherited disorder, a birth defect, mental retardation, or developmental delay.
- A woman who is pregnant or plans to become pregnant at or after age 35. (Some chromosomal disorders occur more frequently in children born to older women.)
- Abnormal test results that suggest a genetic or chromosomal condition.
- An increased risk of developing or passing on a particular genetic disorder on the basis of a person's ethnic background.
- People related by blood (for example, cousins) who plan to have children together. (A child whose parents are related may be at an increased risk of inheriting certain genetic disorders.)

A genetic consultation is also an important part of the decision-making process for genetic testing. A visit with a genetics professional may be helpful even if testing is not available for a specific condition, however.

What Happens during a Genetic Consultation?

A genetic consultation provides information, offers support, and addresses a patient's specific questions and concerns. To help determine whether a condition has a genetic component, a genetics professional asks about a person's medical history and takes a detailed family history (a record of health information about a person's immediate and extended family). The genetics professional may also perform a physical examination and recommend appropriate tests.

If a person is diagnosed with a genetic condition, the genetics professional provides information about the diagnosis, how the condition is inherited, the chance of passing the condition to future generations, and the options for testing and treatment.

During a consultation, a genetics professional will:

- Interpret and communicate complex medical information.
- Help each person make informed, independent decisions about their health care and reproductive options.
- Respect each person's individual beliefs, traditions, and feelings.

A genetics professional will NOT:

- Tell a person which decision to make.
- Advise a couple not to have children.

- Recommend that a woman continue or end a pregnancy.
- Tell someone whether to undergo testing for a genetic disorder.

How Can I Find a Genetics Professional in My Area?

To find a genetics professional in your community, you may wish to ask your doctor for a referral. If you have health insurance, you can also contact your insurance company to find a medical geneticist or genetic counselor in your area who participates in your plan.

Several resources for locating a genetics professional in your community are available online:

- GeneTests from the University of Washington provides a list of genetics clinics around the United States and international genetics clinics. You can also access the list by clicking on “Clinic Directory” at the top of the GeneTests home page. Clinics can be chosen by state or country, by service, and/or by specialty. State maps can help you locate a clinic in your area. See <http://www.genetests.org/>.
- The National Society of Genetic Counselors offers a searchable directory of genetic counselors in the United States. You can search by location, name, area of practice/specialization, and/or ZIP Code. See <http://www.nsgc.org/resource/link.cfm>.
- The National Cancer Institute provides a Cancer Genetics Services Directory, which lists professionals who provide services related to cancer genetics. You can search by type of cancer or syndrome, location, and/or provider name at the following Web site: http://cancer.gov/search/genetics_services/.

Genetic Testing

This section presents information on the benefits, costs, risks, and limitations of genetic testing.

What Is Genetic Testing?

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. Most of the time, testing is used to find changes that are associated with inherited disorders. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. Several hundred genetic tests are currently in use, and more are being developed.

Genetic testing is voluntary. Because testing has both benefits and limitations, the decision about whether to be tested is a personal and complex one. A genetic counselor can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of testing.

What Are the Types of Genetic Tests?

Genetic testing can provide information about a person’s genes and chromosomes. Available types of testing include:

- **Newborn screening** is used just after birth to identify genetic disorders that can be treated early in life. Millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes mental retardation if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most states also test for other genetic disorders.
- **Diagnostic testing** is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disorder.
- **Carrier testing** is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.
- **Prenatal testing** is used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. It cannot identify all possible inherited disorders and birth defects, however.
- **Preimplantation testing**, also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder. It is used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro fertilization. In-vitro fertilization involves removing egg cells from a woman's ovaries and fertilizing them with sperm cells outside the body. To perform preimplantation testing, a small number of cells are taken from these embryos and tested for certain genetic changes. Only embryos without these changes are implanted in the uterus to initiate a pregnancy.
- **Predictive and presymptomatic types of testing** are used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Presymptomatic testing can determine whether a person will develop a genetic disorder, such as hemochromatosis (an iron overload disorder), before any signs or symptoms appear. The results of predictive and presymptomatic testing can provide information about a person's risk of developing a specific disorder and help with making decisions about medical care.
- **Forensic testing** uses DNA sequences to identify an individual for legal purposes. Unlike the tests described above, forensic testing is not used to detect gene mutations associated with disease. This type of testing can identify crime or catastrophe victims, rule out or implicate a crime suspect, or establish biological relationships between people (for example, paternity).

How Is Genetic Testing Done?

Once a person decides to proceed with genetic testing, a medical geneticist, primary care doctor, specialist, or nurse practitioner can order the test. Genetic testing is often done as part of a genetic consultation.

Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. For example, a procedure called a buccal smear uses a small brush or cotton swab to collect a sample of cells from the inside surface of the cheek. The sample is sent to a laboratory where technicians look for specific changes in chromosomes, DNA, or proteins, depending on the suspected disorder. The laboratory reports the test results in writing to a person's doctor or genetic counselor.

Newborn screening tests are done on a small blood sample, which is taken by pricking the baby's heel. Unlike other types of genetic testing, a parent will usually only receive the result if it is positive. If the test result is positive, additional testing is needed to determine whether the baby has a genetic disorder.

Before a person has a genetic test, it is important that he or she understands the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. The process of educating a person about the test and obtaining permission is called informed consent.

What Is Direct-to-Consumer Genetic Testing?

Traditionally, genetic tests have been available only through healthcare providers such as physicians, nurse practitioners, and genetic counselors. Healthcare providers order the appropriate test from a laboratory, collect and send the samples, and interpret the test results. Direct-to-consumer genetic testing refers to genetic tests that are marketed directly to consumers via television, print advertisements, or the Internet. This form of testing, which is also known as at-home genetic testing, provides access to a person's genetic information without necessarily involving a doctor or insurance company in the process.

If a consumer chooses to purchase a genetic test directly, the test kit is mailed to the consumer instead of being ordered through a doctor's office. The test typically involves collecting a DNA sample at home, often by swabbing the inside of the cheek, and mailing the sample back to the laboratory. In some cases, the person must visit a health clinic to have blood drawn. Consumers are notified of their results by mail or over the telephone, or the results are posted online. In some cases, a genetic counselor or other healthcare provider is available to explain the results and answer questions. The price for this type of at-home genetic testing ranges from several hundred dollars to more than a thousand dollars.

The growing market for direct-to-consumer genetic testing may promote awareness of genetic diseases, allow consumers to take a more proactive role in their health care, and offer a means for people to learn about their ancestral origins. At-home genetic tests, however, have significant risks and limitations. Consumers are vulnerable to being misled by the results of unproven or invalid tests. Without guidance from a healthcare provider, they may make important decisions about treatment or prevention based on inaccurate, incomplete, or misunderstood information about their health. Consumers may also experience an invasion of genetic privacy if testing companies use their genetic information in an unauthorized way.

Genetic testing provides only one piece of information about a person's health—other genetic and environmental factors, lifestyle choices, and family medical history also affect a person's risk of developing many disorders. These factors are discussed during a consultation with a doctor or genetic counselor, but in many cases are not addressed by at-home genetic tests. More research is needed to fully understand the benefits and limitations of direct-to-consumer genetic testing.

What Do the Results of Genetic Tests Mean?

The results of genetic tests are not always straightforward, which often makes them challenging to interpret and explain. Therefore, it is important for patients and their families to ask questions about the potential meaning of genetic test results both before and after the test is performed. When interpreting test results, healthcare professionals consider a person's medical history, family history, and the type of genetic test that was done.

A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic mutation, identify an increased risk of developing a disease (such as cancer) in the future, or suggest a need for further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, health professionals typically cannot use a positive test result to predict the course or severity of a condition.

A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing may be required to confirm a negative result.

In some cases, a negative result might not give any useful information. This type of result is called uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because everyone has common, natural variations in their DNA, called polymorphisms, that do not affect health. If a genetic test finds a change in DNA that has not been associated with a disorder in other people, it can be difficult to tell whether it is a natural polymorphism or a disease-causing mutation. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

What Is the Cost of Genetic Testing, and How Long Does It Take to Get the Results?

The cost of genetic testing can range from under \$100 to more than \$2,000, depending on the nature and complexity of the test. The cost increases if more than one test is necessary or if multiple family members must be tested to obtain a meaningful result. For newborn

screening, costs vary by state. Some states cover part of the total cost, but most charge a fee of \$15 to \$60 per infant.

From the date that a sample is taken, it may take a few weeks to several months to receive the test results. Results for prenatal testing are usually available more quickly because time is an important consideration in making decisions about a pregnancy. The doctor or genetic counselor who orders a particular test can provide specific information about the cost and time frame associated with that test.

Will Health Insurance Cover the Costs of Genetic Testing?

In many cases, health insurance plans will cover the costs of genetic testing when it is recommended by a person's doctor. Health insurance providers have different policies about which tests are covered, however. A person interested in submitting the costs of testing may wish to contact his or her insurance company beforehand to ask about coverage.

Some people may choose not to use their insurance to pay for testing because the results of a genetic test can affect a person's health insurance coverage. Instead, they may opt to pay out-of-pocket for the test. People considering genetic testing may want to find out more about their state's privacy protection laws before they ask their insurance company to cover the costs.

What Are the Benefits of Genetic Testing?

Genetic testing has potential benefits whether the results are positive or negative for a gene mutation. Test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care. For example, a negative result can eliminate the need for unnecessary checkups and screening tests in some cases. A positive result can direct a person toward available prevention, monitoring, and treatment options. Some test results can also help people make decisions about having children. Newborn screening can identify genetic disorders early in life so treatment can be started as early as possible.

What Are the Risks and Limitations of Genetic Testing?

The physical risks associated with most genetic tests are very small, particularly for those tests that require only a blood sample or buccal smear (a procedure that samples cells from the inside surface of the cheek). The procedures used for prenatal testing carry a small but real risk of losing the pregnancy (miscarriage) because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. In some cases, genetic testing creates tension within a family because the results can reveal information about other family members in addition to the person who is tested. The possibility of genetic discrimination in employment or insurance is also a concern.

Genetic testing can provide only limited information about an inherited condition. The test often can't determine if a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.

A genetics professional can explain in detail the benefits, risks, and limitations of a particular test. It is important that any person who is considering genetic testing understand and weigh these factors before making a decision.

What Is Genetic Discrimination?

Genetic discrimination occurs when people are treated differently by their employer or insurance company because they have a gene mutation that causes or increases the risk of an inherited disorder. People who undergo genetic testing may be at risk for genetic discrimination.

The results of a genetic test are normally included in a person's medical records. When a person applies for life, disability, or health insurance, the insurance company may ask to look at these records before making a decision about coverage. An employer may also have the right to look at an employee's medical records. As a result, genetic test results could affect a person's insurance coverage or employment. People making decisions about genetic testing should be aware that when test results are placed in their medical records, the results might not be kept private.

Fear of discrimination is a common concern among people considering genetic testing. Several laws at the federal and state levels help protect people against genetic discrimination; however, genetic testing is a fast-growing field and these laws don't cover every situation.

How Does Genetic Testing in a Research Setting Differ from Clinical Genetic Testing?

The main differences between clinical genetic testing and research testing are the purpose of the test and who receives the results. The goals of research testing include finding unknown genes, learning how genes work, and advancing our understanding of genetic conditions. The results of testing done as part of a research study are usually not available to patients or their healthcare providers. Clinical testing, on the other hand, is done to find out about an inherited disorder in an individual patient or family. People receive the results of a clinical test and can use them to help them make decisions about medical care or reproductive issues.

It is important for people considering genetic testing to know whether the test is available on a clinical or research basis. Clinical and research testing both involve a process of informed consent in which patients learn about the testing procedure, the risks and benefits of the test, and the potential consequences of testing.

Gene Therapy

This section presents information on experimental techniques, safety, ethics, and availability of gene therapy.

What Is Gene Therapy?

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Researchers are testing several approaches to gene therapy, including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or “knocking out,” a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease.

Although gene therapy is a promising treatment option for a number of diseases (including inherited disorders, some types of cancer, and certain viral infections), the technique remains risky and is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures.

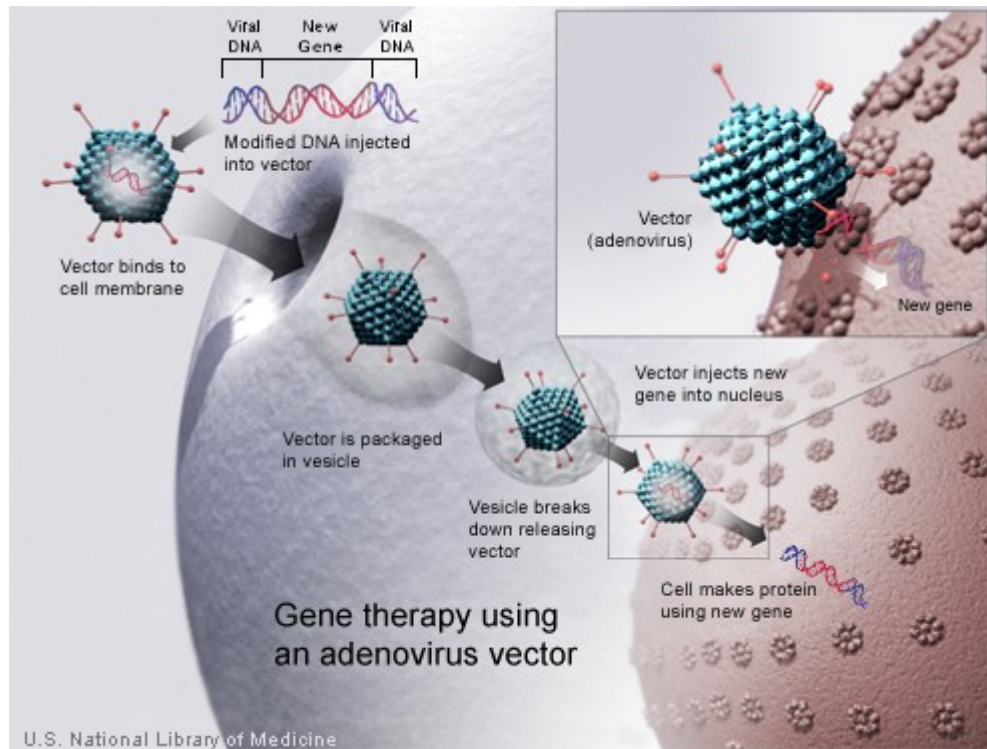
How Does Gene Therapy Work?

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein.

A gene that is inserted directly into a cell usually does not function. Instead, a carrier called a vector is genetically engineered to deliver the gene. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are modified so they can't cause disease when used in people. Some types of virus, such as retroviruses, integrate their genetic material (including the new gene) into a chromosome in the human cell. Other viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

The vector can be injected or given intravenously (by IV) directly into a specific tissue in the body, where it is taken up by individual cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in a laboratory setting. The cells containing the vector are then returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein.

Researchers must overcome many technical challenges before gene therapy will be a practical approach to treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body.



A new gene is injected into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein.

Is Gene Therapy Safe?

Gene therapy is under study to determine whether it could be used to treat disease. Current research is evaluating the safety of gene therapy; future studies will test whether it is an effective treatment option. Several studies have already shown that this approach can have very serious health risks, such as toxicity, inflammation, and cancer. Because the techniques are relatively new, some of the risks may be unpredictable; however, medical researchers, institutions, and regulatory agencies are working to ensure that gene therapy research is as safe as possible.

Comprehensive federal laws, regulations, and guidelines help protect people who participate in research studies (called clinical trials). The U.S. Food and Drug Administration (FDA) regulates all gene therapy products in the United States and oversees research in this area. Researchers who wish to test an approach in a clinical trial must first obtain permission from the FDA. The FDA has the authority to reject or suspend clinical trials that are suspected of being unsafe for participants.

The National Institutes of Health (NIH) also plays an important role in ensuring the safety of gene therapy research. NIH provides guidelines for investigators and institutions (such as universities and hospitals) to follow when conducting clinical trials with gene therapy. These guidelines state that clinical trials at institutions receiving NIH funding for this type of research must be registered with the NIH Office of Biotechnology Activities. The protocol, or plan, for each clinical trial is then reviewed by the NIH Recombinant DNA Advisory Committee (RAC) to determine whether it raises medical, ethical, or safety issues that warrant further discussion at one of the RAC's public meetings.

An Institutional Review Board (IRB) and an Institutional Biosafety Committee (IBC) must approve each gene therapy clinical trial before it can be carried out. An IRB is a committee of scientific and medical advisors and consumers that reviews all research within an institution. An IBC is a group that reviews and approves an institution's potentially hazardous research studies. Multiple levels of evaluation and oversight ensure that safety concerns are a top priority in the planning and carrying out of gene therapy research.

What Are the Ethical Issues surrounding Gene Therapy?

Because gene therapy involves making changes to the body's set of basic instructions, it raises many unique ethical concerns. The ethical questions surrounding gene therapy include:

- How can "good" and "bad" uses of gene therapy be distinguished?
- Who decides which traits are normal and which constitute a disability or disorder?
- Will the high costs of gene therapy make it available only to the wealthy?
- Could the widespread use of gene therapy make society less accepting of people who are different?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence, or athletic ability?

Current gene therapy research has focused on treating individuals by targeting the therapy to body cells such as bone marrow or blood cells. This type of gene therapy cannot be passed on to a person's children. Gene therapy could be targeted to egg and sperm cells (germ cells), however, which would allow the inserted gene to be passed on to future generations. This approach is known as germline gene therapy.

The idea of germline gene therapy is controversial. While it could spare future generations in a family from having a particular genetic disorder, it might affect the development of a fetus in unexpected ways or have long-term side effects that are not yet known. Because people who would be affected by germline gene therapy are not yet born, they can't choose whether to have the treatment. Because of these ethical concerns, the U.S. Government does not allow federal funds to be used for research on germline gene therapy in people.

Is Gene Therapy Available to Treat My Disorder?

Gene therapy is currently available only in a research setting. The U.S. Food and Drug Administration (FDA) has not yet approved any gene therapy products for sale in the United States.

Hundreds of research studies (clinical trials) are under way to test gene therapy as a treatment for genetic conditions, cancer, and HIV/AIDS. If you are interested in participating in a clinical trial, talk with your doctor or a genetics professional about how to participate.

You can also search for clinical trials online. ClinicalTrials.gov, a service of the National Institutes of Health, provides easy access to information on clinical trials. You can search for specific trials or browse by condition or trial sponsor. You may wish to refer to a list of gene therapy trials that are accepting (or will accept) patients.

The Human Genome Project and Genomic Research

This section presents information on the goals, accomplishments, and next steps in understanding the human genome.

What Is a Genome?

A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that organism. In humans, a copy of the entire genome—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus.

What Was the Human Genome Project and Why Has It Been Important?

The Human Genome Project was an international research effort to determine the sequence of the human genome and identify the genes that it contains. The Project was coordinated by the National Institutes of Health and the U.S. Department of Energy. Additional contributors included universities across the United States and international partners in the United Kingdom, France, Germany, Japan, and China. The Human Genome Project formally began in 1990 and was completed in 2003, 2 years ahead of its original schedule.

The work of the Human Genome Project has allowed researchers to begin to understand the blueprint for building a person. As researchers learn more about the functions of genes and proteins, this knowledge will have a major impact in the fields of medicine, biotechnology, and the life sciences.

What Were the Goals of the Human Genome Project?

The main goals of the Human Genome Project were to provide a complete and accurate sequence of the 3 billion DNA base pairs that make up the human genome and to find all of the estimated 20,000 to 25,000 human genes. The Project also aimed to sequence the genomes of several other organisms that are important to medical research, such as the mouse and the fruit fly.

In addition to sequencing DNA, the Human Genome Project sought to develop new tools to obtain and analyze the data and to make this information widely available. Also, because advances in genetics have consequences for individuals and society, the Human Genome Project committed to exploring the consequences of genomic research through its Ethical, Legal, and Social Implications (ELSI) program.

What Did the Human Genome Project Accomplish?

In April 2003, researchers announced that the Human Genome Project had completed a high-quality sequence of essentially the entire human genome. This sequence closed the gaps from a working draft of the genome, which was published in 2001. It also identified the locations of many human genes and provided information about their structure and

organization. The Project made the sequence of the human genome and tools to analyze the data freely available via the Internet.

In addition to the human genome, the Human Genome Project sequenced the genomes of several other organisms, including brewers' yeast, the roundworm, and the fruit fly. In 2002, researchers announced that they had also completed a working draft of the mouse genome. By studying the similarities and differences between human genes and those of other organisms, researchers can discover the functions of particular genes and identify which genes are critical for life.

The Project's Ethical, Legal, and Social Implications (ELSI) program became the world's largest bioethics program and a model for other ELSI programs worldwide.

What Were Some of the Ethical, Legal, and Social Implications Addressed by the Human Genome Project?

The Ethical, Legal, and Social Implications (ELSI) program was founded in 1990 as an integral part of the Human Genome Project. The mission of the ELSI program was to identify and address issues raised by genomic research that would affect individuals, families, and society. A percentage of the Human Genome Project budget at the National Institutes of Health and the U.S. Department of Energy was devoted to ELSI research.

The ELSI program focused on the possible consequences of genomic research in four main areas:

- Privacy and fairness in the use of genetic information, including the potential for genetic discrimination in employment and insurance.
- The integration of new genetic technologies, such as genetic testing, into the practice of clinical medicine.
- Ethical issues surrounding the design and conduct of genetic research with people, including the process of informed consent.
- The education of healthcare professionals, policy makers, students, and the public about genetics and the complex issues that result from genomic research.

What Are the Next Steps in Genomic Research?

Discovering the sequence of the human genome was only the first step in understanding how the instructions coded in DNA lead to a functioning human being. The next stage of genomic research will begin to derive meaningful knowledge from the DNA sequence. Research studies that build on the work of the Human Genome Project are under way worldwide.

The objectives of continued genomic research include the following:

- Determine the function of genes and the elements that regulate genes throughout the genome.
- Find variations in the DNA sequence among people and determine their significance. These variations may one day provide information about a person's disease risk and response to certain medications.

- Discover the 3-dimensional structures of proteins and identify their functions.
- Explore how DNA and proteins interact with one another and with the environment to create complex living systems.
- Develop and apply genome-based strategies for the early detection, diagnosis, and treatment of disease.
- Sequence the genomes of other organisms, such as the rat, cow, and chimpanzee, in order to compare similar genes between species.
- Develop new technologies to study genes and DNA on a large scale and store genomic data efficiently.
- Continue to explore the ethical, legal, and social issues raised by genomic research.

What Is Pharmacogenomics?

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions.

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma.

APPENDIX B. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as “clinical” or “professional” guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute⁹:

- National Institutes of Health (NIH); guidelines consolidated across agencies available at <http://health.nih.gov/>
- National Institute of General Medical Sciences (NIGMS); fact sheets available at <http://www.nigms.nih.gov/Publications/FactSheets.htm>
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: <http://www.nlm.nih.gov/medlineplus/healthtopics.html>
- National Cancer Institute (NCI); guidelines available at <http://www.cancer.gov/cancertopics/pdq>
- National Eye Institute (NEI); guidelines available at <http://www.nei.nih.gov/health/>
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at <http://www.nhlbi.nih.gov/guidelines/index.htm>
- National Human Genome Research Institute (NHGRI); research available at <http://www.genome.gov/page.cfm?pageID=10000375>
- National Institute on Aging (NIA); guidelines available at <http://www.nia.nih.gov/HealthInformation/Publications/>
- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at <http://www.niaaa.nih.gov/Publications/>

⁹ These publications are typically written by one or more of the various NIH Institutes.

- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at <http://www.niaid.nih.gov/publications/>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at <http://www.niams.nih.gov/hi/index.htm>
- National Institute of Child Health and Human Development (NICHD); guidelines available at <http://www.nichd.nih.gov/publications/pubskey.cfm>
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at <http://www.nidcd.nih.gov/health/>
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at <http://www.nidcr.nih.gov/HealthInformation/>
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at <http://www.niddk.nih.gov/health/health.htm>
- National Institute on Drug Abuse (NIDA); guidelines available at <http://www.nida.nih.gov/DrugAbuse.html>
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at <http://www.niehs.nih.gov/external/facts.htm>
- National Institute of Mental Health (NIMH); guidelines available at <http://www.nimh.nih.gov/healthinformation/index.cfm>
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at http://www.ninds.nih.gov/health_and_medical/disorder_index.htm
- National Institute of Biomedical Imaging and Bioengineering; general information at <http://www.nibib.nih.gov/HealthEdu>
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at <http://nccam.nih.gov/health/>
- National Center for Research Resources (NCRR); various information directories available at <http://www.ncrr.nih.gov/publications.asp>
- Office of Rare Diseases; various fact sheets available at http://rarediseases.info.nih.gov/html/resources/rep_pubs.html
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at <http://www.cdc.gov/publications.htm>

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.¹⁰ Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic

¹⁰ Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINEplus (<http://medlineplus.gov/> or <http://www.nlm.nih.gov/medlineplus/databases.html>).

citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine¹¹:

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: http://www.nlm.nih.gov/databases/databases_bioethics.html
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: <http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html>
- **NLM Online Exhibitions:** Describes “Exhibitions in the History of Medicine”: <http://www.nlm.nih.gov/exhibition/exhibition.html>. Additional resources for historical scholarship in medicine: <http://www.nlm.nih.gov/hmd/index.html>
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: <http://www.ncbi.nlm.nih.gov/>
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: http://www.nlm.nih.gov/databases/databases_population.html
- **Cancer Information:** Access to cancer-oriented databases: http://www.nlm.nih.gov/databases/databases_cancer.html
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: <http://www.profiles.nlm.nih.gov/>
- **Chemical Information:** Provides links to various chemical databases and references: <http://sis.nlm.nih.gov/Chem/ChemMain.html>
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): http://www.nlm.nih.gov/databases/databases_space.html
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: http://www.nlm.nih.gov/databases/databases_medline.html
- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: <http://sis.nlm.nih.gov/Tox/ToxMain.html>
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: http://www.nlm.nih.gov/research/visible/visible_human.html

¹¹ See <http://www.nlm.nih.gov/databases/index.html>.

The NLM Gateway¹²

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.¹³ To use the NLM Gateway, simply go to the search site at <http://gateway.nlm.nih.gov/gw/Cmd>. Type **Cowden syndrome** (or synonyms) into the search box and click **Search**. The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	530
Books / Periodicals / Audio Visual	0
Consumer Health	11
Meeting Abstracts	0
Other Collections	0
Total	541

HSTAT¹⁴

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.¹⁵ These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.¹⁶ Simply search by **Cowden syndrome** (or synonyms) at the following Web site: <http://text.nlm.nih.gov>.

Coffee Break: Tutorials for Biologists¹⁷

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries.

¹² Adapted from NLM: <http://gateway.nlm.nih.gov/gw/Cmd?Overview.x>.

¹³ The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

¹⁴ Adapted from HSTAT: <http://www.nlm.nih.gov/pubs/factsheets/hstat.html>.

¹⁵ The HSTAT URL is <http://hstat.nlm.nih.gov/>.

¹⁶ Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

¹⁷ Adapted from <http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html>.

Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.¹⁸ Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.¹⁹ This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: <http://www.ncbi.nlm.nih.gov/Coffeebreak/>.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **MD Consult:** Access to electronic clinical resources, see <http://www.mdconsult.com/>.
- **Medical Matrix:** Lists over 6000 medical Web sites and links to over 1.5 million documents with clinical content, see <http://www.medmatrix.org/>.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see <http://www.mwsearch.com/>.

¹⁸ The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

¹⁹ After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

APPENDIX C. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called **Fact Sheets** or **Guidelines**. They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on Cowden syndrome can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

This section directs you to sources which either publish fact sheets or can help you find additional guidelines on topics related to Cowden syndrome. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at <http://health.nih.gov/>. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are **health topic pages** which list links to available materials relevant to Cowden syndrome. To access this system, log on to <http://www.nlm.nih.gov/medlineplus/healthtopics.html>. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for **Cowden syndrome**:

Birth Defects

<http://www.nlm.nih.gov/medlineplus/birthdefects.html>

Bone Diseases

<http://www.nlm.nih.gov/medlineplus/bonediseases.html>

Breast Cancer

<http://www.nlm.nih.gov/medlineplus/breastcancer.html>

Cancer

<http://www.nlm.nih.gov/medlineplus/cancer.html>

Cancer in Children

<http://www.nlm.nih.gov/medlineplus/cancerinchildren.html>

Genetic Testing

<http://www.nlm.nih.gov/medlineplus/genetictesting.html>

Osteoporosis

<http://www.nlm.nih.gov/medlineplus/osteoporosis.html>

Ovarian Cancer

<http://www.nlm.nih.gov/medlineplus/ovariancancer.html>

Skin Pigmentation Disorders

<http://www.nlm.nih.gov/medlineplus/skinpigmentationdisorders.html>

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **<http://www.nlm.nih.gov/medlineplus/>**. Simply type a keyword into the search box and click **Search**. This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

Healthfinder™

Healthfinder™ is sponsored by the U.S. Department of Health and Human Services and offers links to hundreds of other sites that contain healthcare information. This Web site is located at **<http://www.healthfinder.gov>**. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **[geneticalliance.org](http://www.geneticalliance.org)**

Source: www.geneticalliance.org

http://www.geneticalliance.org/ws_display.asp?filter=diseases_what_is&char=M&s_Diseases=

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is “crawled” and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to Cowden syndrome. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for

professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: <http://health.nih.gov/index.asp>. Under **Search Health Topics**, type **Cowden syndrome** (or synonyms) into the search box, and click **Search**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- Family Village: <http://www.familyvillage.wisc.edu/specific.htm>
- Google: http://directory.google.com/Top/Health/Conditions_and_Diseases/
- Med Help International: <http://www.medhelp.org/HealthTopics/A.html>
- Open Directory Project: http://dmoz.org/Health/Conditions_and_Diseases/
- Yahoo.com: http://dir.yahoo.com/Health/Diseases_and_Conditions/
- WebMD®Health: http://www.webmd.com/diseases_and_conditions/default.htm

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to Cowden syndrome. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with Cowden syndrome.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about Cowden syndrome. For more information, see the NHIC's Web site at <http://www.health.gov/NHIC/> or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at <http://sis.nlm.nih.gov/dirline.html>. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. Simply type in **Cowden syndrome** (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at <http://healthhotlines.nlm.nih.gov/>. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: <http://www.rarediseases.org/search/orgsearch.html>. Type **Cowden syndrome** (or a synonym) into the search box, and click **Submit Query**.

Resources for Patients and Families

The following are organizations that provide support and advocacy for patient with genetic conditions and their families²⁰:

- Genetic Alliance: <http://geneticalliance.org>
- Genetic and Rare Diseases Information Center:
http://rarediseases.info.nih.gov/html/resources/info_cntr.html
- Madisons Foundation: <http://www.madisonsfoundation.org/>
- March of Dimes: <http://www.marchofdimes.com>
- National Organization for Rare Disorders (NORD): <http://www.rarediseases.org/>

For More Information on Genetics

The following publications offer detailed information for patients about the science of genetics:

- What Is a Genome?:
http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html
- A Science Called Genetics: <http://publications.nigms.nih.gov/genetics/science.html>
- Genetic Mapping: <http://www.genome.gov/10000715>

²⁰ Adapted from the National Library of Medicine: <http://ghr.nlm.nih.gov/ghr/resource/patients>.

ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference:
<http://www.nlm.nih.gov/medlineplus/encyclopedia.html>
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.):
<http://www.medterms.com/Script/Main/hp.asp>
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.):
<http://www.intelihealth.com/IH/>
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: <http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html>
- On-line Medical Dictionary (CancerWEB): <http://cancerweb.ncl.ac.uk/omd/>
- Rare Diseases Terms (Office of Rare Diseases):
<http://ord.aspensys.com/asp/diseases/diseases.asp>
- Technology Glossary (National Library of Medicine) - Health Care Technology:
<http://www.nlm.nih.gov/archive/20040831/nichsr/ta101/ta10108.html>

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at <http://www.nlm.nih.gov/medlineplus/encyclopedia.html>. ADAM is also available on commercial Web sites such as drkoop.com (<http://www.drkoop.com/>) and Web MD (http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a).

Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization):
<http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical>
- Patient Education: Glossaries (DMOZ Open Directory Project):
http://dmoz.org/Health/Education/Patient_Education/Glossaries/
- Web of Online Dictionaries (Bucknell University):
<http://www.yourdictionary.com/diction5.html#medicine>

COWDEN SYNDROME DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

3-dimensional: 3-D. A graphic display of depth, width, and height. Three-dimensional radiation therapy uses computers to create a 3-dimensional picture of the tumor. This allows doctors to give the highest possible dose of radiation to the tumor, while sparing the normal tissue as much as possible. [NIH]

Abdomen: That portion of the body that lies between the thorax and the pelvis. [NIH]

Aberrant: Wandering or deviating from the usual or normal course. [EU]

Adaptability: Ability to develop some form of tolerance to conditions extremely different from those under which a living organism evolved. [NIH]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenoma: A benign epithelial tumor with a glandular organization. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adenosine Triphosphate: Adenosine 5'-(tetrahydrogen triphosphate). An adenine nucleotide containing three phosphate groups esterified to the sugar moiety. In addition to its crucial roles in metabolism adenosine triphosphate is a neurotransmitter. [NIH]

Adenovirus: A group of viruses that cause respiratory tract and eye infections. Adenoviruses used in gene therapy are altered to carry a specific tumor-fighting gene. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerobic: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

Airway: A device for securing unobstructed passage of air into and out of the lungs during general anesthesia. [NIH]

Airway Obstruction: Any hindrance to the passage of air into and out of the lungs. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alleles: Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental process. [NIH]

Alpha-1: A protein with the property of inactivating proteolytic enzymes such as leucocyte collagenase and elastase. [NIH]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH₂) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH₂) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form

proteins. [NIH]

Amnion: The extraembryonic membrane which contains the embryo and amniotic fluid. [NIH]

Amniotic Fluid: Amniotic cavity fluid which is produced by the amnion and fetal lungs and kidneys. [NIH]

Ampulla: A sac-like enlargement of a canal or duct. [NIH]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

Anesthesia: A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

Aneuploidy: The chromosomal constitution of cells which deviate from the normal by the addition or subtraction of chromosomes or chromosome pairs. In a normally diploid cell the loss of a chromosome pair is termed nullisomy (symbol: $2N-2$), the loss of a single chromosome is monosomy (symbol: $2N-1$), the addition of a chromosome pair is tetrasomy (symbol: $2N+2$), the addition of a single chromosome is trisomy (symbol: $2N+1$). [NIH]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Antigens: Substances that are recognized by the immune system and induce an immune reaction. [NIH]

Anuria: Inability to form or excrete urine. [NIH]

Anus: The opening of the rectum to the outside of the body. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Aqueous: Having to do with water. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Atypical: Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccid, rodlike or bacillary, and spiral or spirochetal. [NIH]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

Base Sequence: The sequence of purines and pyrimidines in nucleic acids and polynucleotides. It is also called nucleotide or nucleoside sequence. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Bewilderment: Impairment or loss of will power. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

Blastocyst: The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass which becomes the embryonic disc. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood pressure: The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

Blood vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bronchi: The larger air passages of the lungs arising from the terminal bifurcation of the trachea. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Buccal mucosa: The inner lining of the cheeks and lips. [NIH]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Cardiovascular disease: Any abnormal condition characterized by dysfunction of the heart and blood vessels. CVD includes atherosclerosis (especially coronary heart disease, which can lead to heart attacks), cerebrovascular disease (e.g., stroke), and hypertension (high blood pressure). [NIH]

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

Cause of Death: Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Cycle: The complex series of phenomena, occurring between the end of one cell division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell Movement: The movement of cells from one location to another. [NIH]

Cell Respiration: The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [NIH]

Cell Survival: The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

Centromere: The clear constricted portion of the chromosome at which the chromatids are joined and by which the chromosome is attached to the spindle during cell division. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Chin: The anatomical frontal portion of the mandible, also known as the mentum, that contains the line of fusion of the two separate halves of the mandible (symphysis menti). This line of fusion divides inferiorly to enclose a triangular area called the mental protuberance. On each side, inferior to the second premolar tooth, is the mental foramen for the passage of blood vessels and a nerve. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromosomal: Pertaining to chromosomes. [EU]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chromosome Fragility: Susceptibility of chromosomes to breakage and translocation or

other aberrations. Chromosome fragile sites are regions that show up in karyotypes as a gap (uncondensed stretch) on the chromatid arm. They are associated with chromosome break sites and other aberrations. A fragile site on the X chromosome is associated with fragile X syndrome. Fragile sites are designated by the letters "FRA" followed by the designation for the specific chromosome and a letter which refers to the different fragile sites on a chromosome (e.g. FRAXA). [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Cirrhosis: A type of chronic, progressive liver disease. [NIH]

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at <http://cis.nci.nih.gov>. [NIH]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

Codon: A set of three nucleotides in a protein coding sequence that specifies individual amino acids or a termination signal (codon, terminator). Most codons are universal, but some organisms do not produce the transfer RNAs (RNA, transfer) complementary to all codons. These codons are referred to as unassigned codons (codons, nonsense). [NIH]

Colon: The long, coiled, tubelike organ that removes water from digested food. The remaining material, solid waste called stool, moves through the colon to the rectum and leaves the body through the anus. [NIH]

Colonoscopy: Endoscopic examination, therapy or surgery of the luminal surface of the colon. [NIH]

Colorectal: Having to do with the colon or the rectum. [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the

alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

Concentric: Having a common center of curvature or symmetry. [NIH]

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Confusion: A mental state characterized by bewilderment, emotional disturbance, lack of clear thinking, and perceptual disorientation. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Constriction: The act of constricting. [NIH]

Consultation: A deliberation between two or more physicians concerning the diagnosis and the proper method of treatment in a case. [NIH]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Cornea: The transparent part of the eye that covers the iris and the pupil and allows light to enter the inside. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary heart disease: A type of heart disease caused by narrowing of the coronary arteries that feed the heart, which needs a constant supply of oxygen and nutrients carried by the blood in the coronary arteries. When the coronary arteries become narrowed or clogged by fat and cholesterol deposits and cannot supply enough blood to the heart, CHD results. [NIH]

Corpus: The body of the uterus. [NIH]

Cutaneous: Having to do with the skin. [NIH]

Cytochrome: Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption

maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

Cytosine: A pyrimidine base that is a fundamental unit of nucleic acids. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Death Certificates: Official records of individual deaths including the cause of death certified by a physician, and any other required identifying information. [NIH]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Dementia: An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

Deoxyribonucleic: A polymer of subunits called deoxyribonucleotides which is the primary genetic material of a cell, the material equivalent to genetic information. [NIH]

Deoxyribonucleic acid: A polymer of subunits called deoxyribonucleotides which is the primary genetic material of a cell, the material equivalent to genetic information. [NIH]

Deoxyribonucleotides: A purine or pyrimidine base bonded to a deoxyribose containing a bond to a phosphate group. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Diploid: Having two sets of chromosomes. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Discrimination: The act of qualitative and/or quantitative differentiation between two or more stimuli. [NIH]

Disorientation: The loss of proper bearings, or a state of mental confusion as to time, place, or identity. [EU]

Duodenum: The first part of the small intestine. [NIH]

Electrolytes: Substances that break up into ions (electrically charged particles) when they are dissolved in body fluids or water. Some examples are sodium, potassium, chloride, and calcium. Electrolytes are primarily responsible for the movement of nutrients into cells, and the movement of wastes out of cells. [NIH]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endocrine System: The system of glands that release their secretions (hormones) directly into the circulatory system. In addition to the endocrine glands, included are the chromaffin system and the neurosecretory systems. [NIH]

Endometrial: Having to do with the endometrium (the layer of tissue that lines the uterus). [NIH]

Endometrium: The layer of tissue that lines the uterus. [NIH]

Endoscope: A thin, lighted tube used to look at tissues inside the body. [NIH]

Endoscopic: A technique where a lateral-view endoscope is passed orally to the duodenum for visualization of the ampulla of Vater. [NIH]

Enteroscopy: An examination of the small intestine with an endoscope. The endoscope is inserted through the mouth and stomach into the small intestine. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Erectile: The inability to get or maintain an erection for satisfactory sexual intercourse. Also called impotence. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Esophageal: Having to do with the esophagus, the muscular tube through which food passes from the throat to the stomach. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Excrete: To get rid of waste from the body. [NIH]

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

Eye Color: Color of the iris. [NIH]

Eye Infections: Infection, moderate to severe, caused by bacteria, fungi, or viruses, which occurs either on the external surface of the eye or intraocularly with probable inflammation, visual impairment, or blindness. [NIH]

Facial: Of or pertaining to the face. [EU]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Fathers: Male parents, human or animal. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibroid: A benign smooth muscle tumor, usually in the uterus or gastrointestinal tract. Also called leiomyoma. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Frameshift: A type of mutation which causes out-of-phase transcription of the base sequence; such mutations arise from the addition or deletion of nucleotide(s) in numbers other than 3 or multiples of 3. [NIH]

Frameshift Mutation: A type of mutation in which a number of nucleotides not divisible by three is deleted from or inserted into a coding sequence, thereby causing an alteration in the reading frame of the entire sequence downstream of the mutation. These mutations may be induced by certain types of mutagens or may occur spontaneously. [NIH]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Products, rev: Trans-acting nuclear proteins whose functional expression are required for HIV viral replication. Specifically, the rev gene products are required for processing and translation of the HIV gag and env mRNAs, and thus rev regulates the expression of the viral structural proteins. rev can also regulate viral regulatory proteins. A cis-acting antirepression sequence (CAR) in env, also known as the rev-responsive element (RRE), is responsive to the rev gene product. rev is short for regulator of virion. [NIH]

Gene Therapy: The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [NIH]

Genes, env: DNA sequences that form the coding region for the viral envelope (env) proteins in retroviruses. The env genes contain a cis-acting RNA target sequence for the rev protein (= gene products, rev), termed the rev-responsive element (RRE). [NIH]

Genetic testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genomics: The systematic study of the complete DNA sequences (genome) of organisms. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Germ Cells: The reproductive cells in multicellular organisms. [NIH]

Germline mutation: A gene change in the body's reproductive cells (egg or sperm) that becomes incorporated into the DNA of every cell in the body of offspring; germline mutations are passed on from parents to offspring. Also called hereditary mutation. [NIH]

Germ-Line Mutation: Any detectable and heritable alteration in the lineage of germ cells. Mutations in these cells (i.e., "generative" cells ancestral to the gametes) are transmitted to progeny while those in somatic cells are not. [NIH]

Gland: An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

Glucose: D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

Goiter: Enlargement of the thyroid gland. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Granule: A small pill made from sucrose. [EU]

Granulocytes: Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

Guanine: One of the four DNA bases. [NIH]

Hair Color: Color of hair or fur. [NIH]

Hamartoma: A focal malformation resembling a neoplasm, composed of an overgrowth of mature cells and tissues that normally occur in the affected area. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Hemochromatosis: A disease that occurs when the body absorbs too much iron. The body stores the excess iron in the liver, pancreas, and other organs. May cause cirrhosis of the liver. Also called iron overload disease. [NIH]

Hemodialysis: The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal concentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobinopathies: A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [NIH]

Hemophilia: Refers to a group of hereditary disorders in which affected individuals fail to make enough of certain proteins needed to form blood clots. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

Hereditary mutation: A gene change in the body's reproductive cells (egg or sperm) that becomes incorporated into the DNA of every cell in the body of offspring; hereditary mutations are passed on from parents to offspring. Also called germline mutation. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Histones: Small chromosomal proteins (approx 12-20 kD) possessing an open, unfolded structure and attached to the DNA in cell nuclei by ionic linkages. Classification into the various types (designated histone I, histone II, etc.) is based on the relative amounts of arginine and lysine in each. [NIH]

Homologous: Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Human papillomavirus: HPV. A virus that causes abnormal tissue growth (warts) and is often associated with some types of cancer. [NIH]

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Implantation: The insertion or grafting into the body of biological, living, inert, or radioactive material. [EU]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infancy: The period of complete dependency prior to the acquisition of competence in walking, talking, and self-feeding. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins,

intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

Informed Consent: Voluntary authorization, given to the physician by the patient, with full comprehension of the risks involved, for diagnostic or investigative procedures and medical and surgical treatment. [NIH]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Inositol: An isomer of glucose that has traditionally been considered to be a B vitamin although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1379) Inositol phospholipids are important in signal transduction. [NIH]

Intestinal: Having to do with the intestines. [NIH]

Intestines: The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

Ions: An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

Iris: The most anterior portion of the uveal layer, separating the anterior chamber from the posterior. It consists of two layers - the stroma and the pigmented epithelium. Color of the iris depends on the amount of melanin in the stroma on reflection from the pigmented epithelium. [NIH]

Karyotype: The characteristic chromosome complement of an individual, race, or species as defined by their number, size, shape, etc. [NIH]

Kidney Failure: The inability of a kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake. In the acute form (kidney failure, acute), it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema. The chronic form (kidney failure, chronic) is irreversible and requires hemodialysis. [NIH]

Kidney Failure, Acute: A clinical syndrome characterized by a sudden decrease in glomerular filtration rate, often to values of less than 1 to 2 ml per minute. It is usually associated with oliguria (urine volumes of less than 400 ml per day) and is always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in blood urea nitrogen (BUN) and serum creatinine concentrations. [NIH]

Kidney Failure, Chronic: An irreversible and usually progressive reduction in renal function in which both kidneys have been damaged by a variety of diseases to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. Chronic kidney failure requires hemodialysis or surgery, usually kidney transplantation. [NIH]

Larynx: An irregularly shaped, musclocartilaginous tubular structure, lined with mucous membrane, located at the top of the trachea and below the root of the tongue and the hyoid bone. It is the essential sphincter guarding the entrance into the trachea and functioning secondarily as the organ of voice. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Leiomyoma: A benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the uterus and the gastrointestinal tract but can occur in the skin and subcutaneous tissues, probably arising from the smooth muscle of small blood vessels in these tissues. [NIH]

Leucocyte: All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipomatosis: A disorder consisting of the accumulation of abnormal localized, or tumor-like fat in the tissues. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Lymphocytes: White blood cells formed in the body's lymphoid tissue. The nucleus is round or ovoid with coarse, irregularly clumped chromatin while the cytoplasm is typically pale blue with azurophilic (if any) granules. Most lymphocytes can be classified as either T or B (with subpopulations of each); those with characteristics of neither major class are called null cells. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Lysine: An essential amino acid. It is often added to animal feed. [NIH]

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

Malformation: A morphologic defect resulting from an intrinsically abnormal developmental process. [EU]

Malignancy: A cancerous tumor that can invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant tumor: A tumor capable of metastasizing. [NIH]

Mammography: Radiographic examination of the breast. [NIH]

Medical Records: Recording of pertinent information concerning patient's illness or illnesses. [NIH]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Meiosis: A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

Melanoma: A form of skin cancer that arises in melanocytes, the cells that produce pigment. Melanoma usually begins in a mole. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Meningioma: A type of tumor that occurs in the meninges, the membranes that cover and protect the brain and spinal cord. Meningiomas usually grow slowly. [NIH]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Retardation: Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Miscarriage: Spontaneous expulsion of the products of pregnancy before the middle of the second trimester. [NIH]

Mitochondria: Parts of a cell where aerobic production (also known as cell respiration) takes place. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monosomy: The condition in which one chromosome of a pair is missing. In a normally diploid cell it is represented symbolically as $2N-1$. [NIH]

Morphological: Relating to the configuration or the structure of live organs. [NIH]

Mosaicism: The occurrence in an individual of two or more cell populations of different chromosomal constitutions, derived from a single zygote, as opposed to chimerism in which the different cell populations are derived from more than one zygote. [NIH]

Mucocutaneous: Pertaining to or affecting the mucous membrane and the skin. [EU]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Mutagens: Chemical agents that increase the rate of genetic mutation by interfering with the function of nucleic acids. A clastogen is a specific mutagen that causes breaks in chromosomes. [NIH]

Myotonic Dystrophy: A condition presenting muscle weakness and wasting which may be progressive. [NIH]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at <http://cancer.gov>. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Neoplasia: Abnormal and uncontrolled cell growth. [NIH]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neuroendocrine: Having to do with the interactions between the nervous system and the endocrine system. Describes certain cells that release hormones into the blood in response to stimulation of the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neurotransmitter: Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. Among the many substances that have the properties of a neurotransmitter are acetylcholine, norepinephrine, epinephrine, dopamine, glycine, γ -aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclear Envelope: The membrane system of the cell nucleus that surrounds the nucleoplasm. It consists of two concentric membranes separated by the perinuclear space. The structures of the envelope where it opens to the cytoplasm are called the nuclear pores (nuclear pore). [NIH]

Nuclear Pore: An opening through the nuclear envelope formed by the nuclear pore complex which transports nuclear proteins or RNA into or out of the cell nucleus and which, under some conditions, acts as an ion channel. [NIH]

Nuclei: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by

polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nurse Practitioners: Nurses who are specially trained to assume an expanded role in providing medical care under the supervision of a physician. [NIH]

Oliguria: Clinical manifestation of the urinary system consisting of a decrease in the amount of urine secreted. [NIH]

Oncology: The study of cancer. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysosomes; plastids; and vacuoles. [NIH]

Osteoporosis: Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related (or senile) osteoporosis. [NIH]

Ovaries: The pair of female reproductive glands in which the ova, or eggs, are formed. The ovaries are located in the pelvis, one on each side of the uterus. [NIH]

Oxidative Phosphorylation: Electron transfer through the cytochrome system liberating free energy which is transformed into high-energy phosphate bonds. [NIH]

Palate: The structure that forms the roof of the mouth. It consists of the anterior hard palate and the posterior soft palate. [NIH]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Papillomavirus: A genus of Papovaviridae causing proliferation of the epithelium, which may lead to malignancy. A wide range of animals are infected including humans, chimpanzees, cattle, rabbits, dogs, and horses. [NIH]

Paternity: Establishing the father relationship of a man and a child. [NIH]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

PDQ: Physician Data Query. PDQ is an online database developed and maintained by the National Cancer Institute. Designed to make the most current, credible, and accurate cancer information available to health professionals and the public, PDQ contains peer-reviewed summaries on cancer treatment, screening, prevention, genetics, and supportive care; a registry of cancer clinical trials from around the world; and directories of physicians, professionals who provide genetics services, and organizations that provide cancer care. Most of this information is available on the CancerNet Web site, and more specific information about PDQ can be found at <http://cancernet.nci.nih.gov/pdq.html>. [NIH]

Pelvis: The lower part of the abdomen, located between the hip bones. [NIH]

Penis: The external reproductive organ of males. It is composed of a mass of erectile tissue enclosed in three cylindrical fibrous compartments. Two of the three compartments, the

corpus cavernosa, are placed side-by-side along the upper part of the organ. The third compartment below, the corpus spongiosum, houses the urethra. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharynx: The hollow tube about 5 inches long that starts behind the nose and ends at the top of the trachea (windpipe) and esophagus (the tube that goes to the stomach). [NIH]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nerves, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Physical Examination: Systematic and thorough inspection of the patient for physical signs of disease or abnormality. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absence of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plastids: Self-replicating cytoplasmic organelles of plant and algal cells that contain pigments and may synthesize and accumulate various substances. Plastids are used in phylogenetic studies. [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polyp: A growth that protrudes from a mucous membrane. [NIH]

Polyposis: The development of numerous polyps (growths that protrude from a mucous membrane). [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

Postmenopausal: Refers to the time after menopause. Menopause is the time in a woman's life when menstrual periods stop permanently; also called "change of life." [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for

the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Predisposition: A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

Progeny: The offspring produced in any generation. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Prone: Having the front portion of the body downwards. [NIH]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Edema: An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Pyrimidines: A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and uracil) and form the basic structure of the barbiturates. [NIH]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radioactive: Giving off radiation. [NIH]

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

Radiology: A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [NIH]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Refer: To send or direct for treatment, aid, information, or decision. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [NIH]

Renal cell carcinoma: A type of kidney cancer. [NIH]

Reproductive cells: Egg and sperm cells. Each mature reproductive cell carries a single set of 23 chromosomes. [NIH]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Retinoblastoma: An eye cancer that most often occurs in children younger than 5 years. It occurs in hereditary and nonhereditary (sporadic) forms. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Ribonucleic acid: RNA. One of the two nucleic acids found in all cells. The other is deoxyribonucleic acid (DNA). Ribonucleic acid transfers genetic information from DNA to proteins produced by the cell. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA

attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

Scatter: The extent to which relative success and failure are divergently manifested in qualitatively different tests. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Sclera: The tough white outer coat of the eyeball, covering approximately the posterior five-sixths of its surface, and continuous anteriorly with the cornea and posteriorly with the external sheath of the optic nerve. [EU]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Sclerotic: Pertaining to the outer coat of the eye; the sclera; hard, indurated or sclerosed. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

Signs and Symptoms: Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Smooth Muscle Tumor: A tumor composed of smooth muscle tissue, as opposed to leiomyoma, a tumor derived from smooth muscle. [NIH]

Social Work: The use of community resources, individual case work, or group work to promote the adaptive capacities of individuals in relation to their social and economic environments. It includes social service agencies. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

Soma: The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Somatic cells: All the body cells except the reproductive (germ) cells. [NIH]

Somatic mutations: Alterations in DNA that occur after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Stillbirth: The birth of a dead fetus or baby. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Supportive care: Treatment given to prevent, control, or relieve complications and side effects and to improve the comfort and quality of life of people who have cancer. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Systemic: Affecting the entire body. [NIH]

Terminator: A DNA sequence sited at the end of a transcriptional unit that signals the end

of transcription. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyroid Gland: A highly vascular endocrine gland consisting of two lobes, one on either side of the trachea, joined by a narrow isthmus; it produces the thyroid hormones which are concerned in regulating the metabolic rate of the body. [NIH]

Thyroid Hormones: Hormones secreted by the thyroid gland. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tonsil: A round-to-oval mass of lymphoid tissue embedded in the lateral wall of the pharynx situated on each side of the fauces, between the anterior and posterior pillars of the soft palate. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Trachea: The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Translation: The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [NIH]

Trinucleotide Repeat Expansion: DNA region comprised of a variable number of repetitive, contiguous trinucleotide sequences. The presence of these regions is associated with diseases such as Fragile X Syndrome and myotonic dystrophy. Many chromosome fragile sites (chromosome fragility) contain expanded trinucleotide repeats. [NIH]

Trinucleotide Repeats: Microsatellite repeats consisting of three nucleotides dispersed in the euchromatic arms of chromosomes. [NIH]

Trisomy: The possession of a third chromosome of any one type in an otherwise diploid cell. [NIH]

Tumor suppressor gene: Genes in the body that can suppress or block the development of cancer. [NIH]

Tumour: 1. Swelling, one of the cardinal signs of inflammations; morbid enlargement. 2. A new growth of tissue in which the multiplication of cells is uncontrolled and progressive; called also neoplasm. [EU]

Ultraviolet radiation: Invisible rays that are part of the energy that comes from the sun. UV radiation can damage the skin and cause melanoma and other types of skin cancer. UV radiation that reaches the earth's surface is made up of two types of rays, called UVA and UVB rays. UVB rays are more likely than UVA rays to cause sunburn, but UVA rays pass

deeper into the skin. Scientists have long thought that UVB radiation can cause melanoma and other types of skin cancer. They now think that UVA radiation also may add to skin damage that can lead to skin cancer and cause premature aging. For this reason, skin specialists recommend that people use sunscreens that reflect, absorb, or scatter both kinds of UV radiation. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

Vitamin A: A substance used in cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Warts: Benign epidermal proliferations or tumors; some are viral in origin. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Windpipe: A rigid tube, 10 cm long, extending from the cricoid cartilage to the upper border of the fifth thoracic vertebra. [NIH]

Womb: A hollow, thick-walled, muscular organ in which the impregnated ovum is developed into a child. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

Yeasts: A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are *Saccharomyces cerevisiae*; therapeutic dried yeast is dried yeast. [NIH]

Zygote: The fertilized ovum. [NIH]

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