

Understanding Genetics: A District of Columbia Guide for Patients and Health Professionals

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UNDERSTANDING GENETICS



A GUIDE FOR PATIENTS AND HEALTH PROFESSIONALS

DISTRICT OF COLUMBIA DEPARTMENT OF HEALTH | GENETIC ALLIANCE

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PREFACE

Over the past few decades, advances in genetics and genomics have exceeded our greatest expectations and have revolutionized the way we think about health. While genetics has been traditionally associated with pregnancy, birth defects, and newborn screening, almost every disease is influenced in part by an individual's genetic make-up. Therefore, it is important to consider the impact of genetics for any condition throughout a patient's lifetime.

The purpose of the manual is to provide a genetics educational resource for patients and health professionals in the District of Columbia and increase awareness of specialty care in genetics. The manual opens with a basic introduction to genetic concepts followed by a description of the different types and applications of genetic tests. Information is also provided about diagnosis of a genetic disease, family-history taking, newborn screening, and genetic counseling. Helpful resources are included to assist in patient care, patient and professional education, and specialty genetics services in the District of Columbia and surrounding areas. At the end of each section, a list of selected references is provided if any additional information is desired. In addition, a series of consumer fact sheets are provided to be copied and offered to patients. These take-home resources will be critical in helping patients understand some of the basic concepts and applications of genetics.

This manual was created by Genetic Alliance with funding from the District of Columbia Department of Health. Genetic Alliance is an international coalition comprised of more than 600 advocacy, research, and healthcare organizations that represent more than 14 million people. With a 20-year history as a 501(c)(3) not-for-profit organization, Genetic Alliance is dedicated to improving the quality of life for everyone living with genetic conditions. Strategically situated at the crossroads of the genetics community, Genetic Alliance provides technical assistance to advocacy organizations, builds and sustains robust information systems to empower an active and dynamic network of stakeholders, and actively works for public policies that promote the translation of basic research into therapies and treatments. In particular, Genetic Alliance identifies solutions to emerging problems and works to reduce obstacles to rapid and effective translation of research into accessible technologies and services that improve human health.

The mission of the Department of Health is to promote healthy lives, prevent illness, provide equal access to quality healthcare services, and protect the safety of all in the Nation's capital. This project was made possible through funding from the U.S. Department of Health and Human Services Health Resource and Services Administration, Grant # 5 H91 MC 00228-03. Additional print copies can be obtained from the Children with Special Health Care Needs Division, DC-DOH Maternal and Family Health Administration at (202) 671-5000. The manual will also be available online (<http://www.geneticalliance.org>) in a downloadable format and updated regularly.



CHAPTER 1 : GENETICS 101

Understanding the underlying concepts of human genetics and the role of genes, behavior, and the environment will be important to appropriately collecting and applying genetic information and technologies during clinical care. This chapter provides some fundamental information about basic genetic concepts including cell structure, the molecular and biochemical basis of disease, major types of genetic disease, laws of inheritance, and impact of genetic variation.

Almost every human trait and disease has a genetic component, whether inherited or modifying the body's response to environmental factors such as toxins or behavioral factors such as exercise. Understanding the underlying concepts of human genetics and the role of genes, behavior, and the environment will be important in improving disease diagnosis and treatment. This section presents a broad overview of basic genetics concepts and the molecular and biochemical basis of disease.

1.1 CELLS, GENOMES, DNA, AND GENES

Cells are the fundamental working units of every living system. All the instructions needed to direct their activities are contained within a DNA (deoxyribonucleic acid) sequence. DNA from all organisms is made up of the same chemical units (base pairs) abbreviated as A, T, C, and G. The human genome (total composition of genetic material within a cell) is packaged into larger units known as chromosomes—physically separate molecules that range in length from about 50 million to 250 million base pairs. Human cells contain two sets of chromosomes, one set inherited from each parent. Each cell, except sperm and eggs, contains 23 pairs of chromosomes—22 autosomes (numbered 1 through 22) and one pair of sex chromosomes (XX or XY). Sperm and eggs contain half as much genetic material (e.g., only one copy of each chromosome).

Each chromosome contains many genes, the basic physical and functional units of heredity. Genes are specific sequences of bases that encode instructions on how to make proteins. The DNA sequence is the particular side-by-side arrangement of bases along the DNA strand (e.g., ATTCCGGA). Each gene has a unique DNA sequence. Genes comprise only about 2% of the human genome; the remainder consists of non-coding regions, whose functions may include providing chromosomal structural integrity and regulating where, when, and in what quantity proteins are made. The human genome is estimated to contain 20,000-25,000 genes.

Although each cell contains a full complement of DNA, cells use genes selectively. For example, the genes active in a liver cell differ from genes active in a brain cell since each cell performs different functions and therefore requires different proteins. Different genes can also be activated during development or in response to environmental stimuli such as an infection or stress.

1.2 MAJOR TYPES OF GENETIC DISEASE

Many, if not most, diseases have their roots in genes. Genes—through the proteins they encode—determine how efficiently foods and chemicals are metabolized, how effectively toxins are detoxified, and how vigorously infections are targeted. Genetic diseases can be categorized into three major groups: single-gene, chromosomal, and multifactorial.



Thousands of diseases are known to be caused by changes in the DNA sequence of single genes. A gene can be changed (mutated) in many ways resulting in an altered protein product that is unable to perform its function. The most common gene mutation involves a change in a single base in the DNA—a misspelling. Other mutations include the loss (deletion) or gain (duplication or insertion) of a single or multiple bases. The altered protein product may still retain some function but at a reduced capacity. In other cases, the protein may be totally disabled by the mutation or gain an entirely new but damaging function. The outcome of a particular mutation depends not only on how it alters a protein's function but also on how vital that particular protein is to survival.

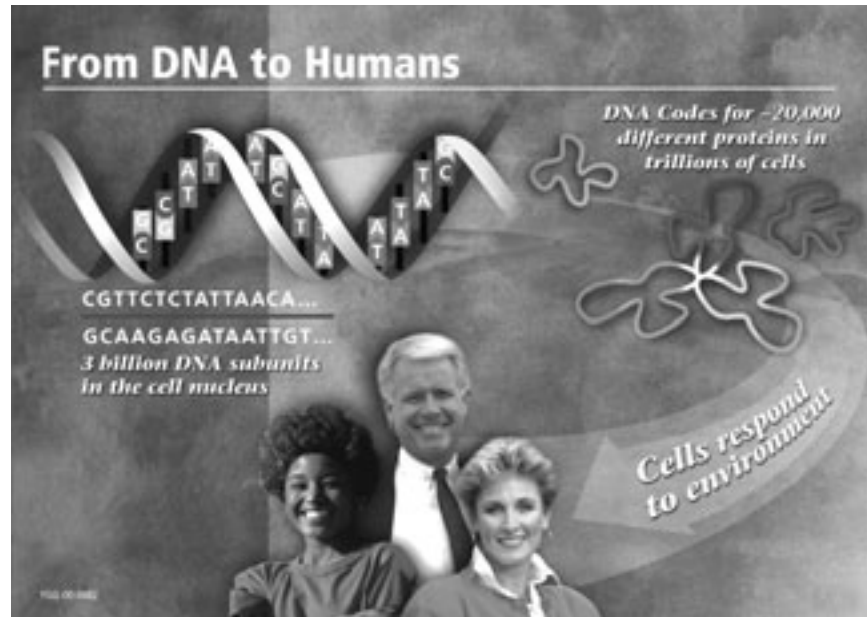


IMAGE CREDIT: U.S. Department of Energy Human Genome Program, <http://www.ornl.gov/hgmis>.

In addition, genetic diseases can be caused by larger changes in chromosomes. Chromosomal abnormalities may be either numerical or structural. The most common type of chromosomal abnormality is known as aneuploidy, an abnormal chromosome number due to an extra or missing chromosome. A normal karyotype (complete chromosome set) contains 46 chromosomes including an XX (female) or XY (male) sex chromosome pair. Structural chromosomal abnormalities include deletions, duplications, insertions, inversions, or translocations of a chromosome segment. [See Appendix H for more information about Chromosomal Abnormalities.]

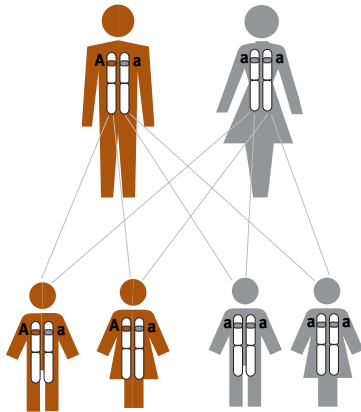
Multifactorial diseases are caused by a combination of genetic, behavioral and environmental factors. The underlying etiology of multifactorial diseases is complex and heterogeneous. Examples of these conditions include neural tube defects, diabetes, and heart disease. While multifactorial diseases can recur in families, some mutations can be acquired throughout an individual's lifetime such as in cancer. All genes work in the context of environment and behavior, both at the cellular and global perspectives. Alterations in behavior or the environment, such as diet, exercise, exposure to toxic agents, or medications can all have influences on traits that are at least in part genetically determined.

1.3 LAWS OF INHERITANCE

The basic laws of inheritance are important in order to understand patterns of disease transmission [See Appendix B for more information about Classical Mendelian Genetics (Patterns of Inheritance).] Single-gene diseases are usually inherited in one of several patterns depending on the location of the gene (i.e., chromosomes 1-22 or X and Y) and whether one or two normal copies of the gene are needed for normal protein activity. There are five basic modes of inheritance for single-gene diseases: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and mitochondrial.

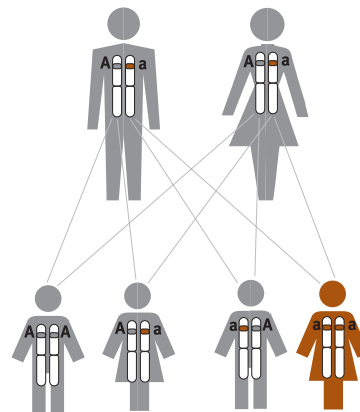
Genetic diseases caused by chromosomal abnormalities are generally not inherited, but usually occur as random events during the formation of reproductive cells. Below are a sample pedigree of each type of inheritance pattern and overview of family history patterns:

■ Affected ■ Unaffected



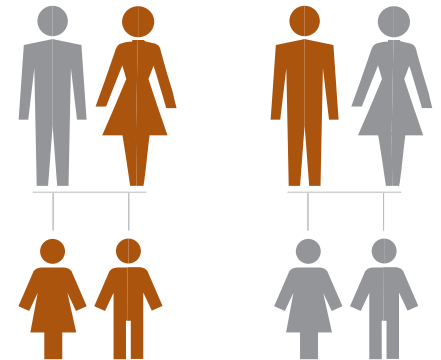
AUTOSOMAL DOMINANT

- Individuals carrying one mutated copy of a gene in each cell will be affected by the disease
- Each affected person usually has one affected parent
- Tends to occur in every generation of an affected family



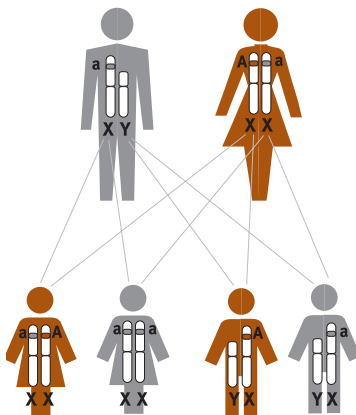
AUTOSOMAL RECESSIVE

- Affected individuals must carry two mutated copies of a gene
- Parents of affected individual are usually unaffected and each carry a single copy of the mutated gene (known as carriers)
- Not typically seen in every generation.



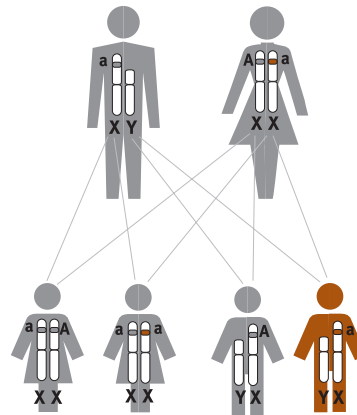
MITOCHONDRIAL

- Only females can pass on mitochondrial conditions to their children (maternal inheritance)
- Both males and females can be affected
- Can appear in every generation of a family



X-LINKED DOMINANT

- Females are more frequently affected than males
- Fathers cannot pass X-linked traits to their sons (no male-to-male transmission)



X-LINKED RECESSIVE

- Males are more frequently affected than females
- Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation
- Both parents of an affected daughter must be carriers
- Only mother must be carrier of affected son (fathers cannot pass X-linked traits to theirs)



1.4 GENETIC VARIATION

All individuals are 99.9 percent the same with respect to their DNA sequence. Differences in the sequence of DNA among individuals are called genetic variation. Genetic variation explains some of the differences among people, such as physical traits and also whether a person has a higher or lower risk for certain diseases. Genetic variation is referred to as mutations or polymorphisms. While mutations are generally associated with disease and relatively rare, polymorphisms are more frequent and their clinical significance not as straightforward. Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide is altered. SNPs occur every 100 to 300 bases along the 3-billion-base human genome. A single individual may carry millions of SNPs.



While some genetic variation may cause or modify risk to disease, others may result in a neutral phenotype or result in no detectable phenotype. For example, genetic variants in a single gene account for the different blood types A, B, AB, and O. Understanding the clinical significance of genetic variation is a complicated process due to the limited knowledge of which genes are involved in a disease or condition, and the multiple gene-gene and gene-behavior-environment interactions likely to be involved in complex, chronic diseases. New technologies are enabling faster and more accurate detection of genetic variants in hundreds or thousands of genes in a single experiment.

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Online Mendelian Inheritance in Man. Available at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>



CHAPTER 2 : DIAGNOSIS OF A GENETIC DISEASE

All diseases have a genetic component. However, the extent to which genes contribute to disease varies and much remains to be learned. Advances in understanding the genetic mechanisms behind these disease enables the development of early diagnostic tests, new treatments, or interventions to prevent disease onset or minimize disease severity. This chapter provides information about the importance of clinical signs such as family history that may be suggestive of a genetic disease, the different uses of genetic testing, and the different types of genetic diseases

All diseases have a genetic component. Mutations may be inherited or developed in response to environmental stresses such as viruses or toxins. The ultimate goal is to use this information to treat, cure, or, if possible, prevent the development of disease.

2.1 HISTORY AND PHYSICAL EXAMINATION

The diagnosis of a genetic disease requires a comprehensive clinical examination composed of three major elements:

1. a physical examination
2. a detailed medical family history
3. clinical and laboratory testing if available.

While primary care providers may not always be able to make a definitive diagnosis of a genetic disease, their role is critical in collecting a detailed family history, considering the possibility of a genetic disease in the differential diagnosis, ordering testing as indicated and, when available, appropriately referring patients to genetic specialists.



IMAGE CREDIT: U.S. Department of Energy Human Genome Program, <http://www.ornl.gov/hgmis>.

2.2 RED FLAGS FOR GENETIC DISEASE

There are several factors that raise the possibility of a genetic disease in a differential diagnosis. One major factor is the occurrence of a condition among family members that is disclosed when the family history is obtained (see Chapter 3 on Pedigree and Family-History Taking). The occurrence of the same condition in more than one family member (particularly first-degree relatives), multiple miscarriages, stillbirths, and childhood deaths are all suggestive of a genetic disease. Additionally, family history of common adult conditions (heart disease, cancer, dementia) that occur in two or more relatives at relatively young ages may also suggest a genetic predisposition.

Other clinical symptoms that are suggestive of a genetic disease include developmental delay/mental retardation and congenital abnormalities. Dysmorphologies often involving the heart and facies as well as growth problems are suggestive of a genetic disorder caused by an inherited mutation, spontaneous mutation, teratogen exposure, or unknown factors. While these clinical features may be caused by a number of factors, genetic conditions should also be considered as part of the differential diagnosis, particularly if the patient expresses several clinical features together that might be indicative of a syndrome (e.g., mental retardation, distinct facies, and heart defect). Some physical features may appear unique or slightly different than the average such as wide-set or droopy eyes, flat face, short fingers, and tall stature. While these rare and seemingly mild features may not immediately be suggestive of a genetic disease to a primary care provider, an evaluation by a genetics specialist may be helpful in ruling in/out a genetic disease.



While many genetic conditions appear during childhood, a genetic condition should not entirely be ruled out in adolescents or adults. Often a genetic disease can remain undetected for several years until an event such as puberty or pregnancy triggers the onset of symptoms or the accumulation of toxic metabolites manifests in disease. In these cases, a detailed family history and physical examination should be performed and a referral to a genetics specialist if indicated.

2.3 USES OF GENETIC TESTING

Genetic tests can be used for many different purposes. Table 2.1 lists some of the major uses of genetic testing.

- The most widespread use of genetic testing is **newborn screening** [See Chapter 4 for more information about Newborn Screening]. Almost every newborn in the U.S. is screened for several genetic diseases. Early detection of these diseases can lead to interventions to prevent the onset of symptoms or minimize disease severity.
- **Carrier testing** can be used to help couples to learn if they carry—and thus risk passing to their children—a recessive allele for genetic diseases such as cystic fibrosis, sickle cell anemia, and Tay-Sachs disease. This type of testing is typically offered to individuals who have a family history of a genetic disorder and to people in 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 diagnostic testing** is used to detect changes in a fetus's genes or chromosomes. This type of testing is offered to couples with an increased risk of having a baby with a genetic or chromosomal disorder. A tissue sample for testing can be obtained through amniocentesis or chorionic villus sampling. [See Appendix E for more information about Prenatal Diagnosis.]
- Genetic tests may be used to confirm a **diagnosis** in a symptomatic individual or used to monitor **prognosis** of a disease or response to treatment.
- **Predictive or predispositional** genetic testing can identify individuals at risk of getting a disease prior to the onset of symptoms. These tests are particularly useful if an individual has a family history of a specific disease and an intervention is available to prevent the onset of disease or minimize disease severity. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer.

Table 2.1
Uses of Genetic Tests

- Newborn Screening
- Carrier Testing
- Prenatal Diagnosis
- Diagnostic/Prognostic
- Predictive/Predispositional

2.4 TYPES OF GENETIC TESTING

Several different methods are currently used in genetic testing laboratories. The type of test will depend on the type of abnormality that is being measured. In general, three major types of genetic testing are available—cytogenetic, biochemical, and molecular testing to detect abnormalities in chromosome structure, protein function, or DNA sequence, respectively.

2.4.1 Cytogenetic Testing. Cytogenetics involves the examination of whole chromosomes for abnormalities. Chromosomes of a dividing human cell can be clearly analyzed under a microscope. White blood cells, specifically T lymphocytes, are the most readily accessible cells for cytogenetic analysis since they are easily collected from blood and are capable of rapid division in cell culture. Cells from other tissues such as bone marrow (for leukemia), amniotic fluid (prenatal diagnosis), and other tissue biopsies can also be cultured for cytogenetic analysis.

Following several days of cell culture, chromosomes are fixed, spread on microscope slides and then stained. The staining methods for routine analysis allow each of the chromosomes to be individually identified. The distinct bands of each chromosome revealed by staining allow for analysis of chromosome structure.

Table 2.2 Types of Protein Changes Resulting in Altered Function

- No protein made
- Too much or too little protein made
- Mis-folded protein made
- Altered active site or other critical region
- Incorrectly modified protein
- Incorrectly localized protein (build-up of protein)
- Incorrectly assembled

2.4.2 Biochemical Testing. The enormous numbers of biochemical reactions that routinely occur in cells require different types of proteins. Several classes of proteins exist to fulfill the multiple functions, such as enzymes, transporters, structural proteins, regulatory proteins, receptors, and hormones. A mutation in any type of protein can result in disease if the mutation ultimately results in failure of the protein to correctly function (see Table 2.2 for how proteins may be altered in a genetic disease).

Clinical testing for a biochemical disease utilizes techniques that examine the protein instead of the gene. Depending on the function, tests can be developed to directly measure protein activity (enzymes), level of metabolites (indirect measurement of protein activity), and the size or quantity of protein (structural proteins). These tests require a tissue sample in which the protein is present, typically blood, urine, amniotic fluid, or cerebrospinal fluid. Because proteins are more unstable than DNA and can degrade quickly, the sample must be collected and stored properly and shipped promptly according to the laboratory's specifications.

2.4.3 Molecular Testing. For small DNA mutations, direct DNA testing may be the most effective method, particularly if the function of the protein is not known and a biochemical test cannot be developed. A DNA test can be performed on any tissue sample and require very small amounts of sample. For some genetic diseases, many different mutations can occur in the same gene and result in the disease, making molecular testing challenging. For example, more than 1,000 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) can cause cystic fibrosis (CF). It would be impractical to sequence the entire CFTR gene to identify the causative mutation since the gene is quite large. However, since the majority of CF cases are caused by approximately 30 mutations, this group of mutations is first tested before more comprehensive testing is performed.

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CHAPTER 3 : PEDIGREE AND FAMILY-HISTORY TAKING

Health care professionals have known for a long time that common diseases - heart disease, cancer, and diabetes - and even rare diseases - like hemophilia, cystic fibrosis, and sickle cell anemia - can run in families. If one generation of a family has high blood pressure, it is not unusual for the next generation to have similarly high blood pressure. Therefore, family history can be a powerful screening tool and has often been referred to as the best “genetic test.”

Both common diseases and rare diseases can run in families. Therefore, family history can be a powerful screening tool. Family history should be updated on each visit and patients should be made aware of its significance to their health.

3.1 IMPORTANCE OF FAMILY HISTORY

Family history holds important information about an individual's past and future life. Family history can be used as a diagnostic tool and help guide decisions on genetic testing for the patient and at-risk family members. If a family is affected by a disease, an accurate family history will be important to establish a pattern of transmission. In addition, a family history can even help to exclude genetic diseases, particularly for common diseases where behavior and environment play strong roles. And lastly, a family history can identify potential health problems that an individual may be at increased risk for in the future. Early identification of increased risk can allow the individual and health professional to take steps to reduce risk by implementing lifestyle changes and increasing disease surveillance.



While many of the well-known genetic disorders are of childhood onset, many complex, adult-onset conditions can also run in families. For example, about five to ten percent of all breast cancers are hereditary. These cancers may be caused by mutations in particular genes, such as BRCA1 or BRCA2. An individual may be at high risk of hereditary breast cancer and genetic testing should be considered if her family history includes more than one first-degree (mother, sister, or daughter) or second-degree relative (aunt, grandmother, or cousin) with breast or ovarian cancer, particularly if the diagnosis of breast or ovarian cancer in those relatives occurred at a young age (50 or younger).

Another example of an adult-onset disease that can be inherited is Alzheimer disease. Although about 75 percent of Alzheimer disease cases are sporadic, 25 percent Alzheimer disease cases are hereditary. Hereditary Alzheimer disease is an extremely aggressive form of the disease and typically manifests before the age of 65. Three genes that cause early-onset Alzheimer disease have been identified.

Notwithstanding the importance of family history to help define occurrence of a genetic disorder within a family, it should be noted that some genetic diseases are caused by spontaneous mutations, such as for single gene disorders like Duchenne muscular dystrophy and hemophilia A as well as for most cases of Down syndrome, chromosomal deletion syndromes, and other chromosomal disorders. Therefore, a genetic disorder cannot be ruled out in the absence of a family history.



3.2 HOW TO TAKE A FAMILY MEDICAL HISTORY

A basic family history should include three generations. To begin taking a family history, start by asking the patient about his/her health history and then ask about siblings and parents.

Questions should include:

1. General information such as names and birthdates
2. Family's origin or racial/ethnic background
3. Health status
4. Age and causes of death
5. Pregnancy outcomes of the patient and genetically-related relatives

It may be easier to list all the members of the nuclear family first and then go back and ask about the health status of each one. After you have taken the family history of the patient's closest relatives, go back one generation at a time and ask about aunts, uncles, grandparents, and first cousins.

3.3 PEDIGREES

One way to record a family history is by drawing a family tree called a "pedigree." A pedigree represents family members and relationships using standardized symbols (see below). As patients relate information to you about their family history, a pedigree can be drawn much quicker than recording the information in writing and allows patterns of disease to emerge as the pedigree is drawn. Since the family history is continually changing, the pedigree can be easily updated on future visits. Patients should be encouraged to record information and update their family history regularly.

PEDIGREE SYMBOLS



Male



Female



Adopted



Deceased
Diagonal line used to show that a person has died.



Pregnancy loss
Include the number of weeks if known.



Still birth
Include the number of weeks if known.



Divorced/not together
Diagonal line used to show parents are divorced or not together.

WHAT IF THERE IS LIMITED INFORMATION ABOUT FAMILY MEMBERS?

1. If you do not know names and ages of family members, but do know the number of boys and the number of girls, you can do this:



Example: This shows that there are 5 boys and 3 girls.

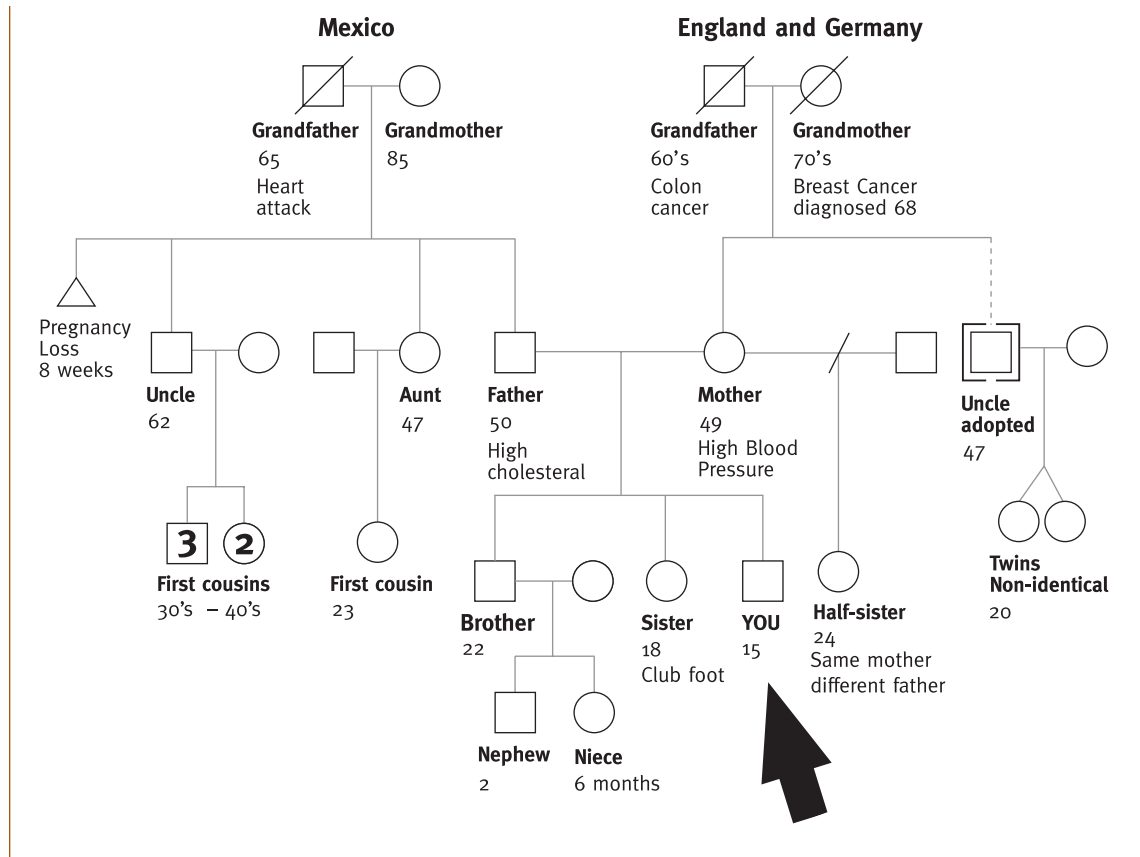
2. If you do not know the number of boys and the number of girls, use a diamond with a number inside it (if total is known) or "?".



Example: This shows that there are 8 children.

The sample pedigree below contains information such as age or date of birth (and, for all family members who have passed on, age at death and cause of death), major medical problems such as cancer, heart disease, and diabetes and age of onset, birth defects such as spina bifida and cleft lip, learning problems and mental retardation, and vision loss/hearing loss at a young age. For family members with known medical problems, ask whether they smoke, what their diet and exercise habits are, if known, and if they are overweight.

SAMPLE PEDIGREE



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CHAPTER 4 : NEWBORN SCREENING

Almost every child born in the United States undergoes state-mandated newborn screening. For each state, a small blood sample (“heel stick”) is collected from each newborn within 48 hours of birth and sent to a laboratory for testing for a panel of genetic disorders. Newborn screening programs may screen for up to 50 diseases, including phenylketonuria (PKU), sickle cell disease, and hypothyroidism. About 3,000 newborns test positive each year for one of these severe disorders. In the event that a newborn screens positive for one of the disorders, screening allows early intervention that can lead to significant reduction in disease severity and possibly even prevention of the disease. This chapter provides an overview of newborn screening programs and the specific conditions and procedures for the District of Columbia, Virginia, and Maryland.

Newborn screening is the first public health program for genetic conditions. In the U.S., newborn screening programs are state-mandated and the diseases screened in each state may vary. Efforts are underway to develop a national newborn screening program. New technologies have enabled substantial expansion of newborn screening programs.

4.1 OVERVIEW OF NEWBORN SCREENING

Each year, more than 95% of all children born in the United States (at least 4 million babies) are tested for a panel of diseases that, when detected and treated early, can lead to significant reduction in disease severity and possibly even prevention of the disease. About 3,000 newborns test positive for one of these severe disorders.

Within 48 hours of a child's birth, a sample of blood is obtained from a "heel stick," and the blood is analyzed for up to 50 diseases, including phenylketonuria (PKU), sickle cell disease, and hypothyroidism. The sample, called a "blood spot," is tested at a state public health or other participating laboratory.



4.2 NEWBORN SCREENING PROGRAMS

Since newborn screening is a state-operated program, each state differs slightly in which diseases are included in newborn screening programs depending on disease prevalence, detectability, treatment availability, outcome, and overall cost effectiveness. Typically, each state has an advisory committee that reviews and selects which diseases are screened for based on current scientific and clinical data. Increasingly, tandem mass spectrometry is being used for newborn screening of up to 50 additional metabolic disorders from dried blood-spot specimens. A recent report commissioned by the US Health Resources and Services Administration recommended uniform screening for 29 genetic diseases. Efforts are underway to examine the feasibility of instituting uniform newborn screening policies.

4.2.1 District of Columbia. Since 1980, the mission of the District of Columbia Newborn Screening Program is to detect, diagnose, and treat every newborn baby who tests positive for certain inherited genetic disorders. This program can mean the difference between life and death for a newborn. It can also prevent life-threatening complications and serious chronic consequences such as mental retardation, developmental disability, liver disease, blindness, neurological degeneration, malnutrition, and death.

The vision of the Newborn Metabolic Screening Program in the District of Columbia is that all newborns are screened for metabolic disorders prior to hospital discharge. The Program's purpose is to require all hospitals in the District of Columbia to screen for 40 inherited genetic disorders that are treatable by diet, vitamins and/or medication, or by anticipatory measures to prevent attacks.



The overall goal of the Program is to ensure that every infant born in the District is screened for 40 inherited genetic disorders and that infants identified with abnormal screening results receive timely and appropriate follow-up, to treat inherited diseases before the onset of clinical symptoms.

Program Objectives:

- To assure that all infants born in the District of Columbia are screened and that testing is processed within 5 days of birth.
- To assure that all families and affected infants receive timely and appropriate confirmatory testing, counseling, and treatment.
- To assure that all newborns diagnosed with a metabolic disease or hemoglobin abnormality are entered into and maintained on appropriate medical therapy.

4.2.1.1 DISORDERS SCREENED. Final rulemaking to amend DC Law 3-65 was published and made effective on November 4, 2005. The amendment expands the current panel of newborn screening disorders in the District of Columbia from seven to 40 disorders. The expanded panel includes screens for inherited hemoglobinopathies and 39 metabolic disorders. Every infant born in a District of Columbia hospital and birthing center will be screened for the following disorders. See the consumer fact sheet on newborn screening for a brief description of the diseases.

1. 2,4-Dienoyl-CoA reductase deficiency
2. 2-Methylbutyryl-CoA dehydrogenase deficiency
3. 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
4. 3-Methylglutaconyl-CoA hydratase deficiency
5. 3-OH 3-CH₃ glutaric aciduria or 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG)
6. 5-Oxoprolinuria (pyroglutamic aciduria)
7. Argininemia
8. Argininosuccinic acidemia (ASA)
9. Beta-ketothiolase deficiency (BKT)
10. Biotinidase deficiency (BIOT)
11. Carbamoylphosphate synthetase deficiency (CPS def.)
12. Carnitine uptake defect (CUD)
13. Citrullinemia (CITR)
14. Congenital adrenal hyperplasia (CAH)
15. Congenital hypothyroidism
16. Cystic fibrosis (CF)
17. Galactosemia
18. Glucose-6-Phosphate dehydrogenase deficiency (G6PD)
19. Glutaric acidemia type I (GA-I)
20. Hemoglobinopathy
21. Homocystinuria
22. Hyperammonemia, hyperornithinemia, homocitrullinemia syndrome (HHH)
23. Hyperornithine with gyrate deficiency
24. Isobutyryl-CoA dehydrogenase deficiency
25. Isovaleric acidemia (IVA)
26. Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHADD)
27. Malonic aciduria

28. Maple syrup urine disease (MSUD)
29. Medium chain acyl-CoA dehydrogenase deficiency (MCADD)
30. Methylmalonic acidemia
31. Multiple acyl-CoA dehydrogenase deficiency (MADD)
32. Multiple carboxylase deficiency (MCD)
33. Neonatal carnitine palmitoyl transferase deficiency-type II (CPT-II)
34. Phenylketonuria (PKU)
35. Propionic acidemia (PROP)
36. Short chain acyl-CoA dehydrogenase deficiency (SCAD)
37. Short chain hydroxy acyl-CoA dehydrogenase deficiency (SCHAD)
38. Trifunctional protein deficiency (TFP)
39. Tyrosinemia type I (TYRO-I)
40. Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)

4.2.1.2 PROCEDURES AND FOLLOW-UP. Every live born infant shall have an adequate blood test for all disorders defined in the District of Columbia Newborn Screening Requirement Act upon informed consent by the parent. The initial screening is to be done in the hospital and may be repeated, as necessary, prior to discharge. When a live birth occurs in a hospital or birthing center, the physician shall have a blood specimen by filter paper of the infant's blood taken prior to the infant's discharge from the hospital or birthing center. The infant's blood for these tests shall be collected not earlier than 24 hours after the first feeding following birth and no later than when the infant is one week old. If the infant born in a hospital or birthing center is discharged before 48 hours after birth, a blood specimen shall be collected prior to discharge. In this case, the newborn must be tested again prior to one week of age. The hospital or birthing center should provide written notice of this requirement to the parents, guardian, or other legally responsible person.

The hospital or birthing center must inform the parent about the purpose of testing and must document in the newborn's health record that the parent was educated about the test and that the parent gave consent or non-consent to test. Each specimen is forwarded to a single laboratory designated by the Mayor, in accordance with the DC Newborn Screening Law. The blood sample and the required patient information must be sent to the approved laboratory on the day of collection for an adequate test.

The laboratory performing blood tests for the purpose of satisfying legal requirements for testing newborns shall report all such test results to the hospital where the birth occurred. The results shall be part of the infant's medical record. The laboratory shall report all results to the Department of Health, Maternal and Family Health Administration, Children with Special Health Needs Division's Metabolic Screening Program on the day testing is completed of all positive and inconclusive test results and this report shall include the patient's required information.

The Children with Special Health Needs (CSHCN) Newborn Metabolic Screening Program notifies the infant's parent(s) and the newborn's physician about abnormal findings, and assists in securing appropriate follow-up testing and treatment when indicated. CSHCN refers critical infants to specialists within the District of Columbia that offer evaluation, treatment and counseling services. Specialty centers for endocrinology, hematology, and medical genetics are located throughout the District of Columbia. For newborns with presumptive positive results (except for G6PD and Sickle Cell Trait), the following steps should be taken by



CSHCN to notify parents/guardians and follow-up with confirmation of the screening result and intervention as needed:

- Notify newborn's parent(s)/guardian by telephone within 24-48 hours following receipt of abnormal screen result from the laboratory.
- Recommend immediate pediatric/primary physician/clinic appointment.
- Recommend immediate evaluation by a Specialty Treatment Center.
- Recommend family testing and counseling.
 - Verify infant's demographic information.
 - Obtain name, telephone number, and address of the infant's physician.
 - Assist with scheduling physician appointment.
- If there is no designated physician, seek a physician or refer the infant directly to a Special Treatment Center.
- If mother's telephone number is disconnected or incorrect, call the birthing hospital/maternity center to verify the telephone number or request telephone numbers of other family members to contact.
- If unable to locate and DC address is located in Ward 5, 6, 7, or 8, request DC Healthy Start to make a home visit. For other DC Wards, contact DC Medicaid to obtain additional information.
- If unable to locate and residence is in Maryland or Virginia, contact MD or VA Newborn Screening Program for assistance.
- Document each telephone contact with family, including name of contact persons, address, telephone number, date, and time. Enter information into DC Newborn Screening case management information system (in development).
 - Send Parent Letter and disorder fact sheet by mail. Document mailing date.
 - Follow-up with mother/physician to assure that doctor appointments are kept. If doctor appointments have not been kept, assist the parent in scheduling and maintaining appointments. If after counseling the parent on the impact of lack of follow-up care and the parent still fails to comply, referral to Child Protective Services should be made.
- Notify newborn's pediatric/primary care physician by telephone within 24-48 hours following receipt of abnormal screening result from the laboratory.
- Recommend immediate pediatric/primary care physician appointment
- Recommend immediate evaluation by specialty treatment center.
- Recommend family testing and counseling.
- If physician is unavailable, report all information to office/clinic nurse.
- Assist with scheduling physician appointment for infant and report back to mother by telephone.
- Obtain name of preferred Specialty Treatment Center. Fax Specialty Treatment Center Referral form to the Specialist, if necessary.

- Fax Pediatrix Screening Test Result Report, Physician Letter, Physician Alert, and List of Specialty Centers. Request that test results and supporting information are included in the infant's medical record.
- Document each telephone contact with physician/nurse, including name, address, telephone number, date and time, and Fax date. Enter information into the DC Newborn Screening case management information system.
- Contact the Specialty Treatment Center within two weeks for follow-up.
- Obtain final diagnosis, name of treatment, and treatment start date. Enter information into DC Newborn Screening case management information system.
- For non-compliant family, contact infant's parents and physician, social worker, outreach worker, or other medical, social, or financial personnel as appropriate.

For newborns screening positive for Sickle Cell Trait and G6PD, the following steps should be taken to notify parents/guardians and follow-up with confirmation of the screening result and intervention as needed:

- Refer infant for follow-up testing and counseling.
- Notify the newborn's parents by mail within 48 hours following receipt of screening result from the laboratory.
- For those with Sickle Cell Trait, mailing includes Parent Letter and Sickle Cell Trait fact sheet.
- For those with G6PD, mailing includes parent letter, parent alert, physician alert, and G6PD fact sheet.
- Recommend confirmatory testing of infant. Infants with G6PD should be retested between six and 12 months of age.
- Recommend parent testing and counseling by family physician and genetic counselor.

In the event that unacceptable results are returned, the following steps should be taken to notify the parents/guardians and re-schedule a second screening:

- The laboratory contacts the submitting hospital to request a repeat screen. The submitting hospital is responsible for repeating unacceptable samples.
- The laboratory notifies the CSHCN of the unacceptable result.
- The submitting hospital is responsible for contacting the newborn's parent(s) to arrange for a repeat/second screen.
- The submitting hospital shall submit a second screen to the laboratory before the infant is one week old.
- CSHCN will notify the newborn's parent(s) by mail within 48 hours following receipt of the unacceptable screening result from the laboratory.
- CSHCN will follow-up with the infant's parent(s), hospital and/or laboratory within one week to confirm repeat screen and obtain results.

For more information on the DC Newborn Screening Program, contact the DC Department of Health at (202) 671-5000.



4.2.1.3 UNIVERSAL NEWBORN HEARING SCREENING. All infants born in the District of Columbia are required by law to be screened at birth for hearing loss. The DC Hears program works for early detection of hearing loss and provides services for all children from birth to five years of age who have been diagnosed with hearing loss or deafness, regardless of their level of income. DC Hears provides free hearing screening and loaner amplification to all DC children in need of services. If hearing loss is not discovered early, the child could experience delays in speech, language, emotional, and educational development.

There are two tests for screening newborn hearing: OAE (otoacoustic emissions) and ABR (auditory brainstem response). A baby may be given one or both of these tests. In the OAE test, a soft rubber earpiece is placed in the baby's ear canal to deliver a soft sound. This test measures how well the baby's inner ear responds to sound. In the ABR test, earphones are placed over the baby's ear canal to deliver sound. This test measures how the brain responds to sounds. Typically, testing is done when the baby is asleep and not aware of the testing. Results are available immediately after testing.

Passing the hearing screening indicates that the baby's hearing is within the normal range at the time of the test. However, some babies with a family history of hearing loss, repeated ear infections, or serious illness may develop hearing loss later. The child's hearing and speech should be monitored as he or she grows.

Not passing the hearing screening indicates that the baby should have a second hearing test. The second screening should occur while the baby is still in the hospital or within two weeks after leaving the hospital. If the baby does not pass the initial hearing screening, it does not mean that the baby has permanent hearing loss since most babies pass the second screening. Often babies can have fluid, blockage, or debris in the ear that clears up on its own. If further testing shows that a baby has hearing loss, an audiologist along with an ear/nose/throat specialist can best determine the next steps. Treatment will depend on the type and degree of hearing loss. If hearing loss is permanent, hearing aids or special services may be recommended. Infants can be fitted with a hearing aid as young as one month of age.

4.2.2 Virginia. The Pediatric Screening and Genetics Services, a unit within the Division of Child and Adolescent Health, Virginia Department of Health administers the Virginia Genetics Program and the Virginia Early Hearing and Intervention Program. Newborn screening is offered to families with new babies as a service through the Virginia Department of Health.

4.2.2.1 DISORDERS SCREENED. All infants less than six months of age who are born in Virginia are currently screened for a number of genetic disorders. Any infant whose parent or guardian objects on the grounds that the tests conflict with his religious practices or tenets will not be required to receive screening.

Effective March 2006, the number of genetic diseases screened is 28, utilizing both traditional laboratory and tandem mass spectrometry (MS/MS) methods.

1. 3-hydroxy 3-methyl glutaric aciduria (HMG)
2. 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
3. Argininosuccinic acidemia (ASA)
4. Beta-Ketothiolase deficiency (β KT)
5. Biotinidase deficiency (BIOT)
6. Carnitine uptake defect (CUD)
7. Citrullinemia (CIT)
8. Congenital adrenal hyperplasia (CAH)
9. Congenital hypothyroidism (CH)
10. Cystic fibrosis (CF)
11. Galactosemia (GALT)
12. Glutaric acidemia type I (GA I)
13. Hemoglobin Sickle/Beta-thalassemia (Hb S/ β Th)
14. Hemoglobin Sickle/C disease (Hb S/C)
15. Homocystinuria (HCY)
16. Isovaleric acidemia (IVA)
17. Long chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
18. Maple syrup urine disease (MSUD)
19. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
20. Methylmalonic acidemia (mutase deficiency) (MUT)
21. Methylmalonic acidemia (Cbl A, B)
22. Multiple carboxylase deficiency (MCD)
23. Phenylketonuria (PKU)
24. Propionic acidemia (PROP)
25. Sickle cell anemia (Hb SS disease)
26. Trifunctional protein deficiency
27. Tyrosinemia type I (TYR I);
28. Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)

4.2.2.2 PROCEDURES AND FOLLOW-UP. The initial screening tests are performed by the Virginia Department of General Services, Division of Consolidated Laboratories Services (DCLS). Currently, it takes three days to process and complete screening on a routine sample. DCLS also performs repeat tests on infants up to six months of age. A second routine newborn screening test is not mandated in Virginia because it is costly and has not been shown to yield an increase in the number of cases. A second screen is required only when an abnormal test result occurs or when a sample has been collected when the infant is less than 24 hours of age.

Results are mailed back to the submitter (usually the hospital of birth) and the primary health care provider listed on the filter paper device for all newborn screening tests. In addition, the health care provider/physician listed on the filter paper device is also notified by telephone within 24 hours regarding all critically abnormal results.

Questions regarding the interpretation of results should be directed to the Virginia Department of General Services, DCLS, Newborn Screening Section at (804) 648-4480 ext. 170. Questions regarding procedures for follow-up should be directed to the Newborn Screening Nurse, Pediatric Screening and Genetic Services, Division of Child and Adolescent Health, Virginia Department of Health at (804) 864-7714 or (804) 864-7715.



The Virginia Department of Health has retained the services of metabolic, medical and endocrinology consultants to provide assistance with test interpretation, diagnostic testing, and treatment of affected infants. There are four Regional Genetic Centers that provide genetic testing, counseling, and education for all residents, especially those with very limited resources.

Virginia Commonwealth University Health System

Medical College of Virginia Hospitals
Genetics Program
P.O. Box 980033
Richmond, Virginia 23298

Eastern Virginia Medical School

Department of Pediatrics
Division of Medical Genetics
601 Children's Lane
Norfolk, Virginia 23507-1921

University of Virginia

Division of Medical Genetics
Department of Pediatrics
Box 386
Charlottesville, Virginia 22908

Fairfax Genetics & IVF Institute

Genetics Program
3020 Javier Road
Fairfax, Virginia 22031



In addition, two metabolic treatment programs are available for children identified through the Newborn Screening Program and provision of food products for management of PKU. Metabolic treatment procedures are recommended and such treatment is provided for infants in medically indigent families by the following health-care providers. The health-care providers offer physician and nutrition consultation.

University of Virginia

Division of Medical Genetics
Department of Pediatrics
www@virginia.edu

Virginia Commonwealth University

Medical College of Virginia Campus
School of Medicine
Department of Pediatrics
lduncan@hsc.vcu.edu

For more information on the Virginia Newborn Screening Program, see <http://www.vahealth.org/genetics/servgp.htm#newbornscreening>.

In addition, providers should consult the following web-site for answers to frequently asked questions: http://www.vahealth.org/genetics/Newborn%20Screening%20Facts_404.pdf.

4.2.2.3 UNIVERSAL NEWBORN HEARING SCREENING. The Code of Virginia requires that all hospitals with newborn nurseries and all hospitals with neonatal intensive care services will screen the hearing of all newborns prior to discharge and report to the Virginia Department of Health. Hospitals are also required to inform the parent and the child's primary health care provider about the infant's risk status and/or screening results and recommendations for follow-up. Persons who provide audiological services are required to: 1) report children who are at risk for hearing loss, children who fail to pass a hearing screening, and children identified with hearing loss to the Virginia Department of Health; and, 2) to give parents information about hearing loss, including choices about learning communication, and to refer them to local early intervention services.

For more information, see <http://www.vabealth.org/hearing/index.htm>

4.2.3 Maryland. All Maryland residents are eligible for newborn screening services. Clinical services are charged on the sliding fee scale with all types of third party payment accepted and no patient is refused service for inability to pay. The Maryland Department of Health and Mental Hygiene's laboratory charges a nominal fee to analyze newborn screening specimens. (The charge is currently \$42 per child and covers as many screening specimens as may be needed.) The Department of Health and Mental Hygiene determines whether specimens are satisfactory and which tests shall be employed.

4.2.3.1 DISORDERS SCREENED. This program identifies and follows-up on newborn babies with any one of 32 rare and serious disorders of body chemistry. Maryland implemented expanded screening using tandem mass spectrometry in November 2003. Cystic fibrosis will be added in the near future. Testing is performed at either the State Public Health Laboratory or the commercial laboratory Pediatrix.

1. 2-Methylbutyryl-CoA Dehydrogenase Deficiency
2. 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG CoA Lyase Deficiency)
3. 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC Deficiency)
4. 3-Methylglutaconyl-CoA Hydratase Deficiency
5. Argininosuccinic aciduria
6. Argininemia/Citrullinemia
7. Biotinidase deficiency
8. Carnitine/Acylcarnitine Translocase Deficiency
9. Carnitine Palmitoyl Transferase II Deficiency (CPT II Deficiency)
10. Congenital Adrenal Hyperplasia
11. Galactosemia
12. Glutaric Acidemia Type I
13. Homocystinuria
14. Hypothyroidism
15. Isobutyryl-CoA Dehydrogenase Deficiency
16. Isovaleric Acidemia
17. Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)
18. Maple Syrup Urine Disease (MSUD)
19. Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)
20. Methylmalonic Acidemia (MMA)
21. Mitochondrial Acetoacetyl-CoA Thiolase Deficiency (3-Ketothiolase Deficiency)
22. Multiple Acyl-CoA Dehydrogenase Deficiency (MADD or Glutaric Acidemia II)



23. Multiple Carboxylase Deficiency
24. Phenylketonuria (PKU)
25. Propionic Acidemia (PA or PPA)
26. Short Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)
27. Short Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (SCHAD)
28. Sickle Cell Disease
29. Trifunctional Protein Deficiency (TFP Deficiency)
30. Tyrosinemia
31. Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

4.2.3.2 PROCEDURES AND FOLLOW-UP. Newborn screening is voluntary in Maryland, in that the informed consent of the child's parent/guardian must be obtained before testing. However, the regulations place the responsibility for the implementation of newborn screening on the institution in which the child is born and require the institution to offer screening to any child born in Maryland. There are about 600 out-of-hospital births yearly and the person legally responsible for filing the birth certificate is responsible for offering testing.

Maryland offers screening for babies twice: initially, after 24 hours of milk feedings and then again at about 2 weeks of age. The initial specimen is usually collected at the hospital just before discharge. Specimens drawn before 24 hours of age are not fully satisfactory. Tests run on such specimens are less sensitive in detecting many of the metabolic disorders. Therefore, if the initial specimen is drawn before the baby is 24 hours old, a repeat specimen is requested before the child is 2 weeks old. A subsequent specimen (the third in these cases) is still recommended at the next pediatric visit. The utility of this later screen, given the earlier repeat, is being evaluated.

Normal results on initial specimens are reported by mail from the laboratory to the hospital. Subsequent specimens are usually submitted by the child's pediatrician. Normal results on subsequent specimens are reported by mail from the laboratory to the child's pediatrician. The laboratory includes a copy of the results on any previous specimens submitted on that child. The laboratory also sends a copy of the reports on all subsequent specimens back to the hospital in which the child was born.

Abnormal results are always phoned by the lab to the Office for Genetics and Children with Special Health Care Needs (OGCSHCN), the medical arm of the newborn screening program. OGCSHCN immediately notifies the baby's physician and arranges referral for definitive diagnostic work-up. A physician (board certified in pediatrics and genetics), a nurse, and a genetic counselor handle the calls. The laboratory also sends the child's physician and the hospital copies of the abnormal laboratory report by mail.

Genetic counseling and long-term case management are offered to diagnosed cases. The comprehensive care of patients with inherited metabolic disorders is coordinated with medical geneticists at the following Genetics Centers. Additional consultants/referrals services can be found at <http://www.fha.state.md.us/genetics/html/referrals.html>.

Johns Hopkins Hospital
 Center for Medical Genetics
 600 N. Wolfe St. Blalock 1008
 Baltimore, MD 21287-3914
 (410) 955-3071

Children's National Medical Center

Department of Medical Genetics
 111 Michigan Ave. N.W.
 Washington, DC 20010-2970
 (202) 884-2187

University of Maryland

Division of Human Genetics
 100 N. Greene St. Room 414
 Baltimore, MD 21201-1595
 (410) 328-3335

For more information about services available for diagnosed cases, please see <http://www.fha.state.md.us/genetics/html/newprog.html>.

For more information on the Maryland Newborn Screening Program, see http://www.fha.state.md.us/genetics/html/nbs_ndx.html.

4.2.3.3 UNIVERSAL NEWBORN HEARING SCREENING. A law was passed during the 1999 Maryland Legislative Session, mandating the establishment of the Universal Infant Hearing Screening Program within DHMH. This law requires that every baby born in a Maryland hospital must be screened for possible hearing loss effective July 1, 2000. OGCSHCN is responsible for administering this program, which identifies and follows-up on newborn babies screened for hearing impairment or at risk for developing hearing impairment.

A baby's hearing is now screened shortly after birth while still in the hospital. Risk factors that might make a baby more likely to have a hearing problem are also collected. The Maryland Infant Hearing Screening & Follow-Up Program helps to ensure that all babies who fail a screening receive follow up testing and early intervention if needed. **For more information, see** http://www.fha.state.md.us/genetics/html/inf_hrg.html

SELECTED REFERENCES

Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
<http://mchb.hrsa.gov/programs/genetics/committee/>

American Academy of Pediatrics—Metabolic/Genetic Screening
<http://www.medicalhomeinfo.org/screening/newborn.html>

March of Dimes <http://www.marchofdimes.com>

National Newborn Screening and Genetics Resource Center <http://genes-r-us.uthscsa.edu>





CHAPTER 5 : GENETIC COUNSELING

As members of a health care team, genetic counselors provide information and support to families affected by or at risk of a genetic disorder. They serve as a central resource of information about genetic disorders for other health care professionals, patients, and the general public. This chapter provides an overview of the role of genetic counselors, and their approach to educating patients and identifying individuals/families at risk of a genetic disorder. In addition, some useful resources are provided where patients may be referred to for additional information.

Genetic counselors play an important role in providing expert genetic services. They are trained to present often complex and difficult-to-comprehend information to families and patients about genetic risks, testing, and diagnosis; discuss available options; and provide counseling services and referrals to educational and support services.

5.1 ROLE OF GENETIC COUNSELING

Genetic counselors work as part of a health care team, providing information and support to families affected by or at risk of a genetic disorder. They help to identify families at possible risk of a genetic disorder, gather and analyze family history and inheritance patterns, calculate risks of recurrence, and provide information about genetic testing and related procedures. In particular, genetic counselors can help families to understand the significance of genetic disorders in the context of cultural, personal, and familial situations. Genetic counselors also provide supportive counseling services, serve as patient advocates, and refer individuals and families to other health professionals and community or state support services. They serve as a central resource of information about genetic disorders for other health care professionals, patients, and the general public.

The most common indications for genetic counseling include advanced maternal age, family history of a genetic condition, and suspected diagnosis of a genetic condition. **For more information about genetic counseling or to find a genetic counselor in your area, please see the National Society of Genetic Counselors' web-site at <http://www.nsgc.org>.**

5.2 PROCESS OF GENETIC COUNSELING

In general, a genetic counseling session aims to:

- Increase the family's understanding about a genetic disease(s), the risks and benefits of genetic testing and disease management, and available options.
- Identify with the individual and family the psychosocial tools required to adjust to potential outcomes.
- Reduce the family's anxiety.

It is not unusual for multiple genetic counseling sessions to occur and, at a minimum, include a pre-testing and post-testing session. During the initial genetic counseling visit, the genetic counselor will determine why the patient/family is seeking genetic counseling, identify what information they wish to obtain from the session, collect and record a family history, and assess and record the psychosocial history of the patient.

Among the topics discussed during a pre-test session are the clinical presentation of the condition(s) the patient may be at risk for, the pattern of genetic inheritance of the condition, risk of recurrence, available testing procedures and test limitations, reproductive options, and follow-up procedures if needed. General questions relating to suggested treatment, therapy, and the function of related proteins are also addressed. Referrals may be made to specialists regarding specific issues which fall outside the scope of genetic counseling practice.





If the patient decides to have genetic testing performed, the genetic counselor is often the point person to communicate the results to the patient/family. However, the post-test session involves more than the provision of medical information and often focuses on helping families cope with the emotional, psychological, medical, social, and economic consequences of the test results. In particular, psychological issues such as denial, anxiety, anger, grief, guilt, or blame are addressed and, when necessary, referrals for in-depth counseling are offered. Information about community resources and support groups are provided to the patient/family.

If the genetic test is positive, testing should be considered in additional relatives of this individual. Genetic counseling referrals for other family members for risk assessment are then discussed and it may be necessary to refer relatives to other genetic counselors due to geographical and other constraints.

At the conclusion of the genetic counseling sessions, the patient should be offered a written summary of the major topics discussed. The summary is often provided in the form of a letter which serves as a permanent record of the relevant information discussed, as well as relaying additional information that may have become available after the final counseling session. The patient may also choose to share the letter with other family members.

5.3 PATIENT EDUCATION

Patients rely most upon their primary health care providers for information related to their condition. In general, though, your patients will require information you may not have. Before providing patients with any educational materials, please be sure to review that the information is produced by a credible source and is current.

Books and pamphlets are most widely distributed and appreciated by patients, even by patients who are web-savvy. Patient advocacy groups generally provide the best and most up-to-date information on specific conditions. The organizations listed below are excellent sources of information about genetic diseases that can be helpful to patients:

Genetic Alliance

4301 Connecticut Ave, NW

Suite 404

Washington, DC 20008

Ph: (202) 966-5557

Fax: (202) 966-8553

URL: <http://www.geneticalliance.org>

E-Mail: info@geneticalliance.org

Genetic and Rare Diseases Information Center (GARD)

P.O. Box 8126

Gaithersburg, MD 20898-8126

Ph: (888) 205-2311

TTY: (888) 205-3223

Fax: (240) 632-9164

URL: <http://www.genome.gov/Health/GARD>

E-mail: GARDinfo@nih.gov

National Organization of Rare Diseases (NORD)

55 Kenosia Avenue

PO Box 1968

Danbury, CT 06813

Ph: (203) 744-0100

TTY: (203) 797-9590

Fax: (203) 798-2291

URL: <http://www.rarediseases.org/>

E-mail: orphan@rarediseases.org

SELECTED REFERENCES**Genetic Alliance–Disease InfoSearch** http://www.geneticalliance.org/ws_display.asp?filter=diseases

Provides accurate and reliable information developed by the advocacy organizations which form the Genetic Alliance. Users can search for information about advocacy support groups related to specific genetic conditions, the clinical features of a wide number of genetic conditions, and updates on management, treatment, and other related topics.

International Society of Nurses in Genetics <http://www.ISONG.org>**March of Dimes** www.marchofdimes.com (Spanish <http://www.nacersano.org/>)

Provides information about improving the health of babies by preventing birth defects, premature birth, and infant mortality.

MedlinePlus <http://www.nlm.nih.gov/medlineplus/>

MedlinePlus has extensive information from the National Institutes of Health and other trusted sources on over 700 diseases and conditions. There are also lists of hospitals and physicians, a medical encyclopedia and a medical dictionary, health information in Spanish, extensive information on prescription and nonprescription drugs, health information from the media, and links to ongoing clinical trials.

National Human Genome Research Institute–Health <http://genome.gov/Health/>

The site provides useful information about basic genetics concepts, genetic conditions, current research, and valuable tools to help make genetics an important tool in determining health.





CHAPTER 6 : INDICATIONS FOR A GENETIC REFERRAL

Referrals to genetic specialists should be considered if a physician suspects a patient is at risk of or is affected with a genetic disorder. Genetic specialists can help identify the appropriate tests to order (genetic or additional laboratory tests), consider the family history, and provide information about the treatment and long-term outcomes for patients diagnosed with a genetic disorder, including recommendations to other medical specialists. This chapter provides a brief overview of points to consider that may indicate when a genetics referral is appropriate.

A referral to or consultation with a genetic specialist may be indicated for several reasons. In general, a consultation with a genetic specialist should be considered if a hereditary condition is suspected. Symptoms that may suggest a genetic disorder are listed in Chapter 3 (“Red flags for genetic disease”). For conditions such as cancer and diabetes, specific clinical guidelines are available.

Patients meeting any of the following criteria should be considered for recommendation to a genetics specialist.

FAMILY HISTORY

- One or more members with mental retardation, an inherited disorder, or a birth defect
- One or more members with early deaths due to known or unknown medical conditions
- One or more members with adult onset health conditions such as cardiovascular disease, dementia and cancer, particularly if onset is early
- Couples who would like testing or more information about genetic conditions that occur frequently in their ethnic group

DEVELOPMENTAL DELAY/GROWTH

- Those who have or are concerned that their child might have an inherited disorder or birth defect due to developmental delay or failure to reach milestones
- Couples whose infant has a genetic disease diagnosed by routine newborn screening

REPRODUCTIVE ISSUES

- Women who are pregnant or planning to be after age 35
- Women who have experienced multiple pregnancy losses, including babies who died in infancy
- People concerned that their jobs, lifestyles, or medical history may pose a risk to the outcome of pregnancy. Common causes of concern include exposure to radiation, medications, illegal drugs, chemicals, or infections
- Couples who are first cousins or other close blood relatives
- Pregnant women whose ultrasound examinations or blood testing indicate that their pregnancy may be at increased risk for certain complications or birth defects





A genetics specialist can provide assistance through a variety of ways—a formal or informal consultation, a genetic counseling session, or a genetic evaluation. A genetics specialist can provide a more accurate assessment of the risk or confirm the diagnosis of a genetic disease. A diagnosis may be made primarily through genetic testing, or a combination of testing, clinical examination, and family history. They are able to provide management options or referrals to specialists as needed depending on the disease, advice to primary care practitioners about a genetic condition, prognoses, treatment and long-term outcome, and recommend educational materials to patients and families.

The primary genetics specialists to be considered for referral are clinical geneticists and genetic counselors. While these specialists can play a major role in the diagnosis and education of family members of a genetic disorder, other medical specialists may be required for

appropriate treatment or intervention such as surgeons, nutritionists, social workers, psychologists, and occupational therapists. The requirements for a referral will vary from system to system. In general, though, a genetics referrals require the following information:

- Patient information
- Name and address of the referrer
- Reason for the referral
- Information about the suspected diagnosis, if known
- Family history

SELECTED REFERENCES

Cancer Genetics Service Directory http://www.cancer.gov/search/genetics_services/

March of Dimes—Genetics and Your Practice <http://www.marchofdimes.com/gyponline/index.bm2>

National Society of Genetic Counselors <http://www.nsgc.org/resourcelink.cfm>



CHAPTER 7 : PSYCHOLOGICAL & SOCIAL IMPLICATIONS

Genetic disorders impact not only the physical health, but also the psychological and social well-being of patients and their families. Understanding the unique aspects of genetic information and anticipating reactions to genetic tests and diagnoses can help guide a course of action to minimize distress and maximize benefit for both the patient and family. Referrals to specialists or support groups can also help address the psychological well-being of the patient and family.

An increased genetic risk or diagnosis can substantially impact medical management as well as the psychological and social well-being of the patient and family. The personal and permanent nature of genetic information raises a range of issues and emotions including guilt, fear, and helplessness. Specialists such as genetic counselors, social workers, psychologists, or support groups can be extremely helpful to patients and families as they deal with these difficult issues.

7.1 GENETIC INFORMATION VS. OTHER MEDICAL INFORMATION

Genetic information, like other medical information:

- Has the potential to help or harm patients and must be considered in making patient care decisions.
- Is complex, demanding thoughtful, critical communication of risks and uncertainties.
- Will arise in your practice. It is helpful to think through how you will respond in the face of inevitable questions, some of them involving difficult judgments.

In addition, genetic information, unlike much of medicine:

- Provides information about family members and relatives. Disclosure of family information can often be helpful to family members, but also can lead to breaches of confidentiality that must be considered and addressed proactively.

7.2 A LIFETIME OF AFFECTED RELATIONSHIPS

Genetic disorders have powerful effects on families. Like many chronic conditions, they may require continual attention and lack cures or treatments. They have implications on the health of relatives, too—a genetic diagnosis for one family member may mean other blood relatives are also at risk, even if they currently show no symptoms. In addition to the long-term medical implications of a disorder, genetic disorders present emotional challenges and special reproductive implications including the risk that additional offspring will inherit the condition, screening choices such as prenatal and newborn testing, and difficult treatment options.



7.3 IMPACT LEVELS

The psychosocial effect of a genetic disorder varies by the nature of the condition and the relationship of a person to the affected individual. Every family is different and it is difficult to predict how people will react to a genetic diagnosis. It's helpful to think in advance about some of the possible reactions, though, so you can react quickly and minimize distress.

7.3.1 Patients. A genetic diagnosis generally provides great benefit to patients. It helps patients understand their disorders, especially when the conditions are rare and the patients have struggled for a diagnosis. Oftentimes, patients spend years living with conditions without knowing their names or causes. Diagnoses usually lead to improved treatment options and access to support services. They can also help other family members make decisions about their own lives.

A genetic diagnosis may lead to negative reactions, too. The science of genetics can be confusing, and patients are often frustrated until they understand the nature of their condition. Patients identified with a mutation may consider themselves at fault or “broken” or interpret their diagnoses as leading to something they cannot fight. A genetic diagnosis can lead to fears about insurance and employment discrimination.

How a patient reacts to a diagnosis varies from individual to individual and is affected by many factors including gender, education, and religious and cultural beliefs. By being aware of these differences and understanding your patients' backgrounds, you will be able to communicate with your patients better and be more effective.

7.3.2 Parents. The diagnosis of a genetic condition can have stressful effects on a relationship. For adult-onset diseases, unaffected spouses may view their partners differently and the diagnosis can lead to a breakdown in communication. Couples with an affected child often face difficult decisions related to family planning since future offspring may be at higher risk. Depending on the condition, parents may be faced with hard choices regarding prenatal testing and termination of pregnancy. The magnitude of these decisions and sense of loss has an impact on the individuals involved and on their interpersonal relationship. Also, a genetic disorder may create a situation where long-term caregiving is necessary. Those couples who are able to communicate their experience with others are most likely to move forward.

7.3.3 Family. Given the shared nature of genetic information, it is important to consider the family unit. Unaffected family members should not be forgotten in the case of a genetic disorder. When one family member is diagnosed for a mutation, spouses, siblings, and parents who do not have the mutation often feel guilt that loved ones are affected when they are not. Siblings of children with special needs sometimes feel neglected because parents need to focus more time and effort on their siblings. Including unaffected family members in the planning of care for individuals with special needs can help them come to grips with their own emotional issues. Adults diagnosed with a genetic condition considering beginning or expanding their family will need to consider the risk of a having an affected child and/or their ability to care for the child.

In cases where a test is predictive, other family members may misinterpret the results of a genetic test as a diagnosis rather than an indicator of risk for a condition. It is important to keep in mind that results of a genetic test may be difficult to understand, not only for patients, but for their families too. In some cases, a genetic test may reveal the risk status of other family members who may not wish to know of this information, thereby encroaching upon others' autonomy or privacy.

The financial burden of a chronic genetic condition, too, can lead to stress among family members. If the family is already struggling financially, it may be intimidated by the costs associated with caring for a child with special needs. You can help your patients by referring them to such as the DC Health Families which ensures affordable health care for children, including doctor visits, prescription medicines, and transportation to appointments. Knowing that resources exist can help ease the stress caused by a genetic diagnosis.

In general, support or advocacy groups and community resources can provide ongoing support to patients and their families with genetic conditions. Support groups can help share experiences about caring for a family member affected with a genetic condition, how to cope with a new diagnoses, obtain healthcare or other services, and heal. Members of support groups know first-hand what it means to be faced with a diagnoses and to need accurate, up-to-date information, and helping individuals stay connected with their community helps fight the feelings of isolation that often surround families who may be living with a genetic condition.

7.3.4 Communities. Genetic testing can lead to issues for communities, not just individuals. Genetics has been used in the past to stigmatize and discriminate along ethnic or racial lines, and underserved or underrepresented communities often view genetic research and/or services with distrust. They may feel that the results of a genetic test or newborn screening will be used segregate their communities. These fears are often in addition to more general issues with the medical establishment, including differences in communication styles and language and diverse cultural beliefs.

Members of the deaf community, for example, may oppose hearing tests for fear that deafness will be considered a disability rather than a lifestyle. In general, it is a good idea to understand the communities where your patients are from so you can present information and options in ways to promote trust and understanding.

7.4 COPING MECHANISMS

When a newborn is first diagnosed with a congenital abnormality, parents are often overcome with concern for their child. Some common reactions include fear, confusion, and grief that their



child is not “normal,” guilt that they did something to cause the condition, and anger that there does not seem to be a solution, that God caused this, or that the other parent is to blame. The fact that a medical cure or treatment does not exist often comes as a great surprise to parents. This further adds to parents concern about their ability to care for the child in the future, too. How care providers react makes a big impact on how parents cope with negative feelings and can help them focus on the challenges and blessings of the newborn child.



Suggestions that can help parents cope with the birth of a child with an inherited condition include:

- For regular routine visits, focus on the child's well-being and not solely on the child's genetic condition. Talk about the newborn's personality, feeding patterns, and other personal traits and always remember that the newborn is an infant first and an infant with special needs second.
- Provide realistic expectations for the future and models for coping. The parents are likely to be asked many well-intentioned questions by relatives and friends, and parents will be better able to respond if they've asked the questions themselves already.
- Explain the genetics of a condition in an understandable manner and consider referring the parents to a genetics specialist—either a clinical geneticist, genetic counselor, or genetics nurse.
- Emphasize that you are aware of the difficulty of the situation and each parent has his or her own way of coping with the stress and caring for an infant with medical needs. It may be helpful for families to share their feelings with others and referrals to social workers, psychologists, or support groups may facilitate these discussions.
- Identify resources such as support groups which focus on the condition in question. Support groups can help families overcome feelings of isolation often associated with a rare congenital condition, provide first-hand experience about caring for an infant with that particular condition, provide information about expectations for the affected infant, and suggest coping mechanism for both parents and siblings to adjust to new challenges.

SELECTED REFERENCES

Genetic Alliance <http://www.geneticalliance.org>

National Organization for Rare Diseases <http://www.nord.org>

Organizations for Support Groups & Information (Genetic/Rare Conditions)
<http://www.kumc.edu/gec/support/grouporg.html#specific>

Burke W, Fryer-Edwards K, and Pinsky L E (eds). *Genetics in Primary Care (GPC): A Faculty Development Initiative*. 2001. <http://genes-r-us.uthscsa.edu/resources/genetics/pdfs/gpc-completedoc.pdf>



CHAPTER 8 : ETHICAL, LEGAL, AND SOCIAL ISSUES

Over the past decade, many ethical, legal, and social implications (ELSI) associated with genetic testing and research have been raised. In order for genetic testing to be used safely and appropriately, these issues should be discussed with patients so that they are aware of the risks and benefits associated with testing. This chapter provides a brief overview of these issues with descriptions of some of the major ELSI concerns related to genetic testing.

Several major concerns have arisen regarding the use and potential misuse of genetic information. Genetic information may differ from other health information because of its long-term implications for an individual and his or her family. Issues span from analytical and clinical validity of a genetic test to potential discrimination by health insurers or employers to the duty to disclose genetic information to potentially affected family members.

To protect patients from additional distress related to genetic conditions, care providers should be aware of the relevant ethical, legal, and social issues related to genetics in health care. Genetic specialists may be able to address patient concerns and questions regarding these issues. A brief discrimination of the major ELSI issues related to genetic testing is provided below:

Communicating test results. It is critical that genetic test results are discussed with patients in an understandable manner. As many genetic tests will not provide simple positive/negative results, but potentially inconclusive tests or risk estimates/probabilities, it is important that patients understand the extent of the information actually provided from a genetic test. Results should be released only to those individuals for whom the test recipient has given consent for information release. Means of transmitting information should be chosen in advance (e.g., by phone, in person) to minimize the likelihood that results will become available to unauthorized persons or organizations. Under no circumstances should results with identifiers be provided to any outside parties, including employers, insurers, or government agencies, without the test recipient's written consent.

Direct-to-consumer tests. A number of companies market genetic tests directly to consumers without requiring permission from a physician. Patients should be cautious when considering direct-to-consumer genetic testing and encouraged to discuss these options with their healthcare professional. Some of these companies may play off consumer fears and offer unvalidated or bogus tests or their laboratories may not be properly certified.

Duty to disclose. The results of a genetic test may have implications for a patient's family members. However, health care providers have an obligation to the person being tested not to inform other family members without the permission of the person tested, except in extreme circumstances. If a health professional believes family members may be at risk, the patient may be encouraged to discuss test results with other family members. In general, families are opposed to doctors informing at-risk members without their consent, even in cases where the disease is easily preventable. The duty to inform varies by state, and courts have ruled on differing sides in different cases.



The American Society of Human Genetics suggests that disclosure to at-risk individuals is permissible when the following criteria are met:

- Attempts to encourage disclosure on the part of the patient have failed
- Harm is highly likely, serious, imminent and foreseeable
- At-risk relatives are identifiable
- Disease is preventable, or medically accepted standards for treatment or screening are available
- The harm from failing to disclose outweighs the harm from disclosure

Genetic discrimination. When considering genetic testing, a major concern often raised is the potential of discrimination based on genetic information. Since genetic test results are typically included in a patient's medical record, patients should be aware that the results may be accessible to others. As a result, genetic test results could affect a person's insurance coverage or employment. More than 30 states have legislation prohibiting genetic discrimination. However, the scope of these protections differ slightly from state to state. No federal legislation has been passed despite several attempts over the last decade.

In addition, members of minority communities often fear that genetic information will be used to stigmatize them. Health providers should be sensitive to the fact that some groups may mistrust the use of genetics as a health tool.

Informed consent. To help ensure that patients understand the risks and benefits of health care choices, informed consent is an important part of the medical-decision making process. For patients considering genetic testing, the following items should be carefully discussed and understood before consent is obtained:

- Testing is voluntary
- Risks, limitations and benefits of testing or not testing
- Alternatives to genetic testing
- Details of the way in which the test is performed (e.g., what type of sample is required, accuracy of test, turn-around-time, etc.)
- Privacy/confidentiality of test results
- Potential consequences related to results including
 - Impact on health
 - Possible emotional and psychological reactions
 - Treatment/prevention options
 - Ramifications for family

Privacy. Genetic information has enormous implications to an individual and his or her family. The privacy of that information is a major concern to patients. In particular, who should have or needs access to that information is a major issue. In order to protect personal genetic information and to avoid inclusion in a patient's medical record, some patients may wish to pay for genetic testing out-of-pocket if possible.

Psychosocial impact. Every individual will respond differently to news of their genetic tests results—whether negative or positive. As there is no right or wrong response, health professionals should refrain from judgment and help the patient understand what the test results mean with respect to their own health, available interventions or follow-up, and risks to their family. An individual may respond to genetic information on several levels—the individual level, family level, or on a community and society level. Referrals to genetic counselors, psychologists, or social workers should be made as needed.

Reproductive issues. Genetic information is routinely used to inform reproductive decisions and medical care. Advanced maternal age, family history, multiple miscarriages, or drug and alcohol exposure are risk factors for genetic conditions for which preconception or prenatal genetic testing may be considered. As these procedures carry several risks and benefits, parents should carefully consider and discuss these options with a physician or genetic counselor. Providers should take a non-directive stance, especially when the only options for treatment and management are termination of pregnancy.

Societal values. Genetic information can raise several questions of personal responsibility, personal choice versus genetic determinism/fate, and concepts of health and disease. Responses to these issues will be influenced by personal factors, family values, and community and cultural beliefs. While genetic information may influence one individual to change their lifestyle or behavior in order to reduce risk or disease severity, others may choose to respond differently. Health professionals should be respectful and sensitive to cultural and societal values and work with the patient to define the appropriate course of action for them with respect to genetic testing and follow-up care.

Test utility. The useful application of genetic tests will depend on the correct interpretation of test results and if the information provided is helpful in guiding medical care and treatment. However, for some genetic conditions, the utility of genetic test results may be limited if no treatment is available or if the results are inconclusive. These issues should be discussed with patients or parents of patients when a genetic test is being considered. Even if a test is not considered to be medically useful, a patient or the family may still gain benefit from testing. Clinical guidelines should be consulted for recommended follow-up care and treatment.

Test validity. Several issues regarding test validity should be considered prior to ordering a genetic test. The analytical and clinical validity of a test are generally measured as test specificity, sensitivity, and predictive value. This information should be shared with the patient as they consider whether or not testing is appropriate for them. Since most genetic tests are offered as services, they are not approved by the Food and Drug Administration. However, genetic tests (or any other clinical laboratory test) should be ordered from CLIA-certified laboratories only.

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American Medical Association. Why Physicians should Know the Legal and Ethical Issues Raised by Genetic Information and Technology. *Genethics* 2000

<http://www.ama-assn.org/ama/pub/category/3719.html>

American Society of Human Genetics—Professional Disclosure of Familial Genetic Information (*Am J Hum Genet*, 62:474-483, 1998)

<http://www.ashg.org/genetics/ashg/pubs/policy/pol-29.htm>

Lehmann LS, Weeks JC, Klar N, et al. Disclosure of familial genetic information: perceptions of the duty to inform. *Am J Med Genet* 2000; 109(9): 705-11.

March of Dimes—Genetics and Your Practice (Financial, Ethical, Legal and Social Issues (*FELSI*))

<http://www.marchofdimes.com/gyponline/index.bm2>

U.S. Department of Energy—Ethical, Legal, and Social Issues

http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml





CHAPTER 9 : PATIENT STORIES & CONSUMER PROFILES

This chapter contains four stories about inherited cancer, newborn screening, late-onset disease, and family history told from the perspective of a patient or consumer. For some patients, diagnosing a genetic condition can be a challenging and lengthy process involving many doctors and office visits, examinations, testing, and months or years of stress and uncertainty. For other patients, the lack of treatment or effective interventions can prove to be extremely frustrating and difficult to comprehend. These stories can help both health professionals and patients understand the issues faced by patients and families affected with a genetic condition and how they overcame and dealt with these issues.

I. INHERITED BREAST AND OVARIAN CANCER

At a family dinner, Samantha and her family were talking about the recent diagnosis of Samantha's sister, Louise. Just 38 years old, Louise had detected a lump in her left breast and was diagnosed with breast cancer. She was recovering from the mastectomy she had chosen to have in order to increase her chances of survival. It was still too painful to talk about their mother's death, years ago, of breast cancer at the age of 48, but from the silence in the room, it was obvious that it was on everyone's mind. It was also believed that a great-aunt had died of some form of cancer although no one was really certain.

The high incidence of cancer deaths in Samantha's family was cause for concern. Samantha and her husband were considering having another child. They had two healthy sons but wished for a little girl. She was only 34 years old, but what if Samantha developed breast cancer in 10 years? Would she be able to care for her children? Could she pass on the risk of breast cancer to her daughter?

Samantha met with her family doctor to discuss her family history of breast cancer. She asked if there was any way she could find out if she was at risk for the disease and if there was anything that could be done to prevent the disease from occurring. Her doctor referred her to a genetic counselor who specialized in inherited cancer to discuss what Samantha's risk was given her family history and the types of genetic testing available. The genetic counselor told her that a small percentage of all breast cancers were inherited. Two genes had been discovered that caused a proportion of inherited breast cancer called BRCA1 and BRCA2. Genetic testing was available to women who had a family history of breast and/or ovarian cancer. A positive result would indicate that Samantha had a much higher risk of cancer, but it was not a 100 percent certainty that Samantha would develop breast cancer.

Samantha and her husband were overwhelmed by the information provided by the genetic counselor and felt that they needed to talk to someone who had experienced this situation. They found a support group in their community and spoke with the director who also had a family history of early-onset breast cancer and had decided to undergo genetic testing herself. After several weeks, they decided to undergo genetic testing. Her sister Louise was tested first to identify the specific mutations in BRCA1 or BRCA2, and once they knew that she had a particular mutation in BRCA1, they tested Samantha's blood. Samantha found out that she was a carrier of a mutation in the BRCA1 gene.

II. THE VALUE OF NEWBORN SCREENING

We brought our 7lb 5oz baby boy home on April 14th. After a tiring but blissfully happy first week of 4 am feedings and little sleep, our pediatrician called to say that one of the tests done with the blood spot collected from our son at birth for newborn screening came back positive. My husband and I both thought it had to be a mistake and that the samples must have been mixed up. Our son Zachary was a completely health and happy baby boy.



The positive result was for a disease called homocystinuria. The following week, we took Zachary back to the hospital to have him re-tested. The second test also came back positive. There was no doubt that Zachary had this disorder although he seemed completely healthy. The doctor told us that children with this rare genetic disorder were unable to break down excessive protein into other amino acids and that in order for him to have a normal life, he would have to be put on a special low protein diet. I had so many questions about would happen to Zach—how different would he be from other children; would his development be delayed; would he be able to walk and talk and go to school with other kids?

After talking with other parents of children affected with homocystinuria, several pediatricians, a geneticist at an academic medical center located two hours away, and nutritionists, we gained some confidence that we could take care of Zachary and provide him with a normal childhood. Zachary has been on a low protein diet for almost 10 years now and his disease is under control. He is in the 5th grade and a very active and bright child. He is doing well in school, plays soccer and baseball, and does all the things any other 10-year would do—birthday parties, Little League, Boy Scouts, etc. By detecting Zachary's condition at a very early age before any symptoms developed and adjusting his diet, Zachary is a bright and healthy boy.

III. ALPHA-1 ANTITRYPSIN DEFICIENCY

Growing up, I was busy and energetic like everyone else. Rarely did I have to go to the doctor. The only real problems I remember were the coughing spells I would occasionally suffer, but I blamed them on my father's smoking habit.

During a routine physical, my doctor noticed high levels of alanine aminotransferase (ALT) on my liver function tests and referred me to a liver specialist. He diagnosed me with alpha-1 antitrypsin deficiency. Though I felt fine, the specialist ordered a liver biopsy and referred me to another specialist, a lung doctor. Everything moved very fast and I didn't understand half of the information I was told and I had no idea what to expect. After a second liver biopsy and a session with a genetic counselor, hours educating myself and my family, I am beginning to understand what it means to be diagnosed with alpha-1 antitrypsin deficiency.

To understand my own health risks and to understand my children's risks of developing alpha-1 antitrypsin, I had a genetic test performed. However, to avoid the risk of genetic discrimination, I have kept the initial genetic testing results out of my medical record.

While it was scary to find out about the disease initially, it has enabled me to possibly change the course of the disease process. For example, I have become a sort of health nut as a result of all of this. I exercise daily, watch my diet, avoid smoky environments and pollutants, and watch my alcohol intake. While everyone should do these things, it is imperative that I do them to help prevent the early onset of disease symptoms. Early diagnosis may have saved me from living a more dangerous lifestyle and damaging either my lungs or my liver. This is one disease where lifestyle changes can result in a longer life when diagnosed early.

IV. TYPE II DIABETES

Sarah was 26 years old when she was diagnosed with Type II diabetes. She had had a recurrent skin infection for almost a year. At first it was a nuisance and since she had no health insurance, it was just something she had to put up with. Then, she seemed to develop an unquenchable thirst and was always drinking water. Despite her increased drinking habits, she managed to lose almost 40 pounds. Finally, the pain from the skin infection became so excruciating that she had no choice but to go to the emergency room. There, they officially diagnosed her with Type II diabetes although she had likely been affected with the disease for some time.

Even without the diagnostic blood tests and a clinical examination, Sarah's high risk of diabetes should have been noted many years ago. Of notable significance, her grandfather, mother, and two cousins have diabetes. Although Type II diabetes is likely caused by a combination of genetic and environmental factors, the high prevalence of diabetes in her family strongly suggested that Sarah was at high risk and a healthy diet and regular exercise could have helped prevent the early onset and severe symptoms she now experiences. Second, Sarah was always a large child and constantly ate foods high in fat and sugar.

Now, at the age of 41, the damage from the disease has devastated the life she was trying to make for herself. Over the past 5 years, she had had two toes on her left foot amputated, her eyesight was rapidly deteriorating, at least four teeth had to be pulled, and she was admitted twice with life-threatening flu infections. Although she refuses to believe it, her doctors have repeatedly told her that just by knowing her family history and a commitment to a healthier lifestyle, much of this could have been prevented.





CHAPTER 10 : D.C. COMMUNITY HEALTH PROGRAMS & CENTERS

This chapter contains contact information about D.C. Community Health Programs and Centers that provide healthcare services, consultation, and testing to patients in need. The Genetics Services Program provides clinical genetic services to pediatric and prenatal clients of the community health centers of the PBC and at DC General Hospital. Services provided include genetic counseling and education; family history taking; physical examinations; diagnostic procedures; laboratory screening and testing; evaluation and diagnosis; treatment and management; referrals; and follow-up services. In addition, information about transportation services, interpreters, governmental agencies, and other health services are provided.

ADVISORY COMMITTEES

Children with Special Health Care Needs Advisory Board

Jacqueline McMorris, MD, Chair
(202) 727-7449

Lead Screening Advisory Committee

Muriel Wolf, MD
(202) 535-2626

Mayor's Advisory Committee on Metabolic Disorders

Mary Tierney, MD, Chair
(202) 727-7449

COMMUNITY SERVICES AND HEALTH CLINICS

Assessment Center for Hearing Impaired Children and Youth

Kendall School, Gallaudet University
800 Florida Ave, NE
(202) 651-5340 (TTY/V)
(202) 651-5000

Center for Child Development/CNMC

111 Michigan Ave, NW Room 3800
(202) 884-5467

Clearinghouse on Disability Information Office of Special Education and Rehabilitative Services

330 C Street, SW, Room 3132
Switzer Building
(202) 205-8241

Clinica Del Pueblo

2831 15th Street, NW
(202) 462-4788

Community Health Care, Inc./ Upper Cardozo Health Center

3020 14th Street, NW
(202) 745-4313
(202) 745-4300

DC Family Voices

(800) 394-5694
www.familyvoices.org

Easter Seal Society

2800 13th Street, NW
(202) 232-2342
(202) 387-4434
www.eseals.org

Faces of Our Children

(866) FACES 11
www.facesofourchildren.org

Healthy Babies Project (Wards 5 & 6)

801 17th Street, NE
(202) 396-2809

Howard University Hospital Family Health Center

2339 Georgia Ave, NW
4th Floor
(202) 865-3250

Howard University Speech and Hearing Clinic

The John H. Johnson School of Communications
525 Bryant Street, NW
(202) 806-7690

HSC Pediatric Center

1731 Bunker Hill Road, NE
Pediatric Audiology and Hearing Clinic
(202) 832-4400
(800) 226-4444

Kiwanis Orthopedic Clinic

5255 Loughboro Road, NW
(202) 363-1148

Lions Club

Vision Screenings
(301) 577-7800



Mary's Center for Maternal and Child Care, Inc.

2333 Ontario Road, NW
 Washington, D.C. 20009
 Main Phone: (202) 483-8196
 Direct Phone: (202) 483-8319
 Fax: (202) 797-2628
info@maryscenter.org

National Dissemination Center for Children and Youth with Disabilities (NICHCY)

(800) 695-0285
 (202) 884-8200
www.nichcy.org

National Heart, Lung, and Blood Institute (NHLBI) (NIH)

Collection and Storage of Umbilical Cord
 Blood for Sickle Cell Disease
 (301) 594-8381
patientrecruitment.nhlbi.nih.gov/sicklecell.aspx

National Rehabilitation Information Center (NARIC)

(800) 346-2742
www.naric.com

Parent and Child Center

1719 13th Street, NW
 (202) 462-3375

Pediatric AIDS/HIV Care

450 M Street, NW
 (202) 347-5366

PSI Services, Inc. Early Developmental Intervention Program

770 M Street, SE
 (202) 547-3870

Scottish Rite Center for Childhood Language Disorders (CNMC Affiliate)

1630 Columbia Road, NW
 (202) 939-4703

Sibley Hospital Washington Speech and Hearing

5255 Loughboro Road, NW
 (202) 537-4010

Sickle Cell Association of the National Capital Area, Inc. (SCANCA, Inc.)

(202) 635-0240
www.scanca.org/index.html
scanca@scanca.org

Washington Free Clinic

1525 Newton Street NW
 Washington, DC 20010
 Phone: (202) 667-1106
 (Provides primary care and prenatal and pediatric care. Services are offered in both Spanish & English and translators are available for other languages as needed)

CONFIRMING LABORATORIES**Children's National Medical Center**

Clinical Metabolic Laboratory
 111 Michigan Avenue
 Washington, DC 20010
 (202) 884-3996
 Dr. Steven Kahler

Pediatric Screening

110 Roessler Road
 Pittsburgh, PA 15220
 (866) 463-6436

ENDOCRINOLOGY**Children's National Medical Center**

Department of Endocrinology
 111 Michigan Avenue
 Washington, DC 20010
 (202) 884-2121

GENETIC CONSULTS/METABOLIC AND GENERAL GENETICS/PRENATAL GENETICS

Children's National Medical Center

Genetics, Metabolism and the Center for Prenatal Evaluation
111 Michigan Avenue
Washington, DC 20010
(202) 884-2817

George Washington University Medical Center—The Wilson Genetics Center

2025 Eye Street, NW
Washington, DC 20052
(202) 741-3096

Howard University Hospital

Department of Pediatrics and Child Health
Howard University Hospital
2041 Georgia Ave, NW, Room 6B02
Washington, DC 20060
(202) 865-1592
(202) 865-1920

GOVERNMENT AGENCIES

DC Commission on Mental Health Services

Parent and Infant Development Program
51 N Street, NE
Suite 700C
(202) 724-5383

DC Department of Human Services

Income Maintenance Administration
(202) 724-5506

Medical Assistance Programs/Public Assistance Service Centers

- Anacostia Services Center, 2100 MLK, Jr. Ave, SE, (202) 645-4614
- Congress Heights Services Center, 4001 South Capital Street, SE, (202) 645-4525
- Eckington Services Center, 51 N Street, NE, (202) 724-5555
- Fort Davis Services Center, 3851 Alabama Ave, SE, (202) 645-4500
- Kennedy Services Center, 508 Kennedy Street, NW, (202) 576-7268
- Northwest Services Center, 1207 Taylor Street, NW, (202) 724-7900

DC Department of Parks and Recreation

Therapeutic Recreation Services Branch
3030 G Street, SE
(202) 645-3995

DC Office of Early Childhood Development

1717 14th Street, NW, Suite 700
(202) 727-1839

Maternal and Family Health Administration

825 North Capitol Street, NE, 3rd Floor
(202) 671-5000

• *Children with Special Health Care Needs Bureau*

The purpose of the Children with Special Health Care Needs Bureau is to improve the health outcomes for this population group by facilitating access to coordinated primary and specialty health care and other services in partnership with their families and community organizations. (Newborn Metabolic Screening Program, Newborn Hearing Screening Program, Genetic Services Program, Sickle Cell Disease Program, Medical Home for CSHCN, Transitional Services for CSHCN, Epilepsy Program, Vision Screening Program, Childhood Lead Poisonings Prevention Program)

• *Perinatal and Infant Care Bureau*

The purpose of the Perinatal and Infant Health Bureau is to improve perinatal outcomes for high-risk pregnant and parenting women, and improve the health and development of their infants into early childhood. The current overarching goal is to reduce infant mortality and perinatal health disparities in the District of Columbia. (Healthy Start Program)



- *Nutrition and Physical Fitness Bureau*

The purpose of the Nutrition and Physical Fitness Bureau is to provide food, health and nutrition assessments and interventions, education and referral services to District families, infants, children, and seniors to affect dietary habits, foster physical activity, decrease overweight and obesity rates and thus improve health outcomes among the population.

- *Child, Adolescent and School Health Bureau*

The purpose of the Child, Adolescent and School Health Bureau is to improve the health and well-being of all District school-age children and adolescents. Primarily the group will seek to enhance access to preventive, dental, primary, and specialty care services for all school-age children, and contribute to the development of a coordinated, culturally competent, family-centered health care delivery system for this population.

- The **Healthline** provides District of Columbia residents with information, outreach, counseling, referrals, and transportation to prenatal and well-baby appointments. The toll-free number is (800) MOM-BABY.

- The **(800) MOM-BABY** hot line is physically located at 33 N Street, NE, Second Floor, Washington, DC 20002. This location also houses the **Parent Resource Center**, with free pregnancy testing, food, clothing, literature, videotapes, and referrals for other public health services.

Medical Assistance Administration (MAA)

(DC Medicaid) (202) 442-5988

General Information: (202) 698-2043,
(202) 724-7316

DC Medicaid Eligibility: (202) 724-5506

DC Medicaid (for recipients): (202) 724-5506

Mental Retardation & Developmental Disabilities Administration (MRDDA)

429 O Street, NW
(202) 673-7657

Women, Infants and Children Supplemental Food Program (WIC) Headquarters

2100 MLK, Jr. Ave, SE, Suite 409
(202) 645-5662
(800) 345-1942

HOSPITALS

Children's National Medical Center

111 Michigan Ave, NW
(202) 884-5000
www.cnmc.org

George Washington University Hospital

901 23rd Street, NW
(202) 715-4000
www.gwhospital.com

Georgetown University Hospital

3800 Reservoir Road, NW
(202) 687-2000
www.georgetownuniversityhospital.edu

Greater Southeast Community Hospital

1310 Southern Avenue, SE
(202) 574-6000
www.greatersoutheast.org

Hadley Memorial Hospital

4601 MLK, Jr. Ave, SW
(202) 574-5700
www.doctorscommunity.com/welcome.htm

HSC Pediatric Center

1731 Bunker Hill Road, NE
(202) 832-4400
www.hfscsite.org

Howard University Hospital

2041 Georgia Ave, NW
(202) 865-6100
www.hu Hosp.org

National Rehabilitation Hospital

102 Irving Street, NW
(202) 877-1000
www.nrhrehab.org

Providence Hospital

1150 Varnum Street, NE
 (202) 269-7000
www.provhosp.org

Sibley Memorial Hospital

5255 Loughboro Road, NW
 (202) 537-4000
www.sibley.org

Washington Hospital Center

110 Irving Street, NW
 (202) 877-7000
www.whcenter.org

HOTLINES**DC Government Citywide Call Center**

(202) 727-100

HSC Health Care System

(800) DCYOUTH

IMMUNIZATION WALK-IN CLINICS

(For Uninsured and Underinsured District of Columbia Residents You Must Bring Proof of Residency; Driver's License, Non-Driver ID, Current Utility Bill, Lease; No appointment necessary—please Bring Immunization Records)

Congress Heights Community Health Center

3720 Martin Luther King Jr. Avenue, SE
 3rd Floor
 (Near Martin Luther King Jr Ave. & S. Capitol St.)
 Wednesdays 5pm
 (Limited Numbers Seen)

District of Columbia Developing Families Center

801 17th Street, NE, Washington, DC
 (Between Benning Rd and Maryland Ave. on 17th Street near Hechinger Mall)
 2nd & 4th Tuesday of each month, 4:30 pm
 (Limited Numbers Seen)

DOH/Immunization Program

1131 Spring Road, NW,
 Washington, DC
 (Corner of 13th & Spring Road)
 Monday & Tuesday 10 am
 (Limited Numbers Seen)

Israel Baptist Church

1251 Saratoga Avenue, NE, Washington, DC
 (off 12th Street and Rhode Island Ave., near Brentwood Road)
 1st Wednesday of each month 4:30 pm
 3rd Saturday of each month 12 pm
 (Limited Numbers Seen)

Reeves Municipal Center

2000 14th Street, NW, Washington, DC
 (Corner of 14th & U Streets)
 Thursdays 4:30 pm
 (Limited Numbers Seen)

INTERPRETERS**Chinatown Service Center**

900 Mass Ave, NW
 (202) 898-0061

Clinica Del Pueblo

2831 15th Street, NW
 (202) 462-4788

Indochinese Community Center (ICC)

1628 16th Street, NW
 (202) 462-4330

Korean Community Service Center of Greater Washington (KCSC)

7720 Alaska Ave, NW
 (202) 882-8270

Translators and Interpreters Guild

2007 North 15th Street, Suite 4
 (703) 522-0881
www.ttig.org



LATINO CLINIC

La Clínica del Pueblo

2831 15th Street, NW
 Washington, DC 20009-4607
 Phone: (202) 462-4788
 (half block from Columbia Heights Metro
 Station)

PEDIATRIC HEMATOLOGY

Children's National Medical Center

Hematology Department
 111 Michigan Avenue
 Washington, DC 20010
 (202) 884-2140

Georgetown University Hospital

Pediatric Hematology/Oncology
 3800 Reservoir Road, NW
 Washington, DC 20007

Howard University Hospital (DC GAPS)

(Dr. Sohail Rana)
 Department of Pediatrics and Child Health
 2041 Georgia Ave, NW, Room 6B02
 Washington, DC 20060
 (202) 865-4583
 (202) 865-4346 (fax)

TRANSPORTATION

Metro/Washington Metropolitan Area Transit Authority

Reduced Fares Disability ID Card
 600 5th Street, NW
 (202) 962-1245
 (202) 962-2568

MetroAccess

(301) 562-5361
 (301) 588-7535



CHAPTER 11 : CONSUMER FACT SHEETS

Family History (Fact Sheet from CDC) * Basic Genetic Information * Dominant and Recessive Genetic Diseases * X-linked Genetic Diseases * What is a Chromosome Abnormality? * Understanding Genetic Testing * Deciding Whether to Have a Genetic Test * Prenatal Diagnosis * Birth Defects & Congenital Disorders * Newborn Screening

Family History Is Important for Your Health

adopted from CDC's Family History Fact sheet

<http://www.cdc.gov/genomics/public/famhix/fs.htm>

Most of us know that we can reduce our risk of disease by eating a healthy diet, getting enough exercise, and not smoking. But did you know that your family history might be one of the strongest influences on your risk of developing heart disease, stroke, diabetes, or cancer? Even though you cannot change your genetic makeup, knowing your family history can help you reduce your risk of developing health problems.



Family members share their genes, as well as their environment, lifestyles, and habits. Everyone can recognize traits that run in their family, such as curly hair, dimples, leanness, or athletic ability. Risks for diseases such as asthma, diabetes, cancer, and heart disease also run in families. Everyone's family history of disease is different. The key features of a family history that may increase risk are:

- Diseases that occur at an earlier age than expected (10 to 20 years before most people get the disease);
- Disease in more than one close relative;
- Disease that does not usually affect a certain gender (for example, breast cancer in a male);
- Certain combinations of diseases within a family (for example, breast and ovarian cancer, or heart disease and diabetes).

If your family has one or more of these features, your family history may hold important clues about your risk for disease. People with a family history of disease may have the most to gain from lifestyle changes and screening tests. You can't change your genes, but you can change unhealthy behaviors, such as smoking, inactivity, and poor eating habits. In many cases, adopting a healthier lifestyle can reduce your risk for diseases that run in your family. Screening tests (such as mammograms and colorectal cancer screening) can detect diseases like cancers at an early stage when they are most treatable. Screening tests can also detect disease risk factors like high cholesterol and high blood pressure, which can be treated to reduce the chances of getting disease.



LEARNING ABOUT YOUR FAMILY HISTORY

To learn about your family history:

- ask questions,
- talk at family gatherings, and
- look at death certificates and family medical records, if possible.

Collect information about your grandparents, parents, aunts and uncles, nieces and nephews, siblings, and children. The type of information to collect includes:

- major medical conditions and causes of death,
- age of disease onset and age at death, and
- ethnic background.

Write down the information and share it with your doctor. Your doctor will:

- assess your disease risk based on your family history and other risk factors,
- recommend lifestyle changes to help prevent disease, and
- prescribe screening tests to detect disease early.

If your doctor notices a pattern of disease in your family, it may be a sign of an inherited form of disease that is passed on from generation to generation. Your doctor may refer you to a specialist who can help determine whether you have an inherited form of disease. Genetic testing may also help determine if you or your family members are at risk. Even with inherited forms of disease, steps can be taken to reduce your risk.

WHAT IF YOU HAVE NO FAMILY HISTORY?

Even if you don't have a history of a particular health problem in your family, you could still be at risk. This is because

- your lifestyle, personal medical history, and other factors influence your chances of getting a disease;
- you may be unaware of disease in some family members;
- you could have family members who died young, before they had a chance to develop chronic conditions such as heart disease, stroke, diabetes, or cancer.

Being aware of your family health history is an important part of a lifelong wellness plan.

WHERE YOU CAN FIND MORE INFORMATION

For more information on CDC's Office of Genomics and Disease Prevention, visit <http://www.cdc.gov/genomics>.

The following Web sites provide additional information on family history:

CDC's Family History Web site for the Public, <http://www.cdc.gov/genomics/public/fambhist.htm>

U.S. Surgeon General's Family History Initiative, <http://www.hhs.gov/familyhistory/>

National Society for Genetic Counselors, <http://www.nsgc.org/consumer/familytree/>

Basic Genetic Information

- Cells are the body's building blocks. Inside most cells is a nucleus—the center of the cell. The nucleus contains threadlike structures called chromosomes made up of smaller structures called genes.
- Genes direct the structure and function of your cells which make up all of your body's organs and tissues.
- Genes are inherited from your parents and determine how you will look.
- Genes come in pairs. One gene comes from your father and one from your mother. This is why you look like your parents.
- Genes also contain instructions for how you age, what diseases you are at risk for or may get in the future as you grow older, or what diseases you might pass down to your children.
- Some genes are stronger, or dominant, and they take over directing your body for that function.
- Some genes are weaker, or recessive, and need the presence of a like partner to become active and make a difference.
- Changes (also called mutations) can sometimes happen in a gene. Changes in a gene may cause cells or organs not to work correctly, leading to a disease. Changes in a gene may also lead to improvement in your body's ability to cope with disease. Changes in the genes can be inherited from your parents or happen due to the environment you live in—the chemicals you are exposed to, through the air you breathe, the food you eat, or the water you drink.
- Whether the specific set of genes you inherited from your parents—or any changes that occur to them during your lifetime—promote health or produce disease may depend on both environmental and behavioral factors. Proper exercise and nutrition can help delay or prevent disease, while smoking and lack of exercise can increase your chances of disease.
- You can take special tests—genetic tests—to see what specific genes are present in your body. These tests can sometimes tell you what diseases you might have or might develop later, and what diseases you might pass along to your children.
- Newborn babies also take genetic tests to look for diseases that might harm the baby or cause mental retardation if they are not treated immediately. These tests are done just after the baby is born so that interventions and treatment can be started immediately to protect the baby from these diseases. If a disease is found, a doctor will help you understand what treatment your baby needs. Sometimes you may be asked to see a genetic counselor.



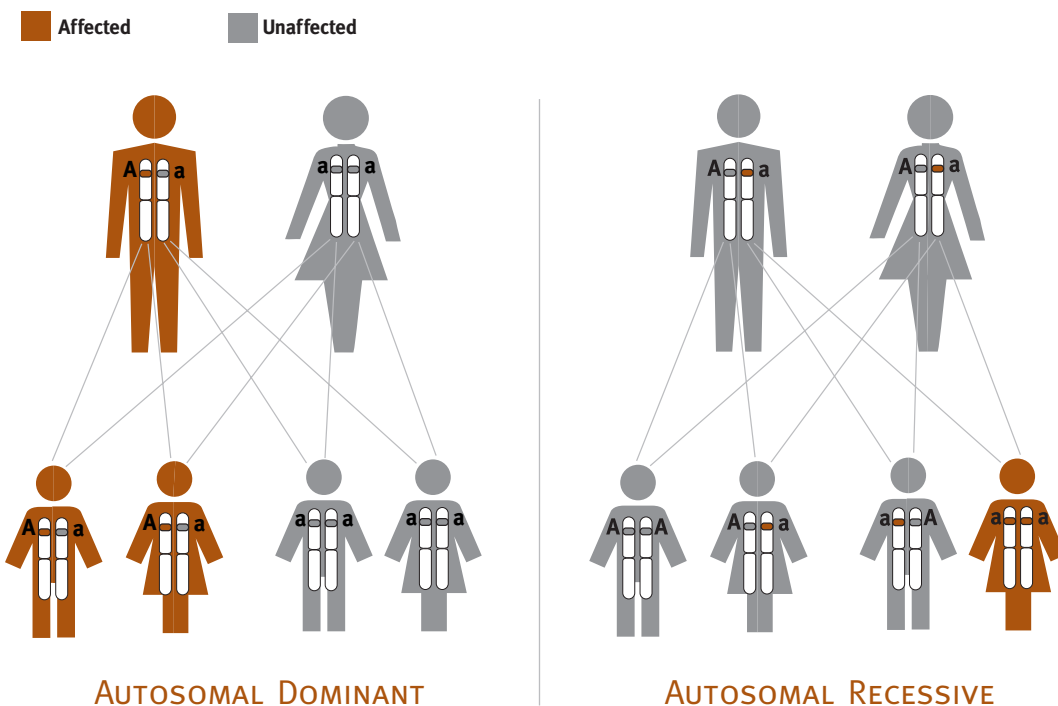
Dominant and Recessive Genetic Diseases

The basic laws of inheritance are important in order to understand how diseases are passed on in a family. For almost every gene, a person has two copies of each gene—one copy from your father and one copy from your mother. Changes to either copy of the gene or both copies of the gene can result in a wide range of effects. Some changes result in relatively minor or undetectable changes; these types of changes are often called single nucleotide polymorphisms (“snips”) or gene variations.

Other DNA changes in a gene can result in changes to the corresponding protein which can lead to disease. These changes are often known as mutations. Diseases caused by mutations in a single gene are usually inherited in a simple pattern, depending on the location of the gene and whether one or two normal copies of the gene are needed. For certain functions in the body, you need two copies of a gene to work normally. For other functions, only one copy is necessary.

There are two major modes of inheritance for single-gene diseases: recessive and dominant. When a person inherits a mutation in one of the two copies of a gene, disease may develop if both copies are required for normal function. In this case, the mutated gene is dominant and the person develops a genetic disease. Dominantly inherited genetic diseases tend to occur in every generation of a family. Each affected person usually has one affected parent.

If a person inherits a mutation in one copy of a gene, but does not develop a disease, the mutated gene is recessive. For a recessively inherited disease to develop, both copies of the gene must be mutated. This can happen when both the mother and father carry a copy of the mutated gene and pass each copy onto the child who will then have two copies of the mutated gene. Recessive genetic diseases are typically not seen in every generation of an affected family. The parents of an affected person are generally not affected.



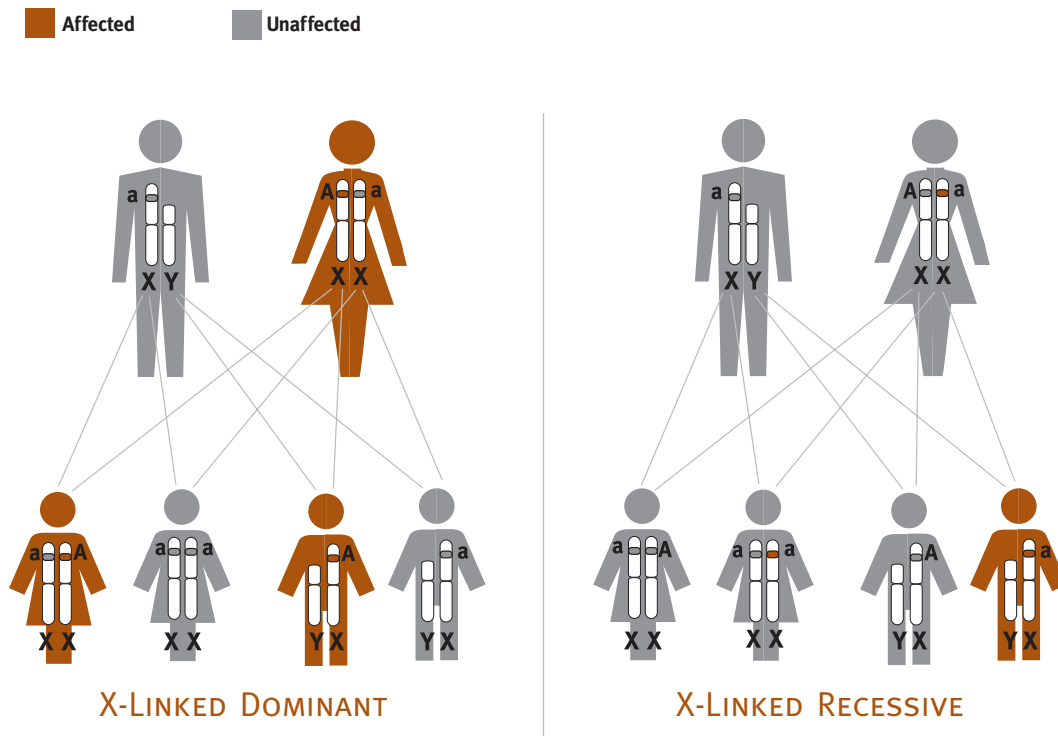
X-linked Genetic Diseases

For genes located on the sex chromosomes (X or Y), the inheritance patterns are slightly different than for genes located on the other chromosomes (1-22). This is due to the fact that females carry two X chromosomes (XX) and males carry a single X and Y chromosome each (XY). Therefore, females carry two copies of each X-linked gene similar to all other genes, but males carry only one copy of X-linked and Y-linked genes.

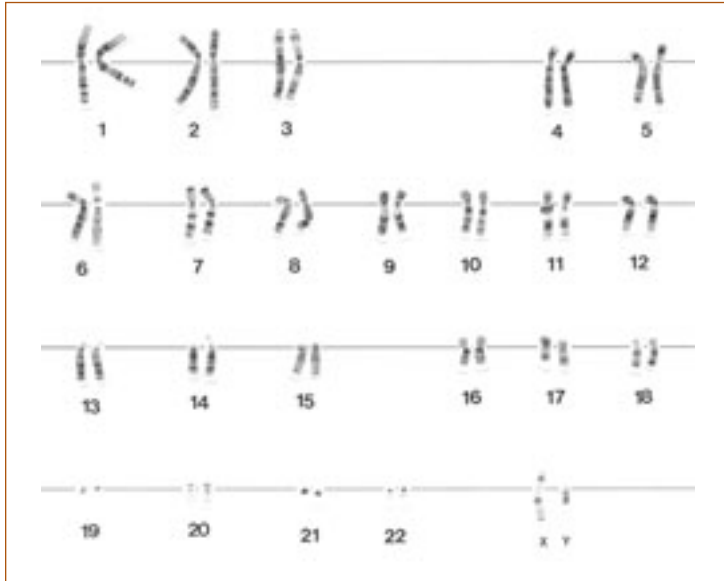
Since males only have one X chromosome, any mutated gene on the X chromosome will result in disease. But because females have two copies of X-linked genes, diseases caused by mutated genes located on the X chromosome can be inherited in either a dominant or recessive manner. For X-linked dominant diseases, a mutation in one copy of an X-linked gene will result in disease. Families with an X-linked dominant disorder often have both affected males and affected females in each generation.

For X-linked recessive diseases to occur, both copies of the gene must be mutated in order for disease to occur in females. 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 since they only pass on the Y chromosome. In contrast, affected mothers can pass the mutated X-linked gene to either their son or daughter.



What is a Chromosome Abnormality?



Almost every cell in our body contains 23 pairs of chromosomes for a total of 46 chromosomes. Half of the chromosomes come from our mother and the other half come from our father. The first 22 pairs (called autosomes) are numbered according to size—the largest chromosome is chromosome 1. The 23rd pair are the sex chromosomes X and Y—females have 2 X chromosomes and males have an X and Y chromosome each. All of the information that the

body needs to work comes from the chromosomes. Each chromosome contains thousands of genes which direct the body's development, growth, and chemical reactions.

Although most everyone has a complete set of chromosomes, sometimes pieces of chromosomes can be switched or moved. In general, as long as all of the material is present, the majority of children with rearranged chromosomes do not develop any health problems. However, when sections of or entire chromosomes are missing or extra copies are present, miscarriage, infant death, or disease usually occurs. For example, an extra copy of chromosome 21 results in Down syndrome.

Chromosome abnormalities usually happen as a result of an error when cells grow and divide. Errors can occur when eggs or sperm are formed, resulting in either too many chromosomes or not enough chromosomes. Or, errors could occur during the early developmental stages of the fetus, also resulting in an abnormal number of chromosomes. The age of the mother and certain environmental factors can increase the risk of a chromosomal abnormality.

Testing can be performed to examine the chromosomes of the fetus. The two types of testing available are amniocentesis and chorionic villus sampling. In both cases, the cells from the baby are grown and processed in the laboratory so that the chromosomes can be studied. Pictures of the chromosomes viewed under a microscope are taken and the chromosomes are then arranged by size and paired together. The picture of the arranged chromosomes is known as a karyotype. The karyotype is evaluated for size and structure of the chromosomes.

Understanding Genetic Testing

Genetic testing involves examining a person's DNA found in blood or other tissues for some abnormality linked to a disease or condition. DNA is actually a chemical alphabet composed of four units that make up all of the genes or genetic material found inside our cells. Genes are important for our body's normal development and functioning. Each gene is unique due to the order of the four DNA units.

When a mistake happens affecting part or all of the gene, this can result in an abnormal function or change in our body leading to disease. The mistake can be fairly large or very small and different types of genetic tests are used to identify the specific gene abnormality. Genetic tests can be used to look for gene abnormalities in persons suspected of having a genetic disease based on symptoms the person may be having or because a close relative has a genetic disease.



The most common type of genetic testing is newborn screening. Almost every baby born in the United States has a blood sample tested for abnormal or missing genes or proteins. Early detection can allow the doctor to prescribe drugs or to place the baby on a specific diet in order to prevent or reduce the severity of a disease. Another type of testing known as carrier testing can help determine the risk of parents passing on a mutation to their child. And predictive gene testing can determine the risk of a healthy person developing a disease in the future.

Genetic testing is not always 100 percent accurate. Even when genetic testing positively detects a mutation, the test may or may not be able to determine when or what symptoms of the disease may show, which symptoms will occur first and how severe the disease will be, or how the disease will progress over time. If a test is negative, an individual may still be at risk for a disease. Therefore, it is important to speak to a health professional such as a genetic counselor to help you understand the benefits and risks of genetic testing and to answer any questions you may have before and after testing.



Deciding Whether to Have a Genetic Test

The decision to have a genetic test is a personal and sometimes difficult one. While a genetic test can determine the presence of a gene abnormality and/or identify an increased risk of disease, a genetic test cannot predict when a disease will develop or how severe the disease will be. Meeting with genetic health professionals can be extremely helpful in understanding and thinking through many of these issues.

Genetic counselors are trained health professionals in the areas of medical genetics and counseling. They work as members of a health care team, providing information and support to families who have members with birth defects or genetic disorders and to families who may be at risk for a variety of inherited conditions. Genetic counselors are trained to help persons as they consider testing, when they receive the results, and in the weeks and months afterward.

When deciding whether or not to have a genetic test for you or your child, several issues should be considered. In addition to the medical issues to be considered, genetic testing also raises some ethical and legal issues you should be aware of. Below is a list of some of the issues you should discuss with your physician or genetic counselor:

- What treatments are available for this genetic disease?
- What impact would the genetic test results have on your family?
- What happens if the results are uncertain or inconclusive?
- What are the risks for future pregnancies?
- What is the cost of the test and will my insurance cover it?
- Who will have access to the test results?
- What emotional support services are available?
- Do other family members have a right to know the test results?
- What is the risk of discrimination by my employer or insurer?

Prenatal Diagnosis

Prenatal diagnosis refers to testing performed during a pregnancy. Prenatal diagnosis is helpful for determining the outcome of the pregnancy, planning for possible complications during delivery, planning for problems that may occur in the newborn, deciding whether to continue the pregnancy, and finding conditions that may affect future pregnancies.

A common reason for prenatal diagnosis is the mother's age. According to professional guidelines, prenatal diagnosis should be offered to women who will be over the age of 35 years at the time of delivery because they have a higher risk of having a child with a genetic condition such as Down syndrome. Children with Down syndrome have a distinct facial appearance and mental retardation; however, the severity of the disease can vary greatly from child to child. The disease is caused by a chromosomal abnormality that can be detected through genetic testing, namely three copies of chromosome 21.

In addition, women who have had a previous child with a genetic condition, if the parents are carriers of a genetic mutation, or if there is a family history of a genetic condition would be eligible for prenatal diagnosis and should discuss the procedure with their doctor or a genetic counselor. Also, positive screening tests (triple screen, quadruple screen, first trimester screen) or abnormal findings on ultrasound are reasons for diagnostic testing.

Several types of prenatal diagnosis are available depending how far along the pregnancy is and what type of disorder is being tested. Chorionic villus sampling (CVS), amniocentesis, periumbilical blood sampling (PUBS), and fetoscopy are some examples of common procedures

used to obtain a sample from the baby for further testing.



Amniocentesis and chorionic villus sampling are both invasive procedures that carry a risk of miscarriage. Amniocentesis involves removing a sample of amniotic fluid from the uterine cavity by a syringe through the abdomen. The technique is generally performed at 15 to 20 weeks gestation. In CVS, the baby's cells are removed from an

area around the baby known as the chorion with a syringe inserted through the cervix or abdomen. CVS can be performed as early as nine week's gestation, but based on safety data, it is typically performed 10 to 13 weeks' gestation. This allows the results of any diagnostic assays to be available at an earlier stage of pregnancy. Both samples contain the baby's cells that can be grown in the laboratory for genetic testing.



Birth Defects/Congenital Abnormalities

A birth defect is a problem that happens while a baby is developing prior to birth. Congenital abnormalities refer to features or conditions that a baby is born with, as opposed to conditions that develop later in life. About one in 33 babies is born with a birth defect in the U.S.

A birth defect may cause physical or mental disabilities. It can affect almost any part of the body and can range from mild to severe. Some birth defects can be corrected by surgery or other medical treatments and children can lead normal lives. But some birth defects are very severe and can cause the baby to die. Some birth defects are easily detected, such as a club foot or cleft lip, but others such as heart defects or hearing loss may require x-rays and special tests.

Some of the most common birth defects to occur affect the heart. About one in every 200-300 babies is born with a heart defect. Depending on the type and severity of the heart defect, some can be corrected by surgery. Other common birth defects are called “neural tube” defects. Neural tube defects are due to abnormal development of the baby’s spine and brain. They affect about one in a 1,000 babies. These defects are often very severe, causing early death. Birth defects of the lip and the roof of the mouth are also common. They are referred to as cleft lip and cleft palate. They affect about one in 700-1,000 babies.

Many birth defects are caused by multiple factors—both genetic and environmental factors. For example, risk of neural tube defects is increased in families with a history of neural tube defects, but the risk can be reduced with folic acid supplementation. Uncontrolled medical conditions of the mother such as diabetes can also lead to birth defects such as heart defects. Some medicines such as Accutane are also known to cause birth defects.

To learn more about your risk of having a baby with a birth defect, please talk with your doctor or a genetic counselor. In particular, women should consult their doctor before becoming pregnant to begin multi-vitamin supplements containing folic acid, to get help with managing their medical conditions, decide which medications are safe to take, and to avoid exposure to alcohol, drugs, and smoking.

Newborn Screening (DC/Virginia/Maryland)

Each year, more than 95% of all children born in the United States (at least 4 million babies) are tested for a panel of diseases that, when detected and treated early, can lead to significant reduction in disease severity and possibly even prevention of the disease. About 3,000 newborns test positive for one of these severe disorders.

Within 48 hours of a child's birth, a sample of blood is obtained from a "heel stick," and the blood is analyzed for up to 35 treatable diseases, including phenylketonuria (PKU), sickle cell disease, and hypothyroidism. The sample, called a "blood spot," is tested at a state public health or other participating laboratory.

Newborn screening programs began in the U.S. in the 1960's with the work of Dr. Robert Guthrie, who developed a screening test for PKU. PKU is an inherited metabolic disease that is caused by a mutation in an enzyme responsible for metabolism of the amino acid phenylalanine. Children who are identified early can avoid foods with phenylalanine, thereby avoiding buildup of the amino acid which can lead to brain damage and mental retardation. When Dr. Guthrie also introduced a system for collection and transportation of blood samples on filter paper, cost effective wide scale genetic screening became possible.

In general, newborn screening is performed for conditions that, when detected and treated early, can lead to significant reduction in disease severity and possibly even prevention of the disease. The panel of newborn diseases screened for varies from state to state, and decisions for adding or deleting tests involve many complex social, ethical, and political issues. Usually, newborn population screening disorders are selected based on disease prevalence, detectability, treatment availability, outcome, and overall cost effectiveness. It is possible to screen for many disorders at birth and soon more will be possible. The American College of Medical Genetics and the March of Dimes recommends that all babies be screened for a core panel of 29 disorders. However, each state decides which disorders to include in its newborn screening panel.

OVERVIEW OF NEWBORN DISORDERS SCREENED IN DC, VA, AND MD

2,4-Dienoyl-CoA reductase deficiency—an autosomal recessive genetic disorder characterized by a deficiency of 2,4 Dienoyl-CoA Reductase necessary for the degradation of unsaturated fatty acids with an even number of double bonds. Symptoms include sepsis, hypotonia, decreased feeding, and intermittent vomiting. Low carnitine levels can be detected and respiratory acidosis may occur.

2-Methylbutryl-CoA dehydrogenase deficiency—an autosomal recessive genetic disorder resulting from a defect in the metabolism of the branched chain amino acid isoleucine. Symptoms include poor feeding, lethargy, hypoglycemia, and metabolic acidosis. Symptomatic patients display developmental delay, seizure disorders, and progressive muscle weakness in infancy and childhood.

3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)—a progressive autosomal recessive genetic disorder characterized by failure to thrive, hypotonia, muscle atrophy, seizures, mental retardation, and dermatological changes.



3-Methylglutaconyl-CoA hydratase deficiency—an autosomal recessive genetic disorder involving an enzyme in the metabolism of the amino acid leucine. Symptoms appear in a wide range of clinical severity and may include acute life-threatening cardiopulmonary symptoms soon after birth, psychomotor retardation, hypotonia, failure to thrive, microcephaly, seizures, and spasticity. Some patients may have acute episodes of vomiting, metabolic acidosis, and lethargy progressing to coma.

3-OH 3-CH₃ glutaric aciduria or 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG)—an autosomal recessive genetic disorder. Symptoms may include metabolic acidosis, hypoglycemia, sensitivity to dietary leucine, carnitine deficiency, hepatomegaly, fever, somnolence, and coma. If this disorder is untreated, it is likely to result in death during childhood.

5-Oxoprolinuria (pyroglutamic aciduria)—a group of autosomal recessive genetic conditions including glutathione synthetase deficiency, glutamylcysteine synthetase deficiency, and 5-oxoprolinase deficiency caused by a deficiency of one (1) of three (3) enzymes in the gamma glutamyl cycle and characterized by metabolic acidosis, hemolytic anemia, electrolyte imbalance, and jaundice.

Argininemia—an autosomal recessive genetic condition that presents from two (2) months to four (4) years of age. Symptoms include progressive spastic paraplegia, failure to thrive, delayed milestones, hyperactivity, and irritability, with episodic vomiting, hyperammonemia, seizures, microcephaly, and cerebral atrophy resulting in mental retardation.

Argininosuccinic acidemia (ASA)—an autosomal recessive genetic disorder of the urea cycle. Symptoms are hyperammonemia accompanied by lack of appetite, vomiting, listlessness, seizures, and coma. Onset is usually at birth, but symptoms may not be noticeable for days or weeks. The build up in ASA, if too high, ultimately causes a build up in ammonia. Build up of ammonia is toxic and can cause brain damage. ASA is also characterized by excessive urinary excretion of argininosuccinic acid, epilepsy, ataxia, mental retardation, liver disease, and friable, tufted hair.

Beta-ketothiolase deficiency (BKT)—an autosomal recessive genetic disorder characterized by recurrent severe metabolic acidosis. Symptoms include increased plasma glycine level, metabolic acidosis, episodic ketosis, vomiting, dehydration, coma, and cardiomyopathy, with on average onset of five (5) to twenty-four (24) months.

Biotinidase deficiency (BIOT)—an autosomal recessive genetic disorder characterized by a lack of the enzyme biotinidase that can lead to seizures, developmental delay, eczema, and hearing loss that are treated with free biotin. Symptoms include hypotonia, ataxia, alopecia, seborrheic dermatitis, and optic nerve atrophy. Metabolic acidosis can result in coma and death.

Carbamoylphosphate synthetase deficiency (CPS def.)—an autosomal recessive genetic condition that presents within seventy-two (72) hours with symptoms of lethargy, vomiting, hypothermia, respiratory alkalosis, and seizures progressing to coma. Survivors of the newborn period have recurrent episodes of hyperammonemia associated with viral infections or increased dietary protein intake. Some patients have a later onset with less severe symptoms.

Carnitine uptake defect (CUD)—a class of autosomal recessive genetic disorders characterized by hypoketotic hypoglycemia, seizures, vomiting, lethargy progressing to coma, cardiomyopathy, and hepatomegaly. This disorder includes carnitine palmitoyl transferase deficiency type I and carnitine acylcarnitine translocase deficiency.

Citrullinemia (CITR)—an autosomal recessive genetic disorder characterized by a deficiency of argininosuccinic acid synthetase, hyperammonemia accompanied by lack of appetite, vomiting, listlessness, seizures, and coma. Onset is usually at birth, but symptoms may not be noticeable for days or weeks. When left untreated, brain damage, coma, and death will occur.

Congenital adrenal hyperplasia (CAH)—a set of inherited disorders that occurs in both males and females as a result of the excess production of male hormones and an underproduction of the enzyme 21-hydroxylase, severe acne, excess facial or body hair, early development of pubic hair, receding scalp hairline, menstrual disturbances in females, and infertility in males and females in its mild form and ambiguous genitalia in newborn girls and salt and hormonal imbalances in girls and boys in more severe forms. If not treated, CAH can cause heart failure and death within a few days from birth. CAH cannot be cured; however, it can be effectively treated.

Congenital hypothyroidism—is caused by a biochemical defect that reduces thyroid hormone secretion and consequently causes a deficiency in the circulating hormone thyroxine. This deficiency in thyroxine can result from the absence of a thyroid gland, incomplete gland development, thyroid inflammation resulting from autoimmune disorders, hereditary defects in thyroid hormone synthesis or an inability to synthesize thyroxine because of dietary iodine deficiency. Among infants and children, untreated hypothyroidism is usually characterized by slowed growth and development, decreased mental capacity, and a characteristic facial appearance. Mental retardation can be prevented, and these patients can be expected to develop normally if detected early through screening and treated with hormone replacement therapy.

Cystic fibrosis (CF)—an autosomal recessive genetic disorder characterized by progressive chronic damage to the respiratory system, chronic digestive system problems, and can affect other organs. CF affects mucus-producing glands producing thick mucus that can obstruct air passages in the lungs, affects sweat and salivary glands, and blocks enzymes secreted by the pancreatic duct. Cystic fibrosis can cause lung disease, failure to grow, clubbed fingers and toes, muscular weakness, and visual impairment.

Galactosemia—a rare inherited disorder that causes a certain kind of sugar to build up in the body. This sugar is called galactose. An infant with galactosemia is missing one of the enzymes that converts galactose into glucose. Most galactose comes from milk sugar in a form called lactose. Galactose builds up in the body and can cause damage to the brain, eyes, liver, and kidneys. Damage can be stopped by eliminating milk, breast milk, and other dairy products from the diet.

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)—G6PD is an inherited condition causing little or no G6PD in the red blood cells. G6PD deficiency does not cause growth problems or change ability to learn or participate in normal activities. Anemia can happen when a person with G6PD deficiency takes certain medicines or eats certain foods. The effects of G6PD can be avoided if certain foods and medicines that might change red blood cells are not consumed. After initial screening, additional blood studies are necessary to confirm the diagnosis between six to 12 months of age.



Glutaric acidemia type I (GA-I)—an autosomal recessive enzyme deficiency genetic disorder characterized by hypoglycemia, dystonia, and dyskinesia. After a period of apparently normal development, the disorder may appear suddenly and present as vomiting, metabolic acidosis, hypotonia, and central nervous system degeneration. It is not yet known how or why Glutaric acid causes brain damage, yet damage occurs when a crisis causes an acidic environment in the blood created by excess protein byproducts. Crises can be provoked by common childhood illnesses such as colds, flu, ear infections, stomach virus, fever, etc.

Hemoglobinopathy—a class of disorders caused by the presence of abnormal hemoglobin production in the blood, due to genetic variations that can result in production of hemoglobin with different structures or thalassemias and reduction in the amount of normal hemoglobin produced. This term includes the following hemoglobin variants: HbS, HbC, HbE, HbD, and alpha/beta thalassemias.

Homocystinuria—this metabolic disorder results from a deficiency of one of several enzymes needed by the brain for normal development. If untreated, it can lead to dislocated lenses of the eyes, mental retardation, skeletal abnormalities, and abnormal blood clotting. A special diet combined with dietary supplements may help prevent most of these problems.

Hyperammonemia, hyperornithinemia, homocitrullinemia syndrome (HHH)—an autosomal recessive genetic disorder that may present at birth or in later childhood. Newborns on high protein formulas or foods may vomit with feeding, refuse to eat, become lethargic, or develop hyperammonemic coma. Patients gravitate to diets low in milk and meat during childhood.

Hyperornithine with gyrate deficiency—an autosomal recessive genetic disorder characterized by slow progressive vision loss leading to blindness. Myopia and decreased night vision appear as early symptoms in the patient's teens and early twenties.

Isobutyryl-CoA dehydrogenase deficiency—an autosomal recessive genetic disorder involving the inability to metabolize valine with a highly variable presentation.

Isovaleric acidemia (IVA)—an autosomal recessive genetic disorder caused by a defect in the breakdown of the molecule isovaleryl-CoA that presents in acute or intermittent episodes. IVA can present as an acute episode of illness during the first few weeks of a newborn's life, or it may present chronically with intermittent episodes of illness throughout life. Both forms of IVA are caused by the same biochemical defect. Infants who survive an acute neonatal episode will go on to exhibit the chronic intermittent form. Symptoms of acute IVA are attacks of vomiting, lack of appetite, and listlessness; lethargy, neuromuscular irritability, and hypothermia are other characteristics. Episodes can be triggered by upper respiratory infections or by excessive consumption of high-protein foods. Early detection through newborn screening and good treatment of IVA generally leads to normal development. Permanent neurologic damage can occur if an acute episode is not prevented or is misdiagnosed.

Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHADD)—an autosomal recessive genetic disorder characterized by failure to oxidize fatty acids due to a missing or malfunctioning enzyme. Symptoms include hypoglycemia, lethargy, failure to thrive, cardiomyopathy, and developmental delay. Early identification and treatment can prevent life-threatening episodes.

Malonic aciduria—an autosomal recessive genetic disorder caused by a deficiency of malonyl-CoA decarboxylase (MCD) with a variable presentation ranging from acute neonatal onset to later in childhood. Symptoms include developmental delay, seizures, hypotonia, diarrhea, vomiting, metabolic acidosis, hypoglycemia, and ketosis.

Maple syrup urine disease (MSUD)—babies with MSUD are missing an enzyme needed to process three amino acids that are essential for the body's normal growth. When these are not processed properly, they can build up in the body, causing the urine to smell like maple syrup or sweet, burnt sugar. These babies usually have little appetite and are extremely irritable. If not detected and treated early, MSUD can cause mental retardation and physical disability. Protein foods containing those amino acids can prevent these outcomes.

Medium chain acyl-CoA dehydrogenase deficiency (MCADD)—an autosomal recessive genetic disorder characterized by inability to convert fat to energy. Fasting is not tolerated well in people with MCADD. Symptoms generally begin in infancy or early childhood, however, there are some with no apparent symptoms at birth. Low blood sugar, seizures, brain damage, cardiac arrest, and serious illness can occur very quickly in children who are not feeding well. Some experience recurrent episodes of metabolic acidosis, hypoglycemia, lethargy, and coma. If not detected and treated appropriately, MCADD can result in mental retardation and death. Those treated are expected to have normal life expectancy.

Methylmalonic acidemia—one of two variations of an autosomal recessive genetic disorder caused by an enzymatic defect in the oxidation of amino acids characterized by lethargy, failure to thrive, vomiting, dehydration, respiratory distress, hypotonia, and hepatomegaly. Acute episodes may include drowsiness, coma, and seizures, with subsequent developmental delays. This disorder includes methylmalonic acidemia CblA, methylmalonic acidemia CblB, and methylmalonic acidemia mutase deficiency.

Multiple acyl-CoA dehydrogenase deficiency (MADD)—an autosomal recessive genetic disorder, also known as glutaric acidemia type II, with three (3) different clinical presentations. Symptoms include hypotonia, hepatomegaly, severe nonketotic hypoglycemia, metabolic acidosis, and variable body odor of sweaty feet.

Multiple carboxylase deficiency (MCD)—an autosomal recessive genetic disorder characterized by a biotin deficiency. Symptoms include seizures, developmental delay, eczema, and hearing loss. Other symptoms are immune system impairment, skin rashes, hair loss and mental retardation that are treatable with oral biotin supplements.

Neonatal carnitine palmitoyl transferase deficiency-type II (CPT-II)—an autosomal recessive genetic disorder of mitochondrial fatty acid oxidation that presents in three (3) forms. The classic form has adult onset of exercise-induced muscle weakness, often with rhabdomyolysis and myoglobinuria that may be associated with renal failure. A second form that is often fatal between three (3) and eighteen (18) months of age with symptoms of hepatomegaly, non-ketotic hypoglycemia, cardiomyopathy, hypotonia, and muscle weakness. A severe form presents in newborns with non-ketotic hypoglycemia, cardiomyopathy, hypotonia, muscle weakness, and renal dysgenesis in some patients.



Phenylketonuria (PKU)—an autosomal recessive disorder that affects the way the body is able to use a part of all food proteins called phenylalanine which is an amino acid. The body uses amino acids as building blocks for body growth and repair. Unless found and treated early, PKU can cause the body to become overloaded with phenylalanine which can prevent the brain from developing as it should leading to severe mental retardation and other problems. When this disorder is detected early, feeding an infant a special formula low in phenylalanine can prevent mental retardation. A low-phenylalanine diet will need to be followed throughout childhood and adolescence and perhaps into adult life.

Propionic acidemia (PROP)—an autosomal recessive genetic disorder characterized by protein intolerance, vomiting, failure to thrive, lethargy, and profound metabolic acidosis. If not treated early, brain damage, coma, seizures and death can occur.

Short chain acyl-CoA dehydrogenase deficiency (SCAD)—an autosomal recessive genetic disorder of fatty acid beta oxidation with a usual clinical onset between the second (2nd) month and second (2nd) year of life, with some presenting within a few days of birth and some in adulthood. Symptoms include hypotonia, progressive muscle weakness, developmental delay, and seizures. Symptoms worsen with seemingly innocuous illness that may lead to lethargy, coma, apnea, cardiopulmonary arrest, or sudden unexplained death.

Short chain hydroxy acyl-CoA dehydrogenase deficiency (SCHAD)—an autosomal recessive genetic disorder of mitochondrial fatty acid beta oxidation for which a complete spectrum of presentation has not been defined. Most patients have hypoglycemia as the major symptom along with seizures, neurologic sequelae or death as the outcome. Several present in the first days or months of life with hypoglycemic seizures secondary to hyperinsulinism. Some patients present after one (1) year with acute onset of vomiting, lethargy, and hyponatremic seizures.

Trifunctional protein deficiency (TFP)—an autosomal recessive mitochondrial fatty acid oxidation genetic disorder characterized by an inability to break down long-chain fatty acids into an energy source. Metabolic crises can occur when fasting, as well as hypoglycemia, lethargy, hypotonia, myopathy, failure to thrive, cardiomyopathy, and neuropathy. Severe untreated cases may present as SIDS.

Tyrosinemia type I (TYRO-I)—an autosomal recessive genetic disorder that causes severe liver disease in infancy. Affected persons develop cirrhosis of the liver and eventually require liver transplantation. The most severe form causes symptoms within the first months of life. These infants experience poor weight gain, enlarged liver and spleen, swelling of the legs, increased tendency of bleeding. Even with therapy death frequently occurs within six (6) to nine (9) months of life for those with the severe form. Children with a less severe form also suffer from enlargement of the liver, spleen, poor weight gain, vomiting and diarrhea.

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)—an autosomal recessive genetic disorder in which the body cannot oxidize fatty acids because of a missing or mal-functioning enzyme. Symptoms include hypoketotic hypoglycemia, hepatocellular disease, and cardiomyopathy. Fatal infantile encephalopathy may be the only indication of the condition.



APPENDIX

District of Columbia Department of Health–Integrated Health Data System
Classical Mendelian Genetics (Patterns of Inheritance) * Genetic Testing
Methodologies * Teratogens/Prenatal Substance Abuse * Prenatal Diagnosis
Maternal Serum Marker Screening * Single-Gene Disorders * Chromosomal
Abnormalities * Pharmacogenetics * Cultural Competencies in Genetics
NCHPEG Principles of Genetics for Health Professionals * CDC Genomic
Competencies for the Public Health Workforce

APPENDIX A. DISTRICT OF COLUMBIA DEPARTMENT OF HEALTH—INTEGRATED HEALTH DATA SYSTEM

As part of an overall plan to improve health care delivery, the Washington, D.C. Department of Health is creating an integrated health data system. Currently under construction, this system will house a patient's full medical records, starting with newborn screening results.

Advantages to this program include:

Full Information. When patients are responsible for conveying complex information to a provider, information may be miscommunicated or omitted. An integrated data system will better allow a provider to know a patient's existing conditions and aid in development of safe and effective treatments.

Portability. In the current system, a patient's medical records may be housed at separate clinics. An integrated data system makes it easy for a patient to share his or her information with a new provider.

Lower Costs. Information collecting and distribution consumes an enormous amount of time. An integrated data system will streamline these processes and save time and money.

Improved Understanding. Consolidating information will allow public health officials to understand and address health concerns better.

The details of how this system will be integrated into your practice will be given to you when the system is closer to completion.



APPENDIX B. CLASSIC MENDELIAN GENETICS (PATTERNS OF INHERITANCE)

The basic laws of inheritance are important in understanding patterns of disease transmission. The inheritance patterns of single gene diseases are often referred to as Mendelian since Gregor Mendel first observed the different patterns of gene segregation for selected traits in garden peas and was able to determine probabilities of recurrence of a trait for subsequent generations. If a family is affected by a disease, an accurate family history will be important to establish a pattern of transmission. In addition, a family history can even help to exclude genetic diseases, particularly for common diseases where behavior and environment play strong roles.

Most genes have one or more versions due to mutations or polymorphisms referred to as alleles. Individuals may carry a ‘normal’ allele and/or a ‘disease’ or ‘rare’ allele depending on the impact of the mutation/polymorphism (e.g., disease or neutral) and the population frequency of the allele. Single-gene diseases are usually inherited in one of several patterns depending on the location of the gene and whether one or two normal copies of the gene are needed for the disease phenotype to manifest.

The expression of the mutated allele with respect to the normal allele can be characterized as dominant, co-dominant, or recessive. There are five basic modes of inheritance for single-gene diseases: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and mitochondrial.

Genetic heterogeneity is a common phenomenon with both single-gene diseases and complex multi-factorial diseases. It should not be surprising that multiple affected family members may experience different levels of disease severity and outcomes. This effect may be due to other genes influencing the disease phenotype or different mutations in the same gene resulting in similar, but not identical phenotypes. Some excellent resources for information about single-gene diseases is the Online Mendelian Inheritance in Man (OMIM; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>) and GeneTests/GeneClinics (<http://www.genetests.org>).

PATTERNS OF INHERITANCE

Autosomal Dominant

- Each affected person has an affected parent
- Occurs in every generation

Autosomal Recessive

- Both parents of an affected person are carriers
- Not typically seen in every generation

X-linked Dominant

- Females more frequently affected
- Can have affected males and females in same generation

X-linked Recessive

- Males more frequently affected
- Affected males often present in each generation

Mitochondrial

- Can affect both males and females, but only passed on by females
- Can appear in every generation

INHERITANCE PATTERN	DISEASE EXAMPLES
Autosomal Dominant	Huntington's disease, neurofibromatosis, achondroplasia, familial hypercholesterolemia
Autosomal Recessive	Tay-sachs disease, sickle cell anemia, cystic fibrosis, phenylketonuria (PKU)
X-linked Dominant	Hypophatemic rickets (vitamin D-resistant rickets), ornithine transcarbamylase deficiency
X-linked Recessive	Hemophilia A, Duchenne muscular dystrophy
Mitochondrial	Leber's hereditary optic neuropathy, Kearns-Sayre syndrome

APPENDIX C. GENETIC TESTING METHODOLOGIES

As the number of genetic tests has expanded rapidly over the last decade, so have the different types of genetic testing methodologies used. The type of test employed will depend on the type of abnormality that is being measured. In general, three categories of genetic testing are available—cytogenetic testing, biochemical testing, and molecular testing—to detect abnormalities in chromosome structure, protein function and DNA sequence, respectively.

Cytogenetic Testing. Cytogenetics involves the examination of chromosomes and their abnormalities. Chromosomes of a dividing human cell can be clearly analyzed in white blood cells, specifically T lymphocytes, which are easily collected from blood. Cells from other tissues such as bone marrow, amniotic fluid, and other tissue biopsies can also be cultured for cytogenetic analysis. Following several days of cell culture, chromosomes are fixed, spread on microscope slides and then stained. The staining methods for routine analysis allow each of the chromosomes to be individually identified. The distinct bands of each chromosome revealed by staining allow for analysis of chromosome structure.

Fluorescent in situ hybridization (FISH) is a process which vividly paints chromosomes or portions of chromosomes with fluorescent molecules to identify chromosomal abnormalities (e.g., insertions, deletions, translocations and amplifications). FISH is commonly used to identify specific chromosomal deletions associated with pediatric syndromes such as DiGeorge syndrome (del22) and cancers such as chronic myelogenous leukemia (BCR-ABL 9;22) and B-cell Lymphoma (IgH-BCL2 14;18).

Biochemical Testing. Clinical testing for a biochemical disease utilizes techniques that examine the protein instead of the gene. Many biochemical genetic diseases are known as ‘inborn errors of metabolism’ since they are present at birth and disrupt a key metabolic pathway. Depending on the disease, tests can be developed to directly measure protein activity (enzymes), level of metabolites (indirect measurement of protein activity), and the size or quantity of protein (structural proteins). These tests require a tissue sample in which the protein is present, typically blood, urine, amniotic fluid, or cerebrospinal fluid. Because proteins are more unstable than DNA and can degrade quickly, the sample must be collected and stored properly and shipped promptly according to the laboratory’s specifications.



A variety of technologies enable both qualitative detection and quantitative determination of metabolites such as high performance liquid chromatography (HPLC), gas chromatography/mass spectrometry (GC/MS), and MS/MS. In addition, bioassays may employ fluorometric (e.g., beta-galactosidase), radioisotopic (e.g., galactosemia), or thin layer chromatography (e.g., mucopolysaccharidosis) methods.

Molecular Testing. Direct DNA analysis is possible only when the gene sequence of interest is known. For small DNA mutations, direct DNA testing may be the most effective methodology, particularly if the function of the protein is not known and a biochemical test cannot be developed. A DNA test can be performed on any tissue sample and require very small amounts of sample. Several different molecular technologies can be used to perform testing including direct sequencing, polymerase chain reaction-based assays (PCR), and hybridization. PCR is a commonly used procedure used to amplify targeted segments of DNA through repeated cycles of denaturation (heat-induced separation of double-stranded DNA), annealing (binding of specific primers of the target segment to parent DNA strand), and elongation (extension of the primer sequences to form new copy of target sequence). The amplified product can then be further tested, such as by digestion with a restriction enzyme and gel electrophoresis to detect the presence of a mutation/polymorphism.

For some genetic diseases, many different mutations can occur in the same gene and result in the same disease, making molecular testing challenging. For example, more than 800 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) can cause cystic fibrosis (CF). It would impractical to sequence the entire CFTR gene to identify the causative mutation since the gene is quite large. However, since the majority of CF cases are caused by approximately 30 mutations, this group of mutations is first tested before more comprehensive testing, such as sequencing, is performed.

For more information about genetic testing, see <http://www.genetests.org/>.

APPENDIX D. TERATOGENS/PRENATAL SUBSTANCE ABUSE

A teratogen is any agent that causes an abnormality following fetal exposure during pregnancy. Teratogens are usually discovered after an increased prevalence of a particular birth defect. For example, in the early 1960's, a drug known as thalidomide was used to treat morning sickness. Exposure of the fetus during this early stage of development resulted in cases of phocomelia, a congenital malformation in which the hands and feet are attached to abbreviated arms and legs. Teratogens can also be found at home or the workplace. The effect is related to type of agent, dose and duration and time of exposure. The first half of pregnancy is the most vulnerable.

Teratogenic agents include infectious agents (rubella, cytomegalovirus, varicella, herpes simplex, toxoplasma, syphilis, etc.); physical agents (ionizing agents, hyperthermia); maternal health factors (diabetes, maternal PKU); environmental chemicals (organic mercury compounds, polychlorinated biphenyl or PCB, herbicides and industrial solvents); and drugs (prescription, over-the-counter, or recreational). In general, if medication is required, the lowest dose possible should be used and combination drug therapies and first trimester exposures should be avoided.

The types or severity of abnormalities caused by a teratogenic agent is also dependent on the genetic susceptibilities carried by the mother and fetus. For example, variation in maternal metabolism of a particular drug will determine what metabolites the fetus is exposed to and the duration of exposure. The genetic susceptibility of the fetus to a particular teratogenic agent will also have an effect on the final outcome.

Two of the leading preventable causes of birth defects and developmental disabilities are alcohol and smoking. Alcohol use in pregnancy has significant effects on the fetus and the baby. Alcohol can pass from the mother's blood stream through the placenta to the fetus. Since alcohol is broken down more slowly in a fetus than in an adult, alcohol levels tend to remain high and stay in the baby's body longer. Birth defects associated with prenatal exposure to alcohol can occur in the first three to eight weeks of pregnancy, before a woman even knows that she is pregnant.

Fetal alcohol syndrome is a group of abnormalities in babies born to mothers who consume alcohol during pregnancy. It is the most common known non-genetic (non-inherited) cause of mental retardation in the U.S. Several educational materials in English and Spanish are available from the CDC at <http://www.cdc.gov/ncbddd/fas/faspub.htm>.



In 2001, the estimated prevalence of smoking during pregnancy for all U.S. women was 11.4%, ranging from 3.9% in DC to 26.2% in West Virginia. Smoking nearly doubles a woman's risk of having a low birth-weight baby as a result of poor growth before birth, preterm



delivery or a combination of both. Premature and low birth-weight babies face an increased risk of serious health problems during the newborn period, chronic lifelong disabilities (e.g., cerebral palsy, mental retardation) and possibly death. More recent studies have suggested a possible link between prenatal smoking exposure and behavioral problems in later childhood and adolescence.

In addition, almost three percent of pregnant women use illicit drugs such as marijuana, cocaine, Ecstasy and other amphetamines, and heroin. These drugs can cause low birth-weight, withdrawal symptoms, birth defects, or learning or behavioral problems.

More information about specific teratogens can be found the following web-sites:

- Organization of Teratogen Information Services http://otispregnancy.org/otis_about_us.asp
- Reprotox—an online Information System on Environmental Hazards to Human Reproduction and Development <http://reprotox.org/>
- Teratogen Information System (TERIS –online version Shepard's Catalog of Teratogenic Agents <http://depts.washington.edu/-terisweb/teris/>
- March of Dimes <http://www.marchofdimes.com>

APPENDIX E. PRENATAL DIAGNOSIS

Prenatal diagnosis can provide a range of information to parents at risk of having a child with an abnormality as well as to provide reassurance and reduce anxiety. In addition, prenatal diagnosis may also be used to identify treatable maternal health problems that can affect the baby's health. Prenatal diagnosis requires the collaboration of several specialists including obstetrics, ultrasonography and genetic counseling. The most common indication for prenatal diagnosis is advanced maternal age (>35 years of age) due to the increased risk of chromosomal abnormalities. Another reason is that screening tests or ultrasound show increased risk.

Two procedures are predominantly used for prenatal diagnosis—amniocentesis and chorionic villus sampling (CVS). Both are invasive procedures that carry a small risk of miscarriage. Amniocentesis involves removing a sample of amniotic fluid from the uterine cavity transabdominally by syringe. The amniotic fluid contains fetal cells that can be cultured for laboratory assays. The technique is generally performed 15 to 20 weeks' gestation. Early amniocentesis (<15 weeks) carries a higher risk of fetal loss and less amniotic fluid can be obtained.

In CVS, fetal tissue is removed from the villous area of the chorion either transcervically or transabdominally. CVS can be performed as early as nine week's gestation, although it is generally performed at 10 to 13 weeks' gestation which is a safer window. This allows the results of any diagnostic assays to be available at an earlier stage of pregnancy.

Other types of prenatal diagnostic procedures include cordocentesis and preimplantation genetic diagnosis. Cordocentesis is a procedure used to obtain a sample of fetal blood directly from the umbilical cord under the guidance of advanced imaging ultrasound. Cordocentesis is typically performed at 18 weeks' gestation or after if prenatal testing from amniotic fluid or chorionic villi samples is not conclusive. Testing of a fetal blood sample can be performed in only a few days. Cordocentesis also carries a risk of miscarriage.

Preimplantation genetic diagnosis is performed on embryos prior to implantation. Couples who choose to undergo in vitro fertilization may choose to have the embryos tested if they are at-risk for a genetic disease. One or two cells are removed from zygotes and biopsied at the six to ten-cell stage. The cells are analyzed using PCR-based methods or FISH. Unaffected embryos are then selected for implantation. This procedure is still relatively new and under development and the risks involved are still being studied.

Several types of laboratory analyses may be performed on fetal samples including cytogenetic analysis, DNA-based analysis, biochemical assays, and fluorescence in situ hybridization (FISH). [See Appendix C—Genetic Testing Methodologies.] Although prenatal diagnosis cannot be used to rule out all fetal defects, many diseases and birth defects can be detected through a combination of prenatal diagnostic procedures.



APPENDIX F. MATERNAL SERUM MARKER SCREENING

Early in their pregnancy, all women are offered screening of several blood markers that can indicate increased fetal risk for certain genetic diseases and birth defects. Between 15 and 21 weeks' gestation, a maternal serum sample is screened for alpha-fetoprotein (AFP), estriol and human chorionic gonadotropin (hCG). In addition, a fourth marker, inhibin-A, is included in some screenings.

AFP was the first protein marker to be associated with fetal abnormalities that was easily detectable in the mother's blood. The fetus synthesizes high levels of AFP early in development, but the level in maternal serum is normally much lower. High concentrations of AFP in maternal serum are associated with open neural tube defects. During early development, the neural tube gives rise to the brain and spinal cord. Improper closure of the neural tube during development can result in birth defects such as spina bifida and anencephaly. Open neural tube defects affect about 2,500 babies each year. In spina bifida, the arches of the vertebrae in the lumbar region fail to fuse. Varying degrees of severity of spina bifida can occur affecting the backbone and the spinal cord, sometimes leading to partial paralysis and bladder and bowel control problems. Anencephaly is a condition in which the brain and skull are severely underdeveloped. Babies with anencephaly are stillborn or survive only a short period of time after birth.

It was later found that decreased AFP levels were associated with Down syndrome. About one in 800 babies is born with Down syndrome, caused by an extra copy of chromosome 21 (trisomy 21). Maternal serum AFP levels combined with maternal age, along with additional markers found in maternal serum (estriol and human chorionic gonadotropin (hCG)), provide a sensitive serum screening test. Low levels of MSAFP and estriol, along with high levels of hCG suggest an increased risk of Down syndrome. Low levels of all three markers suggest an increased risk of Edward syndrome (trisomy 18). The inclusion of a fourth marker, inhibin-A, in the maternal serum screen further improves the accuracy in predicting risk of Down syndrome.

The baby's risk of neural tube defects, Down syndrome and trisomy 18 is calculated based upon the levels of the three (or four) markers measured plus additional factors such as the woman's age, weight, multiple pregnancies, race, and whether she has diabetes requiring insulin treatment. Since this is a screening test, an abnormal test result only indicates an increased risk and does not diagnose a birth defect or genetic disease. Additional testing would need to be performed to diagnose a birth defect or genetic disease. Approximately 5-7% of women will have a false positive result, most commonly due to an inaccurate gestational age.

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American College of Obstetricians and Gynecologists (ACOG). *Maternal Serum Screening for Birth Defects.* ACOG Education Pamphlet APO89, April 2000.

March of Dimes. Fact Sheet—*Blood Screening for Down Syndrome and Neural Tube Defects.* Available at http://www.marchofdimes.com/professionals/14332_1166.asp

APPENDIX G. SINGLE-GENE DISORDERS

Single gene disorders are among the most well-understood genetic disorders given their straightforward inheritance patterns (recessive or dominant) and relatively simple genetic etiology. Although the majority of these diseases are rare, in total, they affect millions of Americans. Some of the more common single-gene disorders include cystic fibrosis, hemochromatosis, Tay-Sachs, and sickle cell anemia.

Even though these diseases are primarily caused by a single gene, several different mutations can result in the same disease but with varying degrees of severity and phenotype. But even the same mutation can result in slightly different phenotypes. This may be caused by differences in the patient's environment and/or other genetic variations that may influence the disease phenotype or outcome. For example, other genes have been shown to modify the cystic fibrosis phenotype in children who carry the same CFTR mutation. In addition, for some disorders such as galactosemia, mutations in different genes can result in similar phenotypes.

Genetic testing is available for many single-gene disorders, however, the clinical examination is extremely important in the differential diagnosis particularly in patients with no family history. For some genetic conditions, patients can often be treated for their symptoms or modify their diets to prevent the onset of symptoms if diagnosed at an early age (newborn screening). However, despite advancements in the understanding of genetic etiology and improved diagnostic capabilities, no treatments are available to prevent disease onset or slow disease progression for a number of these disorders.

Some useful resources to bookmark include GeneTests and OMIM. GeneTests (<http://www.genetests.org>) is an online genetic testing laboratory database providing information about conditions and laboratory testing services. The Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>) database is a comprehensive resource that provides information about the genetic etiology, clinical symptoms, and a bibliography. Of over 5,000 known genetic conditions, the molecular basis is known in almost 2,000.

CONDITION	GENE (CHR. LOCATION)	INHERITANCE PATTERN
Congenital Deafness (nonsyndromic)	Connexin 26 (13q11)	Recessive
Tay-Sachs	hexosaminidase A (15q23)	Recessive
Familial hypercholesterolemia	LDL receptor (19p13)	Dominant
Sickle cell anemia	Beta-globin (11p15)	Recessive
Duchenne muscular dystrophy	Dystrophin (Xq21)	X-linked Recessive
Cystic Fibrosis	CFTR (7q31)	Recessive
Hemochromatosis	HFE (6p21)	Recessive
Huntington disease	Huntington (4p16)	Dominant



APPENDIX H. CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities may be either numerical or structural. The most common type of chromosomal abnormality is known as aneuploidy, an abnormal chromosome number due to an extra or missing chromosome. Most aneuploid patients have trisomy (three copies of a chromosome) instead of monosomy (single copy of a chromosome). Down Syndrome is probably the most well-known example of a chromosomal aneuploidy, caused by an extra copy of chromosome 21 known as trisomy 21. While a trisomy can occur with any chromosome, the condition is rarely viable. The major chromosomal aneuploidies are trisomy 13, trisomy 18, Turner Syndrome (45, X), Klinefelter syndrome (47, XXY), 47XYY, and 47XXX.

Structural chromosomal abnormalities result from breakage and incorrect rejoining of chromosome segments. A range of structural chromosomal abnormalities that result in disease exist. Structural rearrangements are defined as balanced if the complete chromosome set is still present though rearranged, and unbalanced if there is additional or missing information. Unbalanced rearrangements include deletions, duplications, or insertions of a chromosome segment. Ring chromosomes can result when a chromosome undergoes two breaks and the broken ends fuse into a circular chromosome. An isochromosome can form when an arm of the chromosome is missing and the remaining arm duplicated.

Balanced rearrangements included inverted or translocated chromosomal regions. Since the full complement of DNA material is still present, balanced chromosomal rearrangements may go undetected since it may not result in disease. A disease can arise as a result of a balanced rearrangement if the breaks in the chromosomes occur in a gene, resulting in an absent or non-functional protein, or if the fusion of chromosomal segments results in a hybrid of two genes producing a new protein product whose function is damaging to the cell. For example, a chimeric gene is observed in many cases of chronic myelogenous leukemia as a result of a translocation between chromosomes 9 and 22. Part of the chimeric gene is made up of a proto-oncogene, a gene that normally regulates cell proliferation and differentiation. The disruption of the normal function of this gene results in uncontrolled cell growth leading to leukemia.

APPENDIX I. PHARMACOGENOMICS

Pharmacogenomics is the study of how an individual's genetic make-up affects the body's response to drugs. Pharmacogenomics holds the potential for drugs to be tailored to an individual's genetic make-up, sometimes referred to as "personalized medicine." Environment, diet, age, lifestyle, and health status all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.

The impact of an individual's genetic make-up on drug response and outcome has actually been known since the 1950's but has been re-ignited by the sequencing of the human genome. Genetic variation in drug targets or genes involved in drug disposition can result in a different drug responses and outcomes for a given group of patients treated with the same drug. At this early stage of pharmacogenomics research, the development of clinical tests and targeted drugs is slow due to the limited knowledge of which genes are involved with each drug response. Since many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time-consuming and complicated.



The cytochrome (CYP) P450 family of liver enzymes is responsible for breaking down more than 30 different classes of drugs. DNA variations in genes that code for these enzymes can influence their ability to metabolize certain drugs. Less active or inactive forms of CYP enzymes that are unable to break down and efficiently eliminate drugs from the body can lead to drug toxicity.

It is hoped that new findings from genetic studies will facilitate drug discovery and allow drug makers to produce treatments better targeted to the cause of specific diseases. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells. In addition, physicians will be able to analyze a patient's genetic profile and prescribe the best available drug therapy from the beginning rather than relying on the traditional trial-and-error method of matching patients with the right drugs. Pharmacogenomics aims to improve the likelihood of an improved outcome and reduce risk of serious adverse responses. Pharmacogenomics has the potential to dramatically reduce health care costs associated with the more than 2 million hospitalizations each year in the U.S. as a result of adverse drug response and multiple drug prescriptions and patient visits.



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APPENDIX J. CULTURAL COMPETENCY IN GENETICS

Cultural competency involves attitudes, policies, and structures that enable health professionals to work effectively cross-culturally. The term “cultural competence” represents a process of working towards a greater understanding and respect for different beliefs. It does not imply that anyone can truly achieve full “competence” in any particular culture. Health professionals should have the capacity to value diversity, manage dynamics of difference, and adapt to the cultural contexts of the communities they serve. Health organizations and services should acquire and institute cultural knowledge across all aspects of policy making, administration, practice, service delivery and involve systematically consumers, key stakeholders, and communities.

In genetics, cross-cultural genetic services focus on the health beliefs and cultural customs of the patient and family. Culturally and linguistically appropriate health care services may include interpreter staff, translated written materials, culturally-sensitive discussions about treatment, and knowledgeable clinical and support staff. The provision of these kinds of services has the potential to improve patient outcomes and the efficiency and cost-effectiveness of health care delivery. In particular, reproductive issues and pediatric care may raise culturally-unique issues that require culturally-sensitivity discussions about treatment and care.

While smaller health care facilities may lack comprehensive culturally and linguistically appropriate services, larger health organizations may be able to provide a wider range of services. Please refer to the available genetic specialists and their affiliated institutions in the D.C. Healthcare Alliance Providers Directory.

In addition, the following links may be helpful for health professionals learning about different ethnocultural beliefs and diversity issues:

National Center for Cultural Competencies at Georgetown University Center for Child and Human Development <http://gucchd.georgetown.edu/ncccl/index.html>

Assuring Cultural Competence in Health Care: Recommendations for National Standards and an Outcomes-Focused Research Agenda
<http://www.pcusa.org/nationalhealth/advocacy/standard-hc.pdf>

Cross Cultural Health Care Program <http://www.xculture.org/>

Diversity Rx <http://www.diversityrx.org/>

EthnoMed <http://www.ethnomed.org/>

JAMARDA Resources <http://www.jamardaresources.com/>

The National Multicultural Institute <http://www.nmci.org/>

March of Dimes–GENE (Genetics Education Needs Evaluation) Project
<http://www.marchofdimes.com/geneproject>



APPENDIX K. NATIONAL COALITION FOR HEALTH PROFESSIONAL EDUCATION IN GENETICS (NCHPEG)—PRINCIPLES OF GENETICS FOR HEALTH PROFESSIONALS

NCHPEG's publication *Core Competencies in Genetics Essential for All Health-Care Professionals* (Jan 2001) continues to provide basic guidance to a broad range of individuals and groups as they plan educational initiatives in genetics and genetically based health care. The current document, *Principles of Genetics for Health Professionals*, responds to requests for additional guidance about the content that should constitute basic instruction in genetics for those in health care. The principles focus on basic biology related to genetics.

A. PRINCIPLES RELATED TO BIOLOGICAL VARIATION

1. Genetics is the study of heritable biological variation.
2. Genetics in the health-care setting concerns heritable variation that is related to health and disease.
3. Molecular biology is the study of the structures and functions of macromolecules such as nucleic acids and proteins.
4. Genomics is the study of the constitution of entire genomes; that is, all of the genetic material in an organism.
5. Proteomics is the study of the structure and functions of the protein products of the genes in the genome.
6. Individual genetic variation that leads to biochemical and molecular individuality results in part from the variable sequences of the four bases that are central components of the DNA molecule.
7. Mutations introduce additional variation, but not all mutations have biological significance. Some can be deleterious in varying degrees; others, fewer in number, may provide selective advantages that are useful to evolution. There would be no differential selection, and therefore no evolution, without mutation and variation. This principle helps to explain phenomena such as the emergence of bacterial strains that are resistant to antibiotics, as well as the obvious human differences we recognize in everyday life.
8. Human variation results from the interactions among variable gene products and environmental factors that vary from person to person in kind, duration, and intensity. Variation is expressed at the molecular level in differences in sequences of amino acids and therefore in the structure and function of proteins that maintain physiological systems. It also is expressed in disease, which is a result of some incompatibility between homeostatic variation and the individual's experience with the environment. Because that is the case, genetics and genomics are the most basic sciences for health care and for education of health professionals.
9. There is no fixed type—no archetypical individual—in a species, including *Homo sapiens*. A species comprises a population of unique individuals that may vary in each of their traits, including metabolism, immune responses, morphology, and behavior, and, therefore, in expression of disease.

10. There are no sharp genetic boundaries between populations of human beings around the globe, and there is more genetic variation within populations than between them. These facts make the designation of biological races scientifically untenable and make the grouping of people by phenotypes such as skin color a poor predictor of other traits.
11. The genotype for a given trait is the gene(s) associated with that trait. The phenotype is the expression of the genotype. That expression is mediated by protein gene products that work in the context of experiences with the environment, through development, maturation, and aging.
12. Some human traits, including diseases, result primarily from the action of the product of one gene. Other human traits, including most common diseases, result from the products of more than one gene acting in concert with the influence of environmental variables, which vary in kind, duration, and intensity through time.
13. The development of disease reflects three time frames: a) the evolutionary history—biological and cultural—of our species, which has produced the genome common to all of us; b) the individual developmental history of each person, which interacts with the products of his or her genes, and c) the more immediate factors that results in the expression of disease at a particular moment.
14. The phrase “the gene for,” as in “the gene for phenylketonuria,” can be misleading. It can imply erroneously that only genetic influences are responsible for a given trait or disease, discounting the influence of the environment. The phrase also can suggest that only one gene is associated with a given trait when there may be genetic heterogeneity, of alleles and modifiers, as well as multiple loci. The blood-group substances and hemoglobin variants demonstrate such heterogeneity.
15. Genetically based health care, which now embraces genomics, is uniquely positioned to provide insights into prevention because it acknowledges the individuality of each patient and the biological and environmental influences that produce that individuality. Genetically based care focuses primarily on the person who has the disease, not on the disease itself. It asks, “Why does this person have this disease at this point in his or her life?” and it recognizes that individual variation in genes, development, and experiences means that each person has his or her own version of each disease.

B. PRINCIPLES RELATED TO CELL BIOLOGY

1. Classic cell theory holds that all life is made of cells and that all cells come from pre-existing cells.
2. Cells pass through a series of structural and functional stages known as the cell cycle. The cell cycle, which includes processes leading to cell division, is under genetic control. Cancer results from one or more disruptions in that cell cycle. Because most of these disruptions occur in somatic cells (as opposed to germ cells) all cancer is genetic, but not all of it is inherited.
3. Cell division produces new cells.
4. Mitosis, one aspect of cell division, helps to ensure genetic continuity from one generation of somatic cells to the next. Human somatic cells contain 46 chromosomes (the diploid number): 22 pairs of autosomes and one pair of sex chromosomes (X and Y).



5. Human germ cells, sperm and ova, contain 23 chromosomes (the haploid number). A special process of cell division—meiosis—occurs in the precursors to germ cells. Meiosis has two major biological effects: it reduces the number of chromosomes from 46 to 23 and it increases genetic variation through independent assortment and through the exchange of genetic material between maternal and paternal chromosomes (crossing over). Meiotic variations can result in abnormalities of chromosome number or structure.

6. In *Homo sapiens* and in other animals, the fungi, and plants, cells contain a nucleus that includes the chromosomes, the carriers of most of the genetic material (DNA).

7. Human cells also contain mitochondria. Because mitochondria were free-living organisms early in the evolution of life, they carry their own DNA, which now specifies proteins that are useful to us. Mutations in mitochondrial DNA can cause health problems.

C. PRINCIPLES RELATED TO CLASSICAL (MENDELIAN) GENETICS

1. Our understanding of the behavior of chromosomes during meiosis allows us to make predictions about genotype from one generation to the next.

2. Some traits are inherited through an autosomal dominant pattern of inheritance, others through an autosomal recessive pattern. Still others, those traits associated with genes on the X chromosome, follow somewhat different patterns of transmission because the male has only one X chromosome.

3. Traits, not genes, are dominant or recessive. It is convenient, even traditional, to refer to genes as dominant or recessive, but today it is anachronistic, because of our new knowledge of how protein gene products influence phenotype.

4. Aberrations in the behavior of chromosomes during meiosis can result in structural or numerical alterations that have serious consequences for growth and development. Some of these aberrations occur more frequently in the offspring of older mothers. Others arise more frequently during the formation of sperm. We can detect many chromosomal aberrations prenatally. They account for a significant proportion of fetal death, and to a lesser extent, death in infancy.

5. Our understanding of genes in populations allows us to make predictions about the presence of genes in individuals and in given populations and, therefore, about the variable frequencies of disease phenotypes.

6. During the last two decades, research has uncovered genetic mechanisms that extend our understanding of non-mendelian inheritance and that provide biological explanations for heretofore-unexplained observations. These mechanisms, such as imprinting, trinucleotide repeats, and epigenesis, however, do not alter our fundamental understanding of the rules that govern genetic and molecular processes.

D. PRINCIPLES RELATED TO MOLECULAR GENETICS

1. DNA and RNA are information molecules; they store biological information in digital form in a well-defined code.
2. DNA is the primary information molecule for virtually all life on earth; this is but one piece of evidence for the relatedness of all life through evolution.
3. DNA does very little by itself. It is a stable storehouse of genetic information, but it takes proteins to put the information to use. DNA's transcription and the translation of its information into protein are accomplished by protein-mediated mechanisms. Similarly, the functions of the organs and body are carried out by sets of proteins whose properties and actions are not likely to be understood or predictable by our current knowledge of single genes or proteins.
4. The structure of DNA lends itself to replication. DNA replicates with great accuracy, which is critical to the proper transmission of genetic information from one generation of cells to the next and from one generation of organisms to the next.
5. Sometimes errors arise during DNA replication, and evolution has produced mechanisms that repair such mistakes. In fact, some of those mechanisms present in *Homo sapiens* are conserved evolutionarily all the way back to the bacterium *E. coli*. When repair mechanisms fail, mutations may remain. Some may become the basis for evolutionary change.
6. In most biological systems, the flow of information is: DNA to RNA to protein. The processes by which this occurs are replication of the DNA, transcription of the DNA into messenger RNA, and translation of the messenger RNA into protein.
7. DNA is susceptible to damage by environmental insults such as radiation and certain chemicals, and the damage that occurs to our DNA during the course of our lives can contribute to aging and the onset of cancer. Damage that occurs in the DNA of germ cells—sperm and ova—is not completely repaired. Evolution is a possible result of these new, heritable variations.
8. A gene is a segment of DNA. Some genes code for the production of structural proteins (collagen, for example) or enzymes (lactase, for example). Other genes are regulatory, helping to control such processes as prenatal development and ongoing cellular functions.
10. A gene occupies a particular place on a chromosome—a locus. A gene can have two or more alternative forms—alleles—but only one allele at a time can occupy a given locus on a given chromosome.
11. Because proteins direct the operations of cells, such statements as “gene-environment interaction” are inaccurate. The interaction is actually between the environment—for example, oxygen, food, drug, or antigen—and the protein products of the genes.

E. PRINCIPLES RELATED TO DEVELOPMENT

1. The human life span comprises three major phases: development, including embryological development and growth after birth until maturation; maturation; and aging. Progression through the stages is continuous, however, and apart from birth it is difficult to tell where one ends and the next begins.



2. Although virtually all human beings proceed through the same developmental stages, there are individual differences in the rate of progression.
3. Embryological development begins with the fusion of sperm and ovum. This event restores the diploid number and initiates a complex series of events that involves an increase in the number of cells; differentiation of the zygote into the specialized cells, tissues, and organs that make up a new, individual organism; and growth of the organism itself.
4. Embryological development is under genetic control. That is, particular genes must be turned on and off at the correct time to ensure proper development.
5. Development is not, however, the simple unfolding of a genetic program resulting in a predictable end product. It involves the influence of maternal mitochondrial genes and gene products at the time of fertilization, as well as significant and variable non-genetic factors such as communication between cells, the migration of cells within the developing embryo, the proper spatial orientation of the embryo, and the effects of environmental influences. These factors render the precise outcome of development unpredictable and contribute to the uniqueness of each individual, the hallmark of life on earth.
6. Biologists have discovered a set of genes, called homeotic genes, that are central to embryological development of the body plan. These genes are highly conserved throughout evolution, and the genes even appear in the same order on the chromosomes of species as distantly related as round worms, fruit flies, mice, and human beings. Biologists therefore are able to study the genetic and molecular aspects of human development by studying those processes in other species.
7. The Human Genome Project has provided the complete DNA sequences of all human genes and will allow more detailed analysis of the genetic regulation of development. Likewise, the ability to analyze the protein products of genes involved in development will improve our understanding of the many and varied complex steps that produce a new individual.
8. The evolutionary changes that lead to the production of new species undoubtedly result from rare, beneficial changes during embryological development of individual organisms. Most embryological changes will be small, however, because the system will not tolerate major deviations from the basic developmental plan.
9. Environmental agents such as radiation or drugs can interfere with embryological development, resulting in birth defects and, more likely, fetal death. Various technologies allow detection of some of these abnormalities in utero.
10. Unlike development in species whose newborns are juveniles, development in *Homo sapiens* continues throughout infancy, and there is a long juvenile period. This requires prolonged parental investment and also exposes the still-developing organism to the possibility of environmental insults.
11. Change continues throughout the lifespan in the form of maturation and aging, always building upon, and constrained by, what has come before, and providing the substrate for subsequent events.
12. Some diseases that have their onset in middle age or old age may actually have had their origins much earlier in the individual's developmental history.

F. PRINCIPLES RELATED TO NEW GENETIC TECHNOLOGY

1. Advances in technology allow us to analyze and manipulate the genetic material in ways that were not possible even a few years ago.
2. These technologies allow us to identify, isolate, and test for genes associated with disease, and in the future, perhaps for traits that have no clinical significance.
3. Like all technologies, genetic technologies are fallible, can have unintended consequences, and may serve the interests of entities apart from the patient.
4. The growth of information technology in concert with the expansion of genetic technology is a great boon to genetically based health care and to basic research, but it also raises concerns about the use of genetic information.

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APPENDIX L. CDC–GENOMIC COMPETENCIES FOR ALL PUBLIC HEALTH PROFESSIONALS AND CLINICIANS

EXCERPTED FROM CDC'S GENOMICS COMPETENCIES FOR THE PUBLIC HEALTH WORKFORCE

GENOMIC COMPETENCIES FOR ALL PUBLIC HEALTH PROFESSIONALS

A public health professional within his/her professional field and program is able to:

- Apply the basic public health sciences, (including behavioral and social sciences, biostatistics, epidemiology, informatics, environmental health) to genomic issues and studies and genetic testing, using the genomic vocabulary to attain the goal of disease prevention
- Identify ethical and medical limitations to genetic testing, including uses that don't benefit the individual
- Maintain up-to-date knowledge on the development of genetic advances and technologies relevant to his/her specialty or field of expertise and learn the uses of genomics as a tool for achieving public health goals related to his/her field or area of practice
- Identify the role of cultural, social, behavioral, environmental and genetic factors in development of disease, disease prevention, and health promoting behaviors; and their impact on medical service organization and delivery of services to maximize wellness and prevent disease
- Participate in strategic policy planning and development related to genetic testing or genomic programs
- Collaborate with existing and emerging health agencies and organizations, academic, research, private and commercial enterprises, including genomic-related businesses, agencies and organizations and community partnerships to identify and solve genomic-related problems
- Participate in the evaluation of program effectiveness, accessibility, cost benefit, cost effectiveness and quality of personal and population-based genomic services in public health
- Develop protocols to ensure informed consent and human subject protection in research and human subject protection in research

GENOMIC COMPETENCIES FOR PUBLIC HEALTH PROFESSIONALS IN CLINICAL SERVICES EVALUATING INDIVIDUALS AND FAMILIES

The public health clinician, as appropriate to discipline, agency or program, is able to:

- Apply basic genomic concepts including patterns of inheritance, gene-environment interactions, role of genes in health and disease, and implications for health promotion programs to relevant clinical services

- Demonstrate understanding of the indications for, components of, and resources for genetic testing and/or genomic-based interventions
- Describe ethical, legal, social, and financial issues related to genetic testing and recording of genomic information
- Explain basic concepts of probability and risk and benefits of genomics in health and disease assessment in the context of the clinical practice
- Deliver genomic information, recommendations, and care without patient or family coercion within an appropriate informed-consent process

SELECTED REFERENCE

Centers for Disease Control and Prevention. Office of Genomics and Disease Prevention. Genomics Competencies for the Public Health Workforce. Available at <http://www.cdc.gov/genomics/training/competencies/comps.htm>

