MOLECULAR GENETIC PATHOLOGY

GOALS AND OBJECTIVES

Molecular Diagnostics

Goals:

The goal of this fellowship is to understand the pathogenesis of a variety of common inherited diseases, recognize the utility of molecular profiling of acquired diseases for diagnosis and treatment and appreciate pharmacogenetics testing to enable precision medicine for appropriate drug therapy and dosing. The trainee will obtain extensive knowledge in laboratory techniques, results interpretation, and management skills in preparation as a Laboratory Director for a high complexity molecular diagnostics lab.

Objectives:

Patient care:

- To learn how molecular diagnostics testing is integrated into patient care
- To learn to correlate morphologic and clinical findings with DNA results
- To understand ethical and clinical implications of genetic testing

Medical knowledge:

- To understand laboratory assays used in molecular diagnostics
- To learn the specificity, sensitivity, limitations, and interpretations of each assay
- To understand the pathogenesis of inherited and acquired diseases
- To develop an investigatory and analytic thinking approach to molecular diagnostics

Interpersonal and communication skills:

- To use effective writing skills in preparing complex interpretive and NGS reports
- To develop effective oral communication and presentation skills by providing continuing education presentation to laboratory personnel, interesting case presentation to genetics professionals and 1 hour laboratory medicine rounds to CP faculty and residents
- To develop leadership and teaching skills through daily interactions with residents and laboratory staff

Professionalism:

- To demonstrate respect and compassion for patients
- To complete all tasks in an accurate, precise and timely manner

- To work effectively as a team player and treat fellow colleagues, technical and administrative staff with respect
- To enhance professional development by keeping abreast of new developments in molecular diagnostics

Systems-based practice:

- To understand the importance of proficiency testing in the Molecular Diagnostics lab and understand how it is measured
- To evaluate in a critical manner the need for genetic testing
- To understand quality control and quality assurance issues in molecular diagnostics
- To understand the implications of molecular diagnosis as it relates to patient insurability
- To understand the managerial aspects of the molecular diagnostics laboratory, focusing on cost-effectiveness of testing and the clinical utility of an assay

Practice-based learning

- To use case-based learning as a tool for additional insight into the molecular basis of disease pathogenesis
- To understand the ACMG/AMP guidelines for reporting of germline and somatic sequence variants
- To locate, appraise and assimilate pertinent evidence from scientific studies
- To demonstrate effective problem solving skills, using a wide variety of information resources

NEXT-GENERATION SEQUENCING (NGS)

Goals and Objectives:

Trainees will gain skills in the interpretation of NGS data for the diagnosis of inherited disorders and acquired diseases utilizing whole exome sequencing (WES) or exome-based NGS panel testing in the clinical genomics lab or a disease specific 50 gene myeloid panel. Trainees will actively participate in the interpretation of NGS results, variant classification and preparation of clinical reports.

Rotation Faculty: Laura Lee, M.D., Ph.D., Interim Medical Director of Clinical Genomics

PATIENT CARE

- To learn to incorporate germline and somatic clinical NGS testing into patient care.
- To learn to correlate clinical and morphologic findings with NGS results.
- To understand ethical and clinical implications of NGS testing.

MEDICAL KNOWLEDGE

- To understand the laboratory techniques used for NGS on the Illumina platform.
- To understand the importance of levels of evidence for the interpretation of NGS results.
- To gain experience with the application of ACMG/AMP criteria for the classification of germline and somatic NGS variants.
- To understand the importance of computer processing of NGS data.

INTERPERSONAL AND COMMUNICATION SKILLS

- To prepare detailed, accurate, and clearly written NGS reports using the Genosity portal.
- To actively participate in Clinical Genomics Lab group huddles.
- To present at least two interesting cases at biweekly and/or monthly conferences attended by clinical colleagues.

PROFESSIONALISM

- To demonstrate respect and compassion for patients and other team members.
- To review patient results and prepare clinical NGS reports in a timely fashion.
- To work effectively as a member of a diverse team that includes pathologists, genetic counselors, variant scientists, clinical geneticists, medical technologists, and business/finance managers.

SYSTEMS-BASED PRACTICE

- To maintain clear communication about cases with the clinical team as appropriate.

- To gain familiarity with issues surrounding insurance pre-authorization for clinical germline NGS testing by attending at least two regularly held meetings with the finance team.
- To attend a monthly Anatomic Pathology Molecular Improvement Team meeting to observe efforts to streamline somatic NGS workflow processes from pre-analytic to post-analytic phases.

PRACTICE-BASED LEARNING

- To review and learn from NGS interesting case files.
- To become familiar with sources of valid and useful information for the assessment of NGS data.
- To learn how to investigate and interpret possible unexpected findings.

SITUATIONS IN WHICH EVEN AN EXPERIENCED RESIDENT MUST CALL AN ATTENDING:

- When there is contact by an attorney, a relative, or any party not secured by HIPAA requesting information.
- When there is contact by an upset clinician.
- When a possible specimen loss or misidentification has occurred.
- When a preliminary or final diagnosis is requested.
- When unusual results are observed, and the resident is unsure how to troubleshoot the situation to avoid delays in repeat testing.
- When there may be a conflict involving the resident and another laboratory professional.
- When the resident is unsure how to process a unique laboratory specimen.
- When important data processing systems unexpectedly fail.

MOLECULAR INFECTIOUS DISEASES

Goals: The Molecular Infectious Diseases Rotation is intended to educate the fellow in the role of the molecular laboratory in the diagnosis, treatment, and prevention of infectious diseases through a one-month rotation. The fellow will gain familiarity with the design and interpretation of nucleic acid-based testing for pathogenic microorganisms using specimens obtained from body fluids or fresh/processed tissues.

Rotation Faculty: David Gaston, M.D., Ph.D., Medical Director

General Learning Objectives:

Patient care

Demonstrate ability to:

- Utilize molecular microbiology skills for the diagnosis and treatment of infectious diseases.
- Interpret results from molecular microbiology testing.
- Effectively communicate molecular microbiology results and issues to others.
- Synthesize laboratory and clinical information to facilitate timely clinical decision-making and optimize molecular test utilization.

Medical knowledge

Demonstrate knowledge of:

- Pathogenesis of important infectious diseases at the molecular level.
- Test principles and methods used to molecularly identify microbial pathogens in clinical specimens.
- Safety issues related to the clinical laboratories.
- Epidemiology and infection control considerations related to the clinical laboratories.
- Specialized and referral molecular testing for infectious diseases.

Interpersonal and communication skills

Demonstrate ability to:

- Interact productively with laboratory staff and non-laboratory personnel.
- Participate in formal and informal medical education of trainees at all levels.

Professionalism

Demonstrate ability to:

- Provide helpful, timely consultations, including participation on the Microbiology Diagnostic Management Team.
- Establish effective and respectful team-oriented interactions with others.
- Seek resolution of general or collective problems with an attitude of personal responsibility.

Systems-based practice

Demonstrate knowledge of:

- Role of molecular microbiology in the delivery of health care.
- Laboratory management practices.
- Mechanisms and role of quality assurance in the clinical laboratory.
- Organization, structure, and operation of laboratory outreach services.
- Informatics and laboratory information systems.
- Regulatory issues.
- Laboratory testing in the effectiveness and cost of health care.

Practice-based learning and Improvement

Demonstrate ability to use:

- Effective problem-solving skills in clinical and molecular microbiology.
- Medical literature for self-learning and to teach others at the molecular level.
- Case-based learning for insight into the pathogenesis, diagnosis, and therapy of infectious diseases.

- Cognitive skills in molecular microbiology as tools to understand and improve technical aspects of microorganism detection and identification.

Specific Learning Objectives:*

- Preferred and suboptimal specimen types
- Nucleic acid extraction
- Endpoint PCR and detection methods
- Real-time PCR
    - Qualitative
    - Quantitative
    - Methods of amplification product detection
- Target multiplexing
- Non-PCR NAATs (including isothermal techniques)
- Inhibition controls and normalization standards
- DNA sequencing
    - Major applications
    - Sanger method
    - Next-generation technologies (including Illumina and Ion Torrent)
    - 16S and other universal primer assays
- Molecular Automation
- Mass spectrometry
    - MALDI-TOF
    - LC-ESI
- Contamination detection and prevention
- Development, validation, and implementation of molecular techniques for infectious disease diagnosis and monitoring

- Molecular testing and diagnostic stewardship
- Biosafety and infectious-disease testing

*Not all listed systems and methods are implemented in MIDL. Fellows should recognize that their individual training experiences are shaped by local practices, policies, regulations, care-delivery models, patient populations, and technological environment. Thus, fellows are encouraged to consciously expand their knowledge to encompass a broader range of established practices, technologies, and clinical problems represented in MIDL.

CYTOGENETICS- MGP

Goals:
This rotation is designed to provide a basic understanding of the principles and utility of clinical cytogenetics in acquired (cancer) and constitutional (pre- and postnatal) chromosome studies. Fellows will receive exposure to karyotyping, FISH (fluorescence in situ hybridization) and microarray analysis. The rotation will cover classical chromosomal syndromes as well as microdeletion and duplication syndromes. In addition to constitutional chromosome abnormalities, many of the recurring anomalies acquired in neoplasia and the clinical utility of these findings will be discussed in detail. We will also devote time to discuss the unique challenges of prenatal diagnostics. Fellows will have an opportunity to understand the managerial aspects of the cytogenetics laboratory including the qualifications and certification requirements of personnel, accreditation by CAP and other agencies, licensing requirements and proficiency testing. Maintenance of a log of cases reviewed is required upon completion.

***Rotation Faculty*:** Ashwini Yenamandra, Ph.D., Director ; Rebecca Smith PhD Assistant Director

Objectives:

Patient Care:

- To participate in processing of culture material, including bone marrow and peripheral blood samples, and solid tumors
- To become familiar with fluorescent in situ hybridization and microarray analysis as diagnostic cytogenetic techniques
- To understand cytogenetic and patient counseling issues using cytogenetic and microarray tools

Medical Knowledge

- Learn gross morphology of human chromosomes, and the International System for Human Cytogenetic Nomenclature (ISCN, 2020)
- To become familiar with autosomal and sex chromosome abnormalities
- To understand classical chromosomal syndromes and newly recognized micro-deletion-duplication syndromes
- To become familiar with constitutional chromosome study by preparing cultures, performing Giemsa banded metaphase spreads, analysis using computer imaging to make a karyotype from own blood sample
- To become familiar with acquired chromosomal abnormalities in tumors and correlation with morphology
- To develop an investigatory and analytic thinking approach to cytogenetic analysis and correlation with disease

Interpersonal and Communication Skills

- To develop proficiency in presentation of cytogenetic findings to pathologists, medical students, and clinicians

- To present an interesting or challenging cytogenetics case, with clinicopathologic correlation, and in-depth discussion with review of pertinent literature, as a continuing education presentation to laboratory personnel
- To learn to generate effective reports containing karyotype/clinical correlation, diagnostic and prognostic significance in case of acquired chromosome aberrations, and estimation of recurrence risk in case of constitutional anomalies
- Attend the monthly Genetics Laboratory conference (1st Wednesday of every month at 9 am) and be prepared to discuss an interesting cytogenetics case to the group

Professionalism

- To demonstrate understanding of ethical issues involved in cytogenetic testing
- To demonstrate respect, compassion, and integrity in observing and participating in counseling encounters in the VUMC Pediatrics-Genetics Division

Cytogenetics Training Checklist

WEEK 1

Didactic I and II
I: Introduction to clinical cytogenetics: Types and origin of chromosome abnormalities
II: Introduction to Cancer cytogenetics

Laboratory activities:
1. Become familiar with general functions of the laboratory including referral pattern, accessioning, set-up, culturing and harvesting of many different types of specimens. Understand the importance of the quality of chromosome spreads needed for cytogenetic analysis and general QA/QC of the laboratory
2. Become familiar with human chromosome structure and morphology, and the International System for Human Cytogenetic Nomenclature (ISCN, 2009)
3. Learn to identify numerical abnormalities and gross structural changes
4. Opportunity to perform hands on testing on a peripheral blood sample including:
a) Initiate culture to generate dividing cells
b) Harvest cultured cells and prepare slides
c) Stain slides using standard Giemsa banding technique
d) Learn how to choose appropriate metaphase spreads for analysis
e) Learn to create karyotypes using the laboratory computerized imaging system

WEEK 2

Didactic III, IV and V:
III: Principles of cytogenomic microarray analysis
IV: Hemepath FISH
V: Solid tumor FISH

Laboratory Activities:

1. Be involved in the processing of various cultures including bone marrows of adult and pediatric cases, peripheral bloods, leukemic bloods, lymph node biopsies, soft tissue tumors, etc.
2. Understand QA/QC issues involved in clinical cytogenetics and standard of care in constitutional vs. acquired chromosome changes
3. Become familiar with FISH procedures and the advantages and limitations of the technique, including the observation of at least one FISH procedure
4. Review of clinical cytogenetics and FISH cases: normal, abnormal and highly complex cases
5. Understand QA/QC issues involving prenatal diagnosis, culture failure, culture contamination, etc.
6. Observe technologist analysis of microarray cases; perform analysis of at least 4 cases for discussion with directors

WEEK 3

Didactic VI and VII:
VI: Microdeletion/duplication syndromes
VII: Prenatal cytogenetics

Laboratory Activities:
1. Perform analysis of a minimum of 6-8 microarray cases, write reports and review abnormal cases with directors
2. Learn to use genomic databases to aid in CMA case review and understand reporting of CMA abnormalities
3. Continue to review clinical cytogenetics and FISH cases: normal, abnormal and highly complex cases
4. Review of CAP proficiency testing cases
5. Interesting case/topic presentation to technologists (may be done in any week)

Resources on site in laboratory

1. Cancer Cytogenetics 3rd ed. By Sverre Heim and Felix Mitelman

2. Color atlas of Genetics 3rd ed. by Eberhard Passarge

3. An international System for Human Cytogenetic Nomenclature , ISCN 2020

4. Genetics in Medicine by Nussbaum, McInnis, and Willard. (Thompson and Thompson)

5. WHO Classification of Tumors of Haematopoietic and Lymphoid tissues , 4th Edition, 2008

6.The Principles of Clinical Cytogenetics, 2nd ed (Gersen and Keagle)

CLINICAL GENETICS

Goals:
The goal of this rotation is to provide a working knowledge of medical genetics including dysmorphology, inborn errors of metabolism, adult late onset genetic disease, prenatal diagnosis, and cancer genetics.
Rotation Faculty: Angela Grochowski (Peds)

Objectives:

Patient Care

- To understand how to evaluate the family and clinical history of the patient, perform an examination to develop a differential diagnosis for the patient and to order appropriate laboratory testing to assist in the analysis
- To learn how to review biochemical, cytogenetics and/or molecular genetic results to establish a diagnosis
- To understand how to calculate risk assessment based on family history and laboratory data
- To observe (LGG only) and learn how testing for metabolic diseases is performed

Medical Knowledge

- To understand how to identify and distinguish between mendelian and mitochondrial inheritance, chromosomal abnormalities and multifactorial disorders
- To understand principles of genetic disease including, but not limited to: genetic anticipation, penetrance, imprinting, genetic and allelic heterogeneity and X inactivation
- To understand the pathogenesis of genetic diseases
- To understand the mechanism of disease by understanding the causative effects of missense, nonsense, frameshift, duplication, deletions, promoter and splice site variants

Interpersonal and Communication Skills

- To understand the various components in patient reports
- To develop effective oral communication skills when dealing with patients and their families

To develop oral presentations skills by presenting interesting casesProfessionalism

- To demonstrate respect and compassion for patients
- To work effectively as a team player and treat fellow colleagues, technical and administrative staff with respect

Systems-based Practice

- To utilize on-line web based genetic data bases to understand genetic diseases for information on diagnostics and management guidelines
- To utilize on-line in house data bases for patient chart review and laboratory results

Practice-based learning

- To use case-based learning as a tool to assimilate pertinent data from genetic databases and the scientific literature to formulate a differential diagnosis
- To demonstrate effective problem solving skills

Clinic Attended	
Pediatric and Biochemical Genetics	**Maintain Log of Cases**
Hereditary Cancer	**Maintain Log of Cases**

Prenatal	**Maintain Log of Cases**