HAMILTON REGIONAL LABORATORY MEDICINE PROGRAM

LAB CONNECTIONS

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WHAT'S NEW

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CLINICAL GEN(ETICS)OMICS SERVICE

Genetics in clinical diagnostics is undergoing a revolution in scale and thereby blurring the boundaries between what were classically considered two distinct clinical genetic specialities: clinical molecular genetics and clinical cytogenetics. Specifically, the discipline of clinical molecular genetics is focused on analysis of single locus or gene-specific changes down to a resolution of single nucleotide, while clinical cytogenetics techniques were designed to analyze entire genomes but only at the low resolution of microscopically detectable changes. Major advances in genomic technologies over the past decade are now allowing analysis of entire human genomes at the single nucleotide resolution. In light of this, and the ever-growing demand for a widening range of genetic testing across expanding lists of medical conditions, it is no surprise that genomic technologies are now being quickly adapted in the clinical genetic laboratories. This trend is bound to continue in the coming decade, as the clinical need further advances the requirement for clinical utilization of genomic technologies.

Perhaps the greatest challenges facing geneticists in the clinical genomics era are the abilities to interpret the large number of genetic variants identified in each patient, differentiate between normal genetic variation and pathogenic mutations, and correlate the genomic data with clinical outcomes. These are formidable tasks given the large amount of normal genetic variation among humans. An individual genome contains an average of 3-4 million single nucleotide polymorphisms (SNPs) and small insertions/deletions (indels), of which 250-300 are loss-of-function variants in annotated genes and 50-100 are variants previously implicated in inherited disorders. In addition, each genome is marked by approximately 100 copy number variants (CNVs), which are large regions of DNA (average size 250,000 bp, often encompassing one or more genes) that are deleted or duplicated. Lastly, there is epigenetic variation manifest primarily through methylation of CpG dinucleotides. Approximately 1% of the human genome is comprised of CpG dinucleotides, 70% of which are methylated. Fully 20% of these methylated CpG sites exhibit intra- and inter-individual methylation differences (dynamic methylation), accounting for tissue-specific and individual-specific gene expression profiles. Moreover, methylation profiles change during development and with age, adding yet another layer of normal variation.

Collectively, more than 0.5% of the human genome shows copy number variation or sequence variation, which is further compounded by epigenetic variability due to dynamic methylation. Most of this genetic and epigenetic variability falls within the spectrum of normal human diversity, and is not associated with overt human disease. As our capacity to analyze gene panels and genomes increases, so will our need to develop and implement bioinformatic capabilities to predict and differentiate between benign and pathogenic variants.

At the HRLMP Clinical Genetics Laboratories, we are making significant inroads in development and utilization of clinical genomics across major diagnostic technologies including clinical chromosome microarray analysis (CMA), next generation sequencing (NGS), and clinical epigenomics including clinical DNA methylation microarrays (CDMA).

Under Dr. McCready's leadership, we have significantly broadened and improved our CMA (microarray) based services. This technique has now replaced some of the major indications for G-banded karyotyping. Currently, we provide a state-of-the-art, high resolution microarray test (Affymetrix Cytoscan HD) as a first tier test for the genetic investigation of patients with autism, neurodevelopmental disorders and/or multiple congenital anomalies. The Affymetrix array test is also available for prenatal genetic testing of pregnancies with an abnormal ultrasound and normal aneuploidy testing for chromosomes 13, 18, 21, X and Y. This has resulted in significantly higher diagnostic rates compared to the classical G-band karyotyping (3-20% improved diagnostic yield of CMA compared to karyotype depending on the clinical indication). A very exciting development is availability of novel chemistries and microarray platforms which allow us to begin transitioning this technology from fresh tissue specimens (blood, bone marrow, amniotic fluid) to archival specimens such as formalin-fixed paraffin-embedded (FFPE) tissue blocks. This will enable us to further expand this service particularly in oncology diagnostics.

As CMA technology is allowing for orders of magnitude increase in our capability to detect pathogenic losses or gains of genomic regions, similar advances in genetic analysis of single nucleotides (DNA base) is revolutionizing genetic testing of single gene and multi-gene disorders. Pathogenic mutations at the level of single nucleotides are currently predominantly detected using the classical Sanger sequencing, one gene and one patient at a time. New sequencing technologies such as NGS are now allowing us to perform genetic analysis at the single nucleotide resolution for multiple genes, large gene panels, or entire genomes thereby significantly increasing our clinical sensitivity. Alternatively, genetic testing of 10's to 100's of patients can be analyzed in parallel, thereby increasing the testing capacity, and decreasing the technical time and cost. Under the direction of Dr. Waye and Dr. Sadikovic, we are in the process of validating the NGS technology to replace our current Sanger-based testing for BRCA 1 and BRCA2 breast cancer predisposition genes. This process involves developing custom informatics and network solutions for data generation, long-term storage, retrieval and analytical procedures as a pipeline for NGS development, which is likely to be the primary diagnostic technology in clinical genetic labs in the coming years. With the technological and informatics pipeline in place we aim to rapidly utilize and expand this technology across our constitutional and oncology services.

While chromosome and DNA alterations can be effectively detected by microarray and NGS technologies, defects in mechanisms which regulate gene activation require use of yet another novel technology. In other words, genes can be inappropriately turned off or on in absence of any DNA mutations, which can lead to pathogenesis. One such epigenetic mechanism is DNA methylation. Currently there are a number of clinical genetic tests designed to detect such abnormalities in single genes both in constitutional and in cancer genetics. However, other than single gene DNA methylation tests, there are currently no clinical genome-wide DNA methylation tests that would allow for analysis of all 26,000 genes in a single test. Dr. Sadikovic is the lead PI on a multicentre multinational study which uses Illumina microarray technology and is focused on genome-wide testing of DNA methylation in a cohort of 1,000 patients with developmental delay, intellectual disability, and various epigenetic phenotypes, a study which will be completed in the next two years. The key objectives of this study are to develop a reference DNA methylation profile, test the clinical utility of this test, and ultimately introduce DNA methylation microarrays in clinical genetics service. In addition to constitutional epigenetic

defects, DNA methylation abnormalities are a hallmark oncologic defect across the spectrum of leukemias and solid tumors, which represent the next challenge and opportunity for clinical epigenomics.

It is important to emphasize that both a person's genotype and their environmental exposures influence their phenotype. Development of technologies allowing us to profile entire genome and epigenome of an individual or a diseased organ/tissue is only the first step in deciphering which of these changes carry clinical relevance. While these genomic technologies are rapidly moving from research into clinical genetic laboratories, our capacity to interpret genomic changes continues to be one of the limiting factors in clinical utilization. It will take years, even decades, to harness the full potential of genomic technologies. The HRLMP Genetics Laboratory is poised to meet these challenges, to build on our successes in implementation of clinical genomics into service thus far, and become innovation leaders in this field. Our professional staff team includes Dr. John Waye, Head of Molecular Genetics; Dr. Elizabeth McCready, Head of Molecular Cytogenetics; Dr. Bekim Sadikovic, Head of Advanced Molecular Diagnostics and Associate Head of Cancer Genetics; and Dr. Ron Carter, Director of Genetics and Head of Cancer Genetics.

Dr. Bekim Sadikovic, Ph.D., DABMG, FACMG
Dr. John Waye, Ph.D., DABMG, FACMG

Education News

Mylène Vincent joined the Department of Pathology and Molecular Medicine on November 18, 2013 in the role of Director of Administration and Finance. Mylène replaced Nancy Balfoort who left to take up the position of Director, Administration and Finance for the Faculty of Engineering.

Mylène is a results-oriented manager with 12 years diversified experience in the operations, administrative and strategic management of academic organizations centered on science and education. She obtained her Bachelor of Commerce degree with a major in Marketing and minors in Accountancy and Music at Concordia University in Montreal.

Mylène comes to us from the University of Toronto where she was Manager of Finance and Operations with the Department of Chemical and Physical Sciences. Prior to this she held the position of Manager of Administration with the Department of Chemical and Biological Engineering at the University of British Columbia.

On Saturday, October 26th, the HRLMP hosted its 6th **Annual Rapid Fire Showcase**. The day was wet and dreary, but more than 100 participants from across HRLMP and neighbouring hospitals came to hear about what's happening within HRLMP. In fact, attendance at this year's Rapid Fire Showcase surpassed all previous years.

The theme of "Emerging Technologies and Methodologies" set the stage for a series of 12 presentations by Medical Laboratory Technologists from across all disciplines. Topics included new instrumentation for flow cytometry, allergy testing, Cytogenetics microarray, colon cancer screening and automation in Transfusion Medicine. Attendees were introduced to Alfred, the new rapid urine screening system in Microbiology. We learned how the Neonatal Transport Team at McMaster is utilizing point of care testing to provide better care to their littlest patients. We saw the vital role that the cytotechnologist plays during the collection of Endobronchial Ultrasound-Guided Transbronchial (EBUS) fine needle aspiration. The history and mortality of Middle Eastern Respiratory Syndrome (MERS) was discussed, and case studies from several different laboratories demonstrated the interesting and unusual cases that keep us doing what we do every day.

A big thank you goes out to all of our speakers who did a tremendous job sharing their experiences and their passion for laboratory medicine.

Watch for more details of next year's Rapid Fire Showcase scheduled for the fall of 2014.

News from Connections

The Connections editorial board is pleased to welcome **Dr. Elizabeth McCready** who will represent Genetics. She takes over from **Dr. John Waye**, who has represented Genetics for several years. Welcome to Dr. McCready and thank you to Dr. Waye for his past service.

Hematology News

Congratulations to Special Hematology Laboratory – Winners of the People's Choice Best Film Award at the HHS Film Festival!!

The Special Hematology Laboratory at JHCC was awarded the People's Choice Best Film Award for their film "What's So Special About the Special Hematology Laboratory".

This is a tremendous accomplishment and a demonstration of true creativity!

There were over 70 film submissions from departments across HHS and, of these, only 14 were selected for production. The films were viewed and voted on by over 5,900 HHS employees across all campuses. Thanks to everyone in the laboratory for taking the time to showcase to the HHS world what you do and how we contribute to the BEST CARE for ALL .

A special thanks to Wendy Patterson for conceptualizing, directing and participating in the video.

The Core Lab at MUMC is getting into the Holiday Spirit!

Microbiology News

Things are very busy in Microbiology as we evolve into an automated laboratory. The WASPs (walk away, automated, specimen processing systems) are being validated and WASPLab (total laboratory automation) has arrived from Italy and is currently being installed.

The staff in microbiology have been very patient as we make this transition, and despite working under challenging conditions, are full of Christmas Cheer!

With a lot of help from managers, educators and the clinical staff, Hamilton has fully transitioned from charcoal based culture swabs to E-swabs. Thank you to everyone who helped make this possible!

Microbiology is changing our urine culture screen procedure from urinalysis to the Alfred 60 and HB&L system from Alifax on **January 14, 2014**. This revolutionary urine screening system inoculates the urine into a broth and then rapidly detects the growth of bacteria. It will identify urines with no growth in as little as 5 hours of incubation.

Virology has extended their hours to ensure rapid turn around of results as "flu season" is upon us! The laboratory will be operating from 08:00-23:00, 7 days per week on regular non-holiday days.