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(Fund)amental Changes to Sex Differences in Research: Women's Health From Cells to Clinic

Educating Medical Students to Deliver Transformative Health Care in a Changing Society

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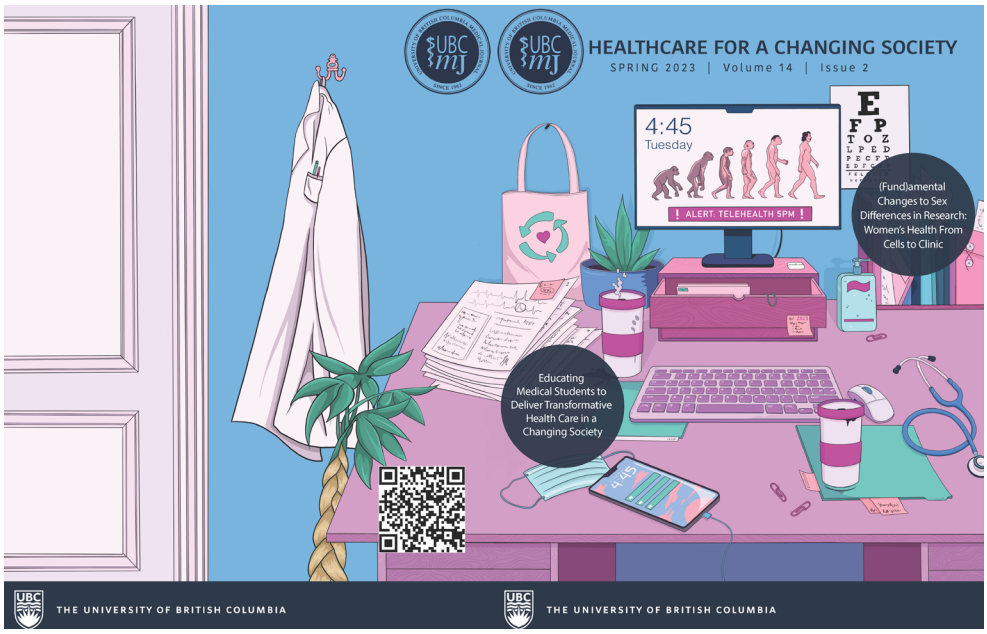

In this issue, we explore the evolution of healthcare in a changing society. Entries in this issue investigate the ageing population, novel therapies and innovations, and emerging themes in healthcare. The cover art for this issue reflects how healthcare has changed with a progressing society through a representation of human evolution surrounded by new technological advances. As society evolves, this issue serves to remind that healthcare must adapt to address arising challenges and meet the needs of the population.

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Healthcare for a changing society

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As society evolves, the field of healthcare must adapt to address challenges and meet the changing needs of the population. With the emergence of new technological advancements, novel infectious diseases and treatments, an ageing population, and initiatives to improve the healthcare system, healthcare is rapidly evolving. In particular, the COVID-19 pandemic has demonstrated the importance of an amenable and responsive healthcare system and that our approach to healthcare must evolve alongside changing societal needs. In this editorial, we explore noteworthy trends in healthcare, discuss the challenges and opportunities that arise from a changing society, and potential implications for patients, providers, and the society. While change may be unpredictable, it is imperative for healthcare providers and policymakers to be willing to adapt to meet population needs in this evolving landscape.

Notably, artificial intelligence (AI) is rapidly becoming a new trend in healthcare. With the ability to analyze large quantities of data and identify minute details, AI has the potential to revolutionize the healthcare system and how care is delivered. AI can be widely applied in healthcare, including in medical imaging analysis, pharmaceutical development, genomic data analysis, and personalized treatment plans. By automating routine tasks, AI has the potential to improve the efficiency of healthcare delivery, reduce costs, and aid healthcare providers in making more accurate predictions about patient outcomes. For instance, ChatGPT, a recently released large language model, was able to use the patient information provided to construct a correctly structured medical note and provide suggestions for future treatments.[1] Furthermore, ChatGPT demonstrated modest prediction accuracy in imaging protocols in breast cancer screening and breast pain assessment, suggesting its potential ability to serve as a tool to complement radiologic decision-making.[2] However, there are limitations in utilizing AI in healthcare. Recurring concerns in the majority of studies testing the use of ChatGPT in medicine were ethical, legal, and transparency issues, risk of bias, and limited medical knowledge.[3] Moreover, ChatGPT was found to be unable to sufficiently answer medical questions due to the lack of medical expertise and experience of healthcare providers.[1] Ultimately, human healthcare providers remain crucial in medical practice as they provide the personal perspective and expertise largely valued by patients.[3] However, AI may still serve as an important accompanying tool in the healthcare setting. While there will be challenges in implementing AI in healthcare, such as privacy and ethical considerations, AI is uniquely poised to transform the healthcare industry in the coming years.

Another such adaptation is the increased use of telemedicine, which has allowed for virtual consultations with healthcare providers. Although telemedicine had been available in the past, it was reintroduced during the COVID-19 pandemic to decrease disease transmission. In 2020, telehealth visits skyrocketed to 52.7 million, which was a 51.9 million increase from 2019.[4] As well, Medicare healthcare costs decreased to 289 million in 2020 from 1.1 billion in 2019.[4] Overall, telemedicine has increased access to care, reduced patient travel burden, decreased healthcare system spending, and improved efficiency for healthcare providers. Virtual care is particularly important for the ageing population, who may face mobility or transportation challenges, by providing them the opportunity to receive necessary medical care from their homes.[5] However, telemedicine poses disadvantages such as confidentiality and privacy breaches and difficulty in rapport-building due to lack of in-person patient-physician interactions. Further investigations are needed to address these challenges. In addition to telemedicine, remote patient monitoring (RPM) devices are a novel innovation in healthcare. RPM systems, such as digital heart rate and rhythm monitors, allow patient physiologic data to be forwarded to their physicians in real-time.[6] RPMs thus allow patients to track their own health and improve efficiency of clinical monitoring. However, it is important to consider potential barriers to virtual care and RPMs, such as access to technology, internet connectivity, and technological literacy, to ensure equitable access for all. Nonetheless, telemedicine will remain essential in healthcare delivery.

Furthermore, the COVID-19 pandemic has instigated a monumental shift in the demographic of patients presenting to hospitals, particularly emergency departments, which has created a myriad of new challenges for our healthcare system. Chiefly, younger and previously healthy individuals have been documented at higher rates in hospital admissions.[7] Not only are patient demographics changing but their reasons for admission are also shifting, such as in the case of new-onset or recurrent COVID-19 infection exacerbation.[8] There have also been increases in social admissions related to issues rooted in poverty and substance use, which further complicate our system's response to this demographic shift.[7,9] Moreover, without a commensurate increase in healthcare funding and development, patient wait times are expected to rise under the projection of nearly one million new immigrants to Canada between 2023 to 2024, all of whom will need adequate care services.[10] Altogether, these factors contribute to immense pressures on our healthcare system, which have since manifested itself in ways including staff shortages and hospital bed availability.[11,12] Needless to say, healthcare infrastructure investment, increased funding for multidisciplinary care, and better patient care models are needed to face the growing demand for services. Already, there have been tremendous strides towards this end, such as the new payment model for British Columbia (BC) physicians which projects to improve the availability of family physicians across the province.[13] Ultimately, further developments are certainly needed.

Finally, there have been tremendous strides made in policymaking with the goal of increasing care accessibility and reducing stigma in the healthcare system. For instance, Canadians continue to face challenges in accessing healthcare in rural communities. While approximately 18% of Canadians reside in rural areas, only 8% of the physicians practicing in Canada serve these communities.[14,15] Rural communities face difficulty acquiring and retaining family physicians, requiring rural-based solutions to improve access to care. In response to these challenges, the Government of Canada has proposed the provision of $26.2 million over the course of four years, starting in 2023, and an increase of maximum forgivable student loans by 50% to support healthcare workers in underserved rural or remote communities.[16] Furthermore,

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efforts have been made to reduce barriers and stigma preventing access to essential support and services. As of January 2023, Health Canada granted the decriminalization of personal possession of certain drugs in British Columbia and endorsed providing information on health and social support services and treatment and recovery programs to adults in possession of these substances.[17] Ultimately, policies should be improved upon to meet the needs of our changing society. Policies that address social determinants of health are needed to ensure equitable access to healthcare for all. By continuously adapting policies to address challenges as they evolve, we can work towards a healthcare system that truly meets the needs of our changing society.

In "Healthcare for a Changing Society", we as the Co-Editors in Chief at the University of British Columbia (UBC) Medical Journal focus attention on how new innovations and shifting population needs transform the field of healthcare. This issue's first feature article is written by Dr. Olusegun Oyedele, an associate professor in the UBC Faculty of Medicine, who examines the changing landscape of medical education. The second feature article is written by Catie Futhey and Dr. Liisa Galea, a professor in the UBC Department of Psychology, who discusses the exploration of sex differences in research throughout history.

Ultimately, our rapidly evolving society necessitates a corresponding change in healthcare to meet the needs of the population. Advancements in AI, emergence of an ageing population, shift in demographics, and changes in public health policies are only a few factors driving rapid change in the healthcare field. The COVID-19 pandemic has demonstrated the importance of having a responsive and adaptable healthcare system as well as healthcare providers and policymakers willing to adapt to meet population needs. While this dynamic landscape presents challenges, it provides opportunities for growth and innovation. As we continue to navigate healthcare in a changing world, it is imperative to consider the potential implications for patients, providers, and society as a whole.

Conflict of interest

The authors of this editorial are the Editors in Chief at the UBCMJ and the opinions shared in this editorial piece are based on that role.

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Educating medical students to deliver transformative healthcare in a changing society

Olusegun Oyedele[1]

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Abstract

Healthcare delivery has undergone profound changes in recent years. This is in part due to the latest global pandemic, but also due to increasing healthcare costs, unprecedented technological innovation, the ubiquitous presence of social media, and increased need for social justice in healthcare. Medical education must respond to these changes or risk training physicians and other healthcare workers who will be unprepared for the future of work in this sector. New models of medical curricula that encompass a systemic approach and include currently neglected competencies within core physician training may prove to be transformational and help to future-proof the health professions.

Change is inevitable but being unprepared is not

Healthcare delivery, and the medical education that shapes it, have changed radically in the past two decades.[1-3] According to van der Lee et al., medical curricula should focus on the future of healthcare,[4] and as such, considerations of the impact of local and global trends must factor into the training of future healthcare workers. Towle addressed this in her 1998 article, opining that "medical education will need to recognize and respond to the context in which it operates" and "create an educational system which is better able to respond to changes in the outside world..."[3] In keeping with this identified need for medical education to anticipate and recognize global changes, this editorial is an invitation to those actively engaged in medical education to consider how changes in healthcare delivery and the worldwide trends that continue to shape societal perceptions, will impact and shape medical education. We must as a collective ask: How should those tasked with training physicians and other healthcare workers for this new era respond?

A changing landscape of healthcare delivery

There is unanimous agreement among observers that healthcare delivery is undergoing a major shift both in North America and globally.[2,3,5,6] Access to data, primarily driven by a revolution in technology has placed high quality medical information in the hands of patients, quite literally. Add to this the re-energized focus on patient advocacy, and the correct insistence on ethical, compassionate and patient-centred delivery of healthcare by regulatory authorities, it becomes clear that the trend of empowered patients driving change in the healthcare system will continue.[7-10] The consistent feedback that patients give, when asked about their interaction with physicians, is that physicians are extremely poor at communicating details of the patient's own care with them.[3,11-13] It is an open question whether the advent of telehealth and other technologies for remote patient-doctor communication have mitigated or compounded communication problems between doctors and their patients. Nevertheless, patients are increasingly finding their voice and demanding more robust and communicative care from their doctors, as well as systems-wide improvement in healthcare delivery. The funders of healthcare, private and public, are also demanding efficiency in the use of allocated resources, where patient concerns are addressed using the best evidence possible.[14,15] In some cases, this can mean a change in the personnel delivering patient care, and a redefinition of the traditional roles of members of the healthcare team. This phenomenon is already taking place within the context of interprofessional and community healthcare.[16,17] In fact, some procedures which were once the domain of family physicians and specialists are now being competently undertaken by other members of the healthcare team.[3,18-20] In the Canadian context, there is ongoing spotlight on the harm that was perpetrated on generations of Indigenous peoples by the healthcare system, and on efforts to redress historical injustice.[21-24] Current ways of thinking about the practice of medicine and of delivering healthcare, along with our existing models of medical education will have to adapt and respond to these challenges, trends and tensions.

A changing world

Since healthcare delivery and medical education do not exist in a vacuum, it is important to examine the aspects of local, national and global societal change that form the milieu in which healthcare students are trained and in which they will practice.[3,25]

Foremost among the drivers of our changing societies around the world is the speed of information access and transmission, including emergent artificial intelligence. "Breaking news" and instant information are literally at our fingertips. With this, perhaps unwittingly, we have granted control to powerful individuals and commercial interests who shape our perceptions for good or ill.[26,27] Information can range from news about life-saving fundraising endeavors,[28] to the metastasis of misinformation that, among other woes, egregiously creates mass hysteria and xenophobic outbreaks of violence against the 'other'.[29] The world's ongoing unpredictable relationship with the COVID-19 pandemic is a poignant case in point, where large numbers of people have been convinced by the information diet available on their social media echo chambers, that, among other beliefs, COVID-19 is a means of mind (and body) control by 'the government'.[30-33] The scourge of such misinformation is ongoing and proliferating in spite of best efforts. Delivering evidence-based healthcare to a skeptical population and training doctors that will deliver such healthcare will continue to be a preeminent challenge of the 21st century.

How medical curricula might change

Medical educators working in the frontline of healthcare delivery and educational thought have grappled with future-proofing medical curricula for some time.[4,34] Two papers[35,36] have inspired my thinking on what may be the path forward, if medical education, at undergraduate, postgraduate and continuing medical education (CME) levels, is to adapt successfully to the forces that are shaping healthcare on all fronts. In discussing the context of global heath training in medical schools, Eaton and colleagues[35] describe three models of medical education, which are also applicable in the context of the present article. These are the 'additive', 'integrated' and 'transformational' models, each

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successive model requiring more innovative thinking, collaborative drive among multiple stakeholders, as well as institutional imagination and commitment. In the transformational model, the curriculum itself becomes a tool for not only transforming the students as future practitioners, but also of changing the learning environment.[35] In her paper, Lucey[36] advocates adopting a systems approach to undergraduate medical education, which would encompass "expanded competencies" such as "measuring and improving quality, safety and costs within complex systems", among others.[36]

In a recent group meeting with the graduating class of 2023, I asked the group what they would have said to their year-one selves, knowing what they know now. A member of the group volunteered without hesitation: "I would tell my year-one self to buckle up and get ready for the ride!" That admonition seems appropriate not only for beginning medical students, but also for the entire community of people invested in the enterprise of medical education and healthcare at UBC and beyond.

Conflict of interest

The author has declared no conflict of interest.

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(Fund)amental changes to sex differences in research: Women's health from cells to clinic

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Abstract

The exclusion of women from biomedical research has existed historically from preclinical models to clinical trials, leading to a disparity in the medical evidence which may be applied to women, as well as a lack of focused, women-centred research. Despite recent advances made by major North American funding agencies, these discrepancies still exist as many studies are not organized in a manner conducive to uncovering sex and gender differences. This commentary aims to consolidate the historical timeline of exploring sex differences in research and outline the clinical significance of analyzing by sex and gender for precision medicine outcomes.

The terms *sex* and *gender* are interactive and evolving concepts that can be difficult to classify into neat boxes. For the purposes of using categorical variables to generate research, however, it is important to arrive at standardized definitions. The United States National Institute of Health (NIH)'s Office of Research on Women's Health defines sex as "a biological classification that is encoded in every person's DNA"[1], and gender as "the socially constructed roles, behaviours, expressions, and identities of girls, women, boys, men, and gender-diverse people".[1] Sex manifests in genetics, hormones, and physical features including gonads and internal and external genitalia. Gender identity is an important part of gender, but both sex and gender are intertwined. Neither term is binary, and the recognition of the non-binary nature of sex and gender will provide invaluable insight into health and disease states that may otherwise be overlooked. *Female* and *male* are words used to describe sex, whereas the terms *woman* and *man* pertain to gender, each carrying a unique host of sociocultural differences. Although this article will not focus on these populations directly, it is critical to recognize that intersex, transgender, and non-binary individuals face disproportionate intersecting healthcare disparities. These disparities span from insufficiently targeted biomedical research to downstream multifactorial barriers to care and must be addressed.[2] Here, the word *female* will be used when describing biological differences whereas *women* will be used to describe research on gender. Not all articles distinguish between sex and gender correctly,[3] and it is important to understand that not all people who possess XX chromosomes or ovaries, or who menstruate recognize themselves as women. The term *women's health* in medicine refers to both biological and social determinants between the sexes and genders.

History of and rationale for sex and gender disparities in research

Women have faced a legacy of obstacles in clinical research. Precipitated largely by the tragically harmful effects of the approved drugs thalidomide and diethylstilbestrol on unborn fetuses in the 1950s and 1960s, women were prohibited from participating in clinical research from 1977 until 1993. The FDA lifted the restriction in 1993 with the advent of the NIH Revitalization Act which mandated the inclusion of women and minorities.[4]

It follows then that several decades' worth of medical knowledge is built on males as the default sex. Indeed, between 1997 and 2000, 8 out of 10 drugs withdrawn from the market by the FDA posed a greater risk to human females.[4] Unfortunately, this mandate of inclusion did not translate into an appropriate and rigorous increase in the analysis of sex differences, broadening this male bias in research beyond the years of overt prohibition. A 2015 survey of NIH-funded randomized control trials found that fewer than a third were analyzed by sex or provided an explanation for excluding this statistical analysis.[5] The 2016 NIH Research for All Act required the consideration of sex as a biological variable (SABV) in NIH-funded vertebrate animal and human studies, or a strong justification for its exclusion.[6] The Canadian Institutes of Health Research (CIHR) policies went further than the inclusion of males and females in preclinical studies by mandating sex and gender-based analysis (SGBA).[7] In 2010, obligatory boxes asking about whether and how sex or gender was to be considered in the grant that was being submitted were imposed. However, it was not until 2019 that SGBA in the proposal itself was set as part of the evaluation criteria for each grant. Even so, recent analyses of funded grants at CIHR do not show a large uptake in SGBA, with under 3% of funded grants ultimately considering sex and/or gender in the projects.[8]

What began as a safety and political concern has metamorphosized into a disparity perpetuated by funding, lack of awareness of the importance of sex and gender, and accessibility. Despite the uptick in initiatives, insufficient funds are being devoted to substantiating the new funding agencies' recommendations for SABV/SGBA: increased sample sizes may be needed to adequately power studies to uncover differences by sex although stratification by sex can in some cases serve to increase statistical power.[9] Moreover, females have historically been considered "too complex" to study, a complexity attributed to fluctuating hormone levels in the estrous and menstrual cycles in rodents and humans, respectively. However, females are not more variable than males on a variety of physiological traits[10]—and the notion that females are too difficult to study has been argued to be overtly sexist.[11] This does not, however, mean hormonal profiles are not important for health, merely that the hormonal variability itself is comparable between sexes. Therefore, this exclusion from preclinical animal models to clinical trials is ungrounded and unacceptable.

Why studying sex differences matters

Significant differences exist between males and females in all facets of medicine: time to diagnosis, disease onset, progression, severity, symptom manifestation, as well as the efficacy of or adverse reactions to vaccines and treatments. These differences exist in many conditions spanning all organ systems, for which many of the underlying mechanisms remain

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unclear. They are in part hormonal and chromosomal, but there are significant influences from gendered factors.[12] Symptoms manifesting differently in the sexes suggest a need to overhaul our governing disease classification system to better reflect broad differences in physiology and may in part explain why human females are diagnosed later than human males for a variety of diseases.[13] Without a deeper more fundamental understanding of sex differences which starts in the preclinical stage, we run the risk of delaying diagnoses, treatment, and pathologizing what is simply different. This remains an issue today because the mere inclusion of both sexes in a study population does little to target the discovery of differences; in fact, failure to analyze properly by sex may misconstrue diverging data entirely.[9] See Figure 1 for a graphical representation of this.

Remarkably, in a 2009 survey of immunological papers, 75% of articles in animal models failed to even *specify* sex, let alone provide sex-based analyses.[19,20] Unfortunately these discouraging statistics did not waver in the context of the ongoing pandemic: just 4% of COVID-19 clinical trials registered on *ClinicalTrials.gov* between January 2020 and January 2021 explicitly reported a plan to include sex or gender as an analytical variable.[21] This disparity, along with the widespread ineligibility of pregnant and breastfeeding women in vaccine clinical research,[22] may have also contributed to greater vaccine hesitancy in women.[23] Women also experience significantly more adverse events following immunization than men,[24] a phenomenon which perhaps is not an issue of their immune system phenotype *overreacting* to stimulus, but just that vaccination doses or programs must be adjusted to target a

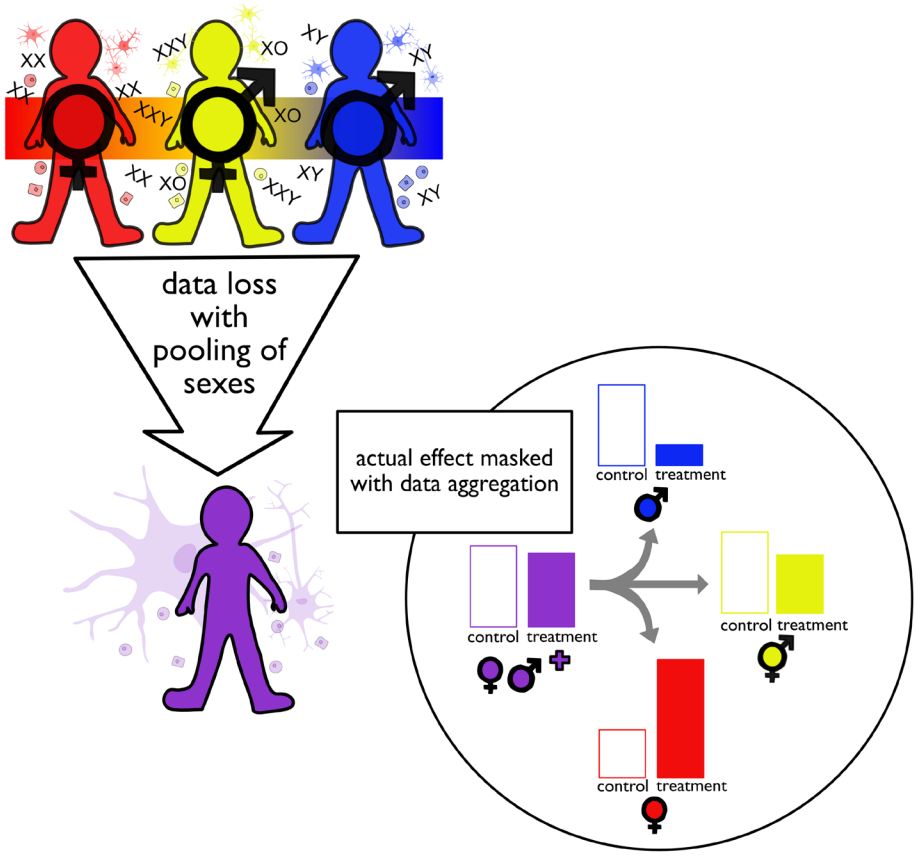

Figure 1: Artistic representation of intricacies in sex differences and potential for information loss with inappropriate (or absent) analysis methods. The graphs showcase that simple inclusion is not sufficient and has the capacity to miss potentially valuable information specific to sex.

For example, cardiac symptoms can present quite differently in women and are often labeled as "atypical"[14]—a puzzling term to be used to describe half the population. Further, the immune system is strikingly different in males and females, with women mounting more robust immune responses to vaccines[15] and a markedly different prevalence pattern in autoimmune disease. It is estimated that 80% of autoimmune disease sufferers are women,[16] with 95% of Hashimoto's thyroiditis cases being women.[17]

Medicine begins in animal models, the results from which inform the early clinical trials which translate into clinical practice. Since the outcomes we see in animals, largely derived from studies in *male* animals, trickle down into the care we receive at the doctor, these studies must also be as reflective of the population as possible.[18] fundamentally different system.

Preclinical discoveries in neuroscience also alert us to divergent systems that deserve further research attention. Entirely distinct pathways underlying chronic pain are observed between male and female rodents,[25] indicating different treatments are needed. In fact, a study conducted at the University of British Columbia (UBC) compared animal and human neuroscience and psychiatry studies from six high-impact journals from 2009 and 2019 and posited that despite an increase in the percentage of papers reporting the inclusion of both sexes, in 2019, only 19% reported using optimal design for elucidation of these differences and just 5% analyzed by sex as a discovery variable—that is, it was not ignored or used as a covariate in the analyses.[3] Indeed, further analysis showed that in human psychiatry publications, 72% of the papers that examined sex in this way

found a statistical difference between human males and females on the variable of interest in the studies, further underscoring the need to study and examine, rather than control for, sex.

Sex-specific medicine

Beyond these differences between males and females, it remains crucial to deconstruct diseases restricted to the processes of just one sex. The same analysis of neuroscience and psychiatry literature mentioned above found that a mere 3% of all human and animal studies analyzed in 2019 were female-only, versus 27% focusing on conditions that affect males alone.[3]

Menstrual cycle phase is a clinically significant factor amidst different conditions, which highlights the urgency of female-centred health research: premenstrual status is noted as an *amplifying cofactor* in anaphylaxis severity in the World Allergy Organization Guidelines,[26] and even influences concussion recovery.[27] Other so-called *catamenial*—that is, related to the cyclicity of the menstrual cycle—disorders also exist, and pertain to conditions such as pneumothorax[28] and epilepsy,[29] which are generally considered outside the scope of conversations involving hormones.

These findings have the propensity to affect a large proportion of the population and are ripe with discovery potential, but the resources, infrastructure, and educational means for researchers and downstream healthcare providers are simply not present. It is difficult, then, to establish accurate prevalence, incidence, and morbidity of such conditions atop a fractured foundation.

In the clinical context: A conversation with Dr. Sherri Hayden

For a clinical perspective, we spoke with Dr. Sherri Hayden, a clinical neuropsychologist of 30 years at UBC Hospital and Alzheimer's Clinic deeply involved in the Women's Health Research Cluster. She maintained that despite recent advances in research direction, she has yet to see this take shape clinically in an appreciable way. Neurology remains a male-dominated field, and the lack of female representation in leadership, as well as clinical roles, is especially conducive to the perpetuation of these discrepancies. Women physicians are often more likely to adhere to clinical guidelines, provide more preventative care, and use more patient-centred communications.[30] In fact, a retrospective study of patients undergoing surgical procedures across Ontario showed that those who had female surgeons experienced significantly better outcomes in procedures and postsurgical care, and had lower readmission and mortality rates.[31] This representation of women in medicine is therefore valuable for not just women, but all patients regardless of sex or gender.

Dr. Hayden emphasized the importance of a sustainable action plan hinged on awareness and making the clinic a welcoming environment. The former may be achieved through representation with women occupying more medical leadership positions and women's health-oriented mentorship programs, and the latter is critical to ensure valuable care-determining information is not dismissed. Dr. Hayden described that "[some patients] have dismissed their confusion or loss of mental faculties as 'just hormonal' for so long that by the time we're seeing them in the clinic, they have mid-stage Alzheimer's Disease." This disregard for one's symptoms may be inadvertent or bias-driven on the part of the physician, or after ingesting a lifetime of societal expectations by the patients themselves. Physicians are more likely to confine a woman's pain to a psychological diagnosis,[32] and a report released by the British Columbia Women's Health Foundation in 2019 pronounced that over half of women in the province felt that a physician had diminished or overlooked their symptoms.[33] By delaying treatment and mitigation measures, these sex and gender discrepancies are only perpetuated.

Going forward

The process of dismantling these research paradigms has been slow but optimistic: federal funding agencies have courses on sex and gender differences in research,[1] and reviews of guidelines for design and analyses exist.[34] In 2022, the Canadian Government announced a funding call for a National Women's Health Research Initiative with $20 million over 5 years dedicated to closing these gaps in health research and quality care access.[35] Although these actions are promising, the $20M investment is 0.4% of the 5-year CIHR budget, and given that females are 50% of the population, this suggests that women's health is vastly underfunded. Medical leaders must try to integrate these new findings into practice to reflect a more equilibrated society across sex and gender. Properly designed and analyzed research may be an investment upfront but starting at these early stages in the medical discovery pipeline will save money long-term in preventing erroneous downstream practices.[18] Several steps to rectify the understudied phenomenon of sex and gender in medical research have been outlined,[3] calling on funders, researchers, and publishers to ensure sex and gender are attended to in studies. However, initiatives must also be prioritized in medical education. In Canada, the University of Toronto has a unique *Women Neurology* elective for neurology residents[36] which could be adopted across other institutions and clinical specialties, or even introduced earlier on in medical school. Funded educational initiatives for medical students and clinicians who have direct communication channels to the general public through patients are also critical. This is a larger issue embedded in centuries of societal customs and expectations, but starting with the evidence and facilitating such quality evidence to be generated and taught, will be an invaluable step forward. Sex differences and gender experiences should be top of our clinician's minds to begin to correct the long-standing biases and disparities in health outcomes.

Conflict of interest

The author has declared no conflict of interest.

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Lipoprotein (a) screening in British Columbia

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Abstract

Lipoprotein (a) (Lp(a)) is a type of low-density lipoprotein (LDL) that is associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD). Lp(a) levels in the blood are primarily determined by genetics and are not affected by lifestyle changes or statin therapy. In 2021, the Canadian Cardiovascular Society (CCS) updated its guidelines on dyslipidemia management and cardiovascular disease prevention, recommending that all individuals over the age of 40 undergo a one-time measurement of Lp(a). While Lp(a) testing is currently available in British Columbia (BC), lowering Lp(a) through pharmacological intervention remains unproven in reducing the risk of ASCVD in the long term. Proprotein convertase subtilisin/Kexin type 9 inhibitors (PCSK9i) are the only Health Canada-approved medications that can lower Lp(a) but are only covered for treating familial hypercholesterolemia as an adjunct to statins and ezetimibe. As a result, Lp(a) testing currently serves as a tool for risk stratification to help guide shared decision-making regarding statin initiation for general primary prevention or other non-pharmacological measures.

Introduction

Cardiovascular disease (CVD) is a leading cause of all-age disability-adjusted life years in Canada, ranking second to cancer.[1] To combat this issue, the Canadian Cardiovascular Society (CCS) provides guidelines for managing various CVDs. In 2021, the CCS updated its dyslipidemia management guidelines for the prevention of CVD. These updates build upon the 2016 guideline and include guidance on the utility of Apolipoprotein B (ApoB), non-high-density lipoprotein-Cholesterol (non-HDL-C), and lipoprotein (a) (Lp(a)) testing, when to use coronary artery calcium scoring, the benefits of icosapentethyl, and lack of cardiovascular (CV) benefit of omega-3 fatty acids.

Notably, the 2021 CCS guideline is the first in Canada to recommend a one-time Lp(a) test in everyone over 40 years of age, a practice recommended by the European guidelines since 2010.[2] These updates will aid healthcare professionals in preventing and managing CVD.

Commonly measured lipid parameters

Since the introduction of lipid screening at age 40 in the 1998 Canadian lipid guidelines, lipid screening has been widely adopted and validated across Canada.[3] The 2021 CCS guidelines recommend a non-fasting standard lipid profile (total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C and triglycerides (TG)), along with fasting glucose or Hemoglobin A1C, estimated glomerular filtration rate (eGFR) and Lp(a) measurement for both men and women over 40, or earlier if other risk factors, family history, or family history of premature CVD are present (Figure 1).[4] The standard lipid profile provides a baseline value of atherogenic particles and possible treatment targets if lipid-lowering therapy is indicated.

While TC is a helpful measure of total plasma cholesterol, it does not accurately quantify atherogenic particles.[5,6] For instance, TC can be within the normal range but be predominately made up of LDL-C, which may more significantly elevate atherogenic risk.[5]

LDL-C measurement distinguishes cholesterol carried in LDL particles and is a good indicator of a patient's general atherogenic state. However, in patients with elevated TG , The Friedewald equation can be used to estimate LDL-C fails to differentiate between intermediate-density-lipoprotein (IDL), very-low-density-lipoprotein (VLDL), and LDL.[7,8]

Since 2012, the CCS guideline recommends using non-HDL-C or ApoB as better markers for atherosclerosis in patients with TG>1.5mmol/L. (Figure 1) ApoB provides greater insight into a patient's atherogenic state than LDL-C alone since all ApoB-Containing lipoproteins, including remnant chylomicrons, VLDL, and Lp(a), contribute to atherosclerosis.[9,10] Similarly, non-HDL-C, which can be tested at no additional cost, can be used as an indirect marker since all particles besides HDL contribute to atherosclerosis.[11] However, it is up to the ordering physician's discretion to choose between ApoB and non-HDL-C.

What is Lp(a) and why screen?

Lp(a) is a type of lipoprotein that increases risk of CVD in a dose-dependent manner. Lp(a) is unique in its composition as it is composed of an LDL particle bound to apolipoprotein-a (apo(a)), which is produced and secreted by hepatocytes.[12] The link between Lp(a) and myocardial infarctions (MI) was first recognized when data from the original Framingham study showed that Lp(a) levels were able to distinguish patients with coronary artery disease (CAD) from normal individuals independent of smoking or hypertension.[13] Over the next two decades, Lp(a) research fell out of popularity due to a prospective trial showing Lp(a) levels in patients with fatal or non-fatal acute MI were indistinguishable from matched controls.[14,15] However, recent studies unequivocally demonstrated that Lp(a) is a risk factor for ASCVD. [16,17]

Evidence in support of Lp(a) screening comes from the strong association between some Lp(a) single nucleotide polymorphisms (SNP) and increased risk for CAD. Notably, SNPs in the Apo(a) gene, LPA, were associated with a variable level of plasma Lp(a) and higher expression of Lp(a) with elevated CAD risk.[18] These SNPs have been found to be most prevalent in African American, South Asian, and European individuals.[17]

Patients with Lp(a) levels between the 90th and 95th percentile (levels greater than 117 mg/dl) have a 2.7- fold hazard ratio for increased risk of MI, independent of other cardiovascular risk factors.[19] Lp(a) levels are also important in the secondary prevention of ASCVD, with elevations correlated with the recurrence of adverse CVD events.[16]

There are two leading theories for Lp(a)'s atherogenicity. First, Lp(a) can directly deposit into the atherosclerotic plaque. This is especially significant when TG levels surpass 1.5 mmol/L.[20] Furthermore, it is thought that Lp(a)'s apo(a) facilitates even greater uptake into the intimal vasculature than LDL.[21] Second, increased Lp(a) concentrations

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in the blood lead to increased endothelial dysfunction.[22] Thus, Lp(a) directly contributes to atherogenic plaque formation and contributes to vascular dysfunction.

Lp(a) testing is available in BC; however, only patients with a history of complex dyslipidemia outlined on requisitions will have testing costs covered. As complex dyslipidemia has no diagnostic criteria, it is up to the discretion of the ordering physician to make this distinction. Identifying patients with elevated Lp(a) plasma levels can aid in CVD risk stratification and guide the decision to start lipid-lowering therapy.

Few medications have been shown to reduce Lp(a), and none have yet been shown to reduce long-term CVD risk. The only pharmacological options approved by Health Canada are PCSK9 inhibitors which show improved outcomes in patients with elevated Lp(a) and reduced Lp(a) levels.[23,24] Nonetheless, in BC, PCSK9i is currently only covered in patients with familial hypercholesterolemia who do not reach target LDL-C despite statin and ezetimibe therapy.[23,25,26] Inclisiran, a small interfering RNA (siRNA)-based PCSK9 inhibitor currently approved by the United States Food and Drug Administration, has been shown to lower Lp(a) by approximately 20% but is not available in Canada, and its long-term benefits in CVD have yet to be studied.[27-29]

Although niacin was previously thought to affect Lp(a), the HPS2-THRIVE and AIM-HIGH trials have recently shown that extended-release formulations of niacin do not effectively lower Lp(a).[30-32]

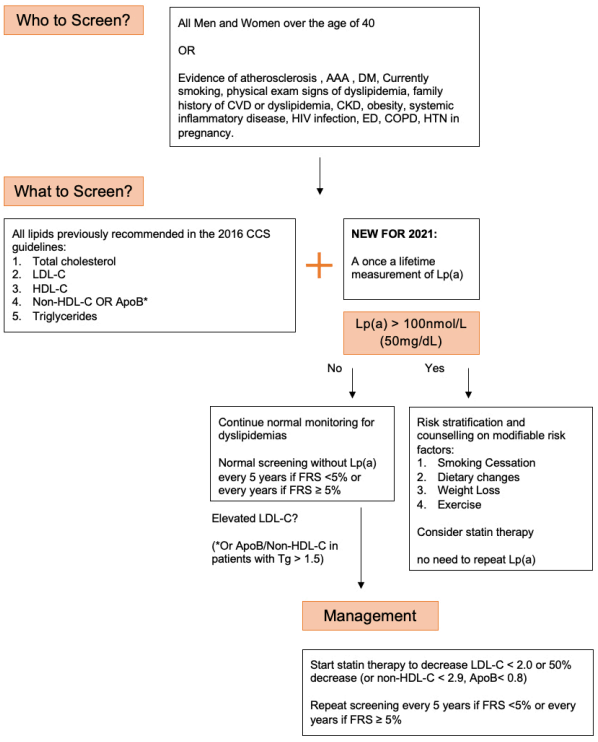

Figure 1: Algorithm for Lp(a) screening. Adapted based on current CCS 2021 guidelines for the management of dyslipidemias. *The choice of Non-HDL-C or ApoB is left at the discretion of the ordering physician. Non-HDL-C has no additional cost. Both non-HDL-C and ApoB are more accurate markers for the atherosclerotic state than LDL-C, particularly in patients with TG> 1.5 mmol/L. Abbreviations: AAA, abdominal aortic aneurysm. DM, diabetes mellitus. CVD, cardiovascular disease. CKD, chronic kidney disease. ED, erectile dysfunction. COPD, chronic obstructive pulmonary disease. HTN, hypertension. CCS, Canadian Cardiovascular Society. LDL-C, low-density lipoprotein- cholesterol. HDL, high-density lipoprotein- cholesterol.

Who should get screened for Lp(a)?

The current CCS guidelines suggest that individuals should undergo initial lipid screening at 40 years of age (Figure 1).[4] The previous complete lipid screening panel compromised TG, TC, HDL-C, LDL-C, and either ApoB or non-HDL-C as determined by the ordering physician. The latest guideline recommends adding a once-a-lifetime Lp(a) test to this panel. Of note, Lp(a) levels are primarily determined by genetics and are not significantly influenced by the additive effects of lifestyle modification, statins, and ezetimibe. Therefore, there is no need to monitor Lp(a) over time.[4]

What to do with screening results?

According to the CCS guidelines, the upper limit of normal for Lp(a) is > 100 nmol/L or 50mg/dL.[4] For primary prevention of ASCVD, Lp(a) levels above 30 mg/dL increase ASCVD risk in a graded manner. (19) The INTERHEART study data set also supports that patients with Lp(a) level greater than 100 nmol/L have a 48% higher risk of MI.[33,34] However, there is currently no established method to incorporate Lp(a) levels into available stratification tools such as the Framingham risk score.[35]

While statins do not decrease Lp(a) levels, intensifying or starting statin therapy in patients with elevated Lp(a) can help reduce the total atherosclerotic load by reducing LDL-C (Figure 1). The 2019 HEART UK guidelines recommend cardiovascular risk modification when Lp(a) is elevated and high-intensity statins to target a 50% reduction in non-HDL-C.[2]

Conclusion

Lp(a) is a lipoprotein particle similar in structure to LDL-C but is uniquely characterized by its apo(a) component. Lp(a) is known to play a role in atherogenic plaque formation. Unlike many other lipid parameters, the amount of Lp(a) in circulation is almost entirely genetically determined by SNPs in the LPA gene. Currently, the only pharmacological intervention approved in Canada for reducing Lp(a) levels are PCSK9 inhibitors, although their use is restricted to patients with familial hypercholesterolemia who have failed to reach targets with statins and ezetimibe.

While elevated levels of Lp(a) are associated with an increased risk of coronary events, there is limited long-term evidence that interventions lowering Lp(a) provide an ASCVD risk-benefit. However, measuring Lp(a) levels once in a patient's lifetime is recognized as a valuable tool for assessing cardiovascular risk. As such, the 2021 CCS guidelines support this one-time Lp(a) screening in individuals over the age of 40. Results from this testing can help with risk stratification and identify patients who may benefit from future pharmacological interventions for lowering Lp(a).

Conflict of interest

The authors have no conflicts of interest to declare.

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Review of systemic therapy options for the treatment of cholangiocarcinoma in Canada

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Abstract

Cholangiocarcinoma, cancer of the biliary tract, is a rare malignancy with a poor prognosis. However, the incidence of cholangiocarcinoma is on the rise globally. Currently, complete surgical resection is the only curative treatment for localized disease while there is no cure for more advanced cholangiocarcinoma. In recent years, there have been several developments of adjuvant and palliative chemotherapies, especially with regards to targeted molecular therapies. Some of these treatments are now approved and funded in Canada. The purpose of the review is to provide a general overview of current cholangiocarcinoma systemic therapies, with a focus on Canadian standards of care.

Background

Cholangiocarcinoma is a cancer arising from the biliary tract. It is a rare gastrointestinal (GI) cancer that accounts for approximately 3% of all GI malignancies.[1] The cancer is associated with an advanced state at presentation and a poor prognosis with 5-year survival rates ranging from 8-40%, due to the lack of adequate screening methods and effective targeted therapy.[2] Data have also shown that the incidence and mortality of cholangiocarcinoma have been rising globally over the past decades.[3] In Canada, the mortality rate for cholangiocarcinoma has risen from 1.71 per 100,000 inhabitants in 2000 to 2.71 per 100,000 inhabitants in 2014, but data on regional patterns of incidence and prevalence is limited.[1]

Cholangiocarcinoma can be further categorized into three subtypes based on location: intrahepatic cholangiocarcinoma (ICCA), extrahepatic cholangiocarcinoma (ECCA), and perihilar cholangiocarcinoma (PCCA). Among the three subtypes, the incidence of ICCA has most substantially increased globally, which can be potentially linked to increases in the incidences of its risk factors such as obesity, hepatitis C infection, and chronic liver disease.[3]

Currently, the only potentially curative treatment for cholangiocarcinoma is surgical resection, which can only be performed for patients with localized disease. Adjuvant chemotherapy is typically provided after definitive resection with the goal of reducing risk of recurrence. It is the current standard of care in Canada, but the true benefit of such therapy has been widely debated over the years. For more advanced disease, palliative chemotherapy has been associated with a modest survival benefit, and increasingly, there is interest in investigating targeted therapies for molecular subgroups of cholangiocarcinoma. With many novel therapies on the horizon, this review aims to provide a general overview of current cholangiocarcinoma treatment, with a focus on Canadian standards of care. The funding information for drugs included in this review is based on provincial funding available in British Columbia as of 2022[7,15,21].

Treatment for Localized Disease

Localized cholangiocarcinoma can be treated with definitive surgery. Currently, there is no evidence for neoadjuvant chemotherapy (therapy given prior to definitive resection); however, there is now evidence supporting the role of adjuvant chemotherapy.

One of the landmark clinical trials in cholangiocarcinoma is the BILCAP trial, which assessed the use of six months of capecitabine, an oral fluoropyrimidine, as adjuvant chemotherapy.[4] The trial ran between 2006 and 2014 in the UK, and recruited 447 subjects with resected cholangiocarcinoma, with 223 in capecitabine group and 224 in observation group with no chemotherapy given. Using intention-to-treat analysis, the median overall survival was 51.1 months in capecitabine group and 36.4 months in observation group, with the mortality rate of patients in the capecitabine group being 81% of that of the observation group (HR 0.81, 95% CI, 0.63-1.04; p=0.097). Serious adverse events were observed in 21% of patients receiving capecitabine and 10% of patients in observation group. Although the survival benefit in the intention-to-treat analysis did not quite reach statistical significance, the per-protocol analysis was associated with an improvement in overall survival, with an adjusted hazard ratio of 0.75 (95% CI, 0.58-0.97; p=0.028). Given the high unmet need and absence of alternative adjuvant therapies, adjuvant capecitabine is now widely adopted as a standard of care option in Canada.[5-7]

Other completed phase III trials to this date have not shown clear survival benefit of other adjuvant therapies. Examples of these trials include the PRODIGE 12 trial that investigated combined gemcitabine and oxaliplatin chemotherapy,[8] the ESPAC-3 trial that looked at leucovorin-modulated fluorouracil and gemcitabine therapies,[9] and the trial performed by Takada et al. that investigated combined mitomycin C and 5-fluorouracil therapy.[10]

However, it is worth noting that an ongoing trial in Japan, the JCOG1202 trial, has shown promising data during the interim analysis.[11] The group investigated the use of S-1, another oral fluoropyrimidine-based therapy, which consists of 3 drugs - ftorafur, gimeracil, and oteracil, as adjuvant chemotherapy for patients with cholangiocarcinoma, gallbladder cancer, and the cancer of the ampulla of Vater. The median overall survival was longer in the treatment group (n=218) versus the surgery-alone group (n=222) with a hazard ratio of 0.69 (95% CI, 0.51-0.94; p=0.008), and a subgroup analysis showed favourable results in patients with cholangiocarcinoma. More data from the trial would be helpful to determine the safety and efficacy of the drug. S-1 therapy is currently not available in North America.[7]

Treatment for Advanced Disease

For patients presenting with advanced metastatic and/or unresectable disease, treatments are of palliative intent. The standard first-line palliative chemotherapy protocol in Canada is the combined therapy of gemcitabine and cisplatin.[5,6] The evidence supporting the therapy was from the ABC-02 clinical trial in the UK, which showed median

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overall survival of 8.1 months in the cisplatin group versus 11.7 months in the combined cisplatin-gemcitabine group.[12] The rate of death among patients in the cisplatin group was 36% lower than the combined cisplatin-gemcitabine group (HR 0.64, 95% CI, 0.52-0.8, p<0.001). Adverse events were also observed to be similar in both groups.

The second-line regimen approved in Canada, FOLFOX (folinic acid, fluorouracil, and oxaliplatin),[5,6] was also studied in the UK in the ABC-06 trial.[13] This trial compared patients who received active symptom control only (n=81) to patients who received FOLFOX plus active symptom control (n=81). The overall survival was significantly longer in the FOLFOX group, with a median survival of 6.2 months versus 5.3 months. The hazard ratio was 0.69 (95% CI, 0.5-0.97; p=0.031). However, higher incidence of adverse events was also observed in the treatment group, including three chemotherapy-related deaths.

Recent advances in immunotherapies have also shed some new light on the treatment of advanced cholangiocarcinoma. In the randomized, placebo-controlled phase 3 TOPAZ study, Oh et al. investigated the use of the PDL-1 immune checkpoint inhibitor, durvalumab, in addition to the standard gemcitabine-cisplatin treatment.[14] Results presented in 2022 showed a statistically significant increase in overall survival in the durvalumab plus gemcitabine-cisplatin group (N=341) in comparison to gemcitabine-cisplatin alone (N=344), and the mortality rate of patients in the durvalumab plus gemcitabine-cisplatin group is 80% of that of the gemcitabine-cisplatin group (HR 0.8, 95% CI, 0.66-0.97; p=0.021). The improvement in median survival was modest (12.9 months vs 11.3 months) but the proportion of patients alive at two years was twice as high in the durvalumab arm (24% versus 12%). Adverse events were not significantly increased with the addition of durvalumab to standard chemotherapy. Durvalumab received a Health Canada indication in September 2022, but it is not yet approved for funding in Canada.[15]

Treatments Targeting Molecular Subgroups

In recent years, tumour molecular profiling has been able to identify potentially actionable genomic aberrations which may respond to targeted therapies. Drugs that target molecular subgroups in advanced cholangiocarcinoma have been of interest in recent research. Progress in this area has been summarized below.

IDH1

Mutation of isocitrate dehydrogenase 1 (IDH1), an enzyme involved in the production of a key substrate in glucose metabolism — α-ketoglutarate — has been implicated in various cancers.[16] In cholangiocarcinoma specifically, 20% of all patients with ICCA have this mutation.[17] The result of the phase III ClariDHy trial reported in 2021 has suggested that inhibition of IDH1 by an oral drug named ivosidenib may improve overall survival of patients with previously-treated advanced cholangiocarcinoma that harbour an IDH1 mutation.[17] Median survival improved from 5.1 months in the placebo group (N=61) to 10.3 months in the treatment group (N=126) after adjusting for crossovers (HR 0.49; 95% CI, 0.34-0.70; p<0.001). Ivosidenib is not yet approved for use in Canada.[7]

FGFR2 Fusions

Fibroblast growth factor receptors (FGFRs) have been another target for oncologic molecular therapies. FGFRs are responsible for activating signaling pathways for cellular proliferation and survival.[18] The fusion of FGFR genes would result in increased activation of the pathway, leading to oncogenic transformation of the cells. The fusion of FGFR genes have been reported in approximately 15% of ICCA.[18] Pemigatinib, a selective FGFR 1-3 inhibitor, was investigated in a recent phase II trial, FIGHT-202.[19] In the trial, it was shown that for patients with previously-treated advanced cholangiocarcinoma with FGFR2 fusions or rearrangements, objective responses (any measurable response to treatment) were achieved in 38 out of 107 patients (36%), with three complete responses (absence of detectable cancer). A phase III trial, the FIGHT-302 study, is now enrolling patients to investigate the use of pemigatinib in the first-line setting.[20] Pemigatinib received Health Canada approval in 2021 but is not yet funded for use in Canada.[21]

BRAFV600E

Mutated forms of the BRAF gene, which codes for the B-Raf protein that is involved in the regulation of cellular growth and proliferation, have been found in 5% of all cholangiocarcinoma.[22] Dabrafenib is a potent B-Raf inhibitor, whereas trametinib selectively inhibits a downstream target of B-Raf — the mitogen-activated protein kinase (MEK) protein.[23] The combination of dabrafenib and trametinib was studied for BRAF-mutated cholangiocarcinoma as a part of the single-arm phase II ROAR trial.[22] The overall response rate (the rate of any measurable response to treatment) was 20 out of 43 patients (46%) with BRAF V600E mutation when assessed by an independent reviewer. Nine patients (21%) had treatment-related serious adverse events. While promising, BRAF inhibitors are not currently approved for use in BRAF-mutated cholangiocarcinoma in Canada.[7]

HER2

The human epidermal growth factor receptor 2 (HER2) protein amplification and overexpression has been extensively studied in breast cancer.[24] However, recent studies have shown that mutations of the HER2 gene are present in 5-20% of ECCA and gallbladder cancer as well.[25] In a phase II clinical trial named MyPathway, the investigators have shown that using pertuzumab and trastuzumab — monoclonal antibodies that target HER2, 9 out of 39 patients (23%) with HER2 mutations achieved partial responses (decrease in the size of a tumour or the extent of cancer in the body).[26] In another trial named HERB, the overall response rate is 36.4% (N=22) for HER2 positive patients when given trastuzumab deruxtecan, a drug made up of the monoclonal antibody trastuzumab that has been covalently linked to the topoisomerase II inhibitor deruxtecan.[25] No phase III trial has been done up to this date, and the treatment is not approved nor funded in Canada.[7]

While the most researched molecular subgroups are described above, Table 1 provides a more comprehensive overview of clinical trials of various targeted therapies. Potential involvement in clinical trials or use of newer molecular treatments approved in Canada have opened new doors for patients with advanced cholangiocarcinoma with possibilities of longer overall survival. Tumour molecular profiling in cholangiocarcinoma is recommended to identify patients who may benefit from a targeted therapy approach, as an alternative or addition to the standard chemotherapies, or be eligible for potential clinical trials.

Conclusion

Cholangiocarcinoma is an uncommon GI malignancy with increasing incidence and prevalence in Canada. For patients presenting with resectable disease, the use of adjuvant capecitabine chemotherapy after surgery is a current standard of care. The clinical trial of S-1 has shown some promising interim results, but more research is needed to elucidate the safety and efficacy of the drug regimen.

For the majority of patients who present with advanced disease, cisplatin and gemcitabine combination therapy remain the first-line

Molecular Target	NCT Number	Trial Phase	Completed	Drug Name	Study Population	Study Location	Notable Results	Further Trial
IDH1	NCT02989857	III	Yes	Ivosidenib	Patients with previously treated local advanced or metastatic cholangiocarcinoma	International *	Progression-free survival significantly improved with ivosidenib compared with placebo (median 2·7 months vs 1·4 months; hazard ratio 0·37; 95% CI 0·25-0·54)	No
	NCT02746081	I	Yes	BAY1432032	Patients with isocitrate dehydrogenase-1 (IDH1)-R132X-mutant advanced solid tumors, 12 of whom have ICCA	International	5/12 patients with stable disease	No
FGFR2	NCT02924376	II	Yes	Pemigatinib	Patients with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocation who have failed at least 1 previous treatment	International	38/107 patients with mutated FGFR2 achieved OR **	Ongoing phase III
	NCT02150967	II	Yes	Infigratinib	Patients with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations	International	25/108 patients (83 with FGFR2 fusions) achieved OR	Ongoing phase III
	NCT02699606	II	No	Erdafitinib	Asian patients with previously treated advanced cancers with FGFR genetic alterations, 14 of whom have cholangiocarcinoma	China, Korea, Taiwan	8/14 patients with FGFR fusions achieved OR	No
	NCT02052778	II	No	Futibatinib	Patients with ICCA with FGFR2 gene rearrangements	International	23/67 patients with ICCA who has FGFR2 rearrangements achieved OR	No
	NCT02265341	I	Early Termination	Ponatinib	Patients with advanced biliary tract cancer with FGFR2 fusions	United States	1/12 patients with FGFR mutations achieved OR	No
BRAF	NCT02034110	II	Yes	Dabrafenib and trametinib combination therapy	Patients with BRAF V600E-mutated rare cancers, 43 of whom have biliary tract cancer	International	20/43 patients with BRAFV600E mutation achieved OR	No
HER2	NCT02091141	II	No	Pertuzumab and trastuzumab combination therapy	Patients with metastatic solid tumours with HER2 overexpression, including 39 patients with cholangiocarcinoma	United States	9/39 patients with HER2 expressing tumour achieved OR	No
	JMACCT ID: JMA-IIA00423	II	No	Trastuzumab deruxtecan	Patients with unresectable or recurrent biliary tract cancer with HER2 overexpression	Japan	8/22 patients with HER2 expressing tumour achieved OR	No
EGFR	NCT00033462	II	Yes	Erlotinib	Patients with unresectable or metastatic cholangiocarcinoma, hepatocellular carcinoma, and gallbladder cancer, number of patients with cholangiocarcinoma unknown	United States	3/42 patients with EGFR expressing tumour achieved OR	No
	NCT00356889	II	Yes	Erlotinib and bevacizumab combination therapy	Patients with metastatic or unresectable cholangiocarcinoma	United States, Singapore, Australia	6/49 patients with EGFR expressing tumour achieved OR	No
dMMR	NCT02628067	II	No	Pembrolizumab	Patients with multiple types of unresectable and/or metastatic solid tumors, 22 of whom have cholangiocarcinoma	International	9/22 patients with dMMR tumour achieved OR	No
PD-L1	NCT02829918	II	No	Nivolumab	Patients with advanced cholangiocarcinoma or gallbladder cancer who have failed 1 or 2 systemic therapies	United States	5/46 patients with refractory biliary tract cancer achieved OR (assessed by independent reviewer), with 27/46 achieving disease control	No
TRK	NCT02576431	II	No	Larotrectinib	Patients with TRK fusion-positive local advanced or metastatic solid tumours, 2 of whom have cholangiocarcinoma	International	41/55 patients with TRK fusion-positive tumours achieved OR; 2/55 patients have cholangiocarcinoma	No

Table 1. Clinical trials for targeted molecular therapies.[27-41]
* International: Greater than 3 locations

standard of care in Canada. However, the landscape of therapeutic options in advanced disease has been rapidly evolving in recent years. The use of the immunotherapy agent, durvalumab, is associated with improved survival in metastatic disease when combined with first-line cisplatin and gemcitabine. Of great interest is the evolving landscape of actionable molecular subgroups with targeted therapies that have been associated with evidence of clinical efficacy — most notably IDH1, FGFR2, BRAFV600E and HER2, although more clinical trials would be needed to further evaluate the true benefits of these drugs.

Future research needs to focus on improving the efficacy of the curative-intent adjuvant therapies for patients with localized disease. In the setting of metastatic disease, there is a need to continue pursuing a precision medicine approach by identifying targeted therapies informed by molecular subgroups. This would require expanded access to tumour molecular profiling. Better therapies are also needed for the majority of patients with advanced cholangiocarcinoma that do not harbor any actionable mutations.

Conflict of interest

SG has received research funding outside of the submitted work, as well as speakers fee from Incyte Canada. SG is an advisor for AstraZeneca and Incyte Canada.

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The mental health toll of the social media scroll

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Abstract

The global pandemic has forced society to adapt, living by extension through our devices for work, play, and daily interactions. Consequently, we have seen significant changes in the mental wellbeing of social media users, with studies demonstrating associations with poorer mental health outcomes, sleep quality, tic disorders, and eating disorders. Conversely, studies have also shown the protective effects of social media in mitigating anxiety and promoting active living. In this article, we aim to critically analyze the literature on the impact of social media use on mental health and suggest recommendations.

In Canada, it is estimated that 32.2 million people are on social media, approximately 84.9% of the Canadian population.[1] A 2021 survey polling 1,622 Canadian households estimated that 74% of Canadian youth aged 7–17 have used social media in the last month.[2] TikTok usage has surged, with users in Canada spending up to 27 hours/week online which is 4 hours greater than the general Canadian average.[3] Today, in a world where daily and pervasive internet use has become the norm, we are relying on technology more than ever to stay connected. However, online social interactions do not necessarily confer the same benefits as face-to-face activities. In this article, we aim to explore the benefits and detriments of social media use on mental health in this ever-changing digital world and provide key recommendations.

Exploration

In April of 2020, Alonzo et al. published a systematic review on the relationship between active social media use, sleep quality, and common mental health outcomes including anxiety, depression, and psychological distress, among youth aged 16–25. They found significant associations between excessive social media use and poor mental health outcomes as well as between excessive social media use and poor sleep quality.[4]

One phenomenon that has been garnering attention since the start of the COVID-19 pandemic is the onset of "tic-like" attacks in people without established tic disorders.[5] For these new referrals, most cases were reported in adolescent girls and consist of motor and phonic tics or functional tics.[5] For example, Hull and Parnes describe 6 adolescent girls with new onset tic-like movements who all shared the common factor of exposure to a specific social media personality on TikTok before symptom onset.[6] There appeared to be no biological predisposition for the disorder such as a family history or childhood symptoms of tics.[6]

A striking outcome of the pandemic is the doubling of eating disorder admissions at children's hospitals across the country.[7] In response to this increase, the British Columbia (BC) government announced in June 2021 plans to invest $6.6 million to assist in virtual peer support and eating disorder services across the province.[8] A link between social media use and disordered eating behavior has been well researched. In 2017, Turner and Lefevre examined 680 social media users following health food accounts and assessed their orthorexia nervosa symptoms using a standardized questionnaire. They concluded that increased Instagram use was associated with a higher prevalence of orthorexia symptoms. TikTok was not included in this study.[9] However, Logrieco et al. examined this gap by identifying that even anti-pro-anorexia content on TikTok may paradoxically trigger harmful behaviors.[10]

Research has also shown the protective value of social media as a coping mechanism for anxiety during the pandemic. Cauberghe et al. conducted a survey amongst Belgian adolescents during lockdown, examining feelings of loneliness and anxiety and whether social media use would be helpful to cope with these feelings. In their study, they identified that loneliness had a greater negative impact than anxiety on adolescents' happiness levels. They also found that social media had a significantly positive effect on happiness level for adolescents dealing with anxious feelings, but not for those dealing with loneliness.[11] In this way, we can see that the use of social media may be helpful in select contexts.

Recommendations

Without a doubt, our digital world has a direct influence on our daily lives and requires careful management. One potential recommendation would be to reduce global screen time. Oberle et al. studied the relationship between recreational screen time and extracurricular participation against mental health symptoms in adolescents across British Columbia. The team established that participants who engaged in more extracurricular participation than screen time had an association with lower levels of anxiety and depressive symptoms among other outcomes. In contrast, screen time >2 hours a day was associated with higher levels of anxiety and depressive symptoms.[12] The study suggests that online social interactions in the midst of a pandemic do not necessarily provide the same benefits that may be accrued via face-to-face extracurricular activities.

Cunningham et al. conducted a meta-analysis which was the first of its kind to examine associations between depressive symptoms and time spent using social networking sites, intensity of social networking use, and problematic social networking use (determined by a high frequency of use with symptoms such as dependence, tolerance, and withdrawal of social media, assessed by questionnaires). Sixty-two studies were analyzed and the results suggest that to target depressive symptoms associated with social media use, interventions should target people who have patterns of problematic social networking use rather than people who spend a lot of time or browse with high intensity on social networking sites.[13] Given this information, a key recommendation in combating adverse mental health outcomes with social media use is to identify patterns of addictive and problematic social networking.

Hull and Parnes suggest that the spread of functional tics post-social media exposure is a possibility[6]. The studies that Tuner and Lefevre as well as Logrieco et al. conducted associate increased social media use with higher tendency towards eating disorders and harmful behaviours.[9,10] One recommendation is for health care providers to take a brief history of the social media usage of patients who present with functional tic disorders as well as patients who present with eating disorders to help delineate if it is playing a factor into the disease processes.

Conclusion

In healthcare, we must begin to acknowledge the impact of our daily interactions with technology on our mental wellbeing. One of the

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internet's oldest social networking platforms, Facebook, has been online for less than two decades, and yet, we are seeing the profound and pervasive impact social media use is having on daily life. With the recency of the global pandemic, we wondered what more there is to learn in the social media domain that will continue to evolve and be utilized daily. It brings into question the implications of further entrenching ourselves into our devices and the concept of living in a future of virtual reality. It presents itself with the enticing premise of staying "connected," but depending on the way we choose to operate our devices, it may come at the expense of a disconnect of our own mental wellbeing, or serve as a powerful aid in our toolbox of coping strategies. Therein lies an opportunity for further study to elucidate the mental health toll of the social media scroll.

Conflict of interest

The authors have no conflicts of interest to declare.

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An analysis of the family physician shortage in British Columbia

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Abstract

Due to a shortage of family physicians, many British Columbians do not have access to a family doctor. Compounding this deficit, the 2021 census reflects that British Columbia has experienced remarkable population growth since 2016. Further, more currently practicing family physicians are leaving their practices and fewer Canadian medical graduates (CMGs) are choosing to pursue family medicine. The government of British Columbia has recently announced significant changes to alleviate the current crisis. In this commentary, the reasons behind these trends, the implications of the government of British Columbia's recent announcements, and the possibility of further interventions are analyzed. These policies require a critical lens to assess whether they will adequately address the physician shortage and the challenges that are currently experienced by family physicians. It is possible that some proposed policies will not achieve their intentions, and some may even cause unintended harm. Moving forward, collaborative efforts between front-line physicians, professional organizations like the College of Family Physicians of Canada (CFPC), and provincial ministries of health are necessary to benefit patients within an appropriate timeframe.

Introduction

There is a widening gap between supply and demand that exists in healthcare, leaving one in five British Columbians without a family doctor.[1] Compounding this deficit, British Columbia is one of the fastest growing provinces in Canada with a population growth of slightly over 316,000 people since 2016.[2] For many newcomers, this growth represents a fresh start in a new province or a retirement in the Okanagan. However, questions exist about whether this population growth is sustainable. While this is a complex issue and cannot be attributed to a single factor, the unavailability of family doctors could be partially explained by a wavering interest in family medicine residencies by Canadian medical graduates (CMGs). In the 2022 Canadian Resident Matching Service (CaRMS) match, 30.7% of CMGs selected family medicine as their first-choice specialty.[3] This represents a decrease from 38.5% of CMGs choosing family medicine as their first-choice discipline in the 2015 cycle,[4] and is much further away from the goal of 45% set by the College of Family Physicians of Canada (CFPC).[5] Additionally, recent polling by the BC College of Family Physicians reflects that approximately 40% of British Columbians are worried their family doctors will retire or close their practices.[6] This is concerning because two and a half new physicians are required to replace each older physician who retires, according to the Canadian Medical Association Journal.[7] A crisis is developing. To find a cure, it is crucial to reflect on the reasons behind the statistics outlined above and what the province is currently doing to address the issue. In this commentary, the underlying reasons behind these trends, the implications of recent announcements by the government of British Columbia, and possible further interventions are analyzed.

A good place to begin is to address the decreased interest in family medicine as a first-choice discipline for CMGs. Across Canada, many residency spots in family medicine typically remain unfilled at the end of the match cycle,[8] but none of these unfilled seats were in British Columbia in 2022.[9] The government of BC has announced an addition of 40 seats in family medicine residency by 2024/2025, which is a good first step to increasing the supply of family physicians.[10] For this to be beneficial, the demand (CMGs entering family medicine) must fill the supplied positions since there are significant costs associated with physician-training resources.[11] Osborn et al. conducted a survey in 2017 among Canadian medical students regarding influencing factors when deciding between front-line residency programs and specialist residency programs.[12] Categories that positively influenced medical students towards choosing family medicine residencies included the work-life balance, the strong physician-patient relationships that could be formed, and the relatively short duration of the residency program (two years).[12] Unfortunately, negative perceptions of family medicine, such as lack of prestige among colleagues, along with misconceptions of incompetence and unimportance of family physicians have been perpetuated at multiple levels of medical education (medical students, residents, fellows, and faculty).[13] Further, research in Canada performed in 1998 has detailed interactions involving professional conflict between family physicians and specialists, particularly with respect to the mutual educational benefit of each party.[14] It has been suggested that this may negatively influence trainees' decisions to pursue a career in family medicine.[14] However, more recent cohort studies performed in 2021 contradict these findings and reveal the feeling among family medicine residents that they are valued by specialists in other fields.[13] This suggests that the CFPC and faculties of medicine across Canada have effectively modified the hidden curriculums of medical schools, which are the underlying themes that subtly contribute to medical education apart from the formal curriculums.[13,15] This is thought to have improved perspectives on family medicine, since perceptions of a career can be formed by experiences in medical school and the learning environment where a student is trained.[13,15] Therefore, positive experiences in medical school generate an eagerness to further explore a specialty. Moving forward, a positive lens is essential to encourage students to pursue family medicine.

The education of new family physicians is equally as important as retaining practicing family physicians. Why are family physicians considering leaving their practices early for retirement or to preferentially work as hospitalists? Hospitalists are physicians who primarily focus on the medical care of hospitalized patients, and most hospitalists are trained in family medicine.[16] As full-time hospitalists may aggravate existing shortages of family physicians, the CFPC actively promotes family physician hospitalists to also spend part of their time in community practice.[17] According to a news release by the CFPC, insufficient administrative support and stagnant payment models are making it more difficult for family physicians to maintain private practices.[18] Further, some family physicians are choosing to retire earlier than expected, in part due to burnout suffered during the COVID-19

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pandemic.[19,20] Since the beginning of the pandemic, an estimated 170,000 patients across Canada were enrolled with retiring physicians and forced to find a new family doctor.[19] Reasons behind the early retirements include concerns for a physician's own health (since most of this retiring cohort were over the age of 75) and reduced revenue due to the increased costs of infection control measures and the decrease in appointments during the height of the pandemic.[19] These effects were most strongly experienced by physicians in fee-for-service models, where physicians are compensated for each patient they attend to, stimulating increased advocacy for implementing a modernized payment model.[21] This is an issue that the government of British Columbia has attempted to target with upcoming changes. With fewer family physicians feeling that the government perceives their profession as essential to today's healthcare system,[13] the new payment model to be implemented in British Columbia promises to compensate physicians more adequately in appreciation of "the value of longitudinal, relationship-based care."[22] The new model compensates for time spent with patients, number of patients attended to, the size of the practice, the complexity of the patients in the practice, administrative work done by family physicians, and indirect patient care.[22] Hopefully, these changes will not only make family practices more sustainable for currently practicing physicians, but also influence medical students to pursue family medicine.

It will take time for the supply of family physicians to meet the demand of British Columbians since training medical students and changing stigmas surrounding family medicine could take many years. In the meantime, there are additional measures that could be examined to improve the accessibility of front-line care in the short and long-term. Some of these measures have already been announced by the BC government, alongside the proposed changes to the payment model for family physicians in British Columbia. These include giving pharmacists the power to alter and renew prescriptions for a broader range of drugs and conditions.[10] Pharmacists will also be enabled to administer a wider range of drugs either by injection or intranasally.[10] Beyond this, the government is trying to extend the validity of prescriptions to two years so that people with mental health and substance-use disorders will be able to acquire essential medications without the need to visit a physician, especially since many do not have access to a primary care provider.[10] One concern is that this policy could inadvertently harm people who suffer from mental illness and addiction. Since patients would be capable of accessing prescribed medications without the need to consult a physician before renewing their prescriptions, they might not receive adequate care from a holistic perspective. A holistic perspective of medicine extends beyond the medications a patient takes and considers the psychological, familial, societal, ethical, and spiritual dimensions of health.[23] Such a policy might limit opportunities for physicians to re-evaluate the effectiveness of patients' treatment plans, which are highly individualistic for people who suffer from mental illnesses such as mood and anxiety disorders.[24] This creates opportunity for inappropriate prescription in patients who are not responding well to their current medications, but continue to renew their prescriptions without speaking with their family doctors. This can have significant adverse effects, particularly in cases where antidepressants are in long-term use.[25]

The Ministry of Health is also seeking to enable pharmacists to prescribe for minor ailments and contraception.[10] Due to this, is there a concern of scope creep for family physicians? Scope creep is the term used when the traditional boundaries of healthcare professions are expanded and overlap with the responsibilities of other healthcare professions, namely medical doctors. In previous analyses of scope creep between nurse practitioners and family physicians, scope creep has been identified as a concern for some family doctors.[26] Dr. Bourgeois-Law makes a compelling argument that the integration of allied health professionals allows patients to benefit, particularly since some allied health professionals are more willing to work in rural and underserved regions compared to family physicians.[26] Perhaps this research could be applied to the current situation, where pharmacists or nurse practitioners can manage patients that are incapable of accessing family physicians, a harsh reality for many British Columbians. However, according to the BC College of Family Physicians, experiences with family physicians are more satisfying to surveyed patients (7.3/10) than experiences with nurse practitioners (6.7/10) and walk-in clinics (6.5/10).[6] These findings reflect that longitudinal care by a family physician is preferred to care from allied health professionals or walk-in clinics when possible, but relying on allied health professionals to improve the accessibility of healthcare in rural communities, prevent illness, and manage chronic and episodic diseases is an immediate action that can benefit patients in the long-term.[27] Therefore, expanding the role of pharmacists in British Columbia is a change that prioritizes population health and will hopefully confer similar benefits to those that nurse practitioners contribute.

The changes discussed above are good first steps to addressing the current inaccessibility of family physicians, but additional measures could be considered to ensure that the response is adequate to meet the needs of British Columbians. It may seem like a viable option to streamline the process for international medical graduates (IMGs) to become licensed and practice in Canada. This could effectively increase the supply of physicians amid the current physician shortage. According to a focus group consisting of physicians, residents, and other healthcare professionals, IMGs are rich sources of clinical and cultural knowledge with experience and a quality education.[28] However, there are some challenges to integrating foreign-born IMGs into the landscape of Canadian healthcare. In particular, the focus group mentioned communication skills (nuances of the English language; tone of speech; subtle communication cues), differences in clinical practice (uncommon diagnoses; care of the opposite sex; attending to mental health concerns), differences in medical education and principles (patient-centered care; ethical principles; unease during feedback), and cultural differences (gender roles; gender equality; personal space and boundaries) as areas that must be improved upon to treat patients in the Canadian medical system.[28] One population not considered by the focus group were Canadians who traveled abroad for medical school but are seeking to return to Canada to practice medicine. Currently, Canadian-born IMGs face significant red-tape when it comes to returning to their home country. This includes multiple board examinations, competition with CMGs for residency seats that are preferentially offered to CMGs, Return-of-Service (ROS) agreements, and a lack of preference for Canadian-born IMGs over foreign-born IMGs.[29] Residency positions are a limited resource due to the financial constraints on physician training that limit the number of seats that can be offered.[29] However, strategic IMGs who apply for residency in Canada are encouraged to apply for family medicine to increase their likelihood of matching.[29] For physicians who completed their medical training and residency in another country prior to immigrating to Canada, provisional licenses are sometimes provided by the government to meet immediate needs

in locations that suffer from a physician shortage.[30] Under provisional licensure, internationally trained physicians can practice medicine under certain restrictions, since they technically have not completed all certification and regulatory requirements to obtain independent licensure yet.[31] Unfortunately, once these physicians complete their Canadian licensing exams, they often decide to leave the underserved area that they previously practiced in under provisional licensure. For example, in studies performed between 1995 and 1999, Newfoundland and Labrador only retained 7% of their IMGs over a ten-year period.[32] However, more recent data suggest this trend is beginning to reverse direction; more fully licensed IMGs are continuing to practice in the same locations that they were placed in when working under the constraints of the provisional license.[32] Nevertheless, this approach may not generate as much long-term positive change as it may have initially seemed to if it were implemented by underserviced communities in British Columbia. Further, opening British Columbia's doors to more provisionally licensed IMGs could have a detrimental impact on neighbouring provinces since large proportions of newly licensed IMGs leave Newfoundland and Labrador, Nova Scotia, Manitoba, and Saskatchewan in favour of Ontario, Alberta, or British Columbia.[32] Therefore, because of the distribution of licensed IMGs when they are given the choice, provinces that receive more IMG physicians would benefit at the expense of provinces that struggle to retain their physicians. Due to this, loosening restrictions on IMGs could exacerbate disparities in healthcare between Canadian provinces. In summary, there are significant financial and systemic challenges to hiring more IMGs to increase the supply of family physicians, but it presents a reserve of medical expertise that may be relied on under provisional licensure to alleviate the current shortage of family physicians.

There is more work to be done to secure a promising future for family medicine. Some interesting concepts proposed recently include implementing family medicine-specific streams in undergraduate medical education programs[33] and extending the length of family medicine residencies from two years to three to better prepare family physicians to serve today's population.[34] Queen's University will be the first undergraduate medical program in Canada to offer the family medicine-specific stream of admission, allocating 30 additional seats to the new stream in fall 2023.[33] The details of this program are still in the early stages of development, and further research will be needed to determine the effect of this program over time.[33] The CFPC is also planning to extend the length of family medicine residencies from two years to three, citing that necessary curriculum expansions which discuss geriatric care, technology, mental health and addiction, racism and colonialism, among other topics, cannot be adequately covered within the current two-year family medicine residency.[35] However, some physicians are concerned that lengthening training could worsen shortages in both family and emergency medicine and that these changes will require additional funding from provincial ministries of health.[35]

The circumstances of Canada's changing demographic, outdated healthcare models that fail to support family practice, and fallout from the COVID-19 pandemic have created the perfect storm in which many Canadians are unable to access a family physician. The government of British Columbia has been proactive in their approach to today's crisis by recognizing that changes are required and has thankfully responded to the pleas of family physicians. As a medical student, recognizing the value of family medicine in the context of Canada's changing healthcare ecosystem is fundamental to medical education regardless of which specialty one may choose in the future.

Conflict of interest

The authors have no conflicts of interest to declare.

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An interview with Dr. Rybicki: Implementation of integrated clinical 3D printing labs in hospitals

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Abstract

As technology becomes increasingly central to improved function and quality of life, Canadian healthcare must begin to prioritize precision and personalized medicine. The implementation of hospital-based, multi-departmental, 3D clinical printing programs across major Canadian hospitals can revolutionize how doctors engage in surgical planning, prosthesis development, and medical education. In this article, we learn about the Ottawa Hospital's 3D printing program from Dr. Rybicki, the former Chief of Medical Imaging at The Ottawa Hospital and Chair of the Department of Radiology at the University of Ottawa. We discuss expansion and implementation of similar programs in other Canadian hospitals.

Hospital-based 3D printing technologies are the new wave in healthcare and are currently being heralded forward by the United States. 3D printing involves creating printable layers using models, such as computed tomography (CT) scans. Thousands of 2D layers are then printed to make 3D objects. Clinical applications include complex surgical planning beyond cross-sectional imaging, medical device printing, and clinician education and training. Canada has a rich history of adopting these technologies, with an example being Dr. Shi-Joon Yoo creating the congenital heart disease 3D printing program at the Hospital for Sick Children in Toronto.

The Food and Drug Administration has defined three potential scenarios for 3D printing within healthcare facilities.[1] 3D Printing Medical Device Production Systems (MDPS) are kits from the traditional manufacturer with specific instructions, materials, and equipment to 3D print medical devices. Scenario 1 refers to healthcare facilities using MDPS to 3D print the device, while traditional manufacturers are responsible for designing the MDPS and complying with regulatory requirements. Scenario 2 states development, production, and regulatory requirement compliance is by a "traditional" manufacturer, who is co-located in the hospital. In Scenario 3, the healthcare facility would replace a traditional manufacturer in all aspects, not using the pre-designed MDPS and allowing for greater creativity. Health Canada will most likely adopt a similar strategy as they released a guidance document for manufacturers in 2019 which aligns with many of the FDA's points.

Figure 1. Drs. Leonid Chepelev (left) and Adnan Sheikh (right), holding a full scale anatomic model of the pelvis 3D printed at The Ottawa Hospital. This model was used for planning a patient with traumatic injury requiring reconstruction, photo from May 2017.

Dr. Rybicki is an internationally-celebrated cardiovascular radiologist and clinical 3D printing researcher. With Dr. Yoo as his role model, he helped co-found the Ottawa Hospital's first comprehensive fully integrated, medical 3D printing lab and program within the Department of Medical Imaging in 2016 with fellow radiologists, Dr. Adnan Sheikh and Dr. Leonid Chepelev (Figure 1). In 2015, Dr. Rybicki founded the 3D Printing Special Interest Group in the Radiological Society of North America and became the Editor-in-Chief of the peer-reviewed journal, 3D Printing in Medicine.[2] The journal is the leading publication in the field with impactful papers on COVID-19,[3,4] evaluations of new technology,[5] and workflows for augmented and virtual reality.[6,7]

Dr. Rybicki recently published an editorial titled: The impact of regulation, reimbursement, and research on the value of 3D printing and other 3D procedures in medicine.[8] He highlights his personal opinions on the changing 3D printing regulation in healthcare facilities and the need to balance safety, efficacy, and value. He explains that 3D visualization is often seen as time-consuming and reserved for tough cases. However, this would be an oversimplification of its use. Instead, healthcare facilities must determine the value of in-hospital 3D printing services using a Quality to Cost ratio. Quality comprises of safety, provider usefulness, and patient benefit. As the use of simple 3D printing services continues to expand in North America, we will see lower cost individualized devices, increased accessibility, and more effective operations using customized models. The effectiveness is evidenced by a study conducted at Harvard Medical School, where 3D models were superior to imaging and 3D visualization for surgical approach and resectability of complex thoracic tumors.[9] These trends in 3D printing would increase the Quality to Cost ratio. As such, it is important to understand the growing utility and barriers to the implementation of 3D printing services in healthcare.

In an interview with Dr. Rybicki, we discussed the journey of starting the Ottawa Hospital's 3D printing program, including his inspiration, current utilities of the technology, barriers to implementation, and advice for other hospitals.

Tell us about what inspired you to start an integrated 3D Printing Program at the Ottawa Hospital, the first of its kind in Canada.

Although I am currently a Professor of Clinical Radiology at the University of Cincinnati, I was the Chair of the Department of Radiology at the University of Ottawa in 2016. 3D printing services as a fully functioning orderable was not available in Canada at the time. Coming into my role, I brought my expertise in this area from my experiences working at Harvard Medical School and the Massachusetts Institute of Technology. It was natural to want to fill the gap in patient care and expand our clinical services, given my experience in American hospitals. Having all aspects of the manufacturing process completed in the hospital allowed for faster printing, more cost-effective devices, and more readily available personalized devices. It also led to students

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learning to use the technology and close collaboration between radiology and various surgical disciplines.

What types of parts did you 3D print at the Ottawa Hospital?

The group 3D printed all varieties of anatomic models for teaching and education, customized prostheses, models for surgical and procedural planning (Figure 2), and surgical guides. We printed models and guides for maxillofacial and cardiac procedures, tumor resection, and other complex bone reconstructions. Over time, we saw the program expand to involve many more surgical disciplines with increasingly creative applications and more technologically adept staff. I was not on as staff at the Ottawa Hospital during the COVID-19 pandemic, but I know that Drs. Chepelev and Sheikh printed multiple devices that were limited in the supply chain.[10]

Figure 2. 3D printed anatomic model of the aortic annulus looking into the left ventricle in a patient being considered for percutaneous repair of the aortic valve. The white rigid material emulates calcification. The clear, flexible material emulates the myocardium and aorta. Image was 3D printed at The Ottawa Hospital and used for intervention at The Ottawa Heart Institute.

Tell us about some of the barriers to implementing in-house 3D printing programs at a medical center.

The biggest barrier to starting this program was the cost. We were fortunate to receive funding from two generous donors. Even as a small-scale operation, the costs were significant, needing printers, materials, software, and human resources.[11] My role as Chief of Medical Imaging enabled me to allocate resources in the interest of eastern Ontario patients. We were able to set up the laboratory in six months. We trained University of Ottawa students to manipulate the software and produce medical devices.

Financing and training individuals will be a barrier to implementation in other hospitals, especially if the physician spearheading the initiative cannot lobby for system-wide changes. Medical 3D printing services not being reimbursed or having billable codes is another large financial roadblock to implementation across large hospitals in Canada. Significant time and effort are put into the clinical consultation, device design, software workflow, and compliance to regulation. While the direct impact on the "bottom line" reimbursement may not be obvious, it is there. I believe that medical 3D printing pays for itself and pays forward by enabling procedures that would not be possible and by reducing operative room costs from shorter procedure times.[12]

What are the main takeaways other Canadian hospitals can get from the success of the Ottawa Hospital 3D printing program?

You can have a fully integrated radiology department and provide that extra level of service for patients. A lot of previously near impossible complex surgeries become feasible. It is enormously helpful for surgical planning, student education, personalized guides, and devices. The scope for 3D printing applications is limitless and we are only skimming the surface of its use in medicine. For any department heads thinking about implementation of these services to their hospital, I recommend reading through the 3D Printing in Medicine journal.[2] There are dozens of articles on 3D printing applications to various clinical situations and infrastructure development for hospital-based 3D printing facilities. I encourage medical students and residents to read about these technologies and practice working with them as I expect increased clinical utility in the several decades to come.

In conclusion, while there are many roadblocks to implementing in-hospital 3D printing services, the many benefits to provider capabilities and patient care must be considered. Increased introduction of these technologies will mitigate several of these barriers while lowering healthcare costs and improving wait times. Canadian hospitals should look to how they can get involved as 3D printing technologies continue to grow and explore new frontiers such as bioprinting cellular matrixes for transplants and grafts.

Conflict of interest

The authors have no conflicts of interest to declare.

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Healthcare implications to Canada's aging population

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Abstract

The United Nations Sustainable Development Goals (SDGs) are a global call to action to achieve peace and prosperity for people and the planet by 2030 and to ensure that no one is left behind. Notably, the third goal of the 17 objectives is to achieve good health and well-being for all individuals at all ages. With this goal in mind, we highlight the importance of carefully considering the changing healthcare needs of our growing population in Canada. The increase in life expectancy coupled with the increasing age of the baby-boomer generation means that our healthcare system will face new challenges in the coming years. More research is needed to fully understand the healthcare needs of this older adult population who have or will soon reach 65 years of age. Herein we comment on the impact of an aging population, provide reasons for challenges, and propose necessary solutions.

Aging Canadians

The age of Canada's population has been rising for decades. This trend will continue as the baby boomer generation (aged 56–75 as of 2022) continues to age. This growth is also due to a change in the Canadian life expectancy which has increased by almost 7 years since 1980.[1] However, an increase in life expectancy does not necessarily accompany an improvement in older adult health outcomes.[2] Since advanced age is associated with increased morbidity, there will be a greater demand for healthcare services and associated healthcare costs. The 2021 Census reports more than 800,000 people aged 85 and older living in Canada which is double the value two decades ago.[1] It is expected that this will increase as baby boomers reach this age demographic.

As a member state of the United Nations (UN), Canada is committed to taking action towards the achievement of the UN Sustainable Development Goals by 2030. The third goal is to achieve "good health and well-being for all at all ages", which includes Canada's aging population. As such, the healthcare needs of the baby boomer population must be considered and prioritized as more of these individuals reach age 65 and older.[3] We must continually monitor and evaluate programs, policies, and interventions that are aligned with this framework such that appropriate considerations are made for our aging citizens.[4] In this commentary, we describe the impact of age on the healthcare system, the needs of baby boomers, and the current and future solutions.

Impact on the healthcare system

The healthcare costs due to an aging society occurs from the combination of increased morbidity and the cost of diseases associated with advanced age.[5] In 2013, over 44% of provincial and territorial health care budgets were allocated to support the needs of Canadians aged 65 and older.[6] Moreover, this value increases with each age group. In 2017, Canadians aged 85–89 cost triple the average per-capita dollar healthcare expenditure by provincial and territorial governments.[7] In terms of future projections, Globerman S. demonstrates that the share of total healthcare expenditures on those aged 65 and over will be 60.3% in comparison to 45.7% in 2019.[7] Notwithstanding, he highlights that the impact of inflation and healthcare technology will likely hold greater significance as determinants of healthcare costs but the contributions of the aging population remain non-trivial. In a recent healthcare utilization cohort study conducted in Ontario, researchers found that the percentage of the population admitted to the hospital has declined by 25% over the past 25 years. However, there is still a higher total number of admitted patients which is attributed to the increase in population.[8] Similarly, they noted that the percent of the population admitted to the Intensive Care Unit (ICU) was relatively unchanged but there was an increase in the total number of ICU patients. While young adults accounted for the greatest increase in emergency department visits, adults over the age of 50 accounted for the greater volume of inpatient resource utilization.[8] This affirms the need for resource allocation that supports the growing number of people over the age of 65.

In addition to rising expenditures, it cannot be assumed that the baby boomer generation will have the same needs as the previous generations. This population is more demographically diverse which will inevitably impact how they interact with and use healthcare services.[9] For instance, a study in 2016 found that younger baby boomers utilize specialist care more than primary care in contrast to older baby boomers. This difference was attributed to increased comorbidities in the younger cohort.[10] Baby boomers, as a generation, need a responsive healthcare system that integrates care from various healthcare professionals (e.g., physicians, pharmacists, social workers, and physiotherapists) to address their multiple chronic health issues.[6] Furthermore, they have had fewer children than their parents which will decrease the number of available family caregivers to support their complex care needs.[11] This underscores the need for other types of caregivers or aids to assist in retention of their independence. The latter requires improved health literacy so that they can take control of personal decision making and in turn manage their own health. This is especially important considering that baby boomers take on the burden of most lifestyle-related chronic illnesses. According to an Australian study, baby boomers are more educated than the previous generations and report increased internet usage which has been shown to improve health literacy. However, the study reports that they lack confidence in differentiating between quality of sources despite their ability to find health information on the internet.[12] More research is needed to garner a complete picture of health literacy in this population. Overall, it is evident that there will be a greater demand for healthcare services, which is exacerbated by increased retirement in healthcare occupations, poor support provided to care providers, short-staffing, inadequate pay, and the extreme COVID-19-related burnout and burden on physicians and nurses during the pandemic.[9,13]

A vulnerable population

To effectively address the impact of an aging population on our healthcare systems, we need a fundamental understanding of the challenges this population faces. In Canada, older adults have a high prevalence of chronic diseases in comparison to younger age groups. This includes

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hypertension, periodontal disease, osteoarthritis, heart disease, diabetes, osteoporosis, cancer, chronic obstructive pulmonary disease (COPD), asthma, and mood and anxiety disorders.[4,14] Notably, 73% of individuals over the age of 65 have at least one of these 10 chronic diseases.[15] This is in addition to normal aging processes, including sensory changes (e.g., hearing or vision loss), alterations in muscles strength and fat percentage, urologic changes, and immune decline.[14] Physical function may also become impaired leading to decreased walking speed, physical disability, falls, and frailty.[14] Frailty increases an individual's vulnerability to stressors leading to cognitive impairment, while disabilities may impede an individual's ability to contribute to their family and society.[16] Psychological and cognitive function are impacted by diseases such as dementia and declining mental health. Data currently show a decrease in new cases of dementia in the 65+ age group, yet it is expected that this will rise as the population continues to age.[17]

The poverty rate for seniors in Canada aged 65 and over is 4.7% which is lower than all other age groups. This is in part due to pension plans and the Guaranteed Income Supplement afforded to low-income seniors.[18] These plans are essential financial infrastructure put in place by the government that allow seniors to retire while maintaining income security and avoiding poverty and marginalization. However, it is also important to provide seniors with the opportunity to continue working should they choose to do so. This involves dismantling existing attitudes of ageism and ableism that exist in mainstream society.[19,20] These can be particularly pervasive in the workplace where employers are reluctant to hire older adults due to beliefs that they are difficult to train.[19] This discriminatory treatment based on age excludes them from the opportunity to learn and the ability to work.[19] Some seniors are also at risk of experiencing abuse (where abuse is defined as any action or inaction that may cause harm) such as those who are isolated or dependent on others.[21] Experiencing abuse further places them at risk to be re-victimized by increasing their likelihood of developing more health problems.[21]

A united solution

The Government of Canada has developed a comprehensive set of steps to support aging Canadians such as establishing information sessions to support health literacy and creating affordable housing to help seniors age in place.[22] While it is important to recognize the work that has been done, it is also important to highlight that more research is needed to understand the unique needs of baby boomers. Currently, we must continue to support healthy aging, improve equitable access to healthcare services, transform discriminatory attitudes, and establish appropriate geriatric training for all healthcare professionals.[19] We need healthcare measures that encourage healthy living through preventative approaches while also improving access to pharmacological interventions that help manage chronic diseases. The former can be achieved through healthy eating and regular exercise which are linked to increased life expectancy and reduction in incidence of age-related disease.[5] The reduction of morbidity through lifestyle changes may also prevent an increase in public healthcare costs.

Incorporating technology, such as the increasingly used virtual and telehealth, has improved access to healthcare. Wearable devices are used to monitor chronic conditions, track sleep disturbances, survey motion in frail patients while allowing the patient to remain in their home environment and simultaneously decreasing the burden on healthcare systems.[23] While wearable devices and telemedicine have improved adherence to medical advice (i.e., treatment plans) in the older population, mobile health apps have had the opposite effect.[23] Design considerations must be made to ensure that cognition, physical ability, and perception of older adults are considered to prevent additional barriers to access.[24]

The financial security of older adults also influences their ability to access healthcare. Consequently, appropriate policies and social protections should be developed to support Canadians over the age of 65 who wish to remain in the workforce while also fostering a change in societal attitudes to address age bias in the workforce.[19] Lastly, the Canadian Medical Association recommends an increase in geriatric training with respect to curricula in medical schools, licensure, continuing education, and specializations.[9,25] In the coming years, Canada will continue to experience changes in the healthcare landscape, and it is critical we are prepared to provide good health and well-being for all. By collectively addressing the evolving healthcare needs of our population we will ensure that no one, including older Canadians, will be left behind.

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Partnering with patients and the public for better healthcare: What can medical students do?

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Abstract

"Bringing Patients and Society Back into the Social Accountability of a Medical School" is a recently completed project that highlighted eight evidence-informed principles to help Canadian medical schools engage directly with members of the public and patients for medical education. In this article, the authors highlight the two principles most actionable by students (Co-production and Partnership/Shared Decision-Making) and reflect on their experiences in the project as medical students. A novel recommendation for improving patient and public engagement from a student's lens is included.

Introduction

"Bringing Patients and Society Back into the Social Accountability of a Medical School" is a recently completed project that will help Canadian medical schools engage directly with members of the public and patients. One outcome of the project was a set of eight evidence-informed guiding principles for the sustainable engagement of patients and the public in the delivery of medical education (Table 1). Students have a crucial role in integrating these principles into their clinical interactions and in student-led groups. Ultimately, increased knowledge of engaging patients will help medical students in their future roles as advocates and collaborators.

#	Principle name	Summary
1	Accountability	Includes transparency, shared outcomes, feedback, maintaining relationships
2	Inclusion	People with diverse perspectives are sought and invited to participate. Engagement processes are accessible.
3	Reciprocity	Relationships are mutually beneficial, based on trust and mutual respect.
4	Partnership/Shared Decision Making	University and community partners have equal voices and share power to make decisions.
5	Co-Production	University and community partners work together to co-develop and co-design engagement processes and activities.
6	Two-Way Communication	Communication is open and honest, with clear expectations on both sides.
7	Supports	Community partners receive the support and information they need to participate fully.
8	Different Levels of Engagement	There are diverse opportunities for the community to engage in medical education (from classroom to committee).

Table. 1 Summary of the 8 evidence-informed principles for patient/public engagement.[4]

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The two most actionable principles by students are co-production and partnership/shared decision-making. In this article, we demonstrate how these principles can apply to medical students looking to improve their engagement with patients and the public.

Key principles

Co-Production

Co-production means university and community partners working together to co-develop and co-design engagement processes and activities. For students, this principle is relevant to student-led groups that interface with patients or members of the public. For example, groups and clubs that focus on women's/men's health, refugee health, political advocacy, Indigenous health, or LGBTQ2+ health. Here, there is a great opportunity to enrich these initiatives by including people with lived experience as partners.

Applying the principle of co-production, we encourage student leaders to ask how often members of the target populations are involved in the development/action of those clubs. Increased involvement could help strengthen the impact of student-led clubs. Committing to co-production could lead to new ideas and initiatives that would provide more valuable opportunities for medical students and members of the public to learn together.

Partnership/Shared Decision-Making

Shared decision-making (SDM) is another guiding principle of engagement that is relevant to students. SDM has been described as an antidote to paternalistic styles of medicine, as the preferred model of care from patient perspectives, and even as a method to improve medication compliance and reduce inappropriate use.[1-3] The central characteristic of SDM is the offering of choice; SDM involves providing patients with choices, which is essential for decision-making, and requires practitioners to understand patient preferences.[2]

In the development of a medical learner, SDM is often considered a fourth-year or resident-level skill. As learners, we are in a unique space to practice collaboration and develop those skills. For instance, we are often given more time for individual assessments so that we can have partnership-building discussions which may feel impractical to those with larger patient loads. Trying to practice SDM can be a tool for our clinical learning. By striving to provide patients with choices, we push ourselves to think of multiple management plans and analyze different considerations.

For trainees more focused on information-gathering and diagnosis, as opposed to developing management plans, exploring values and expectations can be a powerful way to practice SDM. Simply asking "what are your thoughts about how we can help" can be an entry point to collaborative discussion – and may even impress your preceptors along

the way.

Reflections

K.O.

After hearing feedback from patients/members of the public directly, I found it uplifting how passionate and interested the participants were in getting involved with the medical school. It was common for the participants to state they were interested in multiple levels of involvement, from directly working with students to co-creating parts of the curriculum. I realized how important authentic engagement with the medical school can be for members of the public, and the critical role they play in the development of our medical curriculum.

Unfortunately, many of the participants experienced challenges when trying to engage with medical schools, leading to many opportunities for engagement that are not being utilized fully. These ranged from administrative hurdles to feelings of tokenism and non-authentic engagement. Working with patients and the public is crucial, and we should act to remove the barriers to their engagement.

J.W.Y.

I became involved with this project as a fourth-year medical student, with little knowledge of the formal theory behind community engagement within medical education. However, this project was far from being a dry academic pursuit; I was thrilled to discover it was one based on connections and relationship-building. I have learned so much over the last year, which I owe almost entirely to the inspiring people I worked alongside and spoke to throughout the process. In many ways, being involved in this project has shown me the humanistic ways in which academic research can be conducted.

Conclusions and recommendations

In conclusion, we propose an actionable, structural change that would help align UBC medical students with the principles and goals outlined in this project's summary report.[4] Specifically, we would like to address the recommendations to better prepare patients/public in their engagement roles and to develop mechanisms by which patients/public know their contributions are valued.

Community partners play an important role in UBC medical education as guest lecturers, clinical skills patients, or even clinical skills teachers. However, the interaction between these partners and the student body is usually limited to the teaching session itself, and there are few ways to communicate appreciation once the session ends.

We propose the development of a new medical undegraduate society (MUS) position, which we will call "Engagement Liaisons", to help foster safer and more fulfilling experiences for those who volunteer their time to help medical learners. For example, when patients or community members present as guest lecturers, Engagement Liaisons could meet them beforehand to explain the context of what students have been learning, answer any questions they have, and generally be a familiar face in the audience during their presentation. Afterward, Engagement Liaisons could collect messages or 'thank you' notes from the student body and pass those along to the presenter. By building bridges between patients and students, the proposed "Engagement Liaison" position could have the potential to create opportunities for co-production and shared decision-making, potentially paving the way for a more patient-centered curriculum in a way that better serves the needs of patients and communities. While the proposed "Engagement Liaison" positions are an idea for potential future development and not a formal proposal to the MUS at this time, this is just one of the many changes which could be made. We hope this example inspires readers to brainstorm and stimulates new ideas of their own to integrate co-production and shared decision-making into medical education.

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Conflict of interest

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Child welfare in a changing country: A children's health perspective

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Abstract

Canada's foster care "system" has devolved over the past decades to rely increasingly on institutional and group settings as the number of foster families declines. Living in these short-term, formal environments, rather than family-based foster care, has been shown to have negative impacts on children's health. Children who enter foster care are already more likely to have chronic health conditions than their peers who remain with their families of origin. This commentary presents an argument for the centrality of the child welfare system as a social determinant of health. Canada needs a national child welfare strategy that is informed by communities and supported by healthcare practitioners.

Introduction

The 2021 Census marked the second-ever count of Canada's more than 42,000 children living in foster care.[1] As the country looks to the results of this estimation, it is clearer than ever that Canada needs a national child welfare strategy. The history of child welfare in Canada, which ranges from the injustice of residential schools to the silos of modern-day agencies, reveals a deep disinterest in the social environments that surround and raise our nation's children. For the sake of children's health and well-being, Canada needs to expressly prioritize a health strategy for children and youth in care.

Foster care: Snapshot of the present

The current system of fostering was designed in and for an era with one or both parent(s) working at home. This model fails to address the modern wages lost, emotional labour output, and social stigma associated with caregiving work. As social norms have changed, our child welfare system—currently siloed in province- and territory-specific legislation—has not, resulting in a critical lack of family environments for children in foster care.[2] This quiet crisis is affecting the health status and medical care of children and adolescents across the country.

The number of foster families has been declining in all provinces in Canada.[2] Foster care, the placement of a child in the home of someone who is not the child's parent and who is compensated for care provided, was a 1960s-era evolution from the orphanages and institutions that previously housed children whose parents could not provide care.[3] At this time, many provinces were also moving to deinstitutionalize persons with disabilities, who along with children in care, were in need of community placements.[3] At present, the child welfare legislations of most provinces include kinship, foster, and residential care facilities as options for children in care. Kinship care is placement with relatives other than parents. As kinship care is not formal adoption, it is often not financially compensated, leaving family members weighing the financial costs of caring for their loved ones.[4] Residential care facilities, which include "group homes," are facilities with paid staff that are more likely to house adolescents and those children with behavioural difficulties requiring professional support or a higher caregiver-to-child ratio.

These institutions were created to provide a home-like environment for children who had been removed from their homes. In recent years, however, there have not been enough in-home and residential care facility placements.[5] With more demand than supply, provinces are forced to place children and youth in hotels, motels, apartments, and other short-term lodgings, subcontracting human resources companies to staff them around the clock. Existing foster and group homes are asked to prepare for children that may fall outside their age and ability mandates.[5]

Impacts on child health

Short-term, ever-changing placements are patently deleterious to children's health. Children enter nonparental care with more health concerns than their counterparts living at home, with between 30-50% having a chronic medical condition.[6] Beal and Greiner's 2015 model of social antecedents of nonparental care and their contributions suggest three main contributors to the poor health of children entering care: poverty, parent availability, and safety.[6] Common medical problems at entry to care include asthma and respiratory conditions, developmental delays, and skin conditions.[7] Chronic medical conditions such as asthma can be challenging for families with consistent primary and emergency care access to manage; it is doubtful that children staying in hotels with rotating staff supervision are receiving the consistent care they need. More significant medical and behavioural needs have been found to contribute to placement breakdown and delayed reunification with parents, theorized to be due to the increased demands of caring for a child with medical or behavioural needs.[8] With 70% of Canadian children in care having a history of behavioural or mental health treatment, compared to 17–22% of children in the general population,[9] this high-needs group is the standard rather than the exception. Viewing these children as outliers contributes to a system ill-equipped to meet their needs.

The health risks faced by children in care are substantial and have been going unnoticed. Many are removed from an unsafe environment and thrust into a cycle of unstable placements. With a shortage of caregiving environments, children can be placed hundreds of kilometres from their home communities.[10] These vulnerable children, who are likely to have health comorbidities, may lose access to their primary care providers. As there is currently no policy regarding healthcare for children in care, they have no priority for access to primary care in their new or temporary communities. These children are at grave risk of slipping through the cracks.

Towards care of communities

To address the lack of in-home placements, foster families and kinship homes must be compensated in a manner that recognizes the value of creating healthy, well-adjusted, and resilient children, who will grow up to form the foundation of society. Involvement in the child welfare system is plainly a social determinant of health. Children with a history of interrupted attachment, unaddressed medical needs, and traumatic experiences require a health strategy that integrates justice, education, and healthcare. A recent commission published in The Lancet Child & Adolescent Health recommends that national-level policies begin with a detailed stakeholder analysis of parties that hold influence over the country's child welfare system.[11] From there, thorough data on the

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current system must be collected, and barriers to change should be identified.[11] As healthcare practitioners, it is difficult to provide evidence-based care without evidence. Therefore, it is imperative to advocate for a focus on the health of children in care, which will bring this evidence to light. If Canada intends to prioritize the health of children in foster care, our fragmented care system must be aligned under the leadership of a national strategy.

Conflict of interest

The authors have no conflicts of interest to declare.

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Vaccines for opioid use disorder: A promising treatment in the fight against the opioid crisis?

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Lauren Gorfinkel's article published in the fall 2021 issue of the UBCMJ presented a novel pharmaceutical approach in the management of cocaine use disorder.[1] Gorfinkel highlights the need for preventative measures given that stimulant-related hospitalizations have risen sharply, especially in the context of the coronavirus disease 2019 (COVID-19) pandemic.[1] Additionally, stimulants are increasingly implicated in fatal overdoses.[2]

As of March 2022, the opioid crisis has resulted in over 6,000 deaths in British Columbia (BC) since it was declared a public health emergency in April 2016.[3] The COVID-19 pandemic has further escalated the crisis with an alarming 95% increase in apparent opioid toxicity deaths in the second year (2020) of the COVID-19 pandemic compared to the first year (2019), due in large part to illicit fentanyl.[4] As the death toll continues to climb, it is worth considering the applicability of vaccinations towards managing opioid use disorder (OUD).

According to the BC Center for Disease Control, harm reduction services in BC include take home naloxone kits, opioid agonist therapy, and supervised consumption sites.[5] Opioid vaccines could be a valuable harm reduction tool and an intervention for those who have struggled to control substance usage with conventional treatments. Opioid vaccines offer long-term protection, low abuse potential, limited drug-drug interactions, and compatibility with other opioid therapies.[6] Furthermore, opioid vaccines do not interact with endogenous opioids or their receptors.[6]

Research into opioid vaccines has yielded optimistic findings. A recent study evaluated vaccines containing antibodies with affinity for fentanyl-contaminated heroin in the peripheral circulation, thereby preventing the opioids from accessing the central nervous system.[7] Another study tested a bivalent vaccine capable of binding and neutralizing both heroin and fentanyl in the circulatory system.[8] While these treatments have shown promise in animal models, clinical trials in humans have yet to demonstrate success.[9] Another concern is the inability of the vaccine to target structurally different opioids.[6,10]

Although opioid vaccines are in early stages of development, they have the potential to be novel treatments for OUD. Some challenges to consider include cost of implementation, vaccine hesitancy, and vaccine side effects. Animal trials have thus far demonstrated a good safety profile, long-term protection, and lack of abuse liability.[6] Once efficacy is demonstrated in humans, opioid vaccines may drastically affect the course of a growing crisis.

Conflict of interest

The authors have no conflicts of interest to declare.

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The struggle continues: How the Indigenous peoples of Canada have fared through the pandemic

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The Indigenous peoples of Canada have historically faced healthcare inequities. Colonization and colonial healthcare policies have been noted as having substantial negative impacts on the health of Indigenous people.[1] Indeed, over the course of European colonization, public health policies were used to further colonist agendas, for instance, when Indigenous people were removed from their communities and sent for treatment at Indian hospitals.[2] Decades later, there has been a concerted effort to highlight these atrocities and promote reconciliation through the Truth and Reconciliation Commission (TRC). It has been seven years since the TRC published its 94 calls to action, of which seven (calls 18 to 24) are related to health.[3] An independent review, however, has found no progress on these seven calls in the last several years.[4] As we approach the two year mark of the COVID-19 pandemic, it is prudent to review the progress of reconciliation in Indigenous healthcare.

Firstly, the response to the COVID-19 pandemic by the Canadian government has failed to account for structural limitations of Indigenous communities. Social distancing and hygiene practices, for instance, have been endorsed by health organizations in preventing the spread of COVID-19. However, these measures do not take into account factors such as housing, access to food and water, income, poverty, overcrowding, and limited health infrastructure "which are often inadequate in Indigenous communities."[2] Many First Nations communities on reserves still lack access to clean water, and the housing crisis has left 23% of First Nations people living on-reserve in overcrowded housing.[5,6] As an already at-risk population with high rates of chronic illnesses, these social inequalities further increase risk of COVID-19 infection.[6] The situation is further exacerbated by underfunding as "measures to limit the spread of COVID-19 in First Nations communities in Canada represent less than one percent of the federal government's funding."[5,7] Consequently, Indigenous communities in Canada reported their highest infection rates ever with the arrival of the Omicron variant in January of this year (1596.7 per 100,000) after initially keeping rates of COVID-19 infection low in their communities last summer, 2021 (84.2 cases per 100,000).[4,8]

Apart from the structural inequalities, there continues to be inherent discrimination in the healthcare system.[2] In November of 2020, a 230 page report reviewing racism in BC's healthcare was released.[9] The report describes a disturbing pattern of racism in BC healthcare. Detailed are responses from almost 9000 individuals, 84% of which reported experiencing some form of discrimination while receiving healthcare. Additionally, over one-third of healthcare workers responded as having witnessed indigenous-specific racial discrimination. The experiences arise from stereotypes about drug seeking behaviour or intoxication which lead to medical mistakes, rough treatment, denial of service, or mismanagement. The report found that these experiences "limits access to medical treatment and negatively affects the health and wellness of Indigenous peoples in B.C".[9]

Evidently, there is further work to be done in Indigenous healthcare reconciliation.[10] The process begins with acknowledgement of the mistreatments and an understanding of the "culture as cure" concept, which suggests that "when health interventions in Indigenous communities are holistic and informed by cultural knowledge or local spiritual worldviews, they are more likely to achieve success and advance wellness."[10] For instance, vaccine hesitancy surrounding COVID-19 cannot be addressed without first acknowledging Canada's history with healthcare racism and experimentation. A vaccine clinic in Saskatoon responded to the cultural needs of the Indigenous population through offering smudging by Indigenous healthcare workers and was able to vaccinate up to 250 patients a day last year.[4,11] Furthermore, as per the TRC calls to action, reconciliation involves allowing Indigenous communities and organizations to empower themselves through self-determination and implementation of culturally safe coping strategies.[3] Many Indigenous communities enforced strict measures on who can enter their communities which resulted in lower rates of COVID-19 and lower fatality rates in 2020.[2]

It has been recently said that "Canada has barely scratched the surface of the TRC health calls to action."[4] As we move past the COVID-19 pandemic, a key step in the right direction will be for healthcare workers to have a conversation regarding the current experience of the Indigenous peoples with healthcare in Canada. Dialogue should begin with acknowledging the reality of systemic racism and colonialism, and obtaining more data to better understand the impact of racism in health disparities experienced by Indigenous peoples before launching effective interventions.[1] Additionally, there must be a continued effort to provide culturally safe care as well as self-determination of Indigenous peoples, as their guidance will be invaluable in making healthcare more accommodating of their cultural needs.[2] Only then can we hope to address the healthcare inequalities experienced by Indigenous peoples.

Conflict of interest

The authors have no conflicts of interest to declare.

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Perspectives in medicine: A spotlight on the world of machine learning in healthcare

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Abstract

Machine learning (ML) can potentially improve healthcare delivery. The use of technologies such as Heartflow can give rich diagnostic information, bypassing the need for costly and invasive testing. Surgical aids such as Dr. Eitan Prisman's 3D printed surgical guides can help reduce OR times while improving patient prognoses. While the use of ML in healthcare is promising, it is essential to be vigilant and properly validate such tools before implementation. ML has been developed for many different areas of healthcare. ML makes use of data and algorithms to "learn" to perform various tasks in an iterative training process. I was curious about the impact of this technology throughout the various medical subspecialties in British Columbia (B.C.), and the perspectives of physicians within these actively transforming fields.

Machine Learning in Radiology

I first discussed the implementation of ML with Dr. Jonathon Leipsic, a clinical professor of Radiology and Cardiology at the University of British Columbia (UBC) Faculty of Medicine. Dr. Leipsic has been involved in cardiovascular and cardiopulmonary research for the past 15 years. For much of that time, he has engaged in research on the utilization of ML to help enhance the work of radiologists.

Tell me about a current project of yours which utilizes ML as a part of clinical practice.

Beyond our internal collaborations within UBC I work closely with Heartflow, who develop tools to compute physiology from computerized tomography (CT) scans of the heart. To do that, they developed deep learning algorithms to extract the anatomy upon which fluid dynamics can be applied. This computer vision has allowed the extraction of features which are not available to the human eye.[1]

If you have a patient with suspected coronary disease, these are the patients that we want to send for FFRCT to aid in that decision.[2] *An AI (artificial intelligence) algorithm extracts the anatomy from the CT and computational fluid dynamics are applied to solve for pressure and flow.*

For context, traditional fractional flow reserve (FFR) is a measure that uses a pressure wire during a coronary angiography to check the blood flow in various arteries, a procedure which is both invasive and requires an additional dose of radiation.[3] FFRCT is an alternative of comparative accuracy which derives an FFR reading from a CT scan, and has the advantages of being less invasive and bypassing the need for FFR evaluation through coronary angiography.[1,4]

How do you think this will affect the delivery of medical care, from the perspective of the physician, and the patient?

An element [of the advantages of FFRCT] is the ability to answer questions that previously could not be answered by clinicians. The task of quantifying the physiologic burden of plaque lesions on the heart realistically cannot be done by humans reproducibly. It used to be that when a patient had suspected coronary artery disease, we would do a CT and recommend the patient come back for a stress test. But that involves a patient taking another day off to come in for another test. Instead of having the patient do another study, we can extract a greater richness of information from one test. Overall, I think this new technology will drive efficiency, drive quality, and open doors to answer questions that were previously unanswered.

Can you explain more about the improvements in quality and efficiency?

There was a randomized trial presented on November 6, 2022 at the American Heart Association, looking at the pathway using FFRCT versus traditional evaluative pathways involving invasive angiographies.[5,6] *What it showed was that the pathway involving FFRCT was a much more efficient utilization of resources and reduced the rate of unnecessary invasive assessments. This has the opportunity to improve patient outcomes*[7] *and drive a reduction in cost. Furthermore, it provides greater diagnostic certainty and richer information with which to inform decisions.*

In our conversation, Dr. Leipsic indicated that it took 12 years to collect and evaluate the evidence to validate Heartflow as a diagnostic tool. While this may disqualify the technology for some as "emerging," this period was critical in defining the appropriate use of this technology. Indeed, it seems that FFRCT is most effective when anatomical evaluation is uncertain.[2] By careful evaluation and research, the indications for FFRCT have been well defined and the benefit of its correct use have been ratified, lending it considerable strength as a diagnostic tool.

Machine Learning in Surgery

Next, I investigated the impact of ML on the world of surgery. Dr. Eitan Prisman is a clinical professor of Otolaryngology at UBC and a head and neck cancer surgeon. He is the founder of a lab that looks at incorporating 3D printed guides to enhance the efficiency and quality of facial reconstructions. His lab uses ML to generate cutting guides to support bone reconstructions in the wake of surgical cancer removals.[8]

Tell me about a current project of yours which utilizes ML as a part of clinical practice.

As you know, I treat patients with advanced head and neck cancer. A lot of the cancers I end up treating arise from inside of the mouth and invade down into the bone, and to clear the cancer I need to remove the bone itself. This has huge impacts on a patient's essential functions of life, such as swallowing, breathing, cosmesis, and talking. An accurate reconstruction is required to restore those functions, allow them to go through radiation, and fully recover.

The problem is that we can't just put in [a] plate or a free bone because it will die. You need to put in vascularized tissue, so we have to transplant other parts of the patients' body, [such as the tibia] into the jaw. But there is no other jaw in the body; we're left trying to use carpentry techniques to harvest the bone from somewhere else.

Without surprise, there are many patients who have tremendous complications, even after a pretty decent reconstruction. Even if the transplant survives, you may not be putting the bone in an accurate position;

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it needs to be right up against the native jaw in order for it to heal.

To improve those outcomes, we've been leveraging computational mechanics instead of doing surgery on the fly. Figuring out how you need to cut the original [tibia] in the OR to restore the curved bone of the jaw is a very tedious and challenging process. Not surprisingly, these procedures are fraught with multiple complications, including long OR time, long hospital stays, the need for tracheostomies and G-tubes.

What we do instead is first 3D print a patient-specific cutting guide for the transplanted bone with slots where we can make the cuts so that in the end it all fits together, like a puzzle, to recreate the jaw or the maxilla wherever we want. We print those guides out, send them for sterilization and bring them into the operating room to help guide our reconstructions.

How do you think this will affect the delivery of medical care, from the perspective of the physician, and the patient?

The effects have been huge. We've decreased our tracheostomy rates from eighty percent to twenty percent. Our OR time has decreased from five to three hours. We've decreased the time between when the transplant is removed from its blood supply and then reconnected to the blood supply in the head and neck from around one hundred minutes to around fifty-five minutes.[9]

Further than that, since we have lowered our rate of tracheostomies, the length of stay in the hospital for a patient is significantly shorter. Our complications rates are quite a bit lower... We're not having to reoperate on these patients, which also wastes a lot of resources. The cost-benefit is tremendous, and we're just trying to measure the extent of that now.

The evidence for Dr. Prisman's reconstructive technology is still emerging, though the current data are consistent with his descriptions.[9] Similar technology has been developed and validated in its effectiveness.[10] However, the cost for these third-party technologies is hard to justify, often over $3000 per use, whereas Dr. Prisman's lab has been able to create similar in-house technology at a cost of less than $300 per use.[11-12] Proper evaluation and implementation of this in-house technology has the potential to improve patient outcomes post-reconstruction.

Limitations and Considerations

These new tools are exciting for many reasons. However, in my discussion with Dr. Leipsic, he raised an important consideration with regards to emerging technology:

I think that when we integrate a new tool, we have to make sure that it is validated thoroughly and thoughtfully. There is a paper by Fryback and Thornbury[13] *that highlights how technology needs to be evaluated, involving a number of studies to generate evidence on whether a tool could work. I am cautious of excitement over non-validated tools or tests without robust evidence. As physicians, we have to understand how to integrate and use these tools for the better in our patient care and check our ego at the door.*

Conclusion

The technologies explored in this article lend a sense of optimism for the future of ML in medicine. The prospect of improving the care that medical providers can give while increasing the cost and time effectiveness of such procedures is exciting. We need to be cautious and properly evaluate these new technologies to ensure that we are achieving these goals. However, with a provision towards intellectual honesty, we will be able to leverage this technology to improve the lives of patients.

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Conflict of interest

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BEST-CLI trial publishes new international results on the management of chronic limb-threatening ischemia

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Introduction

Results from the landmark Best Endovascular vs. Best Surgical Therapy in Patients with Chronic Limb-Threatening Ischemia (BEST-CLI) randomized control trial were published in The New England Journal of Medicine on November 7, 2022. This highly anticipated multi-centre international study, led by Drs. Alik Farber, Matthew Menard, and Kenneth Rosenfield,[1] sought to determine whether surgical revascularization or endovascular therapy provides the best outcomes for patients with chronic limb-threatening ischemia (CLTI), a form of peripheral artery disease (PAD).[2] Impacting more than 200 million adult patients globally,[2-4] PAD disproportionately impacts older adults, with more than 20% of adults over 80 years old being affected.[4] Stemming from atherosclerotic disease of arteries supplying the extremities,[4] PAD manifests as intermittent claudication on exertion and impaired distal blood flow, which can present as diminished pulses, pallor, peripheral cyanosis, and cold temperature.[3] Lifestyle modifications and medical therapies—using agents to address thrombosis, dyslipidemia, hypertension, and hyperglycemia—are recommended but are typically too slow to reverse the advanced limb ischemia. In patients with CLTI, revascularization or use of either surgical bypass or endovascular therapy is indicated in order to prevent limb loss.[5] In order to determine which of these techniques was associated with the best outcomes, defined by lower rates of major reintervention (to include above the knee amputation or death),[2] the BEST-CLI trial studied 1830 patients with infrainguinal PAD from across the world.[2]

Surgical bypass, endovascular therapy and the best-CLI trial

Once a PAD patient exhibits signs of CLTI, acute limb ischemia, or their PAD limits their lifestyle, revascularization is often considered.[6] This involves either endovascular therapy, which entails the use of balloon angioplasty, stents,[6] or surgical bypass, which may involve the use of an autogenous conduit to revascularize the diseased artery.[2,7] Prior to the BEST-CLI trial, the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial, which enrolled 452 patients from 27 hospitals in the UK, found that although surgical bypass incurred more first-year financial costs than endovascular therapy, there was no significant difference in outcomes or quality of life.[8] Because the BASIL trial did not distinguish between amputation-free survival in the two interventions,[2] the BEST-CLI trial provides valuable insight into the differences between the two approaches.

One thousand eight hundred thirty patients from 150 centres, including the Vancouver General Hospital, across five countries were enrolled in the BEST-CLI trial.[2] Prior to randomization, each patient received an ultrasound that was used to classify them into either cohort 1, if they had a sufficient saphenous vein conduit, or cohort 2, if they did not.[2] Because there are various techniques and variations of bypass and endovascular therapy, surgeons were given the liberty of using specific techniques based on their clinical judgement.[2] Outcomes were assessed at the following timepoints after randomization: 3 months, 6 months, and every subsequent 6 months until 84 months.[2]

In the cohort with a sufficient saphenous vein conduit, 42.6% (n=709) of patients who received a surgical bypass and 57.4% (n=711) of patients who received endovascular therapy experienced either death or a major adverse limb event (P <0.001).[2] Further, surgical bypass patients required fewer reinterventions (9.2%) after their procedure than endovascular therapy patients (23.5%).[2] However, among patients in cohort 2 who did not have a sufficient saphenous vein conduit, major adverse limb events occurred similarly in those who underwent surgical bypass (42.8%, n=194) and those who received endovascular therapy (47.7%, n=95; Hazard ratio=0.79, 95% CI 0.58-1.06; P=0.12).[2] Thus, patients with a sufficient saphenous vein conduit, who underwent bypass surgery, experienced fewer major adverse limb events than those who were treated using endovascular therapy, but the results were comparable between the two groups in patients without a sufficient saphenous vein conduit.[2] The study did, however, have several limitations. Firstly, prior to the beginning of data collection, the investigators determined that the trial would require 2100 patients for statistical significance to be achieved, but enrolment was ultimately halted after 1830 patients due to funding limitations.[2] Furthermore, the study enrolled primarily male patients, so it is uncertain how the results would apply to female patients.[2]

Conclusion

The findings of this trial will likely have significant impacts on clinical decision making among vascular surgeons and interventionalists involved in the management of CLTI, and is therefore of interest to medical students who are in training today. This trial has the potential to inform clinical decisions between surgical bypass and endovascular therapy based on the presence of a sufficient saphenous vein conduit. Specifically, these findings provide evidence that patients who have received a great saphenous vein conduit experience fewer major adverse limb events if they undergo surgical bypass, as opposed to endovascular therapy. The presentation and management of CLTI, which preferentially affects older patients, is an increasingly relevant topic for medical students in the context of an ageing population. Here, we present and summarize the recent international, multi-centre BEST-CLI clinical trial along with relevant background on CLTI, to inform students of the condition and new developments in its management. We encourage readers of this article to read the entire publication by Farber et al. in *The New England Journal of Medicine*, as the full paper provides further subgroup analyses.

Conflict of interest

The authors have no conflicts of interest to declare.

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Specific Submission Criteria

Academic Research

Research articles report student-driven research projects and succinctly describe findings in a manner appropriate for a general medical audience. The articles should place findings in the context of current literature in their respective disciplines. UBCMJ currently accepts both full length articles and research letters.

If in your manuscript you acknowledge anyone for a contribution that goes beyond administrative assistance, you must obtain written permission from that person to publish his or her name (a) where the manuscript or article contains any material(s) (including text, images or other media) or other contribution(s) which belong to others, the author(s) are solely responsible for obtaining permission in writing from the owner(s) for its publication in the article.

Reviews

Reviews provide an overview of a body of scientific work or a medical trend. Reviews may outline a current medical issue or give insight into the principles of practice of a clinical field. Authors may choose to review the etiology, diagnosis, treatment, or epidemiology of a specific disease. Articles may also provide a survey of literature dealing with philosophy and social science as it pertains to medicine.

Case and Elective Reports

Case Reports describe patient encounters in a clinical or public health setting. The case should provide a relevant teaching point for medical students, either by describing a unique condition OR by presenting new insights into the diagnosis, presentation, or management of a more common condition. A template form to be used by the authors to obtain documented consent is provided on our website. The patient's consent form should be retained by the authors for a period of five years. Please do not provide the patient's name or signature directly to the UBCMJ.

Elective Reports provide a specific description of the scope of practice of a medical specialty and/or training program, and recall the student's impressions and reflections during and upon completion of the elective.

News and Letters

This section includes articles that touch on current events in the field of medicine, significant medical advances, or brief summaries of research in an area. Note that submissions to this section do not require extensive elaboration on the methods or results of the review process.

Commentaries

Commentaries are intended to provide a platform for intellectual dialogue on topics relevant to the study and practice of medicine. Submissions should correspond to one of the following categories:

- Subjective pieces relevant to medical studies, life as a future physician, or the current social context of medicine.
- Clinical perspectives on an interesting research study or area of focus.

Correspondence

For any questions related to your submission, please contact the appropriate Section Editors.

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