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MCMASTER UNDERGRADUATE HEALTH SCIENCES JOURNAL

MEDUAMPLIFY LOCAL: SOUNDING THE ALARM

THE CODE RED PROJECT AND POVERTY'S GRIP ON HEALTHCARE IN HAMILTON

HEALTH POLICY REVIEW

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RESEARCH INSIGHT: LAY SUMMARIES

SHARING SCIENCE MADE SIMPLE: EXPLORING THE QUALITY AND READABILITY OF PUBLISHED LAY SUMMARIES

DECEMBER 2023

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DEAR READER...

Welcome to Issue 44 of The Meducator! From translational research collaborations to coordinated responses to global pandemics, the Health Sciences field has become increasingly globalized. Such interconnectivity has reshaped healthcare, but also unveiled intersecting structural and sociopolitical barriers to equitable care delivery. Amid these challenges, a critical assessment of disparities in healthcare is vital. Yet equally important is recognizing earnest efforts to address these gaps. The heroic figure depicted on Issue 44's cover, illustrated by Arim Yoo and Elaine Wang, embodies healthcare professions, researchers, and community leaders in their pursuit to overcome these challenges.

Editors Matthew Olejarz and Aditya Misra open Issue 44 by exploring novel health developments around the world, ranging from AI-powered sepsis detection in the United States to the discovery of exclusomes in Switzerland. Through extensive literature review, Riyad Asgarali and colleagues explore phage therapies as an emerging alternative to antibiotics. Shifting to Industry Insight, Jacqueline Chen and Ria Patel investigate chronic kidney disease and appraise novel drugs from AstraZeneca, United Therapeutics, and Qidni Labs. In Research Insight, Anjana Sudharshan and colleagues examine the quality and readability of published lay summaries by leading 900 McMaster students in applying the Flesch Reading Ease Formula to 200 lay summaries from 4 journals. Finally, in an Interview Spotlight, Dr. Margaret McKinnon shares her experience working with trauma-related conditions as a clinical neuropsychologist.

We take tremendous pride in our journal's emphasis on grounding evidence-based research in social determinants of health. In MeduAmplify Local, Florence Deng and colleagues examine the Code Red Project, interrogating poverty's grip on healthcare in Hamilton while Elizeveta Kirichek and colleagues discuss gender-affirming care for youth in another MeduAmplify. Next, we introduce MeduGallery featuring artist Mishal Hossain's "In Her Image", a powerful centrefold illustration depicting the complexities in medical diagnoses for marginalized women.

We cannot express enough appreciation for our 95 talented and passionate staff members, faculty reviewers, and the supportive McMaster community, who worked alongside us throughout the 44th publication cycle. In particular, we thank our executive team: Alex, Anna, Arim, Audrey, Cindy, David, Elaine, Eric, Florence, Jacqueline, Jeffrey, Nishaad, Raymond, Serena, and Tharani, for their extraordinary leadership. Lastly, we extend our deepest gratitude to you, our reader, for your continued support of our publication.

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MEDPULSE

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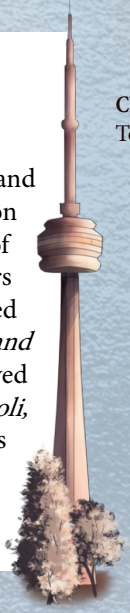
A Potential Cause of Childhood Allergies
CANADA | August 2023

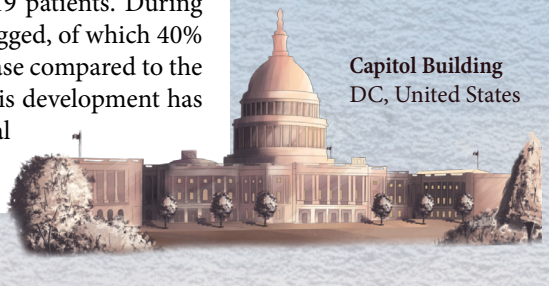
A new study led by researchers at the University of British Columbia and the British Columbia Children's Hospital has found that delayed maturation of gut bacteria within the first year of life may be a key indicator of pediatric allergic disease diagnoses by the age of five.[1] The researchers observed that common allergic diagnoses were consistently associated with depletions in the bacteria *A. hadrus, F. saccharivorans, E. hallii, and B. wexlerae* in infants' stool samples.[1] Additionally, the researchers observed that enrichments in the bacteria *E. lenta, C. innocuum, E. faecalis, E. coli, and T. nexilis* were correlated with allergic diagnoses.[1] These imbalances in the gut microbiota resulted in a weakened intestinal lining and increased inflammatory response and can be a significant factor to predisposing children to allergies within the first five years of life.[1]



CN Tower
Toronto, Canada

Sepsis Detection using Artificial Intelligence
UNITED STATES | July 2022

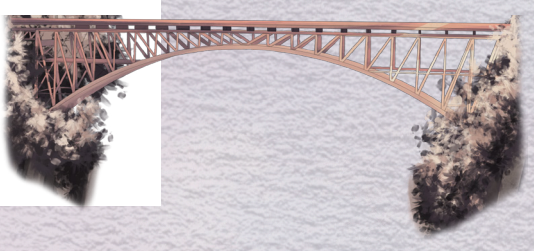
Johns Hopkins University has recently developed an analytical system guided by artificial intelligence (AI) to detect early signs of sepsis.[2] Sepsis is a condition that can develop from bacterial infections. Progression may result in septic shock, a drastic drop in blood pressure, which has a mortality rate of around 50%.[3] Based on clinical data, this AI model may reduce mortality rates by up to 20%. The model was first used to retrospectively screen 173,931 patients and subsequently deployed for 469,419 patients. During the deployment phase, 82% of patients were flagged, of which 40% were confirmed sepsis cases, a significant increase compared to the 2-5% accuracy of existing diagnostic tools.[4] This development has the potential to save thousands of lives in clinical settings.[4]



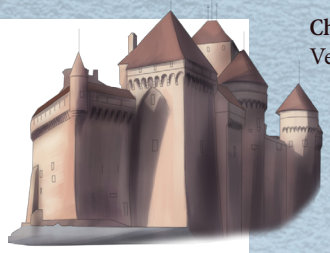
Capitol Building
DC, United States

Reports on HIV and Sexual Reproductive Health Services in Zimbabwe
ZIMBABWE | September 2023

There are significant socioeconomic and political barriers to accessing sexual and reproductive health (SRH) related care in Zimbabwe.[5] In 2020, various initiatives were undertaken to improve services and care related to SRH.[6] These interventions include counseling in general health and risk reduction, increased HIV screening, and delivery of antiretroviral therapy.[7] Screening for STIs has increased from around 2,730 screens per year to 16,298 screens between 2020 and 2022. Additionally, treatment was made available for those who tested positive. For those who tested negative, 2,114 qualified for pre-exposure prophylaxis, and a total of 2,010 HIV self-testing kits were distributed. To continually observe these improvements, the Government of Zimbabwe plans to open more sites and increase the capacity for care to improve the SRH of its people.[6]



Victoria Falls Bridge
Victoria Falls, Zimbabwe



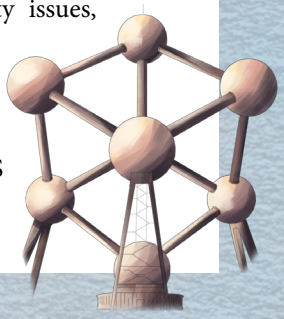
Chillon Castle
Veytaux, Switzerland

The Discovery of a New Organelle
SWITZERLAND | September 2023

Researchers at ETH Zürich have discovered a new organelle in mammalian cells called the exclusome, which stores DNA rings called plasmids.[8] In typical eukaryotic cells, DNA is stored in the nucleus. However, in certain cancer cells, plasmids that do not code for proteins are pinched off, sent out of the nucleus and stored in the exclusome alongside extracellular plasmids.[8] By maintaining cell organization, the exclusome helps prevent potential disruptions to the overall functioning of the cell.[8] Current research suggests that the exclusome may be an evolutionary precursor to the cell nucleus, potentially offering insights into the cellular evolution of eukaryotes.[8]

Paper Straws May be More Harmful than Plastic Straws
BELGIUM | August 2023

A new study conducted at the University of Antwerp tested for the presence of perfluoroalkyl substances (PFAS) in straws made from paper, bamboo, stainless steel, plastic, and glass.[9] Thirty-nine straw brands were examined, and PFAS were found in almost all types, with plant-based materials containing higher concentrations.[9] PFAS may be consumed by drinking through such straws and bioaccumulate.[10] In high concentrations, PFAS may cause liver damage, thyroid disease, fertility issues, and cancer.[10] Despite the eco-friendly appeal and recent social movements to adopt sustainable single-use food products, the high concentrations of PFAS raise concerns about increased exposure to harmful pollutants.[9]



The Atomium
Brussels, Belgium

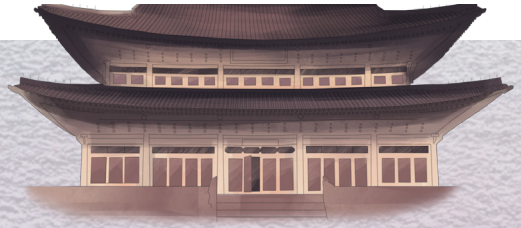
Christ the Redeemer
Rio de Janeiro, Brazil

Avian Influenza in South American Countries
BRAZIL | MARCH 2023

In May 2022, bird flu (H5N1) started to spread in North and South America. The virus was found to infect birds and mammals across 16 countries. Human cases of H5N1 were first identified in Ecuador in January 2023. As a response to the outbreak, the Pan American Health Organization gathered in Rio de Janeiro and discussed methods to halt the spread of H5N1.[13] One suggested precaution was to improve biosecurity in animal facilities, where the virus can circulate easily. In addition, veterinary authorities were advised to educate those working near sources of infection.[14]

Microbial Cell Factories for Sustainability
SOUTH KOREA | July 2023

Researchers at the Korea Advanced Institute of Science & Technology have been exploring the possibility of using microorganisms to produce food and cosmetic compounds.[11] Modifying the genetic material of a microorganism can produce desired novel compounds.[12] Currently, many synthetically-derived compounds, such as fructose, vanillin, and salicylic acid, require the use of extensive resources and create large carbon and water footprints. In contrast, microorganisms create much smaller footprints while requiring a fraction of the land to operate. This advancement could alleviate much of the environmental stress caused by large industries and provide a more sustainable alternative to conventional production techniques.[11]



Gyeongbokgung Palace
Seoul, South Korea

References can be found on our website: www.themeducator.org

PATHOPROFILE

RABIES

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INTRODUCTION

Rabies is a lethal zoonotic disease responsible for the deaths of 60,000 people annually.[1,2] Rabies virus (RABV) is a lyssavirus prototype with a mortality rate of nearly 100% after symptom onset.[1,3-4] Following an incubation period of 1-3 months after exposure, hosts develop encephalitis leading to two possible symptomatologies. A clinical presentation of RABV is encephalitic rabies, characterised by hydrophobia, agitation, and hypersalivation. Alternatively, RABV may also present as paralytic rabies, characterised by muscle weakness and paralysis. Both types eventually result in a comatose state followed by death.[2,3] Despite mass vaccination campaigns in developing nations aiming to reduce infection across mammalian populations, the virus continues to gain prevalence in novel species and geographic areas, proving to be a threat of increasing magnitude.[1]

DIAGNOSIS & TRANSMISSION

RABV is a mammalian-borne disease, with dog bites contributing to 99% of all rabies cases in humans. Minor exposures caused by superficial lesions are more likely to be unrecognised and subsequently unreported.[1,3] RABV transmission occurs most commonly through contact between the saliva of an infected animal, and the mucosal membrane, or impaired skin barrier, of the recipient.[1] RABV can infect most cell types, and there are many mechanistic differences leading to infection in humans.

This results in varied pathogenesis and clinical presentation.[1] The incubation period of RABV is variable, but typically lies within 20-90 days, during which the host is asymptomatic due to a lack of immune response. Once symptoms arise in later stages of the disease, the viral load is intractably high and more difficult to combat.[1,4] Thus, rapid diagnosis is essential for maximising patient outcomes. This is often done using magnetic resonance imaging to detect lesions and swelling in the brain, in addition to standardised laboratory tests to detect RABV and its antibodies.[4] When using fluorescence antibody testing in RABV infection diagnosis, it is important to use multiple sample sources, such as tears, hair follicles, saliva, and urine, for the highest possible likelihood of disease identification.[5]

MECHANISM

In hosts, RABV generally infects peripheral nerves at the motor end plate of neuromuscular junctions, and may also infect muscle cells. RABV binds to nicotinic acetylcholine neuronal receptors via its glycoprotein, the viral determinant of RABV infection.[6] After receptor-mediated endocytosis, RABV is packaged in endosomal transport vesicles and retrogradely transported along axons.[6] In the neuronal cell body, RABV releases viral RNA polymerase and a strand of viral RNA in the cytoplasm, containing the N, P, M, G and L genes, encoding nucleoprotein, phosphoprotein, matrix protein, glycoprotein, and large RNA polymerase protein, respectively.[6-8] The accumulation of viral proteins leads to the formation of cytoplasmic inclusion bodies, which are the site of viral RNA synthesis.[6,9] During replication, full-length, positive-stranded RNA is replicated from the viral genomic RNA, acting as a template for progeny negative-stranded RNA production.[9] During the assembly process, the nucleoprotein, phosphoprotein and large polymerase proteins form a helical ribonucleoprotein (RNP) complex, while encapsulating the negative-stranded genomic RNA.[8,9] The matrix protein forms a capsule around the RNP complex before migrating to the postsynaptic neuronal membrane to bind the glycoproteins.[8,9] Newly synthesized RABVs are then transmitted to neighbouring presynaptic neurons in a viral glycoprotein-dependent manner, initiating the cycle once again.[6]

RABV primarily uses motor pathways to the spinal cord, disseminating throughout the central nervous system (CNS).[10] Initial symptoms of encephalitic RABV may include fever, malaise, cough, pain, paresthesia, or pruritus at the bite site.

Subsequently, patients develop hydrophobia, hypersalivation, lacrimation, and pupil dilation, all of which are signs of autonomic dysfunction and indicate that the infection has spread to the brain.[11] Encephalitic RABV mainly involves extensive neuronal damage and inflammation to the brain stem, cerebrum, and limbic system, leading to increased aggression and other behavioural changes.[12] In contrast, paralytic RABV is categorized by flaccid muscle weakness, particularly in the laryngeal muscle.[10] The spread of RABV to the CNS leads to a condition called 'bulbar paralysis', which involves the dysfunction of muscles innervated by the glossopharyngeal, vagus, and hypoglossal nerves. These nerves innervate various muscles in the throat, including the laryngeal muscle, thus leading to difficulty in swallowing, voice changes, and eventually, respiratory failure with virus progression. The pathogenesis of paralytic RABV is poorly understood, but it often causes extensive neuronal damage to the medulla and the spinal cord.[12] The absence of a significant immune response to the infection and diminished number of peripheral B lymphocytes may be correlated with the appearance of paralytic RABV. After the dissemination of RABV in the CNS, it will then spread to peripheral non-nervous tissues, like the salivary glands, allowing for transmission of the virus to its next host.[11]

TREATMENT

After symptom onset, rabies is almost always fatal. However, this can be prevented through vaccination before or following exposure.[2] The intradermal rabies vaccine is highly effective in preventing infection when coupled with routine wound management, even following exposure to a severe dog bite. The administration of rabies immunoglobulins may also be recommended to neutralise RABV at the inoculation site for patients who experienced a high-risk exposure.[2] Pre-exposure prophylaxis is also recommended for certain at-risk populations, such as those working in veterinary settings, laboratories, and other high-incidence settings.[2] The Milwaukee Protocol was the standard treatment protocol for RABV infection from 2004 to 2015, but is no longer recommended.[13,14] However, this treatment plan is still used despite controversies surrounding its risks.[13,14] The Milwaukee Protocol involves inducing a comatose state and administering high doses of antivirals and sedatives such as ketamine and barbiturates.[13] It was later updated to advise against coma induction after repeated adverse patient outcomes, and introduced the use of benzodiazepines in conjunction with ketamine usage to minimise suffering and autonomic nervous system dysfunction.[13] As the onset of clinical symptoms is a likely predictor of eventual death, it is imperative to reassess the best course of action for surveillance and preventive measures worldwide.[1,2]

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CURRENTS OF CHANGE

GALVANIC VESTIBULAR STIMULATION

doi: 10.35493/medu.44.06

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INTRODUCTION

Galvanic vestibular stimulation (GVS) is an electrode-mediated method of non-invasive electrical stimulation. Its ability to modulate vestibular neuronal activity through electrical currents makes it a coveted diagnostic and therapeutic tool for vestibular and neurodegenerative disorders.[1] Although more robust clinical research is needed before wide-spread implementation, GVS shows promise as a safe, cost-effective, and accessible therapeutic tool for neurological rehabilitation.[2]

MODE OF ACTION

GVS procedures administer a small direct current to a patient's mastoids through large-surface electrode current delivery.[3] Typically, two electrodes are placed behind each ear of the patient, situated on top of each respective mastoid process. These electrodes deliver the current in a modulated waveform to enact a desired neurophysiological response, such as a head tilt.[1] The fundamental mechanism of GVS relies on the activation of primary otolithic neurons and primary semicircular canal neurons, which are both associated with the vestibular system.[1]

The vestibular system is located within the inner ear, and is bordered by the middle ear and temporal bone.[4] It conveys vital sensory information to the brain regarding head position, spatial orientation, and body motion.[4] The vestibular system contains a bony and membranous structure known as the vestibular labyrinth, which is targeted by GVS.[5] The vestibular labyrinth contains the otolithic neurons and the semicircular canals.[6] The otolithic neurons are associated with the otolith organs, responsible for detecting static and transient head displacements. Static displacements refer to changes in head orientation due to gravitational effects, such as head tilting, which alter the spatial alignment of the head relative to the gravitational force.[6] In contrast, transient displacements pertain to head movements characterized by linear translation without simultaneous angular rotation (e.g., moving forward in a car without head tilting).[3] The semicircular canals and otolithic neurons are responsible for sensing angular head movement in three-dimensional space to relay information to the central nervous system, sustaining balance and spatial orientation.[6]

The electrical current applied through the electrodes to the mastoid process stimulates a flow of ions to the otolithic organs and semicircular canals, activating primary otolithic neurons and primary semicircular canal neurons.[3] This induces a variety of vestibular sensations as the brain interprets the signals as changes in head position, movement, or orientation. Simulated vestibular sensations include the modulation of muscle activity and the induction of virtual sensations of motion.[2] For example, modulation of muscle activity can be seen through the body's attempt to compensate for changes in head tilt by activating the deep cervical flexor muscles.[2] Similarly, GVS has been used in virtual reality studies to induce virtual sensations that stimulate the action of flying in a plane, including turning left and right, through the application of specific current waveforms to each mastoid process.[3]

CLINICAL APPLICATIONS

GVS has a wide range of applications with respect to vestibular rehabilitation, particularly in cases of Parkinson's disease (PD) and bilateral vestibular hypofunction (BVH).[1] Current ongoing research is investigating the potential of GVS in addressing the unique challenges of PD, a neurodegenerative disorder that affects movement and balance.[2] GVS is also being explored in relation to BVH, a pathology in which the vestibular system's function is reduced, leading to spatial disorientation and instability.[10] These studies aim to unlock valuable insights into the specific benefits of GVS for individuals dealing with PD and BVH, paving the way for tailored interventions and improved quality of life for those affected by these conditions.

PD is characterised by slowed movements and balance difficulties, leading to an increased risk of falling due to postural instability.[2] Wood et al., found that 68.3% of all PD patients have reported a heightened sense of body swaying and falls due to the vestibular disturbances in PD.[7] However, the use of GVS with current intensity varying between 0.1 and 0.7 mA producing a noisy waveform (randomised current amplitudes) resulted in a reduction of PD-induced body sway by 23±13% in 67% of patients.[8] Similarly, a study utilising GVS with a sinusoidal current waveform also using a 0.1-0.7 mA current intensity demonstrated a significantly reduced sway path with GVS (0.73±0.3m) compared to the control (0.93 ± 0.5m, $p \leq 0.01$).[9] The findings further demonstrate that GVS can potentially reduce body swaying of PD patients and minimise PD-related patient falls.[9]

BVH is a condition that stems from defects in the vestibular organs or vestibulocochlear nerves which leads to difficulty in maintaining balance and affects over 95 million adults worldwide.[10] In an attempt to mitigate the lack of stability in BVH patients, a study used noisy GVS (nGVS) and found that the root mean square (RMS) of the patients' BVH-induced body sway decreased as a result of GVS application (higher RMS signifies higher instability), as illustrated in *Figure 1.*[11]

Overall, GVS has a wide range of clinical applications and is particularly involved with the modulation of muscle activity and the induction of virtual sensations of motion. Further research is required to understand the full scope of the clinical applicability of GVS.

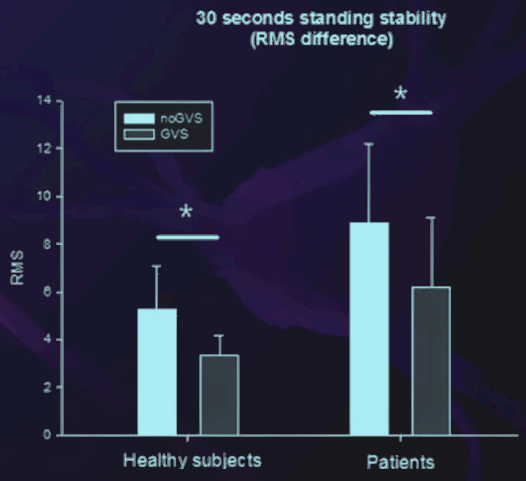

Figure 1. The results emphasise the impact of GVS on BVH patients and the decrease in sway as a result of GVS. The mean RMS was 8.86 ± 3.31 without nGVS application and 6.19 ± 2.29 with nGVS application ($p = 0.018$). In the healthy group, the mean RMS was 5.27 ± 1.79 without nGVS and 3.36 ± 0.80 with nGVS in standing condition ($p = 0.005$). Adapted from the source figure, focusing on plot (A).[11]

LIMITATIONS & FUTURE DIRECTIONS

Recent meta-analyses have advised caution in interpreting favourable GVS-findings, citing small sample sizes and a high heterogeneity of stimulation protocols. For example, the largest GVS-mediated balance rehabilitation study only consisted of 42 participants. However, no existing studies have illustrated GVS as ineffective in combating vestibular rehabilitation.[12] Studies with larger participant cohorts and more rigorous controls must be conducted before introducing GVS into clinical practice.

The question of whether fixed intensity GVS or subject-specific nGVS is more effective in modulating balance remains unsettled due to disparities in stimulation protocols across studies. While both types of nGVS improved postural balance in PD, only fixed intensity nGVS yielded improved balance in both control and case groups. Studies examining both nGVS types delivered differing intensities of GVS, rendering comparisons invalid. More standardised studies comparing stimulation types are required before identifying the most effective delivery of nGVS.[12]

Further research is also required before the clinical use of nGVS in the management of BVH. The underlying mechanism for functional improvements related to nGVS have been attributed to stochastic resonance –the phenomenon in which noise enhances the response to stimuli.[13,14] To understand the exact mechanism of these effects, conducting more *in vivo* studies examining the effects of nGVS in the cortical and vestibular regions may be beneficial. Additionally, Helmchen et al. observed no response to imperceptible nGVS in healthy participants and BVH patients, despite observing strong responses to perceptible GVS in both groups. The authors suspect that these results are due to the lack of weak background vestibular stimulation. Investigation of the effects of nGVS on higher regions of the CNS can provide insights into their role in nGVS-mediated BVH treatments.[13]

The effects of GVS on vestibular performance underscores its potential as a viable, non-invasive treatment option for PD and BVH patients. With further research, this technology has the potential to become standard clinical practice in the field of vestibular rehabilitation.

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SOUNDING THE ALARM

The Code Red Project and Poverty's Grip on Healthcare

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INTRODUCTION

Hamilton is a city of dichotomies. Its dense inner-city and sprawling suburbia constitute a unique microcosm of larger, global wealth inequalities. The entrenchment of poverty has rippling effects on healthcare access and outcomes both within Hamilton and globally, exacerbating discrepancies in the social determinants of health between high-income and low-income populations.[1] Despite having universal healthcare, Canada inadequately addresses healthcare concerns in low-income and homeless populations nationwide and, notably, within Hamilton.

HEALTH IMPLICATIONS IN THE HOMELESS POPULATION

Unfortunately, the effects of homelessness are permeating into the healthcare sector. The relationship between homelessness and health is complex and bi-directional: homelessness can influence health status, and poor health status can result in dispossession.[2] The homeless population in Canada experience a myriad of health inequities and face poor health outcomes in comparison to the housed population.[2] People experiencing homelessness tend to have more emergency department visits and hospitalizations, with higher rates of acute health conditions and mortality.[3] A 2009 study by Hwang et al. found that Canadians experiencing homelessness had a reduced life expectancy compared to the national average of 81 years.[2,4]

The homeless population experiences higher rates of almost all chronic diseases and physical health issues than the general population.[3] These conditions include seizure disorders, diabetes, chronic respiratory tract disease, musculoskeletal illness, dental problems, and tuberculosis.[3] They also experience more general injuries, leading to poor health outcomes. Common injuries tend to relate to the unsafe conditions associated with homelessness, such as using fire to cook food and sleeping on uncomfortable surfaces.[2]

In addition to physical health, mental health issues such as depression, drug addiction, stress, and suicide are prominent among the homeless population.[3] The most common mental illness is alcohol use disorder, with less common conditions being personality disorders, anxiety disorders, affective disorders, drug dependency, and psychotic illness.[2] Unfortunately, many of the basic mental health needs are not addressed, rendering it difficult for those experiencing homelessness to reintegrate back into their respective environments, perpetuating the cyclic nature of poverty.[2] A 2001 study by McCormack et al. found that self-sufficiency and community engagement within homeless populations is contingent on experiencing the feeling of being healthy, underscoring the importance of having equitable access to inclusive physical and mental healthcare.[5]

The homeless population often encounters intersectional barriers, which prevent access to high quality healthcare services. Many people experiencing homelessness report a lack of health insurance or access to healthcare resources, as well as personal barriers such as inadequate social support and feeling isolated from others.[3] The homeless population also experiences difficulty in obtaining consultations with physicians, harm reduction materials, and adequate information regarding available healthcare services.[3] Upon receiving healthcare services, they frequently experience stigmatisation and dehumanisation from healthcare professionals.[6] Inappropriate care and treatment can exacerbate feelings of social isolation and depression, contributing to a vicious cycle of poverty.[3]

THE CODE RED PROJECT

Published in April 2010 by the Hamilton Spectator, the Code Red Project is a seven-part examination of the glaring disparities in health determinants across Hamilton neighbourhoods, mirroring broader implications of poverty on health. Through maps, stakeholder insights, and statistics, the project spurred industry and public discussion.[7]

"Part one: Worlds Apart" maps Hamilton's health status, referencing chief health outcome indicators including average age at death, emergency room (ER) usage, and pre- and post-natal care. Notably, one West Mountain neighbourhood had an average life expectancy of 86.3 years, however, a North End neighbourhood had an average life expectancy of 65.5 years—a difference of an entire generation.[1]

Part two unveils differences in ER dependence due to lack of primary care access. One inner-city neighbourhood averaged $2,060 per person for hospital bed, ER visit, and ambulance use, a drastic uptick from the $138 per person spent on the same services in a Flamborough neighbourhood.[8] Ironically, areas with the best health outcomes are located farthest away from Hamilton's primary hospitals in the inner-city. It is indicative that ER dependence can be predicated on socio-economic hurdles, such as a lack of transportation or family physicians, as well as language barriers.[8] Parts three to five encapsulate the intense struggle within the cycle of poverty, beginning from low birth weights to incongruent high school dropout rates (41.9% to 2.4%).[7] The educational discrepancy later leads to differences in property values ($87,000 in inner-city areas compared to $500,000 in affluent suburbia) and higher rates of low-income seniors stuck in costly acute care limbo.[9,10] The historical and current decline of manufacturing jobs in lieu of high technology positions is a notable exacerbating factor.[7]

Part six hones in on the mental illness implications of poverty, where 25 out of 27 neighbourhoods with the highest rates of psychiatric-related ER visits are in areas with the highest poverty rates.[7]

and Ontario Provincial Legislature since its publication.[7] As a result, the City of Hamilton upstarted neighbourhood development strategies. At McMaster University, the Dean of the Faculty of Health Sciences attributed this series as the primary reason for the relocation of McMaster's health campus and medical centre from the west end of the city to downtown Hamilton.[7] Conjunctly, the McMaster Children's Hospital relocated a Children's Treatment Centre from the North End to a site surrounded by prominent, high-poverty Code Red neighbourhoods.[7]

The Code Red project uncovered the degree of Hamilton's income and health disparities, disseminating health information to urge systematic and legislative change.

HOMELESSNESS

The City of Hamilton is working towards a plan to end chronic homelessness by 2025 through rights-based, intersectional approaches that value person-centred and sustainable models that provide long-term solutions.[11] Homelessness and poverty require intersectoral approaches that fuse health and social services. Collaboration between the healthcare sector, governments, and housing services allows for better identification of issues related to poverty and homelessness and the implementation of appropriate solutions as coordinated action leads to policies that create health equity.[12] A greater emphasis has been placed on analyzing outcomes beyond housing to evaluate the effectiveness of current programs. Strides are being taken to connect individuals to financial assistance through the Homelessness Prevention and Shelter Diversion interventions, which focus on coupling financial support with case management for those at risk of homelessness. Furthermore, various housing types are provided for the diverse needs of the homeless population, such as emergency shelters, permanent supportive housing, and transitional housing.[11]

The Greater Hamilton Health Network's (GHHN) 2022-2023 Integrated Strategic Plan takes an intersectoral course of action to improve the quality of decisions made by the Ontario Health Team.[13] One of their main objectives is to implement socio-demographic data to improve health outcomes for equity-seeking priority groups, like the low-income and homeless populations.[14] By taking a multifaceted approach as a part of their Strategic Plan, the GHHN works to create a stronger system that supports the intersection between health and social services to improve overall health outcomes, especially for those in vulnerable communities facing poverty and homelessness.

CONCLUSION

Homelessness and poverty are not independent issues but rather a result of unique intersections between various systemic factors and oppressive planes. Considering the established relationship between poor health outcomes and low socioeconomic status, an intersectoral approach is required to mitigate the effects of poverty in healthcare access. The City of Hamilton is moving towards a more promising model that prioritizes a person-centred approach to ensure that vulnerable and underrepresented populations, as well as the political, environmental, social, and technological impacts, are taken into consideration when evaluating current conditions. Though the most impactful actions must be taken on a large scale, individual efforts can be taken through self-education, legislation and policy related advocacy and supporting grassroot organizations working to assist low-income and homeless populations. The combination of systemic and individual work will pave the way for a future where healthcare access and outcomes are no longer contingent on income level or neighbourhood of residence.

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EDITED BY: PARTH ARORA & ZAHRA TAUSEEF

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A Critical Review of **Phage Therapy as an Emerging Antibiotic Alternative**

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ABSTRACT

In 2019, nearly 5 million deaths worldwide were attributed to antimicrobial resistance (AMR), underscoring its profound threat to global public health.[1] AMR causes traditional antibiotics to lose effectiveness against bacterial infections due to the emergence of resistant bacteria. Consequently, phage therapy, which employs bacteria viruses to combat bacterial infections, has become a potential solution.[2] Phages can enhance antibiotic sensitivity by targeting bacterial mutants, influencing the evolution of populations and impacting receptors responsible for antibiotic efflux from cells.[3]

Despite the advantages, several limitations to the use of bacteriophages exist. Phage-Antibiotic Synergy (PAS) may address these limitations. PAS describes the phenomenon of improved antimicrobial effect caused by stimulated phage replication in the presence of sublethal concentrations of antibiotics.[4] Phage-antibiotic therapy has effectively reduced the emergence of phage-resistant and antibiotic-resistant strains simultaneously.[3]

INTRODUCTION

Phage therapy, a century-old clinical approach first used by Felix d'Hérelle in 1919, has recently gained prominence as a potential alternative to antibiotics.[5,6] It involves utilizing bacteriophages, viruses that specifically infect bacteria, to combat bacterial infections.[2] Studies have shown promising results for phage therapy in treating bacterial infections in humans, animals, and plants, including multidrug-resistant pathogens such as *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Mycobacterium abscessus*.[4,6,7] Phage therapy mainly uses obligately lytic phages to kill their respective bacterial hosts while leaving human cells intact and reducing the broader impact on commensal bacteria that often results from antibiotic use.[6,7]

There remain challenges to overcome before phage therapy can be considered a practical alternative to antibiotics. These challenges include the safety, efficacy, and regulation of phage therapy, as well as the complexity of host-pathogen interactions.[5] However, novel phage strains and strategies have been developed to enhance the specificity and safety of phage therapy.[8] Additionally, investigations into the pharmacokinetics and pharmacodynamics of phages *in vivo* may provide valuable insights into the optimal dosing and administration routes for phage therapy.[9]

This critical review aims to provide a comprehensive exploration of phage therapy and its developments in case studies and clinical trials while also looking at the PAS which plays a crucial role in addressing AMR.[8,9] Subsequently, an evaluation is conducted on the limitations hindering the widespread adoption of phage therapy. Finally, we outline potential research directions that can pave the way for optimising phage therapy and PAS in the ongoing battle against AMR.

REVIEW FINDINGS: BACKGROUND

The viral replication cycle of a phage involves the infection of a bacterial host, replication of the phage genome, and the release of new phages to infect other bacterial hosts. Phages can have different replication cycles within the bacterial host, including lytic, lysogenic, and pseudolysogenic life cycles.[35] By integrating their genetic material into the host cell's genome, lysogenic phages can persist in the host and continue to produce new phages over time, potentially providing a longer-lasting treatment than lytic phages. Pseudolysogenic and chronic cycles are important areas of ongoing research, but their significance in phage therapy is not yet fully understood.[10]

Currently, to target and eliminate pathogenic bacteria, phage therapy takes advantage of lytic phages. They are the preferred option for therapeutic purposes as they kill their bacterial hosts by attaching to their surface receptors.[10] Once attached, the phages inject their genetic material into the cell. The phage genetic material takes control of the bacterial cell's machinery and begins producing new phages at a rapid pace. The sheer volume of new phages causes the bacterial cell to burst open, releasing a swarm of new phages ready to infect other bacterial cells. In contrast, lysogenic phages do not outright kill the bacteria; rather they integrate their genome into the host cell, which may harbor AMR or toxin genes. Bioengineered lytic phages are used clinically to overcome the constraints of using naturally occurring phages, such as a limited host range and poor infectivity. To maximize the therapeutic impact, lytic phages are compiled into preparations called "phage cocktails", which consist of multiple phages proven to have *in vitro* efficacy against the target pathogen.[5,6] The administration methods include topical application, oral ingestion, and intravenous injection, dependant upon the type of infection and site specificity. Early successes include the treatment of a patient with a multidrug-resistant *Staphylococcus aureus* (MRSA) infection using a cocktail of phages without antibiotics.[11] Phage cocktails can target distinct types of bacteria, and through the use of multiple phages, provide a broad-spectrum approach to infection prevention.[10] Yet, the increased complexity from the additional phages also raises the risk of eventually compromising the efficacy. Overly complex cocktails can lead to dysbiosis, horizontal gene transfer, and even phage resistance.[12] An *in vitro* study conducted in 2022 demonstrated that a two-phage cocktail in combination with the antibiotic imipenem successfully resulted in the synergistic delay of the carbapenemase-producing *K. pneumoniae* growth.[13] However, it is also apparent that isolated applications of phage therapy independent of antibiotics have generally led to more negative results than positive. This includes Leitner et al. who failed to substantiate that phage therapy was more effective than antibiotics in treating cases of urinary tract infections.[14] Despite the failures, they provided insight into the administration routes for various types of infections, as well as the concentration of phages that avoids toxicity but still achieves a therapeutic effect.[15] A faster recovery rate with vastly reduced side effects can be

achieved using phages versus antibiotics, given higher precision in targeting solely harmful bacteria whilst sparing healthy ones.[11]

CASE STUDIES, CLINICAL TRIALS, AND ONGOING DEVELOPMENTS

Recent advancements in phage therapy unveil promising strides in diverse clinical applications. However, while there are plenty of reports on pre-clinical *in vitro* and *in vivo* use, there is a lack of rigorously-conducted clinical trials; most human findings are from individual cases or case series. One noteworthy progression in personalized medicine involves the targeted use of topical bacteriophage therapy for chronic non-healing wounds, as highlighted in the comprehensive study by Gupta et al. The research showcases substantial improvements in wound healing, revealing that seven patients achieved complete healing by day 21 through the application of a tailored bacteriophage cocktail.[16] These findings underline the potential of personalized phage therapy in addressing challenging cases of chronic non-healing wounds.

In addition, developments in personalized medicine concentrate on tailoring bacteriophage-based therapeutic cocktails to treat resistant bacterial infections. A case report conducted by Schooley et al. delineates the success of personalized bacteriophage therapy in treating a patient with a disseminated resistant *Acinetobacter baumannii* infection. The report demonstrates the efficacy of personalized approaches through significantly improved patient outcomes including a reduction in pressor requirements, coma recovery, and improved mental status and renal function.[17] This underscores the potential of personalized phage therapy as a valuable intervention in challenging scenarios of antibiotic-resistant infections.

Ryan et al. and Altamirano et al. shed light on the efficacy of PAS in eradicating bacterial biofilms. These studies emphasize the significant impact of PAS in overcoming challenges posed by biofilm formation and drug-resistant bacteria.[18,19] The findings suggest a promising strategy for enhancing treatment outcomes in cases where traditional therapies fail, providing valuable insights into the dynamic interplay between phage therapy and antibiotics in combating resilient bacterial populations.[18,19]

While preclinical evidence affirms the overall effectiveness of phage therapy in animal models, a review and meta-analysis by Gómez-Ochoa et al. bring attention to a crucial gap between research and clinical practice. The study demonstrates the need for future preclinical trials to align with clinical trials, emphasizing the need for informed translation of findings into clinical applications.[20] This recognition serves as a call to action for refining research methodologies to ensure a seamless transition to clinical use.

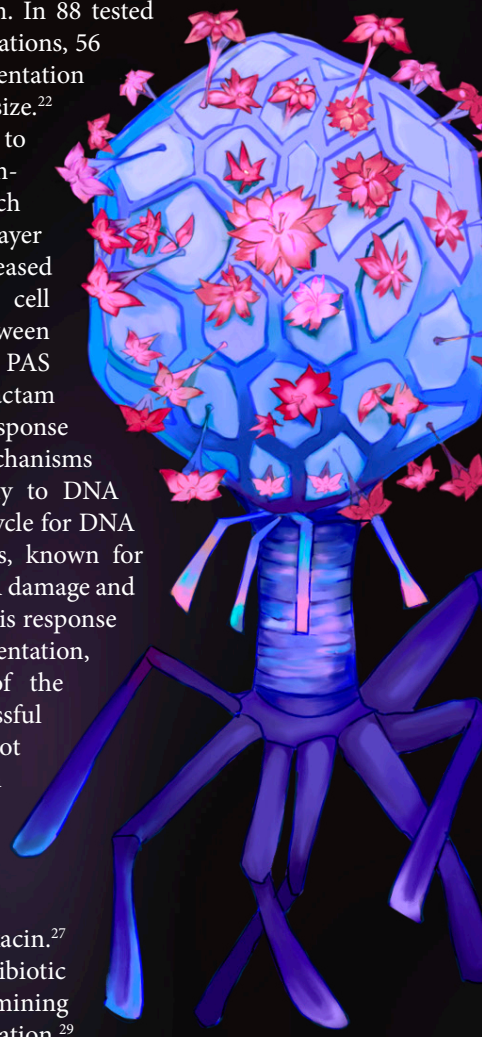
A study conducted by Borin et al. focuses on the λ phage and *Escherichia coli* model system and provides insights into the effectiveness of phage training. Phage training involves exposing bacteriophages to their target bacterial hosts over a period, allowing the phages to evolve and adapt to the bacteria's defenses.[22] While the results of this study are promising, the generalizability of phage training to diverse clinical scenarios with various bacterial strains and infections remains uncertain.

PHAGE–ANTIBIOTIC SYNERGY

PAS refers to the phenomenon where phage production increases in the presence of sublethal concentrations of certain antibiotics.[23,24] PAS allows enhanced bacterial suppression, increased biofilm penetration, and reduced capacity of bacteria to develop resistance against either therapy option. Employing low doses of antibiotics and phages can effectively manage antibiotic-resistant bacteria. While bacteria have developed defenses against antibiotics, they remain vulnerable to phages. This approach tips the balance in the coevolutionary "arms race" between phages and bacteria.[22] Furthermore, PAS also makes use of the mechanism of phage steering, wherein phages are able to specifically select resistive strains of bacteria, thereby reintroducing antibiotic sensitivity.[25] PAS was found to be evident in a variety of processes, including plaque assessments, bacteria filamentation, and clinical case experiments.[24,25]

Plaque assessments are one of the most known demonstrations of PAS. Comeau et al. found that phages stimulated with sublethal β-lactam and quinolone antibiotics increased plaque size.[24] By implementing antibiotics, there is a corresponding increase in plaque size and diameter through simulated phage activity due to increased bacteria inhibition.[25] An *in vitro* study conducted in 2021 observed that the production of progeny bacteriophages was heightened, which may eliminate more bacteria.[26]

Another PAS indicator is bacterial filamentation and elongation. In 88 tested phage and antibiotic combinations, 56 demonstrated bacterial filamentation and increased plaque size.[22] Filamentation is related to disturbances in penicillin-binding proteins (PBPs) which affect the peptidoglycan layer and cell wall, leading to increased phage attachment and cell lysis.[24] The correlation between bacterial filamentation and PAS can be justified through β-lactam antibiotics and SOS-response mechanisms.[27] SOS mechanisms in bacteria respond globally to DNA damage by halting the cell cycle for DNA repair.[28] β-lactam antibiotics, known for inhibiting PBPs, induce DNA damage and trigger the SOS response. This response causes bacterial filamentation, an abnormal elongation of the cell, promoting successful phage predation. While not universal, cell filamentation enhances susceptibility to phage infection, observed in filamentation-inducing antibiotics like ceftazidime, cephalexin, and ciprofloxacin.[27] The specific choice of antibiotic is also important in determining the level of filamentation.[29]



PAS has also been successfully implemented in clinical experiments. For instance, a study in 2020 reported a case of a patient with a urinary tract infection (UTI) of *Klebsiella pneumoniae* that resisted all the tested antibiotics, excluding tigecycline and polymyxin B.[30] After tigecycline failed to treat the UTI, the patient participated in a successful phage therapy with a phage cocktail III and trimethoprim-sulfamethoxazole (SMZ-TMP) antibiotic combination. In particular, from a series of common antibiotics used for UTI treatment, SMZ-TMP was selected specifically due to its strong synergistic effect with phage cocktail III. When the phage cocktail III was applied on its own, it only inhibited growth for 12 hours. SMZ-TMP applied individually was unable to result in any sign of inhibition of bacterial growth. However, the SMZ-TMP and phage cocktail III combination resulted in complete recovery. This case demonstrated major potential for treatment with the application of PAS antibiotic and bacteriophage synergism as a phage therapy strategy.[30]

LIMITATIONS

Despite recent advances, there are still several limitations to phage therapy such as the narrow host range of phages and the lysogenic phenomenon.[31] If the bacteria community is stable, presence of the lysogenic phage may cause harm to the host by strengthening the community.[31] While obligately lytic phages are the predominant choice in current trials, there are instances where the usage of temperate phages may be crucial. This need arises from the fact that obligately lytic phages may not always be available, as exemplified in the study by Derick et al.[6] In this study, engineered phages were employed to address a disseminated *Mycobacterium abscessus* infection, emphasizing the potential significance of incorporating temperate phages in certain therapeutic contexts.

A fundamental limitation of using self-replicating entities such as phages is the potential for rapid evolution and genetic mutations. Phages can mutate quickly to adapt to changing conditions, including the development of resistance.[2] This adaptability can make it challenging to predict and control the effectiveness of phage therapy over time. Additionally, the complex interactions between phages and bacteria in the bodily environment may introduce uncertainties in treatment outcomes.

Pharmacological limitations are also a concern for phage therapy.[32] Clinical trial results of phage treatment of bacterial infections show a low to moderate efficacy, and the variation in infection clearance between subjects within studies is often large.[32] *In vivo*, the pharmacokinetics and pharmacodynamics of phages are virtually unknown, and there is a lack of standardization due to the great variation of phages, bacteria, and infections.[32]

Another limitation of phage therapy is the bacteria mutation dynamics that can outpace phages.[27] Bacteria can evolve resistance to phages by developing mutations that prevent phages from attaching to their surface receptors.[33] In addition, phages can select for small colony variants (SCVs) that are resistant to antibiotics.[34] SCVs are slow-growing bacteria that can evade the immune system and persist in chronic infections.[34] However, recent research has shown that combining phage therapy with antibiotics can address this limitation.[34] By following the administration of phages with antibiotics, the limitation of SCVs can be addressed.[33,34]

Finally, the high cost of phage therapy can be prohibitive, costing thousands of dollars for a single treatment.[36] The personalized approach of finding or engineering the correct phage is time-consuming and expensive. As phage therapy is developed, the cost may decrease, but new infections and the need for multiple rounds of treatment pose additional challenges.

CONCLUSION

In conclusion, the promise of PAS in addressing AMR is evident, yet it is crucial to acknowledge the persistent challenges and complexities of phage therapy. Intricate interactions between phages and bacteria reveal gaps in our understanding, particularly in instances where bacterial strains are unknown and complex. Phage training and steering, while intriguing, cannot be guaranteed universally, adding a layer of uncertainty to the applicability of phage therapy. Moreover, the efficacy of phage therapy proves to be variable across different infections, emphasizing the need for a nuanced approach that is tailored to the specific characteristics of each bacterial strain. Additional complexities surrounding phage therapy include limitations such as narrow host range, the lysogenic phenomenon, and pharmacological uncertainties. Despite intriguing developments in laboratory settings and ongoing research showcasing PAS, the journey towards establishing phage therapy as a widely applicable solution is still in its early stages. The lack of definitive references to successful clinical trials raises questions about the current practicality of phage therapy in real-world scenarios. As we navigate these challenges, further research to uncover the mechanisms involved is imperative to determine the true potential and limitations of phage therapy in the ongoing battle against AMR.

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PLEASE TELL US ABOUT YOUR BACKGROUND. HOW DID YOU GET INVOLVED IN PSYCHIATRY, MENTAL HEALTH, TRAUMA, AND BEHAVIORAL NEUROSCIENCE?

I'm the Homewood Chair of Mental Health & Trauma and a Professor and the Associate Chair of Research in the Department of Psychiatry and Behavioral Neurosciences at McMaster. I'm also a licensed clinical neuropsychologist. My interest in trauma and mental health research stands both from longstanding academic work and my own personal experience. Over 20 years ago, I was onboard an aircraft that ran out of fuel midway over the Atlantic and we were prepared for the ditching of the aircraft. Fortunately, we made it to a military airstrip where we made a rough landing. The back of the plane was on fire and we evacuated. I developed post-traumatic stress disorder (PTSD) following that incident. This shifted my area of interest from working in aging and dementia to mental health and wellbeing. I'm really grateful for the treatment that I received but also the opportunity to give back. It's really important to challenge the stigma around mental health

WE NOTICED YOU HAVE A SPECIAL INTEREST IN MILITARY, VETERAN, PUBLIC SAFETY, AND HEALTHCARE WORKER POPULATIONS. EXPANDING ON THIS POINT, COULD YOU TELL US MORE ABOUT YOUR RESEARCH IN THIS AREA?

The Trauma and Recovery Research Unit consists of 45 members in three different streams of research. Our first area of research focuses on better understanding the impact of the COVID-19 pandemic on the mental health and wellbeing of public safety personnel and healthcare workers. Another area of research focuses on developing novel treatment interventions for trauma-related illnesses. Here, we focus on what are often ignored aspects of PTSD and trauma –for example, dissociation, feelings of guilt and shame, moral injury, moral distress. Those particular areas are often not the subject of treatment interventions in developing and testing new treatments. Finally, we have a military mental health and wellbeing stream where we're focused on areas of particular importance to the Canadian Armed Forces (CAF). For instance, characterizing experiences of military sexual trauma in equity-deserving groups and developing interventions. We travel to CAF bases to deliver training around trauma-informed approaches and methods of taking disclosures of sexual trauma. We also focus on women's experiences in the military –particularly female veterans. So, we've really been trying to develop a lot of research surrounding the experiences of equity-deserving groups in the CAF.

WE NOTICED THAT A VITAL COMPONENT OF YOUR WORK HINGES ON DEVELOPING TREATMENT INTERVENTIONS TO TREAT TRAUMA-RELATED CONDITIONS. HOW DO YOU TRANSLATE YOUR RESEARCH AND KNOWLEDGE INTO REAL-WORLD TREATMENTS? HOW DO YOU DEVELOP AND TEST THESE INTERVENTIONS?

Although I enjoy being a researcher, I think it's really important to collaborate with people with lived experience; for example, individuals who have experienced trauma and clinicians who work with these individuals. The first treatment intervention we became involved in was cognitive rehabilitation using the Goal Management Training approach developed at Baycrest Centre in Toronto. As a clinical neuropsychologist, I would talk to patients about their cognitive difficulties that they lacked treatment for. We began conducting randomized control trials for Goal Management Training in public safety personnel receiving inpatient care at Homewood Health Centre. We plan on completing pre- and post-treatment neuroimaging to offer treatment options for difficulties in memory attention and executive functioning. Right now, we're also working on a psychoeducation approach involving "bottom-up" therapy for post-traumatic stress symptoms. We're providing people with strategies to help regulate bodily arousal and get them back to an optimal zone where they're able to process information without feeling distressed or underwhelmed. 30% of individuals with post-traumatic stress conditions may present as having a dissociative subtype, where they don't feel present in their body but are present in the world around them and have a hyperarousal presentation. For example, the typical symptoms of PTSD include high levels of arousal and irritability. We're trying to target both facets of post-traumatic response through bodily regulation and grounding either the traditional term.

CAN YOU DESCRIBE YOUR FEDERALLY-FUNDED $2.96 MILLION DOLLAR STUDY, HEALTHCARE SALUTE, TO OUR READERS? WHAT IMPLICATIONS AND FINDINGS IN THE FIELD OF PTSD RESEARCH DO YOU HOPE TO FIND?

This stemmed from an initial donation that we received from Home Health Centre to understand the mental health and wellbeing impacts of the pandemic on healthcare workers. I was very fortunate to provide mental health support on ICU and COVID units regionally to understand the experiences of our healthcare performers. We wanted to first identify the problem to characterize the experiences of healthcare workers and public safety personnel over time. We discovered that many healthcare workers were experiencing a lot of moral distress around the pandemic. For example, healthcare workers would turn away visitors from a critically ill child or provide care for families holding on to hope, not knowing if invasive or painful treatments would be effective. We wanted to develop a suite of online tools and resources for health care workers. Through funding from the Public Health Agency of Canada, we developed Health Care Salute, a website that's available to anyone who would like to access it. Here, we have educational material about moral injury and moral distress. We have an approach to help cope by providing education around symptoms and expected responses to high levels of trauma. We talked about how to provide trauma-informed care to healthcare workers and other individuals who have experienced trauma. There are tools to monitor how one is doing and when to reach out to help. Importantly, we have a navigator model which provides access to information on free resources across Canada to support the mental health and wellbeing needs of healthcare workers.

WHAT ADVICE DO YOU HAVE FOR READERS THAT MAY BE INTERESTED IN EXPLORING THIS FIELD IN THE FUTURE?

Follow your passion. When I was in graduate school, I wanted to do something that I could go to a dinner party or talk to people about, and I would feel really passionate about. I spent a lot of time trying to figure out how to do that kind of work that I was most interested in. That same passion has allowed me to carry on with my career because I really love what I do. I want to use research as a way to give back and to serve. Often research can be framed as somebody who is trying to build a career with publications and grants and so on. All that's true, but in our lab, we focus on service. So how can we serve those who serve us across Canada? How do we help women who have experienced early life developmental trauma, sexual trauma, for example? Wanting to give back through research. When you have a greater purpose surrounding your research where you can see the tangible impact it has on others –that's another way of moving forward with your career. Whether that involves traveling to military bases and doing intervention work or developing new treatments. Really, it's important to not only characterize the impacts of trauma but to try to do something about it. We want to try to help shape policy. We want to look at problems that are major issues for our country. How can we use research to help with those problems? That's been our orientation or our approach. For those who are starting out, it's important to volunteer or be involved in research labs during your undergraduate training. Thinking about when you're applying to graduate school or medical school, what sort of experiences can you talk about? You want to be reflecting upon your learning. So if somebody asks you, "what did you learn from that experience?" you can respond to that question: what did patients teach you? Because patients are our best teachers. And be persistent. Many of the graduate students in my lab are people who email me many, many times. So I would say also be persistent around you know, being interested in working somewhere.

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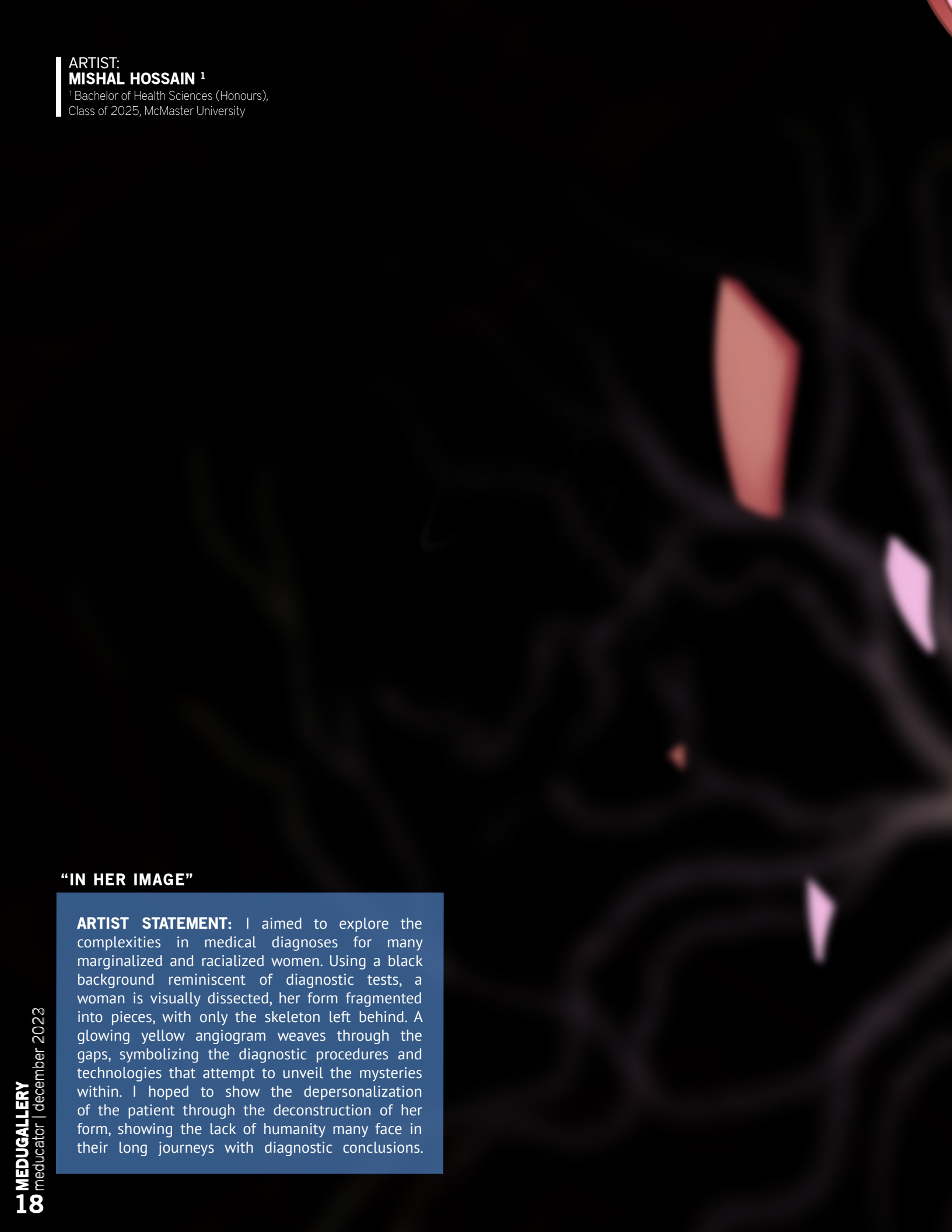
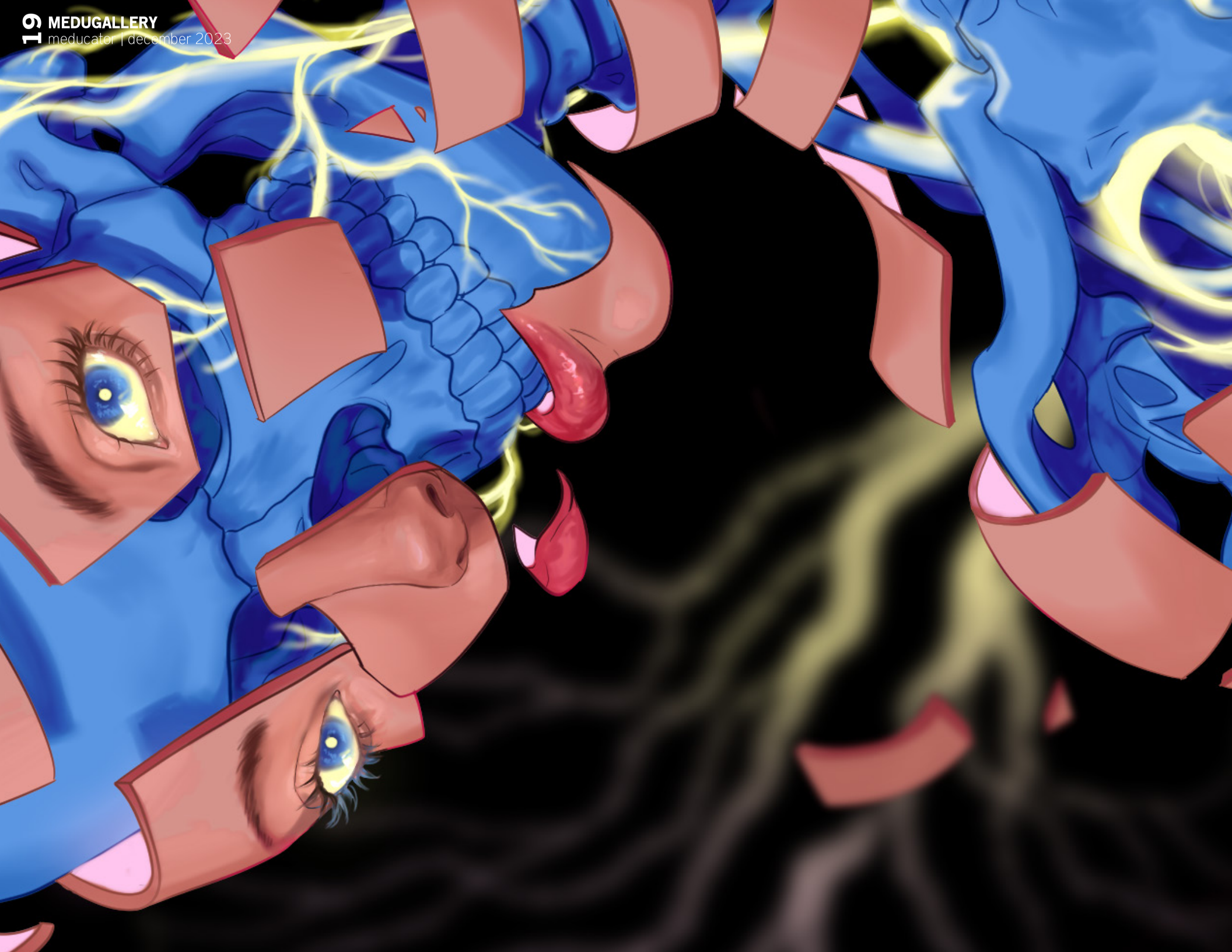


"IN HER IMAGE"

ARTIST STATEMENT: I aimed to explore the complexities in medical diagnoses for many marginalized and racialized women. Using a black background reminiscent of diagnostic tests, a woman is visually dissected, her form fragmented into pieces, with only the skeleton left behind. A glowing yellow angiogram weaves through the gaps, symbolizing the diagnostic procedures and technologies that attempt to unveil the mysteries within. I hoped to show the depersonalization of the patient through the deconstruction of her form, showing the lack of humanity many face in their long journeys with diagnostic conclusions.



CHRONIC KIDNEY DISEASE

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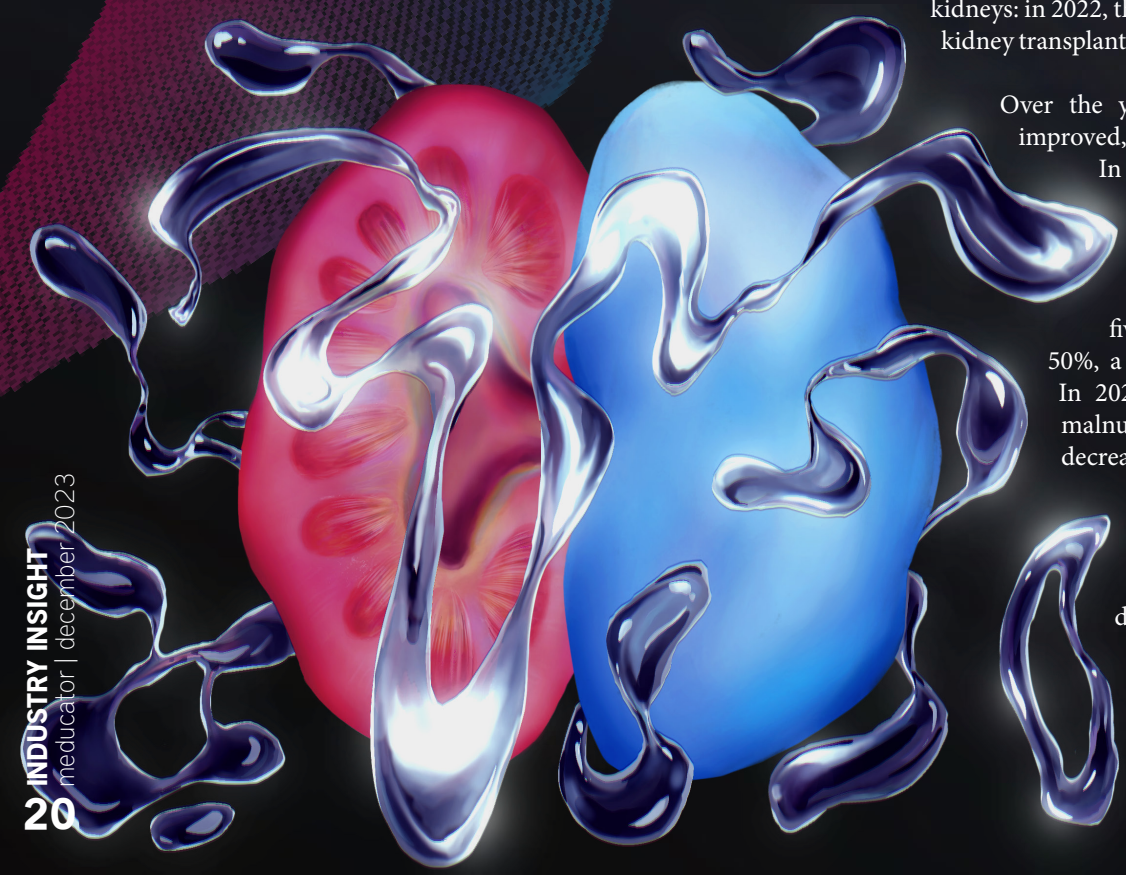
WHAT IS CHRONIC KIDNEY DISEASE?

Chronic kidney disease (CKD) is defined as low filtration function in the kidneys, protein in the urine, or functionally-important structural abnormalities.[1] Low filtration function is associated with waste build-up in the bloodstream and difficulty in excreting salt and water, leading to fluid build-up.[1] CKD may worsen over time, and some individuals with CKD may experience kidney failure, at which point dialysis or transplantation is required to replace kidney function.[1]

CKD may be caused by diabetes, renovascular disease, glomerulonephritis, polycystic kidney disease, and various genetic and environmental factors. In 2023, approximately four million Canadians live with and 11-13% of the global population are affected by CKD.[2] This disorder has a 50% five-year mortality rate and is associated with lower quality of life compared to other chronic diseases, including sickle cell anemia, cancer, and cystic fibrosis.[3] CKD's comorbidities, such as diabetes, are increasing in prevalence and can increase the risk of developing CKD.[3] Thus, the rates of CKD are also set to rise.[3] Annual CKD management costs across Canada total $40 billion, with dialysis treatment for people with end-stage kidney disease (ESKD) costing $100,000 per patient.[3]

CURRENT TREATMENTS

Current treatments for ESKD include hemodialysis, peritoneal dialysis (PD), and kidney transplantation.[4] Hemodialysis can be used to replace kidney function by filtering a patients' blood to remove urea, salts, and other toxins. This process is intrusive and resource-intensive, involving three to four hour sessions three times a week. PD is a less resource-intensive home-based modality associated with less fluctuation in fluid status and provides similar life expectancy but better wellness outcomes.[4] PD works by adding and removing dialysis fluid to the bloodstream via a bag implanted to the peritoneum lining.[5] Kidney transplants surgically replace a malfunctioning kidney with a healthy donor kidney. However, transplants require lifelong immunosuppressive treatment and may eventually fail. Nonetheless, patients who undergo kidney transplantation had a 1.2 in 100 annual death rate compared with 16.5 in 100 for dialysis patients.[6] There is, however, a shortage of kidneys: in 2022, there were 2,813 individuals in need of a kidney transplant in Canada and 1,195 kidneys donated.[7]



Over the years, these techniques have rapidly improved, increasing in efficiency and efficacy. In 1998, the one-year mortality rate of dialysis patients was 25%, primarily due to infection, cardiovascular conditions, and comorbidities, such as high blood pressure.[8] In 2012, the five-year mortality rate was recorded at 50%, a significant improvement from 1998.[9] In 2023, many related conditions such as malnutrition and high blood pressure have decreased due to improvements in dialysis efficiency, quality, and accessibility. During the same timeframe, the 10-year survival rate for recipients of kidney transplant from deceased donors increased from 60.5% to 66.9%.[8,9] The long-term negative effects of kidney grafts likewise decreased due to the refinement of immunosuppressive therapies.

ASTRAZENECA

AstraZeneca, partnering with Columbia University, investigated genetic markers of CKD enabling researchers to determine a genetic diagnosis in 10% of CKD patients.[11] AstraZeneca is currently developing genomic databases to identify urinary biomarkers for CKD to create more efficient screening tools. Furthermore, new target treatments are being tested with organ-on-a-chip and 3-D bioprinted models, which can simulate the anatomy and physiology of a real kidney. Subsequently, researchers can conduct more accurate and reliable preliminary testing while reducing some of the financial and physical burden of traditional *in vivo* testing.

Ionis Pharmaceuticals licensed ION532, a drug targeting a prominent genetic driver for kidney disease gene APOL-1, to AstraZeneca for $30 million USD for commercialization.[12,13] ION532 has not yet been clinically tested, but has secured an additional $30 million USD investment upon development.[14]

BAXTER

Healthcare company Baxter International and medical device company Theranova launched an expanded hemodialysis (HDx) treatment, which reportedly "filters a wider range of molecules from the blood than conventional hemodialysis."[15] HDx combines specific filtration techniques to resemble a kidney's natural function.[16] Baxter's post-hoc found that HDx reduced hospitalization rates by 45%, resulting in a $6,098 USD reduction in associated costs per patient. Compared to the most medically effective non-expanded hemodialysis treatment available, the cost of dialysis with Thernaova's HDx was on average $4,772 USD lower per patient.[17]

UNITED THERAPEUTICS

A promising treatment for ESKD is xenotransplantation, which is currently being researched by United Therapeutics (UT).[18] Xenotransplantation involves transplanting cells or organs across different species. Pigs have been identified as the most acceptable donor species for humans, and significant progress is made in modifying the porcine genome to reduce immunological barriers and incompatibilities between pigs and humans.[19] Given that organ transplant supply remains relatively stable while demand increases annually, xenotransplantation could potentially address unmet needs by providing a renewable source of lifesaving organs.[19]

Current research focuses on assessing function and xenograft rejection. Montgomery et al. observed promising results in the prognosis of transplanted kidneys from genetically modified pigs supplied by UT into two human recipients who were declared neurologically dead.[18] Moments after reperfusion, the xenografts in both recipients began to produce urine. The measured platelet, white blood cell counts, and inflammatory markers at various time intervals remained stable and within normal ranges.[18] These results support the viability and potential clinical value of xenotransplantation, providing alternatives to transplants and reducing organ shortages in CKD.[18] As of March 2023, UT funded Johns Hopkins' researcher and surgeon Dr. Kazuhiko Yamada and Dr. Andrew Cameron with $21.4 million USD to perform pre-clinical research and study the outcomes of xenotransplantation in living patients.[19]

QIDNI

Qidni Labs, a Kitchener-based startup, is working on addressing the accessibility of dialysis machines to improve CKD patient outcomes in rural areas, disaster zones, and emergency settings.[20] While traditional dialysis requires 120 liters of purified water per dialysis, Qidni dialyzers require significantly lower amounts of water.[20] By simultaneously providing equivalent quality, time, and price of dialysis, Qidni has been able to reduce water consumption and address the associated filtration costs by using readily-accessible saline solutions available in pharmacy settings.[20]

Additionally, Qidni has developed implantable bioengineered kidneys that use a nanofiltration system to mimic the organ's function and drain waste products into the bladder. The company founder, Dr. Morteza Ahmadi, successfully tested a prototype in a pig, which utilizes ultrathin nanoporous silicon membranes.[21] In 2013, Ahmadi et al. noted the material's fragility and potential to provoke an immune response, suggesting that the membrane should be coated with a biocompatible material.[21] Qidni Labs continues to research and develop novel implantable maintenance-free portal devices that could free patients from dialysis machines.[21]

THE FUTURE OF CKD

The CKD treatment market continues to focus on research and development of more viable treatments for patients and economies alike. As research and industry innovations in this domain progress, the scientific and economic future for kidney failure treatments is promising.

REVIEWED BY: DR. SERGI CLOTET-FREIXAS & DR. CATHERINE CLASE

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References can be found on our website, www.themeducator.org

HEALTH POLICY REVIEW

ONGOING DEBATE ON MEDICALLY-ASSISTED DEATH IN CANADA

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INTRODUCTION: LEGISLATIVE & HISTORICAL CONTEXT

In 2016, Canada introduced Bill C-14, the Medical Assistance in Dying (MAiD) Act, providing an end-of-life care option for a rapidly increasing number of Canadians.[1] MAiD includes active and passive methods, known as voluntary euthanasia, administered by a designated medical professional, and assisted suicide, the provision of medication by a medical professional to self-administer.[2] The House of Commons and Senate passed Bill C-14 following the Supreme Court's unanimous decision in *Carter v Canada*. This case challenged the prohibition of physician-assisted death, decreeing it an infringement on the Canadian Charter of Rights and Freedoms.

Under Bill C-14, medical and nurse practitioners providing MAiD were deemed exempt from criminal liability of homicide.[2] Eligible patients must be at least 18 years old and fulfill multiple criteria: possess decision-making capacity, be suffering from an incurable illness, disease, or disability in an irreversible state of decline, intolerable physical or psychological suffering, as well as a "reasonably foreseeable" natural death. This criterion involved safeguards, where requests required voluntary informed consent, two independent witnesses, a ten-day waiting period, and consent at the time of MAiD.[3]

Although the definitions of intolerable suffering vary, many patients request MAiD due to a loss of autonomy, independence, enjoyment, or a fear of future suffering due to their health condition.[4] In 2021, Bill C-7, an amendment to the MAiD Act, put forth revised eligibility criteria waiving the requirement of "reasonably foreseeable" natural death in response to public discourse suggesting an *"unconstitutional exclusion"* of patients who meet all other eligibility criteria.[3] New strengthened safeguards were implemented for such applicants. Notably, a 90-day observation period from the initial assessment and the day MAiD is provided, subject to alteration considering any imminent loss of capacity during that time.[3] Meanwhile, several safeguards were waived for naturally foreseeable deaths. Specifically, the ten-day waiting period and the requirement of final consent were both removed to avoid patients' suffering from fear of losing decisional capacity over the waiting period, or from refusing pain medication to preserve their ability to provide final consent.[3]

In March of 2024, MAiD eligibility laws stand to change further with the implementation of Bill C-39, stipulating that individuals solely suffering from a mental illness will gain eligibility.[5] The rapid progression from prohibiting MAiD to the widened current and foreseeable scope of legalized eligibility has sparked substantial public scrutiny and ethical debate.

THE ARGUMENT OF AUTONOMY & RIGHTS

A 2018 qualitative case series study, while Bill C-14 was in effect, found a common sentiment about MAiD among Vancouver recipients; the vast majority concurred that their ailments compromised their quality of life through constant struggles with health function and a loss of purpose.[4] Patients were confident, well-informed, and unapprehensive about pursuing MAiD. In cases of great suffering and end-of-life palliative care, many supporters argue that one should have the autonomy to choose MAiD.[4]

Proponents often argue that MAiD gives patients autonomy when suffering from a disempowering health condition. Through decriminalizing MAiD, the Canadian government sought to affirm the autonomy and dignity of persons suffering from grievous or irremediable medical conditions to seek MAiD.[2] Upon discussion of eligibility expansion, many advocates in the media argue that assisted death is a matter of personal choice, and restrictive criteria against non-foreseeable death and persons with disabilities are paternalistic against those who are suffering.[6] In the same vein, some argue that individuals with mental illness should not be restricted from choices available to others who are suffering. In a CBC opinion piece, one such individual seeking MAiD argues that there is a disconnect between the opinions of health experts and the lived experience of individuals who have a mental illness, where all health efforts have been futile.[7] Therefore, excluding such individuals, while they may meet all other eligibility requirements, infringes on their autonomy.[7] Medically providing individuals with the support needed to die peacefully, without pain, and comfortably by their own choosing is also often seen as more dignified than unpleasant or unpredictable alternatives.[6] In this context, MAiD accessibility seeks to grant autonomy, empowerment, and dignity to all individuals suffering from intolerable health issues in their medical decisions.

Many also concur that access to MAiD is a matter of preserving rights. *Carter v. Canada* was a catalyst, from which the Supreme Court of Canada found that laws upholding MAiD prohibition directly violated Canadians' Section 7 Charter rights to "life, liberty, and security of the person". Though MAiD prohibition laws sought to protect vulnerable persons from suicide, *Carter* argued that this law was overbroad. The Court agreed that the prohibition disproportionately denied the rights of individuals who are not vulnerable through its overbreadth.[2] The alterations pushed forth by Bill C-7 were prompted by *Truchon v. Canada*, where the Supreme Court of Quebec ruled that restricting MAiD from people without a "reasonably foreseeable" natural death also directly violated these Charter rights by preventing people with grievous and incurable medical conditions from making decisions about their own bodily integrity.[2,3,8] The incoming consolidation of Bill C-39, including individuals suffering only from mental illness within the fold of eligibility, rests upon a similar justification of preserving constitutional rights. MAiD was decriminalized with carefully designed safeguards to protect Canadians' rights and safety, primarily formed by the Special Joint Committee on MAiD, a Parliamentary group handling the review and provision of MAiD laws.[9]

MAID AND PALLIATIVE CARE

While the Canadian Government considers MAiD a method of alleviating suffering, healthcare practitioners are concerned that MAiD expansion is becoming a method to relieve suffering caused by a system that lacks sufficient palliative care. The 2023 Access to Palliative Care Report in Canada describes the persistent issue that those in the early stages of their life-limiting diagnoses are often ineligible for palliative care.[10] Instead, half of all palliative patients lived for less than 22 days, indicating that palliative care primarily serves as end-of-life care. This inadequacy in palliative care access may decrease quality of life and increase symptom burden, which may contribute to the choice of seeking MAiD.[11] In a qualitative study by Pesut et al., nurses providing MAiD further discussed the tensions between a system focused on relieving suffering through MAiD and the undue suffering seemingly caused by this lack of access to specialized care.[12] One nurse states, "[Our] healthcare system contributes to suffering [...] but then uses that very suffering to activate access to MAiD", which may indicate a focus on increasing MAiD access over delegating more attention towards improving patients' access to care.[12]

However, it should be noted that improved access to palliative care may have a limited effect in reducing MAiD requests. A cohort study conducted by Seow et al. found that 88% of terminally ill patients, mainly with a cancer diagnosis, received more intensive and earlier palliative care, despite cancer constituting 65.6% of MAiD provisions in 2021.[13] Although these patients had access to earlier, more proactive, and higher quality of palliative care, their increased incidence of MAiD requests indicates that improved palliative care minutely decreases the likelihood of terminally ill patients requesting MAiD. Thus, it is argued that although access to palliative care may have modest effects in increasing patients' quality of life, establishing MAiD availability continues to be essential to preventing undue suffering in terminally ill patients.

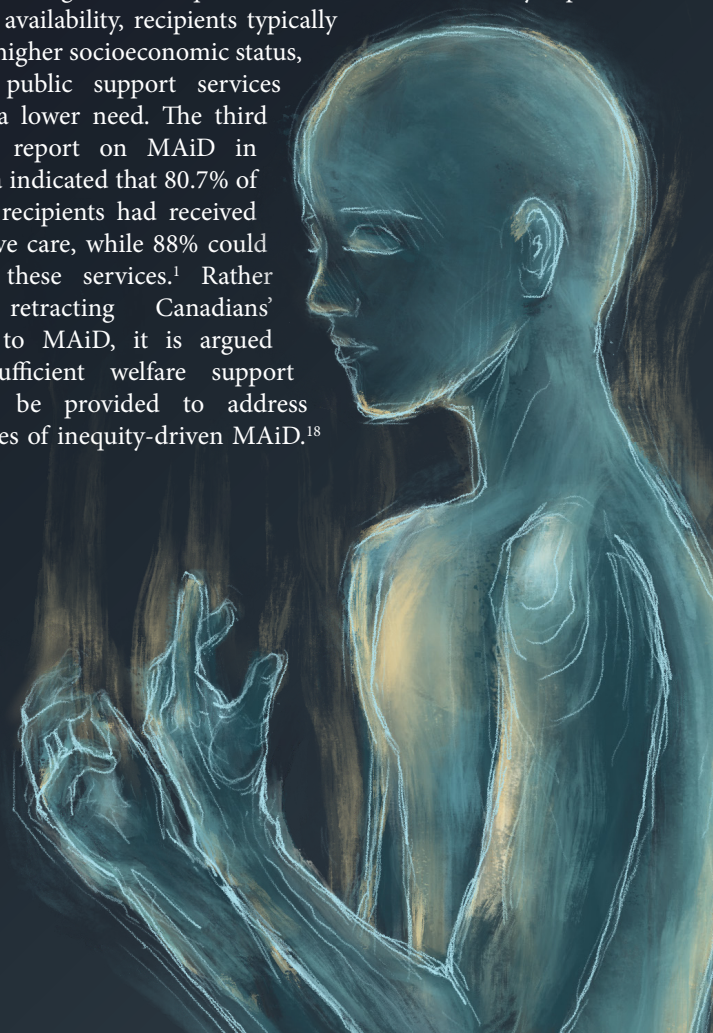
THE ISSUE OF STRUCTURAL VULNERABILITY

Structural vulnerabilities refer to the impacts of demographic attributes such as socioeconomic status, sex, gender, race, or ethnicity on one's position in social hierarchies.[14] Public and academic discourse on MAiD remains concerned with individuals' structural vulnerabilities to exploitation or coercion from existing social inequities.

The final report of the Expert Panel on MAiD and Mental Illness notes that reflection on such factors that "constrain decision-making, frame choices, and limit life options" is imperative.[14] The stigmatization of some demographic attributes may lead to instabilities in housing, employment, and social support, thereby contributing to an individual's suffering. Structural vulnerability also indirectly contributes to suffering by reducing care accessibility, which can occur by many social determinants of health. Social variables influence illness and recovery trajectory, as resource inequities can bring about and perpetuate originate health disparities.[15] In a recent study involving a group of Canadians living with mental illness, researchers explored MAiD with respect to mental illness and social health determinants.[15] Socioeconomic disadvantages, limited mental health support, stigma, and discrimination constitute a "social facet of suffering" that many MAiD recipients experience. Many also critiqued the availability and coverage for MAiD as opposed to more comprehensive mental health support.[15]

Although MAiD aims to preserve patients' autonomy, detractors of MAiD legalization provide an alternate perspective.[16] The president of the Canadian Association of MAiD Assessors and Providers noted that "Our health system is woefully inadequate in serving [the Canadian] population with [social service] resources," as outlined in a 2023 review of the Canadian MAiD program.[16] Ultimately, this suggests autonomy is compromised in many groups due to structural vulnerabilities. Further, released by the Parliamentary Budget Officer, the 2020 cost analysis of MAiD notes that Canada's healthcare costs dropped by a net $86.9 million since legalization, and predicts a drop of a net $149 million upon eligibility expansion with Bill C-7.[17] With such framing, MAiD enables structural vulnerabilities and undignified living conditions by diverting pricier alternatives of expanding welfare and palliative care services. Given the coercive and pressured influence of poverty, racialization, disability, systemic healthcare imbalances, and limited social support services, it is argued that MAiD undermines autonomy in end-of-life care.[6] The removal of safeguards, notably in Bill C-7 and the incoming C-39, does not equalize marginalized groups as intended because they were not equal beforehand.[6]

It is, however, essential to note that some studies find that structural vulnerabilities are not significantly impactful in driving MAiD. In 2023, Downar et al. evaluated palliative care and structural vulnerabilities in Canada, concluding that socioeconomic deprivation does not considerably increase MAiD usage.[18] Though MAiD requests could be driven by poor service availability, recipients typically have a higher socioeconomic status, where public support services are at a lower need. The third annual report on MAiD in Canada indicated that 80.7% of MAiD recipients had received palliative care, while 88% could access these services.[1] Rather than retracting Canadians' access to MAiD, it is argued that sufficient welfare support should be provided to address instances of inequity-driven MAiD.[18]



IMPLICATIONS OF MAID ON HEALTHCARE

With its legalization in 2016, the demand for MAiD services has increased exponentially, especially with the addition of Bill C-7, which deemed the eligibility criteria of a "reasonably foreseeable death" as unconstitutional. Healthcare professionals who provide MAiD have reported changes in the population, particularly in increasing visibility and normalization of the procedure.[3] However, the growing demand for MAiD services faces a looming issue concerning the number of willing MAiD providers, as MAiD is an optional "add-on" responsibility for physicians and nurse practitioners.[19, 20] By nature, the responsibility of being a MAiD provider is highly regulated, emotionally taxing, and laden with various potential ethical and moral quandaries.[20] Thus, the increase in demand for MAiD services and the number of new MAiD providers has not been proportional, as demonstrated in the 2021 federal report.[19] Despite a 32.4% increase in MAiD throughout 2020, there was only a 17.2% increase in providers over the same period.[1,19]

Accessing MAiD is a laborious process for both physicians and patients. Two independent physicians or nurses must evaluate a patient to ensure the individual meets the eligibility requirements.[21] Furthermore, MAiD cases are rarely straightforward, causing additional strain on MAiD practitioners who must navigate the ambiguity of a referral for a final decision.[22] In addition to complex cases, the legislative criteria of eligibility are vague, causing the assessment to be subject to interpretation.[3] Oftentimes, there are also disagreements between providers, patients, and other stakeholders involved in the process. In a qualitative study about navigating Bill C-7, assessors expressed relief when receiving relatively straightforward referrals that could be deemed eligible.[3] A sense of guilt and sadness was associated with deeming a patient ineligible for MAiD.[3,20]

Therefore, it is also crucial to examine the mental health and psychological impact of providing MAiD. A study by Dholakia et al. on the emotional impact on healthcare providers involved with MAiD reported polarizing emotions. There were positive emotions of reward and relief of providing a valuable service. At the same time, recurring themes of powerlessness, guilt, emotional exhaustion, and vicarious suffering were reported among healthcare providers.[14]

CONCLUSION

Discussions of loosening MAiD eligibility requirements are steadfast into 2024, primarily concerning the current exclusion of "mature minors" and individuals suffering only from mental illness and "mature minors"–as in, minors possessing the decisional capacity to choose or reject a given treatment.[5] Bill C-39, which stands to include patients suffering only from mental illness within the fold of eligibility, was postponed from March of 2023. The one-year extension intends to provide additional time to prepare for safe and equitable MAiD assessment and provision guidelines.[5,9]

Proponents of MAiD advocate for the preservation of patient autonomy and Canadians' Charter rights to "life, liberty and security of the person". However, concerns regarding the contribution of inadequate palliative care access to the suffering underlying MAiD requests continue to arise among healthcare practitioners. Additionally, individuals remain concerned about issues of structural vulnerabilities among marginalized groups and coercion to MAiD. The increasing demand for MAiD services is met with the shortage of willing providers due to the unique emotional and mental burdens associated with providing MAiD. Therefore, there is a need for improved support and organizational structures to ensure the service is sustainable. Though there are several observed benefits of MAiD accessibility in healthcare, particularly protecting autonomy and rights, increasing public concerns about social vulnerability and insufficiencies in palliative care suggest a need for policy review and reform. This nuanced debate surrounding MAiD access and expansion will continue to grow as the Canadian healthcare system develops.

THIS HEALTH POLICY REVIEW WAS ANONYMOUSLY REVIEWED BY AN ASSOCIATE PROFESSOR OF MEDICINE AT MCMASTER UNIVERSITY.

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RESEARCH INSIGHT

SHARING SCIENCE MADE SIMPLE: EXPLORING THE QUALITY AND READABILITY OF PUBLISHED LAY SUMMARIES

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ABSTRACT

Lay summaries exist to bridge the gap that separates the scientific community from the general public. To foster improved science communication, this study examined the overall quality and readability of published lay summaries across peer-reviewed journals. We obtained 200 lay summaries published in four science journals: eLife, PLOS Medicine, Proceedings of the National Academy of Science (PNAS), and the Journal of Hepatology. Over 900 students across three semesters participated as raters of each summary using a rubric developed to assess the overall quality, accuracy, and accessibility of lay summaries across these journals. The Flesch Reading Ease formula was used to determine the readability of the highest and lowest scoring summaries from each journal. eLife and the Journal of Hepatology had the highest and lowest mean scores for overall quality of 15.6 and 11.7 out of 20, respectively. There were statistically significant differences in accuracy and accessibility found across all journals ($p<0.0001$). eLife had the highest scoring lay summary for readability. The differences in and lack of consistent scoring across journals with the rubric indicate that deficits exist in the overall quality and readability of published lay summaries. These findings may support the development of guidelines that incorporate elements of the rubric used to write effective lay summaries.

INTRODUCTION

Scientific journals are the predominant medium for communicating research findings. Scientists have the necessary training to read and contextualize scientific articles, however, the general public may lack these skills.[1] This is a significant issue as non-specialist audiences are key stakeholders in scientific research through their roles as patients, research participants, and members of society, and need to be informed of important advancements.[2,3] Unlike technical abstracts, lay summaries are designed to communicate research to the general public in an accessible format.[4] These texts are typically 250 to 300 words of relevant summary content that clarify complex ideas, and are free of jargon.[5,6] Further, scientific journals use the passive voice while lay summaries use the active voice to foster greater reader engagement.[7]

The Importance of Lay Summaries

Lay summaries benefit both the general public and the scientific community. Greater accessibility facilitates higher visibility of research, correlating with increases in the number of citations and future scientific collaborations.[8] Additionally, lay summaries extend the reach of research articles on social media and news platforms, removing the barrier for general audiences to understand and engage with relevant science.[9] This translation of knowledge can increase public interest in science, leading to greater public participation in research.[10] Lay summaries can help to combat misinformation, particularly in the health sciences.[10] Accuracy and accessibility are essential to a powerful lay summary. Accuracy refers to making information easier to understand without compromising the clear communication of facts. Accessibility refers to the removal of barriers to public understanding, such as jargon. Many researchers find it challenging to write lay summaries that accurately and accessibly communicate findings to the public.[3] This is troubling as lay summaries are the strongest defense against a reporting practice known as spin –the biased and inaccurate translation of scientific information, leading to misinterpretations.[11] Disparities in these aspects may be due to a lack of consensus and training on instructions to write lay summaries across peer-reviewed journals.[12] For example, PLOS Medicine requires authors to include a bullet point-structured summary of their research that is accurate and accessible to non-scientists.[13] However, apart from omitting technical terminology and acronyms, the terms accurate and accessible are not further defined.[13] According to a sentiment analysis published in the Cambridge University Press, the readability of scientific writing has declined, while the use of scientific jargon has increased over the past three decades.[14] The Flesch Reading Ease (FRE) score is a readability measure that assesses how easily a piece of text can be understood. Applying the FRE to scientific abstracts has revealed that the average number of syllables per word and the average sentence length in scientific abstracts have steadily increased since 1960.[14] More than 20% of abstracts currently have an FRE score at the post-secondary level, well-above the target of 8th and 9th grade students.[15] These findings indicate that current science communication efforts may not effectively convey research findings to general audiences.

Knowledge Gap and Research Question

This study builds on data collected from three semesters of undergraduate students in the LIFESCI 2AA3 course at McMaster University. The aim of this ongoing research is to help establish a gold standard for the quality of lay summaries across peer-reviewed journals. This study compares the quality of selected lay summaries across journals using a rubric to assess overall quality, including accuracy and accessibility, and the FRE score to assess readability. This investigation also explores the potential of this rubric in helping to establish guidelines for writing lay summaries.

RESEARCH DESIGN

This study analyzed 200 lay summaries from four reputable (impact factor of 3 or higher) scientific journals: eLife, PLOS Medicine, Proceedings of the National Academy of Science (PNAS), and Journal of Hepatology. These journals were selected as they consistently publish lay summaries alongside articles. Fifty lay summaries were assessed from each journal using two methods: a subjective, specially developed rubric to determine accessibility and accuracy, and an objective FRE formula score to determine readability. Over 900 undergraduate students in the LIFESCI 2AA3 participated as raters. Each lay summary was graded by six to nine students using a rubric (Appendix Figure A) created by Dr. Katie Moisse, Assistant Professor and Associate Director of the School of Interdisciplinary Science at McMaster University. The rubric had four categories, each worth five points for a total score for overall quality out of 20. Line 1 asked whether the study's methods, results, and conclusions were accurately summarized, while Line 2 asked the same of the rationale, implications, and limitations. Together, these lines evaluated accuracy. Line 3 assessed the clarity and organization of the writing, and Line 4

assessed whether it was tailored towards non-expert audiences, together evaluating accessibility. The statistical significance of the data was determined using a one-way ANOVA and Tukey Test. The FRE formula was used to calculate readability of the highest and lowest scoring lay summaries on the rubric from each journal, using the total words per sentence and total syllables per word.[16] The numerical scores and the corresponding United States school grade reading level necessary to understand the article were determined using the FRE table (Appendix Table A).[16]

RESULTS

eLife, PLOS, PNAS, and Hepatology had mean total rubric scores of 15.6, 14.7, 13.2, and 11.7, respectively. Total scores were significantly different across the four journals ($p<0.0001$), and between each journal ($p<0.0001$) (Figure 1).

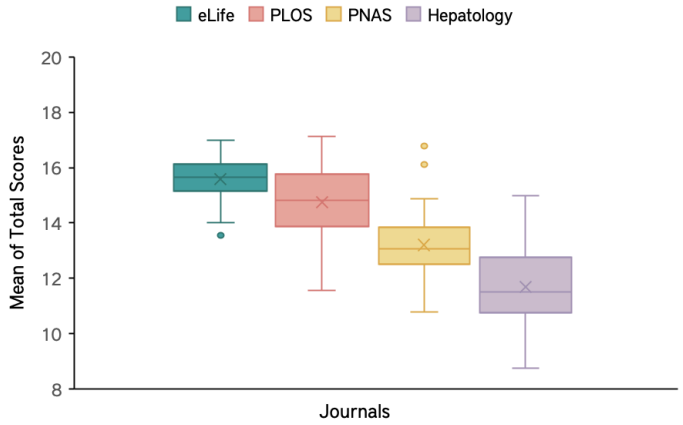

Figure 1. Mean of total scores for each journal using the LIFESCI 2AA3 rubric. Each of the four categories were scored out of five, 1 being strongly disagree and 5 being strongly agree. Each journal received a total score out of 20, which was used to assess overall quality (accuracy and accessibility). Statistically significant differences in quality were found across all journals ($p<0.0001$).

Figure 2A highlights the outlier in the accuracy trend mentioned above; eLife vs. PLOS show no significant differences in accuracy ($p=0.6134$). Of the two, PLOS scored the highest in accuracy with mean scores of 3.9 and 3.6 out of 5 for Lines 1 and 2, respectively. Additionally, Figure 2B highlights the outlier in the accessibility trend mentioned above; PNAS vs. Hepatology show no significant differences in accessibility ($p=0.8752$). Of the two, eLife had the highest accessibility scores of 4.3 and 4.0 out of 5 for Lines 3 and 4, respectively.

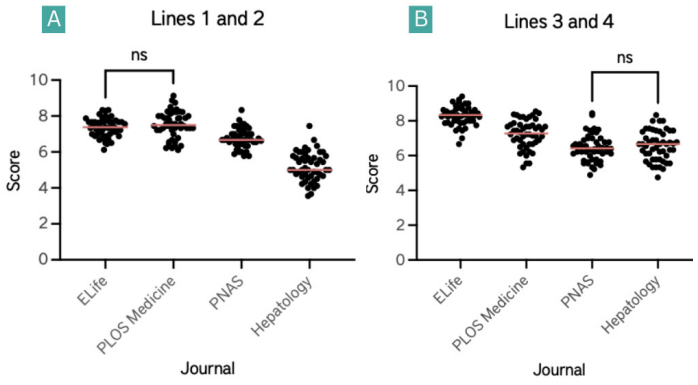

Figure 2. Scatterplot of combined total scores. (A) Lines 1-2 represent accuracy. **(B)** Lines 3-4 represent accessibility. Each dot represents an individual lay summary. The median is represented by the red lines. No statistical significance is indicated by "ns".

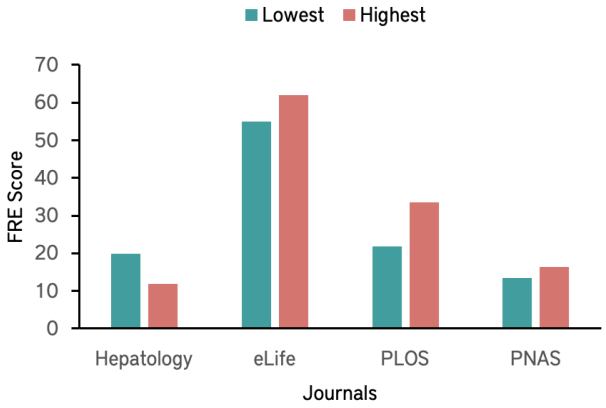

Figure 3. Bar graph with FRE scores for the highest and lowest scoring lay summaries from each journal. The highest scoring lay summary was from eLife, which also had the highest FRE score of 62.0, corresponding to the reading level of an 8th to 9th grade student (Figure 3). Lay summaries from PLOS, PNAS, and Hepatology scored between 10.0 and 30.0 on average, corresponding to university level or higher (Appendix Table 1).

DISCUSSION

Overall Quality

In order to promote effective communication of scientific research, the quality of lay summaries must be improved, as demonstrated by the results of this study. eLife had the highest overall quality, with a mean rubric score that is 1.4 times that of Hepatology, the lowest scoring journal (Figure 1). As seen in Figure 1, eLife also had the smallest range of 3.0 for overall quality, suggesting a greater consistency in scoring across raters of the three semesters for the journal and its published lay summaries. Hepatology scored the lowest for accuracy and overall quality, indicating greater variability in grading. The differences discovered between journals and eLife's high rubric score may be a reflection of the guidelines used to publish their lay summaries, called *eLife digests*. eLife collaborates with freelance writers and science communicators to provide clear and engaging insights into research.[17] Unlike the other journals examined, eLife has invested resources into researching different approaches to translate science for general audiences.[17] *eLife digests* are typically 200-400 words, and are considered to have an optimal length by 90% of non-scientist readers, as found in a 2016 *eLife digest* reader survey.[18] *eLife digests*' high quality scores on the rubric demonstrate the value of a lay summary writing process with clear guidelines to produce accurate and accessible lay summaries.

Readability

As seen in Figure 3, the lowest and highest quality summaries from eLife had the highest FRE score of 52.0 and 62.0, respectively. This, along with the faFct that eLife had the highest score for accessibility and overall quality in this study, suggest that improved readability may contribute to a higher score on the rubric. The average assessed lay summary scored at the undergraduate and graduate level of readability. Thus, many lay summaries may be difficult to understand for individuals without a higher level of education. Studies of lay summaries from a similar level of journals

(impact factor higher than 3) have also demonstrated lower FRE scores. Wen et al. found that while lay summaries published in Autism Research were significantly more readable than their corresponding abstracts, the mean FRE score for lay summaries was 34.39.[19] Shiely and Daly assessed a random sample of lay summaries from randomised controlled trials from the National Institute for Health and Care Research and found a mean FRE score of 42.77. [20] These findings align with the undergraduate literacy level requirement found in this investigation. The restrictive readability illustrates the need for researchers and editors to adopt more accessible writing techniques. As shown in Figure 3, the highest scoring summary from Hepatology on the rubric had a lower FRE score than the lowest scoring summary. This finding suggests that readability scores may not always function as an accurate measure of an individual's comprehension. Studies have found that some general audiences prefer plain-language summaries of medium complexity, written for a reading level between 14-17 years.[21] Hence, a higher FRE score may not necessarily correspond to a higher quality lay summary on the rubric. Additionally, oversimplified lay summaries may not only miscommunicate findings but may also lead to negative public perception.[21]

Implications, Limitations and Next Steps

The findings of this study should be used to inform guidelines for the communication of scientific findings to the public. The scores obtained from the combined dataset of the three semesters of students did not differ significantly from that of each semester alone. Thus, the consistency in gradings for each journal may support the use of the specially developed rubric as a standardized guideline for writing lay summaries. The depth of raters' evaluations in the study was limited by the rubric's design, which featured only four sections to assess accuracy and accessibility. Free-text feedback and thematic coding could be used with the rubric to identify nuanced factors and perceptual differences that may be missed using the current rubric. Readability measures such as FRE are also limited in the scope of their evaluation, as the formulas cannot assess other features that affect a reader's understanding such as headers, visuals, and line spacing. Future research should assess how a lay summary that is written in accordance with the rubric in this study alters the overall comprehension of the text by non-technical audiences.

CONCLUSION

This study explored the overall quality of published lay summaries across peer-reviewed journals. We found significant differences in the overall quality between journals. Additionally, we found differences in readability scores that support the need to use more inclusive writing techniques in science. This research can help improve science communication by supporting guidelines for writing lay summaries across journals.

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APPENDIX

Figure A. LIFESCI 2AA3 lay summary grading rubric.

Does the lay summary accurately summarize the study methods, results and conclusions?	Does the lay summary accurately summarize the study rationale, implications and limitations?	Is the lay summary's writing clean, clear and logically organized?	Is the lay summary's writing tailored to its audience and purpose?	Total

Table 1. Flesch Reading Ease (FRE) Scores.[14]

Reading Ease Score	Reading Level/Grade	Description
90 – 100	5th Grade	Very Easy
80 – 90	6th Grade	Easy
70 – 80	7th Grade	Fairly Easy
60 – 70	8th and 9th Grade	Standard
50 – 60	10th to 12th Grade	Fairly Difficult
30 – 50	College/University	Difficult
0 – 30	Graduate	Very Difficult

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Pathways to Identity:
Navigating Gender-Affirming Care for Youth

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INTRODUCTION

The increasing recognition of transgender and gender non-conforming (TGNC) identities has ushered in a new era in healthcare, where gender-affirming treatment (GAT) has become a common approach to address these populations' specific needs and challenges.[1] According to the 2021 Canadian Census of Population, the proportions of transgender and non-binary people were three to seven times higher for Generation Z and millennials than Generation X and baby boomers.[2] Common GAT methods include talk therapy, hormone replacement therapy (HRT), puberty blockers (PBs), and gender-affirming surgeries. These treatments aim to reduce gender dysphoria which TGNC individuals describe as an incongruence between one's experienced gender and sex assigned at birth.[3] Although treatment access is increasing, fear of social stigmatization can limit the extent to which TGNC youth can access these services.

In Canada, the Common Law Mature Minor Doctrine allows mature children to make autonomous treatment decisions.[4] Access to GATs is a pivotal step towards improving the wellbeing of TGNC youth. Gender dysphoria can lead to severe mental health issues, such as depression, anxiety, and suicidal ideation if left untreated.[5] According to a Canadian review conducted by Kingsbury et al., transgender adolescents showed 5 times the risk of suicidal ideation and 7.6 times the risk of a suicide attempt compared to cisgender, heterosexual adolescents.[6] The impact of GATs on TGNC youth has the potential to significantly reduce the negative impacts of gender dysphoria.[5]

STAGES OF GENDER TRANSITION: SOCIAL AND PHYSICAL ASPECTS

Gender transition or affirmation is a dynamic process whereby an individual affirms their gender identity through social and medical processes.[7] Many individuals transition socially, which involves changing the way TGNC youth present themselves to better align with their gender identity.[8] This may involve using a different name and pronouns, using gender-based facilities, and dressing in clothes associated with their gender identity.[9]

Individuals may also pursue physical transition, using hormonal and surgical treatment to alter their bodily appearance to better align with their desired gender identity.[10]

In Ontario, HRT and PBs can be prescribed through primary care physicians or endocrinologists, while chest and genital affirming surgery requires psychiatric assessment and/or documentation of gender dysphoria.[11] It is important to note that eligibility and insurance coverage for these surgeries vary between provinces and territories. Healthcare providers take note of several factors related to mental health, including discrimination, degree of support from family and peers, and pre-existing mental health conditions, which could impact a patient's decision to transition.[12] While HRT is the starting point for most individuals, every plan will differ based on the patient.[13] Estrogen is administered to exhibit traditionally feminine characteristics, while testosterone is administered to increase traditionally masculine characteristics.[14] Alternatively, PBs are considered to be a fully reversible option to suppress the progression of puberty for youth who have not started or are in the early stages of puberty. Using PBs and subsequent HRT is correlated with improved mental health outcomes and quality of life.[15] These treatments can also provide additional time for patients to reflect upon their gender identity before the potential pursuit of irreversible gender-affirming surgeries.[12,13] Over the past 5 years in Canada, there has been an increase in referrals of youth to specialty clinics offering gender-affirming care, mirroring trends in other countries.[16]

CHALLENGES AND BARRIERS

Ethical concerns surrounding GAT have been raised for TGNC youth, namely the ability of minors to make significant medical decisions while their sense of identity is still forming.[17] During childhood and adolescence, peer and societal influences can impact the decisions of youth who are uncertain of their identity, raising concerns as to whether they are capable of making pivotal decisions without parental consent.[18] Furthermore, some argue gender-affirming surgery is not 'medically necessary' but rather a matter of choice. However, these arguments overlook the consensus from medical professionals that affirming a person's gender identity is essential to their wellbeing.[15] Delaying or denying care can lead to emotional distress associated with transphobia and minority stress.[19-22] This can potentially lead to further mental health detriments, including depression and anxiety. Veale et al. highlights the significant disparities experienced by Canadian TGNC youth, with 74.9% of participants of the Trans Youth Health Survey having disclosed self-harm at least once in 2016.[23] Thus, mental health support is essential to reducing the emotional distress that may accompany gender dysphoria.

There are many negative impacts of delaying treatment for TGNC youth. Sorbara et al. demonstrated that gender-incongruent youth who present to gender-affirming treatment later in life have higher rates of psychoactive medication use and mental health problems.[24] Ensuring that the critical window for care is being met at younger ages can make a significant difference in the use of PBs. A study by Puckett et al., which thematically analyzed common barriers felt by 256 TGNC individuals, concluded that PBs were often a missed opportunity as many did not identify as transgender until after puberty.[25] Using puberty suppression in children and adolescents with gender dysphoria can lead to psychological improvements, such as decreased depression and increased overall functioning.[26] Identified disadvantages of starting PBs later in puberty include unpleasant side effects, such as hot flashes in individuals assigned female at birth, decreased growth velocity, and increased body mass index.[26] This emphasizes the impact of timely care and access to hormonal PBs in TGNC youth.[24]

Each TGNC youth's transition and treatment process is uniquely impacted by structural barriers. These include administrative issues, provider barriers such as denial of care, and care-seeking barriers such as unsupportive guardians.[27] Moreover, limited awareness among healthcare providers about the specific needs of TGNC individuals further restricts access. A study by Puckett et al. indicated that participants felt that there was a lack of knowledge surrounding gender-affirming care, often interfering with access to gender-affirming services.[24] Despite the growing accessibility of GAT, cultural and religious biases add contention to the acceptance of TGNC individuals and their medical treatment. Familial support and affirmation of TGNC youths' gender identities are correlated with improved quality of life and wellbeing.[28] However, a survey completed by Travers et al. demonstrated that only 33% of TGNC youth felt strongly supported by their family, while others did not receive explicit support, or even experienced open rejection.[30]

CONCLUSION

Despite the growing awareness for the challenges faced by TGNC youth and the consistent demonstration of positive mental health outcomes associated with GAT, there remain several barriers to accessing treatment and improving outcomes. In order to be an effective ally for TGNC youth, it is of the utmost important to remain informed of the unique challenges and discrimination faced by this population. By engaging in dialogue to reduce the stigma surrounding GAT, a path can be paved towards providing access to this life-affirming care.

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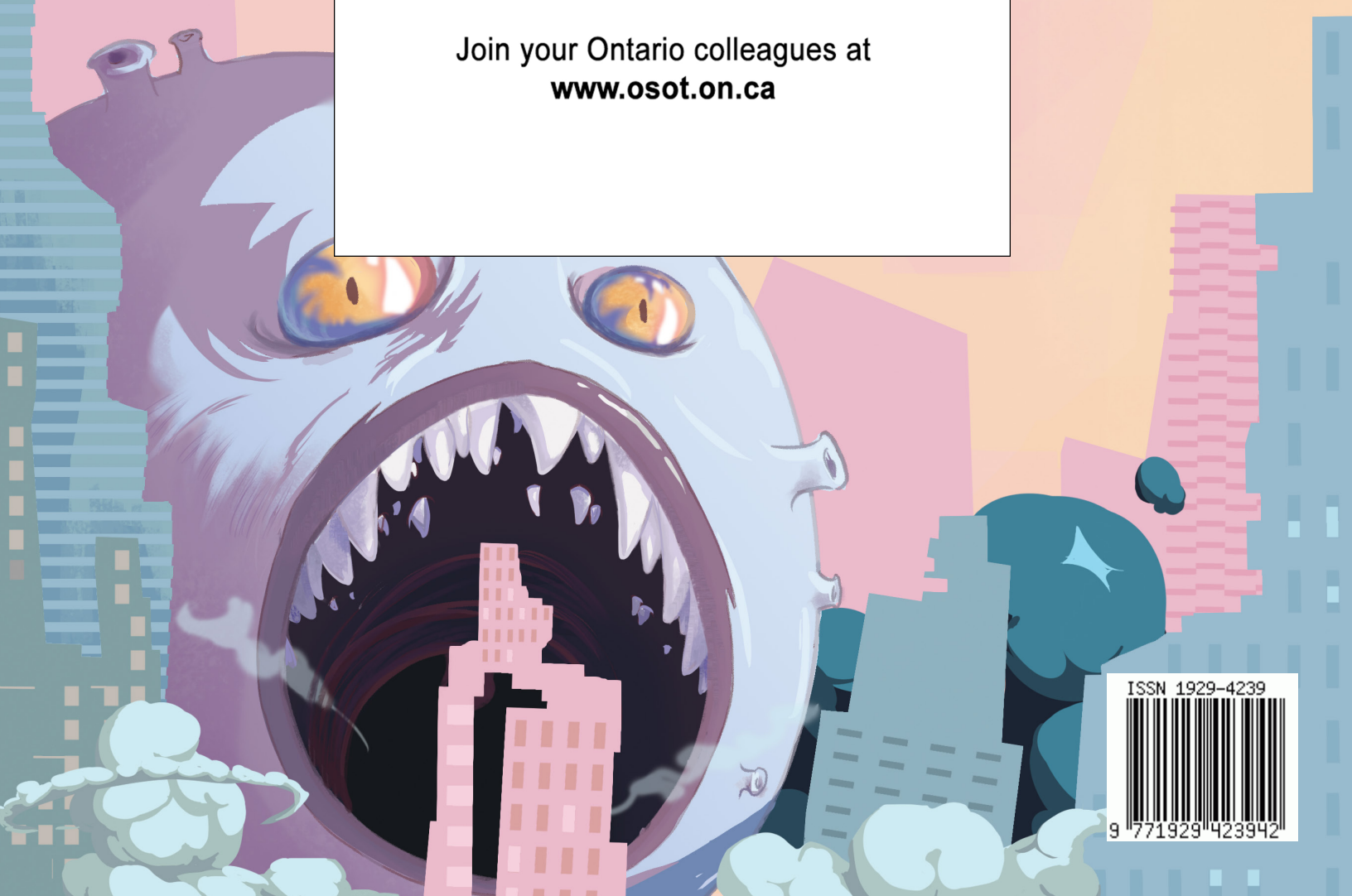

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