MEDICAL GENETICS RESIDENCY PROGRAM
Department of Pediatrics

University of Michigan Health Systems
1500 E. Medical Center Drive
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Ann Arbor, MI 48109-5718

(734) 763-5405/(734) 232-0366
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Biochemical Genetics Goals and Objectives

Director: Elizabeth Ames

The goals and objectives of the Biochemical Genetics rotation is to provide the resident with exposure to all aspects of care of metabolic disease and counseling in accordance with the Residency Review Committee for Medical Genetics expectations and to fulfill criteria for board eligibility by the American Board of Medical Genetics and Genomics.

Patient Care

The resident will become familiar with the evaluation, diagnosis, and management of patients with inborn errors of metabolism including disorders of intermediary metabolism like urea cycle disorders, organic acidemias, disorders of carbohydrate and lipid metabolism, organelle related disorders and numerous other inborn errors of metabolism (IEMs). Residents will gain exposure in performing and expertise in interpreting biochemical analyses relevant to the diagnosis and management of biochemical disorders.

By the end of the rotation the resident should be able to identify signs and symptoms of IEMs, formulate a differential diagnosis, order appropriate tests, and recognize normal variants and complex patterns of metabolites. Residents will be able to manage acute metabolic crises and provide chronic management of patients with an IEM.

Residents should be able to interpret NBS results, collaborate with the primary provider to act upon results in a timely manner, develop a differential diagnosis and order appropriate confirmatory testing and communicate results to families.

Medical Knowledge

Through coursework and didactic sessions with attending physicians, residents will become familiar with fundamental concepts, molecular biology, and biochemistry relevant to IEMs. Residents will also interpret biochemical assays and be familiar with specific metabolites altered in disorders listed above. Residents will become familiar with laboratory procedures and fundamental biochemistry that encompass screening tests, newborn screening, diagnostic tests, technical procedures, quality assurance and interpretation of biochemical genetics results, including recognition of common laboratory test artifacts and normal variants. Residents will develop broad knowledge of basic biochemistry and biology, the application of biochemical methods through the diagnosis and management of genetic diseases and an understanding of the etiology, pathogenesis, clinical manifestations, and management of IEMs.

Residents will be able to formulate and finalize a care plan for a patient with an IEM and apply practice guidelines as appropriate.

Principles of Metabolic Abnormalities: Biochemical Genetics

Residents will gain expertise in interpreting biochemical analyses relevant to the diagnosis and management of human genetic diseases and will develop broad knowledge of basic biochemistry and biology, the application of biochemical methods through the diagnosis and management of genetic diseases and an understanding of the etiology, pathogenesis, clinical manifestations, and management of human inherited biochemical disorders. Residents will learn to apply appropriate diagnostic and therapeutic modalities in the management of inpatients with metabolic disease crises and to provide clinical care directed at selected biochemical disorders.

Objectives:

- Know what is meant by an inborn error of metabolism.
- Understand how to approach and manage infants and children with metabolic disorders in both emergent and chronic situations.
- Become familiar with initial and long-term management issues for the following metabolic disorders including issues related to pregnancy.
- Be familiar with the symptoms, referral basis, history, diagnosis, and management of:
    - Phenylketonuria
    - Galactosemia
    - Homocystinuria
    - Lysosomal Storage Disorders
    - Wilson's Disease
    - Tay Sachs
    - Gaucher Disease
    - Hemochromatosis
    - Maple syrup urine disease
    - Biotinidase deficiency
    - Glycogen storage diseases
    - Disorders of glycoprotein metabolism (CDG)
    - Disorders of peroxisomal biogenesis
    - Urea cycle disorders
    - Disorders of fatty acid oxidation or lipid cholesterol metabolism
    - Organic acidemias
    - Disorders of creatine synthesis
- Understand teratogenic risks of maternal PKU
- Recognize newborn screening metabolites; describe evaluation for abnormal newborn screens
- Gain familiarity with how to identify clinical trials that patients are eligible for
- Be able to counsel patients and families about generals risks and benefits of new and emerging therapies such as ASOs and gene therapy

Mitochondrial Genetics

Objectives:

- Understand the essential nature and functions of mitochondria in metabolism.
- Understand the concept of heteroplasmy.
- Understand the inheritance pattern of mitochondrial diseases.
- Be able to recognize pedigrees and symptoms that may suggest mitochondrial disorders.
- Know how to work-up and manage mitochondrial disorders.
- Learn the counseling issues related to inheritance, penetrance, and expressivity of mitochondrial diseases.
- Know the common mitochondrial diseases and their varied presentations.

Practice-Based Learning & Improvement

Residents will learn to apply appropriate diagnostic and therapeutic modalities in the management of inpatients with metabolic disease crises and to provide clinical care directed at selected biochemical disorders.

Residents will assess self-performance and develop a learning plan.
Residents will critically evaluate and utilize information from diverse sources.
Residents will identify areas for improvement in individual practice.

Interpersonal & Communication Skills

Residents will display effective communication with ordering and consulting physicians and laboratory directors and will have opportunities to improve their communication skills in the laboratory setting.

Residents will display effective communication and relationship development with families and health care team members.

Residents will exhibit the ability to manage conflicts with patients/families and health care teams and participate in team-based care (includes dieticians, social workers, nurses, lab personnel, other physicians, etc).

Residents will exhibit the ability to communicate general and sensitive information with awareness of the social context, demonstrate sensitivity to cultural values in communicating information and be able to provide appropriate information and resources to patients and families with an IEM.

Professionalism

Residents will interact closely with other clinical staff and learn their responsibilities and tasks. Residents will learn how clinical staff communicate with other hospital and laboratory personnel.

Residents will demonstrate caring, honest, and sensitive behavior in all relationships and situations.

Residents should display the ability to manage personal beliefs to avoid any negative impact on patient care and be able to recognize and manage ethical issues in genetics practice.

Residents should complete professional responsibilities in a timely manner.

Residents are expected to recognize limits of their own knowledge and ask for assistance when needed.

Residents should be able to identify and manage situations in which maintaining personal emotional, physical, and mental health is challenged by common and typical clinical care situations.

Systems Based Practice

Residents will learn costs and benefits of diagnostic and therapeutic modalities in the management of patients with IEMs and how these costs are transferred to insurance providers.

Residents will learn to function effectively within different systems; and be able to incorporate and advocate for genetic services to enhance cost-effectiveness of care. Residents should be able to recognize and manage the variation in access to genetic testing; facilitate management and transitions of care teams as the patient ages and participate in identifying system errors and implementing potential systems solutions.

Residents will be able to document essential elements of genetics encounters for patients with IEMs to enhance the transfer of information and patient safety; and utilize decision support tools.

Biochemical Genetics Laboratory Goals and Objectives

Director: Drs. Ayesha Ahmad, Shane C. Quinonez, and Lidong Zhai

The goals and objectives of the Biochemical Genetics Laboratory rotation in the Medical Biochemical Genetics Fellowship Program are to provide the fellow with exposure to the laboratory diagnosis of inborn errors of metabolism. The laboratory rotation will take place in the Biochemical Genetics Laboratory which is part of the Michigan Medical Genetics Laboratory at Michigan Medicine. The Biochemical Genetics Laboratory runs over 1,000 patient samples annually and continues to expand its test catalog. The current test catalog includes plasma amino acid analysis (HPLC), urine organic acids (GCMS), serum methylmalonic acids (LCMS/MS), biotinidase enzyme activity (spectrophotometric analysis), and acylcarnitine analysis (LCMS/MS).

Patient Care

Fellows will be responsible for the interpretation of all biochemical laboratory results run in the biochemical genetics laboratory during their rotation. All interpretations will be reviewed with a laboratory director. Fellows will also be responsible for interpretation of previous years' CAP samples.

Medical Knowledge

Fellows will become familiar with the biochemical laboratory abnormalities and diagnosis of urea cycle disorders, organic acidemias, disorders of carbohydrate and lipid metabolism, lysosomal storage disorders, peroxisomal storage disorders and various other inborn errors of metabolism (IEMs). During their time on the rotation fellows will be responsible for receiving, preparing, running, and interpreting patient samples run in the laboratory. Fellows will gain experience with all tests in the biochemical genetics laboratory catalog. Fellows will be responsible for organizing and directing the biweekly biochemical genetics signout meeting where previous weeks' cases are reviewed with on-call attendings, dieticians, and trainees. Fellows will be responsible for select chapters of the textbook *Physician's Guide to the Laboratory Diagnosis of Inherited Metabolic Diseases.* Fellows will understand the technology, limitations, and turnaround time of all biochemical tests run in the biochemical genetics laboratory.

Practice-Based Learning & Improvement

Fellows will be exposed to the quality improvement and quality assurance practices of the biochemical genetics laboratory. This also includes CAP and ERNDIM (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism) sample analysis and reporting.

Interpersonal & Communication Skills

Fellows will display effective communication with ordering and consulting physicians and laboratory staff and directors and will have opportunities to improve their communication skills in the laboratory setting.

Professionalism

Fellows will interact closely with laboratory staff and directors and learn their responsibilities and tasks. Fellows will learn how laboratory staff communicates with other hospital and laboratory personnel.

Systems Based Practice

Fellows will learn costs and benefits of diagnostic and therapeutic modalities in the management of inpatients with IEM crises and how these costs are transferred to insurance providers. Fellows will have exposure to Soft, the laboratory information system.

Lab safety

It must be emphasized that each fellow/student must exercise care while occupying the laboratory. Patient samples may contain infectious agents and there are a number of dangerous chemicals in use. In addition, the instruments being utilized in the lab are highly sensitive and extremely expensive. Please do not attempt to operate any of these instruments unless supervised.

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Clinical Cancer Genetics Rotation

Directors: Andrea Murad, MS, CGC and Anthony Scott, MD, PhD

Goals:

The primary objective of this rotation is to introduce clinical Medical Genetics residents to the principles and practice of clinical cancer genetics. The Clinical Cancer Genetics Rotation consists of individual tutoring, a case-based program and practical experience in the Cancer Genetics Clinic. At the end of the rotation residents should have:1) a working understanding of oncogenes, tumor suppressor genes and "caretaker genes," 2) an introduction to techniques for cancer risk assessment, 3) the ability to recognize classic familial cancer syndromes based on pedigree analysis and clinical phenotype and 4) an appreciation of the role of genetics in cancer treatment and prevention (eg. precision oncology). Clinical cancer genetics will be framed in the context of a medical genetics model as well as multidisciplinary care including cancer risk assessment, cancer screening/surveillance, and therapeutic oncology.

Resident Responsibilities:

Residents will be asked to fully participate in case-preparation for the clinics that they attend. This may include record review, construction of pedigrees, researching the availability of genetic testing, and preparing risk estimates based on empiric models or Mendelian genetics. Residents will be responsible for dictating clinic notes and patient letters for patients / families the resident sees in clinic. Attendance at weekly clinical case conference, reading and case-based self-study are highly recommended.

Patient Care

Residents will be expected to learn appropriate diagnosis and risk assessment for patients with known or suspected genetic forms of cancer. Residents will help identify appropriate genetic testing options for a given patient given their personal and/or family history of cancer. They also will participate in longitudinal management of patients with hereditary cancer syndromes.

Medical Knowledge

Residents will learn from cases and didactic sessions about specific cancer genetic disorders and their underlying mechanisms (see list below for details).

Practice-Based Learning & Improvement

Residents will learn basics of cancer genetics, testing options, and medical management for a variety of cancer predisposition syndromes. Residents will learn to use several different databases and risk models to assess patients' risks for genetic disorders associated with increased risk for cancer, including consensus criteria used to determine indications for testing and, in some cases, a clinical diagnosis for a hereditary cancer syndrome. Residents will learn how to calculate carrier risks for Mendelian and complex disorders. Residents will learn about how pathologic features of tumors can be used to identify hereditary cancer syndromes and inform treatment and prognosis. They will also learn the role of enhanced cancer screening in the setting of a family history of cancer, in the absence of positive genetic testing.

Interpersonal & Communication Skills

Residents are expected to communicate effectively with other health care providers and with their patients and families, including the benefits and limitations of genetic testing for inherited cancer risk. Residents will learn about privacy and confidentiality in cancer genetics. They will be able to discuss the implications of the Genetic Information Non-Discrimination Act, particularly given the asymptomatic population undergoing testing in this clinic.

Professionalism

Residents will learn the importance of accurate communication of test results and counseling information in the clinical setting. They will also learn basics of how to relay test results to patients in stressful situations.

Systems Based Practice

Residents will learn about cost-effectiveness of genetic evaluation, as well as review cost-benefit analyses for various testing strategies (including multigene panel testing), and how these tests influence care of cancer patients and their families. This includes application of guidelines to ensure appropriate utilization of genetic testing and the availability of self-pay options available for patients who might not meet criteria for inherited cancer genetic testing.

Clinical Cancer Genetics Rotation Curriculum and Schedule

Clinical Experience
In addition to the didactic component, residents will participate in the evaluation and management of patients scheduled in the Thursday Cancer Genetics Clinic. These occur every Thursday morning and every Thursday afternoon (should conflicts arise, there are also virtual clinic options every 2nd and 4th Mondays of the month).

Case studies
During the rotation, residents will complete six case studies that review common hereditary cancer syndromes. They will review their answers with Andrea Murad prior to the end of the rotation..

Suggested didactic focus during the rotation:

Oncogenes, Tumor Suppressor Genes, "Caretaker Genes"

Clinical correl: Familial Adenomatous Polyposis, Lynch

Phenotypic variation and cancer syndromes

Clinical correl: LFS, PTEN Hamartoma Tumor Syndrome

Cancer Risk Assessment

Clinical correl: Hereditary Breast Ovarian Cancer Synd.

Managing Individuals at High Risk

Clinical correl: LFS, von Hippel Lindau Syndrome

Hereditary Pediatric Tumors

Clinical correl: LFS, VHL, Retinoblastoma, Neuroblastoma

MEN and Other Hereditary Cancer Syndromes

Clinical correl: MEN2A,B, BHD, HLRCC, etc.

Recommended Reading

Online Resources:

Elements of Cancer Genetics Risk Assessment and Counseling (PDQ®) http://www.cancer.gov/cancertopics/pdq/genetics/risk-assessment-and-counseling/healthprofessional

National Comprehensive Cancer Network. Guidelines for detection, prevention, and risk reduction. http://www.nccn.org

GeneReviews GeneReviews® - NCBI Bookshelf (nih.gov)

Overview of Cancer Genetics:

Fearon, ER Human cancer syndromes: clues to the origin and nature of cancer. Science. 1997 Nov 7;278(5340):1043-50.

Stoffel EM, Carethers JM. Current approaches to germline cancer genetic testing. Annu Rev Med. 2020;71(1):85-102. doi:10.1146/annurev-med-052318-101009Lu KH, Wood ME, Daniels M, Burke C, Ford J, Kauff ND, Kohlmann W, Lindor NM, Mulvey TM, Robinson L, Rubenstein WS, Stoffel EM, Snyder C, Syngal S, Merrill J, Wollins DS, Hughes KS. ASCO Expert Statement: Collection and Utilization of a Cancer Family History for Oncology Providers. J Clinical Oncology 2014 (epublished ahead of print February 3, 2014).

Stoffel EM, Cooney KA eds. Advances in Inherited Cancers. Seminars in Oncology.43(5). 527-622.

Selected References:

Breast/Ovarian Cancer:

Date last edited: July 29, 2024

Fan X, Wynn J, Shang N, et al. Penetrance of breast cancer susceptibility genes from the eMERGE III network. JNCI Cancer Spectr. 2021;5(4):kab044. doi:10.1093/jncics/pkab044

Bedrosian I, Somerfield MR, Achatz MI, et al. Germline testing in patients with breast cancer: ASCO-Society of Surgical Oncology guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.0222

Quante AS, Whittemore AS, Shriver T, Strauch K, Terry MB. Breast cancer risk assessment across the risk continuum: genetic and nongenetic risk factors contributing to differential model performance. Breast Cancer Res. 2012;14(6):R144. doi:10.1186/bcr3352

Irelli A, Patruno LV, Chiatamone Ranieri S, et al. Role of breast cancer risk estimation models to identify women eligible for genetic testing and risk-reducing surgery. Biomedicines. 2024;12(4). doi:10.3390/biomedicines12040714

Colorectal Cancer:

Stoffel EM, Boland CR. Genetics and Genetic Testing in Hereditary Colorectal Cancer. Gastroenterology. 2015 Oct;149(5):1191-1203.

Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol. 2015;33(2):209-217. doi:10.1200/JCO.2014.58.1322

Coughlin SE, Heald B, Clark DF, et al. Multigene panel testing yields high rates of clinically actionable variants among patients with colorectal cancer. JCO Precis Oncol. 2022;6:e2200517. doi:10.1200/PO.22.00517

Pancreatic Cancer:

Sawhney MS, Calderwood AH, Thosani NC, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. Gastrointest Endosc. 2022;95(5):817-826. doi:10.1016/j.gie.2021.12.001

Everett JN, Dettwyler SA, Jing X, et al. Impact of comprehensive family history and genetic analysis in the multidisciplinary pancreatic tumor clinic setting. Cancer Med. 2023;12(3):2345-2355. doi:10.1002/cam4.5059

Precision Oncology:

Mody RJ, Wu YM, Lonigro RJ, Cao X, Roychowdhury S, Vats P, Frank KM, Presner JR, Asangani I, Palanisamy N, Dillman JR, Rabah RM, Kunju LP, Everett J, Raymond VM, Ning Y, Su F, Wang R, Stoffel EM, Innis JW, Roberts JS, Robertson PL, Yanik G, Chamdin A, Connelly JA, Choi S, Harris AC, Kitko C, Rao RJ, Levine JE, Castle VP, Hutchinson RJ, Talpaz M, Robinson DR, Chinnaiyan AM. Integrative Clinical

Sequencing in the Management of Refractory or Relapsed Cancer in Youth. JAMA 2015; 314 (9): 913-925. PMC: 4758114.

Robinson DR, Wu YM, Lonigro RJ, Vats P, Cobain E, Everett J, Cao X, Rabban E, Kumar-Sinha C, Raymond V, Schuetze S, Alva A, Siddiqui J, Chugh R, Worden F, Zalupski MM, Innis J, Mody RJ, Tomlins SA, Lucas D, Baker LH, Ramnath N, Schott AF, Hayes DF, Vijai J, Offit K, Stoffel EM, Roberts JS, Smith DC, Kunju LP, Talpaz M, Cieślik M, Chinnaiyan AM. Integrative genomics of metastatic cancer. Nature. 2017 Aug 17;548(7667):297-303. Epub 2017 Aug 2. PMID:28783718.

Cobain EF, Wu YM, Vats P, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. JAMA Oncol. 2021;7(4):525-533. doi:10.1001/jamaoncol.2020.7987

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Cytogenetics Rotation for Medical Genetics Residents

Laboratory Director: Lina Shao, M.D., Ph.D., FACMG
Clinical Cytogenetics Laboratory – Pathology
2800 Plymouth Road
Building 35, Room 1400
Ann Arbor, MI 48109

Goals and objectives for residents in the Clinical Cytogenetics Rotation: To learn fundamental concepts, specific knowledge of the field, and the methods that are used, as well as to acquire basic skills in clinical cytogenetics.

Patient Care

Residents will learn appropriate indications for sending karyotypes from peripheral blood, amniocytes, bone marrow, and other tissues. Residents will learn the implications of test results on health and disease.

Medical Knowledge

Cytogenetics is a cornerstone of Medical Genetics, having application to our understanding of abnormal development at every stage and in virtually every tissue of the human body. As chromosomes are the physical embodiment of our genetic blueprints, cytogenetics intersects with molecular genetics, cell biology and development. As such, a general knowledge of some basic concepts in several related areas is required to understand cytogenetics:

List of related concepts/basic knowledge to cover prior to the rotation:

Cell biology: the cell cycle, meiosis, mitosis, chromosome and chromatin structure, recombination; Embryology: Gametogenesis (male and female), fertilization, embryogenesis, placental development: formation of chorionic villi, amniotic fluid; Human genetics: modes of inheritance, autosomal vs. sex-linked inheritance, linkage vs. synteny, expression of phenotypes—penetrance, variable expressivity, anticipation, heterogeneity; Molecular genetics: DNA probes, hybridization techniques, classes of repetitive sequences, unique DNA sequences.

Major concepts and current topics in cytogenetics can be comprehensively covered by reading recent textbooks, reviews and benchmark journal articles in the field. Some of the basic concepts in cytogenetics to be studied are listed below. Additional topics will be determined by the types of samples submitted to the laboratory and abnormalities detected during the rotation. Then, in practice, one can follow the flow of decision-

making in the laboratory and the ultimate interpretation and significance of the results obtained. In this way, one can better understand the importance of having a clinical history and indication for cytogenetic studies provided with the sample for the proper handling of different types of specimens, the importance of integration of the clinical history for the correct interpretation of results, and the significance of the results for further studies, genetic counseling and involvement of additional family members. A reference list and copies of selected references will be provided (see attached).

Basic concepts in cytogenetics and molecular cytogenetics to be acquired by the end of the rotation:

Properties of autosomes vs. sex chromosomes, nondisjunction, trisomy, monosomy, ploidy, mosaicism, X-inactivation, structural rearrangements, meiotic segregation behavior, microdeletions, uniparental disomy, loss of heterozygosity, imprinting, fragile sites, the pseudoautosomal region, polymorphisms, variants, copy number variants, NORs, euchromatin, heterochromatin (facultative, constitutive), constitutional vs. acquired abnormalities.

In addition to general concepts, specific knowledge of the field will be covered, including historical developments, the common cytogenetic abnormalities and syndromes, and the various syndromes that have associated cytogenetic manifestations, as outlined below.

A. Historical landmarks in cytogenetics: use of mitotic inhibitors, mitogens, hypotonic solution, fixative, discovery of the human chromosome number, Lyon hypothesis, chromosome banding methods, prenatal diagnosis, fluorescence in situ hybridization (FISH), molecular cytogenetics, genomic and SNP microarrays

B. The most common constitutional cytogenetic abnormalities and their association with congenital syndromes and spontaneous abortions, especially with regard to phenotype and recurrence risks:
   1) Numerical abnormalities
      a) Autosomal trisomies: +21, +13, +18
      b) Sex chromosome abnormalities: Turner syndrome, including X/XY mosaicism, XXX, XXY, XYY
      c) Mosaicism: confined placental mosaicism, trisomy rescue
      d) Uniparental disomy, copy-neutral loss of heterozygosity
   2) Structural rearrangements
      a) Translocations: Robertsonian, reciprocal, balanced, unbalanced, 3:1 segregation -- eg: the constitutional t(11;22)
      b) Inversions: the inversion loop
      c) Duplication/Deletion syndromes
      d) Microdeletion syndromes: eg. Prader-Willi and Angelman
      e) Copy number variants, variants of uncertain significance; pathogenic vs benign

   3) Chromosome breakage/DNA repair/other syndromes with cytogenetic manifestations: Fragile X, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, xeroderma pigmentosum, Werner syndrome, Roberts syndrome

Practice-Based Learning & Improvement

Methods in cytogenetics and molecular cytogenetics:

An important aspect of the rotation is observation of the methods that are used to obtain a cytogenetic result. Knowledge of routine laboratory procedures used to obtain karyotypes from amniotic fluid, chorionic villus, PHA-stimulated peripheral blood, and bone marrow samples is best obtained by watching and discussing the significance of each step of the process. The specific methods to be observed and to be discussed are outlined below.

A. Cell culture methods and chromosome preparation:
   1) Sample procurement, triage, sample preparation for adherent cell cultures (especially in situ cultures), and suspension cultures: Amniocentesis samples, chorionic villus samples (CVS), mitogen-stimulated peripheral blood samples (including prophase), bone marrow samples.
   2) Slide preparation, banding techniques (G-banding), special stains
   3) Analysis at the microscope, photomicrography, automated scanning
   4) Instrumentation: sterile laminar flow hoods, 5% CO_2 incubators, inverted microscopes, robotic harvester, microscopy (phase contrast, brightfield, fluorescence), automated scanning system for metaphase cells

B. Fluorescence in situ hybridization (FISH):
   1) DNA Probes: chromosome painting, repetitive sequence probes, unique sequence probes, MFISH/SKY, limitations.
   2) Slide preparation, hybridization, detection (counterstains)
   3) Instrumentation: hybridization apparatus, fluorescence microscopy and color imaging
   4) Test Development and Validation:
      a) Metaphase vs interphase FISH analysis
      b) Probe validation, test validation (analytic sensitivity and specificity)
      c) Reportable ranges, cut-offs for an abnormal result

C. Cancer Cytogenomic Microarray and SNP analysis
   1) Indications for microarrays with actionable results
   2) Microarray platforms: Affymetrix Cytoscan HD platform; contains more than 2.6 million copy number markers, including 750,000 SNPs, and median spacing of 0.88 kb within genes.
   3) DNA extraction, QA, chip hybridization and washes
   4) Analysis software, resolution, making calls, QA
   5) Interpretation and reporting: databases, CNVs, runs of homozygosity

D. Analysis, Interpretation and Reporting:
    1) Chromosome identification (karyotyping)
    2) Levels of banding resolution for metaphase chromosomes
    3) Number of cells, colonies appropriate for cytogenetic analysis
    4) Mosaicism issues, chimerism
    5) Maternal cell contamination
    6) FISH analysis (metaphase vs. interphase)
    7) Nomenclature: ISCN 2020, FISH ("ish"), microarray nomenclature

Interpersonal & Communication Skills

Residents will gain an appreciation for the necessity of accurate communication among lab staff and between lab staff and medical professionals.

Professionalism

Residents will learn to interact closely with laboratory technologists, the laboratory director, and other lab staff. Residents will also learn guidelines for sample handling and processing across departments and medical facilities.

Systems Based Practice

Residents will learn multiple aspects of lab management, including turn-around times, costs of tests, sample volumes, and quality control. They will become acquainted with ACMG Practice Guidelines and Laboratory Standards and Guidelines for Clinical Cytogenetics. Residents will also learn about CLIA and other certification.

References with handouts provided:
Medical genetics textbooks with introductory cytogenetics chapters:

Nussbaum RL, McInnes RR, Willard HF. 2016 "Principles of clinical cytogenetics and genome analysis" and "The chromosomal and genomic basis of disease: disorders of the automosmes and sex chromosomes" Ch. 5 and 6. In, *Thompson & Thompson: Genetics in Medicine* 8th Ed., Saunders, Elsevier, Philadelphia, pp. 57-105.

Vogel, F, and A.G. Mitulsky. 1997. *Human Genetics: Problems and Approaches,* 3rd Ed. Springer-Verlag, New York. (Chapter 2 provided)

Confined Placental Mosaicism:

Lestou VS and Kalousek DK. Confined placental mosaicism and intrauterine fetal growth. *Arch Dis Child Fetal Neonatal Ed* 1998; 79:F223-F226. (provided)

Kalousek DK. Confined placental mosaicism and genomic imprinting. *Bailliere's Clinical Obstetrics and Gynaecology* 2000; 14:723-730. (provided)

General References
Counseling issues, recurrence risks:

Gardner RJM, Sutherland GR, Shaffer LG. *Chromosome Abnormalities and Genetic Counseling*, 4th Ed. Oxford University Press, New York, 2012.

Cytogenetic methodology:

Arsham MS, Barch MJ, and Lawce HJ. *The AGT Cytogenetics Laboratory Manual*, 4th Ed. Wiley Blackwell, NJ, 2017.

Gersen SL, Keagle MB, Eds. *The Principles of Clinical Cytogenetics,* 3rd ed. Springer, New York. 2013.

Nomenclature:

ISCN (2020): An International System for Human Cytogenetic Nomenclature. McGowan-Jordan J, Hastings, RJ, Moore, S (Eds.). S. Karger, Basel. 2020.

Constitutional abnormalities:

Schinzel, A. *Catalogue of Unbalanced Chromosome Aberrations in Man*, 2nd Ed. deGruyter: New York. 2001.

Borgoankar, DSI *Chromosomal Variation in Man*, 8th Ed. Wiley-Liss: New York. 1997.

Milunsky A, Ed. *Genetic Disorders and the Fetus, 5th Ed.* Johns Hopkins Univ Press: Baltimore. 2004. Esp. chapter by Lillian Hsu.

Cancer cytogenetics (all neoplasia):

Heim, Sverre and Mitelman, Felix. *Cancer Cytogenetics*, 4th Ed. John Wiley & Sons, Hoboken, NJ. 2015. Chapters 1-4.

Websites

“Atlas of genetics and cytogenetics in oncology and haematology”
http://atlasgeneticsoncology.org/

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Medical Genetics Clinic Goals and Objectives

Director: Wendy Uhlmann, MS, CGC and Anthony Scott, MD, PhD

The primary objective of the Medical Genetics Clinic rotation is to introduce residents to the principles and practice of adult medical genetics. Our Medical Genetics Clinic has a rich history as the first genetics clinic in the country, established in 1941, and currently is one of the few adult medical genetics clinics nationwide. In this rotation, the residents will work closely with our team of clinical geneticists and genetic counselors. They will learn case preparation skills, pedigree construction and family history taking skills, risk assessment and risk communication skills and components of genetic counseling. Residents will obtain understanding of key concepts in adult genetics, including evaluation and work-up of patients for genetic conditions, approach to the physical exam and assessment of dysmorphic features, generating and considering differential diagnoses. They will also learn how to select and order genetic testing, understand insurance coverage issues and implications, relevant legislation (the Genetic Information Non-discrimination Act), interpret and communicate genetic test results.

Patient Care

Residents will provide care in our Medical Genetics Clinic to patients with known or suspected genetic conditions and/or positive family histories. Responsibilities will include case preparation, management of the clinic visit and follow-up post clinic.
Case prep and follow-up skills will include:

- Construct pedigree from family history form or at appointment (if family history form is not returned)
- Review medical records (including MiChart, Care Everywhere and any outside records received)
- Perform literature search to obtain articles about the genetic condition
- Generate differential diagnoses (when indicated)
- Perform risk assessment (think about risks for patient, children/future children, siblings etc.)
- Conduct search of genetic testing laboratories
- Select laboratory and complete paperwork
- Develop Powerpoint counseling aids to use for provision of genetic counseling and develop a plan for the session
- Obtain pertinent patient literature and contact information for national and Michigan chapters of support groups
- Track results of tests/evaluations

- Phone out results
- Write clinic visit summary note/letter
- Present summary of patients at pre-clinic conference

Medical Knowledge

Residents will learn about adult medical genetics from reading, individual weekly meetings with genetic counselors and clinical geneticists, care of patients in clinic and post-clinic conferences. A goal of this rotation is to recognize issues specific to adult patients with a personal and/or family history of a wide spectrum of conditions including:

- Connective tissue disorders (e.g. Ehlers-Danlos syndrome, Marfan syndrome, Osteogenesis imperfecta, Aneurysm syndromes)
- Neurocutaneous conditions (e.g. Neurofibromatosis, Tuberous sclerosis)
- Classic genetic conditions (e.g. Hereditary Hemorrhagic Telangiectasia, hemochromatosis, alpha-1 antitrypsin deficiency, hemoglobinopathies, Turner syndrome, Klinefelter syndrome)
- Chromosome abnormalities and rearrangements (e.g. Translocations)
- Neurological conditions (e.g. ALS, muscular dystrophies, myotonic dystrophy, Charcot-Marie-Tooth syndrome)
- Intellectual disability and/or congenital anomalies
- Atypical diabetes, obesity, and/or lipodystrophy
- Biochemical conditions in adults

Residents generally will also see some patients for preconception counseling and risk assessment. In addition, residents generally will have the opportunity to see patients who, based on family history, are considering predictive genetic testing for Huntington disease, Alzheimer Disease, ALS, or other neurodegenerative disorders. The resident will need to be aware that there are international guidelines for predictive genetic testing and the need for desired insurance coverage prior to testing.
If patients are not seen with some of the above conditions during the resident's rotation, the resident will be encouraged to read about the conditions.

Practice-Based Learning & Improvement

Residents will learn how to work-up, evaluate and provide care for patients seen in an adult medical genetics clinic. Residents will learn to provide risk assessment and risk communication for Mendelian and complex inherited conditions. They will also obtain experience in post-test counseling of genetic testing results (pathogenic variants and variants of uncertain significance).

Interpersonal & Communication Skills

Residents will continue to build on their interpersonal and communication skills by working with a multidisciplinary team that includes clinical geneticists, genetic counselors and other rotators (genetic counseling students, medical students). Residents will be expected to communicate effectively with adult patients ranging from late teens to 80s, sometimes with multiple family members present. Residents will have opportunities to communicate with other clinicians and genetic testing laboratories. Through their work with genetic counselors, residents will learn

about wording, tone and nuances in providing genetic information and assessing patient's understanding and psychological responses.

Professionalism

Residents will be expected to be professional in their interactions, to assume full responsibility for the tasks described above and to comply with HIPAA guidelines in their interactions with patients and the clinical team. Specifically, residents will be expected to be attuned to the privacy and confidentiality issues that genetic information poses, particularly an issue when multiple family members are seen unbeknownst to each other.

Systems Based Practice

Residents will learn about the different databases to access 1) information about genetic conditions (e.g. MedGen, GeneReviews, OMIM) 2) information about genetic testing (e.g. Genetic Testing Registry) and 3) support group information for patients (e.g. MedlinePlus, MedLine Genetics, Genetic Alliance, NORD, Michigan Genetics Resource Center). Residents will also learn the different tasks needed to select and order genetic tests and find out about insurance coverage.

MEDICAL GENETICS RESIDENCY PROGRAM
Department of Pediatrics

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Molecular Genetics and Genomics Laboratory Rotation Goals and Objectives

Director: Chen Yang, Ph.D.

The goals and objectives of the Molecular Genetics and Genomics Laboratory rotation in the Medical Genetics Residency Program are to provide the resident with exposure to all aspects of molecular genetic testing in accordance with the Residency Review Committee for Medical Genetics expectations and to fulfill criteria for board eligibility by the American Board of Medical Genetics and Genomics (ABMGG).

Patient Care

The residents will become familiar with the evaluation, diagnosis and management of genomic disorders, chromosomal aneuploidy, and disorders due to copy number variation; the residents will also become familiar with the methods used in DNA Sanger sequencing and Next-Generation Sequencing (NGS), methylation analysis, Multiplex Ligation-dependent Probe Amplification (MLPA), and bioinformatics relevant to genetics diagnostics. Residents will gain expertise in interpreting molecular results relevant to the diagnosis and management of human genetic diseases and will develop broad knowledge of basic molecular biology, the application of molecular methods through the diagnosis and management of genetic diseases and an understanding of the etiology, pathogenesis, clinical manifestations of human inherited genetic disorders.

Medical Knowledge

Through coursework and didactic sessions with attending physicians, residents will become familiar with fundamental concepts of molecular biology and genetics for Mendelian single gene disorders, imprinting disorders, and genomic disorders. Residents will also be required to interpret the results of molecular genetic assays, including pathogenicity classification of sequence variants and copy number variants. Residents will also learn appropriate nomenclature for genetic variations. Details about the curriculum are attached below.

Practice-Based Learning & Improvement

Residents will learn to apply appropriate diagnostic modalities in the management of patients with genomic and genetic disorders. Residents will also become familiar with laboratory procedures and fundamental molecular biology that encompasses diagnostic tests, including PCR, sequencing, methylation specific MLPA, and SNP based chromosomal microarray analysis (CMA), and allele-specific assays.

Interpersonal & Communication Skills

Residents will learn how laboratory results are communicated to ordering physicians and laboratory directors and will have opportunities to improve their own communication skills in the laboratory setting.

Professionalism

Residents will interact closely with laboratory staff and learn their responsibilities and tasks. Residents will learn how laboratory staff communicates with other hospital and laboratory personnel.

Systems Based Practice

Residents will learn the costs and benefits of diagnostic and therapeutic modalities in the evaluation of patients with genetic disorders, and how these costs are properly billed to patients and insurance providers.

Curriculum:

Week 1

I. Discussion topics:
   - A. Pre-analytical issues: Specimen and Patient demographic requirements - Anticoagulants, fixatives, handling, storage, stability
   - B. Specimen processing from blood, other types of samples
   - C. Nucleic acid extraction, quantitation
   - D. Quality control of nucleic acid extractions

II. Laboratory Procedures:
   - A. Blood sample processing for nucleic acid extraction
   - B. Extraction, Quantitation of nucleic acid
     - Automated “robotic” procedure
     - Manual procedure
   - C. Spectrophotometric quantitation of nucleic acid
   - D. Quality assessment of extracted nucleic acids – gel electrophoresis

III. Discussion topics:
   - A. Nucleic acid analysis: Electrophoresis
     - Agarose gels
     - Capillary electrophoresis
   - B. Nucleic acid detection methods
   - D. Nucleic acid amplification:
     - Polymerase Chain Reaction (PCR)
     - Whole genome amplification

IV. Laboratory Procedures
   - A. PCR based assays

Week 2

I. Discussion topics:
   A. DNA sequencing-based analysis

II. Laboratory procedures:
   A. Sanger
   B. NGS

III. Discussion topics:
   A. DNA copy number analysis

IV. Laboratory procedures:
   A. SNP-based CMA
   B. MLPA
   C. Methylation specific MLPA (MS-MLPA)

Molecular Genetics Laboratory sign-out

Residents will shadow laboratory director for case sign-out and discuss the interpretation and reporting of laboratory results. Residents will be responsible to review relevant clinical information and discuss interpretations of laboratory results.

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Neurogenetic Disorders Residency Training Goals and Objectives

Director: John Fink, M.D., Peter Todd, M.D./Ph.D., Sharan Srinivansan, M.D., Ph.D.

Patient Care

The goals of the Neurogenetic Disorders rotation for Medical Genetics Residents are to develop clinical skills in the principles and practice of genetics related to neurological inherited syndromes. The objectives of the rotation in Neurogenetics are to develop familiarity with diagnosis, management, and genetic counseling of patients (children, adolescents, and adults) with inherited neurologic disorders. The Resident will learn to build a differential diagnosis and to order and interpret appropriate diagnostic testing. The resident will learn the natural history, presentation, complications, molecular basis, inheritance pattern and prevailing treatment for neurogenetic syndromes.

Medical Knowledge

This rotation will consist of primarily outpatient consultations and evaluations, self-study, genetic counseling and development of interdisciplinary team approaches to the care of families with genetic neurologic conditions including hereditary spastic paraplegia, spinocerebellar ataxias, Charcot-Marie-Tooth, dystonia, familial dementia, Tourette's syndrome, Wilson's disease, Niemann-Pick disease, Von-Hipple-Lindau disease, Fabry disease, CADASIL, episodic ataxias, and mitochondrial encephalomyopathies.

Practice-Based Learning & Improvement

The resident is required to calculate recurrence risks, order and interpret the results of diagnostic tools, and preparation of correspondence between referring physicians and families including clinic notes and letters for families. Reading and case-based self study is recommended.

Interpersonal & Communication Skills

Residents will work closely with physicians and nurses in the Neurogenetics clinic. Residents will learn appropriate diagnosis, treatment, and recurrence risk counseling for a variety of neurogenetic diseases.

Professionalism

Medical Genetics Residents will be responsible for attending clinic and inpatient consults. They will work with the attending physician in management of patient inquiries. They are responsible for obtaining the medical history for referred patients in combination with the attending

physician, performing a relevant neurological physical examination and providing appropriate genetic counseling when required.

Systems Based Practice

Residents will learn the costs and benefits of diagnostic tests and studies, and their relevance to care and management of patients with Neurogenetic disorders. Residents will become familiar with the clinical and economic burden of neurodegenerative diseases on patients, families, and society.

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Pediatric Genetics Residency Training Goals and Objectives

Director: Catherine E. Keegan, MD, PhD

The purpose of the Pediatric Genetics Rotation is to provide the resident with exposure to all aspects of Pediatric Medical Genetics in accordance with the Residency Review Committee for Medical Genetics and will aid in fulfillment of criteria for board eligibility by the American Board of Medical Genetics and Genomics. Residents will gain expertise in performing a competent medical genetics diagnostic evaluation, genetic counseling and case preparation skills, genetic, genomic, cytogenetic and metabolic diagnostic testing, and evaluation and management of inpatients and outpatients with known or suspected genetic disorders.

Patient Care

Residents will participate actively in the inpatient and outpatient evaluation and management of patients with a variety of known or suspected genetic and biochemical genetic disorders. This includes taking a complete family history and construction of a pedigree, performing comprehensive genetics-focused physical examinations, selection of appropriate diagnostic studies, follow-up of test results, putting together an appropriate differential diagnosis, understanding treatment modalities and options, and managing inpatients on the Pediatric Genetics Service.

Residents will become competent in collection of tissues, including buccal swabs and skin biopsies.

Medical Knowledge

Conditions and major concepts that residents are expected to gain familiarity with during their Pediatric Genetics rotation:

1. Multiple Malformations/Dysmorphology

Objectives:

- Know the basic underlying mechanisms of normal and abnormal morphogenesis.
- Be able to distinguish between syndromes, field defects, and associations.
- Understand the difference between a malformation, deformation, and disruption.
- Understand how to do an appropriate work up in a patient who presents with multiple anomalies.

- Become familiar with the terminology used in dysmorphology.
    - (see *AJMG* terminology articles, issue 149A, 2009)
- Learn how to take a family history, analyze the pedigree, and assess risks.
- Understand the concepts of minor and major anomalies and know what kinds of studies/evaluations are available (MRI, echocardiogram, etc.) and may be required to determine the extent of anomalies.
- Know the indications for ordering chromosomal microarray testing and the difference between oligonucleotide and SNP microarrays.
- Understand the indications for ordering whole exome sequencing, whole genome sequencing, and NGS-based panel testing and how this technology differs from microarray-based technologies.
- Know that the features of a syndrome may change with age. Different medical problems may occur as an infant grows.
    - Some examples:
        - Williams syndrome
            - ✓ Facial features coarsen with age, joint contractures develop
        - Down syndrome
            - ✓ As individuals with Down syndrome age, there is an increased risk of seizures and early onset Alzheimer's disease
        - Prader-Willi syndrome
            - ✓ Weight management is of paramount importance and obese adults with PWS are at significant risk for heart disease and diabetes

2. Intellectual Disability/Autism

Objectives:

- Understand the difference between syndromic and nonsyndromic ID/autism.
- Become familiar with common syndromic ID/autism disorders.
    - Fragile X syndrome
    - Rett syndrome
    - Kabuki syndrome
- Learn the diagnostic evaluation for syndromic and nonsyndromic ID/autism.

3. Short stature and Overgrowth syndromes

Objectives:

- Become familiar with common syndromes causing short stature and overgrowth.
- Understand the diagnostic evaluation for a patient with short stature or overgrowth.

4. Approach to Multifactorial Diseases in Pediatrics

Objectives:

- Understand the concepts of multifactorial inheritance.
- Understand the concept of empiric recurrence risks.
- Familiarize yourself with genetic counseling issues related to the following common birth defects:
    - Isolated, non-syndromic cleft lip and/or cleft palate
    - Neural tube defects
    - Congenital heart defects

- Congenital hip dysplasia
- Pyloric stenosis

- Understand the risks to fetuses of the above conditions and the medications to treat them, and surveillance during pregnancy (e.g. echocardiograms for congenital heart disease, ultrasound for NTD). Know how to use Reprotox and related resources to assess teratogenicity of various medications that are commonly used in the adult population.

5. Teratogenesis

Objectives:

- Understand the principles of dose, agent, and time of exposure.
- Understand the molecular effects of certain teratogens.
- Understand and learn to recognize the consequences of teratogenic exposures.
- Know the risks of agents known to be teratogenic and those that are not.
- Know how to appropriately counsel women who may have a pregnancy wherein teratogenic exposure potentially has occurred.

6. Chromosome Disorders I -- Aneuploidies

Objectives:

- Become familiar with general clinical presentations of common autosomal and sex chromosome aneuploidies including Trisomy 21, Turner syndrome, Klinefelter syndrome, and other sex chromosome abnormalities.
- Participate in a counseling session of a patient with Trisomy 21, Turner syndrome, or Klinefelter syndrome with one of the pediatric genetic counselors
- Understand the concepts of non-disjunction, translocation and counseling/evaluation for translocation carriers.
- Familiarize yourself with counseling issues for Trisomy 21 at birth and in adulthood.
- Understand reproductive issues for affected individuals including the potential application of assisted reproduction technologies.
- Understand the indications for ordering chromosomal microarrays and how this technology differs from standard karyotypes
- Become familiar with copy number variations and counseling issues that arise in de novo vs. inherited copy number variants

7. Chromosomal Disorders II – Structural Abnormalities

Objectives:

- Know the different types of structural chromosome alterations: deletions, inversions, translocations, duplications.
- Become familiar with the phenotypic characteristics, medical management, and counseling issues of patients with common microdeletion and microduplication syndromes.
- Understand the reproductive risk of having a "balanced translocation" and related genetic counseling issues.
- Understand the reproductive risk of having a Robertsonian translocation, and related genetic counseling issues.

8. Neurocutaneous Disorders

Objectives:

- Know general characteristics of neurocutaneous disorders and understand how to evaluate individuals with these conditions including physical exams, imaging studies, and laboratory studies.
- Become familiar with the diagnostic criteria for, management and counseling issues in Pediatric patients for:
    - Neurofibromatosis Type I and II
    - Tuberous sclerosis
- Know the value and application of DNA diagnostic studies in these conditions.

9. Connective Tissue Disorders

Objectives:

- Become familiar with the general features and learn how to evaluate individuals with suspected connective tissue disorders.
- Know how to do appropriate measurements and specific clinical tests as they relate to diagnostic criteria.
- Understand how to classify connective tissue disorders and what type of laboratory testing is indicated.
- Familiarize yourself with management and genetic counseling issues for the following connective tissue disorders:
    - Osteogenesis Imperfecta
    - Marfan syndrome and other fibrillinopathies
    - Ehlers-Danlos syndromes
    - Stickler syndrome

10. Hematologic Disorders

Objectives:

- Understand the molecular genetic basis, genetic counseling, and genetic testing, of:
    - Hemophilia A & B
    - Inherited thrombophilias
    - Sickle Cell Anemia
    - Thalassemia (a and B)

11. Craniosynostosis Syndromes

Objectives:

- Familiarize yourself with the general approach to the evaluation of craniosynostosis, understanding the distinction between primary and secondary forms.
- Understand the importance of making a specific diagnosis and of arranging for specific molecular testing if indicated.
- Familiarize yourself with the following craniosynostosis syndromes (be able to compare and contrast):
    - Apert syndrome

- Crouzon syndrome
- Carpenter syndrome
- Pfeiffer syndrome
- Non-syndromic coronal synostosis (Muenke syndrome)

12. Neurogenetic Syndromes

Objectives:

- Familiarize yourself with the general approach to evaluating neurological regression and/or deterioration in children.
- Understand the importance of making a specific diagnosis and of using appropriate metabolic and/or molecular testing.
- Understand the concept of predictive genetic testing for adult-onset neurological conditions and be aware of ethical issues and management issues surrounding predictive testing.
- Familiarize yourself with the following neurological disorders:
    - Hereditary Motor and Sensory Neuropathy (Charcot-Marie-Tooth Disease)
    - Brain malformations including microcephaly
    - Inherited neuropathies, including Charcot-Marie-Tooth disease
    - Genetic epilepsies
    - Trinucleotide repeat disorders
    - Inherited Ataxias with late adolescent, adult onset
    - Huntington Disease
    - Myotonic Dystrophy
    - Spinal Muscular Atrophy (Types I, II, III)

13. Skeletal Dysplasias

Objectives:

- Understand how to clinically classify and approach the diagnosis and management of skeletal dysplasias.
- Understand the diagnostic distinctions of the numerous skeletal dysplasias and the chondrodysplasias, including lethal and non-lethal disorders.
- Become familiar with management, DNA testing, and genetic counseling for:
    - Achondroplasia

14. Cardiovascular Disorders

Objectives:

- Become familiar with the approach to the diagnosis and management of cardiovascular syndromes, including:
    - Cardiomyopathies
    - Congenital heart defects
    - Arrythmias
    - Aortopathies

15. Hearing Loss Disorders

Objectives:

- Become familiar with the approach to the diagnosis and management of hearing loss syndromes, including:
    - Syndromic
    - Non-syndromic
    - Environmental

16. Ophthalmologic Disorders

Objectives:

- Become familiar with the approach to the diagnosis and management of ophthalmologic syndromes, including:
    - Malformations
    - Retinitis pigmentosa, both syndromic and non-syndromic
    - Optic atrophy disorders
    - Macular disorders

-

17. Renal Disorders

Objectives:

- Become familiar with the approach to the diagnosis and management of syndromic and nonsyndromic renal disorders, including malformations.

18. Immunodeficiency Disorders

Objectives:

- Become familiar with the approach to the diagnosis and management of immunodeficiency syndromes, including:
    - Primary immunodeficiencies
    - Syndromic immunodeficiencies

19. Pulmonary Disorders

Objectives:

- Become familiar with the approach to the diagnosis and management of pulmonary syndromes, including:
    - Cystic fibrosis
    - Primary ciliary dyskinesia
    - Congenital central hypoventilation syndrome

20. Disorders of Sex Development

Objectives:

- Become familiar with the approach to the diagnosis and management of disorders of sex development, including:
    - Androgen insensitivity syndrome
    - Gonadal dysgenesis
    - Disorders of androgen synthesis
    - Sex chromosome abnormalities

21. Imprinting

Objectives:

- Understand the concept of imprinting and the consequences of mutations involving imprinted genes or chromosomal regions.
- Be familiar with the diagnostic criteria, molecular causes and management of the following imprinted conditions:
  - Prader-Willi Syndrome
  - Angelman Syndrome
  - Beckwith-Wiedemann Syndrome
  - Russell-Silver Syndrome
- Become familiar with the features, diagnostic testing, genetic mechanisms, counseling, and management of uniparental disomy disorders.

22. Mitochondrial Genetics

Objectives:

- Understand the essential nature and functions of mitochondria in metabolism.
- Understand the concept of heteroplasmy.
- Understand the inheritance pattern of mitochondrial diseases.
- Be able to recognize pedigrees and symptoms that may suggest mitochondrial disorders.
- Learn the counseling issues related to inheritance, penetrance, and expressivity of mitochondrial diseases.
- Know the common mitochondrial diseases and their varied presentations.

23. Predictive and Presymptomatic Risk Analysis: Application of Bayes' Theorem

- Become familiar with the general principles of calculating recurrence risk.
- Understand how to utilize Bayes Theorem and conditional probabilities.
- Know how to modify risks based on genetic testing.
- Understand concepts of sensitivity, specificity, positive predictive value and negative predictive value.

Practice-Based Learning & Improvement

Residents will learn to apply appropriate diagnostic and therapeutic modalities in their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and lifelong learning.

Residents will assess self-performance and develop a learning plan.
Residents will critically evaluate and utilize information from diverse sources.
Residents will identify areas for improvement in individual practice.

Residents will learn how to use Genetic Databases for Clinical Genetics

Face2Gene, **www.face2gene.com**

GeneReviews, **http://www.genereviews.org**

Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 1996. World Wide Web URL: **http://www.ncbi.nlm.nih.gov/Omim/**

Interpersonal & Communication Skills

Residents will display effective communication with ordering and consulting physicians and laboratory directors and will have opportunities to improve their communication skills in the clinical setting.

Residents will display effective communication and relationship development with families and health care team members.

Residents will exhibit the ability to manage conflicts with patients/families and health care teams and participate in team-based care (includes dieticians, social workers, nurses, lab personnel, other physicians, etc).

Residents will exhibit the ability to communicate general and sensitive information with awareness of the social context, demonstrate sensitivity to cultural values in communicating information and be able to provide appropriate information and resources to patients and families with genetic disorders.

Residents will learn appropriate counseling for known/unknown diagnoses.
Residents will participate in the following genetic counseling sessions with one of our Pediatric Genetic Counselors:

- Diagnostic CMA/Panel test/whole exome sequencing
- VUS on CMA/Panel test/whole exome sequencing
- Pre-whole exome sequencing
- Trisomy 21 and Turner syndrome or Klinefelter syndrome

Residents will learn appropriate counseling for conditions identified by newborn screening, including:

- Cystic fibrosis
- Inborn errors of metabolism
- Pompe disease and MPS I
- X-linked adrenoleukodystrophy
- Spinal muscular atrophy

Professionalism

Residents will interact closely with other clinical staff and learn their responsibilities and tasks.
Residents will learn how clinical staff communicate with other hospital and laboratory personnel.

Residents will demonstrate caring, honest, and sensitive behavior in all relationships and situations.

Residents should display the ability to manage personal beliefs to avoid any negative impact on patient care and be able to recognize and manage ethical issues in genetics practice.

Residents should complete professional responsibilities in a timely manner.

Residents are expected to recognize limits of their own knowledge and ask for assistance when needed.

Residents should be able to identify and manage situations in which maintaining personal emotional, physical, and mental health is challenged by common and typical clinical care situations.

Residents will learn basic ethical frameworks and applications to genetic cases such as privacy and confidentiality of genetic information.

Systems Based Practice

Residents will demonstrate an awareness of and responsiveness to the larger context and system of health care, including social determinants of health.

Residents will learn costs and benefits of diagnostic and therapeutic modalities in the management of patients with genetic disorders and how these costs are transferred to insurance providers.

Residents will learn to function effectively within different systems and be able to incorporate and advocate for genetic services to enhance cost-effectiveness of care.

Residents should be able to recognize and manage the variation in access to genetic testing, facilitate management and transitions of care teams as the patient ages, and participate in identifying system errors and implementing potential systems solutions.

Residents will also learn how to find and utilize information and services provided by Support Groups/ Foundations to provide information to patients. They will also learn about gene therapy development/trials (understand the rationale for, developing modalities, and limitations of gene therapy for genetic disease). They will also learn about Clinical trials and research - Informed consent issues, dissemination of information issues.

Residents will learn to advocate for patients within the health care system to achieve the patient's and family's care goals, including, when appropriate, end of life goals.