HEALTH SCIENCE INQUIRY
A publication platform for graduate students to discuss, discover, and inquire

CHRONIC DISEASE: NATURE, NURTURE & CONSEQUENCE

Volume 9 / 2018

Art Submissions

Ask An Expert

Spotlight On Careers

Cover Design: Farigol Hakem Zadeh (p. 14)

Health Science Inquiry

TEAM

LETTER FROM THE EDITORS

Dr. Tracy Moreira-Lucas has been a member of the Health Science Inquiry team for eight years and has held a variety of positions including Reviewer, Senior Editor, Executive Editor, and for the past two years, Co-Editor-in-Chief. Just recently, she graduated from the University of Toronto with a Ph.D. in Nutritional Sciences. Her work focused on examining the effect of high vitamin D supplementation on type 2 diabetes risk, more specifically she worked to determine whether supplementation might positively impact oral glucose tolerance and some of the inflammatory pathways involved in the pathogenesis of type 2 diabetes. In her free time, she likes using her nutrition knowledge to modify traditionally indulgent recipes into healthier versions, exploring new restaurants and cuisines, and is embarking on a new passion, painting.

Tanya Miladinovic has been involved with HSI for five years, initially as a Main Submission Author, followed by roles of Senior Editor, Marketing Executive, and most recently, Co-Editor-in-Chief. She is a senior PhD candidate in the Medical Sciences Program at McMaster University, where she is investigating pathways that may contribute to metastatic cancer-induced pain. Specifically, she is interested in patterns of functional neuro-immune interactions within the spinal cord and brain regions implicated in the pain response. Beyond the lab, Tanya dabbles in painting and believes there can be art in unexpected places; she makes effort to exercise creativity in the lab and in her life. You can find her work in this issue, at www.paintedbytan.wixsite.com/paintedbytan, and on instagram@paintedbytan.

Dear Readers,

It is with great pleasure that we present the 9th annual issue of Health Science Inquiry with a focus on Chronic Disease: Nature, Nurture, and Consequence.

Given recent advances in medical therapeutics and technology, individuals are living longer and the risk for developing chronic diseases is becoming a growing concern. Through this issue, we have welcomed commentaries discussing the genetic bases and modifiable contributors to chronic diseases, and the socioeconomic impact as a consequence of chronic disease.

With staff, contributing authors, and artists from across Canada, HSI continues to serve as a national platform for student involvement and discussion. We are continually impressed by the insightful submissions that we receive from Canadian graduate and medical students. We are also deeply grateful to our partner journals, Health Promotion and Chronic Disease Prevention in Canada and Lifestyle Genomics, for their support and commitment to student development. In addition to the Main Submissions, HSI features News Articles and expert testimony highlighting cutting-edge research and novel findings in Chronic Disease.

HSI regularly publishes relevant career information and blog posts on various topics related to scientific discovery and graduate student life, which you can find at healthscienceinquiry.com. We are also dedicated to promoting creative expression within the research community by providing a platform for graduate students to display relevant artwork and to promote a complimentary side of the research world through art and creative expression.

Finally, we would like to thank our dedicated staff for their work on this years issue. The HSI team, consisting of 42 graduate and medical students from various disciplines across the country, represents a broad Canadian voice. We are proud to create this open forum and hope that this publication.

Sincerely,
Tracy Moreira-Lucas & Tanya Miladinovic
Co-Editors-in-Chief

HSI NEWS
Health Science Inquiry

Artificial intelligence and mental illness

—Kevin Dick

Technology has become increasingly present in all corners of our lives. We leave a trail of our digital selves in the wake of our interactions with smart phones, smart devices, social media, and the Internet. Our digital signature provides unprecedented access to the unseen side of human behavior and has increasingly become a viable source of data for research into human health. Furthermore, with the digitalization of medical records, artificial intelligence and machine learning (AI/ML) have been adopted to develop predictive models, clinical decision support systems, and synthesize information from disparate sources. Recently having entered the proverbial AI summer, a period of rapid development and considerable funding, AI/ML applications have become increasingly present in research. Numerous fields are applying AI/ML algorithms in their work, and healthcare stands to benefit substantially from its widespread adoption. Researchers throughout Canada are addressing a broad range of chronic diseases and illnesses with AI/ML as a primary tool.

A key trend in contemporary healthcare has been the emergence of corporate entrants such as IBM, Microsoft, Apple, Facebook, and Alphabet Inc. [1, 2]. Chronic depression and other mental illnesses have been identified as one example of benefitting from the appraisal of the plethora of social media data available for detection and preventative measures. The Ottawa-based company, Advanced Symbolics Inc. (ASI), has recently been contracted by the Canadian Federal Government on a three-month pilot project leveraging social media data to detect suicide-related behavior [3]. Co-founder and Chief Scientist Dr. Kenton White, an adjunct professor of Computer Science at the University of Ottawa, is spear-heading the initiative and ASI will be focusing on suicide-related behavior and measuring ideation (i.e. thoughts), behaviors (i.e. self-harm), and communications (i.e. suicidal threats, plans of suicide). With the use of its patented AI technology Polly, ASI will use randomized, controlled samples of 160,000 Canadians in its representative sample. Polly is trained to learn the patterns using a large labeled corpus for a specific subject or issue and will look to identify and correlate patterns in the segments of the Canadian population who discuss suicide-related behavior based on publicly available but non-personally identifiable online data. When interviewing a representative of ASI about major challenges to this work, privacy concerns were highlighted:

> *"Privacy is of extreme importance to ASI. To maintain privacy, we anonymize our data. All data is taken from public online sites where each user has agreed to allow open access to their accounts and data. The reading of the data is done in compliance with each site's terms and conditions. If an individual on the site has indicated they wish their information to be private, ASI respects the wish. Privacy is preserved using two methods: differential privacy and k-anonymity."*

Differential privacy is a method used to processes personal information (e.g. age, gender, ethnicity) such that individual privacy is preserved: individuals are assigned probabilities for each demographic category and statistical noise is introduced so that it is not possible to determine the specific demographics of an individual [4]. The data is further protected using k-anonymity which removes demographic combinations that are below a small threshold to prevent against individuals being identified based on uncommon demographics. Having been highly successful in other prediction tasks such as correctly predicting the outcome of the Brexit referendum, the Trump election, and the Trudeau-led Liberal electoral victory in 2015, the successes of this pilot project are highly anticipated.

For patients previously diagnosed with mental illness, researchers have turned to AI/ML to assist physicians in treatment recommendation and modification. This is the focus of PhD Candidate Martin Cousineau's work at McGill University. Using medical health records from Douglas Mental Health University Institute in Montreal, he looks to assist physicians

in achieving remission for patients suffering from treatment-resistant depression, a severe form of the major depressive disorder. His work has been used to identify the best initial treatment modification for incoming patients, recommend potential successful treatments, and characterize the current timing decisions between appointments. A variety of ML methods are leveraged in this work including the correction of selection bias introduced by the use of observational data, recommendation systems to personalize individual treatment (among hundreds of possible combinations), and inverse reinforcement learning to infer from the data the weights of multiple variables leveraged by a physician to select the date for the follow-up appointment. By no means trivial, when asked about the challenges in his work, Cousineau highlights the following:

> *"The main challenge in my work consists in the limited suitable data available in comparison with the complexity of the task (e.g., predict the best treatment out of hundreds of possible combinations); there are many missing values which reduce the number of suitable observations. Another important challenge regarding my work pertains to using observational data that may be subject to a selection bias. While methods exist to reduce the effect of this bias, results generally require confirmation with randomized controlled trials (RCTs). My work can however suggest meaningful RCTs to run."*

Despite these obstacles, Cousineau forges forward. His work promises to increase the efficiency of treatment management and ultimately, has the potential to save lives.

Research into utilizing multitudinous digital signatures to address mental illness is still in its infancy and considerable work remains. With the rising adoption of technology, data availability to support these initiatives is anticipated to increase and both ASI and Martin Cousineau express a shared vision of the future where artificial intelligence will significantly improve healthcare and humankind as a whole.

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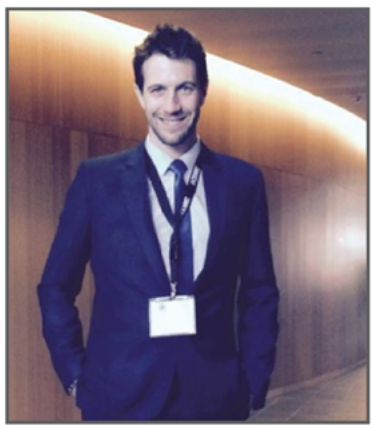

Kevin is a third year PhD candidate in Biomedical Engineering specializing in Data Science and Bioinformatics at Carleton University. He received his BSc in Biology and Computer Science from McGill University in 2014. His doctoral research focuses on improving protein-protein interaction prediction and leveraging context in related complete-graph problems such as protein function prediction and medical diagnosis prediction. As a polymath, Kevin spends his spare time exploring his curiosities at the intersection of the arts and sciences.

HSI NEWS
Health Science Inquiry

The best way forward: simulations and machine learning for optimizing treatment

—Kevin Dick

Happening upon a bifurcation in a road, one is faced with a simple choice: left or right? Without complete information about the paths ahead, this can present a difficult choice. Depending on the context of your journey and the information and knowledge you have, you make an informed decision. In different situations, that decision might be more complex: left, right, go back, stay here... At times it is beneficial to learn more about the paths ahead before committing to one, thereby improving the expected outcome of your final decision. This is an oversimplification of the decision process we as humans perform every day in all situations, and something that Dr. Audrey Durand has used to make quantitatively informed decisions for a plethora of health conditions. As a post-doctoral researcher at the McGill University School of Computer Science, she has helped guide the decision-making process in research on Down syndrome, osteoporosis, heart disease, cancer, and Alzheimer's disease. In an interview with Dr. Durand, we garnered some insights into the state-of-the-art machine learning methods in health care.

Simulations for the Screening of Fetal Down Syndrome

Dr. Durand's first use of computer science in the domain of health care began with the development of simulators to evaluate Down syndrome screening strategies during pregnancy. While prenatal foetus karyotyping is considered the gold standard for the detection of Down syndrome, the use of reliable molecular methods to detect common aneuploidies (the presence of an abnormal number of chromosomes) are considered faster and less expensive. One such method is rapid aneuploidy diagnosis (RAD), which includes techniques such as fluorescence in situ hybridization (FISH) and quantitative fluorescence PCR (QF-PCR). To determine the optimal screening options trading-off various outcomes of Down syndrome prenatal screening such as cost, false positive rate, and number of procedure-related miscarriages, Dr. Durand and collaborators performed a series of computer simulations. These comprised estimating the performance of six screening options recommended by guidelines in the US and Canada, combined with three diagnostic approaches (karyotyping, FISH or QF-PCR) for each end point that cover the main outcomes in Down syndrome prenatal screening. Their work indicated that RAD detected the majority of clinically significant chromosomal abnormalities while remaining the most cost-effective option [1]. These results promise to partially offset the economic and financial burden on contemporary medical systems. Following these successes, Dr. Durand went on to adopt state-of-the-art methods to address similar optimization challenges.

Adaptive Clinical Trials as Bandit Problems

In machine learning, researchers want to teach a computer (known as an "agent") to "understand" a problem and then use it to make subsequent decisions. Dr. Durand's expertise in machine learning (ML) specializes on navigating the exploration-exploitation trade-off. This arises when learning about the problem is conducted simultaneously as the agent is making decisions. Roughly akin to the path-finding example above, Dr. Durand explains:

"...the learning algorithm must balance between acquiring information about the environment, which helps

determining the optimal behaviour, and behaving in what is thought to be the 'best' way given current knowledge. In machine learning, this is known as 'bandits problems'."

Dr. Durand went on to explain that she is currently involved in a project where bandits algorithms are used to guide an adaptive clinical trial in real mice experiments with induced cancer tumours. Given that personalized medicine seeks to customize treatment based on an individual patient's characteristics, the pharmacological treatment strategy can be modelled as a contextual bandit problem which trades-off the collection of information about the treatment believed to be optimal given the current state of the patient and the exploration of lesser known treatments that could improve the current strategy. The pilot project applying this strategy over simulations, in combination with preliminary results from mouse model experiments, showed considerable promise [2], and the subsequent analysis and dissemination of results are forthcoming and highly anticipated.

A New Age of Medicine

In summary, path finding in the face of incomplete information is a challenge ubiquitous in healthcare research as it is in the navigation of our own natural environments. This research looks to quantitatively improve healthcare treatment while remaining cost-effective. Through both her research and vision for the future of healthcare, Dr. Durand is helping to herald a new age of medicine:

"With machine learning, resources can be used more efficiently, meaning that we can save time, money, and more importantly, lives. By automating some procedures, machine learning can even provide some populations with access to services that were otherwise not available. Healthcare is a field that will highly benefit from machine learning."

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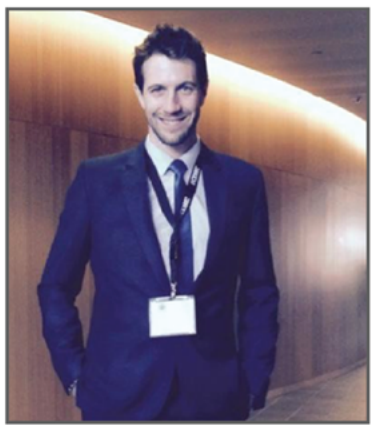

Kevin is a third year PhD candidate in Biomedical Engineering specializing in Data Science and Bioinformatics at Carleton University. He received his BSc in Biology and Computer Science from McGill University in 2014. His doctoral research focuses on improving protein-protein interaction prediction and leveraging context in related complete-graph problems such as protein function prediction and medical diagnosis prediction. As a polymath, Kevin spends his spare time exploring his curiosities at the intersection of the arts and sciences.

HSI NEWS
Health Science Inquiry

Persistent organic pollutants (POPs): a sneaky culprit of chronic disease

—Daniel Robinson

The cause of chronic disease has long been thought to be directly related to genetic predisposition that is, a person's genetic material being the sole factor required to develop chronic disease. As research in the field progressed, a more apparent link between environmental factors and genetics has emerged. Today, we understand chronic disease as an interplay between both genetic predisposition and environmental exposure, where 'genetics loads the gun but environment pulls the trigger' [1].

There are multiple environmental factors that are known to directly contribute to chronic disease. Some better-known examples include lifestyle habits such as diet and exercise in obesity, or the effects of smoking on cardiovascular and lung health. There are also various classes of chemical compounds found within our surroundings that play a critical role in the onset of chronic disease.

One emerging contributor to chronic disease are chemicals known as Persistent Organic Pollutants (POPs). These fat-soluble compounds have been linked to a series of chronic diseases ranging from metabolic issues to carcinogenesis [2]. Regarding the biological basis of disease, it is thought that the structural resemblance between POPs and some hormones produced by our bodies allows POPs to bind and activate hormone receptors within our bodies. This disrupts hormonal balance and endocrine systems which leads to a series of health complications. This is typically manifested through abnormal thyroid functioning, reduced glucose sensitivity, and disruptions in overall energy utilisation, culminating to weight gain and obesity, to diabetes [3], and even to Alzheimer's disease [4].

What is particularly concerning about POPs is their propagated use in many household items: they are present in non-stick compounds that coat kitchen cooking ware (Teflon); they take form as poly-halogenated biphenyl compounds which act as flame retardants used in furniture; and they are the poly-fluorinated compounds used in clothing to repel stains and wrinkles [5]. This widespread use of POPs in many household items in combination with genetic predisposition result in a key interplay that increases the likeliness of developing various chronic diseases.

There are some preventive measures that can be taken to limit exposure to POPs and decrease the likeliness of developing chronic disease. Of primary importance is reducing the number of products that may contain POPs within your household. This means opting for clothing that is not treated with stain-repellents, or furniture that does not contain flame retardants, and having an overall awareness of what constitutes household products. Further, adopting healthy lifestyle and diet habits remains important to reduce the chance of developing chronic disease in general, as reviewed here [6]. Although these measures will not eliminate the risk of developing chronic disease associated with exposure to POPs, it can reduce the general occurrence of chronic disease.

The versatility of POPs has resulted in their presence in many household products, however, given their association with chronic disease means we are using them at a personal and social cost. A continued exposure to persistent organic pollutants will continue to increase the onset of chronic disease. Until stricter regulations regarding the use of POPs in consumer products is introduced, avoiding and limiting exposure to POPs remains a key strategy to prevent chronic disease arising from regular exposure to persistent organic pollutants.

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Daniel received his B.Sc. (hons.) in Biochemistry at the University of Manitoba prior to coming to the University of Ottawa to start his doctoral research. He is currently studying gene regulation in adult muscle stem cells during muscle repair to find ways that could be used to stimulate muscle stem cells to repair muscles in persons affected by muscle degenerative disease. When he is out of the lab, Daniel enjoys staying active, going to the gym, and working with the Canadian Army Reserve in his role as a Signals Officer.

Health Science Inquiry NEWS

An Unfortunate Interaction Between Anti-Psychotic Medication and Obesity

—Logan Townsend

Second generation antipsychotic (SGAs) drugs, like olanzapine, are the current standard-of-care for the treatment of schizophrenia because they are more tolerable than earlier drugs. In recent years, SGAs have been increasingly used for managing a range of common off-label conditions such as anxiety, attention deficit, bipolar, and sleep disorders. Partly because of this off-label use, the number of SGA prescriptions in Canada more than doubled to >7 million annually between 2005-2012. Unfortunately, SGAs have serious metabolic side effects, including weight gain and type 2 diabetes, affecting up to 70% of individuals taking these drugs [1].

Initially, it was believed that the metabolic side effects associated with SGAs were secondary to weight gain, but it is clear that SGAs have direct diabetogenic effects. In both rodents and humans, SGAs cause high blood sugar within minutes [2]. Acute SGA-induced hyperglycemia does not dissipate even after months of continuous use [2], and is linked to adverse effects on the brain, liver, muscle, and fat tissue [3].

Regardless of SGA use, obesity is more prevalent in individuals with schizophrenia compared to the general population. This raises the important question of whether the metabolic dysfunction associated with obesity could alter the acute responses to SGAs. Indeed, olanzapine's side effects mimick many of the metabolic disturbances that characterize obesity, including hyperglycemia, insulin resistance, and glucose intolerance. Moreover, Dr. David Wright at the University of Guelph reasoned that "initial studies [testing the responses to olanzapine] have all used lean, healthy rodents. As individuals taking antipsychotics are often obese and display perturbations in glucose metabolism prior to the onset of taking medication we thought that this could impact the acute metabolic side effects of antipsychotics."

With this in mind, Dr. Wright and I fed ~30 mice a high-fat diet to make them obese. After a month, we confirmed that obese mice displayed the classic characteristics of obesity, like insulin resistance. We then performed a series of experiments comparing the metabolic responses to olanzapine in these obese mice versus their lean counterparts. Overall, Dr. Wright said that "mice fed the high fat diet developed more severe hyperglycaemia with olanzapine treatment and this was associated with a greater degree of insulin resistance and increases in markers of liver glucose production." From Dr. Wright's perspective, these findings have direct implications for humans: "acute side effects of olanzapine and other antipsychotic drugs are even more severe than initially envisioned, as many of the individuals given this drugs are obese and glucose intolerant prior to treatment."

These findings have relevance to not only those with schizophrenia, but the entire patient population who are prescribed SGAs for various conditions. The current obesity epidemic means that those taking SGAs are very likely experiencing more severe side effects than they realize [3]. Moreover, SGAs, especially olanzapine, rapidly cause weight gain meaning that side effects may get progressively worse with chronic use. This cycle may partly explain why SGA use shortens the timeframe of weight gain to diabetes from decades to months [1].

Dr. Wright's group is now working to identify potential ways to alleviate some of Olanzapine's adverse side-effects, particularly glucose regulation. Multiple groups have previously tried using diabetic medications, given that SGAs side effects are similar to many diabetic symptoms, but with only partial success. For example, metformin, the most commonly prescribed anti-diabetic drug, was only partially able to prevent SGA-induced hyperglycemia [2]. We suspect that the moderate success of metformin may be due to the fact that it only functions in the liver, whereas our team's research has shown that olanzapine functions in both the liver and skeletal muscle [3]. Therefore, Dr. Wright believes a more

whole-body intervention will be required. For instance, they very recently published a report showing that exhaustive exercise can completely block the acute olanzapine-induced hyperglycemia [4]. However, exhaustive exercise is a very impractical strategy in humans, especially since it needs to be performed immediately before every olanzapine dose (daily!). For this reason, they are planning to experiment with "exercise mimetics," essentially drugs that attempt to mimic the benefits of exercise, as a novel way to combat the unwanted side effects of SGAs.

Taken together, there appears to be an unfortunate interaction between SGAs, including olanzapine, and obesity. With the increasing prescription of SGAs and epidemic of obesity, these findings have far-reaching implications. It will be important for future work to consider their treatment groups, likely including obese animal models and human participants.

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Logan is a PhD candidate at the University of Guelph. His research looks at metabolic contributors to the development of diabetes. Specifically he focuses on liver and adipose tissue and the effects of interleukin-6. In his spare time he enjoys rock climbing and mountain biking.

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We would like to thank our 2018 judges

Dr. Bruce W. Case, MD, MSc, DOH, FRCP(C)
Departments of Pathology and Epidemiology/ Occupational Health and School of Environment, McGill University

Dr. Case received his MD (1972), Diploma in Occupational Hygiene (1980), and MSc in Epidemiology (1985) from McGill University, where he was a National Health Scholar. His research has focused on tissue-based measurements of exposure and diagnosis of diseases related to elongated mineral particles. In addition to McGill University Dr. Case worked at the Mount Sinai School of Medicine, New York and as Director of the US EPA Center for Environmental Epidemiology at the University of Pittsburgh (1988-1991). His current teaching is focused on social determinants of health and on occupational medicine for McGill medical students, and Professional Development Courses for international occupational hygiene associations.

Dr. Sally Willis-Stewart, PhD
Senior Instructor, School of Health and Exercise Science, University of British Columbia

Dr. Stewart has a PhD in Interdisciplinary Studies (Nutrition, Exercise Physiology and Health Promotion) and is a Sr. Instructor and Director of the Nutrition Education Center for the School of Health and Exercise Sciences at UBC Okanagan. Her teaching, research and educational leadership endeavours and passions are in educating, promoting and facilitating individual health. She has also been instrumental with influencing student health and academic success through course offerings, classroom and campus environment changes, and faculty education.

Dr. David M. Mutch, PhD
Associate Professor, Dept. of Human Health and Nutritional Sciences, University of Guelph

Dr. Mutch leads a nutrigenomics research program that explores how perturbations in fatty acid metabolism influence the development of obesity-related complications. His current research focuses on the roles of fatty acid desaturase (FADS) genes in the synthesis of omega-3 and omega-6 fats, and how they influence adipose tissue function. Dr. Mutch is also interested in personalized nutrition and is investigating if knowledge of FADS genotype can be used to tailor omega-3 dietary intake to improve an individual's cardiometabolic health.

Dr. David W. L. Ma, PhD

Professor and University of Guelph Research Leadership Chair
Director, Guelph Family Health Study and Past-President, Canadian Nutrition Society

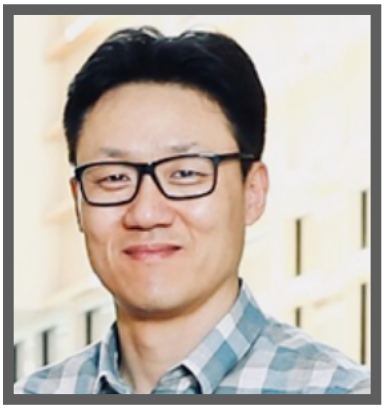
Dr. Ma obtained his PhD in Medical Sciences at the University of Alberta conducting research on the anticancer properties of ruminant fats in breast cancer. He then moved to Texas A&M University where he did postdoctoral research investigating the role of omega-3 fatty acids and folate in colon cancer. He returned to Canada where he joined the Department of Nutritional Sciences at the University of Toronto and later moved to the Department of Human Health and Nutritional Sciences at the University of Guelph. He is also the Past-President for the Canadian Nutrition Society, representing 600+ scientists, health professionals and trainees from across Canada advocating for nutrition research and education.

Dr. Ma's research encompasses investigations to better understand the role of fats in human health and disease. As the Director of the Guelph Family Health Study, a longitudinal cohort study of families with young children he leads a multidisciplinary team of investigators and trainees to better understand determinants of health in young families.

Dr. Keith Lawson, MD, MSc

Surgeon-Scientist Program,
University of Toronto

Dr. Lawson received his MD and MSc (Cancer Biology) at the University of Calgary. He is currently a Urology resident enrolled in the Surgeon-Scientist Program at the University of Toronto, completing a PhD in Molecular Genetics. His current research interests involve the application of functional genomic technologies for the discovery of novel therapeutic targets in renal cell carcinoma.



Dr. John Song Kim, PhD

Associate Professor and Director, Health and Environments Research Centre (HERC) Laboratory, Department of Community Health and Epidemiology, Faculty of Medicine, Dalhousie University

Dr. Kim obtained his PhD in Human Toxicology from the University of Iowa and completed his Masters of Environmental Toxicology at the University of Nebraska Center for Health and Environmental Toxicology. Nanotoxicology and human health risk assessment have been his primary academic and research. In recognition of his contributions to nanotoxicology research, he has served on the Technical Committee for the International Organization for Standardization (ISO) Working Group on Nanotechnology. The primary objective of his research program is to better understand adverse health effects of emerging hazards and exposures (e.g., nanoparticles) on the cardiopulmonary and brain systems by providing more information on its causal factors and mechanisms.

Dr. Renee Lyons, PhD

Bridgepoint Chair in Complex Chronic Disease Research and TD Scientific Director
Collaboratory for Research and Innovation, Bridgepoint Health

TOP ARTICLE SUBMISSIONS

Call for submissions

In October 2017, HSI sent out a call for submissions to graduate students at universities across Canada asking them to submit short (700-800 word) commentaries on various topics related to Chronic Disease under one of the following sub-themes:

1. Nature (Genetic Basis) — 7 articles submitted.
2. Nurture (Modifiable Contributors) — 9 articles submitted.
3. Consequence (Socioeconomic Impact) — 6 articles submitted.

Review and judging process

Beginning in March 2018, each submission was reviewed by two HSI Reviewers who critically assessed each commentary and provided feedback to the authors regarding its content and structure. After receiving their feedback, authors were given three weeks to revise their submission and resubmit to the journal. Our team of Senior Editors reviewed each revised commentary, and using information from the feedback given to them and additional editorial staff input, made a final publication decision. Each submission was then reviewed and scored twice by a team of independent judges not affiliated with HSI.

Winners

The highest scoring submission for each sub-theme were provided with the opportunity to have their articles forwarded via expedited review for possible publication in one of our partner journals: Health Promotion and Chronic Disease Prevention in Canada and Lifestyle Genomics. We received some outstanding submissions, and the editorial team highly commend the authors for their achievement. After tabulating the results, we are pleased to announce the top 3 submissions for the 2018 issue of Health Science Inquiry:

Nature. Mind the gap: genetic variation and personalized therapies for cardiomyopathies.
Authors: Yichi (Tony) Zhang and Aaron MacCosham

Nurture. Diet as a modiable contributor and potential treatment strategy for Major Depressive Disorder.
Author: Caroline Wallace

Consequence. Waiting in transition: Access to rehabilitation care for adults with chronic neurological conditions in Ontario.
Author: Shikha Gupta

Health Science Inquiry

Enhancing the strategies for diagnosis and treatment of hypertrophic cardiomyopathies

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Hypertrophic cardiomyopathy (HCM) was first diagnosed in humans by Robert Teare in 1958 [1]. HCM is the most prevalent chronic genetic heart disease, affecting every 1 in 500 individuals [2,3]. This disease is defined as the pathological myocyte disarrangement that can lead to thickening of the cardiac walls, which cannot be explained by other cardiac or systemic causes [2-5]. Some HCM symptoms include chest pain, shortness of breath, irregular heartbeat, blood flow obstruction, inefficient heart pumping, and heart failure [4,6,7]. The most severe symptom of HCM is sudden cardiac death (SCD) [2,5]. Over the past three decades, several gene mutations that cause HCM have been identified. However, due to the complexity of HCM genetics and symptoms, the diagnosis and management of this disease are challenging. In this article, we will review the discovered human HCM-mutations that are screened during diagnosis, and we will subsequently mention both the advantages and shortcomings of the current HCM management guidelines. Lastly, we will suggest new strategies to enhance the diagnosis and treatment of HCM.

Long after the discovery of HCM, the first genetic mutation that causes the disease (β-Myosin heavy chain-7 (MYH7)) was linked to it by Seidman *et al.* in 1990. To date, more than 1500 gene mutations have been associated with HCM [4,5,7,8]. This disease is generally autosomal dominant with incomplete penetrance, meaning that not all individuals carrying the genes express HCM traits [2,5,8]. The majority of HCM-mutations affect the sarcomeric organization [5]. The known gene mutations linked to HCM are described in **Table 1**.

These genes can be screened in individuals with symptoms of HCM to detect the source of dysfunction. They become more important when discerning the actual HCM disease from HCM phenocopies, which do not carry HCM-genotype, but have HCM-phenotype as the secondary consequence of other conditions. Determining this distinction helps to diagnose the primary source of the disease and to use the correct protocols for managing patients with HCM versus those with HCM phenocopy [8]. However, genetic testing is useful for the diagnosis of around only 60% of all existing HCMs [7]. We speculate that the advancements in whole-genetic and next-generation sequencing will enhance the discovery of additional HCM-causing mutations. Nevertheless, the incomplete penetrance of HCM causes variability in disease phenotype. In addition, the age of onset can further complicate the diagnosis [5,7]. Therefore, because of the existence of such variabilities, genetic testing, although necessary for HCM patients, is not the only diagnostic approach that should be relied upon, especially in the cases of asymptomatic individuals [7].

Based on the current guidelines, genetic counselling and screening are required for asymptomatic first-degree relatives of HCM patients [7,8]. The follow-up tests include determining family clinical history, a physical examination, an exercise test, an echocardiogram, and magnetic resonance imaging [5–7]. If the asymptomatic individual is genotype positive for the known HCM-mutation, regular follow-ups to monitor disease progression are recommended [7,8]. **Table 2** provides a summary of clinical approaches undertaken in relation to HCM genotype-phenotype variability.

Current HCM clinical trials show that several biomarkers can be screened in order to identify genotype positive individuals [10]. Therefore, to enhance HCM diagnosis, we suggest that in addition to the current methods, screening for these biomarkers should be added to the guidelines.

Once HCM is diagnosed, a change in lifestyle is required, such as a reduction of athletic activities, in order to decrease the rate of disease progression and the possibility of SCD [2]. Moreover, surgical approaches that remove or obliterate portions of ventricles are used to manage severe cases [2,3,5]. In patients with high risk of SCD, the possibilities of implanting a cardioverter-defibrillator or heart transplantation are evaluated [2,6]. Furthermore, specific medications, such as β-blockers, $Ca2^{+}$-channel blockers, and anti-arrhythmic drugs, are prescribed [2, 5–7]. Current studies are looking at drugs that may prevent HCM in genotype-positive phenotype-negative individuals [8]. Nonetheless, most of the current HCM drugs affect the disease upstream of the sarcomere in cellular mechanisms. These drugs are less selective for the sarcomere and

Table 1: Gene mutations resulting in HCM (4,5,7-9). Gene frequencies lower than 3% are considered rare.

Family	Subfamily	Protein	Gene	Frequency in Patients
Sarcomeric proteins	Thick Filament	β-Myosin heavy chain	MYH7	25-35%
		Myosin-binding protein C	MYBPC3	20-30%
		Regulatory myosin light chain 2	MYL2	<5%
		Essential myosin light chain 3	MYL3	Rare
		α-Myosin heavy chain	MYH6	Rare
		Titin	TTN	Rare
	Thin Filament	Cardiac troponin T	TNNT2	3-5%
		Cardiac troponin I	TNNI3	<5%
		α-tropomyosin	TPM1	<5%
		Cardiac troponin C	TNNC1	Rare
		α-cardiac actin	ACTC	Rare
	Z-disc	α-actinin 2	ACTN2	Rare
		Myozenin 2	MYOZ2	Rare
		Muscle LIM protein	CSRP3	Rare
		LIM domain binding 3	LDB3	Rare
		Telethonin	TCAP	Rare
		Vinculin/metavinculin	VCL	Rare
Sarcomere-associated proteins	Calcium Handling	Calsequestrin	CASQ2	Rare
		Junctophilin 2	JPH2	Rare
		Phospholamban	PLN	Rare
		Myosin light-chain kinase 2	MYLK2	Rare

can impact other cellular processes. We think that drug molecules that specifically target proteins within the sarcomere have better therapeutic potential than those that are commonly prescribed and are not specific to HCM.

Table 2: Summary of clinical approaches to HCM based on genotype-phenotype relations.

HCM		Phenotype	
		+	-
Genotype	+	Medication and therapy	Annual follow-ups and Screening
	-	1) Checking for HCM phenocopies If none found: 2) Investigating the possibility of new HCM genetic mutations	No follow-up required

Based on the current knowledge of HCM, limitations to HCM diagnosis exist, such as the inabilities of diagnosing asymptomatic individuals and all HCM genetic mutations. We suggested that advancements in genetic sequencing and HCM biomarker screening can solve such problems [8]. Furthermore, we noted that the drugs currently available for HCM patients are not HCM-specific. We believe that while new gene-editing approaches and therapeutics are facilitating ways of preventing, reversing or attenuating HCM phenotypes, we should also consider new tools such as biomarkers and HCM-specific drugs in the diagnosis and treatment of this disease.

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Farigol received her Honours BSc (Physiology) with High Distinction from the University of Toronto. With an extensive family history of cardiovascular diseases and diabetes, she was inspired to contribute to these areas of research. She began her research on myogenic responses in the microvasculature of stroke animal models. She then worked on generating organoid (intestinal buds) from ileal stem cells to study Glucagon-Like peptide-1 and its effects on insulin secretion. She was the recipient of several academic scholarships including the Queen Elizabeth II Graduate Scholarship. Working at the Ted Rogers Center for Heart Research, Farigol's MSc at the University of Toronto research focused on the regulation of Ca2+-cycling proteins in the heart to target their pathophysiology during cardiomyopathies. Farigol is also passionate about the translational aspect of new interventions in science to clinical medicine.

Targeting our aging cells to treat metabolic disease

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Introduction

Aging is the leading predictor of the major chronic diseases that account for the majority of morbidity, mortality, and health costs worldwide [1]. While we cannot reverse our chronological age, we can influence our physiological aging. As our cells age and encounter stress, they become "worn out" and enter a state known as cellular senescence. The discovery of the accumulation of senescent cells in aged and damaged tissues has provided insight into one of the underlying causes of age-related pathology, and has emerged as a potential target for the treatment of chronic diseases [2]. Recently, the accumulation of senescent cells has been associated with metabolic disorders, such as type II diabetes and obesity. Pharmacological targeting of cellular senescence may have significant impact on disease pathogenesis, and could be more effective in preventing the progression of diabetes complications than currently available therapies, which have limited impact on previously existing tissue damage [3]. An emerging class of drugs, termed senolytics, selectively targets senescent cells in diseased tissues, and has shown promising results in pre-clinical trials [1].

Cellular senescence and the secretory phenotype

The cells in our body can undergo a finite number of divisions. With every round of DNA replication, the repetitive DNA sequence at the ends of chromosomes, called telomeres, become progressively shorter until they reach a critically short length that results in cellular senescence. As cells become senescent, they lose the ability to divide and take on a distinct morphology [2]. Although initially identified as a response to the progressive shortening of telomeres, senescence may also be triggered by a variety of other stressful stimuli and cellular insults. Senescence is therefore an essential mechanism for preventing the proliferation of aged and damaged cells. However, when the immune system is unable to effectively clear senescent cells, the cells accumulate and have many pathological effects [4].

Senescent cells also secrete large quantities of over 100 different soluble factors [5], collectively known as the senescence-associated secretory phenotype (SASP). These factors include inflammatory cytokines and chemokines, proteases, fibrotic factors and growth factors that disturb the tissue microenvironment. Beyond its effects on tissue function, the SASP contains factors that induce senescence in neighboring cells, setting off a cascade of events that culminates in the formation of functionally aged and/or diseased tissue. Thus, both the accumulation of senescent cells and the secretsion of pro-inflammatory factors have been shown to contribute to tissue damage and the pathology of metabolic diseases [2] (**Figure 1**).

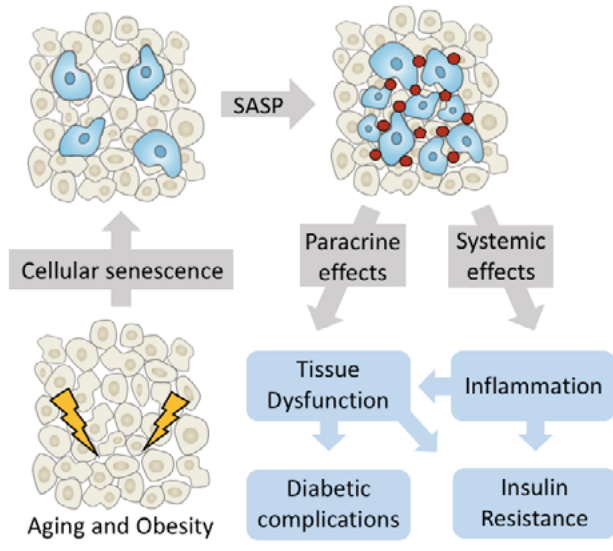

Figure 1: Pathological effects of cellular senescence and its role in driving insulin resistance and diabetes complications. Adapted from [3].

The role of senescence in metabolic disease

Cellular senescence in adipose tissues has been associated with obesity and contributes to its pathological effects. Caloric overload, due to nutritional excess or low energy expenditure, leads to the storage of energy in adipose tissue. When the storage capacity of adipocytes reaches a certain threshold, it triggers a stress response that results in cellular senescence and local inflammation. This

senescence response initiates a cascade of events that give rise to liver steatosis and insulin resistance, two of the hallmarks of metabolic syndrome [6]. Interestingly, when mice were genetically manipulated to block adipocyte senescence, they had a lower body weight and were protected against insulin resistance induced by chronic high-fat diet [7].

Insulin resistance, due to obesity and ageing, is initially compensated by the proliferation of insulin-producing islets of beta cells. This compensatory proliferation leads to proliferative exhaustion, accelerating cellular senescence and contributing to type II diabetes [8]. In turn, metabolic and signaling changes seen in diabetes, such as high circulating glucose, altered lipid metabolism, and growth hormone axis perturbations, create a microenvironment that promotes the induction of cellular senescence. Thus, senescence is part of a diabetic pathogenic loop, acting as both a cause and a consequence of metabolic changes and tissue damage [3].

Cellular senescence as an emerging therapeutic target

The current gold-standard treatment for obesity and type 2 diabetes are glucose-lowering medications that are combined with a diet and exercise regime. However, these treatments do little to ameliorate existing tissue damage, and have a limited effect on the pathogenic loop that is established by senescent cells. Senescent cell-targeted therapies present new opportunities for targeting one of the underlying causes of type 2 diabetes and potentially reversing some of its complications [3] (**Figure 2**).

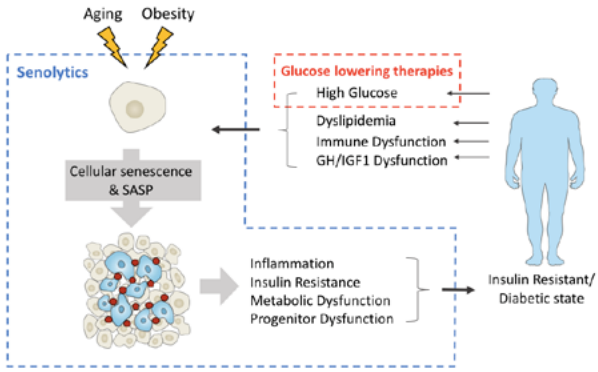

Figure 2: Senolytics present new opportunities for targeting type 2 diabetes and its complications. Adapted from [3].

Senolytics are senescent cell-clearing drugs that typically act either by selectively inducing apoptosis in senescent cells or by preventing senescent cells from secreting harmful factors [1]. Although these drugs are still in the early stages of development, they have shown promise in pre-clinical and clinical trials. Because cellular senescence is a basic aging mechanism that is thought to play a role in numerous age-related diseases, targeting senescent cells could have a widespread impact on individual patients and on a population-wide scale [3].

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The genetics of pain: a bio-psycho-social approach for understanding pain

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Pain is one of the most complex experiences in life due to its subjective nature. Because pain is an intensely personal experience, it is rather difficult to quantify and assess [2]. Most people can judge their own pain but struggle to share the feeling with family, friends, coworkers and health care professionals. This has led to negative stigma directed towards those suffering from chronic pain [1]. As a result, people dealing with chronic pain feel a decrease in effectiveness and productivity and are less motivated to seek treatment [3].

Currently, systematic biology theories indicate pain to be a product of a finely composed balance between the endocrine, immune, and nervous system. However, when one of these systems fail to act, the pain response becomes inharmonious resulting in a chronic problem. Although there is an abundance of literature highlighting the psychological and social significance of chronic pain, understanding how these variables are affected by genetic mechanisms is still in the adolescent stage of research. Biological systems influence cognitive function (and vice-versa), making it crucial to study the interactions between biological and psychosocial aspects of pain.

A host of genes have been recognized for their roles in biological systems that respond to distress, trauma, and injury. For the purpose of this commentary, I will focus on a few that are currently emerging as big players in the field of pain and genetics [7]. COMT is a gene responsible for making an enzyme called catechol-O-methyltransferase. The COMT enzyme aids in regulating neurotransmitter levels in the brain by breaking down neurotransmitters such as dopamine and norepinephrine [4]. SLC6A4 encodes the membrane protein responsible for transporting serotonin from synaptic spaces to pre-synaptic neurons. It has been studied for its role in depression-susceptibility in people experiencing emotional trauma [5]. The protein encoded by the FKBP5 gene is a member of the immunophilin protein family. This family of proteins is heavily involved in regulating the immune system, as well as playing a role in basic cellular processes such as protein folding and trafficking [6]. The OPRM1 gene makes a protein known as the mu (μ) opioid receptor, which is important for regulating reward, pain, and addictive behaviours in our bodys opioid system [5].

These biomarkers, among others, are important in stress, immune and opioid systems. Moreover, they have been previously studied for their potential involvement in people experiencing acute traumatic injuries. This is primarily done by investigating single nucleotide polymorphisms (SNPs) in these genes. SNPs are mutations in our DNA, represented by a change in a single DNA nucleotide, such as a substitution mutation. The normal occurrence of a SNP results in the most common type of genetic variation among people. Typically, a panel of SNPs can be mapped using a database such as the Human Pain Genetics Database which lists SNPs in human genes that were found to have an association with conditions of pain [7]. Currently, clinical researchers are asking why is it that some people recover successfully after an acute traumatic injury while others do not. A person may have an SLC6A4 or COMT SNP that makes them more psychologically resilient to trauma, thereby enabling them to quickly recover from their injury. Another person may have an OPRM1 SNP that results in lower production of opioid receptors, rendering them unable to properly regulate the opioids they need to manage their pain. Investigating a panel of SNPs in genes that are relevant to trauma and stress to determine whether a relationship exists with psychosocial moderators, such as early life adversity events [8] or household income, will certainly shine some light on pain research. Because genetic research in this particular field is still relatively young, there are many SNPs that still need to be studied alongside psychological and social variables [7]. Hopeful findings are on the horizon which will help both researchers and clinicians better understand pain.

It is well understood that a cascade of physiological changes occurs when a person endures almost any form of pain and the level of these changes are facilitated by genetic factors. Furthermore, these changes are also heavily influenced by psychological and societal contributors such as workplace environment, previous trauma, or other lifestyle stressors [9]. A deeper understanding of this bio-psycho-social model will offer a greater appreciation for the unique pain sensation

that many people experience. As a result, clinicians and researchers can implement innovative therapeutic strategies based on their ability to empathize with their patients, as well as biological evidence to help solidify rehab programs unique to each persons genetic makeup.

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Mind the gap: genetic variation and personalized therapies for cardiomyopathies

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The following is an abstract from the top *Nature* article; the full article will be published in an upcoming issue of the journal *Lifestyle Genomics*.

Abstract

Inherited cardiomyopathies, as the name suggests, are forms of heart disease that have strong genetic bases in the form of specific genetic mutations. These diseases have an onset in adolescence and they burden the patients and their families over the entire lifespan, hence they are chronic diseases. There are several different degrees of inherited cardiomyopathies including hypertrophic, dilated, restrictive and arrhythmogenic right ventricular, among others. These categories were established as diagnostic classifications to delineate proper treatment options, but even within these distinct categories there is significant heterogeneity in terms of patient genetics [1]. Therefore, this review supports the role of genetic factors as the primary predictors of patient-specific cardiomyopathies, and argues for using patient-derived induced pluripotent stem cells (iPSCs) and high throughput pharmacogenetic screens to optimize treatment for cardiomyopathies.

Tony Zhang completed his B.Sc. in Kinesiology at Queen's University and his M.Sc. at Carleton University in the Department of Biology. He is currently completing a PhD in Molecular Biology at The University of Texas Southwestern Medical Center in Dallas, Texas under the supervision of Dr. Eric Olson. The Olson lab is interested in studying the role of novel genes and cell populations in skeletal muscle and heart development and regeneration, and Tony is currently studying genes that may play a role in cancer cachexia-induced muscle atrophy.

Aaron received his BA in Psychology from Carleton University and is currently completing a BSc in Biomedical Sciences from the University of Ottawa. In the fall, Aaron will be attending McGill University to pursue an MSc in epidemiology.

A fine balance: the complex interplay between host and microbes in inflammatory bowel disease

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Inflammatory bowel disease (IBD) is one of the most common chronic inflammatory disorders, with millions of people suffering from this debilitating condition [1]. It is characterized by perturbed intestinal barrier function and an infiltration of immune cells beyond the intestinal wall [2]. It is responsible for high levels of morbidity in the form of recurrent bouts of abdominal pain and diarrhea, and an increased risk of severe complications such as colon cancer and fistula [2]. The prevalence of this disorder has increased over the past decade, and this trend has been predicted to continue worldwide [1,3]. However, the etiology of IBD is multifactorial, encompassing genetic, immunological, and environmental components, which has made pinning down causes and designing treatments especially difficult. An environmental component that particularly complicates this equation is the microbiota.

The human gastrointestinal tract is colonized by trillions of microbes, outnumbering our own cells and forming a complex community that we refer to as the gut microbiota. The colon is particularly densely populated, containing over 100 billion microbes per gram and supporting hundreds of different bacterial species [4]. Together, these organisms are able to influence many aspects of host physiology, for example metabolizing nutrients, modulating the immune system, and maintaining the integrity of the gut mucosal barrier. Generally the microbiota interacts symbiotically with the host to maintain a homeostatic state in the gut, and in a healthy adult the microbiota is generally stable and robust to perturbation [5]. However, major shifts in the gut microbiota have been shown to play a significant role in a number of diseases, one of the most prominent being IBD.

In the case of IBD, these alterations are commonly associated with an initial environmental stimulus that triggers inflammation and a shift in the gut microbiota. In healthy individuals, the immune system balances on a knife edge: it dampens the inflammatory response to beneficial resident microbes, while remaining poised to respond to external insults. These insults can include antibiotics, drugs, diet, toxins, and microbial pathogens all of which can be risk factors for the development of IBD [6]. Any one or a combination of these factors can trigger activation of the immune system, transiently provoking inflammation and disruption of the epithelial barrier. In healthy individuals, the resident microbes aid in the maintenance of this homeostasis, exerting a protective effect against development of colitis. This is done through the induction of anti-inflammatory factors; even a limited selection of *Clostridia* strains from the human gut microbiota has been shown to be able to induce the production of regulatory T (Treg) cells, interleukin-10 (IL-10), and transforming growth factor beta 1 (TGF-β1) [7]. In a proportion of individuals, however, the inflammation engendered by the transient stimulus persists, leading to the development of chronic IBD. This maladaptive response is associated with profound and sustained modifications to the microbiota, and a disruption of the symbiotic relationship between host immune system and gut microbes.

The progression of disease is accompanied by the dominance of microbial groups not usually prevalent in the healthy gut. Changes in microbiota composition vary on an individual basis, but usually include a significant increase in abundance of members of the *Enterobacteriaceae* and *Fusobacteriaceae* families [8]. This is commonly accompanied by a corresponding decrease in abundance of *Clostridia*, *Bifidobacteriaceae*, *Ruminococcaceae*, and *Faecalibacterium*, as well as an overall loss of bacterial species diversity [8]. This set of bacteria tends to induce a tolerogenic immune response and mediate anti-inflammatory activity [9]. Ultimately what these alterations boil down to is a shift in the microbiota, favouring microbes that thrive under conditions of inflammation, and serve to further activate the immune response. This leads to a vicious cycle of interactions between the gut microbiota and the host, where inflammation drives a shift in the prevalence of microbes, which triggers more inflammation and further promotes the growth of inflammation-inducing microbes. Consequently, the question becomes: how can we break this cycle? A number of approaches have been used to treat IBD, including 5-aminosalicylate (5-ASA) agents, corticosteroids, immunomodulators, and surgical intervention, but none have proven curative or even

consistently efficacious [8]. Newer treatments involving prebiotics, probiotics, and fecal microbiota transfer have also met with inconsistent success. All of these treatments are complicated by the dramatic variation in microbiota composition and genetics between individuals, making it difficult to even define a 'healthy' versus a 'diseased' microbiota [10]. The severity and increasing prevalence of IBD highlights the need for further study to understand the key contribution of the microbiota in the progression of this disease. The current treatment outcomes indicate a need to take into consideration the interaction of the gut microbiota with host genetic and immunological factors on an individual basis to shed light on this question.

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Juvenile idiopathic arthritis: a heterogenous group of diseases with a heterogenous set of challenges

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Arthritis affects children too. As a matter of fact, juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease, or disease affecting joints and connective tissue, found in children with a prevalence of 16-150 per 100,000 individuals in developed countries [1]. Encompassing all forms of arthritis with unknown etiology that are found in patients aged 16 years and younger, and that persists for more than 6 weeks at a time, JIA is used as an umbrella term to describe a heterogenous group of diseases that are categorized according to a wide range of laboratory and clinical diagnostic criteria, including the number of joints involved, fever, and lymph node enlargement [2]. Currently, there are seven subtypessystemic arthritis (sJIA), enthesitis related arthritis (ERA), oligoarthritis, rheumatoid factor-positive (RF+) polyarthritis, rheumatoid factor-negative (RF-) polyarthritis, psoriatic arthritis, and undifferentiated arthritis [2].

Despite marked advances in management and treatment, JIA remains a disease that results in functional impairments (reduced range of motion, joint swelling, growth abnormalities, etc.), medication-associated morbidity, and long-term disabilities that can incur lasting economical and emotional strain on patients and their families [3]. On average, the annual cost of treating JIA ranges between approximately $3000 to $18 000 per year and can climb even higher for patients receiving biologic agents, such as monoclonal antibodies [4]. In addition to financial costs, JIA takes a toll on quality of life. The lives of children with chronic arthritis are impacted by ambulatory visits, hospitalizations, and interruptions in education, which in turn, augments the burden on their caregivers.

The high degree of inter-patient heterogeneity in clinical manifestations, gene expression, and cellular phenotypes brings about numerous hurdles in differential disease diagnosis and treatment. To begin, recognition of JIA in children can be challenging in itself and it often takes a long time for children who develop this disease to obtain a referral for a pediatric rheumatologist, and a subsequent assessment. Owing to its definition, diagnosis of JIA does not occur prior to 6 weeks of symptom onset, and often is not completed until much later. In British Columbia, Canada, the median amount of time between symptom onset and obtaining a pediatric rheumatologist assessment is 38.3 weeks—almost 9 months [5].

As the most recent system of JIA classification, the diagnostic criteria put forward by the International League of Associations for Rheumatology (ILAR) are based upon clinical manifestations (as mentioned above) [2]. It has been proposed that additional measures are needed to pinpoint the exact condition a child may have in this broad group of diseases [6]. For example, systemic JIA (sJIA) is distinct in the systemic features and inflammatory response that it displays, so much so that there is an up-and-coming consensus for it to be set apart from the other subtypes [7]. The heavy involvement of the innate immune system, along with the major roles that interleukin (IL)-6, IL-1, and IL-18 play, has led many to believe that sJIA should be considered as an autoinflammatory syndrome rather than a classic autoimmune disease like systemic lupus erythematosus (SLE) [7]. Furthermore, due to such findings, and to the knowledge that has been acquired since the introduction of the ILAR classification system, some believe that it is only a matter of time before the all-encompassing term "juvenile idiopathic arthritis" will be phased out [8].

In addition to healthcare practitioners, parents of children who develop JIA also face barriers in understanding JIA pathogenesis. In a study where parental education was used as a measure of socioeconomic status, it was found that the children of parents who had either a university degree or post-graduate training were more likely to be seen by a rheumatologist sooner than those of parents with less education, and is perhaps attributable to their increased mindfulness of clinical abnormalities or familiarity with the healthcare system [9]. This highlights the benefits of educational efforts in promoting awareness of presenting symptoms of JIA that could help parents recognize when to seek medical attention.

The heterogeneity of conditions found within JIA and the classification of diseases creates large compilations of data that pose analytical challenges. Machine learning

methods that take both clinical and biological factors into consideration, have been tested in the development of novel approaches that could be used to dissect these large data sets [10]. High-throughput data analysis could radically improve the efficacy and accuracy of future diagnoses made in the clinic. Such advances could also warrant the development of personalized therapy for patients with JIA, minimizing the time spent arriving at an accurate diagnosis and determining the best courses of therapy. More importantly, children with JIA would not have to wait as long to receive the appropriate treatment, thereby reducing the amount of joint damage that they experience when living with arthritis. Further investigation into the underlying genetic and cellular mechanisms that drive specific JIA phenotypes is needed in order to determine more effective methods for tackling this life-impacting group of diseases.

From a whole-diet perspective, dietary patterns that are high in plant-based foods and lean proteins, and that are based on consuming fresh and minimally processed foods, such as the Mediterranean diet, have garnered attention in the field of nutritional psychiatry for improving mental health. Jacka and colleagues recently conducted a randomized controlled trial (SMILES trial) and showed that a modified Mediterranean diet support group had a greater improvement in the symptoms of depression in clinically depressed individuals than a social support group [8]. Parletta and colleagues also conducted a trial (HELIFMED) comparing a Mediterranean-style dietary intervention and a social support condition as a control, and found similar results [9]. Unsurprisingly, the Mediterranean diet is rich in nutrients that are potentially linked to improved mental health, and that have been consistently associated with lower levels of inflammation.

Although the research to date that directly implicates nutrient intake and diet with improved symptoms of depression is by no means conclusive, it may eventually present an enticing alternative treatment option for MDD. Improving nutrient intake by modifying diet is an accessible lifestyle change with no adverse side effects and may translate to improved mental health. These lifestyle changes have considerable implications for individuals who are unable or do not wish to take antidepressant medication. Moreover, individuals who maintain a healthy diet are more likely to engage in other protective health behaviours that may also help to improve mental health. For these reasons, research on the impact of diet on MDD should focus on clinical populations, and should be considered in clinical settings for the treatment of mental illness.

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LINE-1 DNA methylation as a biomarker of early carcinogenesis

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After sequencing of the human genome in 2003, science turned to the epigenome to improve understanding of the biological processes that dictate how the genetic code is read [1]. The interplay between the genome and epigenome can be described as the union of nature and nurture — while the genetic code remains fixed by nature, the epigenome may be altered. The epigenome is a set of heritable, yet modifiable chemical changes that affect the transcription, translation, and silencing of the genome [1]. The pattern of the epigenome is responsible for gene activation, silencing, and facilitation of tissue-specific gene expression in cells of the human body. Mutations leading to genetic changes in DNA are considered rare, and typically occur in the context of disease processes such as cancer [1]. However, the epigenome is susceptible to change due to environmental factors, and is expected to change across an individual's lifetime [2]. This key characteristic of the epigenome has made it an important topic in chronic disease research [3]. DNA methylation, histone modification, nucleosome modeling, and gene expression regulation by microRNA (miRNA) are known epigenetic regulation mechanisms [3]. This paper explores the potential for DNA methylation to serve as a biomarker of early carcinogenesis.

DNA methylation is a widely studied epigenetic modification in the field of molecular epidemiology, which seeks to understand molecular processes by which known risk factors may cause disease in the human body. Molecular epidemiology techniques are commonly applied to research focused on the etiology of cancer, where long latency periods make it difficult to study the effect of toxins on cancer risk directly. Breaking down the disease continuum allows molecular epidemiologists to study the mechanistic relationships by which lifestyle exposures can lead to disease. For example, to elucidate the mechanism by which body mass index (BMI) may lead to increased colorectal cancer risk, an investigator may study the relationship between BMI and DNA methylation — a known precursor to cancer.

Another consideration of molecular epidemiology research involves the investigation of genetic factors that affect the molecular processes under study. The efficiency of molecular processes in the cell is influenced by an individual's genetics [4]. By incorporating genetic factors into the study of molecular epidemiology, it becomes possible to target those individuals that are at an increased risk of disease due to genetic polymorphisms. When data on lifestyle exposures and genetic factors are combined, a more complete picture of the risk of chronic diseases begins to form. This research can then be directly used to test individuals for genetic variants, as well as create targeted interventions for those at an increased risk. Specifically, genetic screening and development of drugs that may help mitigate deficiencies associated with methylation processes could benefit individuals determined to be at increased risk [5]. In any case, molecular epidemiology allows intervention research to move forward with greater information regarding the biological mechanisms behind disease causation [5].

Biomarkers have become important surrogate endpoints of studies in the quest for improved disease understanding due to their ease of measurement and earlier detection of disease [6]. In a recent review, Strimbu and Tavel define biomarkers as objective indications of medical state observed from outside the patient — which can be measured accurately and reproducibly [6]. Long interspersed nuclear element-1 (LINE-1) DNA methylation is a specific form of DNA methylation, and an established precursor to carcinogenesis. It is specifically linked to colorectal, breast, cervical, head and neck, and kidney cancer, as well as all-cancer mortality, and other chronic diseases [7, 8]. Although the exact role of LINE-1 DNA methylation is not clear, hypomethylation of LINE-1 elements is linked to genomic instability, a known precursor to cancer [3]. Furthermore, LINE-1 DNA methylation is a relatively stable measure, and does not change over shorter time periods [9]. This is an essential component of a biomarker, as a measure with poor stability and daily or monthly fluctuations would be difficult to quantify without consistent measurement and follow-up.

In recent years, microchip-based approaches have been used to quantify DNA methylation over traditional polymerase chain reaction (PCR) based approaches [10]. This approach is able to quantify methylation with

improved reliability and validity over previous methods [10]. It is perhaps these types of advancements in cheaper, easier to use measurement tools that will further propel the use of LINE-1 DNA methylation as a common biomarker for detecting carcinogenesis in its early stages. Basic science studies show that there is biological probability for LINE-1 DNA methylation to lie on the causal pathway between specific lifestyle factors and carcinogenesis [7, 8]. Although some current research suggests that LINE-1 DNA methylation is tissue-specific, methylation measured in leukocyte cells is also associated with colorectal, bladder, and breast cancer risk [8].

Combined, these aspects of LINE-1 DNA methylation demonstrate its potential as a biomarker of early carcinogenesis. Currently, the relationship between the majority of cancer risk factors and LINE-1 DNA methylation has not been established. However, epidemiologic studies investigating these relationships continue to provide new research, allowing for potential future implementation of LINE-1 DNA methylation as a biomarker of early carcinogenesis in clinical work.

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Using precision medicine to reduce falls in individuals with Alzheimer's disease

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Falls are considered a significant public health problem in the older adult population (>65 years) [1]. Consequences of falls can be major injuries such as hip fractures or head traumas, hospitalization and even death [1]. Aside from these more seemingly debilitating outcomes, falls can also lead to adverse psychological effects such as depression and loss of independence [2]. The economic impact of falls is also substantial; in Canada alone the associated direct costs of falls is more than two billion CAD annually [3]. The problem of falls and their consequences is more severe in individuals with Alzheimer's disease (AD), as they fall at least twice as often as cognitively healthy older adults, incur more severe injuries and experience lower recovery rates [4]. Currently, there are approximately 44 million people with AD or other forms of dementia, and this number is expected to triple in the next 40 years [5]. Despite the many studies conducted in an effort to reduce falls, we are still facing their negative impacts. A systematic review of fall prevention programs (e.g. physiotherapy, strength training, medication review) in people with dementia demonstrated that these programs were beneficial for reducing falls only in some of the participants [6]. It is essential to discover a successful fall prevention method for people with AD, as it would lead to a better quality of life for the patients and a lower economic burden for society. Bearing in mind that current fall prevention strategies are not effective for all individuals with dementia, it is time to investigate this matter from a novel perspective.

AD is an etiologically heterogeneous condition caused by different genetic and environmental factors in different individuals [7]. The rate at which people with AD lose their cognitive and physical abilities is determined by the originating factors as well as the constitutional genetic makeup of the patients [8]. This indicates that not all people with AD fall due to a shared etiology or possess the same risk factors for falls [9]. To a great extent, the numerous factors that contribute to falls in people with AD, including severity of cognitive impairment, vision problems, balance and gait impairment and disease co-morbidities, are influenced by the patient's genetic background. Clearly, each patient requires a different approach to the prevention of falls, as the etiology and risk factors for falls vary in different patients. In addition, just by treating the noticeable risk factors (e.g. vision impairment) in a person with AD, the problem of falls cannot be eliminated, as there could be other unknown contributing factors. Since the risk factors can potentially vary among individuals with AD that fall, the genetic make-up or the more in-depth underlying reason for this difference amongst these individuals can be strikingly different as well [9]. In this article we propose that approaches used in precision medicine to determine who should receive which treatment can be highly beneficial to this line of investigation. Besides the patient's original genetic makeup (the genome), which influences the entire progression of the disease without changing during a patient's lifetime, other layers of gene expression regulation (i.e. epigenomics, transcriptomics, proteomics and metabolomics) are highly plastic and can immediately reflect any change in the status of any primary, secondary, or interactive factors that determine the risk of falls in people with AD.8 The improvement and reduction in cost of genomic technologies in recent years have made feasible the exploration of millions of such biomarkers in relation to response to various fall prevention programs. With the improvement in sensitivity and throughput of such tools, we are now able to perform non-invasive liquid biopsies from easily accessible tissues (e.g. peripheral blood plasma, urine and saliva) to search for biomarkers that reflect the biological processes occurring in the more relevant non-accessible organs, e.g. the brain in AD. The advent of highly computational methodologies such as data mining and machine learning has removed the obstacles in interpretability and applicability of the discovered biomarkers in the age of multi-omics [10].

In conclusion, it is imperative to reiterate that the number of individuals with AD is increasing, and fall-related injuries, which are one of the most expensive medical conditions associated with the disease, are also at an incline. While many risk factors for falls have been identified, and they can be used to determine who is most

likely at a higher risk for falling, we lack fall prevention strategies that can be used for every patient with AD. In this commentary, we propose methods used in precision medicine to stratify patients based on their genomic and epigenomic profile and direct appropriate interventions to the specific deficits. Unlike other medical fields, precision medicine using genetics technology has not been used in rehabilitation sciences. This approach can potentially lead to saving time and reducing healthcare costs associated with falls and will also open doors for further investigations in other conditions in the same field.

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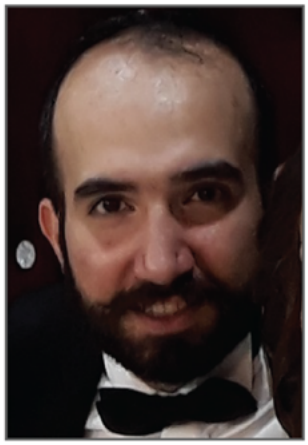

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Oral health for a healthy mind: the unexplored links between oral health and dementia

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"Regular visits to the dentist will keep our teeth healthy." Who has never heard of this recommendation? Still, we often overlook the connection between the mouth and the rest of the body. One such example is the association between oral health and dementia. Dementia is an ailment that chronically impacts the cognitive function of over 46 million patients worldwide [1]. The decline in memory and reasoning caused by dementia can be devastating to its sufferers as well as to families and caregivers of patients afflicted with the condition. As the number of dementia cases nearly doubles every 20 years, the burden to healthcare systems is coming to light. Early diagnosis of dementia-related disorders can help to alleviate some of the symptoms and slow down its progression; hence there is relevance in finding tools that detect dementia and prevent its development. Thus, we will discuss the possible impacts of oral diseases on cognitive function, and potential uses for the screening of dementia.

Several recent studies have attempted to summarize the evidence that correlates oral health conditions with dementia [2-5]. The importance of adequate mental health on the drive and ability to care for oneself is somewhat intuitive. In this context, a deterioration in oral hygiene can be an early sign of dementia. Daly *et al.* found that this general trend was ca observed in a variety of studies, in which dementia patients were at significantly higher risks of developing gum disease of varied intensities, cavities and tooth loss [4]. The authors, however, were conservative in suggesting that dementia caused oral disease, due to the scarcity of well-designed cohort studies on the subject, as well as to the few studies that show no correlation between impaired cognitive function and the above-mentioned oral conditions.

Oral health problems have been implicated as risk factors in the development and progression of dementia. Although less obvious, this association has been explained through different mechanisms, including the level of masticatory stimulation impacting on the cerebral blood flow and the release of inflammatory signaling molecules from localized oral inflammation into the organism, which could lead to neurodegeneration. In addition, decreased brain stimuli caused by missing teeth may reduce cerebral activation, affecting brain function and leading to the development of dementia [2].

Recent systematic reviews showed somewhat contradictory conclusions regarding the connection between tooth loss and dementia. They ranged from identifying positive association [2, 3], in which tooth loss resulted in approximately 20% to 50% increase in the risk of developing dementia, to suggesting no association at all [5]. Although most current literature positively associates tooth loss with dementia, the quality of this evidence is arguable [3, 4]. Diverse confounding factors, such as living conditions, access to dental care, dietary changes caused by tooth loss, level of dexterity, and communication ability across dementia patients, play a major role in hampering the validity of these studies. A promising approach is the Hisayama study, which followed the elderly population of a Japanese town over time [6]. Using neuroimaging, they expected to detect traces of cognitive decline as that population aged independent of behavioural changes. According to their criteria, 11.5% of the individuals developed dementia. Their findings indicated that people with 20 teeth or less were 1.6 times more likely to develop dementia than those with 20 teeth or more. Further studies with varied populations could be conducted to unveil the effect of tooth loss on the maintenance of healthy cognition.

Based on this potential relationship between dementia and oral health, we believe in the necessity of developing strategies to contain a self-feeding cycle of dementia and oral diseases. In this model, poor oral health and tooth loss contribute to dementia, which in turn deteriorate the oral condition of patients and further aggravate their mental disorder (**Figure 1**). Dental care must be included and provided for people with dementia and mild cognitive impairment, with the aim of improving oral health throughout life and minimizing the impact on their quality of life. A recent study assessed the current access to dental prevention advice and the care of patients diagnosed with early-stage dementia [7]. An oral education program was developed to assist nurses and other caregivers on the

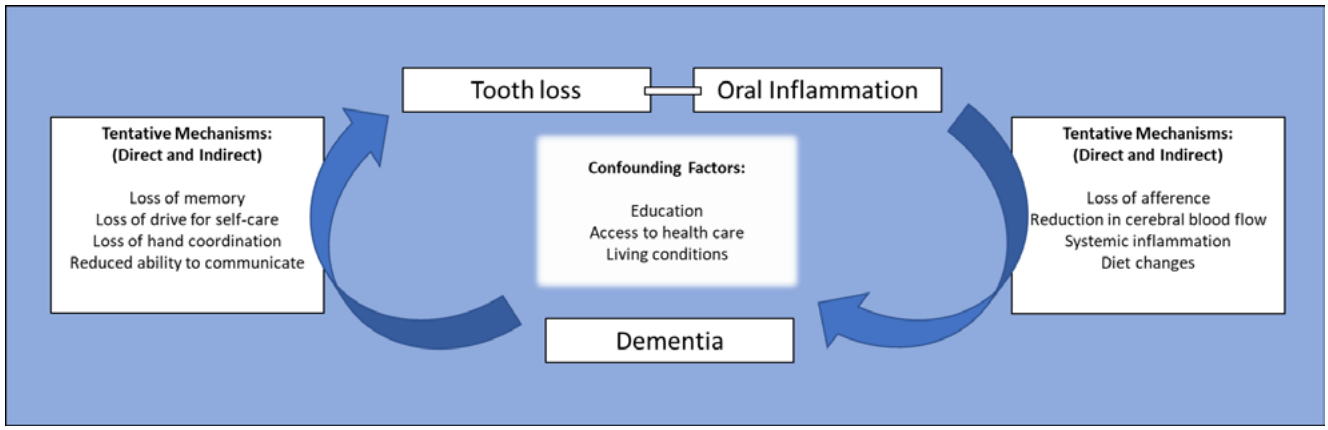

Figure 1: Proposed model. Oral conditions, such as tooth loss and oral inflammation, partially cause or exacerbate the mental disorder (dementia) of the individual, via physiological and social mechanisms. This impaired cognitive function results in deficiencies in oral care that worsen the oral condition. As a result, there is a repeated cycle in which mental and oral health continuously affect each other. Factors such as education, access to the health care system and living conditions can independently influence both health aspects (oral and mental).

oral care of these patients. However, a lack of awareness by health practitioners hindered preventative advice from being adequately provided.

Thus, higher quality health services can be provided following investigations into the association between oral and systemic health, and by translating such findings to the patients. Well-designed longitudinal studies can significantly contribute to determining the nature of the association between tooth loss and dementia. Finding such links may help dentists contribute to the early diagnosis of dementia, resulting in the development of strategies that will prevent it.

Acknowledgement

We would like to thank Dr. Raphael Freitas de Souza (McGill University) for his academic guidance and critical reading of this manuscript.

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Childhood obesity: the importance of diet and physical activity

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It is estimated that 14% of Canadian children are either overweight or obese [1]. These rates have remained relatively stable over the past few years and suggest a dire need for successful interventions. Obesity is a multifactorial disease characterized by increased caloric intake and decreased energy expenditure and is often accompanied by other chronic health conditions and serious economic impacts. Epidemiological evidence suggests overweight and obese children are 4–5 times more likely to develop type 2 diabetes mellitus, 2–6 times more likely to develop hypertension and 2.4 times more likely to develop the metabolic syndrome in later life [2]. Moreover, it is estimated that excess weight and physical inactivity in Canada amount to annual economic burdens of $1 billion and $1.5 billion, respectively [3]. Several risk factors including poor dietary intake, marketing of energy-dense, nutrient-poor foods, physical inactivity and gut microbial composition are believed to play a role in the etiology of obesity. Furthermore, habit-forming behaviour begins in early childhood and tracks into adolescence and adulthood; thus promoting a healthy lifestyle in early childhood is crucial.

Dietary intake in early childhood is important to support energy requirements for appropriate growth and metabolism; however, many children overconsume calories leading to excessive weight gain, fat deposition and altered gut microbial composition. Children who consume a diet characterized by energy-dense, high-fat, low-fibre foods are more likely to develop obesity in later life and the impact of diet on microbial composition is believed to play a significant role [4]. In a recent study comparing fecal microbiota of European children to rural African children, European children typically consumed a high-fat, low-fibre diet and had lower levels of *Bacteroidetes* and higher amounts of *Firmicutes* compared to African children consuming high-fibre, low-fat diets [5]. The ratio of *Firmicutes* to *Bacteroidetes* differs in lean and obese individuals, where greater amounts of *Firmicutes* and lower amounts of *Bacteroidetes* is associated with obesity [6]. In another study, obese adults were randomly assigned to either a low-fat or low-carbohydrate diet to be followed for one year [6]. Weight loss was observed in both groups and was correlated with an increased abundance of *Bacteroidetes* [6]. These bacteria have different genetic components, engage in different metabolic activities and appear modifiable through dietary intake. Therefore, gut microbial composition may partly explain the link between dietary intake and obesity.

The marketing of unhealthy foods to children is big business. Ultra-processed, calorie-dense foods are shamelessly promoted on children's television channels, video games and social media. In recent years, food and beverage television advertising to children has increased by 17% on all stations and by 5% on children-specific stations in Toronto [7]. A systematic review and meta-analysis of 17 studies found unhealthy dietary marketing to children was associated with increased caloric intake during or shortly following exposure and these children were 10% more likely to choose energy-dense, nutrient-poor foods [8]. Moreover, consumption of these types of foods stimulates several neural pathways involved in reward, which may induce addictive-like traits in food consumption, increase unhealthy eating behaviours such as binge eating and further contribute to the rising rates of overweightness and obesity [9]. Overall, these actions play into our evolutionary inclination towards energy-dense foods, making over-consumption easy and in line with normality.

In addition to consuming a healthy diet, physical activity is crucial for energy expenditure and weight management. However, many Canadian children fail to meet physical activity guidelines and, instead, spend several hours each day in sedentary behaviours [10]. A systematic review and meta-analysis using data from 7,351 youth across 5 studies found substituting sedentary time for moderate-to-vigorous intensity exercise significantly reduced body fat percentage by 2.5% [11]. When 60 minutes of sedentary behaviour was reallocated to moderate-to-vigorous physical activity, a 4.5% decrease in body fat percentage was observed [11]. Interestingly, reallocating sedentary time to light physical activity did not yield a significant effect on body composition. This suggests that moderate-to-vigorous physical activity should be promoted and prioritized in daily life, while efforts should be made to reduce time spent in sedentary behaviours. Finally, promoting physical activity

in early childhood is important for instilling healthy lifestyle behaviours and reducing the risk for chronic disease later in life.

Childhood obesity is influenced by a wide array of interacting factors. Many are modifiable. Promoting healthy behaviours and limiting food and beverage advertising in early childhood is crucial for fostering positive attitudes towards a healthy diet and participation in physical activity. Not only do health-promoting behaviours reduce the risk for obesity and other chronic diseases, but they may improve children's gut microbial composition. It is time we act from a personal, public and political perspective to encourage the success of our children and their future.

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Food and beverage marketing: content not suitable for children

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Childhood obesity affects 1 in 7 Canadian children, making it a national public health concern [1]. It is a multifactorial disease that can be attributed to environmental, hereditary, lifestyle, cultural, and social factors [2]. Childhood obesity acts as a precursor to obesity in adulthood, and increases the risk of additional chronic illnesses, such as type 2 diabetes, cardiovascular disease, metabolic syndrome, and cancer [2]. Furthermore, childhood obesity is associated with a reduced quality of life and can substantially impact a child's psychosocial wellbeing [3]. One significant, though often overlooked, contributor to childhood obesity is food and beverage marketing, which within the last half century, has emerged and proliferated into a multi-billion dollar industry in Canada [4].

Children are exposed to hundreds of advertisements per day, 90% of which promote unhealthy products (i.e., calorie-dense, low-nutrient, and high in salt, sugar and fat [4]. The reason for why food and beverage marketing is so detrimental to child health is that exposure to advertisements directly influences food preferences, choices, and eating habits among children [4,5]. In 2016, a meta-analysis by Canadian researchers demonstrated that exposure to unhealthy dietary marketing significantly increased the consumption of, and the preference for, unhealthy food and beverage products in children [5]. Despite the surmounting evidence of the negative implications associated with marketing food and beverage products to children, the practice is becoming more pervasive and the tactics are becoming increasingly extreme. Children are being inundated with food and beverage advertisements across numerous media and technology platforms, including, but not limited to television, websites, online games, video games, smartphone applications, and social media [4]. Less overtly, but still impactful, marketing of food and beverage products also occurs through product placement, celebrity endorsements, and corporate sponsorships of school and recreational events [4,6].

It is not a coincidence that food and beverage companies are focusing specifically on children; in fact, marketers have identified this age demographic as the ideal target for reasons related to their buying and spending power, accessibility, and susceptibility to persuasive messaging [4]. In Canada, children not only have their own money to spend, but also have significant influence over their parents' purchases. In 2006, Canadian children aged 9-14 spent nearly $3 billion, and in 2004, were estimated to have determined $20 billion of their parents' spending [6,7]]. As noted above, children are exposed to numerous sources of advertising, many of which are screen-based. The average Canadian child spends approximately 8 hours per day in front of screens, making them extremely accessible targets for marketing [4]. Finally, children are viewed as impulsive and impressionable consumers who lack the critical thinking skills necessary to comprehend the persuasive language and marketing techniques used in advertisements [4,6]. Until now, the food and beverage industry has largely self-regulated the marketing of its products to children; however, their efforts have been minimal and ineffectual. In 2007, The Canadian Children's Food and Beverage Advertising Initiative (CAI), was implemented with the overall purpose of reducing advertising to children under the age of 12, and improving the nutritional quality of products targeted to them [8]. Though this initiative was promising in principle, it has failed in reality, largely due to the fact that participation of companies is voluntary, and that those involved can be selective about the criteria that they adhere to [4,8]. Interestingly, a recent report by the Heart and Stroke Foundation demonstrated that approximately 75% of the unhealthy advertisements viewed by children are, in fact, from companies that are members of the CAI [4,8].

The legislation of policy has been proposed as a viable option for restricting food and beverage companies from marketing to children [4,6,9]. Policies of this nature have proven to be effective in reducing unhealthy behaviours and improving health outcomes in the past. For example, in 1980, Quebec pioneered legislation to ban all commercial advertising of goods and services to all persons under the age of 13. Since then, the province has reported a 13% reduction in fast food purchases, as well as the lowest rate of obesity in any province in Canada [4,10]. The recently proposed Canadian Bill S-228 (i.e., Child Health Protection Act) would amend the current Food and Drugs

Act to prohibit food and beverage marketing directed at persons under 17 years of age, and would include packaging, advertising, and other forms of promotion [9]. Bill S-228 is a stride in the right direction for health promotion in Canada. The marketing of unhealthy food and beverage products is an exploitive industry that puts children at risk for a myriad of chronic health conditions. Institution of Bill S-228 would not only terminate the predatory and unethical marketing practices of food and beverage companies, but would also support children in making healthy choices about food, potentially lowering national rates of childhood obesity. Researchers, health professionals, policymakers, and parents must continue to advocate for the protection of children and demand accountability from the industry for putting them in harm's way.

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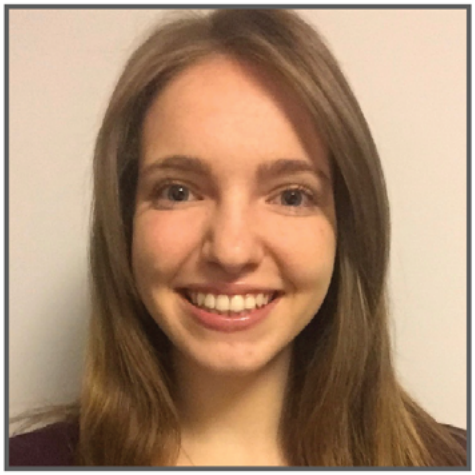

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A call for interdisciplinary collaboration between video game designers and health care professionals to fight obesity

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More than 26% of Canadian adults are obese and 12% of school-aged children are overweight or obese; together, this accounts for an annual health care cost of $3.9 billion in Canada [1]. Obesity contributes to the early development of a number of diseases such as type 2 diabetes, osteoarthritis, colorectal cancer, depression and premature death [1]. Some commonly reported barriers to regular physical activity include lack of time, social support, space to exercise, transportation and funds to buy equipment or join facilities [2].

Ubiquitous and accessible consumer technologies can assist people struggling with obesity to recover and maintain a good quality of life. This is especially true for the new generation of video games—"exergames"—that require exertion in the form of strength training, balance and flexibility activities. Exergames can offer the combination of the benefits of physical activity and the entertaining and motivating factors of video games. They have the potential to increase accessibility and affordability of treatment options while reducing the strain on the health care system. Video games are intrinsically motivating — people engage with them because they are inherently interesting and are designed to be enjoyable [3]. However, commercial exergames have been unable to replicate the recommended exertion requirements as they are primarily designed to maximize entertainment [4]. Video games that are tailor-made for health, on the other hand, lack the graphics and gameplay standards of commercial games [5] and risk losing user interest. The loss in interest is partly due to the fact that tailor-made video games are based on extrinsic motivation. People engage with them because they lead to desirable but separable outcomes which are achieved over time, resulting in loss of interest as results are delayed [3]. Action void of intrinsic motivation will result in failure of any activity-based intervention. Effective game design must include interdisciplinary collaboration between healthcare professionals and video game designers for exergames to be a successful treatment option.

Research on exergames has produced mixed results with variability in data based on the type of game, time spent playing each game, and weight and age of participants. Exergaming results in higher levels of energy expenditure in both adults and children, and higher energy expenditure than in heart sedentary video games [6]. Respiratory exertion while exergaming exhibited respiratory efforts that were comparable to medium intensity aerobic dance [7] and energy expenditure and heart rate similar to brisk walking or jogging [8]. However, the amount of energy expenditure during exergaming is not comparable to the recommended amounts of daily physical activity. Energy expenditure during exergaming falls below the recommended levels for maintaining cardio-respiratory fitness [6]. Exergames also have low half-lives as users get tired of the game and move on to more exciting sedentary videogames; users engaged in exergaming for 6 minutes compared to at least 60 minutes of physical activity per day as recommended by health agencies [7].

Gamification is defined as using game design elements in a non-game context and can be the solution to increase intrinsic motivation in exergames. To understand "fun" in video games, researchers have used the Self Determination Theory (SDT), which emphasizes motivation to perform a behavior (9). Motivation has been identified as the key characteristic for enjoying game play, and enjoyment of engaging in a certain behavior is an important characteristic of motivation. Enjoyment is a function of feeling autonomous (the perception of making in-game choices), competent (being good at the game) and reliable (perception of relating to personal values). The concepts of attractiveness, motivation and incentive are also similar to the concept of Utility Value in the field of economics (10) that quantifies a person's satisfaction from consuming a good or service but emphasizes that a consumer's utility value is difficult to measure and changes from person to person. Based on these principles of gamification it should be noted that (i) exergame as a motivational tool is not designed for people who already engage in traditional physical activity, (ii) there will not be a one-size-fits-all solution and (iii) effectiveness of exergames is a combination of the motivational and physical benefits (10).

Therefore the crux of the issue is that while exergames can be an effective tool to fight obesity, the sports and training science aspects play a secondary role in the design and development process of these games [4]. It is clear that future exergames design and production require significant contribution from health care professionals. In turn health care professionals must concede that exergame design will include addictive elements to intrinsically motivate users. Effective exergames must balance recommendations from physicians and physiotherapists on variables such as the types of exercise, duration, range of motion and speed, while video game designers make the game fun and addictive. The success of exergames can only be achieved through interdisciplinary collaboration between video game designers and health care professionals.

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Stand up for your health: excessive sedentary behaviour as a modifiable risk factor for chronic disease

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Within daily life, there are few more ubiquitous behaviours than sitting. Excessive sitting is a form of sedentary behaviour (SB), which is defined as any waking behaviour in a seated, lying, or reclining position with an energy expenditure of 1.5 metabolic equivalents (i.e., 1.5 times the resting energy expenditure [1]), and has been consistently linked to an increased risk for all-cause mortality and numerous chronic diseases [2]. While SB does not include behaviours such as standing or sleeping, nearly every activity of daily life involves or encourages sitting: transportation, occupations, leisure-time, and household activities. Notably, SB is distinct from physical activity (PA); it is not simply the absence of it or the lack thereof. Rather, SB is a unique contributor to chronic disease risk, independent of PA levels. A recent review by Ekelund and colleagues [3] suggests that high levels of moderate-intensity PA (i.e., 60-75 min/day) can attenuate the detrimental effects of SB; however, these levels of activity are not easily attainable or feasible for population health, with only 1 in 5 Canadians meeting PA guidelines of 150 min/week [4].

Unlike other modifiable health behaviours–such as smoking or PA–SB is an invisible behaviour, in that engagement in it is typically not a conscious or cognitive choice. The excessive accumulation of SB is partially due to a built-up environment; however, factors such as occupation (e.g., manual labour vs. desk-based), education, and societal norms [5,6] all contribute to the average Canadian sitting for 10.8 hours/day [7]. This statistic is especially concerning when the dose-dependent nature of SB is considered: the more an individual engages in SB, the greater their risk of developing chronic health conditions.

Although the field of SB research is young, numerous reviews and meta-analyses have been published in the last decade, consistently and independently linking excessive SB to numerous chronic diseases. Notably, a systematic review by Rezende and colleagues [2] summarizes 27 systematic reviews that assess the association between SB and health outcomes. The authors report that SB is associated with all-cause mortality and cardiovascular mortality, independent of PA and body mass index (BMI), with some reviews reporting as much as a 49% increase in all-cause mortality between individuals who were sedentary for $<$4 hours/day and those who were sedentary for $>$9 hours/day. The same review by Rezende and colleagues reports a positive association between increased SB and risk for cardiovascular disease (5-15%), cardiovascular events (5-17%), type 2 diabetes (20-112%), metabolic syndrome (73%), and an obesogenic effect in youth [2]. There is also emerging evidence that eludes to an association between excessive SB and poor mental health [8].

It is hypothesized that a mechanism for the association between SB and chronic disease risk derives from low levels of lipoprotein lipase (LPL) following both acute and chronic exposure to SB [9], which are associated with an increased risk of cardiovascular disease. SB is also thought to affect carbohydrate metabolism through modifying muscle glucose transporter (GLUT) protein content, which negatively impacts insulin sensitivity and oxidative capacity. It should be noted that these hypothesized mechanisms are inferred from animal models, spinal cord injury studies, and bedrest studies [9]. Establishing the exact mechanism(s) of action of SB and the associated health effects still requires further investigation.

The risk for chronic disease is further amplified through the positive relationship between SB and other health-compromising behaviours, including smoking, alcohol consumption, decreased leisure-time, physical activity, and diet [5]. While the causality of some of these behaviours is still debated, these negative health behaviours compound the risk for chronic diseases, such as obesity, cardiovascular disease, and diabetes.

Although the exact mechanism(s) for the relationship between SB and chronic diseases remain unknown, pragmatic solutions for preventing and attenuating the risks associated with excessive SB are simple, cost-effective, and efficacious. A recent meta-analysis examined

the effectiveness of breaks from SB on metabolic markers, and found that taking short, frequent, light-intensity PA breaks (e.g., walking) from bouts of sitting significantly improved blood glucose and insulin levels [10]. Breaks of moderate-vigorous PA were also more effective in reducing blood glucose and insulin levels than an equivalent single-bout of moderate-vigorous PA, highlighting the distinct benefit derived from taking multiple breaks compared to a single one [10].

Aside from the health benefits of breaking up prolonged SB, the accessibility, simplicity, and cost associated with a SB intervention are ideal. Reducing overall SB by substituting it with standing and/or light physical activity is a simple, effective, and practically free solution that can be done by almost anyone at almost any time.

In sum, excessive SB negatively impacts health through increased risk of several chronic diseases, independent of PA levels. Breaking up bouts of SB with light-intensity PA or reducing overall SB are simple and effective ways for anyone to attenuate the unique risk associated with it.

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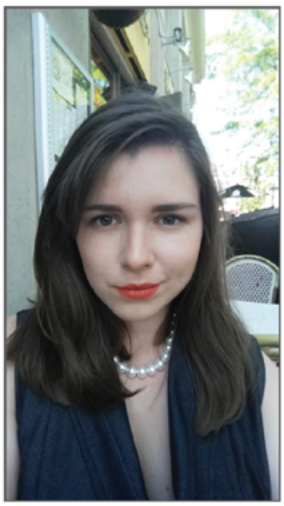

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Yoah received a B.Sc from the University of Waterloo, and his M.A from Western University, and is now a Ph.D candidate at Western University. His research focuses on the impact of excessive sedentary behaviour on subjective well-being in university students. He enjoys playing guitar, mountain biking, and chasing after his dogs."

Food insecurity in Canada and opportunities for chronic disease prevention and management

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Food insecurity, the inadequate or insecure access to food due to financial constraints, affects 12.6% of households or approximately 4 million individuals in Canada [1]. This modifiable social determinant of health independently affects chronic disease at all stages of life. Bold action to combat food insecurity in Canada has the potential to considerably reduce the prevalence of chronic disease and curb healthcare spending. However, Canada currently has no national strategy to address this public health problem and food insecurity prevalence has changed little over the past 10 years.

Since the first Canadian survey measuring hunger, data have consistently demonstrated a relationship between food insecurity and chronic disease after adjustment for household composition and income. Canadian children who experience even a single episode of hunger are more likely to have poorer health than those who never went hungry [2]. Furthermore, youth who experience multiple episodes of hunger are at a higher risk of being diagnosed with a chronic condition. For some, the effects on their well-being persist many years after experiencing hunger, leaving permanent impacts on their health.

A similar relationship exists when observing the proportion of Canadian adults with chronic physical and mental health conditions such as diabetes, heart disease, depression and anxiety. Compared to 9% of adults in food secure households, 34% of adults in severely food insecure households report a diagnosis of 3 or more chronic illnesses (**Figure 1**) [3]. Higher levels of stress and inadequate nutrient intake in food insecure populations are two mechanisms which may explain these observations.

The healthcare burden for food insecure individuals in Canada's publicly-funded healthcare system is a concern for all Canadians. For example, Ontarians in severely food insecure households consume healthcare services costing more than twice that of food secure individuals, including costs for physician services, inpatient stays and emergency room visits [4]. In fact, food insecurity is the single strongest predictor for high-cost healthcare use above education, region of residence, immigration status and even income [5]. This is because food insecurity is a more direct measure of material deprivation — a combined function of assets, savings, shelter costs, food costs and income itself.

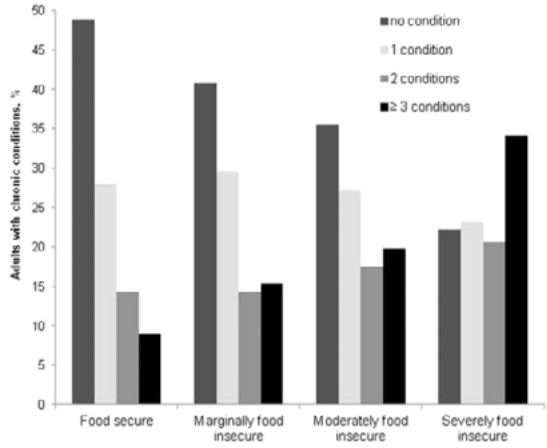

Figure 1: Prevalence of number of chronic conditions among adults, 18–64 years of age, by household food security status (Canadian Community Health Survey, 2007-2008 [3]).

Currently, there are no federal or provincial policies to explicitly reduce food insecurity. The main response by Canadians has been in the form of food charity, an ineffective initiative at addressing the root causes of hunger. Research suggests only a quarter of food insecure households use food bank services and that utilizing these services does not result in food security [6].

Food banks are an unregulated charitable model, providing food often deemed inappropriate for retail sale [7]. Users have reported misalignment between food bank provisions and household needs, inadequate amounts of food due to rationing, stigma associated with the use of charity and sporadic access due to dependence on volunteer-driven labour [7]. The lack of coordinated governmental response represents a missed opportunity to address social determinants of chronic disease in Canada.

Canadian policies to provide support to the most

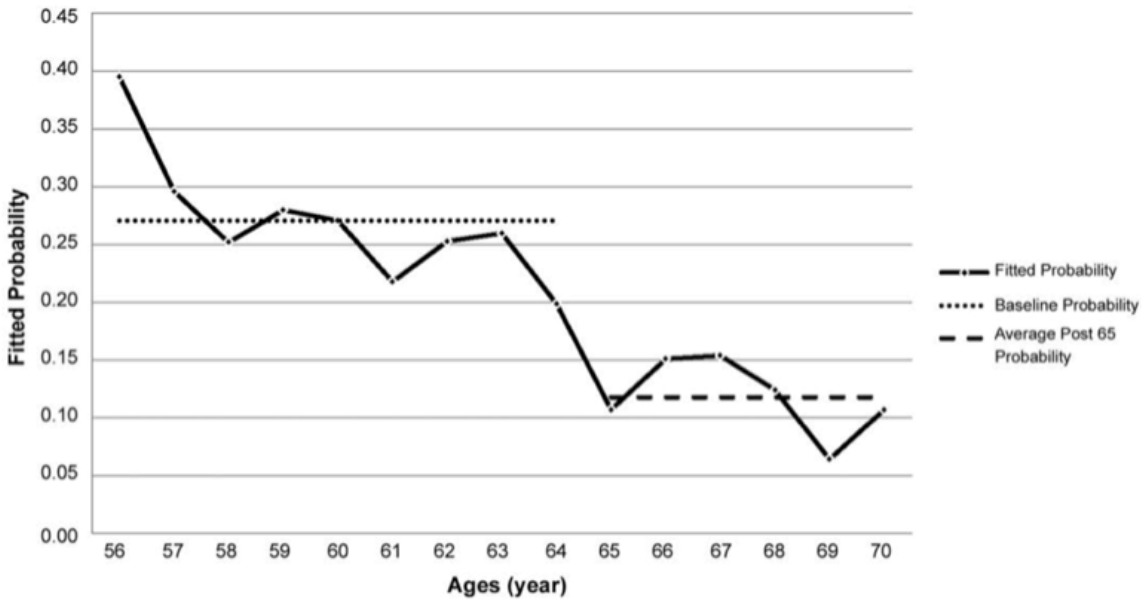

Figure 2: Fitted probability of food insecurity by age from probit regression (Canadian Community Health Survey pooled data 2007–2013 [9]).

economically disadvantaged are currently insufficient in preventing food insecurity. 70% of households dependent on social assistance report an inability to reliably put food on the table, highlighting the inadequacies of these programs to meet basic needs [1]. However, research has shown that improvements to social assistance can be a promising strategy to provide households with basic needs. For example, British Columbia's modest increase in social assistance rates in 2005 resulted in a significantly lower prevalence of food insecurity, highlighting sensitivity to small increases in income [8]. Meanwhile, 62% of food insecure households in Canada rely on income from employment, mostly in the form of low-wage, precarious jobs. This demonstrates the inability of the majority of food insecure individuals to garner a living wage, despite participation in the workforce.

As food insecurity is strongly rooted in inadequate income, a guaranteed annual income holds promise to reduce material deprivation. In fact, an example of a guaranteed income has already been implemented in Canada for seniors. When an adult turns 65, they become eligible for the Old Age Security and Guaranteed Income Supplement programmes. After the age of 65, the prevalence of food insecurity among low-income individuals drops by half, partly due to the significant protection offered by these guaranteed incomes (**Figure 2**) [9]. Expansion of a guaranteed income may similarly reduce food insecurity rates in Canada, with notable impacts on chronic disease prevalence and the ability for individuals to better manage their health.

Despite relative affluence in Canada, food insecurity continues to be a public health concern that has remained largely unaddressed. Lagging action on this social determinant of chronic disease will continue to burden the health of individuals and the Canadian healthcare system. Along with bold efforts to achieve scientific breakthroughs in disease treatment throughout Canada, the fundamentals of providing basic needs in every household should not remain forgotten as an important strategy to reduce the incidence and burden of chronic disease.

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Plant-based diet as a means to prevent and treat chronic disease

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Chronic diseases, such as coronary artery disease, ischemic stroke, diabetes, and some specific types of cancer, were once thought to be prevalent in high-income countries only. However, research shows that these chronic diseases are now affecting populations worldwide [1]. Furthermore, migrants who go from a low-income country to a high-income country often have a dramatic increase in the rate of cancer and cardiovascular disease [2]. Rates of chronic disease among African Americans are similar to Caucasian Americans even though the rate of chronic disease is extremely low in traditional African societies. Not only does it illustrate the cultural environment that promote chronic disease in North America, it also indicates the primary determinants of these diseases are heavily influenced by modifiable environmental factors, such as lifestyle and diet.

Proper diet is essential to prevent chronic diseases. Although there are disagreements as to what the optimal diet is, the Adventist Health study showed that as you incrementally remove more animal products from your diet, you increasingly reduce the risk of developing diabetes [3]. To expand on this, the incidence rate of diabetes was lowest among individuals who identified themselves as vegan, which entails no animal products in their diet. However, the risk increases to those that consume only eggs and dairy (lacto-ovo vegetarian), and again heightens for those consuming fish (pesco-vegetarian). Furthermore, an even higher risk was displayed in a diet that is primarily vegetarian but does incorporate some meat occasionally (semi-vegetarian). Lastly, the typical American non-vegetarian diet, that consists of eating mostly animal based foods on a regular basis ultimately had the highest risk for developing diabetes. Furthermore, in the same study, they found that the vegetarian diet was associated with lower all cause-mortality and disease specific mortality compared with the non-vegetarian dietary pattern [4]. They also demonstrated some associations with lower mortality of the pesco-vegetarian, vegan, and lacto-ovo vegetarian diets when compared with the non-vegetarian diet. Moreover, the incidence rate of colorectal cancer was lower among vegetarian group compared with non-vegetarian group [5]. Pesco-vegetarian had the lowest incidence of colorectal cancer suggesting that fish may provide more protection than meat. This is all highlighted with Canada's newly remodeled food guidelines, removing "poultry" and replacing it with "protein"; recommending reducing and limit the intake of meat products and increase the consumption of plant-based proteins [6]. The World Health Organization (WHO) has even labelled processed meat as carcinogenic [7]. As a result, to prevent chronic diseases, it is recommended to consume more plant-based sources and limit the intake of meat and dairy products, as dairy has also been removed from the guidelines.

The importance of proper diet cannot be expressed enough to prevent the development of chronic diseases. Just like the WHO's guidelines for moderate to vigorous physical activity, argumentatively, diet needs be emphasized even more. Not only can proper diet add to longevity, it can treat and even reverse chronic diseases [8]. A recent study recruited participants with type 2 diabetes and divided them into either an experimental group or control group [8]. Both the experimental group and the control group received an isocaloric (-500 kcal/day) diet. The experimental group received a vegetarian diet whereas the control group received a diet that consisted of foods recommended by conventional diabetic diet. A calorie restricted vegetarian diet had significantly greater improvements to patients' clinical measures than the calorie restricted conventional diabetic diet. Not only did the experimental group lose more weight with the same amount of caloric restriction, they made significant reductions in their diabetes medication, as well as significant improvements in their insulin sensitivity. Lastly, there were significant improvements in both visceral and subcutaneous fat compositions. Therefore, not only does the vegetarian diet provide greater protection from chronic diseases, it also provides improved clinical patient measures than conventional diets.

With the current demographic of our population shifting strongly towards older adults, the numerous comorbidities that develop within this age group place a huge financial burden on the current healthcare system. As a result of

physical limitations and chronic disease, older adults will be transitioning into an assisted living home (9). That being said, it is very hard to get this population to meet the WHO guidelines for physical activity (10), which further emphasizes the importance and impact that food can have in these facilities. However, the meals provided are usually not ideal for the various types of chronic diseases. Policy makers should be concerned with what kind of food facilities are providing, as this could be a simple transition that could result in a huge impact.

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Kirsten Dillon is a Master's student at the University of Western Ontario. As a researcher in the Exercise and Health Psychology Laboratory, her primary focus is the determination of how reducing sedentary behaviour in older adults will affect cognitive decline, physical functioning, sleep and quality of life. Additionally, her research involves using exercise as a means to treat and prevent chronic disease in all populations. Kirsten completed her B.Sc. (hons.) in Kinesiology and Health Science and Psychology at York University while simultaneously captaining the women's varsity volleyball team for five years.

Diet as a modifiable contributor and potential treatment strategy for Major Depressive Disorder

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Top Submission

Much like the recent push in medicine to have physicians consider mental health when treating physical illness, a similar drive is needed for the inverse to occur in psychiatry: to consider physical health when treating mental illness. A novel and promising avenue for this is monitoring and modifying diet. Typically recognized as a critical factor in physical health, diet is a controllable health behaviour that has been associated with mental health resulting from an increased understanding of the interactions between the gastrointestinal tract and the brain [1]. These interactions occur through a bi-directional communication network, aptly termed as the gut-brain axis. This area of study has seen a proliferation in preclinical, clinical, and translational research, and has implicated both diet and nutrition as modifiable contributors to chronic mental illnesses, such as Major Depressive Disorder (MDD) [2].

MDD (also known as clinical depression) is a serious, and often chronic, psychiatric condition that affects approximately 11% of Canadians at some point in their lifetime [3]. Having no clear etiology, MDD is often treated with antidepressant medications that alter neurotransmitter activity in the brain. However, these medications simply treat the symptoms of depression, but not the disorder, itself. With numerous complications arising from the use of antidepressants, focus has now shifted to treatments that target the possible underlying pathophysiology of the disorder.

A consistent finding among patients with depression, and a proposed cause of the disorder, is an increased expression of pro-inflammatory cytokines that lead to neuroinflammation. Once in the brain, pro-inflammatory cytokines reduce the availability of neurotransmitters that are critical for regulating mood, such as serotonin, dopamine, and norepinephrine, by reducing their synthesis [4]. They also reduce neurotransmitter availability by increasing the expression of transporters that reabsorb them into the presynaptic neuron, and by decreasing precursors of these neurotransmitters by activating enzymes that break them down [4]. These alterations in neurotransmitter functioning are associated with changes in reward circuity in the prefrontal cortex and the anterior cingulate cortex, as well as with fear and arousal circuitry in the amygdala and the insula, which manifest as the core features of depression, such as anhedonia and anxiety [4]. Research on the gut-brain axis has helped researchers hypothesize the etiology of this immune activation, and has emerged as a possible treatment target for MDD.

Chronic stress, often a precursor for depression, can cause increased permeability of the gastrointestinal lining, and allow toxins, such as the endotoxin Lipopolysaccharide (LPS), to leak into the bloodstream [5]. LPS is known to elicit a strong global immune response, including a release of pro-inflammatory cytokines. These cytokines can then travel to the brain, cause disruptions in neurotransmission, as described above, and result in a depressive symptomatology [4]. Thus, it is hypothesized that targeting the gut-brain axis and reducing inflammation may alleviate the symptoms of depression.

One of the most direct ways to target the gut-brain axis is through an individual's nutrient intake. While research studying the effects of diet and nutrition on MDD in clinical samples is still in its early stages, several studies have reported robust findings that support the idea that specific nutrient-and diet-based interventions can alleviate depressive symptoms. Nutrients that may be contributing to this effect include polyunsaturated fatty acids (PUFAs), such as omega-3 and omega-6, Vitamin D, and probiotics. A recent review by Deacon and colleagues reported that there is adequate evidence for suggesting that omega-3s have a role in improving depression, but that further research is required [6]. Studies assessing the effects of probiotics on alleviating the symptoms of depression and anxiety in humans also show promise, but there currently exist too many gaps and inconsistencies in the research, as well as a lack of randomized controlled trials from which to draw conclusions [7].

From a whole-diet perspective, dietary patterns that are high in plant-based foods and lean proteins, and that

are based on consuming fresh and minimally processed foods, such as the Mediterranean diet, have garnered attention in the field of nutritional psychiatry for improving mental health. Jacka and colleagues recently conducted a randomized controlled trial (SMILES trial) and showed that a modified Mediterranean diet support group had a greater improvement in the symptoms of depression in clinically depressed individuals than a social support group [8]. Parletta and colleagues also conducted a trial (HELIFMED) comparing a Mediterranean-style dietary intervention and a social support condition as a control, and found similar results [9]. Unsurprisingly, the Mediterranean diet is rich in nutrients that are potentially linked to improved mental health, and that have been consistently associated with lower levels of inflammation.

Although the research to date that directly implicates nutrient intake and diet with improved symptoms of depression is by no means conclusive, it may eventually present an enticing alternative treatment option for MDD. Improving nutrient intake by modifying diet is an accessible lifestyle change with no adverse side effects and may translate to improved mental health. These lifestyle changes have considerable implications for individuals who are unable or do not wish to take antidepressant medication. Moreover, individuals who maintain a healthy diet are more likely to engage in other protective health behaviours that may also help to improve mental health. For these reasons, research on the impact of diet on MDD should focus on clinical populations, and should be considered in clinical settings for the treatment of mental illness.

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Caroline is a PhD candidate in Clinical Neuroscience at Queen's University. Her research interests currently lie in examining the neurobiological relationship between nutrition and mental health to develop novel treatments for depression, as well as searching for biomarkers that will help predict who will respond to these types of treatments. Her doctoral research involves running a clinical trial examining the effects of a probiotic supplement on patients with depression, and how inflammation may be mediating this relationship.

Weighing the costs of obesity: a brief review of the health care, workplace, and personal costs associated with obesity

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Despite being a serious public health concern for decades, obesity was only recognized as a chronic disease by the Canadian Medical Associated in 2015 [1]. Obesity currently affects 25% of the Canadian adult population, with many projections suggesting the prevalence will continue to increase over the next 20 years [2]. The severity of this health issue is amplified by its numerous physical and psychosocial co-morbidities, including but not limited to, type 2 diabetes, cardiovascular disease, osteoarthritis, depression, and reduced quality of life [3,4]. In addition to the myriad of negative health outcomes, there are substantial economic implications associated with the rising prevalence of obesity. The purpose of this paper is to provide a brief overview of the financial impact of obesity on the Canadian health care system and workplace, as well as highlight the personal economic costs experienced by individuals living with obesity as a result of weight bias and discrimination.

Health Care Costs of Obesity

Calculating the economic burden of illness helps policy makers and public health planners determine how and where to allocate health care funds. A Canadian cost-of-illness study conducted by Anis and colleagues demonstrated that the direct costs (e.g., medication, physician, and hospitalization costs) of obesity in 2005 were $3.9 billion. Indirect costs (e.g., costs associated with co-morbidities) of obesity were an additional $3.2 billion, combining for a total of nearly $7 billion [5]. A more recent literature review of Canadian studies estimates that the total annual cost of obesity may be as high as $11 billion, representing 12% of Canada's total health expenditures [6]. Indeed, obesity places a considerable burden on the health care system and will undoubtedly escalate as prevalence of the disease increases.

Workplace Costs of Obesity

Obesity-related costs have become a major concern for employers [7]. Based on self-report data available in 2005, approximately 15.7% of employed Canadian adults (18 to 64 years) were obese [8]. According to a report by Park (2009), obesity was correlated with several negative components of job performance in the Canadian workforce including absenteeism, reduced work activity, and work injury. For example, men who had obesity were nearly three times as likely to be absent from work than their non-obese counterparts [8]. Similarly, Canadian women with obesity were more likely to: [1] report decreased work activities because of a chronic health issue, [2] take a disability day, and [3] experience a work injury than their colleagues with normal weight [8]. The high prevalence of obesity is evident across diverse sectors and environments (e.g., management, clerical, sales and service, transport, manufacturing, and farming), however the impact of obesity appears to be amplified in those occupations that require heavy labour, longer hours (>40 hours), or shift work [8]. While the investigators were unable to quantify the exact costs of lost productivity, the reported proportion of employees with obesity in the Canadian workforce suggests there are substantial financial implications for employers.

Personal Costs of Obesity

The personal costs associated with obesity appear to be less reported on in the literature than health care and workplace costs, including a notable paucity of Canadian studies. Employees with obesity face several negative, work-related stereotypes including but not limited to: being lazy, sloppy, unmotivated, emotionally unstable, less competent, disagreeable, and undisciplined [4]. These stereotypes lead to weight discrimination and stigma, which can create inequities throughout the employment process including hiring, wages, promotions, and termination [4]. Results of a recent study demonstrated that individuals with obesity are discriminated against during job recruitment and tend to be rated less suitable for work by potential employers than their normal weight counterparts [9]. In terms of remuneration, a review conducted by American researchers

found wage inequities between employees with obesity and their non-obese colleagues, with some studies indicating up to 3.4% and 9% decrease in wages for men and women with obesity, respectively [4]. Additionally, workers with obesity were less likely to receive a promotion and had lower rates of wage growth than average weight employees [4]. Finally, findings from qualitative studies have highlighted employees' perceptions that their weight was a major factor in their termination or demotion [4]. Ultimately, weight bias and discrimination in the workplace results in a loss of life chances and significant economic penalties for individuals with obesity [4].

Recommendations for Action

Immediate action must be taken to reduce the financial burden of obesity on the Canadian health care system and work force, and lessen the personal costs experienced by individuals living with obesity. In 2016, Bill 207 was introduced in Manitoba to amend The Human Rights Code to include physical size and body weight as protected characteristics, however it was overturned by the provincial government who deemed it vague and challenging to enforce [10]. Further consideration of protective and antidiscrimination policies is strongly recommended. Future research should examine the effectiveness of workplace health and wellness initiatives for weight maintenance as such interventions could result in reductions of both health care and employer expenditures related to obesity. Research exploring the feasibility of implementing weight bias training as well as anti-discrimination policies within occupational settings is warranted, and if effective, may lessen the economic impact on individuals living with obesity.

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Waiting in transition: access to rehabilitation care for adults with chronic neurological conditions in Ontario

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Top Submission

Chronic neurological conditions in Canada and rehabilitation care

One of the leading causes of chronic disability in the Canadian population is neurological conditions[1] that affect an estimated population of 3.6 million in the community and 170,000 in long-term institutions [1]. Evidence has been established that rehabilitation interventions are effective for functional recovery after neurological trauma, illness or injury [2]. Fundamental to neurological rehabilitation is the appreciation that different patients need systematic care at different stages in their recovery [3]. Systematic care means the adequate amount, intensity and volume of care that is required at the right time to achieve individual health outcomes at every stage in the rehabilitation process. For systematic care, services need to be designed and delivered in such a way to ensure continuity of care for the patients, from hospital to home and then to the community. However, literature highlights that many people with chronic neurological conditions do not receive the right services at the right time and wait at every step in transition [4].

Factors affecting timely access to rehabilitation care

Critical analysis of available literature suggests that there are many factors that play a role at each of the stages of the rehabilitation care pathway [5]. During acute and sub-acute phases, individual's clinical characteristics, especially the motor and cognitive status assessed by functional independence measurement scores, determine whether the patient will receive in-patient rehabilitation or not [6]. However, within inpatient rehabilitation the focus remains on early discharge, given the current policy emphasis on cost shifting to the community and a belief that community-based rehabilitation ensures better recovery [7]. This means that as soon as the patient reaches the community stage, access to rehabilitation care becomes severely restricted as a result of limited resources and policy decisions resulting in restructuring of the current health system (**Figure 1**).

The growth of the 65+ age cohort and increasing rates of chronic conditions has increased the demand for rehabilitation services in Ontario. Despite increasing demand, the Ontario government adopted several structural measures directed towards cost-containment and privatization [7]. Following this restructuring, only partial coverage for rehabilitation services was provided based on eligibility criteria[2]. As a result, individuals who do not meet eligibility have to obtain services available privately or limited by the home-care coordinating agencies [8]. Even for the individuals who meet eligibility criteria, there is capping on the services which means that limited services are provided based on predefined amounts of hours per service. As a result, volume of services provided to the clients are capped with the potential for clients to purchase additional services from provider agencies. Concurrent to this, numbers for therapist-population ratios are concerning. An estimated ratio of therapists to the population is 51 for physiotherapists (PTs) and 36 for occupational therapists (OTs) out of 100,000 in Ontario [9]. Considering that there are more than 5,600 people with neurological conditions per 100,000 people in Ontario, these numbers for PTs and OTs available will further shrink simultaneous to an aging population (**Table 1**).

[1]The 11 most common neurological conditions in Canada are Alzheimer's disease, amyotrophic lateral sclerosis, brain tumors, cerebral palsy, epilepsy, head injury, headaches, multiple sclerosis, Parkinson's disease, spinal injuries and stroke.

[2]Eligibility criteria include: (1) residents aged over 65 or under 20 years, (2) those receiving social support through the Ontario Disability Support Program, Family Benefits or Ontario Works, (3) residents of long-term care facilities and (4) those who are returned to the community following hospital discharge.

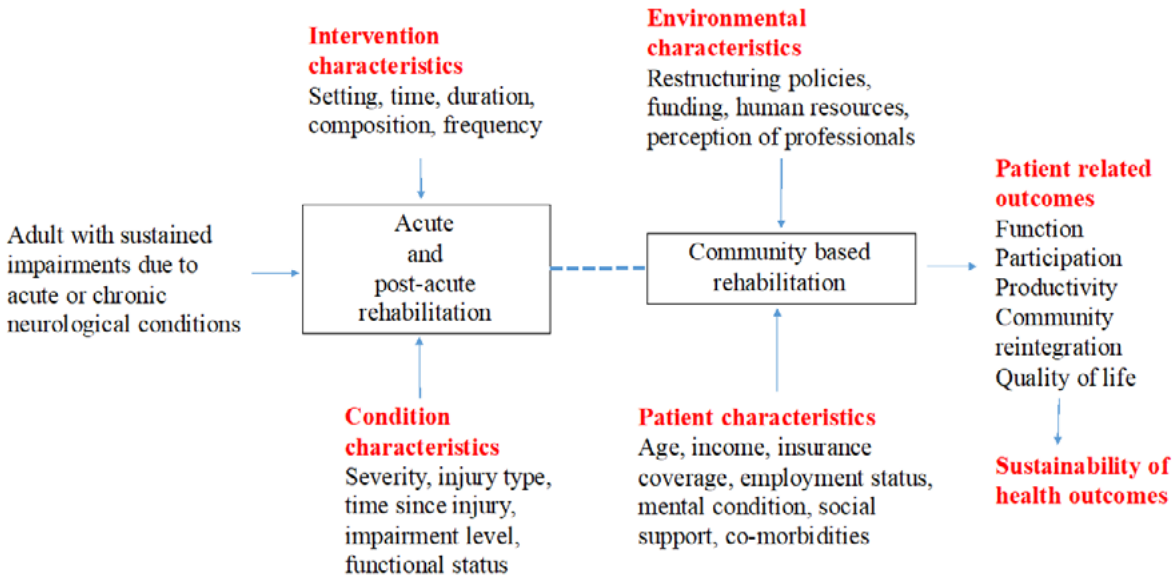

Figure 1: Factors affecting access to timely rehabilitation services across rehabilitation care pathways

Consequences of wait times for rehabilitation care

Withholding necessary care from someone who is in need of services can have unwanted health implications for the person and lead to negative medical outcomes. Consequences of wait times can be serious and grave, especially for adults with neurological conditions, including prolonged suffering from pain, discomfort, loss of function and mental agony [10]. Although in recent years, much attention has been given to limiting waiting times in healthcare, the majority of these initiatives have addressed medical and surgical procedures such as cardiac surgeries, knee replacements and chemotherapy. Home based or community based rehabilitation care has not been considered as medically necessary or something that needs to be provided urgently. Even in the settings where triage, a mechanism of referral prioritization by clinicians, is practiced for rehabilitation services, there is no guarantee of timely access based on need [4].

Conclusion and future directions

It is apparent that adults with neurological conditions have to wait at every step in transition during rehabilitation, from entry to exit from the system, and both time (i.e. limited amounts of hours per service) and timing (i.e. delay) of rehabilitation services affect their trajectory of recovery. This calls into question the appropriateness of the system's response to the rehabilitation care needs of adults living with chronic neurological conditions. Some of the gaps that have been identified in the literature indicate the need to understand how timeliness of care influence the

Table 1: Estimated therapist-population ratio in Canada and Ontario

Estimates	Canada	Ontario
Total Population (2014)	35,544,600	13,685,200
Population with neurological conditions (2015)	3,870,000	770,259
Population with neurological conditions per 100,000 population	10,887	5,600
Total number of PTs (2013)	19,253	6950
Total number of OTs (2013)	14,351	4892
Number of PTs per 100,000 population (2013)	55	51
Number of OTs per 100,000 population (2013)	41	36

patterns of recovery and health outcomes of patients with neurological conditions. Longitudinal research is required to address this gap as understanding these processes will contribute in framing effective systems that ensure timely access to services at all points of transition in the healthcare system.

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Catheter re-use: thrifty or threatening? A commentary on intermittent catheter re-use by individuals with spinal cord injury.

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Spinal cord injury (SCI) is a temporary or chronic condition resulting from damage to the spinal cord which can be sustained traumatically or due to long lasting spinal degeneration. Changes in muscle tone, sensation, and autonomic function (including bladder dysfunction) are often experienced by those with SCI. Bladder dysfunction is experienced by almost all individual living with SCI [1] and can often be physically, medically, and socially debilitating. Some forms of bladder dysfunction include: hyperflexic bladder, where the bladder is spastic and may void spontaneously; or flaccid bladder, in which it is difficult to void and may lead to bladder damage from overfilling [2]. For those living with SCI, intermittent catheterization (IC) is often one of the few options available for bladder voiding and offers a safe, clean, and relatively easy way to void the bladder and is often associated with gaining greater independence [3]. In this mini-review, the issue of catheter reuse due to financial constraints will be discussed. Suggestions for future research directions will also be provided.

During IC, a thin, hollow tube is manually inserted into the urethra to help empty the bladder. The procedure can be carried out by the individual themselves, or with the assistance of a nurse. In many developing countries, including Canada, catheters used for IC are not included under the medical coverage umbrella [4]. Out-of-pocket costs for IC may be a major contributing factor to catheter re-use by individuals with SCI. Catheter re-use is associated with an elevated risk for urinary tract infections (UTIs) and higher risks for urethral trauma [4], but for many individuals living with SCI, still remains the only viable option for somewhat clean catheterization [4]. According to an article by Woodbery *et al.* 2008, 50% of participants surveyed in Canada reported reusing catheters. Although single catheter use and the use of more expensive, pre-lubricated catheters are associated with an almost 20% decrease in UTI risk (compared to 70-80% UTI prevalence rate with catheter re-use in observational studies), individuals are still willing to re-use catheters [4]. Single-use catheters, on average, cost $46/week [6]. Annually, this can add up to a hefty $2,392 (cost for purchasing single use, pre-lubricated catheters), which may be out of reach for individuals of low socioeconomic status. A cost for simply using the bathroom.

Catheter re-use is also associated with increased risk for damage to the urethra. Urethral trauma is most common with the use of non-lubricated catheters (which also tend to be cheaper; [6]. Irritation and damage to the urethra may contribute to increased risk of UTIs and other bacterial infections [5]. Although proper cleaning and re-sterilization of a catheter is necessary in preventing bacteria entering the bladder and reducing the risk for UTIs, current cleaning techniques can range from running the catheter under lukewarm water to the use of household bleach, or other antiseptic solutions. Proper cleaning and sterilization technique for the re-use of catheters has yet to be established and it is unknown whether such technique would be feasible and effective in household settings, due to the complexity of procedure or potential costs associated with the necessary cleaning solutions [7]. Participants from the Hakansson article, for example, reported sterilizing catheters anywhere from daily to weekly, with greatly varying methods [4].

Future research should focus on collaboration with policy makers and work towards better medical coverage that would include catheters for individuals with SCI. Research focusing on associated health risks and proper cleaning techniques may be beneficial as leverage when negotiating policy and medical coverage. In addition, future findings may be used to educate policy makers and other stakeholders on the risks of catheter re-use, bringing the issue of catheter re-use and its associated health risks to the forefront. In the mean time, patient education must remain an important component of the rehabilitation process. Education about the risks of catheter re-use should be clearly conveyed to patients by their nurses and other health care practitioners. Although, unfortunately, many will still re-use catheters due to financial constraints.

Living with an SCI can already prove to be challenging experience; however, it should not be a limiting factor to the quality of life, independence, and health an individual may attain. Simply requiring IC should not be directly associated with avoidable health risks. More work needs to be done at education, research, and policy levels to assure the highest possible standard of health for those living with SCI.

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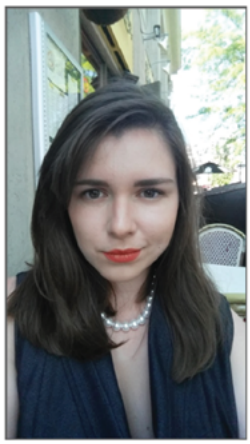

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The hidden impact of an invisible illness: postural tachycardia syndrome

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Introduction

Postural Tachycardia Syndrome (POTS) is an under-recognized [1], debilitating disorder of the autonomic nervous system that primarily affects women of child-bearing age [2]. POTS is characterized by an inappropriately high heart rate upon standing, in association with chronic orthostatic symptoms (3). POTS is estimated to affect 0.1-1% of the North American population [2]. The causes of POTS are not well understood, and are likely multiple pathologies arriving at a similar end presentation [3]. POTS is frequently misdiagnosed, and many patients suffer an extended diagnostic delay [1]. As well, there are no medications approved specifically for POTS treatment [4].

Quality of Life

POTS patients experience significant impacts to their quality of life (QOL) [5], including activity limitation [4], impaired sleep [5] and increased suicide risk [6]. QOL in POTS is comparable to patients with Chronic Obstructive Pulmonary Disease [7], Congestive Heart Failure [7] and Chronic Fatigue Syndrome [1]. Patients often experience exercise intolerance as well as extreme fatigue, limiting everyday activities including tasks as simple as bathing and household chores [4]. In a study of 624 POTS patients, 97.1% reported activity limitations, versus only 31.7% of the health controls [6]. Sleep concerns including lack of refreshing sleep and daytime sleepiness are also reported and contribute to reduced QOL [5]. Interestingly, POTS patients also have a higher suicide risk when compared to healthy controls, however, the exact etiology of this is unknown [6].

Economic, Educational and Social Impact

POTS patients are significantly impacted in multiple aspects of their lives. Patients who are disabled and unable to work have greater impairment in multiple QOL domains including physical functioning and social functioning, compared to those who are able to work [7]. In a recent survey of 3,210 POTS patients age 18 and older, only 46% were currently employed [8] and 70% reported income loss due to their POTS symptoms [8]. This same survey found that 89% of patients missed school days as a result of their symptoms (9). Social impacts are also prevalent in this patient population with 60% of patients reporting they have lost a close friend, and 23% reported the loss of their spouse or partner because of POTS [9].

Diagnosis and Treatment

Diagnostic delay is common for a number of potential reasons including a clinical presentation of non-specific symptoms, no orthostatic measurements in clinic, and a lack of physician knowledge. [10]. Current treatment includes symptom mitigation with medications to lower heart rate, increase fluid volume and increase vasoconstriction [4]. Increasing salt and fluid intake may also aid in symptom management [4]. However, as the etiology of POTS is unclear, the specific underlying mechanisms cannot be directly targeted.

Conclusion

POTS is an invisible illness that has significant impacts on quality of life. However, despite evidence supporting the severity of this illness, POTS remains largely unknown, with many patients waiting years for diagnosis and specialized care. With increased awareness of POTS, patients could benefit from earlier diagnosis and specialized treatment, improved quality of life.

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Health Science Inquiry

Wearable self-tracking technologies and hypertension: opportunities and challenges in the literature

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Wearable consumer self-tracking technologies (STT) automatically measure a host of variables such as geolocation, movement, mood, sleep, heart rate, breathing, and galvanic skin response with the intention of promoting self-awareness and positive behavioural changes [1]. Consumer self-tracking devices are regulated as "low risk" and are intended for general wellness and disease prevention (1), increasing their use in chronic care settings. This review article examines the literature on self-tracking and chronic conditions in order to better understand the risks and benefits to individuals with hypertension, and to identify further directions for research. Hypertension is a complex disorder that is often perceived as preventable and a result of individual inactivity, despite the host of psychosocial and genetic predictors that affect it [2]. Hypertension is often treated with a combination of medication, patient-targeted interventions and lifestyle changes, such as by increasing physical activity, managing stress, and reducing body weight [3]. Individuals with hypertension may turn to wearable STT to promote positive lifestyle changes, though little research has explored the benefits and risks of this practice.

The self-tracking literature thus far has been characterized as either techno-critical or techno-utopian, and the benefit and risks of self-tracking to individuals with hypertension will be reviewed. "Techno-critical" [4] research tends to view self-tracking technologies as surveillance devices that quantify complex bodily functions, while "techno-utopian" [5] perspectives tend to view self-tracking technologies as having the potential to support patients and health care professionals in disease management. This literature will be briefly reviewed in order to demonstrate the area where further understanding of the experiences of self-tracking in individuals with chronic conditions, such as hypertension, could be developed.

Wearable consumer self-tracking devices have been proposed to be tools that support those with chronic conditions such as hypertension, though little research has examined what that experience is like. Wang *et al.* [6] identified that users with FitBits increased their step count and total active minutes, which is a finding that could benefit those attempting to manage their hypertension or high blood pressure through lifestyle changes. Ayobi *et al.* [7] found that self-tracking physical activity supported patients with multiple sclerosis in maintaining or increasing their physical activity levels, and allowing them to feel more motivated and experience more hope in regard to their condition. STT provide longitudinal data for individuals with chronic illness, which can be beneficial to health care providers and in understanding their illness [8]. STT provide opportunities for patients with chronic conditions to objectively record their condition, and to relay that data to their health care professional.

While some evidence indicates that self-tracking can lead to positive outcomes for users, there is concern that the devices may have little benefit or even pose risks to users with hypertension or those who don't otherwise fit the definition of a "target user". Consumer devices have been criticized for lacking reliability [7], which may cause undue worry in users or a false senses of security [8] based on the data. Users with chronic conditions have expressed frustration that self-tracking devices aren't able to accurately capture their experience, and that the goals set by the devices may not be realistic for their differently abled bodies [7]. In Nunes *et al.*'s [9] critical review, it was found that in some conditions, such as hypertension, over-measuring of symptoms makes the condition worse or causes anxiety in patients. Interestingly, many users report simultaneous benefits and challenges of the devices, demonstrating that self-tracking is a complex practice that shouldn't be considered as inherently beneficial or problematic for a particular user. To conclude, further investigation into the experience of individuals with chronic conditions using STT is needed, particularly when considering the lack of research focusing on the experiences of users with hypertension. Currently there is little psychological understanding of STT impact on users with hypertension despite concerns about reliability and suitability. Additionally, while many researchers have criticized self-tracking for its lack of suitability for certain users or applauded its potential to increase efficiency in

the healthcare system, further nuanced and exploratory work that showcases the experiences of users with complex and chronic conditions is needed. In particular, future research would benefit from a more in-depth exploration of the benefits and risks of self-tracking for users with hypertension.

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Exploring immersive technologies: the potential for innovation in whiplash research

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Whiplash-acquired disorders (WAD) are some of the most common injuries acquired as a result of a motor vehicle collision (MVC) [1]. WAD and its associated sequelae often present as neck pain, musculoskeletal deficits or neurological signs [2]. It has been estimated that of the individuals who sustain such an injury, 20 to 50 percent will experience chronic alterations of their activities of daily living as much as 1 year later [1,3]. WAD also imposes a large economic burden on the healthcare system, which leads to billions of dollars spent every year for rehabilitation of these injuries, not including the time spent away from work [4]. WAD represents a huge hardship for sufferers, their caregivers as well as their employers. Given these burdens, whiplash research requires innovation which could be accomplished via virtual-reality (VR) and augmented reality (AR) in order to better understand it.

Despite the socioeconomic burden of WAD, it is unclear as to why some individuals are more predisposed to WAD, or how acute to chronic WAD occurs [3,4,5]. Many traditional models have looked at the biomechanical characteristics of a MVC (e.g., speed/direction of impact, awareness of impending collision) in order to explain the development of WAD [3,4]. The current consensus is that the associations between the biomechanical characteristics of traumatic events, such as a car crash, and clinical symptoms (headache, neck pain) are weak or poorly understood [3,4,5]. As a result, clinicians struggle to explain to patients how they developed their symptoms.

Consequently, new mechanistic models have been developed to explain the curiosity that is WAD. It is believed that the onset of many chronic health conditions, such as WAD or post-traumatic distress, can be linked back to a maladaptive stress reaction to trauma [6]. Other mechanistic models now include both the reaction to a traumatic event (i.e., MVC), as well as pre-existing traits of the individual, both organic (genetics) and non-organic (socioeconomic status, psychological factors) in nature [3,5]. It has also been proposed that approximately 20% of individuals subjected to a 'placebo' MVC will exhibit WAD-like symptoms, despite no physical car collision occurring [4]. This may be due to perceived psychological stress such as anxiety of a perceived impact, but at this point it remains unclear [4]. These models are difficult to empirically assess, as most are in the theoretical stage because it is not ethical to place individuals in real-world car crashes. Furthermore, it is difficult to experimentally manipulate the parameters of a traumatic event under natural circumstances, including capturing of the stress/startle reactions of normal humans in real-world car crashes.

Given the advent of immersive technologies such as VR and AR, the study of stress/startle responses in traumatic incidents could be possible. VR has been described as an interface where the user interacts with 3-D objects with real time feedback [7]. AR can be described as the digital overlap of real space which can be manipulated [7]. VR and AR technologies have had increasing use in the world of medicine, from revolutionizing the ways surgeries are performed to changing the education of anatomy [7]. In clinical applications, VR has been documented to be effective in both the assessment and intervention of range of motion for the cervical spine [8]. In these applications, VR has proven effective as it allows for capture of intended variables in a simulated environment, such that responses are more ecological in nature, as if they happened in the real world [8]. In the field of phobia research, VR has shown to be quite efficacious in producing simulated environments resembling real-world ones, with the goal of promoting behavioural change [9].

While VR has been used for pain assessments and kinematic measures of the neck, to date no investigations have used VR to study the psychosocial domains or possible mechanisms of WAD [8,10]. VR or AR technologies could be radical in their ability to give subjects the perception of driving or being a passenger in a MVC, despite not experiencing an actual car crash. A VR road collision simulator could help develop inroads to why whiplash injuries occur through exploration of the psychosocial domains of WAD without any biomechanical input. In this manner, many of the mechanisms described above to explain WAD can be investigated in a robust fashion. The results of these studies could provide potential new explanations for WAD as well as inform future interventions.

Applications of immersive technologies such as VR and AR are well documented and appear poised to continue progressing [7,8,9,10]. The use of these technologies allows for the types of research that have not been possible to conduct previously and exploration of purely theoretical mechanistic models in WAD research [3,4,5,6]. Truly, the pieces are present for dedicated researchers to help understand the problem that is WAD, and aid in decreasing the burden of this common condition.

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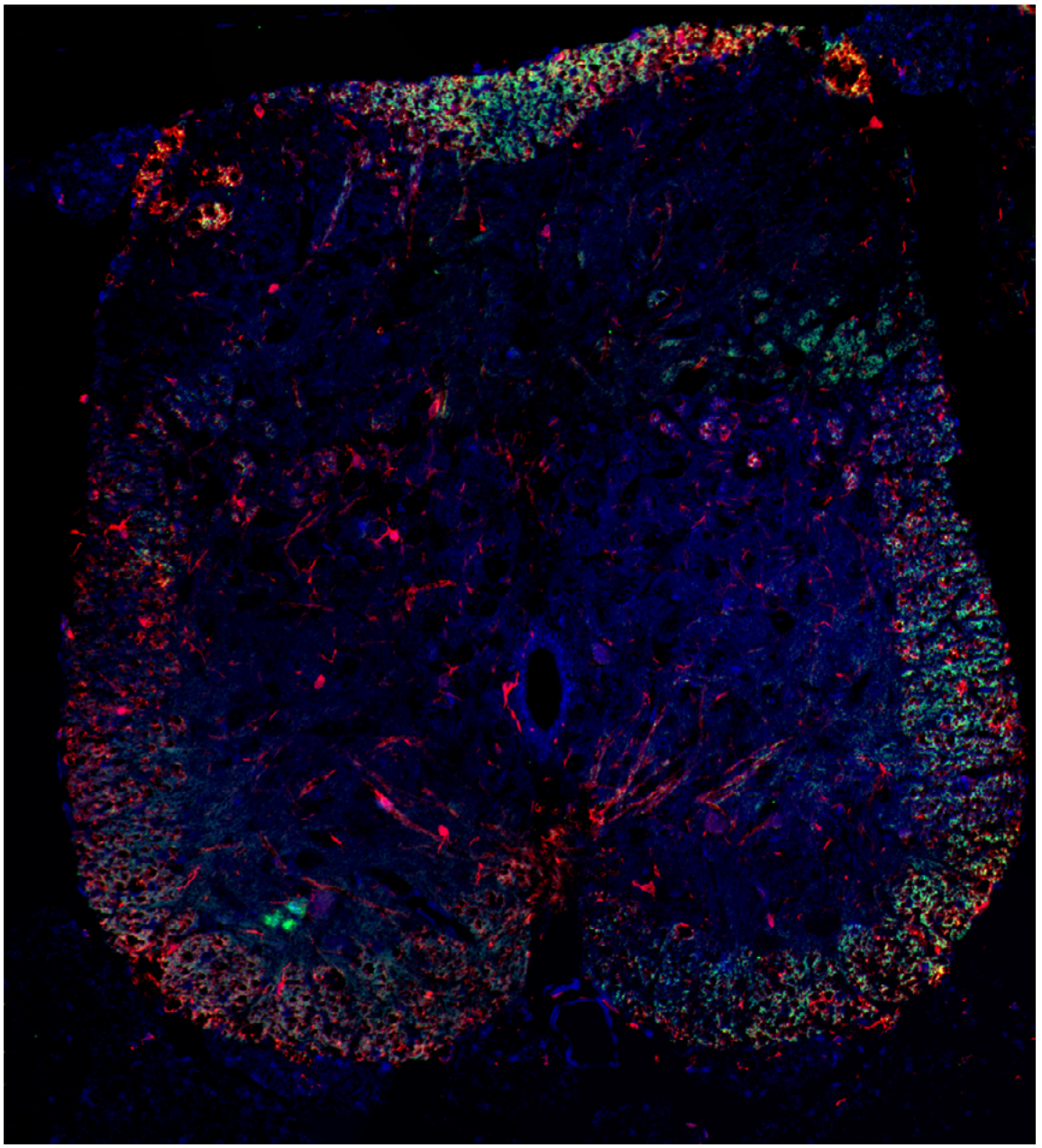
Michael is a first year PhD student in the Health and Rehabilitation Sciences program at Western University, in the Physical Therapy field. He is also a working Physiotherapist, graduating from Western's MPT program in 2017. His PhD research relates to the development of a biopsychosocial framework through which to understand whiplash injuries. Specifically, he is interested in how the human stress response can contribute to the development of whiplash associated disorders.

Shahan is a graduate student in the Pain and Quality of Life Integrative Research Lab (PIRL) at Western University. His research interest are focused on developing Virtual and Augmented Reality (VR/AR) applications for the measurement and management of chronic pain.

Farigol received her Honours BSc (Physiology) with High Distinction from the University of Toronto. With an extensive family history of cardiovascular diseases and diabetes, she was inspired to contribute to these areas of research. Her MSc at the University of Toronto research focused on the regulation of Ca^{2+}-cycling proteins in the heart to target their pathophysiology during cardiomyopathy. Painting is Farigol's lifetime hobby in which she finds peace and freedom of expression. She likes to explore and integrate traditional and modern artistic themes and techniques to create her pieces. "Harmony" is the name of her new work which was inspired by the contemporary Persian carpet patterns and coloration, and was combined with drawings of essential organs within our body.



Tanya Miladinovic is a senior PhD candidate in the Medical Sciences Program at McMaster University. She is investigating pathways that may contribute to breast cancer-induced bone pain. In an effort to characterize novel mechanism-based therapeutics, she is pharmacologically modulating potential underlying signalling pathways and quantifying nociceptive responses and associated patterns of functional neuronal signalling within the spinal cord and brain regions implicated in the pain response. Tanya believes there can be art in unexpected places and makes effort to exercise creativity in the lab and in her life.

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Health Science Inquiry

ASK AN

EXPERT

Dr. Arif Jetha is an associate scientist at the Institute for Work & Health. He is also an assistant professor (status) at the University of Toronto's Dalla Lana School of Public Health. Dr. Jetha's program of research aims at understanding life course differences in the employment participation of people living with chronic disabling conditions. He is specifically interested in understanding early labour market experiences and their impact on key transitions across life. His research takes a systems perspective to understand the role of policy-level factors and organizational conditions in the prevention and management of work disability. Dr. Jetha earned his PhD in behavioural sciences and public health at the University of Toronto, and an MSc in health community and development from the London School of Economics and Politics. He also held post-doctoral fellowships at the Liberty Mutual Research Institute for Safety and the Institute for Work & Health.

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Are we overlooking a vulnerable generation of workers? How to Support Young Adults with Chronic Disease and Disability in the Labor Market

Disclosure: A version of this article was published in the Center for the Promotion of Health in the New England Workplace (CPH-NEW) News and Views

When we think about young adults, we tend to visualize people in good health with a vibrant, active lifestyle. We don't often think about the difficulties faced by young people who live with disabling chronic health conditions, and often lack the knowledge to support them as they enter the labor market. This lack of awareness may have a significant impact on those starting their career with a chronic disease or disability that has no visible signs or symptoms, or is characterized by symptoms that fluctuate in severity such as arthritis or depression.

Research conducted at the Institute for Work & Health in Toronto, Canada helps to illustrate the needs of young workers living with chronic disease and disability, and the challenges they face accessing support within their workplaces.

A survey of young adults living with psychological, learning and physical disabilities found that extended drug coverage, the opportunity to modify the way jobs are performed and flexible scheduling arrangements are most useful supports for finding and sustaining employment [1]. Many of these needs are also reported in studies of older workers with disabilities [2].

Notably many young people in this study indicated difficulties accessing the most needed workplace supports. Out of the more than 150 young adult participants surveyed, three in four touched upon the reluctance to talk about the details of their health condition at work and how this was a barrier to accessing job accommodation and health benefits. Close

to the same proportion of participants thought that their jobs, which were mostly in sales and service sectors, could not be accommodated. Two thirds also talked about negative attitudes towards people with disabilities in the workplace as a reason for not getting help.

Barriers to accessing workplace supports may be intensified for those living with a condition not visible to others or characterized by unpredictable flares of symptoms [3]. Interviews and focus groups conducted with people living with arthritis found that having a condition imperceivable to others enabled them to conceal their condition from others. Yet, many of the young adult participants in the study were worried that their disease would ultimately worsen as they progressed in their career, and acknowledged that they would ultimately have to request formal accommodations or modifications to sustain employment.

Being at an early career phase was also related to a reluctance in requesting assistance out of fear of losing their jobs, limiting opportunities for career advancement or having their colleagues minimize the impact of their health condition. As one young adult study participant described it: I think there's always the misconception that people don't get impairments until later in life and so that can always be something very difficult either to convey to your employer or to your colleagues [who think] maybe you're getting special treatment or you're just a big complainer.

Adding to the findings described in both studies is the changing nature of the labour market that young adults encounter as they start their career. Market pressures, cost cutting and changing social policies in industrialized countries has meant that full-time or permanent jobs are less available to the current generation of young people starting their careers [4]. As a result, young adults living with chronic disease and disability are faced with the challenge of managing their health in non-standard employment situations where formal job accommodations and benefits may not be readily available and job security is a constant concern.

There are several takeaways for employers and policymakers. Primarily, the current generation of young workers living with chronic disease and disability may require employment supports that can be tailored to their needs to encourage engagement in the labor market.

On a positive note, among the most needed workplace supports are those that are low cost, such as flexible scheduling arrangements. Being able to start late or leave early on some days, to work from home on occasion, or to take breaks can make a difference in enabling young people to attend medical appointments or self-manage their health conditions. Offering a work environment where young people have the latitude to modify the way they perform tasks is another low-cost strategy. We suggest that employers provide opportunities for workers to figure out their own ways to complete tasks, identify work-arounds for limitations, or ask for help without repercussions. These are also examples of arrangements that older workers with more job tenure often report feeling more comfortable in accessing [2, 3].

In certain sectors in which young people often work, such as sales and services, it can be difficult for an employer to offer scheduling flexibility or enable an employee to choose the way in which they perform their job tasks. As an important first step, we recommend that communication practices between supervisors and young workers be strengthened as a way to start a dialogue on employment needs and the identification of relevant support strategies. Strengthening communication may be especially important for those living with invisible episodic conditions who may struggle with the decision to talk about their limitations or request formal accommodation [5].

A supportive workplace brings out the best in its employees – not only young adults living with chronic disease and disability, but also in a broader range of workers facing different life circumstances. Therefore, responding to the needs of young workers will also enable organizations to better respond to a range of other issues, including productivity loss, staff retention, morale, and workplace hazards that can contribute to injury or illness [6].

Young adults with chronic disease and disability face a gap with regards to the workplace supports that they most need. This gap can be exacerbated when their conditions are episodic and invisible. By providing flexible strategies and solutions, employers and policymakers can play a critical role in helping young adults living with health conditions find employment and thrive in their working lives. The impact can be important not only for labor market activity, but for quality of life.

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ASK AN

EXPERT

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Getting ready for the future: modifying our epigenome to prevent the effects of developing in an adverse environment.

Our environment is rapidly changing. Since the industrial revolution, life forms have been exposed to increasing amounts and variety of products of human activity. Fortunately, life forms have evolved adaptive mechanisms that have allowed us to cope with different stimuli in our fast-changing world. However, such adaptive mechanisms operate only within limits. Figuring out those limits, and the effects of an adverse environment, is gaining relevance in present days as we are becoming aware of complex gene-environment interactions and that environmental stimuli can significantly impact on human health [1]. It is not uncommon now to read or hear that pollutants, certain kinds of food, etc., can negatively affect our health, which suggests that the thresholds for proper function of our adaptive mechanisms are being surpassed [1]. Emerging genomic editing technologies hold promise to help us in preventing the long-term effects of exposure to an adverse environment.

Adaptation to an adverse environment depends on the capacity of the cell to activate or repress specific genes that function to alleviate stress in specific organs. For example, continued consumption of a high fat diet can cause chronic inflammation, which stresses the heart and reduces its capacity to pump blood [2]. The heart then activates genes promoting enlargement of heart muscle cells, or cardiomyocytes, to preserve contractile function at least temporarily [3]. However, if the stimuli persist, the heart could decompensate and fail. In this example, activation and maintenance of the proper expression of genes promoting cardiomyocyte hypertrophy could be considered key for adaptation of the heart to environmental stimuli. Following the example, if the stimuli were no longer present, mechanisms repressing hypertrophy-promoting genes would be equally important for proper heart function [3]. Mechanisms activating, maintaining and silencing gene expression depend on the accessibility of DNA to regulatory proteins. How accessible a gene is to its regulators, and thus its activity, depends in large part on chemical modifications on DNA, and post-translational modifications on histones and other chromatin components that scaffold DNA inside the nucleus. For example, DNA methylation is associated generally with gene repression. Methylations on the lysine 4 and 36 of histone H3 are associated with relaxed and active chromatin, whereas methylations on lysine 9 and/or 27 favor chromatin compaction and gene repression. Distribution of the broad variety of DNA and histone marks in different combinations at specific loci, and across the genome, is known as the epigenome. The activity of DNA and histone methyltransferases and demethylases is altered by environmental stimuli, resulting in changes in the epigenome translating into global changes in gene expression.

Thus, DNA and chromatin modifiers regulate the epigenome and are key for coordinating the adaptive response of cells and organisms to environmental change.

Epigenetic features composed of multiple chromatin marks can be maintained through multiple cell divisions. Chromatin marks have an important function in stabilizing gene expression patterns in the long-term so that cells and tissues can keep performing tissue-specific functions throughout the life of the organism. Thus, altering the epigenome can cause long-term alterations in gene expression. This has important implications in health. Our own research indicates that altering the epigenome during early embryonic development causes abnormal long-term activation of specific genes that promote heart disease in the adult life [4]. In line with this evidence, numerous studies have demonstrated that exposure to environmental factors that alter the epigenome during fetal development, for example obesity during pregnancy, can program adult disease. This overwhelming evidence is making us realize that complex environment - gene interactions are shaping the future of our health. We are only starting to understand how different environmental factors alter the epigenome, and large efforts are underway to uncover the modifications altered on the specific genes mediating disease development [1]. This knowledge could then be leveraged towards the direction of epigenetic marks to such genes to restore their normal activity using genome-editing tools.

The CRISPR/Cas9 system has recently emerged as a versatile and effective tool for genome editing. The CRISPR (clustered regularly interspaced short palindromic repeats) /Cas9 (CRISPR-associated protein 9) system can be used in genome editing in several ways. It is used for gene inactivation by inducing mutations in unique loci. In this application Cas9 is guided by an RNA fragment containing a short sequence complementary to the target site to induce a cleavage on double stranded DNA. The cells DNA repair system, which is prone to errors, repairs the DNA often introducing insertions or deletions, which then disrupt the target locus [5]. In a second application, an additionally provided DNA template homologous to the target site donates a designed nucleotide combination to induce specific DNA modifications. This application of the CRISPR/Cas9 system has been useful in generating mutant models to investigate the function of genes and intergenic regulatory elements. This application has also allowed for repair of disease-inducing mutations in cellular and animal models, and even in human embryos [6]. In a third application, CRISPR/Cas9 can also be used to recruit epigenetic modifiers. In this application, the endonuclease of Cas9 is inactivated to generate what is known as a dead Cas9, or dCas9. dCas9 is then fused to, for example, histone, or DNA de-methylases, so that instead of inducing a DNA double strand cut, dCas9 recruits epigenetic regulators, which facilitate control of the transcriptional state of the target gene [5] (**Figure 1**). Following the example discussed before, it is exciting to speculate that targeting epigenetic regulators to genes involved in programming disease, for example, those controlling inflammation and cardiac hypertrophy, could be useful for long-term gene control. This approach could potentially translate into ways to prevent the negative effects of developing in an adverse environment, and improve health in future generations.

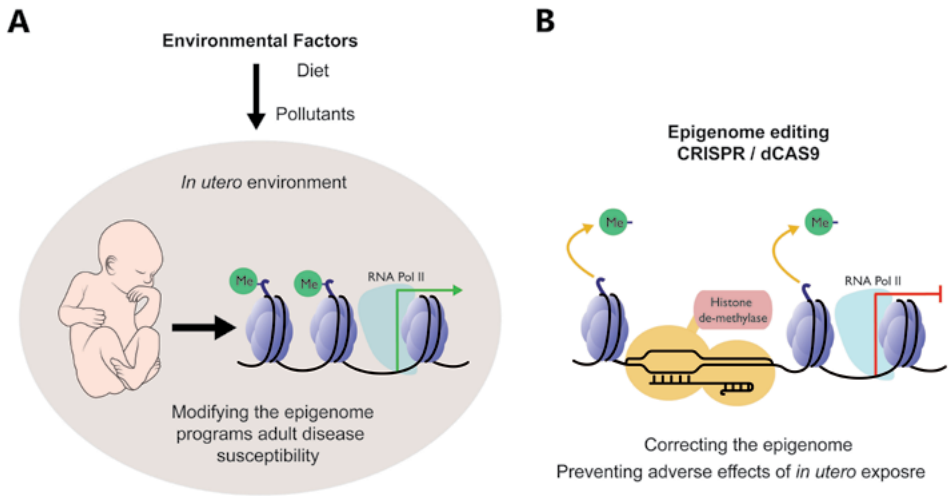

Figure 1: **Modifying our epigenome to prevent the negative effects of developing in an adverse environment.** A) Development in an adverse environment can alter the epigenome, for example by deposition of histone methyl marks (green circles) that promote abnormal activation (green arrow) of disease-promoting genes. B) CRISPR/dCas9 (orange) could be used to target histone de-methylases (pink) to remove (orange arrows) activating histone marks (green circles), correcting the epigenome to restore a normal inactive state on disease-promoting genes (red arrow). *Artwork by Melanie Delgado-Brand.*

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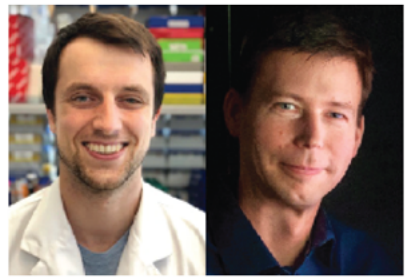
ASK AN



EXPERT

The Kieffer lab has the capacity to address questions from molecular to cellular to whole organism, using model cell lines, differentiated stem cells, zebrafish and genetically engineered rodents. We utilize tissue-specific knockdown or reintroduction of genes, cell transplant and surgical manipulations to address the role of hormone actions in a site-specific manner. We assess the effects of environment on metabolic function with dietary manipulations, from neonates to adults. We have advanced equipment for high-throughput analyses of cellular function and pathways, for whole animal imaging, and for metabolic phenotyping. Through strong networks of collaborators including basic scientists and clinicians, we have assembled and led multidisciplinary teams and effectively engaged researchers across Canada and around the world to support our research enterprise. We actively collaborate with industry, including large pharmaceutical companies, as we strive to translate our findings to the clinical setting.

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How do primary/patient-derived cell models compare to mouse models in the study of chronic disease? Do either of these models carry increased translational potential?

The study of chronic disease has long used animal models to elucidate mechanisms, investigate physiology, and test potential therapies. Among the various animal models, the mouse is one of the most widely used. Genetically, humans and mice share sizeable DNA sequence homology, with many of the disease-related genes being near-identical [1,2]. The ability to create transgenic, knockout, and knockin mice in whole-body or tissue specific manners allows for powerful in vivo studies and research on isolated tissues providing valuable insight into complex physiological and disease processes. However, experimental interventions developed using mouse models do not always translate well into humans. A well-known example of this trend is the TGN1412 anti-CD28 monoclonal antibody developed by TeGenero for the treatment of multiple sclerosis, rheumatoid arthritis, and certain cancers [3]. Toxicity studies performed on mice and non-human primates demonstrated safety at doses hundreds of times higher than what would be introduced into humans. However, the first human clinical trials of this drug at sub-clinical doses caused a cytokine storm and devastating organ failure in all the participating patients, all of whom were fortunately rescued with intervention [4]. Indeed, the majority of drugs that enter clinical trials never reach the marketplace and the limitations of animal models used in drug testing are an important contributing factor [5]. Moreover, mouse models that were created to recapitulate human genetic diseases have frequently had phenotypes that differ from their human counterparts [6] and models that do work use genetically identical or near-identical animals that lack the genomic diversity that is the reality of a human population.

Recent progress in the stem cell field has established a variety of techniques that can be utilized to generate cultures enriched for mature cell populations or tissue-specific organoids from human pluripotent stem cells (hPSCs) and adult

stem cells [7,8]. These unique *in vitro* cellular model systems offer several advantages. Because they have a human genome, they are the most appropriate model for studying human disease-relevant genetic variations. hPSCs can also be maintained in culture for many passages while retaining a healthy genome. This is beneficial for studies that require the generation of cellular materials at a large scale, such as those involving high-throughput drug screening. Under defined culture conditions, hPSCs can be directed to differentiate into a variety of mature cell types. These *in vitro* differentiation processes often align with normal developmental pathways, providing the opportunity to probe deeper into developmental and degenerative processes9.

Patient-derived induced pluripotent stem cells (iPSCs) provide the opportunity to model disease development, uncover unique mechanisms, and test potential therapeutics in a personalized approach. Successful modeling using this method incorporates personalized disease information and the recapitulation of disease development at the molecular, cellular and organ levels. Combined with new state-of-the-art genome editing tools, such as CRISPR/Cas9, hiPSCs can be specifically engineered to remove disease-relevant genetic mutations while retaining the global genomic status of the individual [10]. The inverse is also possible; engineering healthy hPSCs to express individual mutations. These new methods are enabling rapid expansion of sophisticated *in vitro* disease models, offering new platforms to perform biomedical research.

Overall disease modelling using mice or human derived cells each have their own benefits, however the translational value of experiments would be most enhanced by a combination of the two approaches. Studies in mice enable researchers to test hypotheses in a live animal, while the use of stem cells allows for more specific disease modelling and drug screening. Moving forward, researchers should design experiments and interpret results with appropriate consideration of the similarities and differences between these approaches in discovery research.

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Health Science Inquiry

ASK AN

EXPERT

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Patient-derived induced pluripotent stem cells — Bridging the gaps between preclinical and clinical effectiveness in brain illness?

At present, patient-derived central nervous system (CNS) tissue is often only available post-mortem. While these tissues can be helpful during autopsy and when confirming a clinical diagnosis, the obvious barriers in accessing primary human CNS tissue in live patients presents an impediment to developing patient-specific personalized approaches in clinical medicine. Furthermore, ideal access to post-mortem tissues is often limited for both clinicians and researchers, and a delayed post-mortem interval can significantly impact tissue and cellular integrity. As a result, animal models of CNS diseases are frequently used in research and are heavily relied upon when studying disease mechanisms and identifying possible treatment strategies. While certain imaging techniques (CT, MRI, PET, etc) can provide valuable clinical information in vivo, their lack of specificity and detailed resolution at the microscopic level is insufficient in providing detailed cellular mechanisms related to pathophysiological mechanisms of neurodegenerative diseases.

The majority of neurological illnesses rarely occur spontaneously in animals. Researchers have therefore developed animal models that function as extremely valuable tools when attempting to model specific pathophysiological mechanisms related to chronic neurological diseases. Unfortunately, most models do not recapitulate the full spectrum of the human condition and have limited translational potential [1]. For example, experimental autoimmune encephalomyelitis (EAE) is a widely used model and a valuable tool for studying multiple sclerosis (MS). EAE is most commonly induced in rodents and has made a significant impact on understanding how the immune system contributes to the neuropathology observed in MS. Furthermore, the majority of disease modifying therapies that are currently prescribed for MS patients were initially tested and validated in the EAE model [2]. Nevertheless, EAE does not model the entirety of the human condition and the majority of drugs that are successful in EAE often fail in human clinical

trials, thus limiting the applicability of the model. Non-human primate models of EAE can better recapitulate human disease and carry increased translational potential; however, these models are expensive and difficult to implement [3]. The limited translational potential of animal models of most neurodegenerative disorders has been widely documented [1, 4]. It is important to mention that similar disadvantages are observed in modeling other CNS diseases, including Parkinson's disease, Alzheimer's disease, stroke, and ALS. While evidence indicates that many of these failures arise from inadequate internal and external study validity [1], it underscores the unmet need for more optimal models that can help bridge the gap between successful preclinical animal studies and human clinical trials.

The relatively recent discovery that terminally differentiated cells can be reprogrammed to pluripotency, generating induced pluripotent stem cells (iPSCs) [5], provides a novel tool to study the etiology, development, and treatment of disease, including most neurological diseases. Patient-derived iPSCs can be reprogrammed from mature adult cells (often fibroblasts) and selectively differentiated into cells of interest. This not only permits the study of genetic associations with neurodegenerative diseases, but it also allows researchers to study the direct pathological and cellular mechanisms *in vitro* using patient-specific CNS cells. Importantly, using patient-derived iPSCs can circumvent ethical debates that have plagued allogeneic stem cell trials, eliminate concerns of immune rejection, and provide a format/model that may help to move novel therapies from preclinical animal studies to successful human clinical trials.

Certain challenges remain when studying diseases that arise from the dysregulation and/or mutation of multiple genes or those that are associated with strong gene-environment interactions. Using cells derived from MS patients, stable iPSC-derived lines have been successfully generated [6], and primary patient-derived iPSCs have been successfully differentiated into neurons and oligodendrocytes [7-9]. While no differences in the intrinsic properties of iPSC-derived neurons in patients with MS have been reported, recent evidence indicates that neural precursor cells (NPCs) derived from individuals with a progressive form of MS (primary progressive MS) have inherent defects in their ability to respond to myelin injury compared to cells derived from healthy controls [10]. A second critical finding of Nicaise and colleagues was that NPCs derived from iPSCs of patients with progressive MS exhibited marked individual differences [10]. This finding underscores the significant heterogeneity associated with this disease, which is most often reflected in patients' clinical trajectories, responsiveness to certain medications and immune cell profiles/activity.

While still in the early stages, the study of patient-derived cell populations has the potential to help us better understand critical pathophysiological mechanisms related to human CNS disorders. For complex and heterogeneous neurodegenerative conditions, like MS, the best hope for appropriate and successful treatment is a personalized approach, where treatment is tailored to the individual. iPSCs may indeed help determine this "best course" of treatment. For example, the genetic predisposition of certain patients might make them unresponsive to certain treatments or even perhaps predispose them to certain risks associated with a particular treatment. Prior screening of potential treatments *in vitro* using patient-derived iPSCs could reduce these risks and possibly guide optimal treatment strategies for individual patients.

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Spotlight On Careers

Dr. Thomas Durcan

Interview by Rhalena Thomas

Dr. Thomas Durcan is an assistant professor at McGill University and a group leader of the Montreal Neurological Institute (MNI)-induced pluripotent stem cell (IPSC)/CRISPR Platform in Quebec. The Platform was established in 2015 with funding from Brain Canada, the MNI, the Quebec Parkinson's Network and private sources. Having now expanded and grown into the MNI Open drug Discovery platform, the groups works with academic and industry partners to provide iPSC training and to work with these groups to develop iPSC-centric assays that can be adapted for drug discovery assays. All cell-lines, assays and findings with these open assays will be made available under the auspices of the MNI Open-Science initiative. Dr. Durcan received his PhD in cellular and molecular biology from the University of Notre Dame and completed his postdoctoral training with Dr. Edward Fon at McGill University, where his research focused on understanding the function of parkin, a Parkinson's disease-associated protein. In his own lab, Dr. Durcan's research is focused on the cell biology of Parkinson's disease and other neurodegenerative disorders. His group uses induced pluripotent stem cells to understand why these disorders develop.

1. Can you describe your position and typical work day or week?

I have a twofold position: the first is one that has an academic focus, as assistant professor, and the second is as group leader of the iPSC Discovery platform. In my academic capacity, I supervise students, overseeing their projects in the PhD program, I teach classes, and I sit on several committees, where I give my input and provide guidance to students. While doing this, I also work on getting papers published and applying for research grants. My other position is the translational part of the job. While Dr. Fon is the director of the platform and oversees activities, I manage the day-to-day aspects, and ensure that project milestones are met. We have a team of about 15 people working on different aspects of neurodegenerative and neurodevelopmental disorders. We work on developing new assays and stem cell lines, as well as making the assays more high-throughput. My initial engagement in the platform was to form partnerships with other companies. A key partnership was with the Center for Research and Development in Vancouver, who helped us introduce automation and high content screening, through a partnership termed NeuroCDRD. The other key partnership was with the Structural Genomics consortium (SGC), that brought expertise in assay development, leading to the formation of the NeuroSGC tissue platform group within the IPSC discovery platform

Now, more recently, I've been in discussions with Big Pharma. For example, in November, Takeda (the largest Pharmaceutical company in Japan) announced an Amyotrophic Lateral Sclerosis (ALS) partnership termed NeuroTakeda, and we were brought in at an early stage to be part of the meeting. The Japan team and I developed a project plan and budgets in order to initiate the project in December 2017. We now have funding for the next three years to develop new open (publically available) assays for ALS and look for new molecules as therapeutic targets. However, my day-to-day responsibilities are different. I have a lot of meetings, both with the (platform) team and elsewhere. I spend a lot of time answering emails related to projects in and out of the group, as well as other matters. Sometimes, there is trouble shooting that needs to be done. There is a lot of writing to do. I don't do any bench work anymore; it is something that has fallen by the wayside. Now, I'm part of a bigger picture. It's nice being at the bench, but you sometimes get too ultra-focused to the effect that you don't see the whole picture. Most of my planning of the projects involves figuring out how to get the right people (for each position); and making sure that everything gets done on a daily basis. I work with many people within the MNI and other groups including the SGC, CDRD, Takeda and other partners. Together, we take those concepts and put the nuts and bolts in them to make sure that all of the steps get completed.

2. What is the pathway you took from graduate school to your position?

When I finished my postdoctoral fellowship, I was thinking about leaving science, or at least, leaving research and going into publishing. I interviewed with Neuron and Nature Cell biology, but for different reasons it didn't work. When one door closes, another one opens; and it just so happened that at that same time, the lab manager position opened up in Dr. Fon's lab. I was responsible for managing the lab and placing orders for about a year, when the idea of developing a stem cell platform was brought to my attention. I approached Dr. Fon and asked to manage the platform, helping to

bring in Brain Canada funding and setting up the team, with the recruitment of a research assistant for the platform. We started off as a small group with just two or three of us doing everything to set up the platform. In 2015, I was offered the position of assistant professor. In a way, I came into the position by falling through the back door. Now that I have the position, I make sure to work hard each and every day to advance to the next level. I have received the Parkinson's Canada new investigator's award, Michael J. Fox Foundation funding, Kennedy's Disease Association funding, and we have several grant applications that are under review at FRSQ, NSERC and other places.

The position I have isn't a tenure track position, but I am still fortunate enough to have my current position, which lets me do everything an assistant professor on a tenure track would. I teach, write, supervise and do all the administrative work like any other assistant professor. An advantage of my current positions (as assistant professor and associate director of the iPSC Discovery platform) is that I see both the academic and the industry worlds and get to know and work with people in both. In a few years, I might be interested in doing something else and I might consider changing positions (if an opportunity came up in industry). However, right now, I really enjoy what I do here, and there are a lot of exciting things happening to keep me occupied at the MNI for the coming years.

3. Are there other platforms like the one you have here?

Yes, I think the world standards are probably the Harvard Stem Cell institute or the RucDR biologics, which are two large bio-depositories run in a business-like fashion. Our group in Quebec has started later than in many other places and we have been playing catch-up for a while. There are platforms of various sizes in ICM, France, at Oxford, and at Cambridge. I think that it's something that people are recognizing as a good thing to have available. Sometimes, individual labs will do stem cell work on their own. However, consolidating all of the stem cell work can be more valuable because it lets us get better pricing, and allows us to bring in expertise, companies and workshops to benefit surrounding labs. The goal for the first three years of our platform was to build and grow it; it's now there. The current work involves expanding and branding the platform, and in the next three years, we hope to move the platform onto the next level.

The stem cell platform is a hybrid business model. We work with outside users but we also have internal projects. I think it's most similar to the clinical research unit at the MNI, where they work with Pharma and bring in clinic trials. They have a very defined structure. In the first three years in the iPSC platform, we also needed to work on implementing a defined structure. How do you make a structure that is business-like in an academic setting (which is not easy by any means)? We needed to define group units, team leaders, and set specific goals. It could not be 'wishy-washy', we have group meetings and set specific agendas so that everyone knows what they were doing. We need to show concrete progress over the next three years and that we developed new molecules or tools that will push the field forward.

4. Is there a lot of demand in the iPSC platform for people with masters and doctoral degrees?

A problem in academia is that people do a MSc, followed by a PhD and a postdoc, but then what? If you don't want to follow the conventional route (of becoming a professor or working in industry), what do you do? Here, we are providing new opportunities and looking for very diverse staff. We have people from many different nationalities that have settled in Canada and who each bring a distinct mindset, skills and talents. We are always on the lookout for new people although at the moment we have almost reached capacity, but its good problem to have, as now we have to find new ways to grow and expand. We try to attract talent from people at McGill and the MNI who want to stay in Montreal. A lot of people go to a University and do a PhD, but then leave. I don't think that that is a good model. I think that if people work hard and do good work, you should try to keep them, which is the model that is used at Harvard. In doing so, you build a network of people familiar with the institute and who can drive the research forward.

5. How do you envision the future of healthcare research?

Big data and multi-omics will be the next stages of health research. Now, we have the technology and the capacity to do really exciting things. There will be three main groups: biology groups that can work with cells, engineering groups that can actually manipulate cells to grow in a distinct fashion, and computational groups that can test models and fit the data together. I think that when students are trained now, they will start on one aspect of a project and will gradually grow into a big team-based project. We will work the way that physics works, where papers have 20 or 30 authors because everyone is contributing distinct pieces of a puzzle that fits together.

I think that the key to making progress in health research is to open up the data, like we are doing at the MNI with the open science initiative. I think that scientists have been working in closed silos for too long, afraid to speak about their work or engage with patients. We need to get out more and figure out how to engage with patients. There is a disconnect between researchers and patients who go to the hospitals when they get sick. How do we show those patients

what it is that we do and highlight the benefits of their involvement in the research process through cells, DNA or even clinical information? Right now, everything (i.e. medical records) is paper-based and 20 years behind the available technologies. This should not be the case. Instead, there should be an electronic record that goes to a centralized database for each patient so that you can immediately start to put different pieces together. This is ongoing but should be further advanced. If we found something interesting from patient cells using our assays, we could incorporate our findings with the patient data, and we could eventually pinpoint patient stratification. Right now, it is seen as a failure if you test a molecule in 1000 Parkinson's patients and see a response in only 20. However, it is possible that there is a specific signature for those 20 patients that causes them to respond to treatment differently. I think that medicine will be turning towards a patient-centric focus. Using patient stem cells and high throughput screens is one way of getting better treatments.

6. Do you have any advice for grad students interested in pursuing a similar career path?

You have to love science and go into it with an open mind. There are days when this job will wear you down, but there are also days when you will love what you are doing. The truth is that you have to have a passion for it...whether you want to work in industry or academia, you need to have a question. I don't think it matters where you work or know what you want to study once you have that question that you feel will make a difference. Go in with open eyes, not with a defined plan. Science and life throw obstacles and challenges along the way, so it is important to be adaptable. On my first day of grad school, they said 'work hard, play hard' and I've always kept that as a motto. I try to work hard and enjoy life at the same time. I think it is also a good way for grad students to work: *be serious about your work, don't be serious about yourself.*

Spotlight On Careers

Dr. Marie Pierre Fauer

Interview by Rhalena Thomas

Dr. Marie Pierre Faure is the Deputy director of the InstituteTransMedTech (iTMT), Living Lab. The iTMT was created by five founding institutions (Polytechnique Montréal, Université de Montréal, CHU SainteJustine, CHUM and the Jewish General Hospital) with funding from a $35.6M grant awarded in 2016 by the Canada First Research Excellence Fund (CFREF) and $60M in contributions from industry key partners. The iTMT is housed in Polytechnique Montréal and works in a novel method termed "the living lab" to select, fund and carry out translational medical research. The living lab is the cornerstone of the iTMT Institute. Dr. Faure was recruited to build the team and manage the projects of the living lab. She describes a living lab as "a methodology where we put together all the experts around the table to answer questions or work together on projects for any innovation in the healthcare field." In this method of working a group consisting of patients, industry partners, clinicians and academic researchers are all brought together around the table to decide on what are the top priorities for health care. For each project a team with representatives from these categories are brought together and collaborations are formed and defined between industry partners, clinicians and basic researchers. The goal is to create diagnostic, treatment and healthcare solutions most important to the patients, that can move seamlessly from the research stage and be easily implemented into the clinic and continue to be improved by user feedback.

Dr. Faure obtained her PhD in neuroscience from McGill University. She has over 25 years of experience bridging the gap between knowledge and expertise, working toward the innovation of novel healthcare solutions. The living lab group works collectively with researchers, engineers, students, physicians, caregivers, industries, policy-makers, governments and patients, with the goal of designing, developing and implementing innovative technological solutions into the healthcare system, improved disease diagnosis, treatments and healthcare delivery. The iTMT is focused on three main priority groups, which were determined to pose the greatest health risks to Canadians: cancer, cardiovascular illnesses and musculoskeletal disorders.

1. Can you outline the path you took to become the manager of the iTMT Living Lab?

I started my studies in France, where I completed a Medical engineering degree, focusing on imaging in biology. I crossed the ocean and came to Quebec to work at the Jewish General Hospital (Lady Davis Institute) and finish my PhD thesis at McGill University under the supervision of Dr. Alain Beaudet. After completing my graduate studies, I started a biotech company. From there, I worked at three different biotech companies over 20 years. I realized I wanted to work using the Living Lab method (popular in France) and decided to start another company, called C4Care Living Lab. My company became the first Living lab in Montréal, Canada. In 2014, C4Care Living Lab was certified by [the official regulatory group that recognizes and gives accreditation to Living labs], the European organization of Living Lab (ENoLL). As the founder and president of C4Care, my objectives were to find a method for early detection of skin cancer and to follow the patient care journey from the pharmacy to the first line at the medical clinic and through treatments and cancer care. To meet these objectives, we combined convergent technologies to create SkinCheck4LIFE ecosystem; this work was recently published. When Polytechnique received the grant from the Canada First Research Excellence Fund to create the Institute TransMedTech (iTMT), they made me an offer I couldn't refuse: to establish the Living lab approach as part of the iTMT.

2. Can you describe your position at the TransMedTech Institute and one of your current projects?

I only started at Polytechnique seven months ago. My first task was to set up the team for the Living Lab. So far, I have recruited about 10 people that create a guiding council. We put out a call for medical technology projects as well as excellence awards for graduate students, postdoctoral fellows and professionals. I organize and manage the group that determines which projects are selected for support by iTMT. The group consists of researchers, patients, clinicians, industry representatives from a consortium including Polytechnique, Montréal University, CHUM and Jewish General Hospital. The funding all comes from the government rather than industry. The current projects and excellence award winners can all be found on our website. (http://www.polymtl.ca/transmedtech/en/competition-results). We select the initiatives that our group determines have the highest needs to achieve innovations corresponding to iTMT

mission, like the ones that serve the patients that really need help. A current project we are really excited about is working on a way to detect brain tumors early on and to distinguish the difference between a tumor and normal tissue in order to identify the boundary of the tumor within the brain tissue. This project is in collaboration with the Montreal Neurological Institute and we are already making a lot of progress. We have over 30 ongoing research projects. My role is to put together the teams working on each project, get the right experts all together in one room, with the patients and industry partners so that all aspects of the problems are considered. In this way, real solutions can be found and developed. For our industry partners, we try to bring them early in the process and they get to establish intellectual property early to ensure our technologies can be implemented immediately for patients.

3. Do you find any friction between people from different experiences and backgrounds trying to work together

If you are a nice person, you like to put people together and you have a sense of humor, you will find working with a varied group of people very stimulating. In the varied group, you get many new ideas and many ways of working, at the end you will come to a consensus of what would be best for the patients. This is what everyone is working towards. All the people in the team are experts in their fields, the expertise is selected around the medical needs. In the first group meeting, people are a little bit shy. After the second meeting, everyone knows each other and sees the advantages of working in this method. Everyone learns surprising things about the way the others work: perhaps a basic researcher learns something about how a surgery is being done and the surgeon has an idea about something that could be tested in the research lab. Everyone stays in their field of expertise, but collaborate together and a synergy is formed. This collaboration forms quickly and this is what is so stimulating about this way of working.

4. What are your favourite and least favourite parts of your position?

I am person who likes to have every day different from the last. In this position every day is different, I am moving all the time. Each day there are more projects, more researchers, more collaborations. I really enjoy it, when I'm asked how do I see my job, I say "it's not a job, it's a gift". When building your own team, you end up working with people you have a good fit with, even the human resources management are not difficult. It's different from team where you come into a group that already has a way of working. I was able to select my team and I love the people I work with. Each person in the team depends on each other and is made better by the team. At the same time, each person can also work on their own as expert in their field.

5 . Do you have any advice for current masters and doctoral students?

Think what your field will be like in 3-5 years from now. It's not the same as 20 years ago, where you choose a field and you will be there for life. You will no longer spend your whole career in one field. Now you need to be more flexible and open minded. Technology is evolving every day, students need to open their eyes and ears. Realize that if you have a Master's degree today, it is not an end point it's just the beginning of your career. Keep learning new skills in what you enjoy. You want to choose the field and skills that you are passionate about to have a job that you will like. Many students don't know what they want to do next, it's important to expose yourself to different areas. At Polytechnique we expose students to academics, to industry researchers and entrepreneurs to open their mind to different pathways. You may start in academia, switch to industry and then realize you want to be an entrepreneur: life is not a straight line. You need to keep your mind open to opportunities and to what will make you happy and motivated to go to work and study every day in a constantly changing world.

6. What do you see coming up in the next 5 years for health research.

Integration, integration, integration of new healthcare approaches taking into account the patient as part of his own healthcare system. Currently, excellent centers give you the leading experts in the field. Top scientists are already working in the way of a living lab, collaborating and working with many partners. Living labs are now starting to put a label on these collaborations and making them more effective. The projects are becoming more efficient and taking into account everyone's perspective to move quickly from the lab to the bedside. Translating innovation from different disciplines and sectors will give us a better chance to answer user needs. I think in five years the medical field will be more personalized and integrate many more technologies. Hopefully, we keep patients alive with a good quality of life for longer. Using the aggregation and integration of knowledge, we will not be working in isolation anymore, working as a community will become the norm moving forward. I have been on many committees in Montréal, this is the first time I have seen so much energy and desire to work together. The quality of companies and research have never been better. People are ready to work together, we are really in a movement. To survive as a key university and excellency center, you have to open the walls and incorporate the way the world is going right now. Everything is going faster than ever before and students need to be exposed to this world.

Spotlight On Careers

Dr. Stephanie Ross

Interview by Pedrum Mohammadi-Shemirani

Dr. Stephanie Ross is a Scientific Advisor at the Canadian Agency for Drugs and Technologies in Health (CADTH). She completed a BSc in Biology at the University of Toronto, and a MSc in Epidemiology at Cambridge University. She earned her PhD in Health Research Methodology at McMaster University under the supervision of Dr. Guillaume Paré. Her doctoral thesis focused on advancements in the field of cardiovascular disease pharmacogenetics. After graduation, she went on to complete a post-doctoral fellowship in genetic epidemiology at McGill University. From there, she transitioned into industry, starting as a clinical research officer (CRO) before advancing to her current role as Scientific Advisor at CADTH.

CADTH is a non-profit organization that is responsible for providing healthcare decision makers with objective evidence to help make informed decisions on drugs, diagnostic tests and medical devices. CADTH provides recommendations on a healthcare product by assessing the evidence supporting its cost, effectiveness, safety, feasibility and input from patients. As a Scientific Advisor, Dr. Ross is responsible for ensuring all reports produced by CADTH exhibit scientific rigor and consistency. She is also responsible for educating staff and other members, and keeping CADTH up-to-date with the most cutting-edge practices in the field.

1. How did your graduate education prepare you for your career?

First, it provided me with a strong background in biostatistics and epidemiology, which formed the basis for much of my work in health research methodology. I also cultivated strong writing skills by drafting scientific papers about my research and gained the ability to critically appraise epidemiological studies, which is a big part of the job here at CADTH. On a related note, I learned how to effectively communicate scientific research; or more broadly, how to take a complex idea and distill it down so different groups of people can understand the core message. Lastly, I gained experience in project management. It's important to be able to keep track of a project and be able to work with different types of people on a team in order to reach the primary goal.

2. What is your average day/week like?

At CADTH, I'm a part of a broader team which includes managers, CROs, external experts and other Scientific Advisors. These teams will be assigned to a common drug review (CDR). This means that we receive a drug submission from a pharmaceutical company who wants to have a drug funded by the different provinces in Canada for a particular group of people. Our primary goal is to assess the drug safety, effectiveness, cost and feasibility. Thus, it's our responsibility to critically evaluate all of the clinical trials, costs and unmet needs related to the drug. Our findings are then sent to a large committee composed of patient group representatives, policy makers, clinicians and health economists. This committee reviews our report alongside patient group input and their own conclusions to arrive at a final recommendation. Their recommendation is sent to all the provinces, which use this information to decide how to implement the drug in their healthcare systems.

I'm usually working on multiple CDRs simultaneously. As a result, my day consists of multiple meetings with different teams, which consist of clinicians, economists and CROs. My role in these meetings is to ensure that all the members properly understand the scientific studies under review. There is a lot of reading and editing involved. I need to review the studies in the CDR and check the reports that we produce. In addition, I spend time on various committees, such as the Mental Health Working Group, where we promote CADTH research to patients and policy makers in the mental health community.

3. What is your favourite and least favourite part about the job?

My favourite part of the job is the variety. We are always learning about different diseases and evaluating different trials. Every study is unique, so there are always new challenges with minimal repetition. I also love working with different groups of people and sharing ideas in meetings, teaching others about epidemiology and learning about the clinical and

economic perspectives of drug reimbursement.

My least favourite part of the job is that it can get busy and hectic. Our projects tend to come in waves and it can take a bit of time to get used to the workflow, but that's part of what makes it exciting too. Also, I work at our satellite office in Toronto, so it can be challenging having to communicate remotely with team members at the main office in Ottawa or in other locations throughout Canada.

4. What is the current demand for MSc or PhD students in your field?

CADTH is growing and recruiting, so there is a demand for recent graduates. In my specific role as Scientific Advisor, it is very common to hold a PhD degree. However, CROs are a diverse group with a mixture of both MSc and PhD graduates across a variety of fields. We are mostly looking for candidates that demonstrate an ability to critically appraise scientific literature and who love to learn.

5. Do you have any advice for current graduate students who would like to envisage a similar career path?

For general career advice, I cannot stress enough the importance of networking. If you can attend scientific conferences or similar events, talk to different company representatives and learn about their jobs. It can also be helpful to talk to friends that have graduated to learn about what they do, and expand your horizons outside of academia. Also, talk to your supervisor about your career aspirations. They may be able to work with you to achieve your goals, or at least connect you with someone who can help you. If someone was specifically interested in Health Technology Assessment, I would recommend taking a course in Health Economics. There are lots of different positions in this field, which range from Health Canada to CADTH to consulting firms to pharmaceutical companies. However, a solid writing foundation, ability to take feedback, and familiarity with the industry will always be helpful.

Spotlight On Careers

Dr. Elizabeth McCready

Interview by Pedrum Mohammadi-Shemirani

Dr. Elizabeth McCready is both an Associate Professor in the Department of Pathology and Molecular Medicine at McMaster University, and the Head of the Molecular Cytogenetics laboratory in Hamilton. She is also the Program Director for the Canadian College of Medical Geneticists (CCMG) training program at McMaster University. Prior to graduate school, she spent several years working in industry, developing DNA sequence-based tests for clinical laboratories, before settling into her current career path. She earned her PhD in Human Genetics at the University of Ottawa, where her doctoral thesis focused on identifying the genes causing short finger brachydactyly. After graduating from her PhD, she went on to complete two fellowships with the Canadian College of Medical Geneticists (CCMG) in Molecular Genetics and in Cytogenetics.

The CCMG is a national organization that is responsible for educating, certifying, and representing medical geneticists in Canada. They offer a post-doctoral fellowship program for laboratory training in three specialties: biochemical genetics, molecular genetics, or cytogenetics.

What are the requirements?
As a post-doctoral fellowship, all trainees must be MD or PhD holders. Although a background in human genetics is not a requirement, it is highly recommended due to the competitive nature of the program. There are currently only 2 funded fellowships that are available yearly in Ontario. Each training site receives many applications (e.g. McMaster University received approximately 30 last year), from which one is selected to move forward in competition against other sites across the province for the 2 spots.

How long is the program?
The fellowship lasts 2 years on average. Some trainees, particularly in the molecular genetics or cytogenetic specialties, choose to dual specialize by completing a second fellowship. These secondary specialties take an additional year on average.

What do you learn?
The CCMG has mandatory general genetic concepts and specialty-specific concepts that need to be understood from a theoretical standpoint. There is also a lot of importance placed on understanding the quality management systems of a clinical laboratory, and the requirements needed for different levels of accreditation. However, the fellowship is primarily a full-time, hands-on program in a hospital laboratory setting. You will gain experience interpreting laboratory tests and writing reports under the supervision of a certified laboratory geneticist. Depending on the specialty, you will need to complete a number of cases of different types. For instance, you may need 100 cases at the bench performing different lab techniques, and at least 200 consultative cases that include test result interpretation and reporting. Once you have completed all of the required cases by the CCMG, you will submit your logbooks and training documentation to the college and be credentialed. You are then able to sit and write the certifying exams to become a fellow.

What types of jobs are available?
The program certifies you to direct a clinical laboratory in your specialty and prepares you to consult with clinicians on referred cases. Such jobs may be of particular interest for graduate students who are interested in healthcare, working in a hospital setting, and having a more direct impact on patient lives. That being said, unlike MD holders, a PhD fellow is not certified to directly interact with patients and offer clinical management decisions. PhD fellows focus on the laboratory sciences aspects, and consult with or provide results to the requesting physician rather than to the patient directly.

What about other countries?
The equivalent to the CCMG in the United States is the American College of Medical Genetics and Genomics (ACMG), which certifies medical geneticists to work in the USA. There is a reciprocity agreement between these two countries, such that individuals that have completed the CCMG training may sit the ACMG certifying exams without repetition of their training program, and vice-versa.

If you are interested in learning more about the CCMG fellowship program or have any additional questions, please visit their website: https://www.ccmg-ccgm.org/training/frequently-asked-questions.html

1. How did your graduate education prepare you for your career?

My graduate education was tremendously important for my career. It provided me with a solid framework for understanding human genetics, which was essential for my success in both the CCMG training program and my current role, in which I lead a cytogenetics laboratory.

In combination with my experience in industry, it provided me with a better understanding of the differences between research and clinical environments. The latter has stricter requirements, regulatory hurdles and accreditations. For instance, you may spend 2 years validating a product for FDA approval, but if you have insufficient or improper documentation, you may be required to repeat the whole process. These accreditations and quality management systems are necessary in clinical settings because you are dealing with patients' lives.

2. What is your average day/week like?

My laboratory is located in an academic health centre, so I have both clinical service duties for the hospital and academic duties for the university. I am expected to divide my time roughly as follows: 60% on services, 20% on teaching, and 20% shared between administration and research. However, other lab scientists may divide their time differently among these activities depending on their contracts and interests. Furthermore, the role of a laboratory director will be dependent on the hospital. There are community-based hospitals that do not have academic affiliations, and as a result, their lab scientists may not be required to perform academic duties.

The majority of my service work involves triaging requisition forms, reviewing requests for completion, and, if needed, requesting additional information for the samples we receive. Part of the job also involves interpreting results of the test, preparing reports for physicians, and reviewing them for accuracy. In atypical cases, we spend a lot of time preparing the reports and talking to clinicians about the findings.

The academic work primarily involves directing the CCMG training program at McMaster University. We have teaching sessions, supervise the fellows, review their reports, and continually assess their learning progress. I also teach large group and problem-based learning sessions in the medical school, and I supervise some undergraduate thesis projects. My administrative work involves ensuring that we are meeting all our requirements for accreditation of the lab. I also spend time on several different committees, from the local to national level, with the Ministry of Health, Cancer Care Ontario, and the CCMG. With my remaining time, I try to squeeze in some research, which often involves case reports or research that is translational in nature rather than basic science.

3. What is your favourite and least favourite part about the job?

I don't like being stagnant and I always like to learn, so my favourite part is the opportunity to solve a challenging case. We sometimes receive challenging cases that can take several hours to investigate the clinical significance of the observed test result. These are frustrating in the moment, but always educational, and the feeling of satisfaction afterwards is truly rewarding.

My least favourite part is management of deviation from clinical protocols. As a clinical laboratory, quality is imperative since we are dealing with the lives of patients. Treatments might be given based on the results of our tests, so we need to ensure that we are always accurate. The lab and myself understand that we can affect medical decision making. Therefore, we have systems in place to minimize errors as much as possible and take that responsibility very seriously.

4. Do you have any advice for current graduate students who would like to envisage a similar career path?

If someone wants to do the CCMG fellowship, I highly recommend getting involved in human genetics work at a graduate or post-graduate level. It's not a requirement for the training program, but the program is fairly competitive. Even if you are a phenomenal researcher, a lack of exposure to human genetics will put you at a disadvantage relative to other applicants.

For all graduate students, I would stress the importance of perseverance. You need to have goals and strive to achieve them. There will be days when you might question yourself, but if you continue to work hard you will get to where you need to be.