



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.

SELECTED REFERENCES

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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Rothstein M (ed). *Pharmacogenomics: Social, Ethical, and Clinical Dimensions*, Hoboken (New Jersey): John Wiley & Sons, 2003.

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.

Developed by:

Joseph D. McInerney, MA, MS
Executive Director, NCHPEG

Barton Childs, MD
Professor Emeritus of Pediatrics and Biology
The Johns Hopkins School of Medicine

[Reviewed by NCHPEG's working group on content and instruction]



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>

