

2022 Association of Professors of Human and Medical Genetics (APHMG) consensus-based update of the core competencies for undergraduate medical education in genetics and genomics.

Massingham LJ, Nuñez S, Bernstein JA, Gardner DP, Parikh AS, Strovel ET, Quintero-Rivera F. Genet Med. 2022. Oct: 2167-2179. doi: 10.1016/j.gim.2022.07.014. Epub 2022 August 31. PMID: 36040446.

## Box 1. Medical Knowledge

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### Genome Organization/Gene Regulation

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

1. Compare and contrast the organization of the nuclear and mitochondrial genome, including approximate number of nuclear and mitochondrial genes, how nuclear DNA is packaged into chromatin and the process of replication.
2. Describe the process and regulation of gene expression, including the steps of transcription and translation, the impact of gene structure, and the role of regulatory factors e.g., transcription factors, chromatin modifiers, and non-coding RNAs.
3. Explain how genetic variation, in coding and non-coding regions of the genome, influences gene expression and can result in disease.
4. Describe the concept of epigenetics and explain the role of epigenetic mechanisms in the regulation of gene expression and how it can influence disease. Recognize that some epigenetic modifications can change over time.

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### Genetic Variation

**Section Goal:** Apply knowledge of genetic/genomic variation to explain differences in phenotypic expression, disease phenotypes, and treatment options.

1. Describe the types and extent of variation seen in the human genome, including both sequence and structural variation in coding and non-coding sequences.
2. Describe how allelic variation contributes to both normal and pathogenic phenotypic spectrum. Distinguish between rare variants and common polymorphisms.
3. Describe the ways in which variants occurring within coding regions of the genome affect encoded products (e.g., missense (non-synonymous), nonsense, silent (synonymous), frameshift, and aberrant splicing).
4. Describe the mechanisms by which changes in proteins result in disease. Examples include but are not limited to dominant negative, loss-of-function, gain-of-function, and haploinsufficiency.
5. Describe the spectrum of genetic liability; from monogenic disorders predominantly caused by single genes with large effect sizes, to multifactorial/polygenic disorders caused by genetic and environmental factors with smaller effect sizes.
6. Define pharmacogenetics/genomics and explain how the variants in genes involved in drug transport and metabolism contribute to variability in drug response.
7. Describe the principles of genome-wide association studies and how they are used to identify correlations between genomic regions and disease susceptibility. Explain the strengths and limitations of this approach.

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## Population Genetics

**Section Goal:** Apply concepts of population genetics to explain why allele frequencies vary between human ancestral populations, and how it can be used to calculate an estimated predictive disease risk.

1. Compare and contrast genetic and geographic ancestry with the social constructs of race and ethnicity. Give examples of situations in which race, ethnicity, and ancestry correlate with different genetic and environmental risk factors for disease. Explain how these situations may contribute to incorrect inferences about health in individuals and groups.
2. Explain how concepts of population genetics (including population bottlenecks, founder effects, and natural selection) contribute to allele frequency differences across populations. Discuss how these concepts can alter allele frequencies in the population, leading to increased risk in specific populations.
3. Calculate the estimated genotype frequencies within a population using the Hardy-Weinberg equation and describe how they can be used to predict genetic disease risk and carrier status.
4. Explain how the overrepresentation of individuals of European ancestry in research studies and genetic variation databases limits the transferability of these data to people from other ancestral backgrounds. Recognize the limitations and potential harms of making assumptions about an individual based on perceived ancestry and average population risk.

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## Inheritance

**Section Goal:** Apply the basic principles of monogenic and multifactorial inheritance to interpret a family history, estimate disease risk, and explain phenotypic variation.

1. Describe the characteristic features of monogenic inheritance patterns: autosomal dominant, autosomal recessive, X-linked (including manifesting carrier/skewed X-inactivation patterns), and Y-linked.
2. Explain the concept of genotype-phenotype correlation and how factors such as reduced penetrance (including age-dependent penetrance), variable expressivity, genetic heterogeneity (locus and allelic), pleiotropy, modifier genes, *de novo* pathogenic variants, and environmental factors affect the phenotypic expression of a disease and the observed pattern of inheritance.
3. Describe how mitotic errors result in mosaicism and explain how it affects the phenotypic expression of genomic disorders.
4. Describe the underlying genetic mechanisms of non-Mendelian inheritance patterns: mitochondrial, somatic and germline mosaicism, uniparental disomy, parent of origin (epigenetic and genomic imprinting) and repeat expansion disorders. Explain how these phenomena affect phenotype and recurrence risk.
5. Describe the concepts of mitochondrial inheritance (mtDNA), heteroplasmy, and the threshold effect in mitochondrial disorders.
6. Explain the principles of multifactorial inheritance of normal human traits and polygenic disorders.

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## Cytogenetics and Molecular Genetics

**Section Goal:** Apply knowledge of cytogenetics and molecular genetics to recognize 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. Describe the basic principles of molecular and cytogenetic nomenclature used to report G-banded karyotype, fluorescence *in situ* hybridization (FISH), chromosomal microarray analysis (CMA), and sequencing results.
3. Describe the types of structural variation seen in chromosomes (e.g., translocations, inversions, deletions, duplications, copy number variants, etc.). Utilize the presence of a structural variant to explain an individual's risk for a syndrome, reduced fertility, or spontaneous abortion.
4. Contrast the uses and limitations of cytogenetic techniques that detect aneuploidy and structural variation including G-banded karyotype, chromosomal microarray analysis (CMA), and fluorescence *in situ* hybridization (FISH).
5. Contrast the uses and limitations of molecular techniques that detect nucleotide variants, including Sanger sequencing for single genes, next-generation sequencing for multi-gene, exome, and genome analyses.
6. Contrast the uses and limitations of molecular techniques that detect nucleotide repeat expansions or alternative methylation patterns affecting the epigenome. Examples include PCR of repetitive sequences, Southern blot, array-based methylation, methylation-sensitive PCR, and bisulfite sequencing.

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## Biochemical Genetics

**Section Goal:** Apply knowledge of genetics/genomics to explain the etiology, pathogenesis, diagnostic modalities, and rationale for treatment of cancer.

1. Describe the multistep model of cancer pathogenesis and the role that DNA repair, proto-oncogenic, and tumor suppressor genes play in this model.
2. Recognize the types of genetic and epigenetic changes that can result in gain-of-function of proto-oncogenes or loss-of-function of tumor suppressor genes (e.g., Knudson two-hit hypothesis).
3. Explain how cancer is multifactorial in nature and describe the role of different risk factors in cancer development including germline (high, moderate, and low penetrance) pathogenic variants, familial predisposition, environmental factors (smoking, alcohol, diet, estrogen exposure, radiation/UV light), and chance (i.e., sporadic).
4. Explain why germline pathogenic variants associated with hereditary cancer predisposition syndromes are often characterized by earlier onset of cancer, increased risk of multiple cancers in a single individual and patterns of specific cancers in a family.
5. Describe the application of current somatic/tumor and germline testing (cytogenetic, molecular, and epigenetic technologies) to clarify the mechanism of tumorigenesis, evolution, diagnosis, and prognosis of cancer.
6. Describe how genetic testing of the tumor and/or germline can lead to individualized and targeted cancer therapies (precision medicine), and/or long term follow up. Explain the mechanisms of action of these therapies (e.g., Inhibitors of: PARP, PD-1/PD-L1, IDH1/2, tyrosine kinases).

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## Box 2. Patient Care

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### Medical Genetics/Inheritance

**Section Goal:** Demonstrate the ability to gather family history, construct and interpret a family pedigree, assess risk for a genetic disorder, and determine when a clinical genetics evaluation is appropriate.

1. Explain the rationale for referring a patient for a clinical genetic evaluation based upon medical history and physical exam findings that may include congenital anomalies, neurodevelopmental phenotype, unusual physical features or stature, multisystemic disease, early onset, bilateral or atypical disease, and multiple miscarriages or reproductive failure.
2. Use the family history to evaluate indicators for clinical genetics referral including multiple affected family members with the same or significantly overlapping clinical presentation for example: physical findings, developmental delay/intellectual disabilities, clustering of cancers, multiple miscarriages, fetal or early childhood deaths, or sudden cardiac death.
3. Use a family history to construct a three-generation pedigree and interpret for possible mode(s) of inheritance (Mendelian, multifactorial, and mitochondrial) and assessment of associated recurrence risks. Apply the most up-to-date guidelines to document family history using inclusive practices to indicate gender identity, family structure, use of assisted-reproduction technologies, and/or adoption.
4. Recognize that congenital anomalies may have intrinsic or extrinsic causes, may occur in isolation or part of a pattern, and that these anomalies (malformation, deformation, and disruption) may be part of a syndrome, sequence, and association.

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## Genetics and Genomic Testing

**Section Goal:** Identify appropriate indications for genetic and genomic testing for diagnostic and screening purposes. Recognize the implications and limitations of these test results.

1. Explain the difference between screening (i.e., noninvasive prenatal screening (cell-free DNA), newborn screening, carrier screening), and diagnostic or predictive genetic and genomic testing strategies as components in the evaluation of a patient.
2. Discriminate between testing strategies with respect to the type of tissues evaluated (somatic vs. constitutional /germline).
3. Recognize that the optimal approach is to test an affected family member first (informative vs. uninformative testing result) and that predictive genetic testing of unaffected and/or asymptomatic family members has ethical considerations.
4. Select genetic tests most appropriate for a patient's suspected diagnosis. Recognize that testing can result in differences in management (including preventive screening, changes to medication/dosing, surgery).
5. Interpret the results of a cytogenetic (G-banded karyotype, FISH or microarray) 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); 22q11.2 deletion syndrome (DiGeorge syndrome); 7q11.23 deletion (Williams syndrome), deletion 15q11.2 ( Prader-Willi/Angelman syndrome).
6. Recognize the role of biochemical screening studies (e.g., plasma ammonia, plasma acylcarnitine profile, plasma amino acids, and urine organic acids) in the diagnosis of an inborn error of metabolism. Interpret the results in the context of the patient's clinical presentation.
7. Compare and contrast the value, sensitivity, and specificity of molecular and biochemical testing strategies in the diagnosis and management of metabolic disorders.
8. Recognize the benefits and limitations of direct-to-consumer and consumer-initiated testing and how they may impact the patient experience and their care.

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## Cancer Genetics

**Section Goal:** Describe indications for genetic referral related to cancer diagnosis, testing, treatment, and counseling.

1. Assess the likelihood of a hereditary cancer predisposition by evaluating an individual's personal and family history of cancer, including early age of onset of cancer, affected family members, multiple primary cancers, and type of cancer (e.g., *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer, Lynch syndrome).
2. Recognize phenotypic characteristics of syndromic conditions with increased cancer risk that may benefit from a genetic evaluation (e.g., Peutz-Jeghers Syndrome, *PTEN*-Hamartoma Syndrome, Neurofibromatosis Type 1, Tuberous Sclerosis Complex).
3. Recognize the benefits of germline testing in families with hereditary cancer predisposition syndromes including opportunity to improve disease surveillance in genotype positive but asymptomatic family members, provision of surgical and/or other treatment options based on the known patterns and penetrance (high/moderate/low risk) of the cancer type.

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## Reproductive and Prenatal

**Section Goal:** Describe indications for a genetics referral for prenatal genetic counseling, testing, and diagnosis.

1. Recognize the indications and limitations for carrier screening including test characteristics, carrier frequency, and personal/family history.
2. Discuss benefits, and limitations of currently used prenatal screening approaches, including: first and second trimester serum screening, noninvasive prenatal screening, and ultrasound evaluation.
3. Discuss risks, benefits, and limitations of invasive prenatal diagnostic techniques including chorionic villi sampling, amniocentesis, and cordocentesis.
4. Discuss indications for preimplantation genetic testing.
5. Recognize the impact of teratogens (e.g. alcohol, drugs, infectious agents, hyperglycemia secondary to maternal diabetes) on embryonic development, including the effect of dosage, timing and duration of exposure.

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## Treatment and Management

**Section Goal:** Apply knowledge of the genetic disease etiology to the selection of treatment options and management.

1. Outline the principles for management of genetic diseases and describe their appropriate application based on disease pathogenesis. Examples include correction, enhancement or replacement of a defective structural protein or enzyme, dietary treatment, modulation of RNA expression or function, alteration of DNA sequence to modulate gene expression using techniques such as genome editing for somatic and germline therapies, organ transplantation, and stem cell therapy.
  2. Define gene therapy and explain the current techniques. Outline scientific, ethical, and clinical obstacles to widespread implementation of gene therapy.
  3. Recognize how identification of a specific pathogenic variant in an individual could lead to targeted treatment and/or management of disease. Some examples include: *BCR-ABL1* fusion (tyrosine kinase inhibitors such as imatinib), *PML-RARA* fusion (all-trans retinoic acid (ATRA)), exon amenable skipping for Duchenne muscular dystrophy (*DMD*, exon 51- eteplirsen), cystic fibrosis (*CFTR*, G551D- ivacaftor).
  4. Explain how the presence of specific genetic variants that affect drug transport or metabolism in an individual patient (pharmacogenetics) may predict physiological response or adverse reactions to medications and influence medical management. Some examples include: *CYP2C19* (clopidogrel), *CYP2C9* (warfarin), *HLA-B\*1502* (carbamazepine). Refer to PharmGKB.org as a good resource for drug specific information.
  5. Recognize the emerging role of polygenic risk scores in complex conditions and describe how modifications of lifestyle and environment can prevent or mitigate disease in genetically predisposed individuals. Recognize that there may be limited portability of polygenic risk scores developed using data from individuals of one ancestry to individuals of other ancestries.
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**Box 3.** Interpersonal and Communication Skills, Practice Based Learning and Improvement, Professionalism, and Systems Based Practice

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**Interpersonal and Communication Skills**

**Section Goal:** Effectively communicate with patients and healthcare professionals, in an inclusive and sensitive manner, providing clear and understandable information about genetic principles and inheritance.

1. Address fears and concerns of patients and family members regarding genetic testing in order to enable informed decision-making in a respectful, sensitive, and non-directive manner.
2. Describe the role of clinical genetics professionals (e.g., medical geneticists, genetic counselors, clinical laboratory geneticists) in patient care and the process for making appropriate referrals for genetic evaluations.
3. Demonstrate the ability to explain to patients and families the rationale for a genetic evaluation and basic concepts of inheritance.
4. Explain to the patient/family the rationale behind genetic evaluation and the components of genetic testing as they relate to informed consent. These components include potential risks, benefits, and limitations of different types of results (i.e., diagnostic, non-diagnostic, variants of uncertain clinical significance, and secondary findings).
5. Recognize the relevance of patient autonomy in the informed consent/assent for genetic testing of minors (i.e., the unique implication of testing the minor for an adult-onset disorder).
6. Communicate family history and medical history pertinent to genetics with an interdisciplinary team of healthcare professionals.
7. Evaluate personal knowledge and expertise about genetic counseling and testing to decide if and when to initiate pre-test counseling and genetic testing or to refer for specialty services.

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**Practice Based Learning and Improvement**

**Section Goal:** Recognize the strengths and deficiencies in one's own knowledge of clinical genetics and genomics and adopt strategies for self-improvement and lifelong learning.

1. Access reputable resources regarding genetic conditions to inform management and surveillance recommendations. Some resources include: GeneReviews, OMIM, NHGRI Talking Glossary of Genetic Terms, NCBI Genetic Testing Registry, MedlinePlus-Genetics, National Organization for Rare Disorders (NORD), Understanding Rare Chromosome and Gene Disorders (UNIQUE).

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**Professionalism**

**Section Goal:** Demonstrate respect, empathy, accountability, and integrity when interacting with and communicating genetic information to patients, families, and healthcare professionals.

1. Explain how a patient's autonomy (including their own privacy and confidentiality) can conflict with the healthcare provider's duty to warn potentially at-risk family members about genetic health risk.
2. Demonstrate compassion and respect regarding the potential socio-emotional impact of disclosing predictive genetic testing results to patients and families.
3. Validate the individual identity of patients by recognizing how their unique characteristics may influence their decisions regarding genetic testing and management.

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**Systems Based Practice**

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

1. Explain the rationale for inclusion of a disease in a newborn screening program and the criteria that are important for a successful genetic screening program.
  2. Describe ethical challenges related to genetic information, including ensuring privacy and potential discrimination, and the ways in which the Genetic Information Non-Discrimination Act (GINA) aims to address some of these issues.
  3. Identify historical examples of how incorrect assumptions about correlations between the social construct of race and genetic ancestry have been used to justify inequitable and unjust policies and practices in health care and society more widely. Propose ways to minimize these harms in the present and future.
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