Association of Professors of Human and Medical Genetics
MEDICAL SCHOOL CORE CURRICULUM IN GENETICS 2013

APHMG Genetics Competencies Working Group 2012-13:

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INTRODUCTION

Today's physician requires skills to navigate multiple sources of information, judge their validity, decide when and how to apply new scientific findings to their clinical practice, and communicate detailed diagnostic test results to a diverse population of patients. Genetics, previously viewed as a discipline dealing primarily with rare disorders, has experienced a period of dramatic growth that has led to vast increases in our understanding of the fundamental role of genetic mechanisms in health maintenance, disease pathogenesis and treatment response. Many of these advances are attributable to the Human Genome Project and the development of genomic-based technologies. As a result, a comprehensive understanding of the principles of genetics and genomics, from basic science to clinical application, is vital in order for practicing physicians to develop necessary skills and make informed clinical decisions.

In an effort to ensure that medical education reflects our current understanding of genetics/genomics and its impact on medical practice, the Association of Professors of Human and Medical Genetics (APHMG) has developed a Core Curriculum for Medical School Genetics Education [1,2] that has been updated periodically [3]. Here we provide a further update to this core curriculum that reflects advances in genetics and genomics, as well as broader changes in medical training, including the movement towards competency-based education.

Competency-based education (CBE) has attracted renewed attention in recent years [4,5] as a means to ensure that graduating medical students are prepared with the skills required for current medical practice and to meet contemporary healthcare needs. This learner-centered educational paradigm emphasizes outcomes and abilities rather than time in a training program [5]. The Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Medical Specialties (ABMS) established 6 competencies for US residency training [6]. These general competencies are: patient care, medical knowledge, practice-based learning and improvement, professionalism, interpersonal skills and communication, and systems-based practice. The Association of American Medical Colleges (AAMC) adapted these domains for preclerkship clinical skills education in "Recommendations for Clinical Skills Curricula for Undergraduate Medical Education" [7]. Similar frameworks have been adopted by other countries [4,5]. The concept of CBE in medical education was also central to a 2009 joint report by the AAMC and the Howard Hughes Medical Institute that aimed to establish a continuum of specific competencies in the basic sciences for incoming and graduating medical students [8]. The report calls for more competency-based curricula, improved preparation in the basic sciences before medical school, and a greater role of science in the practice of medicine during medical school. While this report urged for competency-based education, its focus was mainly on the domain of Medical Knowledge. Other groups have recently published competencies for foundational sciences in undergraduate medical education, notably for Biochemistry [9]. Currently, the AAMC is embarking upon a "Transition to Residency Competency Project" to develop a description of

measurable clinical skills and clinically relevant scientific skills for which all graduating medical students should demonstrate competence.

With the movement toward competency-based education and the emphasis on active learning, a working group of the APHMG revisited and updated our Genetics Core Curriculum. As this document was developed, we were mindful of the guidance provided by other groups regarding medical education in genetics. The published guidelines for Genetics Education from the AAMC Medical School Objectives Project [10] includes objectives for Knowledge, Attitudes, and Skills that all medical students should demonstrate prior to graduation, and Educational Strategies to foster skills for life-long learning. The European Society of Human Genetics took the approach of categorizing physicians into specialists and non-specialists and developed a set of core competencies for each [11]. Other groups including the National Coalition for Health Professional Education in Genetics (NCHPEG) [2] and the Genetics/Genomics Competency Center for Education [12] have developed competencies for a broader range of health professionals. Although these guidelines are valuable in guiding curriculum development, we felt that a more detailed set of up to date competencies targeted specifically to undergraduate medical students in the United States would be a useful reference and source of standardization for undergraduate medical education in genetics/genomics.

To initiate this process and to identify current trends in medical genetics education, we developed a survey that was administered to 39 North American medical schools. We identified topics of emerging importance that should be included in a medical curriculum (e.g., use of cytogenomic arrays, direct-to-consumer testing and the Genetics Information Nondiscrimination Act) and of topics of declining importance (e.g., linkage studies).

In this current document, we have mapped learning objectives to the ACGME competency domains, and have constructed a set of broad genetics competencies that we believe all graduating medical students should achieve. The intent of this report is to encourage a focus on competency-based education in genetics/genomics and to provide guidance to deans, curriculum committees, and course and clerkship directors regarding the competencies that students should demonstrate with respect to medical genetic knowledge, skills, and behaviors necessary for a future career in medicine.

Given the variety of curricular models employed among medical schools, these guidelines are presented in a way that will allow incorporation into individual curricula, whether genetics be taught as a stand-alone course or integrated in various ways throughout the preclerkship or four-year curriculum. The core curriculum outlined in this document has been organized by the six ACGME competency domains, with broad genetics competencies followed by learning objectives to provide guidance regarding the depth and breadth that should be targeted. The objectives are not intended to be exhaustive, but rather provide a conceptual framework of genetics principles and applications for integration across the four-year curriculum.

MEDICAL GENETICS CORE CURRICULUM

I. MEDICAL KNOWLEDGE

A. Genome Organization/Gene Regulation

Apply knowledge of the human genome structure and function, including genetic and epigenetic mechanisms, to explain how changes in gene expression influence disease onset and severity.

1. Describe the organization of the human genome, including the approximate number of genes, the number of chromosomes, and how DNA is packaged into chromatin.
2. Describe the organization and distribution of the mitochondrial genome.
3. Describe the structure and function of genes.
4. Describe the process and regulation of gene expression, including the steps of transcription and translation, the role of regulatory factors such as transcription factors and noncoding RNAs, and the significance of heterochromatin versus euchromatin.
5. Explain how errors in gene expression can result in disease.
6. Explain how temporal and spatial patterns of gene expression vary throughout the human life cycle, and how gene expression patterns can influence disease.
7. Define the concept of epigenetics, explain the role of epigenetic mechanisms in regulation of gene expression, development and disease, and describe how environmental exposures can influence epigenetic modifications.

B. Genetic Variation:

Apply knowledge of genetic/genomic variation to explain variation in normal phenotypic expression, disease phenotypes, and treatment options.

1. Explain the concept of genetic individuality as it applies to medicine.
2. Describe the types and extent of variation seen in the human genome, including both sequence and structural variation in coding and non-coding sequences (e.g. single nucleotide variants, insertion-deletions, copy number variants).
3. Define the terms mutation and polymorphism and describe their role in both normal human variation and disease.
4. Describe the types of mutations that lead to human disease and their functional consequences, including but not limited to missense, nonsense, frameshift, microdeletion, and splice-site mutations.
5. Explain the basis of genotype-phenotype correlations and how different types of mutations influence clinical outcomes and disease severity.
6. Describe molecular mechanisms of disease, including dominant negative, loss of function, gain of function, haploinsufficiency.
7. Describe the role of allelic variation and its contribution to both normal and pathogenic phenotypic variation.
8. Describe the spectrum of genetic contribution to disease, from disease-causing mutations in Mendelian disorders to genetic and non-genetic susceptibility factors in multifactorial disease.
9. Compare and contrast rare (high risk) vs. common (low risk) genetic variants with respect to their contribution to human health and disease susceptibility.
10. Define the terms pharmacogenetics and pharmacogenomics and explain how genetic variants can affect drug response in individual patients.

11. Describe the principles of genetic linkage analysis and association studies, including the concept of linkage disequilibrium, and how they are used to identify genes contributing to disease. Explain the strengths and limitation of these approaches.
12. Discuss how understanding the pathophysiology of a specific genetic mutation could lead to more effective treatment.
13. Describe the clinical manifestations and pathophysiology of common genetic diseases.

C. Population Genetics

Apply basic concepts of population genetics to explain why allele frequencies vary between human ancestral populations, and to infer and calculate disease risk.

1. Explain genetic variation with respect to geographic ancestry and evolution, and its effect on variation between populations.
2. Explain basic concepts of population genetics, including founder effect and genetic drift.
3. Apply the concepts of the Hardy-Weinberg law to determine genetic risk by calculating carrier frequency, gene frequency and disease frequency.
4. Explain how carrier frequency within populations influences local health care policy and practice.

D. Inheritance

Apply the basic principles of single-gene and multifactorial inheritance to construct a pedigree, interpret a family history, estimate disease risk, and explain phenotypic variation.

1. Compare and contrast Mendelian, monogenic, polygenic, and multifactorial inheritance.
2. Describe the characteristic features of Mendelian inheritance patterns (autosomal dominant, autosomal recessive, X-linked, and Y-linked), and deduce the mode of inheritance from a pedigree.
3. Explain how factors such as reduced penetrance, delayed age of onset, variable expressivity, genetic heterogeneity (locus and allelic), anticipation, pleiotropy and environmental factors affect the phenotypic expression of a disease and the observed pattern of inheritance. Describe the mechanisms that underlie each of these phenomena.
4. Describe the underlying genetic mechanisms of non-Mendelian inheritance, including somatic and germline mosaicism, uniparental disomy, epigenetics and genomic imprinting, unstable repeat expansion and contraction, and chromosomal rearrangements. Explain how these phenomena affect the phenotype and recurrence risk of genetic disorders.
5. Describe the characteristic features of mitochondrial inheritance and explain the role of maternal inheritance and heteroplasmy in mitochondrial diseases.
6. Explain the principles of multifactorial inheritance of normal human traits and the multifactorial nature of complex disorders.
7. Use information in a pedigree to calculate probabilities of transmission for Mendelian traits and diseases.

E. Cytogenetics and Molecular Genetics

Apply knowledge of cytogenetics and molecular genetics to describe the principles, uses and limitations of genetic testing technologies.

1. Describe the structure and function of chromosomes. Compare and contrast their segregation in mitosis and meiosis.
2. Demonstrate a basic understanding of cytogenetic nomenclature.
3. Explain and contrast the uses and limitations of a G-banded karyotype, fluorescence *in situ* hybridization, and cytogenomic arrays, particularly with regard to detection of genomic copy number changes.
4. Describe the types of structural variation seen in human chromosomes (e.g. translocations, inversions, deletions, and duplications), and explain the phenotypic risks associated with these structural variations.
5. Define mosaicism and explain how it affects the phenotypic expression of a chromosomal disorder.
6. Compare and contrast molecular diagnostic techniques used in genetic testing, including (but not limited to) Southern blotting, polymerase chain reaction, DNA sequencing, array comparative genomic hybridization, fluorescence *in situ* hybridization, genomic and expression array-based technologies and next generation sequencing. Explain the utility and limitations of each.
7. Describe the basic concepts of emerging technologies including expression based techniques, exome and whole genome sequencing.

F. Biochemical genetics

Apply knowledge of biochemical pathways and genetic principles to describe, diagnose and treat metabolic disorders.

1. Explain what is meant by an inborn error of metabolism.
2. Describe the underlying genetic defect and pathogenesis for metabolic disorders, such as amino acid disorders, urea cycle defects, lysosomal storage diseases, fatty acid oxidation defects, organic acidurias, and carbohydrate disorders.
3. Describe the underlying mechanisms that contribute to variability in presentation of metabolic diseases, including allelic heterogeneity, environmental factors, and modifier genes.
4. Discuss the rationale for the various approaches to treatment of metabolic disorders.

G. Cancer Genetics

Apply knowledge of genetics/genomics to the development, diagnosis and treatment of cancer.

1. Describe the multistep model of pathogenesis of cancer.
2. Describe the role of oncogenes, tumor suppressor genes and DNA repair genes in the neoplastic process. Explain why germline mutations in these genes are associated with an increased risk of cancer and with inherited and familial cancer syndromes.
3. Differentiate between inherited, familial and sporadic cancers.
4. Compare the genetic/epigenetic mechanisms by which cancers arise, including somatic mutation, epigenetic changes, and germline mutation. Contrast basic laboratory testing strategies for each mechanism.
5. Explain how current cytogenetic and DNA technologies are used to establish the diagnosis, prognosis, treatment and long term follow up of cancer.
6. Explain how genotype of the tumor and/or patient influences rational/targeted drug design and individualized cancer treatment.

II. PATIENT CARE

A. Medical Genetics/Inheritance

Demonstrate the ability to gather family history information, construct and interpret a family pedigree, assess risk for a genetic disorder, and determine when a complete genetics evaluation is appropriate.

1. Recognize the indications to refer for a genetics evaluation, including family history of disease, congenital anomalies, developmental disability, and multiple miscarriages or reproductive failure.
2. Obtain and interpret medical, social, and family histories and physical exam findings in order to determine if a patient is at risk for a genetic disorder.
3. Use a three-generation family history to construct a pedigree and interpret the mode of inheritance.
4. Assess recurrence risks for Mendelian, multifactorial, and mitochondrial disorders.
5. Demonstrate the ability to explain to patients and families the relevance of a genetics evaluation and basic concepts of inheritance.
6. Once a genetic diagnosis has been made, recognize and access appropriate information regarding management and surveillance of the disorder.
7. Recognize that congenital anomalies may have intrinsic or extrinsic causes, and may occur in isolation or part of a pattern. Discriminate between categories of anomalies such as: malformation, deformation, disruption, dysplasia, syndrome, sequence, and association.
8. Provide information about appropriate patient support and resources including genetics support groups, community groups, or other resources that may benefit the patient and their family.

B. Genetic Testing

Identify appropriate indications for genetic testing and recognize the limitations and implications of test results.

1. Recognize the evolving nature and interpretation of genetic testing
2. Explain the roles of screening, diagnostic and predictive genetic testing strategies as components in the evaluation of a patient.
3. Recognize that different tissues and testing strategies may be needed for laboratory diagnosis.
4. Discuss the benefits, limitations and risks of genetic tests, including the ethical concerns associated with genetic testing and the importance of the informed consent process.
5. Explain the potential for genomic testing to be used as a component of personalized health care with a focus on prevention, assessment of disease risk, identification of pharmacogenetic variants and treatment options.
6. Describe the types of test results that are obtained from various genetic and biochemical diagnostic techniques, including positive, negative, ambiguous and variant of unknown significance.
7. Differentiate the indications for standard cytogenetic karyotype, FISH analysis, and cytogenomic array.
8. Interpret the results of a cytogenetic report with respect to common numerical and structural chromosome abnormalities, and recognize their clinical features, etiologies

and prognoses (e.g. trisomy 13, 18, 21; 47, XXY (Klinefelter syndrome); 45,X (Turner syndrome); del 22q; del 5p; etc).

9. Describe the clinical indications of an inborn error of metabolism that would suggest the use of biochemical screening studies such as acylcarnitine profile, plasma amino acids and urine organic acids.
10. Explain how the interpretation and implication of biochemical screening studies are dependent on knowledge of biochemical pathways and the patient specific indications for testing.
11. Recognize clinical scenarios where biochemical testing strategies can provide more clinically applicable results than molecular testing results.

C. Cancer Genetics

Recognize and describe indications for genetic referral for diagnosis, testing, treatment and counseling specifically related to cancer.

1. Differentiate between sporadic, familial, and hereditary cancer based on medical and family history, and identify individuals at increased personal risk for developing cancer.
2. Describe the role of genetic testing, including the benefits, limitations, and ethical implications for cancer patients and their unaffected family members. Recognize that the optimal approach is to test an affected family member first, if available.
3. Recognize the manifestations of common hereditary cancer syndromes.

D. Reproductive and Prenatal Genetics

Recognize and describe indications for a genetics referral for diagnosis, testing and counseling specifically related to prenatal diagnosis.

1. Recognize the indications for preconception and prenatal carrier testing for genetic disorders depending on family history and specific ethnic background.
2. Explain the difference between prenatal screening and diagnosis.
3. Discuss commonly used prenatal screening tests, including first and/or second trimester serum screening, cell free fetal DNA testing, and ultrasound evaluation.
4. Discuss risks, benefits, and limitations of commonly used prenatal diagnostic procedures.
5. Discuss indications for preimplantation genetic diagnosis and the process of implementation.
6. Describe the impact of teratogenic substances on development.

E. Treatment/Management

Apply knowledge of genetic variation and the etiology of genetic disorders to the selection of treatment options and strategies.

1. Describe the following treatment strategies for genetic disease, including when they are best utilized clinically:
    - Organ transplantation, stem cell therapy and regenerative medicine
    - Correction, enhancement, or replacement of a defective structural protein or enzyme
    - Dietary treatment
    - Modulation of RNA expression or function
    - Alteration of DNA sequence

- Alteration of gene expression

2. Explain the basic theories and techniques for gene therapy, and the barriers to its implementation.
3. Describe how modification of non-genetic factors, such as diet, exercise and other lifestyle factors, can prevent or mitigate disease in a genetically-predisposed individual.
4. Explain how genetic variation and knowledge of the patient's genotype might alter medical management of a specific condition.
5. Describe the principles of pharmacogenetics/pharmacogenomics and how they inform dosing of medication by predicting physiological response and adverse drug reactions.

III. INTERPERSONAL AND COMMUNICATIONS SKILLS

Apply knowledge of genetic principles to effectively communicate with patients and professionals regarding genetic information.

1. Describe the role of clinical genetics professionals (e.g. medical geneticists, genetic counselors, clinical laboratory directors) in patient care, and the process for making appropriate referrals for genetics evaluations.
2. Communicate with patients and families regarding genetic information in a culturally sensitive and non-judgmental manner in a way that can be understood by the patient accounting for differences in educational, socio-economic, and ethnic backgrounds.
3. Explain the process for diagnostic and predictive testing of adults and minors, including the risks, benefits, limitations, and implications for other family members, and obtaining informed consent.
4. Clearly communicate family history and medical history pertinent to genetics with an interdisciplinary team of health care professionals.

IV. PRACTICE BASED LEARNING AND IMPROVEMENT

Recognize the strengths and deficiencies in one's own knowledge of medical genetics/genomics, and demonstrate strategies for self-improvement and lifelong learning.

1. Use information technology to obtain reputable current information about genetics. Resources include but are not limited to the following:
   - GeneTests (http://www.genetests.org)
   - Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM)
   - National Human Genome Research Institute (NIH/NHGRI): Health: http://www.genome.gov/Health/
   - NIH Genetic Testing Registry: http://www.ncbi.nlm.nih.gov/gtr/
   - Genetics Home Reference http://ghr.nlm.nih.gov
   - National Organization for Rare Disorders (NORD) http://www.rarediseases.org
2. Demonstrate skills required to stay abreast of advances in genetics that relate to changes in medical practice.

V. PROFESSIONALISM

Demonstrate respect, compassion, accountability and integrity when interacting with and communicating genetic information to patients and peers.

1. Describe how genetic information is different from other medical information and how that difference may affect decisions of health care providers, patients, and their families.
2. Discuss examples of use and misuse of genetic/genomic information and testing results.
3. Recognize the importance of patient confidentiality especially as it relates to the need to reduce public fear and misinformation about genetics.
4. Describe the potential impact of genetic information on insurance coverage and employment status.
5. Demonstrate effective, compassionate and confidential communication regarding genetic information with patients and colleagues.
6. Collaborate with genetics health professionals to provide appropriate care.

VI. SYSTEMS BASED PRACTICE

Explain the ethical, legal and social implications of genetic information, and its impact on public policy.

1. Explain the implications of local, state and federal laws, including the Genetic Information Non-Discrimination Act (GINA), that affect the privacy, confidentiality and potential discrimination related to genetic information.
2. Describe the rationale for newborn and population-based screening, and the factors that are important for a successful genetic screening program.
3. Explain the difference between screening and diagnostic testing and why specific tests may be targeted towards a defined population.
4. Explain implications and limitations of direct to consumer genetic testing, and the need for involvement of a genetics healthcare professional in interpretation of results.
5. Describe the challenges of including genetic information in electronic medical records, including confidentiality, insurance coverage, and other unforeseen issues.

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