Version 1
February 2024

MOLECULAR PATHOLOGY FELLOWSHIP
UNIVERSITY OF CALGARY
GUIDELINES AND OBJECTIVES

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DEFINITION AND SCOPE

Molecular Pathology is a subspecialty within Molecular Diagnostics in Laboratory Medicine, concerned with laboratory investigation of neoplastic disease (solid and hematolymphoid) using nucleic acids (genetic analysis) and other macromolecule (e.g. protein) analysis in the context of screening, diagnosis, prognostication, treatment, surveillance, and follow-up. Molecular pathologists apply a common core of molecular diagnostics knowledge to neoplastic disease that is also relevant in other contexts including germline genetic testing, molecular biochemistry, and molecular microbiology. The purpose of this Molecular Pathology Fellowship is to train fellows in both this common core of molecular knowledge, and specific knowledge pertaining to molecular testing of neoplastic disease. Successful completion of this fellowship will prepare the fellow to become a molecular pathology laboratory director and/or expert consultant to treating clinicians and other pathologists regarding interpreting genomic information in neoplastic disease. This fellowship is not intended to prepare fellows to independently oversee or report germline genetic, molecular biochemistry, or molecular microbiology testing.

ELIGIBILITY REQUIREMENTS

Royal College certification in Diagnostic and Molecular Pathology, Diagnostic and Clinical Pathology, Hematological Pathology, or Neuropathology

OR

Eligibility for Royal College certification in the above listed specialties

FELLOWSHIP OVERVIEW

The Molecular Pathology Fellowship Program is centered at the Arthur J.E. Child Comprehensive Cancer Centre in Calgary, Alberta. This one-year fellowship consists of:

- **6 months of Molecular Diagnostics Core Training**
- **6 months of Molecular Pathology Specialty Training**

The **Core Training** (6 months) involves rotations through multiple laboratories to gain exposure to overlapping core concepts and all specialty streams of Molecular Diagnostics, and Genetic and Genomic Diagnostics. These include neoplastic disease, germline disease, biochemical genetics, and molecular microbiology.

Specific rotations during **Core Training** (6 months) will include:

- Molecular Pathology / Hematopathology (first 8 weeks, and any remaining time during Core Training after the below rotations are scheduled)
- Molecular Genetics Laboratory (4 weeks)
- Cancer Cytogenetics (2 weeks)
- Molecular Microbiology (1-2 weeks)
- Biochemical Genetics (1 week)

An individual fellow's specific time allocation at each site, beyond the minimum requirement, can be negotiated depending on the fellow's interests and the ability of the hosting laboratory to accommodate a longer rotation. Direct experience to cover the learning objectives will be prioritized when possible, with supplementation through independent learning resources and/or preceptor didactics as needed to ensure all content is covered.

The **Molecular Pathology Specialty Training** (6 months) will further focus on molecular testing of neoplastic disease to strengthen and refine specialty-specific knowledge and skills. Topics covered in Core Training may also be covered during the Specialty Training Stream, in greater detail as it pertains to Molecular Pathology specifically.

In addition to clinical service work, longitudinal expectations during the fellowship include attendance of pertinent rounds, teaching sessions, and meetings; assisting with general orientation and teaching of concurrent Molecular Pathology rotators; participation in at least one laboratory management project; at least one departmental, province-wide, or national presentation; and at least one poster at a regional or international conference (see Specific Objectives).

The fellow will be given a minimum of 8 weeks of protected time during the fellowship for scholarly and/or laboratory management activity, including laboratory management project(s), research, and presentation / poster preparation, to fulfill the above expectations. Approval of additional protected time is at the discretion of the Fellowship Director, depending on the scope and nature of ongoing projects and the fellow's progress in meeting training objectives.

There is no on-call service for this fellowship.

EVALUATIONS

Performance evaluations will take the form of weekly low-stakes assessments by the supervising faculty member. These will be integrated into quarterly evaluations at the 3, 6, 9, and 12 month timepoints. Performance evaluation will be based on the Specific Objectives listed below. This includes assessing the fellow's professionalism; quality of their data review and report writing; accuracy of interpretations; consideration and care in working up cases; and ability to answer targeted questions around specific topics or cases. It also includes observing their ability to teach/communicate with others including residents, pathologists, patient-facing clinicians,

technologists, etc., in teaching sessions, patient care rounds, and presentations. The trainee will also be evaluated on their competency carrying out the required laboratory management project(s), presentation, and poster. The quarterly evaluations will be discussed with the fellow and kept on file. If performance is unsatisfactory, the fellow will undergo learner support and/or remediation, as necessary.

CERTIFICATION

Upon successful completion of the fellowship, the fellow will be issued a formal certificate.

SPECIFIC OBJECTIVES

Medical Expert

Core Training objectives include demonstrating and applying knowledge of:

- Human gene and genome structure and function
  - Structure and information content of the human genome
  - DNA, RNA, and protein structure
  - Gene organization and structure
  - Epigenetics and chromatin structure
  - Regulation of gene expression
  - Mitochondrial genetics
  - microRNAs and circulating cell free nucleic acids
- Biospecimen quality and tissue selection for molecular testing
  - Characteristics of different sample types including formalin fixed paraffin embedded tissue (FFPE), fresh tissue, cytology samples, blood, bone marrow, plasma, and body fluids
  - Factors impacting nucleic acid and protein stability including formalin fixation, cold ischemia time, and decalcification
  - Extraction methods, advantages / disadvantages, and potential issues
- Molecular techniques / methods including familiarity with test selection and design, wet lab procedures, QC/QA, and test interpretation, advantages and disadvantages of each technique:
  - PCR-based methods (allele-specific PCR, qPCR, RT-PCR, ddPCR, methylation specific PCR, etc)
  - Gel electrophoresis and capillary electrophoresis for fragment analysis
  - Targeted sequencing
  - Fluorescence in-situ hybridization (FISH) and karyotyping
  - Genomic microarray
  - Identity testing (STR-based)
  - Methylation profiling
  - Next generation sequencing (NGS) / massively parallel sequencing (MPS) including targeted panels, whole exome sequencing, whole genome sequencing, whole transcriptome sequencing
- Data interpretation and bioinformatics / informatics

  - Technical aspects of bioinformatic pipelines
  - Variant calling, annotation and interpretation in somatic and germline settings
  - Detection of pathogens
  - Typing and analysis for pathogen comparison
  - Molecular databases
  - Laboratory information system (LIS)
  - Report formatting
- Variant classes and nomenclature
  - Single nucleotide variant (SNV), insertion/deletion (indel), copy number variant (CNV), loss of heterozygosity (LOH), regions of homozygosity (ROH), structural variation (SV), gene fusion, microsatellite instability, tumor mutational burden
  - Human genome reference sequence versions, and reference transcripts
  - Gene and variant nomenclature rules including Human Genome Variation Society (HGVS); HUGO Gene Nomenclature Committee (HGNC); and International System for Human Cytogenetic Nomenclature (ISCN)
- Laboratory Management, Quality Control, Quality Assurance and Quality Improvement:
  - Standard operating procedures (SOPs)
  - Assay troubleshooting
  - Run QC metrics
  - Sample QC metrics
  - Sample QC requirements (e.g. tissue / DNA quantity, pathologist review, pre & post H&E, microdissection, flow cytometry, tumour cellularity)
  - Optimization, validation and verification of molecular assays with appropriate documentation
  - Apply concepts of sensitivity, specificity, positive predictive value, negative predictive value, accuracy, precision, reference range, reportable range
  - Accreditation requirements (e.g. ISO15189, IQMH, CAP)
  - Post-analytical QA activities (e.g. fail rate, positivity rate, TAT)
  - Budget and cost-effectiveness considerations for molecular testing
  - Regulatory issues
  - Root cause analysis
- Basics / prerequisites of human genetics
  - Genotype and phenotype correlations, penetrance, expressivity
  - Basic principles of Mendelian inheritance and pedigree analysis (eg autosomal dominant, autosomal recessive, X-linked)
  - Basic population genetics and its impact on planning and interpretation of molecular diagnostics assays
  - Variant classes and nomenclature
  - Ascribing clinical significance to different types of gene variants in the germline setting

  - Differences between germline and somatic mutations
  - Awareness of genetic counselling, genetic risk assessment, and ethical considerations of genetic testing
  - Awareness of general principles of biochemical genetics
- Basics / prerequisites of cancer genetics
  - Multistep pathogenesis of cancer with acquisition of cancer hallmarks
  - Oncogenes and tumour suppressors
  - Receptor tyrosine kinases
  - DNA repair pathways
  - Microsatellite instability and genomic instability
  - Tyrosine kinase inhibitors and other targeted therapies
  - Canonical pathways of carcinogenesis (e.g. colon cancer)
  - Ascribing clinical significance to different types of gene variants in the somatic setting
  - Characteristics of circulating tumour cells and circulating tumour DNA
- Basics / prerequisites of microbiology
  - Viral load monitoring
  - Targeted and multiplex detection of pathogens
  - Broad based detection of pathogens (e.g. 16S rRNA, 18S rRNA/ITS)
  - Antimicrobial resistance/anti-viral/anti-fungal/anti-mycobacterial detection
  - Pathogen typing
  - Outbreak investigation assessment and reporting

Molecular Pathology subspecialty training objectives include demonstrating and applying knowledge of:

- Complex genomic testing in neoplasms:
  - Considerations for clinical utility and clinical validity of testing
  - Method selection conditional on clinical and/or technical requirements
  - Validation requirements and planning
  - Preanalytical requirements
  - Quality control and quality assurance measures
  - Test interpretation
  - Reporting requirements
- Indications for testing, application of molecular methods and significance of the findings, in specific cancer sites and histologies; familiarization with the common biomarkers identified in each scenario:
  - Thoracic tumours (e.g. lung cancer)
  - Soft tissue and bone tumours (e.g. sarcoma)
  - Female genital tumours (e.g. ovarian cancer, endometrial cancer)
  - Breast tumors
  - Digestive system tumours (e.g. colorectal cancer, GIST, cholangiocarcinoma)
  - Central nervous system tumours (e.g. gliomas, medulloblastoma)
  - Endocrine and neuroendocrine tumours (e.g. thyroid cancer, neuroblastoma)

  - Hematolymphoid neoplasia (e.g. acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, myeloproliferative neoplasia, chronic lymphocytic leukemia, other mature B-cell neoplasms)
  - Skin tumors (e.g. melanoma)
  - Genitourinary tumors (e.g. prostate carcinoma, bladder carcinoma, renal cell carcinoma)
  - Head and neck tumors, eye and orbit tumors, pediatric tumors
- Knowledge of guidelines:
  - Tumour site-specific (e.g. Lung biomarkers, colon biomarkers, *BCR*::*ABL1*)
  - NGS (validation for cancer panels, bioinformatics, reporting)
  - Variant classification algorithms for somatic variants
  - Diagnostic sequencing (e.g. CLSI, etc.)
  - Reporting requirements
- Germline findings in somatic testing
  - ACMG list of incidental findings
  - Variant allele fraction (VAF) and its utility in this scenario
  - Appropriate reporting and communication of these findings
  - Genetic counselling indications
- Reporting molecular findings in neoplastic disease
  - Essential elements of synoptic reporting of molecular diagnostics results (specimen #, block, adequacy, microdissection, tumour cellularity, results, methods)
  - Other essential reporting components:
    - HGVS, ISCN nomenclature
    - Limitations
    - Coverage of genes on the panel
    - Low coverage exons
    - Recommendations for further testing / counselling

Communicator

- Obtain and accurately discuss appropriate information with staff pathologists and clinicians in difficult cases
- Provide follow-up of assay progress and reporting of preliminary and final results to clinicians as requested or by phone when the case is completed.
- Review final assay results independently and with laboratory attending, and draft preliminary or final reports for the laboratory information system (LIS).
- Communicate effectively and demonstrate caring and respectful behavior when interacting with:
  - Technologists, technicians, lab specialists
  - Lab management
  - Hematologists/Oncologists
  - Pathologists
  - Medical Geneticists

- Molecular Geneticists
- Ob/Gyn
- Other medical specialties
- Family physicians

Collaborator

- Assist the molecular pathologist(s) on service with general orientation and teaching of concurrent rotating residents and other rotators on the Molecular Pathology service (fellows, medical students etc)
- Attend pertinent rounds, teaching sessions and meetings as appropriate (e.g. weekly Molecular Pathology Consensus rounds, semiregular Alberta Molecular Lab Technologist and Scientist Educational Rounds, monthly Molecular Pathology Lab meetings, monthly Molecular Pathology South Med Ops meetings, quarterly Molecular Pathology South Med/Sci/Ops meetings, ad hoc meetings with molecular reagent/equipment vendors, etc)
- Work as a part of a multidisciplinary team in the management and treatment of patients
- Demonstrate a commitment to their patients, profession, and society through participation in profession-led regulation

Leader

- Demonstrate knowledge of molecular laboratory management, including:
  - Molecular lab funding and diagnostic test reimbursement
  - Regulatory approval and funding of cancer therapeutics in Canada / provinces and its relationship to test reimbursement
  - Working with technologists, technicians, laboratory specialists, and lab management
  - Ethical, legal, and regulatory issues pertinent to molecular testing in Canada
- Demonstrate knowledge of the methods of quality control in a molecular pathology lab
- Allocate finite healthcare resources appropriately

Health Advocate

- Oversee the preliminary review of new cases coming into the laboratory to facilitate planning and effective provision of laboratory services to users.
- Recognize how technological advances in molecular biology may apply to improvement in diagnostic pathology
- Respond to individual patient health needs and issues as part of patient care
- Acquire appropriate QA/QC knowledge to ensure patient safety and accuracy of medical reports

Scholar

- Participate in at least one laboratory management project pertaining to molecular pathology over the course of the fellowship. Project options will be discussed with trainees early in the fellowship to find the best possible alignment of their interests with

the current needs and available resources in the Molecular Pathology program. As examples, this may include generating a business plan/project justification with cost and volume analysis, review of send out testing, quality improvement project, design/optimization/validation of a new test, and communication to stakeholders. Publication in peer-reviewed literature is highly encouraged when possible.
- Present at least one departmental, province-wide, or national presentation on a molecular pathology topic of their choosing.
- Present a poster at a regional or international conference.
- Participate in academic half day molecular lectures.
- Function as a continuing medical education resource for molecular pathology laboratory technical/scientific staff
- Apply the principles of critical appraisal to sources of medical information
- Contribute to the creation, dissemination, application, and translation of new medical knowledge and practices

Professional
- Deliver the highest quality of care with integrity, honesty and compassion
- Practice medicine in an ethical manner and with a sensitivity to diverse patient populations
- Exhibit appropriate professional behavior and perform duties in a dependable and responsible manner
- Demonstrate respect for patient confidentiality in all communications
- Demonstrate commitment to excellence and ongoing professional development
- Demonstrate a commitment to their patients, profession, and society through ethical practice

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2. Rosenbaum JN, Berry AB, Church AJ, Crooks K, Gagan JR, López-Terrada D, Pfeifer JD, Rennert H, Schrijver I, Snow AN, Wu D, Ewalt MD. A Curriculum for Genomic Education of Molecular Genetic Pathology Fellows. The Journal of Molecular Diagnostics, 2021, 23:1218–40
3. Velu PD, Cushman-Vokoun A, Ewalt MD, Feilotter H, Gastier-Foster JM, Goswami RS, Laudadio J, Olsen RJ, Johnson R, Schlinsog A, Douglas A, Sandersfeld T, Kaul KL. Alignment of Fellowship Training with Practice Patterns for Molecular Pathologists. The Journal of Molecular Diagnostics, 2022, 24:825–40