THE UNIVERSITY OF BRITISH COLUMBIA

Faculty of Medicine

PRECISION HEALTH SYMPOSIUM

Prioritizing and enabling research in Precision Health

February 2nd, 2023
AMS Student Nest (NEST), UBC
The Great Hall

https://mednet.med.ubc.ca/research/strategic-initiatives/precision-health/

Program at a Glance		
8:30-9:00am	**Registration, Breakfast and Poster Set Up**	Foyer and The Great Hall
9:00-9:05am	**Welcome and Introductions** Dr. Chris Carlsten, Co-Lead, Precision Health	The Great Hall
9:05-9:10am	**Opening Remarks** Dr. Stuart Turvey, Co-Lead, Precision Health	The Great Hall
9:10-9:50am	**Catalyst Grant Award Recipient Presentations** • Dr. Gillian Hanley and Dr. Janice Kwon *"Precision Health Care to Improve the Quality of Life and Long-term Health of People Entering Premature Surgical Menopause"* • Dr. Kasmintan Schrader *"Parent-of-Origin-Aware Hereditary Cancer Diagnostic and Cascade Genetic Testing"* • Dr. Ren Yuan and Dr. Calum MacAulay *"An AI model to predict future lung cancers risk with low-dose screening CT"* • Dr. Catrina Loucks *"Uncovering patient-specific genetic factors that can be used to optimize morphine-based pain relief while avoiding harm"* *Moderator: Dr. Stuart Turvey*	The Great Hall
9:50-10:40am	**Keynote Speaker** Dr. Nadine Caron, University of British Columbia *"The Silent Genomes Project"* *Introduction: Dr. Stuart Turvey*	The Great Hall
10:40-11:15am	**Coffee Break and Poster Viewing**	Foyer and The Great Hall
11:15-11:45am	**Catalyst Grant Award Recipient Presentations *(continued)*** • Dr. Carolina Tropini and Dr. Annie Ciernia *"Metabolite Control of Microbiome-Microglia Communication in Pediatric Inflammatory Bowel Disease (IBD)"* • Dr. Aline Talhouk *"Risk evaluation and omics screening for targeting prevention in endometrial cancer"* • Dr. Sarah Dada *"Use of Long Read Whole Genome Sequencing to Drive Community-Based Patient-Oriented Care for Autism Spectrum Disorder"* *Moderator: Dr. Chris Carlsten*	The Great Hall

11:45-12:30pm	**Keynote Speaker** Dr. Michael Snyder, Stanford University *"Transforming Healthcare with Big Data"* *Introduction: Dr. Chris Carlsten*	The Great Hall
12:30-1:30pm	**Lunch and Poster Viewing and Networking**	Foyer and The Great Hall
1:30-1:35pm	*Move to Breakout Session Rooms*	
1:35-2:10pm *concurrent sessions	**Breakout Sessions 1** Molecular and Adanced Pathology Core (MAPCore) *"Bringing Spatial "Omics" From Glass to Clinic"* **Breakout Session 2** PopData BC *"Using existing data to support precision health research – services through Population Data BC"*	Performance Theatre Room 2306
2:10-2:15pm	*Move to Breakout Session Rooms*	
2:15-2:50pm *concurrent sessions	**Breakout Session 3** The BC Biobank Network *"Provincial Biobanking to Support Precision Health"* **Breakout Session 4** Advanced Research Computing (ARC) *"High performance computing and data management for Precision Health research"*	Performance Theatre Room 2306
2:50-3:00pm	**Coffee Break** *Move to Breakout Session Rooms*	
3:00-3:35pm *concurrent sessions	**Breakout Session 5** The Canadian Urban Environmental Health Research Consortium *"Bringing the environment into precision health: The Canadian Urban Environmental Health Research Consortium (CANUE)"* **Breakout Session 6** Genome Sciences Centre *"How can the Genome Sciences Centre help accelerate your Precision Health project?"*	Performance Theatre Room 2306
3:35-3:40pm	*Move to The Great Hall*	
3:40-3:50pm	**Poster Awards and Closing Remarks** *Presented by: Drs. Chris Carlsten and Stuart Turvey* *End of Symposium*	The Great Hall

Welcome Message from the Precision Health Co-Leads

We are delighted to welcome you to the first ever UBC Faculty of Medicine Precision Health Symposium held at UBC Vancouver-Point Grey academic campus located on the traditional, ancestral, unceded territory of the xʷməθkʷəy̓əm (Musqueam).

This symposium brings together faculty, staff, and students across UBC faculties and departments with the goal to foster collaboration between researchers in the Precision Health field. We are very pleased to welcome our visiting keynotes speakers, Dr. Nadine Caron and Dr. Michael Snyder, and highlight their important research works. We look forward to hearing from the past recipients of the Catalyst Grant awards as well as our Breakout session presentations showcasing a variety or resources and services that can support your research.

We would like to acknowledge support from the UBC Faculty of Medicine which has allowed us to provide opportunities such as the Symposium as well as the Precision Health Catalyst Grant competition. We are able to support and strengthen our leadership in this field.

Lastly, we would also like to acknowledge our event sponsor, Genome BC, for their contributions to this Symposium.

Please enjoy the Symposium presentations and use this an opportunity to meet, connect and learn how you may collaborate with others to further research in Precision Health.

Dr. Chris Carlsten, MD, FRCPC
Professor of Medicine and Head of Respiratory Medicine, UBC
Co-Lead, Faculty of Medicine Precision Health, UBC

Dr. Stuart Turvey, MBBS, DPHIL, FRCPC
Professor of Pediatrics, Division of Allergy and Immunology, UBC
Co-Lead, Faculty of Medicine Precision Health, UBC

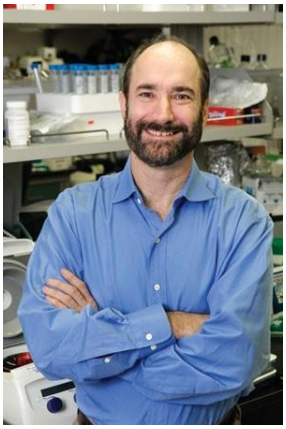
Keynote Speakers

Dr. Nadine Caron, MD, MPH, FRSC
Co-Director, Centre for Excellence in Indigenous Health
Professor, Department of Surgery, UBC Faculty of Medicine

Dr. Caron, a member of the Sagamok Anishnawbek First Nation and a surgical oncologist in northern B.C., is a professor in UBC's Northern Medical Program and department of surgery. She is an active Indigenous physician within BC Cancer, a senior scientist at Canada's Michael Smith Genome Sciences Centre at BC Cancer and Special Advisor on Indigenous Health to the Dean, Faculty of Medicine and Vice-President, Health at UBC.

Dr. Caron is the inaugural First Nations Health Authority Chair in Cancer and Wellness at UBC, a founding co-director of the UBC Centre for Excellence in Indigenous Health and consultant in development of B.C.'s first ever Indigenous Cancer Strategy to improve Indigenous cancer outcomes and experiences in B.C.

Dr. Caron is a co-lead on the Silent Genomes Project, a project that aims to address the genomic divide by reducing access barriers to diagnosis of genetic disease in Indigenous children.



Dr. Michael Snyder, Ph.D.
Chair, Dept. of Genetics, Director, Center for Genomics and Personalized Medicine, Stanford University

Dr. Snyder received his Ph.D. training at the California Institute of Technology and carried out postdoctoral training at Stanford University. He is a leader in the field of functional genomics and proteomics, and one of the major participants of the ENCODE project.

Snyder Lab was the first to perform a large-scale functional genomics project in any organism, and has developed many technologies in genomics and proteomics. These including the development of proteome chips, high resolution tiling arrays for the entire human genome, methods for global mapping of transcription factor binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, de novo genome sequencing of genomes using high throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes, proteomes and regulatory networks.

He has also combined different state-of-the-art "omics" technologies to perform the first longitudinal detailed integrative personal omics profile (iPOP) of person and used this to assess disease risk and monitor disease states for personalized medicine.

Precision Health Catalyst Grant Presenters

Precision Health Care to Improve the Quality of Life and Long-term Health of People Entering Premature Surgical Menopause

Dr. Gillian Hanley, Department of Obstetrics and Gynaecology, Faculty of Medicine; Vancouver Coastal Health Research Institute; Women's Health Research Institute
Dr. Janice Kwon, Department of Obstetrics and Gynaecology, Faculty of Medicine, BC Cancer

Project Aim: Understand how precision medicine can be used to improve the quality of life and long-term health of patients entering premature surgical menopause and apply lessons learned to a wider population of patients who would not be eligible to be seen at the clinic. This involves generating data as a catalyst for a broader project to address quality of life and longer-term health outcomes in this larger and more diverse patient population entering premature surgical menopause.

Parent-of-Origin-Aware Hereditary Cancer Diagnostic and Cascade Genetic Testing

Dr. Kasmintan Schrader, Department of Medical Genetics, Faculty of Medicine, BC Cancer

Project Aim: Generate real-world sensitivity and specificity data for calculation of optimal sample sizes needed to validate Parent of Origin(P-O)-aware genetic testing in additional Hereditary Cancer (HC) and other actionable genes. This involves a characterization of P-O effects in SDHD and SDHAF2 PV carriers, a protocol to assign P-O to SDHD variants to support personalized management recommendations, and a method to assign P-O to alleles of common HC genes and other non-cancer related actionable findings to enable focused CGT strategies.
Co-recipient: Dr. Stephen Yip, Department of Pathology and Laboratory Medicine, Faculty of Medicine; Vancouver Coastal Health Research Institute

Risk evaluation and omics screening for targeting prevention in endometrial cancer

Dr. Aline Talhouk, Department of Obstetrics and Gynaecology, Faculty of Medicine; Vancouver Coastal Health Research Institute; Women's Health Research Institute

Project Aim: Evaluate the utility of omics data obtained from minimally invasive self-testing tools, to predict Endometrial Cancer (EC) pathology and improve screening. This involves determining whether self-collected, at-home minimally invasive vaginal sampling of DNA and/or vaginal microbiome are able to predict malignant endometrial changes and stratify which patients should receive an endometrial biopsy.
Co-recipient: Dr. Anna Tinker; Department of Medicine, Faculty of Medicine; BC Cancer

An AI model to predict future lung cancers risk with low-dose screening CT

Dr. Ren Yuan, Department of Radiology, Faculty of Medicine; BC Cancer
Dr. Calum MacAulay, Department of Physics and Astronomy, Faculty of Science, BC Cancer

Project Aim: Use radiomic features and AI models to identify sub-visual changes of the "normal" lung before future cancer develops within a year and compare to those from the "normal" lung where a future benign nodule develops. This involves developing an AI tool that can predict the risk of future lung cancer from a "normal-looking" lung to human eyes on LDCT and validating it in further prospective studies. This pilot project will lay the groundwork to prospectively evaluate the utility of this AI algorithm using the BC

Lung Screening Program that will launch across BC in April of 2022 and for national and international collaborative studies with other research groups.

Metabolite Control of Microbiome-Microglia Communication in Pediatric Inflammatory Bowel Disease (IBD)

Dr. Carolina Tropini, School of Biomedical Engineering, Faculty of Medicine and Applied Science; Department of Microbiology and Immunology, Faculty of Science
Dr. Annie Ciernia, Department of Biochemistry and Molecular Biology, Faculty of Medicine; The Djavad Mowafaghian Centre for Brain Health

Project Aim: Determine the impact of early life gut inflammation on social behavior and cognition and microbiota-brain communication by capturing the full spectrum of changes and identifying novel metabolites that are altered in pediatric IBD in both sexes. The pilot project predicts that metabolite changes signal to the brain microglia and promote inflammation, which will be examined in future studies.

Uncovering patient-specific genetic factors that can be used to optimize morphine-based pain relief while avoiding harm

Dr. Catrina Loucks, Department of Pediatrics and Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine; BC Children's Hospital Research Institute

Project Aim: Catalyze the identification of clinically-relevant genetic factors that predict the safe and effective use of morphine in children through development of a C. elegans platform to validate the roles of novel genetic variants impacting morphine responses uncovered through a larger grant.
Co-recipient: Dr. Colin Ross, Faculty of Pharmaceutical Sciences, BC Children's Hospital Research Institute

Use of Long Read Whole Genome Sequencing to Drive Community-Based Patient-Oriented Care for Autism Spectrum Disorder

Dr. Sarah Dada, Bioinformatics, Faculty of Science, University of British Columbia, BC Cancer Research Institute, Michael Smith Genome Science Centre

Project Aim: Use new methods of long read whole genome sequencing to ascertain culpable variants within individuals and families with ASD to provide earlier, targeted, and individualized treatment. This involves completing a workup of patient genome and key findings for correlation to variants identified and for translation to precision medicine practice. Patients and families will also receive genetic counseling related to the findings.
Recipients: Drs. Anamaria Richardson, Department of Pediatrics, Faculty of Medicine; BC Children's Hospital Research Institute and Suzanne Lewis, Department of Medical Genetics, Faculty of Medicine; The Djavad Mowafaghian Centre for Brain Health; BC Children's Hospital Research Institute

Breakout Sessions

The BC Biobank Network *Provincial Biobanking to Support Precision Health*	Introduction to the BC Biobank Network, how it operates and how it can support provincial outreach to enable provincial research. Anyone using biospecimens for their research or recruiting participants would benefit from attending this breakout session.
Population Data BC *Using existing data to support precision health research – services through Population Data BC*	This session will be relevant both to people who are just generally curious about using existing data for research, as well as to those who are already using such data but want to hear about new opportunities or ask questions about innovative directions. Learning outcomes: 1) Awareness of linked / linked data sets and other resources available through PopData 2) Understanding of how to add researcher-collected data, where that is desired 3) Introduction to training resources available
The Canadian Urban Environmental Health Research Consortium *Bringing the environment into precision health: The Canadian Urban Environmental Health Research Consortium (CANUE)*	This session will be of interest to anyone interested in incorporating individual level environmental information into their project. Participants in this session will: 1) Gain an understanding of CANUE, its data holdings, and the approach used to gather, document and disseminate environmental exposure data with researchers from across Canada. 2) Learn how to access and make use of CANUE data to leverage information about environmental exposures for precision health research projects. 3) Develop familiarity with research facilitated by CANUE data.
Advanced Research Computing *High performance computing and data management for Precision Health research*	UBC Advanced Research Computing supports cutting-edge research through high-performance and cloud computing, big data storage and transfer services, and more. Whether you need support working with sensitive health data, such as genomics or multi-omics data, or are navigating a data management plan for a grant or project proposal, ARC has a team of experts dedicated to helping you succeed. Join us for our presentation and discover how you can leverage powerful, secure, and reliable computing solutions optimized to meet the needs of your precision health research project

Genome Sciences Centre *How can the Genome Sciences Centre help accelerate your Precision Health project?*	Learn how the Genome Sciences Centre can help accelerate your research. Long read, single cell, short read, whole genome, transcriptome, epigenomics, targeted approaches and more. Technical expertise to help experimental design, large analysis platforms with extensive bioinformatic expertise. Bespoke projects also supported. This session is for anyone who is interested in generating sequence data would benefit from seeing what the GSC can offer to support their projects.
Molecular and Advanced Pathology Core (MAPCore) *Bringing Spatial "Omics" From Glass to Clinic*	Learning outcomes: 1) Examples of how molecular pathology can progress translational discoveries 2) Introduction of MAPcore and overview of services we provide 3) Overview and applications of multiplex immunofluorescence, digital spatial profiling, and HALO image analysis

Poster Presentations

Poster 1

Developing a Conceptual Model for the Massification of Specialized Precision Medicine

Linlea Armstong[1, 2], Leah Prentice[2], Jessica Zambonin [1, 2], Cornelius F. Boerkoel[1, 2]

[1]Department of Medical Genetics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[2]Provincial Medical Genetics Program, BC Women's Hospital

Background: The Provincial Medical Genetics Program has a long history of excellence in applying genetic information to inform care of patients. The traditional approach was highly personalized, labour intensive, and focused on serving the deep needs of a low volume of patients with ultra-rare diseases. The revolution in genetic and genomic diagnostics coupled with increasing opportunities for clinical actionability have accelerated referrals and expectations. The Program's now >50 members must emerge a massified service, with due attention to equity in patient care, consistency, efficiency, ongoing quality improvement, and management of workload for providers. This must maintain the flexibility to accomplish the highly innovative, individualized translational aspects of care required to resolve outstanding precision diagnostic and therapeutic problems in conjunction with local and international clinical and research resources.

Methods: Inspired by the methodology of Stanford's Hasso Plattner Institute's Design Based Thinking, we developed a conceptual model for how providers in an academic translational program can cooperate together to meet high volume demands. We developed an advisory committee, reviewed the literature and the approaches of programs in other jurisdictions, and tested application of concepts to move through the phases of empathizing, defining, and ideating.

Results: A visual model emerged that acknowledges the overlapping key activities of a program providing precision care at a massified scale, while maintaining capacity to meet highly individual and translational needs.

Conclusions: The model holds all members responsible to contribute to defining the standards of care for the Program's care pathways, and supports members to additional differential involvement/specialization across the following key activities: provider to provider consultation, direct patient care via high volume models, academic (quality improvement and teaching), research aligned to needs of Program patients/Program priorities, and enablement of research informed by Program expertise/data but distinct from Program priorities.

Poster 2

Evaluating treatment outcomes in pharmacogenomic-guided care for depression: a rapid review and meta-analysis

Mary Bunka[1,2], Gavin Wong[1,2*], Dan Kim[1,2], Louisa Edwards[1,2], Jehannine Austin[3,4,5], Mary M. Doyle-Waters[2], Andrea Gaedigk[6,7], Stirling Bryan[1,2]

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[3]BC Mental Health and Substance Use Services Research Institute, UBC, Vancouver, BC, Canada;
[4]Department of Psychiatry, University of British Columbia (UBC), Vancouver, BC, Canada;
[5]Department of Medical Genetics, University of British Columbia (UBC), Vancouver, BC, Canada;
[6]Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, MO, USA;
[7]Department of Pediatrics, University of Missouri-Kansas City, Kansas City, MO, USA

Background: Guiding medication choices using pharmacogenomic (PGx) tests offers the prospect of improved remission and response for patients with major depressive disorder. This rapid review examines treatment outcomes in patients undergoing PGx-guided treatment for depression versus unguided treatment.

Methods: Searches in MEDLINE, Embase, PsycInfo, and CENTRAL, plus hand-searches, resulted in 2,289 abstracts. After removing exclusions, two reviewers independently screened 184 full-texts. The first reviewer extracted data from randomized controlled trials (RCTs), including participant characteristics, treatment outcomes, and study discontinuation rates, conducting a critical analysis using the Cochrane Risk of Bias Version 2 (RoB2) tool. The second reviewer checked for accuracy and agreement. Random effects meta-analyses of outcomes, such as response (a 50% improvement on HAM-D17 scale) and remission (scoring in the "non-clinical" range of the HAM-D17), were conducted.

Results: Ten RCTs that enrolled adult patients with moderate-to-severe depression were included. Eight RCTs (n=2,341) reported remission, while seven (n=2,188) reported response. The risk ratio (RR) of remission was 1.46 (95% CI: 1.02-2.08), while that of response was 1.32 (95% CI: 1.00-1.73), in the PGx-guided arm compared to treatment-as-usual. No significant differences were found for total discontinuation, serious adverse events, withdrawal due to adverse effects, or mortality. Risk of bias was deemed high and GRADE certainty in the evidence was very low.

Conclusion: Our comprehensive review of the best available evidence suggests that PGx-guided care for depression is more likely to result in remission and response to treatment than standard of care. Despite the limitations in the evidence base, including high risk of bias and inconsistency between trials, there is confidence in the direction of effect. Though modest, the beneficial effects of PGx for those with moderate-severe depression could have major ramifications for patients and the health system.

Poster 3

Characterizing SHPRH as a Novel Tumour Suppressor Gene in Lung Adenocarcinoma

Sihota TS[1,2], **Chuang YC[1,3]**, Nagelberg AL[1,2], Chow JLM[1], Shi R[1,3], and Lockwood WW[1,2,3].
[1]Department of Integrative Oncology, BC Cancer Research Institute, Vancouver, BC, Canada
[2]Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
[3]Interdisciplinary Oncology Program, University of British Columbia, Vancouver, BC, Canada
Funding by: LCRF, CIHR

Background: Late-stage diagnosis of lung cancer (LC) is associated with poor prognosis and survival, highlighting a need for increased understanding of LC risk factors to support early screening and treatment strategies. LC incidence is a complex interplay of environment and genetics, with the specific genes underlying increased susceptibility still poorly understood. Whole exome sequencing on never-smoker patients with lung adenocarcinoma (LUAD) identified a gene potentially linked to LC initiation: *SNF2 Histone Linker PHD RING Helicase* (*SHPRH*). Due to frequent double allelic disruptions and its chromosomal location within a major LC susceptibility locus, we predict that SHPRH may function as a tumour suppressor in LUAD. This project aims to evaluate the effects of altered SHPRH expression on LUAD development and progression and explore its role in tumour suppression.

Methods: To assess clinical relevance, we analyzed LUAD datasets for SHPRH copy number and expression level differences in association with survival outcomes. To functionally characterize SHPRH's role in LUAD tumorigenesis, a doxycycline-inducible lentiviral vector system was used to conditionally express SHPRH in LUAD cell lines. *In vitro* and *in vivo* assays were performed to assess alterations in tumorigenic potential.

Results: Analysis of the TCGA LUAD dataset (n=230) reveals that SHPRH is mutated or homozygously deleted in 7% of LUADs and 52.2% demonstrate single copy loss. LUAD patients with reduced SHPRH expression have significantly worse overall and progression-free survival outcomes. SHRPH re-expression in cell lines with inactivating alterations reduces anchorage-dependent and -independent colony growth *in vitro*. Implantation of these cells into mice show that SHPRH re-expression significantly reduced tumour burden *in vivo*.

Conclusions: SHPRH expression may be positively associated with better patient outcomes and reduce the tumorigenic potential of LUAD. SHPRH's chromosomal location and potential role as a tumour suppressor may make it a promising clinical biomarker for patients at increased risk for LC.

Poster 4

Use of long read whole genome sequencing for precision diagnosis and treatment of individuals with Autism Spectrum Disorder

Sarah Dada[1,2,3,4], Sally Martell[3,4], Ying Qiao[3,4], Kristina Calli[3,4], Kieran O'Neill[1,2,4], Katherine Dixon[1,2,4], Suzanne Lewis[3,4], Steven Jones[1,2,4]
[1]Michael Smith Genome Sciences Centre
[2]British Columbia (BC) Cancer Agency
[3]British Columbia (BC) Children's Hospital
[4]University of British Columbia
Funding by: Genome British Columbia, BC Cancer Agency

Background: Autism Spectrum Disorder (ASD) is the most common childhood developmental disability, affecting 1 in 58 Canadian school-aged children. ASD is defined by deficits in social communication and interactions, as well as restricted and repetitive behaviours. ASD diagnosis is complex with a highly variable pattern of behavioural symptoms, including co-morbidities (e.g. seizures). ASD is heterogeneous and can be caused genetically by both inherited and *de novo* mutations. Structural Variants (SV) represent substantial genomic diversity. Their role in ASD is undetermined, largely due to limitations in the commonly used short read whole genome sequencing (WGS). Similarly, aberrant DNA methylation is known to be associated with ASD. Long read genome sequencing offers previously unseen insight into the genome of individuals with ASD at a reasonable cost, while deriving small variants, SV, and methylation patterns. My project will derive and integrate previously unseen genomic changes identified from long read genome sequencing with phenotypic (symptom-based) data, to improve diagnosis and treatments in participants with ASD.

Methods: From a cohort of 500 participants with childhood ASD I will identify participants who have no definitive genetic abnormalities from pre-existing short read WGS. Using long read WGS I will analyze and determine the impact of participants' structural variants, their methylome and imprinting, and their small variants. Among possible causal variants I will look for variant association within the original cohort and publicly available data, and integrate the genomic data with the participants' clinical phenotype to resolve the implicated behavioural impacts.

Results: I have currently discovered novel complex large structural variants and associated methylation patterns among several patients.

Conclusion: This project will increase the clinical utility genomic data by providing a stable and defined ASD view of the patient, which will allow us to provide an individualized and cost-effective treatment in an anticipatory, rather than a reactive way.

Poster 5

Identification of a Novel Subtype of Endometrial Cancer With Unfavourable Outcome Using Artificial Intelligence-Based Histopathology Image Analysis

Amirali Darbandsari[1], Hossein Farahani[2,3], Purang Abolmaesumi[1], Samuel Leung[4], Stefan Kommoss[5], David Huntsman[3,4], Aline Talhouk[3], C. Blake Gilks[3,6], Jessica N. McAlpine[7], Ali Bashashati[2,3]

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[6]Vancouver General Hospital, Vancouver, BC, Canada
[7]Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, University of British Columbia, Vancouver, BC, Canada
Funding by: CCSRI, MSFHR

Background: ProMisE was developed by our team as a pragmatic, cost-effective, and clinically applicable molecular classifier for endometrial cancer (EC) patients. ProMisE has four subtypes: (i) *POLE* mutant (*POLE*mut), (ii) mismatch repair deficient (MMRd), (iii) p53 abnormal (p53abn), and (iv) NSMP (No Specific Molecular Profile), lacking any of the defining features of the other three subtypes. Within each subtype, there are clinical/prognostic outliers. This is particularly evident within the largest subtype; NSMP (~50% of ECs), where a subset of patients experience a very aggressive disease course, comparable to patients with p53abn.

Methods: We hypothesized that objective assessment of the digitized hematoxylin and eosin (H&E)-stained histopathology slides of NSMP could potentially identify outliers. We developed an artificial intelligence (AI)-based image analysis model to identify the NSMP cases that had similar histopathological features to the p53abn subtype, as assessed by H&E stain. We used a discovery cohort of 182 and an external validation cohort of 195 NSMP ECs.

Results: Our AI-based image analysis model identified 21 (11.5%) out of the 182 NSMP cases with similar histopathological features as p53abn cases. We refer to these cases as p53abnlike-NSMPs. Compared to the rest of the NSMP cases, these cases had markedly inferior disease-specific survival (DSS) (10-year DSS 58.9% vs. 93.1% (p<3.44e-8)) and progression-free survival (PFS) (10-year PFS 55.1% vs. 91.4% (p<3.76e-06)). These findings were confirmed in our validation cohort, with 10.7% of the 195 patients categorized as p53abnlike tumors with 10-year DSS of 51.3% vs. 82% (p<5.28e-5) and PFS of 56.6% vs. 89.3% (p<2.15e-4).

Conclusions: Utilizing an AI-based approach for histopathology image analysis, we have discovered p53abnlike-NSMPs, a novel subtype of NSMP ECs with morphological features similar to p53abn cases. p53abnlike-NSMPs exhibit similar clinical behavior as p53abn, having noticeably inferior outcome compared to the rest of the NSMP cases in two independent cohorts.

Poster 6

Inhibition of CETP Activates Macrophages to Rescue Mice from Streptococcus Pneumoniae-Induced Sepsis

Haoyu Deng[1,2], Wan Yi Liang[3], Le Qi Chen[3], Tin Ho Yuen[3], Mark Trinder[2,4], Patrick C.N. Rensen[5,6], John H. Boyd[1,2], and Liam R. Brunham[1,2]

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[6]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands

Backgrounds: Sepsis is a leading cause of mortality. Low HDL-cholesterol levels are associated with an increased risk of death from sepsis, and increasing levels of HDL by inhibition of cholesteryl ester transfer protein (CETP) decreases mortality from sepsis in a *APOE*3-Leiden.CETP* mice, a well-established model for human lipid metabolism.

Methods: We studied the effect of the CETP inhibitor, anacetrapib, on *Streptococcus pneumoniae*-induced sepsis in female *APOE*3-Leiden* and *APOA1.CETP* mice. We determined pro-inflammatory cytokines in bronchial lavage (BAL) and blood (ELISA), macrophage function in both blood and BAL (flow cytometry) and abundance of pro-inflammatory macrophages in lung and liver (immunohistochemistry). Western blot was performed to study the mechanism of macrophage activation by CETP inhibition. Finally, we evaluated the effect of anacetrapib in rescuing APOA1.CETP mice after the onset of *S. pneumoniae*-induced sepsis.

Results: CETP inhibition by anacetrapib significantly improved survival of mice from sepsis challenge, which is likely due to the maintenance of high HDL levels. CETP inhibition negatively regulated the host pro-inflammatory response via attenuation of pro-inflammatory cytokine transcription and release, alleviating immune-mediated organ damage, and promoted macrophage activation in the blood and accelerated macrophage infiltration into both the lung and liver. *In vitro* experiments revealed that CETP inhibition significantly decreases caspase-1 and COX-2 protein expression in peripheral blood mononuclear cells and THP1 cells, which likely represents a novel mechanism responsible for improved bacterial clearance during sepsis. In addition, CETP inhibition attenuated pro-inflammatory cytokine production by enhancing the availability of HDL and thereby sequestrating LPS. From a clinical translational perspective, our study unprecedentedly confirms that sepsis-induced mortality in mice can be reduced with CETP inhibition both pre-infection and post-infection.

Conclusions: CETP inhibition appears as a novel treatment option for bacterial sepsis by maintaining high HDL levels to sequester inflammatory pathogen-associated lipids, and activating macrophages to mediate bacterial clearance.

Poster 7

Epitope Compatibility to Guide Deceased Donor Kidney Allocation: Recommendations from a Pan-Canadian Online Public Deliberation

Louisa Edwards[1], Colene Bentley[2], Michael Burgess[3], Ruth Sapir-Pichhadze[4], Teresa Atkinson[5], Jennifer Desjardins[5], Paul Keown[6], Stirling Bryan[1]

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Funding by: Genome Canada, Genome British Columbia, Canadian Institutes of Health Research (awards LSARP 273AMR and GP1-155871). Author RSP is also supported by Fonds de recherche du Quebec—Santé chercheur boursier clinician award (grant no. 254386).

Background: The increasing demand for kidneys, coupled with their scarce supply, necessitates finding ways to reduce rejection and improve transplant outcomes. Longer-lasting kidneys might result from greater epitope compatibility – donor-recipient matching on targeted immune system protein molecules. However, adding epitope-based criteria to deceased donor allocation decisions would alter the current waitlist system for recipients, with transplant outcomes prioritized over wait times. We sought public input to identify trade-offs and guide Canadian policymakers and health professionals in deciding how best to allocate kidneys fairly, should epitope compatibility be adopted.

Methods: Postal invitations were sent to 35,000 randomly-selected households across Canada, with over-sampling of rural/remote locations. Participants were selected to ensure socio-demographic diversity and geographic representation. Five two-hour online sessions were held from November-December 2021. Participants received an information booklet and heard from expert speakers prior to deliberating. During small- and large-group facilitated discussions, participants deliberated on how epitope compatibility could be implemented fairly for transplant candidates, and governance issues. Participants collectively generated and voted on recommendations on these topics. In a final policy panel session, kidney donation and allocation policymakers engaged with participants. All sessions were recorded and transcribed.

Results: Thirty-three participants (18 female, 15 male) took part and generated nine recommendations. There was consensus on adding epitope compatibility to the existing deceased donor kidney allocation criteria. However, participants recommended including safeguards and flexibility around this (e.g., mitigating declining health). They specified that a transition period was needed before implementing epitope compatibility, which included an ongoing comprehensive public education program. Participants unanimously recommended regular monitoring of outcomes of epitope compatible transplants, and noted that this should be publicly shared.

Conclusion: Participants supported adding epitope compatibility to kidney allocation criteria, but wanted safeguards and flexibility around implementation. These recommendations can provide guidance to policymakers regarding including epitope-based deceased donor allocation criteria.

Poster 8

Cellular and Molecular Biomarkers of Long COVID: A Scoping Review

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Funding by: Canadian Institutes of Health Research (177747)

[Abstract] Background: Long-COVID (LC) encompasses diverse symptoms lasting months after the initial SARS-CoV-2 infection. Symptoms can be debilitating and affect the quality of life of individuals with LC and their families. Although the symptoms of LC are well described, the aetiology of LC remains unclear, and consequently, patients may be underdiagnosed. Identification of LC specific biomarkers is therefore paramount for the diagnosis and clinical management of the syndrome. This scoping review describes the molecular and cellular biomarkers that have been identified to date with potential use for diagnosis or prediction of LC.

Methods: This review was conducted using the Joanna Briggs Institute (JBI) Methodology for Scoping Reviews. A search was executed in the MEDLINE and EMBASE databases, as well as in the grey literature for original studies, published until October 5th, 2022, reporting biomarkers identified in participants with LC symptoms (from all ages, ethnicities, and sex), with a previous infection of SARS-CoV-2. Non-English studies, cross-sectional studies, studies without a control group, and pre-prints were excluded. Two reviewers independently evaluated the studies, extracted population data and associated biomarkers.

Results: 23 cohort studies were identified, involving 2211 LC patients [median age 51·8 years, predominantly female sex (61·10%), white (57%), and non-vaccinated (99%)]. A total of 239 candidate biomarkers were identified, consisting mainly of immune cells, immunoglobulins, cytokines, and other plasma proteins. 18 of the 239 candidate biomarkers identified were evaluated by the authors, by means of receiver operating characteristic (ROC) curves.

Conclusions: Diverse cellular and molecular biomarkers for LC have been proposed. Validation of candidate biomarkers in independent samples should be prioritized. Modest reported performance (particularly in larger studies) suggests LC may encompass many distinct aetiologies, which should be explored e.g., by stratifying by symptom clusters and/or sex.

Poster 9

Exploring the value of pharmacogenomic-guided treatment for major depression: a model-based economic analysis

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Funding by: This study was funded by Genome BC, Genome Canada, and Michael Smith Health Research BC.

Background: Pharmacogenomics (PGx) testing, one of the most promising recent genomic advances, can guide prescribing in search of enhanced efficacy and fewer side effects. People with major depressive disorder (MDD) often receive pharmacological treatment, but finding an effective medication can be a lengthy trial-and-error process. Response to antidepressants partly reflects variation in genes that influence medication metabolism. PGx testing, therefore, potentially represents a major therapeutic advance. We sought to establish the cost-effectiveness of PGx for MDD patients.

Methods: We developed a microsimulation Markov model of MDD care pathways in British Columbia (BC), Canada, to evaluate the effectiveness and cost-effectiveness of PGx testing from the public payer's perspective, over 20 years. The model includes unique patient characteristics (e.g., metabolizer phenotypes) and uses estimates derived from systematic reviews, administrative data analyses, and expert judgments. We estimated incremental costs, life-years (LYs), and quality-adjusted life-years (QALYs) for a representative MDD patient cohort in BC. We conducted extensive sensitivity analyses.

Results: PGx testing, if implemented in BC for adult patients with moderate-severe MDD, is predicted to save the health system CAD$848 million, and bring health gains of 11,160 LYs and 63,696 QALYs over 20 years. These savings are mainly driven by slowing or avoiding the transition to refractory (treatment-resistant) depression. PGx-guided care is associated with 47% fewer refractory patients over 20 years. All sensitivity analyses supported the robustness of these findings.

Interpretation: PGx testing offers the opportunity for a major value-promoting investment by health systems; specifically, population health gains combined with health system cost reductions.

Poster 10

SGLT2 inhibitor attenuates doxorubicin-induced cardiotoxicity in iPSC-derived cardiomyocytes

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Funding by: Canadian Institute of Health Research

Background: Doxorubicin is a commonly used chemotherapy drug that treats both adult and childhood cancers, but its clinical usefulness is limited by doxorubicin-induced cardiotoxicity (DIC). The incidence of DIC increases up to 65% at cumulative doses of 550 mg/m^2, which leads to irreversible heart failure and death. Sodium-glucose transport protein 2 (SGLT2) inhibitors are effective glucose-lowering medications that are indicated for type 2 diabetes mellitus treatment. SGLT2 inhibitors have also been demonstrated to be effective for the treatment of heart failure, and may have cardioprotective effects. We hypothesized that the SGLT2 inhibitor, empagliflozin, would be protective against DIC.

Methods: Using our established patient-specific induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) model of DIC, we performed cell viability assay, RNA sequencing, metabolomics assays as well as CRISPR/Cas9 genome editing techniques to evaluate the drug effects of empagliflozin against DIC.

Results: We found that co-treatment of empagliflozin reduced doxorubicin-induced cell death in multiple iPSC-CM lines. Transcriptomic analysis showed that co-treatment with empagliflozin up-regulated fatty acid metabolism and calcium homeostasis in iPSC-CM under doxorubicin treatment. Metabolomic analysis on central carbon metabolism-related metabolites showed increased ketone bodies level when co-treated with empagliflozin. Comparison of doxorubicin-treated SGLT2 and SGLT1 knock-out iPSC-CM lines indicated that the cardioprotective effect of empagliflozin was dependent on the presence of SGLT1, but was independent of the presence of SGLT2.

Conclusions: Our findings identify empagliflozin as a potential cardioprotective agent against DIC. The cardioprotective mechanisms of empagliflozin act via metabolomic alteration in fatty acid and ketone body metabolism, and are dependent on the inhibition of SGLT1. These results provide insight into the future clinical application of SGLT2 inhibitors to prevent cardiac toxic events in cancer patients who received anthracycline therapies.

Poster 11

Characterizing an Arrhythmia-Related Titin Mutation Using Patient Stem Cell-Derived Atrial Cardiomyocytes

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Funding by: Canadian Institutes of Health Research, Michael Smith Foundation for Health Research, Stem Cell Network, University of British Columbia CAPP Program

Background: Atrial fibrillation (AF) is a common heart rhythm disorder that is linked to a greater risk of ischemic stroke and heart failure. Multiple genetic studies have identified an association between protein truncating mutations in the *titin* gene and increased risk of AF. However, the structural and functional consequences of titin mutations in atrial cardiomyocytes and how such mutations lead to arrhythmias are unclear. Our objective was to investigate the cellular effects of titin mutations identified in patients with unexplained AF.

Methods: We identified a titin mutation in a patient with early-onset AF and generated patient-specific induced pluripotent stem cell lines (iPSCs). We used CRISPR/Cas9 homology-directed repair to perform genome-editing of the patient iPSCs and corrected the titin mutation to wildtype. We differentiated titin-mutated and wildtype iPSCs into atrial-like and ventricular-like cardiomyocytes. We characterized cellular electrophysiology by optically mapping voltage and calcium transients and assessed the organization of cardiomyocyte sarcomere structures through immunofluorescent staining of sarcomere proteins and confocal microscopy.

Results: iPSC-derived atrial cardiomyocytes displayed cell type-specific characteristics including faster beat rates (mean±sem, beats/minute: 150.9±21.8 vs. 21.9±3.6; $p = 0.01$) and shorter rate-corrected action potentials ($cAPD_{80}$: 195.9±23.8 vs. 394.7±42.8 ms; $p = 0.048$) compared to ventricular cardiomyocytes. Analysis of sarcomere organization showed poorer structural alignment in iPSC-derived atrial cardiomyocytes with the titin mutation than wildtype (% organization: 66.3±6.8 vs. 88.0±2.9; $p = 0.03$). Similarly, ventricular cardiomyocytes with the titin mutation showed poorer sarcomere organization than wildtype (62.0±3.9 vs. 82.9±2.9; $p = 0.008$).

Conclusions: The titin mutation leads to abnormal sarcomere organization in both atrial and ventricular iPSC-derived cardiomyocytes and this phenotype can be reverted through CRISPR/Cas9 correction of the titin mutation to wildtype. These findings further our understanding of the role of titin in the atria and provide insight to the mechanisms by which titin mutations may promote arrhythmogenesis.

Poster 12

Effects of diesel exhaust exposure on prothrombotic and inflammatory markers in ex-smokers with COPD: a randomized, double-blinded, cross-cover study

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Funding by: Canadian Respiratory Research Network

Background: Inflammation plays a critical role in the pathophysiology of cardiopulmonary diseases such as chronic obstructive pulmonary disease (COPD). Investigating the impact of traffic-related air pollution on prothrombotic and inflammatory markers can inform of the mechanisms for negative health impact of air pollution exposures. The aim of this study was to determine the impact of acute diesel exhaust (DE) exposure on blood and urine prothrombotic and inflammatory markers in those with and without COPD.

Methods: Twenty-nine research participants (age 40-80) were recruited in this randomized, double-blinded, cross-over, controlled human exposure study to DE. Participants included former smokers with mild-moderate COPD (GOLD I and II), former smokers without COPD, and healthy never-smokers. Each participant was exposed to DE (300 μg/m^3 of $PM_{2.5}$) and filtered air (FA) for 2 hours with a 4-week washout period in between. Blood and urine samples were collected at baseline and 24 hours after each exposure. Plasma fibrinogen and serum plasminogen activator inhibitor-1 (PAI-1) concentrations were quantified using ELISAs. Urinary eicosanoids concentrations were quantified via LC-MS/MS. Linear mixed effects models were used for statistical comparisons.

Results: COPD participants showed a significant increase in plasma fibrinogen (1.21 [1.06 to 1.38], p=0.006) after DE exposure relative to FA exposure, but no significant DE-associated change in serum PAI-1. There were borderline significant DE-associated serum PAI-1 changes among healthy participants (1.12 [1.00 to 1.25], p=0.05) and ex-smokers without COPD (0.91 [0.83 to 1.01], p=0.07). COPD participants showed pollution-attributable increase in urinary thromboxane A_2 metabolite concentrations as follows: 11-dehydro TXB_2 (1.45 [1.02 to 2.08], p=0.04); 2,3-dinor-TXB_2(1.45 [1.05 to 2.00], p=0.03).

Conclusions: Acute DE exposure was associated with increased prothrombotic and inflammatory blood and urine markers in participants with mild-moderate COPD. These biomarkers may be a useful tool for precision health in managing environmental exposure risks.

Poster 13

Premature Atherosclerotic Cardiovascular Disease during a Low-carbohydrate High-fat (Ketogenic) Diet: A case series

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Funding by: non-applicable

Background: Low-carbohydrate high-fat (LCHF) or ketogenic diets (KDs) have been promoted for management of several chronic diseases including diabetes and obesity. These dietary patterns are characteristically high in saturated fats and low in carbohydrates in order to induce ketogenesis. A known risk of KDs is that they may trigger hypercholesterolemia. However, there is limited data on their effect on atherosclerotic cardiovascular disease (ASCVD).

Methods: We collected data on lipid levels and cardiovascular risk factors (CV RFs) of patients referred to a specialty Lipid clinic with marked hypercholesterolemia following a KD. We report a case series of 3 individuals with markedly elevated low-density lipoprotein cholesterol (LDL-C) following a KD with subsequent evidence of premature atherosclerosis.

Results: All 3 patients presented with severe hypercholesterolemia (LDL-C >5 mmol/L) during a KD. In all cases, this represented a >2x increase in LDL-C compared to baseline, pre-KD. Patient 1 was a 37-year-old previously healthy male presenting with a myocardial infarction following 2 years of KD (baseline LDL 3.23 vs 9.19 on KD). Patient 2, a 51-year-old male with no known CV RFs adopted a LCHF diet for 4 years and was subsequently found to have diffuse ASCVD in 4 coronary segments on angiography (baseline LDL 4.2 vs 6.87 on KD). Patient 3, a 54-year-old female with probable FH, presented with worsening dyslipidemia and extensive ASCVD requiring coronary artery bypass grafting following 2 years of KD (baseline LDL 5.63 vs 25.62 on KD).

Conclusion: These cases illustrate the extreme hypercholesterolemic response and potential for ASCVD development during LCHF diets, even among young individuals. As case series, no causal relationship can be inferred from these findings. However, these cases highlight the importance of close monitoring of patients on KDs, and the need for more formal studies of the cardiovascular risk associated with this increasingly popular dietary pattern.

Poster 14

Deep Learning Segmentation Model for Automated Detection and Quantification of Evolving Patterns of Pneumonia on CT

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Funding by: VCHRI

Objective: To demonstrate an accurate method the illustrates the abnormal parenchymal tissue while accounting for normal pulmonary anatomy.

Methods: 784 CT scans were categorized into 6 specific patterns and further divided into test (128), training set (524) and validation set (132). We had also used heuristic models such as HU thresholding and vessel segmentation thresholding, in addition to the AI model so that we obtain an improved accuracy.

Results: Model B showed the best diagnostic performance with 99.29% accuracy and background sensitivity of 99.88% in comparison to ground truth. Model C showed a higher sensitivity (46.06%) and lower PPV (66.63%) than Model B (Sn 42.50%, PPV 68.09%). DL based automated detection of lung infection using CT images holds great potential in augmenting healthcare strategies in the management of pulmonary infection, such as evolving patterns of pneumonia. This model also provided percentage estimation of well-aerated lungs, a critical parameter in determining treatment strategies, conventionally limited to only qualitative assessment by human radiologists.

Conclusion: This deep learning segmentation model has significant clinical value in quantifying pulmonary disease, which is difficult to quantify by a human, when considering the effect of temporality and progression of the illness.

Poster 15

Human Germline Heterozygous Gain-of-Function *STAT6* Variants Cause Severe Allergic Disease

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Funding by: CIHR

Background: STAT6 (Signal transducer and activator of transcription 6) is a transcription factor that plays a central role in the pathophysiology of allergic inflammation. We have identified 16 patients from 10 families spanning 3 continents with a profound phenotype of early-life onset allergic immune dysregulation, widespread treatment-resistant atopic dermatitis, hypereosinophilia with eosinophilic gastrointestinal disease, asthma, elevated serum IgE, IgE-mediated food allergies and anaphylaxis.

Methods: The cases were either sporadic (7 kindreds) or followed an autosomal dominant inheritance pattern (3 kindreds). All patients carried monoallelic rare variants in STAT6. Patient variants were modelled in HEK293 cells for luciferase assays and quantification of pSTAT6 through flow cytometry. Jurkat T-cells were stably transfected with patient variants for RNAseq analysis. scRNAseq, dephosphorylation of STAT6, and intracellular cytokine staining were conducted in patient primary T-cells for further characterization of this new disease.

Results: Functional studies established their gain-of-function (GOF) phenotype with sustained STAT6 phosphorylation, increased STAT6 target gene expression, and TH2 skewing. Precision treatment with the anti-IL-4Rα antibody, dupilumab, was highly effective improving both clinical manifestations and immunological biomarkers.

Conclusion: This study identifies heterozygous GOF variants in STAT6 as a novel autosomal dominant allergic disorder. We anticipate that our discovery of multiple kindreds with germline STAT6 GOF variants will facilitate the recognition of more affected individuals and the full definition of this new primary atopic disorder.

Poster 16

Lineage tracing and fate mapping group 2 Innate lymphoid cells

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Introduction: Innate lymphoid cells (ILCs) are frontline immune-modulatory cells involved in the early stages of host defense and maintenance of tissue homeostasis, particularly at mucosal surfaces such as the small intestine, lung, and skin. The ILC family is classified into five major groups: NK, ILC1s, ILC2s, ILC3s, and LTi, based on their developmental trajectories and functional characteristics. Their significance in specific immune responses and diseases is only beginning to be understood, and the mechanisms by which ILCs regulate inflammatory conditions still remains elusive.

Methods: To pinpoint the functional role of ILC2 in vivo, we have now developed Il17rbeGFP-CreERT2 transgenic mice and conducted several experiments (flow cytometry and ScRNA-seq) to show that they express tamoxifen-inducible Cre-ERT2 and GFP under the control of the endogenous Il17rb promoter/enhancer.

Results: This unique mouse model enables selective lineage tracing and fate mapping of Il17rb- expressing ILC2s and ILC2 progenitors across all anatomical locations. It has allowed us to monitor the emergence, development and history of ILC2s throughout life and then to inactive ILC-associated genes in these cells and evaluate how these changes alter homeostatic conditions and disease trajectory in a variety of animal models.

Conclusion: The fact that Il17rb selectively marks ILC2s in vivo demonstrates that Il17rb-eGFP-CreERT2 mice are an attractive tool for studying ILC2 development, migration, and plasticity in homeostatic conditions and inflammatory diseases.

Poster 17

Local Perfusion Index: Investigating User-Specific Variations and Sensor Placement Effects

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Introduction: Photoplethysmography (PPG) is an optical sensor for non-invasive monitoring of cardiac function. PPG measurements can be affected by multiple factors, including blood volume changes, tissue structure, and sensor-to-skin contact. This study aimed to examine perfusion index (PI) across different sensor placements/attachments.

Methods: Experiment1 (E1) involved 3 tests. In E1-Test1, PPG1 and PPG2 were attached to the base of the index finger and the top of the middle finger, respectively. In E1-Test2, both PPGs were removed and re-attached to the same locations. After E1-Test2, participants made some random hand/arm movements. Following that, E1-Test3 was performed (no change in sensor placements/attachments). Experiment2 (E2) involved testing 3 PPGs at 4 body sites, including: Fingers, Forehead, Ears, and Forearm/Wrists. PPG measurements of all tests were used to estimate the heart rate (for verification) and local PI. All tests involved 100s of continuous and synchronized multi-PPG data collection (10 healthy participants).

Results: The findings of both experiments revealed significant variability in the PI range across participants. The outcome of E1 showed that for all participants, PI measurements of each PPG were significantly different before/after sensor re-attachment, and after hand/arm movements. Across all participants, the average PI was lower at the base of the finger compared to the top of the finger. The outcome of E2 suggests that although PI variations exist across the same body sites (e.g., top vs. base of the finger, front vs. side of the forehead), on average, PI was the highest on “Fingers” and was the lowest on the “Forearm/Wrist”.

Conclusions: The findings of this study revealed PI variability across different participants, and PI sensitivity to various sensor placement conditions. Considering the popularity of PPG use in clinical applications and wearable technologies, interpretation of PI measurements should be done with caution, while employing a user-centric approach (informed by anatomical/physiological characteristics).

Poster 18

Multi-focal genomic dissection of synchronous primary and metastatic tissue from de novo metastatic prostate cancer

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Background: *De novo* metastatic castration-sensitive prostate cancer (mCSPC) is highly aggressive, but the lack of routine tumor tissue in this setting hinders genomic stratification and jeopardizes precision oncology efforts. Accurate molecular profiling at diagnosis is imperative for genomics-informed risk stratification and biomarker-guided treatment. Currently, it is unclear the extent that intrapatient heterogeneity impacts clinical cancer genotyping.

Methods: We performed genomic profiling of 607 synchronous primary foci, metastatic lesions, and cell-free DNA from a rare clinical trial cohort of 43 *de novo* mCSPC patients who underwent radical prostatectomy at diagnosis. Surgery is not currently standard practice in this disease setting. All samples were subjected to targeted DNA sequencing using a bespoke prostate cancer-specific panel with a subset having additional whole-exome sequencing.

Results: Sequencing-derived tissue tumor fraction was heterogeneous and low across same-patient foci in ~20% of patients. In samples with high tumor fraction, the genomic landscape of mCSPC closely resembled metastatic treatment-resistant prostate cancer. In same-patient samples, intra-prostate heterogeneity in mutation, copy number, and whole-genome duplication status was pervasive. Phylogenetic modeling demonstrated additional complexity in several patients driven by polyclonal metastatic seeding from the reservoir of primary populations. While the metastatic clones were often identified in the primary site, frequent discordance between select primary foci and synchronous metastases in clinically-relevant genes, plus highly variable per-sample tumor fraction, resulted in false genotyping of the dominant disease, when relying on a single tissue focus. However, *in silico* modeling demonstrated that analysis of multiple prostate diagnostic biopsy cores can rescue misassigned somatic genotypes.

Conclusions: Our work reveals extensive polyclonality that undermines standard precision genotyping in *de novo* mCSPC, nominates practical strategies for improved biomarker profiling and genomics-informed risk stratification and offers deep biological insight into the relationship between primary and untreated metastases.

Poster 19

Using genomic heterogeneity to inform therapeutic decisions for metastatic colorectal cancer: an application of the Value of Heterogeneity framework

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Funding by: RP was supported by a CIHR Doctoral Research Award. The Canadian Centre for Applied Research in Cancer Control (ARCC) is funded by the Canadian Cancer Society.

Purpose: Mutations in *KRAS* and *NRAS* are associated with poor response to cetuximab and panitumumab, two anti-EGFR antibodies for metastatic colorectal cancer (mCRC). Our objective was to evaluate the use of *KRAS* and *NRAS* mutation status to inform third-line anti-EGFR therapy for mCRC in British Columbia (BC), using the value of heterogeneity (VOH) framework.

Methods: We used administrative data to identify mCRC patients who were potentially eligible for third-line therapy in 2006–2019. We compared three stratification policies that were in place during the study period: the unstratified decision, where anti-EGFR therapy was not offered (2006-2009); stratification by *KRAS* mutation status (2009-2016); and stratification by *KRAS+NRAS* mutation status (2016-2019). Using the VOH framework, the value of using *KRAS* or *NRAS* mutation status in treatment selection is expressed as the difference in net monetary benefit (NMB) between the stratified and unstratified (or less stratified) decisions.

Results: We included 2,664 patients in the analysis. At $100,000/LYG, offering anti-EGFR therapy to *KRAS* wild-type patients provides a VOH of $1,565 per patient; further stratification on *NRAS* provides additional VOH of $594. Mean testing cost for *KRAS* only or *KRAS+NRAS* is $215 and $713 respectively; the VOH exceeds the testing cost under both scenarios. Resolving subgroup-specific uncertainty in the *KRAS* and *KRAS+NRAS* decision could provide additional value.

Conclusions: Stratification of anti-EGFR therapy by *KRAS* and *NRAS* provides value at $100,000/LYG. There is diminishing marginal value and increasing marginal costs as the decision becomes more stratified. The VOH framework can illustrate the value of subgroup-specific decisions in a comprehensive way.

Poster 20

Precision Cancer Medicine: The Personalized OncoGenomics Program

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Background: Advances in DNA sequencing technologies, drug development, and understanding of cancer biology and cancer drivers are enabling the delivery of precision genomic medicine to cancer clinics. The use of comprehensive, integrative data provided by whole genome and transcriptome sequencing and analysis (WGTA) presents an opportunity to prospectively align patients to therapies, fuel clinical trials and build rich datasets for future research.

Methods: Patients with incurable cancers of diverse types enrolled in the Personalized OncoGenomics (POG) program underwent WGTA. DNA-based data, including mutations, copy number data, and mutation signatures, were combined with RNA-based data, including gene expression and gene fusions, to generate comprehensive WGTA profiles. WGTA profiles generated for all patients were reviewed by multidisciplinary molecular tumour board members to identify and prioritize alterations and inform systemic therapy.

Results: Over 1000 patient profiles have been generated. Integration of WGTA and clinical data revealed the impact of cancer therapy on the genomic landscape, including alterations associated with therapy resistance, and the mutagenic effects of DNA-damaging platinum therapies and DNA repair gene mutations. Molecular tumour board discussions identified clinically actionable targets for 83% of patients, 37% of whom received WGTA-informed treatments. Therapies were informed by DNA mutation and copy number data, and also by RNA expression data and genome-wide signatures, with an overall clinical benefit rate of 46%.

Conclusions: Integrating RNA expression, genome, and clinical data provided insights into cancer progression and illuminated treatment options for patients. This data resource can be used to support genomics and clinical research, and drive improvements in cancer patient care and outcomes.

Poster 21

Detection of a Novel Disease Causing Splicing Variant in *PHF21A*

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Funding by: BC Children's Hospital Foundation

Background: A 9-year-old girl presented with macrocephaly, dysmorphic features, intellectual disability, and developmental delays. Whole exome sequencing of the patient identified a potentially pathogenic heterozygous variant in *PHF21A* (NM_016621.3: c.153+1G>C). The variant is in the splice donor site of intron 5 and may alter RNA splicing. Previously, only variants in the carboxy-terminal of *PHF21A* have been associated with disease, specifically intellectual developmental disorder with behavioural abnormalities and craniofacial dysmorphism with or without seizures (IDDBCS). We aimed to establish the pathogenicity of the splicing variant.

Methods: Saliva and whole blood samples were collected from the patient and the parents. DNA was extracted from saliva for parental segregation analysis. RNA was extracted from whole blood for RNA sequencing, RT-PCR, and RT-qPCR.

Results: The *PHF21A* variant was identified as *de novo* by parental segregation. RNA sequencing data showed exon 5 is spliced out of 30% of the aligned reads from the patient. Aberrant splicing at exon 5 is not observed in the sequencing reads from the parents. PCR amplification of *PHF21A* showed exon 5 is spliced out in the patient, validating the RNA sequencing results. Additionally, the relative expression of *PHF21A* at exons 3-5 was significantly lower in the patient compared to the parents. No significant differences were observed in the relative expression of *PHF21A* at exons 6-7.

Conclusions: Splicing analysis of *PHF21A* confirmed the deleterious consequence of the variant consistent with the mechanism of disease. Exon 5 of *PHF21A* contains a leucine zipper domain, and removal of this domain is anticipated to impair protein function. This research study provided a diagnosis for the family, ending their diagnostic odyssey, and expands our understanding of spectrum of disease causing variants in *PHF21A*.

Poster 22

Integrin-linked kinase mediates epithelial-mesenchymal transition and osimertinib resistance in EGFR driven lung adenocarcinoma

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Background: Lung cancer leads in cancer-related deaths in Canada. In ~20% of lung adenocarcinoma (LUAD) cases, activating mutations in EGFR drive malignant cell proliferation. Recent advances in LUAD therapies led to the development of the third-generation EGFR inhibitor, osimertinib, which greatly improved clinical outcomes. Regrettably, patients often develop resistance against osimertinib. Epithelial-mesenchymal transition (EMT) is one known resistance mechanism that is also associated with poor outcome. Integrin-linked kinase (ILK) is a protein involved with integrin-mediated signal transduction and was shown to induce EMT in other cancers; recently high ILK expression was correlated to worse prognosis in patients treated with EGFR inhibitors. We hypothesize that ILK is important for EMT and osimertinib resistance in EGFR-driven LUAD.

Methods: We performed Gene-Set-Enrichment-Analysis (GSEA) on publically available databases. We knocked-down ILK with doxycycline-inducible shRNA constructs in HCC4006 and performed AlamarBlue cell viability assays and clonogenic assays to evaluate osimertinib sensitivity and tolerance. Osimertinib-resistant cells were made by dose-escalation and western blots were performed to assess protein levels.

Results: Using GSEA, we found that EMT gene signature is significantly enriched in EGFR-mutant LUAD patients with high ILK expression. When HCC4006, an EGFR-mutant LUAD cell line with high ILK expression, were made to become osimertinib resistant, the cells exhibit strong EMT phenotype demonstrated by amplified levels of NCAD, Vimentin, and SNAIL, along with the loss of ECAD expression. Knocking down ILK in HCC4006 cells sensitizes the cells to osimertinib and reduced the expression of EMT markers in response to osimertinib treatment. Lastly, knocking down ILK during the resistance-transformation process reduced the expression of mesenchymal markers, suggesting that ILK may be important for EMT-mediated osimertinib resistance in LUAD.

Conclusions: Our results demonstrate that ILK is important for EMT in EGFR-driven LUAD and targeting ILK can be a viable strategy to combat osimertinib resistance and this deadly disease.

Poster 23

Early Pregnancy Assessment Clinic (EPAC) Data Registry

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Background: In Canada, it is estimated that up to 25% of females will experience a miscarriage in their lifetime. BC Women's Hospital + Health Centre's Early Pregnancy Assessment Clinic (EPAC) provides care for these patients in the first trimester of pregnancy such as bleeding, cramping, and miscarriage. The services of EPAC are accessible through self-referral or by a provider. EPAC provides access to urgent diagnostic care and provides women multiple options in the case of pregnancy loss such as surgical or medical management. Despite miscarriage is extremely common, there exist several distinct gaps in the literature on complications in the first trimester of miscarriage. The Early Pregnancy Assessment Clinic Data Revision project aims to build evidence to fill these gaps through the creation of a clinical data registry.

Purpose/Significance of the Data Registry Project: The purpose of the Early Pregnancy Assessment Clinic (EPAC) REDCap data registry project is to characterize the patient population within EPAC at BC Women's Hospital & Health Centre. The project aims to improve care for patients at BC Women's hospital as well as other facilities serving these patients. It can be utilized to assist future research opportunities and promote the improvement of the care provided at EPAC by incorporating patient feedback.

Objective (of the Recruitment Project): Determine whether current recruitment methods result in a biased patient sample via a three-month trial of recruitment and recruitment tracking.

Recruitment Method: Utilizing a script, EPAC Nurses (during a Triage Call) obtain consent from patients interested in learning more about the study. A few days later, a study coordinator will contact them directly through phone, email, and mail during which the potential participant will learn more about the research and may then provide consent to participate.

Preliminary Results: The three-month recruitment trial is almost halfway through and, within that range, 168 patients have been referred to EPAC. Of the 168, 65 have agreed to be contacted, 24 have declined to be contacted, and 79 were not approached. Of the 79 who were not approached, the main barrier was English was not their primary language.

Poster 24

Pharmacogenomic testing for major depression: a qualitative study of the perceptions of people with lived experience and professional stakeholders

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Funding sources: Genome BC and Genome Canada (project # B26PMH), Michael Smith Health Research BC (award #18932).

Objectives: With increasing evidence for the clinical utility of pharmacogenomic testing for depression (PGx4Dep), there is a growing need to consider issues related to the clinical implementation of this testing. Perspectives of key stakeholders (both people with lived experience [PWLE] and providers) are critical, but not frequently explored. The purpose of this study was to understand how PWLE and healthcare providers/policy experts (HCP/Ps) perceive PGx4Dep, to inform the consideration of clinical implementation within the public healthcare system in British Columbia (BC), Canada.

Methods: We recruited two cohorts of participants to complete individual 1-hour, semi-structured interviews: 1) PWLE, recruited from patient and research engagement networks and organizations, and 2) HCP/Ps, recruited via targeted invitation. Interviews were audiotaped, transcribed verbatim, de-identified, and analyzed using interpretive description.

Results: Interviews were completed with 17 PWLE (7 with experience of PGx4Dep; 10 without); and 15 HCP/Ps (family physicians, psychiatrists, nurses, pharmacists, genetic counsellors, medical geneticists, lab technologists, program directors and insurers). Visual models of PWLE's and HCP/P's perceptions of and attitudes towards PGx4Dep were developed separately, but both were heavily influenced by participants' prior professional and/or personal experiences with depression and/or PGx4Dep. Both groups expressed a need for evidence and numerous considerations for the implementation of PGx4Dep in BC, including: patient and provider education, technological and clinical support, local testing facilities, and measures to ensure equitable access to testing. PWLE wanted pre-test counselling, emotional support and accessible psychiatric care for patients; HCP/Ps wanted conclusive economic analyses and ongoing evaluation and outcomes monitoring.

Conclusions: Our findings can be used to inform the development of PGx4Dep implementation strategies that have the best chance of being acceptable and effective within the realities of a public healthcare system. Pre-test counselling should address expectations, limitations and misconceptions of PGx4Dep, and PGx test results should be applied in a person-centered manner.

Poster 25

Assessing the utility of pharmacogenomic testing in a treatment-resistant schizophrenia or schizoaffective disorder patient cohort

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Funding by: BC Schizophrenia Society Foundation, James Family Foundation, BC Neuropsychiatry Program, UBC Neuropsychiatric ERIN Research Fund, and VGH and UBC Hospital Foundation, philanthropic commitments from Bob and Beth Baker, and the Djavad Mowafaghian Centre for Brain Health

Background: The UBC MAGERS (Metabolic Explorations in Refractory Schizophrenia) Study is an intensive pilot, multimodal –omics and psychiatric genetic counselling research project conducted in 50 participants hospitalized in the tertiary provincial BC Psychosis Program Unit at UBC Hospital. Participants with severe and treatment-resistant schizophrenia or schizoaffective disorder had mean admission and discharge total Positive and Negative Syndrome Scale Scores of 90.2 and 68.2, respectively. We assessed the relative frequency of poor (PM), intermediate (IM), rapid (RM), and ultrarapid (UM) metabolizers at the drug metabolizing cytochrome P450 (CYP) enzymes most clinically relevant to commonly used psychiatric medications CYP2D6, CYP2C19, and CYP2C in the first 25 participants of our cohort.

Methods: Detailed medication histories were obtained from interviews, review of medical records, and Pharmanet. Whole genome sequencing (WGS) was performed for 25 participants in the BC Genome Sciences Centre and analyzed in UBC's Michael Smith Laboratories. Actionable pharmacogenomic (PGx) variants were extracted using Stargazer in the Psychiatric Pharmacogenomics Lab at the University of Calgary. PGx reports were generated using Sequence2Script Pro software, which integrates inferred medication phenocopies with genotypes, and makes recommendations based on stringent evidence-based guidelines from several databases (CPIC, DPWG, FDA) and resources (PharmVar, PharmGKB, Flockhart Table). A retrospective analysis of participant medication history was completed and cross-referenced with PGx psychiatric medication recommendations.

Results: 11 participants (44%) had at least one PGx guided recommendation. Of the 136 current medications that participants were taking, 19 (14%) had a recommendation: 13 pertained to CYP2D6, 5 to CYP2C19, and 1 to both CYP2D6 and CYP2C19.

Conclusion: At CYP2D6, 32% of the participants were PMs in our cohort, compared to an expected 6.04% based on PharmGKB. Our preliminary results suggest PGx should be routinely considered in individuals with treatment-resistant psychosis, or who have a history of adverse reactions to multiple psychotropic medications.

Poster 26

Early health technology assessment to inform development and pricing of psoriatic arthritis biomarker screening

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Funding by: National Psoriasis Foundation

Background: Developing biomarker tests is a significant resource investment with great uncertainty as to whether the final product will represent good value for money. Early Health Technology Assessment (eHTA) using economic modeling can be used in a product development life cycle to determine the required performance for the product to be cost-effective, and subsequently likely to be listed by payors. We aimed to conduct an eHTA of a biomarker test for psoriatic arthritis (PsA) compared to no screening.

Methods: We implemented a decision analytic model informed by literature. The model followed a cohort of patients aged 45-years with mild psoriasis and in which PsA was prevalent but undetected. The test was assumed to be administered at baseline, and a proportion of patients who screened positive would accept early treatment with a conventional Disease-Modifying Antirheumatic Drug (cDMARD) to slow disease progression. Patients with PsA in the no screening arm were clinically detected. Disease progression was represented by changes in Health Assessment Questionnaire (HAQ) scores. We assumed values for sensitivity, specificity and the probability of treatment acceptance. The time horizon was 40 years.

Results: The model finds the level of sensitivity, specificity and treatment acceptance required for the biomarker to be considered cost-effective and therefore financially viable at different commercial prices. The model also finds several parameters significantly influence these results, including the choice of the subsequent therapies for patients who screen positive, assumptions around disease progression, and the time at which patients are expected to switch from a cDMARD to a biologic DMARD.

Conclusions: Early health technology assessments can help identify required test performance and important clinical assumptions biomarker developers should consider. It can also support a business case for further commercialization. The potential value of a biomarker test for PsA appears to hinge on treatment implications for screened positive patients.

Poster 27

Quantitative immunoglobulin profiling of acutely ill COVID-19 patients reveals associations between isotype response and organ dysfunction and mortality

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Background: Multiple biomarker studies on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have suggested that the antibody response of the infected individual is associated with the disease severity and outcome. However, previous serology studies lacked a detailed understanding of each individual humoral response including isotype and subclass generation. To investigate detailed antibody profiles in acute COVID-19 hospitalized patients, we first needed to generate a new blood test capable of quantifying all anti-SARS-CoV-2 antibody isotypes and subclasses (individually) from a drop of blood, we then applied the assay to assess the associations between antibody profiles and patient outcomes.

Methods: Plasma samples collected from COVID-19 patients (n=137) at day 4 and day 7 after hospitalization were analyzed using the new blood test we developed—ImmunIQ—which provided quantification of anti-receptor binding domain (RBD) IgG, IgA, IgM, IgD, IgE, IgG1-4, IgA1-2 in a single analysis from 4.2 µL of plasma. Statistical analyses of the antibody profiles and patient outcomes (28-day mortality, in-hospital mortality, and organ dysfunction) were performed using logistic regression.

Results: A doubling in anti-RBD IgG concentration from day 4 to 7 after hospitalization was associated with decreased likelihood of death by day 28 (OR 0.56, 95% CI 0.32–0.93). A doubling in IgM concentration from day 4 to 7 was associated with reduced likelihood of invasive mechanical ventilation after day 7 (OR 0.15, 95% CI 0.02–0.67) and with reduced likelihood of vasopressor use after day 7 (OR 0.17, 95% CI 0.03–0.69). Dexamethasone use (n=19) was associated with increased anti-RBD antibody response.

Conclusions: Development of an assay that enabled resolution of an individual's specific humoral response to COVID-19 was essential to this investigation. We found that early increases in specific anti-SARS-CoV-2 antibody isotypes were associated with lower mortality, less use of mechanical ventilation and vasopressor.

Poster 28

Nanopore Long-Read Sequencing of Advanced Tumours from the Personalized OncoGenomics and Marathon of Hope Cancer Centres Network Study

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Funding by: BC Cancer Foundation, Marathon of Hope Cancer Centres Network.

Background: Advances in sequencing technologies have transformed our understanding of cancer and herald an era of targeted precision medicine. The prevailing short-read sequencing technology has limitations including poor alignment to repetitive sequence, inability to detect large structural variants (SVs), incomplete representations of complex SVs, challenges associated with assigning DNA mutations to a specific DNA copy, and an inability to natively identify DNA modifications. Long-read Oxford Nanopore sequencing is well suited to address these challenges.

Methods: Samples were obtained from the Personalized OncoGenomics (POG) program, a precision medicine initiative integrating whole genome and transcriptome analysis (WGTA) into the clinical care of advanced cancer patients in British Columbia. Samples were selected based on biological criteria including epigenetic dysregulation, high SV burden or clinical characteristics of interest. DNA was enriched for long DNA fragments followed by PCR-free library construction optimized for automation and sequencing on the PromethION sequencing platform using R9.4 flow cells. Reads were analysed through a bioinformatics pipeline to evaluate SNVs, indels, SVs, and DNA modifications, with phasing to identify haplotypes.

Results: Long-read sequence was generated for 186 tumour samples and 39 matched peripheral blood samples from 178 POG patients spanning diverse tumour types. Corresponding WGTA short-read data is available for all patients. With a total sequence yield of 18 Tb, we generated a median of 73 Gigabases per sample and a median read length of 20.3 kilobases. Long reads demonstrate the detection of complex SVs and associations between methylation of DNA repair gene promoters and homologous recombination repair deficiency phenotypes that may help identify optimal treatments for a subset of patients.

Conclusions: This initiative represents one of the largest tumour long-read genome datasets sequenced on the nanopore platform, and is a critical resource for exploring the clinical implications of large-scale genomic complexity and DNA modifications in cancer.

Poster 29

Single-Cell Meta-Analysis of Primary Non-Small Cell Lung Cancer Tumours

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Background: Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer. While next-generation sequencing (NGS) has improved the understanding of the development and treatment of NSCLC, bulk sequencing outputs an average signal across all cells in a sample. Single-cell sequencing, on the other hand, enables 'omics profiling of individual cells, thus lending resolution for investigating intra-patient tumour heterogeneity. However, individual studies consist of small cohorts that limit the power of analyses. The objective of this study is to create a single-cell atlas of primary NSCLC tumours' transcriptomes using publicly available data. It is hypothesized that standardized processing and integration of multiple datasets will reveal novel tumour cell subpopulations that lend new insights into NSCLC biology.

Methods: The Gene Expression Omnibus (GEO) was queried for single-cell RNA-seq data from human NSCLC samples. Eligible datasets were acquired using the 10X platform and had publicly available raw count matrices. All datasets were processed using Seurat's default workflow. Malignant epithelial cells were identified based on inferred copy number alterations and analyzed separately using Monocle.

Results: Five studies that meet the inclusion criteria were found in GEO. They span 38 patients and 164,258 high-quality cells. Malignant cells were found to cluster into three distinct subtypes, two of which have not been previously documented in single-cell studies.

Conclusions: A single-cell atlas for primary tumours of NSCLC was created using publicly available data from GEO. Malignant cells were identified and classified into three subtypes. Overall, this study demonstrates how the reuse and re-analysis of data can reveal novel insights for personalized medicine.

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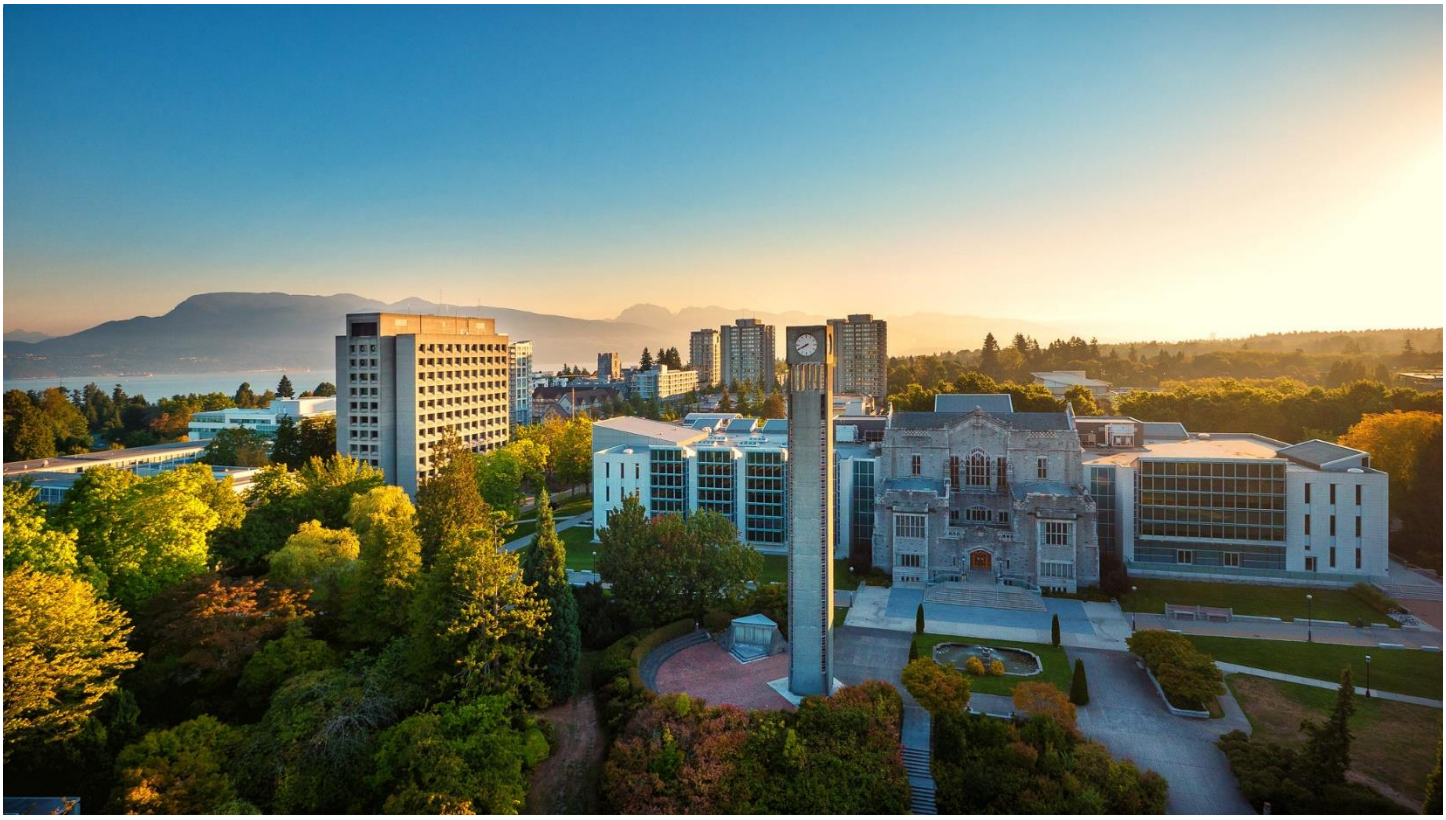

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