

**Association of Professors of Human and Medical Genetics  
MEDICAL SCHOOL CORE CURRICULUM IN GENETICS 2010**

***PREAMBLE***

Genetics is among the most rapidly advancing fields in medicine. Genetic mechanisms are now recognized to play a fundamental role in maintenance of health, in the pathogenesis of disease and response to treatment. For this reason, it is essential for every practicing physician in the 21st century to have an in-depth understanding of the principles of genetics and genomics, from basic science to clinical application.

In an effort to ensure that education in the basic science and medical application of genetics is up to date with the latest advances, the Association of Professors of Human and Medical Genetics (APHMG) and the Association of American Medical Colleges have developed recommendations on what constitutes a Core Curriculum for Medical School Genetics Education. The last version of the APHMG recommendations was published in the American Journal of Human Genetics (1995, 56:535-537), and the AAMC report was in June 2004. The American College of Medical Genetics (ACMG) has sponsored periodic reviews of the genetic content on the United States Medical Licensing Examination (USMLE) and confirmed that all of the question topics could be mapped to the Core Curriculum outlined by the APHMG and AAMC documents. Periodic updates are needed to ensure that the curriculum is current for advances in genetics. The revised recommendations here state the fundamental genetics principles with which all graduating students should demonstrate competence.

This document provides guidance to deans, curriculum committees, and course and clerkship directors regarding the competencies that students should demonstrate with respect to the medical genetic knowledge, skills, and behaviors necessary for a future career in medicine.

Given the variety of curricular models employed, each medical school must find the best way to incorporate genetics teaching into its own curriculum. Genetics provides a unique perspective on the function of the human body in health and disease, and education on the topics cited in this proposal can be integrated throughout a four year curriculum.

This updated curriculum has been mapped to a set of educational objectives as required by the Liaison Committee on Medical Education (LCME) utilizing the competencies set forth by the Accreditation Council for Graduate Medical Education (ACGME) as it relates to graduate medical education. It includes specific objectives in the following broad categories:

- Organization of the genome and regulation of gene expression as it relates to medical genetic diagnosis.
- Genetic variation and the implications for diversity of normal variation and disease.
- Principles of inheritance patterns.
- Clinical, ethical and social implications for diagnosis, family health, prediction, and personalized medicine.

- Importance of genetic testing including cytogenetics, molecular genetics, genome scanning, and biochemical genetics.
- Unique features of the genetics for cancer and pre-natal diagnosis.
- Treatment of genetic conditions including family counseling.

Given the rapid advance of medical genetics, this Core Curriculum is a work in progress, and should be updated regularly.

## **I. Medical Knowledge**

### **A. Genome Organization/Gene Regulation**

- Describe the organization of the human genome, and how DNA is packaged into chromatin.
- Describe the organization and distribution of the mitochondrial genome.
- Describe the structure and function of genes.
- Describe the mechanisms and regulation of gene expression including, transcription, translation, *cis* and *trans*-acting factors, micro RNA's, and chromatin structure.
- Define the concept of epigenetics and explain the role of epigenetic mechanisms in regulation of gene expression and development.
- Explain how patterns of gene expression vary during development and differentiation.

### **B. Genetic Variation and Common Disease**

- Describe the types and extent of variation seen in the human genome, including both sequence and structural variation in coding and non-coding sequences.
- Explain the difference between a polymorphism/non-pathogenic and a pathogenic alteration (mutation).
- Describe the nature of mutation and the mechanisms that produce different types of mutation.
- Explain genetic variation with respect to geographic ancestry and evolution.
- Describe how evolutionary conservation of the human genome and proteins clarifies normal and abnormal function in humans.
- Explain how all disease is due to some combination of genetic and environmental factors.
- Compare and contrast the genetic contribution to single-gene disorders vs. common diseases with complex inheritance including the role of both rare, high risk variants and common, low risk variants.
- Describe the principles of genetic linkage analysis and association studies, and how they are used to identify genes contributing to disease and provide information about biological pathways.

### **C. Population Genetics**

- Know the behavior of genetic variation within populations and be able to define the terms founder effect and genetic drift.
- Explain how genetic variants are distributed among individuals in populations.
- Explain genetic risk of a given condition based on carrier status and carrier frequency of a condition within a population.
- Determine carrier frequencies and incidence of recessive conditions using Hardy-Weinberg Laws.

#### **D. Inheritance**

- Explain what is meant by dominant and recessive phenotypes and alleles.
- Explain how factors such as reduced penetrance, delayed age of onset, variable expressivity and pleiotropy affect the phenotypic expression of a disease and the observed pattern of inheritance. Describe the mechanisms that underlie each of these phenomena.
- Describe the underlying genetic mechanisms of non-Mendelian inheritance including somatic and germline mosaicism, uniparental disomy, epigenetics and genomic imprinting, and unstable repeat expansion and contraction.
- Contrast the inheritance of mitochondrial genome to that of the nuclear genome.
- Explain the principles of multifactorial inheritance as they relate to both normal and abnormal human traits.

#### **E. Cytogenetics and Cytogenomics**

- Describe the structure and function of chromosomes. Compare and contrast their replication and segregation in mitosis and meiosis.
- Demonstrate a basic understanding of cytogenetic nomenclature.
- Describe the use and limitations of cytogenomic array technologies for the detection of genomic copy number changes.

#### **F. Cancer Genetics**

- Describe three mechanisms by which single genes predispose to neoplasia:
  1. Oncogenes
  2. Tumor suppressor genes
  3. DNA repair genes
- Describe the molecular genetic mechanisms that underlie cancers:
  1. Germline mutations
  2. Somatic mutations
  3. Epigenetic changes

#### **G. Molecular Genetics**

- Describe the common molecular diagnostic techniques used in molecular diagnostic testing and how they are used in genetic testing (such as Southern blotting, polymerase chain reaction, DNA sequencing)
- Apply the concept of genetic linkage analysis and genome wide association studies to make a prediction of gene status or genetic risk

#### **H. Treatment**

- Define the mechanism of treatment for genetic disease by:
  1. Organ transplantation
  2. Manipulation of a metabolic pathway
  3. Correction or replacement of a defective structural protein or enzyme
  4. Modulation of RNA expression or function
  5. Alteration of DNA sequence
  6. Alteration of gene expression
- Explain the basic theories and techniques for gene therapy, and the barriers to its implementation.

## **II. Patient Care**

### **A. Genome Organization/Gene Regulation**

- Explain how errors in gene expression can result in disease.
- Explain how epigenetic mechanisms regulate normal gene expression and the implication for normal phenotype variation.
- Explain how altered epigenetic mechanisms contribute to disease phenotypes.

### **B. Genetic Variation and Common Disease**

- Explain how phenotypic variability (including penetrance) is influenced by a combination of genetic variation (polymorphism and genomic copy number variation) and environmental influences.
- Describe the concept of a modifier gene and the contribution to phenotype variability.
- Describe the different types of mutations and their functional consequences.

### **C. Medical Genetics/Inheritance**

- Recognize the indications for a genetics evaluation, including family history of disease, congenital anomalies, developmental disability.
- Demonstrate how to take a three-generation family history and draw a pedigree, and from that information recognize and describe the characteristic features of:
  1. Mendelian inheritance (autosomal dominant, autosomal recessive, and X-linked conditions).
  2. Non-Mendelian inheritance (mitochondrial, imprinting).
  3. Unstable repeat expansions.
  4. Cytogenetic translocations.
- Explain how factors such as genetic heterogeneity (locus and allelic), reduced penetrance, delayed age of onset, variable expressivity, pleiotropy, and environmental factors affect the phenotypic expression of a disease and the observed pattern of inheritance.
- Although many Mendelian disorders can be used to demonstrate genetic principles, all students should be able to describe the clinical manifestations and pathophysiology of the following common diseases (adult polycystic kidney disease, cystic fibrosis, Duchenne/Becker muscular dystrophy, familial hypercholesterolemia, Fragile X, Gaucher, hemophilia, Marfan syndrome, Neurofibromatosis, PKU, and sickle cell).
- Estimate recurrence risks for Mendelian and multifactorial disorders in affected families.
- Describe the role of somatic and germline mosaicism in assessing recurrence risk of Mendelian disease.
- Describe the genetic basis of mitochondrial diseases and identify the inheritance patterns for mitochondrial traits.
- Recognize anomalies that result from disordered embryonic development (congenital anomalies):
  1. Group anomalies into clinically recognizable syndrome complexes.
  2. Describe the impact of teratogenic substances and the need to comprehensively evaluate for non-teratogenic causes of malformations.
- Explain the role of genetic testing for diagnostic purposes in the evaluation of a patient, and in predictive and presymptomatic testing.
  1. Explain the differences between a screening and a diagnostic genetic test.
  2. Explain the limitations of genetic testing (ie: a negative test often does not rule out a clinically diagnosed condition).

- Describe the temporally dynamic nature of the interpretation of test results (eg. Comparative Genomic Hybridization techniques).
- Explain the potential for genetics to be used in providing personalized health care with a focus on:
  1. Prevention
  2. Assessment of disease risk
  3. Pharmacogenetics

#### **D. Cytogenetics and Cytogenomics**

- Differentiate the indications for standard cytogenetic karyotype, FISH analysis and cytogenomic array.
- Interpret the results of cytogenetic tests with respect to common numerical and structural chromosome abnormalities, and be familiar with their clinical features and etiologies (trisomy 13, 18, 21, Klinefelter, 45,X, del22q).
- Define mosaicism and explain how it affects the phenotypic expression of a chromosomal disorder.
- Compare and contrast traditional cytogenetic techniques, such as karyotyping with new techniques such as cytogenomic arrays.

#### **E. Cancer Genetics**

- Based on medical and family histories, be able to:
  1. Differentiate sporadic vs. familial vs. hereditary cancers.
  2. Identify individuals at increased personal risk for developing cancer.
- Describe the role of genetic testing, including the benefits, limitations, and ethical implications for:
  1. Cancer patients
  2. Unaffected family members and other individuals at increased risk for developing cancer

#### **F. Reproductive Genetics**

- Describe the role of preconception and prenatal carrier testing for genetic disorders depending on:
  1. Family history of genetic disease
  2. Specific ethnic background
- Describe the process of genetic and non-genetic prenatal testing, including:
  1. The role of medical and family history in determining risk status
  2. 1<sup>st</sup> and 2<sup>nd</sup> trimester ultrasound
  3. 1<sup>st</sup> and 2<sup>nd</sup> trimester analyte testing
  4. Common indications, risks and benefits of chorionic villi sampling and amniocentesis
  5. Implementation and indications for pre-implantation diagnosis

#### **G. Biochemical Genetics**

- Describe the genetic defect, pathogenesis and rationale for different treatment options for disorders involving inborn errors of metabolism and interpret the results of biochemical diagnostic techniques.
- Describe the importance of public health based, mass-screening of newborns for inherited disorders and its paradigm of prediction, intervention and prevention of genetic diseases.

## **H. Molecular Genetics**

- Be familiar with the interpretation of results obtained from various molecular genetic diagnostic techniques used to detect genetic variations and mutations.
- Discuss the benefits, limitations and risks of molecular genetic tests, including the ethical concerns associated with genetic testing and the importance of the informed consent process

## **I. Treatment**

- Recognize how knowing a patient's genotype can be used to identify a more effective treatment. Cite examples in which knowing the genetic basis for disease makes a treatment difference:
  1. Pharmacogenetics:
    - a. Understand how genetic variation can predict response to medications:
      - i. Hereditary disorders
      - ii. Somatic disorders such as cancer
    - b. Understand how genetic variation can effect proper dosing of medications (e.g., warfarin).
    - c. Understand how genetic variation can predict which patients are at increased risk for adverse effects of medications.
  2. Define genotype and describe the impact of genotype on medical management (eg. Long QT syndrome, Connexin 26).
- Describe how modification of non-genetic factors can prevent or mitigate disease in a genetically-predisposed individual.
- Describe how the discovery of the genetic basis of a phenotype leads to a better understanding of the pathophysiology and development of new treatments.

## **III. Interpersonal and Communications Skills**

### **A. Genetic Counseling**

- Describe the role of genetic counselors in patient care.
- Describe and apply the key principles of pre- and post-test genetic counseling with specific emphasis on:
  1. Techniques to convey difficult medical information, recognizing patient defenses, and respecting the autonomy of patients.
  2. Communication of the limitations of genetic testing and the potential for different interpretations of current genetic test results in the future.
  3. The potentially disconcerting nature of genetic information as the concepts of genetics may be unfamiliar and especially anxiety provoking with regard to diagnostic or predictive tests.
  4. Recognize that genetic information may have implications for an individual, a family, or an entire community or ethnic group.
  5. Communication of genetic information appropriate for individuals of different educational, socio-economic, ethnic, and cultural backgrounds.
- Describe when and how to make appropriate referrals for genetics evaluations, to genetics support groups, community groups, or other resources that may benefit the patient and family.

#### **IV. Practice Based Learning and Improvement**

- Demonstrate knowledge and appropriate use of electronic resources for the clinical diagnosis, testing, and understanding of genetic conditions. Resources that are available but not limited to the following:
  1. GeneTests (<http://www.genetests.org>)
  2. Online Mendelian Inheritance of Man (OMIM) (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>)
  3. Pubmed
  4. On-line family history tools
  5. Patient directed resources:
    - a) Genetics Home Reference <http://ghr.nlm.nih.gov>
    - b) Patient support group websites
    - c) National Organization for Rare Disorders (NORD) <http://www.rarediseases.org>
- Demonstrate skills needed for life long commitment to continuing education to stay aware of advances in genetics as they relate to knowledge and changes in medical practice.
- Describe the implications of genetic variation due to geographic ancestry for disease risk, prevention and treatment.

#### **V. Professionalism**

- Explain how genetic information has been appropriately used and misused to impact targeted populations throughout history.
- Describe the rationale behind genetic exceptionalism, and the arguments against it.
- Describe the potential impact of genetic information on personal health and life insurance, and the legislative response to that concern.

#### **VI. Systems Based Practice**

- Population Screening:
  1. Describe the rationale for newborn screening for genetically determined diseases.
  2. Explain the difference between screening and diagnostic testing, and the need for follow up evaluations in the newborn screening process.
  3. Explain how and why specific tests may be targeted towards a defined population.
- Recognize the importance of patient confidentiality especially as it relates to the need to reduce public fear and misinformation about genetics.
- Be aware of local and federal policies regarding the use or misuse of genetic information.
- Describe the issues involved with genetic privacy including the implications of federal and state regulations such as the Genetic Information Non-Discrimination Act (GINA).