Canadian College *of* Medical Geneticists
Collège canadien *de* généticiens médicaux

CCMG General Knowledge Training Guidelines

Topic	Objectives	Specific knowledge and skills ***By the end of training, all Trainees will be able to:***
1. Human genome structure and heredity	Understand general concepts related to the human genome and inheritance of DNA	a. Describe the information content of the human genome and the elements that predispose to mutation b. Describe the structure of DNA, how it is replicated and maintained (DNA repair mechanisms) c. Describe the chromosomal structure of the human genome d. Describe stages of cell division for mitosis and meiosis e. Describe the medical relevance of mitosis and meiosis f. Describe human gametogenesis and fertilization and the transmission of genomic material
2. Human gene structure and function	Understand general principles of human genetics at the gene level	a. Explain the organization and structure of genes (exons, introns, promoter regions, enhancers, silencers, etc.) b. Explain basic gene expression: transcription through to translation c. Explain gene regulation including transcription, splicing, variation of gene expression between tissues and relevance to medicine and the role of non-coding RNAs d. Explain post-transcriptional mechanisms including post-translational modifications

3. Mendelian single gene inheritance	Understand general concepts of single gene disorders and factors influencing these disorders	a. Describe Mendel's laws of inheritance b. Describe basic principles of Mendelian inheritance c. Understand concepts of penetrance, expressivity, anticipation, hypomorphic alleles and pseudodeficiency d. Explain how epigenetic factors influence phenotype e. X-linked inheritance : describe the effect skewed X-inactivation may have on clinical phenotype in females f. Demonstrate ability to analyze pedigrees for inheritance patterns g. Give examples of conditions where genotype correlates with phenotypic severity
4. Molecular genetics concepts and testing methods	Understand general principles of molecular biology as applied to human health	a. Understand the basic principles of the polymerase chain reaction b. Understand the concepts of nucleic acid sequencing, including Sanger and massively parallel sequencing c. Understand the concepts of targeted assays versus scanning methods d. Understand the basic principles of nucleic acid hybridization assays (e.g. Southern blot, Northern blot) e. Understand the limitations associated with molecular methods (allele drop-out, primer polymorphisms, large deletions etc.) f. Describe the concept of sample identity testing and use as an adjunct method to establish relationship between samples (i.e. maternal cell contamination, sample identity matching) g. Describe mutations using appropriate nomenclature (e.g. HGVS)
5. Significance of gene mutations	Understand general concepts of pathogenicity of genetic variation	a. Describe different classes of gene mutations (missense, nonsense, frameshift, splicing) and their effect on transcription, translation and protein function b. Ascribe clinical significance to different types of gene variants
6. Non-mendelian inheritance	Understand principles of non-Mendelian inheritance	a. Describe common non-Mendelian inheritance and their etiologies, including uniparental disomy, imprinting, mosaicism, unstable triplet repeats, pseudoautosomal inheritance, etc.

		b. Describe implications of non-Mendelian inheritance on genetic diagnostic testing c. Describe implications of non-Mendelian inheritance for clinical genetics including pedigree analysis and counselling
7. Mitochondrial inheritance	Understand principles of mitochondrial inheritance	a. Describe the structure and inheritance of the mitochondrial genome and gene expression b. Understand the basis for clinical heterogeneity in mitochondrial DNA defects c. Describe the role of nuclear and mitochondrial genes in mitochondrial disease d. Describe general features of mitochondrial disorders (multisystemic etc.) e. Recognize maternal inheritance from pedigree information.
8. Pharmacogenomics	Understand principles of pharmacogenomics	a. Describe the concept of drug responsiveness risks and benefits based upon genotype
9. Cytogenetic concepts and tests	Understand general principles of human cytogenetics as applied to human health	a. Describe general principles of cytogenetic methods for chromosome analysis, including karyotyping, genomic copy number assessment and spectral karyotyping. b. Describe appropriate indications for cytogenetic testing c. Distinguish between common cytogenetic variants and pathogenic rearrangements d. Describe general concepts of autosomal and sex chromosomal abnormalities (aneuploidy, translocations, etc.) e. Describe the meiotic segregation of rearranged chromosomes and the effects of recombination events. f. Describe general concepts of sex chromosomal abnormalities (aneuploidy, translocations etc.) g. Describe parent of origin effects and relevance to chromosomal abnormalities h. Describe etiology of chromosome abnormalities (non-disjunction, breakage and repair, non-homologous recombination, uniparental disomy) i. Understand uses and limitations of cytogenetic tests including the limits of

		detection of mosaicism j. Understand the effect of mosaicism on phenotype k. Understand use of appropriate nomenclature (e.g. ISCN)
10. Genomic microarray and copy number analysis	Understand principles and techniques associated with change in copy number analysis	a. Describe the appropriate indications for copy number analysis b. Describe the different techniques that can be used to detect copy number changes including array (CGH, SNP), FISH, qPCR, MLPA, whole genome sequencing; describe the limitations of each including the types of mutations detected c. Understand and describe when additional studies are required to complement or confirm microarray results d. Describe the basic principles used to ascribe clinical significance to copy number changes
11. Cancer genetics	Understand general principles of human cancer cytogenetics and molecular pathology	a. Explain concepts of multistep pathogenesis of cancers including inherited predisposition, oncogene activation, tumor suppressor inactivation, alteration of cell cycle control and DNA repair genes b. Explain and contrast inherited versus somatic mutations c. Describe methods to detect gene expression d. Describe principles of recurrent rearrangement detection using molecular or cytogenetic methods e. Describe the relevance of cytogenetic and molecular analysis to cancer diagnosis, prognosis and monitoring
12. Biochemical genetics	Understand broad categories of Inborn errors of metabolism	a. Describe the structure and functional relationships of intracellular components: nucleus, Golgi, endoplasmic reticulum, mitochondria, lysosomes, peroxisomes b. Describe the different categories of proteins in a cell (structural, enzymes, transport, receptor proteins etc.), their modes of action and means of regulation c. Describe biochemical consequences of a primary enzyme block in a metabolic pathway and the way clinical and pathological signs may be produced. d. Describe the major categories of inborn errors of metabolism: amino acid

		disorders, urea cycle disorders, organic acid disorders, fatty acid oxidation defects, lysosomal storage disorders, mitochondrial disease and peroxisomal disorders e. Understand principles of newborn screening f. Understand concept of pseudo-deficiency (ie. lysosomal disorders) g. Understand the deleterious effects of toxic metabolites on the fetus (e.g., maternal PKU)
13. Complex disorders	Understand the genetic contribution to complex human disease	a. Describe qualitative and quantitative traits; provide examples b. Describe the effect of genetic and environmental modifiers on single-gene disorders c. Define the concepts of multifactorial inheritance including liability model, threshold effects, epistasis, heritability and concordance d. Describe evidence for a genetic contribution to complex traits and common disorders e. Contrast the relative recurrence risks for multifactorial inheritance with single gene disorders and factors that affect risk (such as degree of relationship, sex, severity)
14. Population genetics	Understand concepts of human population genetics	a. Describe key concepts of human genetic variation in populations, including the role of ethnicity and population isolates in human variation b. Describe the Hardy-Weinberg equilibrium c. Demonstrate ability to use the Hardy-Weinberg equilibrium to assess genetic risk d. Understand concepts of population screening and when appropriate to offer screening
15. Genetic counseling	Understand key concepts in genetic counseling and risk assessment	a. Describe common indications for genetic counseling b. Describe the purpose of genetic counseling in specific scenarios c. Describe concepts of counseling: non-directive, awareness of values and biases

16. Risk assessment and calculations		a. Basic Bayesian analysis: demonstrate ability to modify *a priori* risk by one conditional factor b. Calculation of Odds ratios c. Understand basic test performance characteristics: sensitivity, specificity, positive predictive and negative predictive value
17. Developmental genetics and birth defects	Understand key steps in human development	a. Understand key concepts in developmental biology as it relates to normal and abnormal human morphogenesis b. Understand the concepts of morphogenesis, differentiation, pluripotency, specification, determination, embryonic induction, competency, and signal transduction. c. Describe the processes involved in early embryogenesis: fertilization to gastrulation d. Describe the major embryonic cell lineages and the distribution in the fetus and extra-embryonic tissues
18. Prenatal diagnosis	Understand principles of prenatal screening, prenatal diagnosis and related methodologies	a. Articulate the principles of a prenatal screening program b. Differentiate prenatal screening from prenatal diagnosis c. Describe the advantages, disadvantages and limitations associated with prenatal karyotyping, and prenatal rapid aneuploidy detection (RAD) by qfPCR or iFISH d. Describe the advantages and disadvantages of amniocentesis and chorionic villus sampling. e. Describe the risks, benefits, limitations and controversies surrounding the use of emerging technologies such as: • Non-invasive prenatal testing • array CGH on a prenatal sample • exome sequencing on a prenatal sample f. Describe genetic factors that contribute to recurrent pregnancy loss g. Understand the impact of teratogen exposure (e.g. infection, alcohol, medications) and maternal disease (eg. maternal PKU) on fetal development

19. Clinical Genetics	Understand broad categories of genetic conditions and their methods of assessment.	a. Describe methods of assessment of phenotypic variations, syndrome identification and diagnosis, including generally accessible computer diagnostic aids (e.g. OMIM) b. Understand the concept of syndrome and be able to give examples of syndromes associated with the following clinical manifestations: • dysmorphology • Cancer • Neurogenetic conditions • Cardiac genetic conditions • Imprinting disorders • Inborn errors of metabolism (major categories) • Chromosomal syndromes and genomic disorders characterized by recurrent microdeletions and microduplications c. Describe and understand the distinction between genetic screening and genetic testing d. Describe and understand the distinction between genetic testing for the purpose of diagnosis and predictive testing to assess risk for predisposition to monogenic or complex genetic diseases as well as their applications and limitations.
20. Ethics		a. Describe privacy and confidentiality principles as it relates to general practice (e.g. communication with health care providers, reporting, database searches), b. Describe ethical issues that relate to genetic testing in childhood c. Describe informed consent and its role in genetic testing d. Describe issues that relate to consenting for genomic analysis e. Explain incidental finding and provide examples from common tests (not large scale NGS-based sequencing) in which an incidental finding may be uncovered f. Outline the implications related to reporting and/or not reporting incidental findings and secondary findings (actively searching for disease-related pathogenic mutations not related to a patient's indication for testing) g. Describe ways to reduce the risk of incidental findings

		h. Describe the principles of biobanking

Recommended Texts and References:

Thompson and Thompson: Genetics in medicine 7th Edition
Strachan and Read: Human Molecular Genetics
Leonard, Debra: Molecular Pathology in Clinical Practice
Firth, Helen and Hurst, Jane: Oxford Desk Reference Clinical Genetics
Milunsky and Milunsky: Genetic Disorders and the Fetus
Moore, Persaud: The Developing Human
Emery and Rimoin: Essential Medical Genetics
Gardner: Chromosome abnormalities and Genetic Counseling.