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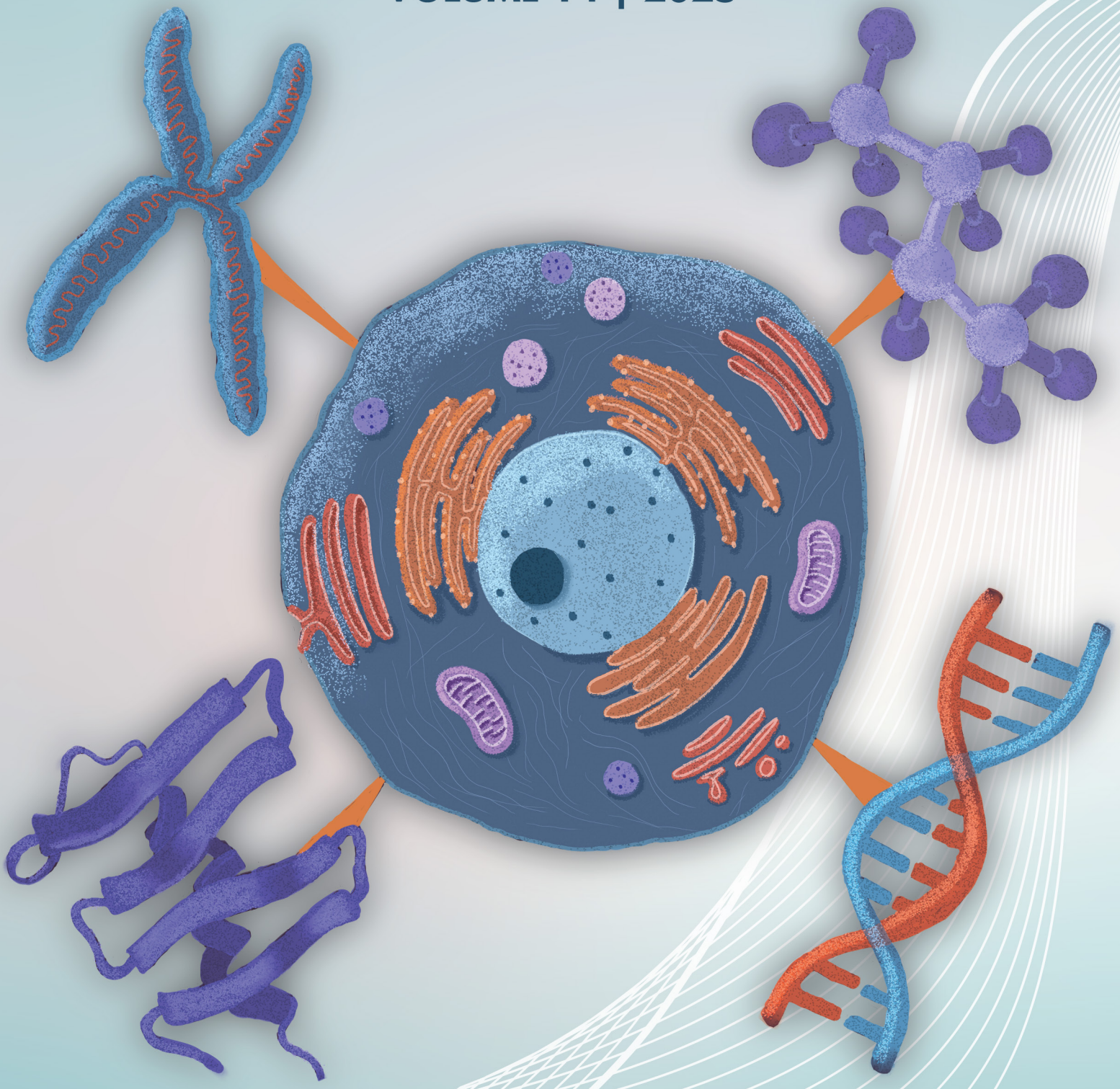
VOLUME 14 | 2025



UNRAVELING COMPLEX DISEASES WITH MULTI-OMICS TECHNOLOGIES

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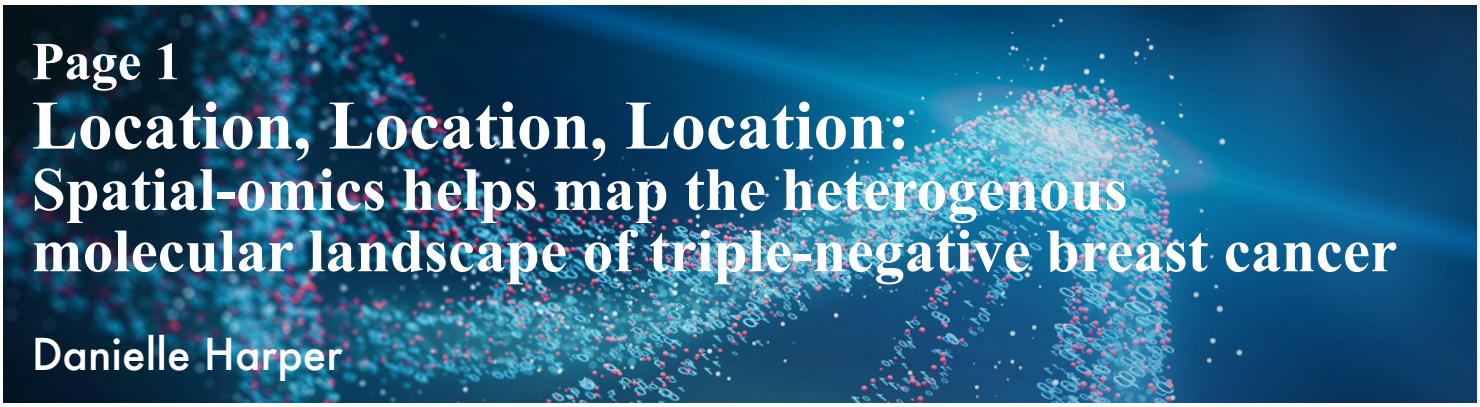
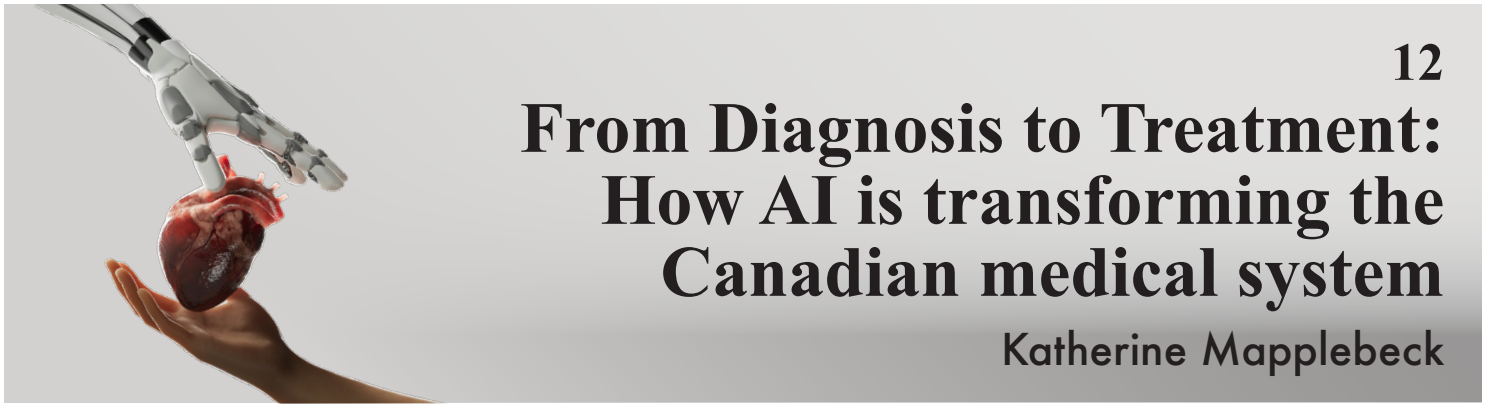
CONTENTS

VOLUME 14 | 2025

NEWS





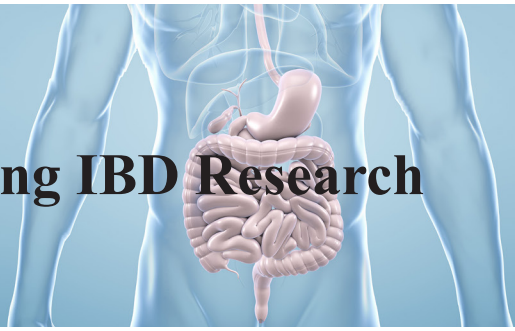
CONTENTS

VOLUME 14 | 2025

ASK AN EXPERT

PROFILE

FEATURE



CONTENTS

VOLUME 14 | 2025

RESEARCH

LETTER FROM THE EDITOR-IN-CHIEF

Jackie Trink, PhD

As I conclude my first term as Editor-in-Chief for HSI, I am excited to present this year's edition of the journal, themed around a cutting-edge and rapidly evolving field: multi-omics. This year's issue highlights the power of integrative, systems-level approaches to understanding health, disease, and the complex biological networks that connect them.

Multi-omics – encompassing genomics, transcriptomics, proteomics, metabolomics, and beyond – represents the forefront of biomedical research. It allows for a comprehensive understanding of human biology by integrating diverse data layers to generate insights that single approaches alone cannot offer.

In this issue, we bring together contributions that span a range of disciplines and methodologies, all unified by a shared focus on multi-omics analysis.

Our incredible team of volunteer staff – students, researchers, writers, artists, and editors from across institutions – worked tirelessly to curate, refine, and elevate each submission. This edition reflects the creativity and scientific curiosity of our dedicated team and collaborators.

This year also marked a period of growth for our journal. We welcomed new volunteers from across Canada and worldwide, enriching our editorial lens and expanding the scope of what our journal can be. It has been especially inspiring to see students from a range of academic levels – from master's to post-docs to medical students – come together to share ideas, challenge conventions, and explore new scientific frontiers.

We believe this issue comes at a pivotal time. As healthcare increasingly moves toward precision medicine, the need for greater understanding in this complex field cannot be overstated. We hope that this edition will not only inform but also inspire graduate and medical students as well as early-career researchers to explore integrative approaches in their own work.

Serving as Editor-in-Chief has been a deeply rewarding experience, full of collaboration, learning, and growth. I am proud of what our team has accomplished and excited to see where next year's edition will take us.

Sincerely,
Jackie Trink, PhD
Editor-in-Chief

Jackie Trink is a first-year medical school at the University of Limerick, Ireland. Previously, Jackie completed her PhD in Medical Sciences in the Faculty of Health Sciences at McMaster University. Here she studied the therapeutic potential of interrupting the interaction of two proteins to prevent the development of fibrosis in both diabetic and non-diabetic kidney disease.

Meet the artist **Giovanni DeCarolis**

MOLECULAR MOSAIC

While multi-omics and the different tools associated with its use in health research are complex and expansive, the beauty of the biological structures is not lost in simplicity. With this piece, I hoped to put that beauty on full display with a minimalist approach that pops with colour and fluidity. I hope that this art can motivate readers to reconsider the barrier to entry for digesting content from the integrated "omes" of research, and transition seamlessly into learning and becoming inspired by the works within this newest edition of Health Science Inquiry.

Giovanni DeCarolis is currently a second-year medical student at the University of Limerick, Ireland. He has a passion for clear and helpful patient-physician communication and hopes to incorporate artwork throughout his career to help facilitate this.

More of Gio's drawings can be found on instagram @drawgiovanni

HEALTH SCIENCE INQUIRY

VOLUME 14 | 2025

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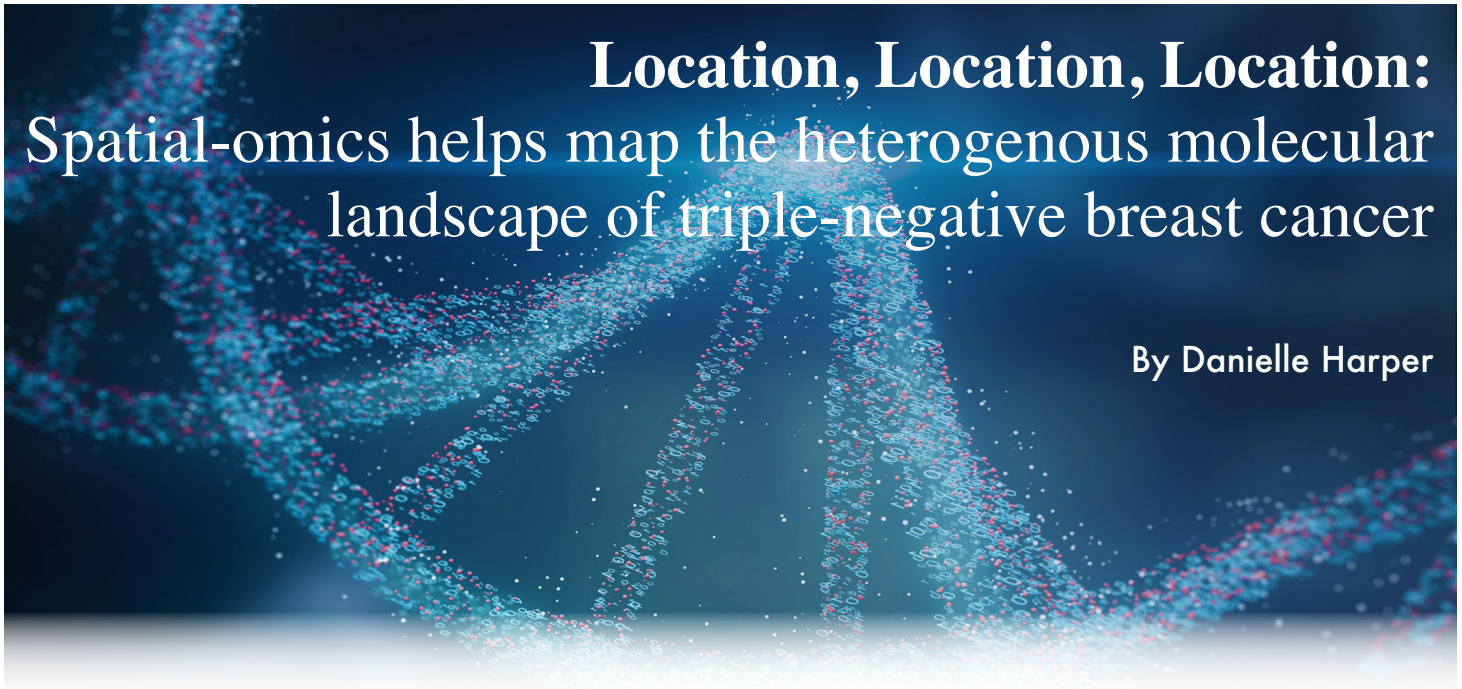

Location, Location, Location: Spatial-omics helps map the heterogenous molecular landscape of triple-negative breast cancer

By Danielle Harper

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype, characterized by a lack of the clinically actionable targets: ER (estrogen receptor), PR (progesterone receptor), and HER2 (human epidermal growth factor receptor 2).[1] The TNBC subtype represents approximately 15%-25% of all breast cancer diagnoses and compared to other subtypes is more commonly diagnosed in premenopausal women.[1] Until recently, surgery followed by cytotoxic chemotherapy and/or radiation were the only treatment options for TNBC patients. Not only do treatment options remain limited, but drug resistance and disease recurrence are common. Up to 30% of TNBC patients develop metastatic disease, when the cancer spreads to distant organs, for which the average life expectancy is just 8-13 months.[2] This poor prognosis underscores the importance of developing new therapeutic approaches for managing TNBC and preventing disease progression.

Recent advances in multi-omics technologies have revealed TNBC to be a heterogenous group of diseases with distinct gene expression profiles. Lehmann et al used bulk RNA sequencing of 386 TNBC tumours to reveal six distinct subtypes with unique therapeutic vulnerabilities.[3] For example, patients with basal-like tumours exhibit upregulated epidermal growth factor receptor (EGFR) signaling, and may respond to EGFR inhibitors, such as lapatinib.[3] Intratumoural heterogeneity, characterized by subpopulations of cells with varying gene expression profiles and propensities for drug resistance, remains a significant challenge in TNBC management.[4] As we learn more about the molecular features of triple-negative tumours, treatment strategies continue to evolve. Attention has recently shifted toward immunotherapy, which leverages the body's immune system to recognize and destroy cancer cells. Immunotherapy offers a promising new avenue for a subset of TNBC patients, but challenges remain in identifying which patients are likely to respond to treatment.

Transcriptomic studies have demonstrated that ~20% of TNBC tumours express PD-L1 (programmed death ligand-1), making them possible candidates for immune checkpoint inhibitor (ICI) therapies.[5] PD-L1 binds to the programmed cell death protein 1 (PD-1) expressed on the surface of T-cells to prevent their cytotoxic function.[5] Monoclonal antibodies that prevent this interaction between PD-L1 and PD-1 allow T cells to recognize and kill the tumour cells. Susceptibility to immune checkpoint blockade has been shown to correlate with the presence of tumour-infiltrating lymphocytes (TILs) within the tumour.[6] However, increasing evidence suggests that not just the presence, but the location of these TILs within the tumour microenvironment (TME) may provide additional prognostic insight and help guide treatment decisions.[7] These novel insights are made possible by advances in spatial-omics technologies.

Spatial-omics is a field dedicated to profiling the molecular characteristics of a tissue in a way that preserves its positional context.[8] Spatial transcriptomics

https://doi.org/10.29173/hsi487
Received 28 March 2025
Accepted 30 June 2025

(ST), for example, is a novel technology that measures gene expression from intact tissues samples, such as tumour biopsies.[9] Traditional bulk RNA sequencing provides the average gene expression signatures within a sample, but ST maps gene expression signatures back onto the tumour sample to reveal spatial patterns. These patterns can provide insights into a tumour's molecular features and potential vulnerabilities. While single-cell RNA sequencing approaches can reveal gene expression patterns associated with a particular cell type, ST goes one step further by providing spatial context for the gene expression profiles of individual cells. In other words, researchers can look at cell behaviour relative to neighboring cells and explore how cell-cell interactions shape tumour progression, metastatic spread, immune responses, and treatment resistance.

Briefly, one approach to ST utilizes tissue sections placed on a glass slide containing immobilized reverse-transcription oligo(dT) primers to capture tissue mRNAs.[9] From there, the mRNA is reverse-transcribed and positional barcodes (short DNA sequences that correspond to a particular XY coordinate on the slide) are incorporated to into the resulting cDNA in order to identify where on the tissue section that mRNA molecule originated.[9] The barcoded cDNA library can then be sequenced and mapped back onto the tissue section to reveal spatial patterns of gene expression.[9]

Hammerl et al. defined three spatial immunophenotypes based on the location of TILs, specifically CD8+ cytotoxic T cells, in TNBC tumour samples.10 CD8+ T cells kill tumour cells by releasing a protein called granzyme. Tumours lacking CD8+ T cells were classed as "ignored", while those bordered by CD8+ T cells were considered "excluded", and tumours with infiltrating CD8+ T cells were deemed "inflamed".[10] Gene-expression patterns unique to each spatial immunophenotype were identified and used to predict treatment outcomes. Both ignored and excluded phenotypes were associated with poor response to anti-PD-1 immune checkpoint blockade therapy, while inflamed tumours were associated with more favourable treatment outcomes.[10] While the concept of "hot" and "cold" tumours (indicating immune infiltration or lack thereof) has been around since the early 2000s[11], spatial approaches offer novel insights into the molecular landscapes of TNBC tumours in order to make rapid and accurate treatment decisions.

A more recent study published in Nature Communications used ST to reveal unique patterns in intratumoural organization across TNBC tumour samples.[12] The authors identified a gene expression signature corresponding to the location of tertiary lymphoid structures (TLS), which are aggregates of immune cells within the TME.[12] This thirty-gene signature was able to distinguish infiltrating immune cells from tumour or non-tumour (stromal) cells. As expected, more TLS within a tumour correlated with a higher response to immunotherapy.[13] The presence of TLS within the tumour is believed to correlate with an adaptive immune response and being able to identify these inflammatory structures offers novel predictive insight that traditional bulk transcriptomic methods lacking spatial resolution would miss.[12]

In addition to identifying where specific subtypes of immune cells are located within a tumour, ST has the potential to shed light on host-tumour interactions. Understanding the relationship between a cell's location within a tumour and its gene expression pattern can provide valuable information about how a cell's behaviour is shaped by its neighbours. For example, a 2023 ST study of colorectal cancer (CRC) reported that macrophages with immunosuppressive gene-expression signatures were concentrated at the invasive front of the tumour (the interface between tumour and normal tissue).[14] These macrophages are thought to adopt a pro-tumourigenic phenotype in response to cancer cell secretion of immunosuppressive human leukocyte antigen-G (HLA-G).[14] These findings suggest that targeting HLA-G or anti-inflammatory macrophages at the invasive front may help slow CRC metastasis.[14] In TNBC, ST revealed that crosstalk between tumour-associated macrophages (TAMs) and CD8+ T cells may promote ICI resistance.[15] TNBC patients who did not respond to ICI therapy had a higher proportion of anti-inflammatory Apolipoprotein E (APOE) expressing TAMs and the physical distance between these APOE+ TAMS and exhausted CD8+ T cells was greater.[15] In a mouse model of TNBC, an APOE inhibitor improved ICI efficacy, suggesting that the presence of APOE+ TAMS may be a biomarker for ICI response.[15] As spatial techniques continue to advance, new insights into cellular interactions within the TME and their therapeutic potential in TNBC will emerge.

Spatial-omics incorporates not only transcriptomic approaches, but also proteomics. Spatial proteomics

(SP), named Nature's Method of the Year for 2024, is used to understand the arrangement of proteins within a tissue sample.[16] While fluorescently-conjugated antibodies have long been used to locate particular proteins in cells/tissues, recent advances in multiplex immunofluorescence technologies have allowed researchers to observe localization of dozens of proteins across a single sample. For example, co-detection by indexing (CODEX) is a method that utilizes DNA-conjugated antibodies to visualize up to 60 different proteins at once.[17] The ability to simultaneously visualize such a wide range of targets can reveal novel interactions that will ultimately provide a more comprehensive map of the TME. Mishra et al. recently applied CODEX technology to reveal a novel interaction between S100 calcium-binding protein A7 (S100A7) and phospholipase A2 (cPLA2) within the breast TME.[18] Using this spatial approach, the authors were able to demonstrate that inhibition of S100A7/cPLA2 signaling led to an increased number of proliferating cytotoxic CD8+ T cells within the tumour.[18] These results suggest that of S100A7/cPLA2 inhibition may sensitize breast tumours to ICI therapy. Experts in cancer immunology agree that spatial-omics are transforming the field. In their Nature Methods Comment[19], Daniela Quail and Logan Walsh, researchers at the Rosalind and Morris Goodman Cancer Institute at McGill University, write "for cancer immunology, in which effective innate and adaptive immune responses rely on cellular interactions, understanding these spatial relationships is critical for uncovering mechanisms of antitumour immunity".

As with any emerging technology, spatial-omics faces several key challenges that must be overcome to unlock its full potential. As discussed in a recent review by Alexandrov et al, spatial-omics experiments yield immense amounts of data, posing significant computational challenges.[20] Data analysis requires robust storage infrastructure and bioinformatic expertise.[20] Fortunately, artificial intelligence and machine learning models are rapidly evolving, and are capable of addressing some of these challenges. Other concerns include reproducibility of results, calling for the need to standardize protocols.[20] This has been partially addressed through the commercialization of specific spatial technologies, including the CODEX platform, but we must also acknowledge the potential financial barriers associated with the use of proprietary reagents and equipment.[20]

The ability to map transcriptional, proteomic, or even metabolomic signatures onto a physical tumour landscape provides novel insight into cell behavior and potential therapeutic vulnerabilities. Identifying patients that are most likely to respond to immune checkpoint blockade therapies is key to improving outcomes for TNBC patients. Spatial-omics approaches are paving the way for biomarker discovery and a deeper understanding of TNBC biology.

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Danielle Harper is a fifth-year PhD Candidate in the Department of Pathology and Molecular Medicine at Queen's University. Her research focuses on calpain protease inhibition as a novel antimetastatic approach for triple-negative breast cancer.

The New Drug Development Playbook

By Sarah Asbury

The deep biology revolution is here. Multi-omics experiments sample an infinitely complex biological system, and the data from a single experiment is often too complex for a single person, even a highly trained one, to understand. The next generation of biotechnology innovators promise to unravel the biology embedded in these experiments using machine learning and artificial intelligence to turn massive troves of data into something translatable and commercializable. Young ambitious start-up companies have raised billions of dollars on their platforms to advance the drug development process into a future that is less expensive, more efficient, and extremely precise. The challenges in drug development are well-known: less than 10% of clinical trials succeed[1], only 5% of eligible oncology patients enrol clinical trials[2], and developing a single new drug costs $2.5 billion USD.[3] The new wave of AI-driven biotechnology companies aims to be the solution by using multi-omics and machine learning to disrupt the traditional drug development model.

One such company is Recursion pharmaceuticals, pioneering cellular cartographers whose venture derives biological maps from multi-omics experiments.[4] They have industrialized the drug development pipeline using an assembly line of robots to conduct gene perturbations at scale and rapidly phenotype results. A silicon-valley darling, Recursion has partnerships with both Nvidia[5] and Google Cloud[6], a motif for the new wave of biotech that has much in common with traditional tech companies. Each multi-omics experiment generates billions of bytes of information, and at scale, that becomes the 23 petabytes of experimental data stored in Recursion's proprietary biological and chemical database[5]. The amount of information generated is incomprehensibly massive and represents deeply entangled relationships between cell genetics, cell composition, and experimental condition measured across imaging, genetic, and molecular modalities.[4] Recursion builds machine learning models, accelerated by Nvidia's compute infrastructure and Google Cloud storage, to interpret these thousands of perturbation experiments.[5,6] The aim is to build a general biological map that can be broadly used to understand any biological condition – an expedition with lofty goals beyond single disease indications.[4,7] Recursion is effectively training a machine learning model to understand entire biological systems, which will inform new disease targets and help design more effective drugs. However, it is not yet known whether these parameters can be gleaned from careful cataloguing of bulk sequencing experiments, biological imaging, and molecular tests.

Once a target is identified, Recursion uses machine-learning accelerated protein target prediction to generate a library of potential drug compounds.[4] Recently, Recursion acquired precision chemistry biotech Exscientia, with expertise in machine learning to automate small molecule synthesis and generate best-in-class therapeutics; their partnership promises to accelerate development and refinement of chemical libraries.[8] Chemical drug candidates in Recursion's

https://doi.org/10.29173/hsi488
Received 28 March 2025
Accepted 1 July 2025

pipeline are put through a series of increasingly more complex biological tests, until finally the best targets are assessed in a futuristic preclinical model which utilizes animal enclosure sensor and video data processed by machine learning algorithms for rapid identification of drug toxicities, optimization of dosages, and identification of the best drugs to bring to clinical trial.[4,9,10]

Recursion's technology is an investment into the multi-omics and deep learning revolution, but whether they can successfully capitalize on it is an open question. The ambiguity is perhaps best represented in their most recent clinical reporting for their drug candidate REC-994, which showed excellent drug tolerance in the Phase II dose escalation clinical trial but no significant improvements in disease.[1,11,12] Regardless, Recursion has been extremely successful in attracting pharmaceutical partnerships, including a recent up-to $12 billion deal with Swiss pharmaceutical company Roche to generate conditional biological maps using their platform.[7] Roche's partnership represents a vote of confidence in their biological mapping platform to accelerate their own drug development pipelines. Recursion's partnership with Sanofi has also been successful, identifying a multi-cancer drug candidate and fast-tracking it to Phase I clinical trials in as little as 18 months – a very impressive timeline for drug discovery.[13] Overall, Recursion's platform for deep multi-omics biological mapping and proven drug candidate acceleration remains an attractive case study for the multi-omics drug development revolution.

Tempus, another pioneer of the AI-driven healthcare revolution, focuses on multi-omic data integration to transform how patients enrol in clinical trials. Drugs increasingly target narrower patient subsets with specific molecular and genetic markers.[2] Founded in 2015, Tempus took advantage of this trend by building the world's largest library of clinical and multi-omic biomarker data alongside software infrastructure to transform their database into actionable insights for physicians, researchers, and allied health professionals.[14,15] Their value is clear: Tempus enables clinicians to quickly identify clinical trials their patient may be eligible for across 2000 healthcare institutions and help researchers recruit eligible patients across the network of 50% of the United States oncologists.[2,15] Comprehensive patient profiles span clinical records, imaging, and molecular information to help match them to clinical trials in what is referred to as the TIME Trial Network.[2] Further, Tempus offers in-house sequencing panels to measure clinical trial eligibility markers, and simultaneously their multi-omic patient database, so that clinical researchers can retrospectively analyze which subsets benefit from their drugs.[16,17] Tempus is revolutionizing the clinical trial management system and cleverly pairing it with their genomics services to create a fully personalized medicine clinical trial ecosystem.

Biomarker-informed clinical trials are popular in modern pharmaceutical clinical pipelines. Indeed, Tempus has been used by 95% of the largest public companies.[15] For example, British pharmaceutical giant GSK partnered with Tempus in 2020 to gain access to Tempus' clinical and multi-omic database.[18,19] They further expanded their partnership in 2022, confirming the value Tempus brought to their clinical trials.[18,19] Tempus' software suite facilitated GSK to rapidly launch a Phase II study and new clinical sites based on areas of concentrated patient eligibility in under 3 months, resulting in GSK partnership renewal. Their collaboration aligns with GSK's clinical strategy: to invest in drugs with genetic validation.[19] These drugs tend to have a deeper biological rationale, and by investing in them, GSK leadership is betting on increased success rate in clinical trials. Janssen also partnered with Tempus starting in 2020, where they joined their TIME trial network to increase enrollment in their United States trials and rapidly open new sites in key institutions based on clinical and molecular traits of local patient populations.[20] Janssen is amongst other large companies – like GSK, Pfizer, and Astrazeneca – that are all taking advantage of the Tempus clinical and multi-omic database and sequencing technologies to further understand which multi-omic biomarkers are predictive of patient response to both standard of care and drugs in clinical development.[15] Tempus represents the realization of precision medicine in clinical trials, using machine learning and multi-omics to enrol the right patients to the right clinical trials at the right time. Although Tempus has attracted major pharmaceutical partners, only longitudinal analysis can determine whether their collaborations have indeed improved clinical trial outcomes.

Insitro, a younger emerging biotechnology company, is also slated to become a major player in the multi-omics and AI-driven drug development revolution. Insitro hopes to combine the ability of multi-omics to make

precise measurements of entire biological systems and the power of machine learning to deconvolve complex experiments into drug insights from multifaceted disease states.[21] Founded in 2018 by Daphne Koller, Insitro had raised $400 million by 2021 to leverage multi-omics and machine learning to make drug development cheaper and less risky.[22,23] Their recent academic paper uses the UK Biobank, a massive multi-omic and clinical phenotyping database with over half a million participants, and demonstrates the company's R&D capabilities.[24] They train a model to predict liver fat content from MRI images, which are costly to produce, from cheaper modalities like blood biomarkers. Using both measured and predicted liver fat content, they identify several novel genetic targets associated with non-alcoholic fatty liver disease.[24] Here they demonstrate the ability of machine learning to expand genetic targets in an academic setting but hope to translate these findings to an actionable drug candidate. Recently, they partnered with Eli Lilly to further develop several potential liver disease drug candidates targeting the genes identified via artificial intelligence.[23] They also saw success in another partnership with Bristol Myers Squibb, delivering a milestone achievement to identify novel genetic targets for ALS drug development.[25] Insitro's early success suggests they may be able to make drug development more efficient and targeted through AI-driven genetic models – but whether these translate to clinical success have yet to be proven.

Advances in sequencing, multi-omics, and machine learning provide the power to analyze biological systems at scale. Biotechnology start-ups are capitalizing on this opportunity, developing ways to make drug development more efficient, more precise, and hopefully, cheaper. Traditional pharmaceutical companies have recognized the value of the new drug development playbook and are thus partnering with ambitious AI-driven companies ready to prove their worth in enhancing clinical pipelines. Underlined by massive databases and machine learning, the deep biology revolution has begun.

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Health Consequences of Wildfire Smoke: Unraveling its Potential Effect on our DNA

By Rohma Ramay

Climate change has resulted in an increased frequency of wildfires across the globe; there is an urgent need to address the health consequences of exposure to smoke from these wildfires. Wildfire smoke is comprised of a complex mixture of gases, vapor, and particles including carbon monoxide, nitrogen oxide, ozone, volatile organic compounds (VOCs), and fine particulate matter (PM2.5). Out of these components, PM2.5 is of particular importance because, due to its small size, it can penetrate deep within the lungs and enter the bloodstream, causing a wide range of health concerns.[1] The World Health Organization (WHO) designates PM2.5 as a substantial threat to public health and PM2.5 exposure has been known to cause both respiratory and cardiovascular effects.[2] Recent research into the mechanism of health effects caused by PM2.5 suggest a role of epigenetic modifications such as changes in gene expression. Here we review emerging evidence on how PM2.5 exposure from wildfire smoke influences gene expression through epigenetic mechanisms.

The Science of Epigenetics

Prior research illustrates that the mechanism of adverse health effects of PM2.5 may be anchored in epigenetics: the change in gene expression resulting from variations in DNA methylation, histone modification, and the function of non-coding RNA molecules. These changes can lead to either a significant increase or decrease gene suppression based on the specific chemical change initiated.[3]

For example, changes in DNA methylation and histone modifications after PM2.5 have been linked to the onset of certain diseases such as dementia, diabetes and hypertension.[4] Since metabolic intermediates are key factors in DNA methylation, disruptions in metabolic homeostasis can alter cell-specific methylation patterns and contribute to diseases like type 2 diabetes.[4] In hypertension, aberrant DNA methylation – particularly in gene regulatory regions – may influence key pathways related to disease pathology. Altered methylation patterns have also been associated with age-related diseases such as dementia.[4,5] This signifies the importance of environmental exposures in shaping the epigenome.[6]

How PM2.5 from Wildfire Smoke Modifies the Epigenome

Researchers conducted a study at the California National Primate Research Center (CNPRC) in which they collected nasal epithelium samples of primates to perform whole genome bisulfite sequencing from two groups of adult female rhesus macaques. One group was born before the 2008 California Wildfires, and exposed to wildfire smoke early in life, while the other group was born in 2009 with no exposure to wildfire smoke in early life.[7] The study identified 3370 differentially methylated regions (≥5% methylation change; $p < 0.05$) and one gene (FLOT2) with significantly altered expression (false discovery rate (FDR) < 0.05, fold-change ≥ 1.2). These alterations primarily affected genes related to

https://doi.org/10.29173/hsi489
Received 28 March 2025
Accepted 1 July 2025

immune processes. These findings suggest that early-life exposure to wildfire smoke may lead to long-term gene modifications.[7]

Another study by Schuller et al. used a genetically engineered mouse strain that lacks the apolipoprotein E (ApoE) gene. ApoE−/− is an established animal model used for environmental toxicology studies due to its increased sensitivity to oxidative stress and inflammation, permitting evaluation of the epigenetic changes produced by exposure to wildfire smoke.[8] Their results showed that after 40 days of exposure, these mouse models expressed sperm DNA methylation changes, which can impact alterations in gene expression.[8] Variation was observed in 3353 differentially methylated regions. Most of this change was hypermethylation which targets a variety of developmental processes.[8] Similarly, another study investigated the intergenerational effects of PM2.5 exposure, highlighting additional epigenetic mechanisms involved. Studies have shown that paternal exposure to PM2.5 may lead to epigenetic changes that predispose first and second-generation offspring to metabolic disorders. Small RNAs (sRNAs) play a critical role in mediating these effects.[9] It was found that piR033435 and piR006695 regulate first-generation sperm methylation by binding to the 3′-untranslated region of *Tet1* mRNA, leading to the hypermethylation of testosterone genes and ultimately, impairing the function of Leydig cells leading to hypogonadism.[9]

A recent study by Jiang et al. (2025) details how PM2.5 exposure disrupts the brain's epigenetic landscape through hyper- and hypomethylation of genes involved in synaptic signaling, inflammation, and neuronal integrity.[10] These alterations were linked to impaired memory, learning deficits, and transgenerational effects due to inherited epigenetic changes. The study highlights DNA methylation of synaptic genes such as SHANK3, histone acetylation linked to amyloid toxicity, and microRNA dysregulation as key mediators of PM2.5-induced cognitive impairment – underscoring the complex pathways through which air pollution can shape long-term brain health.[10]

A 15-year cohort study conducted in Isfahan, Iran, found that long-term exposure to PM2.5 through ambient air pollution was significantly associated with an increased incidence of cardiovascular disease including acute myocardial infarction and ischemic heart disease.[11] The results showed that the risk of non-fatal cardiovascular events rose with higher PM2.5 levels, among older adults, smokers, and individuals with hypertension or diabetes. Thus, higher concentrations of PM2.5 were associated with more pronounced adverse cardiovascular outcomes.[11]

Collectively, these studies highlight the detrimental impact of PM2.5, while many studies involve animal models, their conserved epigenetic response suggests relevance to human physiology and underscores the importance of understanding the effect of PM2.5 on the human epigenome through further studies. Translating animal studies to humans suggests that alterations in gene expression mediated by PM2.5 can also have a significant impact on the developing fetus and cause reproductive abnormalities leading to a variety of health outcomes ranging from neurological effects to changes in the immune response. Therefore, there is a growing need to conduct detailed studies that evaluate the underlying epigenetic mechanisms of PM2.5 exposure in humans.

Can these Epigenetic Changes be Reversed?

Although epigenetic changes from PM2.5 may present long-lasting effects, recent studies suggest that these changes may not be permanent. Since epigenetic changes are largely influenced by environmental factors and lifestyle changes, adjusting these external factors may help restore normal gene expression.[12] For example, PM2.5 can increase the production of reactive oxygen species (ROS) leading to the hypomethylation of the p16INK4a promoter- a regulatory region of the p16INK4a gene involved in senescence (the reversible halt of cellular replication), DNA damage, and tumorigenesis.[12] However, the antioxidant N-acetylcysteine (NAC) may reverse these ROS-mediated epigenetic modifications.[12] Although NAC is not naturally found in foods, dietary intake of cysteine – its precursor – may support antioxidant defenses. Cysteine is abundant in protein-rich foods such as chicken, turkey, yogurt, and eggs, as well as in sulfur-containing vegetables like garlic and onions. Increasing cysteine intake through diet may help reduce oxidative epigenetic damage induced by environmental exposures such as PM2.5.[13]

In contrast, a 2012 review by Ji and Khurana Hershey highlights growing evidence that PM2.5 exposure induces a range of epigenetic changes – such as DNA methylation alterations, histone modifications, and

dysregulated miRNA expression that may persist long after exposure. These changes could even be inherited across generations, emphasizing the importance of early-life exposures in shaping long-term health outcomes.[14] However, it is important to consider that individual susceptibility to PM2.5 may also be influenced by genetic predisposition and social determinants of health, which could act as confounding variables when evaluating the epigenetic and health outcomes of PM2.5 exposure. While further research is still required to understand the mechanism of potential reversal of epigenetic changes, supplementation with antioxidants and lifestyle changes in diet can potentially aid in reducing the downstream health risks associated with wildfire smoke.

With the growing body of research outlining the epigenetic effects of PM2.5, there is an urgent need for reform in both government and environmental policies to reduce unwanted exposure to these pollutants. Some of these changes would include air quality monitoring, stricter wildfire prevention laws, and public health surveillance initiatives.[15] Further research is required to delineate the mechanisms behind epigenetic alterations and to better understand the health effects that this exposure may cause. Current findings demonstrate adverse effects of PM2.5 on gene expression through histone modification, DNA methylation, and changes in non-coding RNA function. Given the increased frequency of wildfires due to climate change, there is a strong need to study the health effects of PM2.5 exposure and the long-term consequences of it, especially in areas that are more susceptible to wildfire events. Without adequate research and policy-driven action, the health consequences of PM2.5 exposure through wildfire smoke could not only affect current populations but potentially future generations as well.

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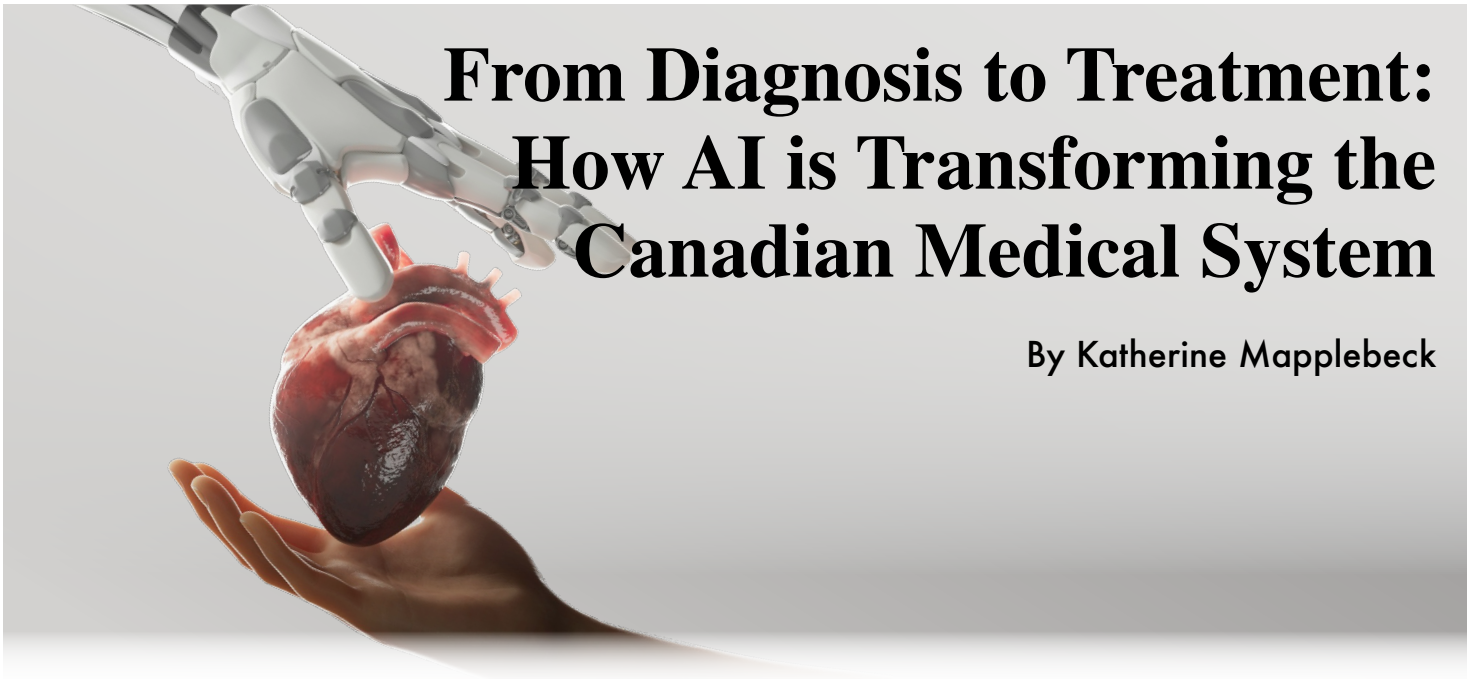

From Diagnosis to Treatment: How AI is Transforming the Canadian Medical System

By Katherine Mapplebeck

Artificial intelligence (AI) *was once confined to science fiction, popularized by futuristic films and mainstream media. Today, it is no longer a futuristic concept but an integral part of daily life. Defined as computer systems capable of performing tasks that are commonly associated with human intelligence, AI is now revolutionizing the Canadian medical system. From predictive analytics of patient data to advanced imaging and robotic-assisted surgery, AI is enhancing accuracy, efficiency, and patient outcomes across the country.*

Predictive Analytics

AI is helping to make significant strides in clinical decision-making through predictive analytics, which involves using patient data to predict health outcomes. A notable example is an AI initiative at Unity Health Toronto, which is reported to have reduced unexpected in-hospital deaths by 26%.[1] The algorithm identifies internal medicine and general surgery inpatients that are suspected to deteriorate, undergo transfer to the ICU, or die within 48 hours. The system runs every hour, analyzing over 150 variables (e.g., vitals, labs, demographics), and automatically pages medical teams when a high-risk threshold is reached.

Dr. Muhammad Mamdani, co- author of the study and Vice President of Data Science and Advanced Analytics at Unity Health Toronto, explained that their team trained the algorithm on data from over 20 000 patients. "When a physician predicted whether a patient would die or go to the ICU, they were right less than one-third of the time," says Dr. Mamdani. When their algorithm was trained on the same variables, it correctly predicted outcomes 70% of the time.[1]

The algorithm, called CHARTWatch, trained on data from over 20 000 patients, includes a diverse range of patient demographics to improve its accuracy and mitigate bias. Initial challenges associated with implementing CHARTWatch included skepticism from clinicians, alarm fatigue (a desensitization to frequent alerts), and technical issues such as sodium levels being misinterpreted as missing data. Endorsement from a highly respected physician at Unity Health Toronto helped drive acceptance of CHARTWatch into clinical practice at St. Michael's Hospital.

While the system is not yet widespread across Canada, its promising results suggest it could become a model for hospitals nationwide. Internationally, similar systems like the UK's National Early Warning Score (NEWS) algorithm are being adopted, demonstrating global momentum toward AI-assisted monitoring.[2] "Healthcare is pretty slow to adopt, so I don't see things radically changing overnight. I think it will take some time. But as we become more comfortable with AI and the benefits it can provide us, the more value that it can give us," says Dr. Mamdani.

https://doi.org/10.29173/hsi493
Received 28 March 2025
Accepted 1 July 2025

Imaging for Lung Transplant Evaluation

AI is also a promising tool for diagnostic measures and imaging. Researchers at the University Health Network in Toronto have spearheaded a study that uses machine learning – an AI subset where systems learn from data without explicit programming – trained on Ex Vivo Lung Perfusion (EVLP) imaging data.[3] EVLP assesses lungs that are isolated outside of the body for potential transplantation.[4]

The machine learning model, InsighTx, analyzes over 1300 EVLP X-rays to identify patterns associated with lung injury and transplant success.[3] This allows clinicians to better assess donor lung viability, complementing human interpretation and reducing reliance on subjective judgment. While complete diagnostic accuracy statistics (e.g., sensitivity and specificity) are still under evaluation, early results suggest the model improves detection of subtle lung damage that might be overlooked by clinicians.[3] Challenges include the need for larger datasets and external validation to ensure results are generalizable.[3]

Robotic Surgery

AI also helps surgeons in robotic-assisted procedures. The da Vinci Surgical System was introduced into Canadian hospitals in 2008 and has increased precision in minimally invasive procedures.[5] AI integration has enabled the system to assist with intraoperative decision-making, enhancing dexterity and reducing complication rates. Studies have shown that robotic-assisted surgeries using da Vinci systems are associated with shorter hospital stays and lower post-operative complication rates compared to traditional surgery.[5] However, costs remain high, and surgical teams require extensive training. Ongoing research focuses on refining AI algorithms to further improve surgical outcomes and expand access.[5]

The Future of Artificial Intelligence in Canadian Healthcare

The progress made by AI is promising, however, major ethical considerations still arise in the discussion of AI in healthcare. Potential benefits of AI initiatives should not be outweighed by breaches to ethical guidelines in medicine. Bias assessments of AI systems may also be limited by a lack of race and ethnicity data in Canadian hospitals.[6] Furthermore, maintaining patient confidentiality and informed consent is paramount, especially since AI systems operate using sensitive health data. CHARTWatch, for example, functions within hospital firewalls and allows for patients to opt-out of the program. Finally, broader trust-building with the public is essential, which includes transparent communication about AI's role in patient care coupled with robust privacy safeguards to foster greater acceptance. Additionally, there is one key component missing from AI: empathy. Empathy will always be a vital component of providing the best standard of care, as patients and family members encountering the healthcare system are experiencing some of the most distressing moments of their lives.

Looking ahead, AI in Canadian healthcare will continue to evolve across prognostic, diagnostic, and therapeutic domains. Areas for future research include improving algorithm transparency, integrating more diverse patient data to reduce bias, and evaluating cost-effectiveness to ensure equitable access. Importantly, experts emphasize that AI should not replace healthcare professionals but instead optimize and improve what they already do.[7]

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Ask an Expert with Dr. Eric Brown
Rethinking bacterial testing: How host-mimicking conditions are transforming antibiotic research

By Kyla Krajcovic

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Since the beginning of antibiotics, scientists have cultured bacteria on nutrient-rich media, such as Mueller-Hinton broth or nutrient-dense agar formulations.[1] The problem? We don't need antibiotics to work in broth, we need them to work in the human body. Inside the host, bacteria often face nutrient scarcity, and their physiology and behaviour change dramatically in response. This means that how bacteria respond to antibiotics during laboratory testing can differ significantly from how they behave during an active infection. This mismatch may have caused researchers to overlook key survival mechanisms that only emerge in nutrient-limited environments – mechanisms that could be targeted by new drugs.[1]

According to the WHO, only 12 new antibiotics were approved between 2017 and 2022, 10 of which belonged to existing classes which were already associated with antimicrobial resistance.[2] This stagnation in antibiotic discovery may be due in part to the use of non-physiological testing conditions. For example, the type II fatty acid synthesis pathway was used as a drug target – until Poulsen et. al. showed that some gram-positive bacteria bypass it by scavenging fatty acids from their host.[3] Nutrient-limited environments within the host can induce adaptive bacterial behaviours that are hidden under nutrient-rich lab conditions and overlooking this can lead researchers to pursue ineffective drug targets.

Dr. Eric Brown and his team at McMaster University have been working on this problem for the last decade. A professor of biochemistry and an expert in bacterial physiology, Dr. Brown leads a lab focused on understanding how bacteria behave under nutrient scarcity – conditions that more closely resemble those faced during an infection.

Simulating Infectious Conditions

In the body, nitrogen is limited in the large intestine[4], methionine is scarce in the nasal cavity[5], and host defences actively sequester metal ions like iron and zinc away from invading bacteria[6]. To simulate these stresses in the lab, Brown's team uses nutrient-limited media containing only glucose, ammonium chloride, and essential salts and phosphates, which are starkly different from traditional nutrient-rich broths.[7] In this scarce environment, *E. coli* was shown to require 119 additional genes for survival compared to nutrient-rich conditions.[7] Many of these genes are involved in biosynthesis of amino acids, vitamins and nucleotides, or nutrient scavenging from the environment.[7] The Brown Lab has been studying these newfound pathways as potential drug targets – ones which may be missed under standard testing conditions.

What Antibiotic Research is Missing

For decades, antibiotic development has focused on targeting essential bacterial processes: protein translation, DNA replication, and cell wall synthesis. Now, the Brown Lab is shifting this perspective by studying genes that only become essential under infection-like, nutrient-limited stress. Which nutrients are absolutely required for bacterial survival in the host? Which vitamins or amino acids? Do these vulnerabilities

https://doi.org/10.29173/hsi499
Received 28 March 2025
Accepted 2 July 2025

vary by pathogen or by site of infection? These are the questions driving the Brown Lab's search for the next generation of antibiotics.[8,9]

The Biotin Block

One major discovery from Dr. Brown's lab is a molecule called MAC13772 that inhibits biotin synthesis in bacteria, ultimately leading to bacterial death by forming a biotin blockade. However, this compound only works in nutrient-limited media, because rich media contains biotin, allowing the bacteria to grow and survive without need for the synthesis.[10] This may explain why this compound has been previously overlooked: mouse models, commonly used in early testing have significantly higher biotin than humans. Bacteria colonizing mice therefore do not need to synthesize their own biotin for survival – it is readily available the host.[10] For this reason, the drug appeared ineffective in mice even though it may have worked in humans. To combat this, the Brown Lab implemented streptavidin – a molecule that tightly binds biotin – to lower the available biotin levels in the test mice.[10] With these new mice, the biotin synthesis pathway once again became necessary for bacterial survival. This underlines the importance of validating antibiotic targets in models that better reflect human biology.

Siderophores: A Trojan Horse Strategy

In a recent study, the Brown lab explored how *Klebsiella pneumoniae* – a multi-drug resistant bacterium – responds to antibiotic compounds in human blood. Surprisingly, some antibiotics seemed to promote bacterial growth rather than inhibit it.[11] In human blood, *K. pneumoniae* is starved for iron. To survive, it sends out siderophores, which are small, iron-scavenging molecules that sequester iron from the environment. The team discovered that the antibiotic compound they were testing was acting as a siderophore itself and promoting bacterial proliferation.[11] Turning this challenge into an opportunity, the Brown Lab chemically linked a beta-lactam antibiotic to a siderophore, creating a 'Trojan horse' compound. This conjugate was able to exploit the bacteria's iron uptake mechanisms: when the siderophore delivered iron to the bacteria, it also smuggled the antibiotic into the cell, where it would inhibit cell wall synthesis and effectively kill the pathogen.[11] This strategy underlies the mechanism of cefiderocol, a novel antibiotic being investigated in Dr. Brown's lab. Cefiderocol has been approved for treating complicated urinary tract infections and hospital-acquired pneumonia caused by gram-negative bacteria. However, real-world data is still being collected to inform its safety and effectiveness across various patient populations.[12]

Building Bacterial Signatures

Dr. Brown's lab also uses omics techniques like metabolomics, gene-chemical interaction mapping, and promoter activity tracking to uncover how new antibiotic compounds work, especially under nutrient-limited conditions.[13] A promoter is a regulatory DNA sequence that helps to initiate transcription. Tracking promoter activity allows researchers to assess gene expression levels, revealing which genes are upregulated or downregulated in response to a drug.[13] Since few antibiotics have been tested in this way, Dr. Brown's team has had to do the groundwork: systematically deleting individual bacterial genes, then exposing the bacteria to antibiotic compounds while under nutrient stress. If deleting a gene makes the bacteria more vulnerable to a drug – or, conversely, makes the drug less effective – it reveals that gene's role in the drug's mechanism of action.[14] By gathering information about these responses across a bacterial genome, the team builds a repertoire of unique chemical-genetic "signatures" for each compound.[13] These signatures can then be compared to those of new antibiotics to help predict how these drugs will work.[1]

Extensive testing has generated mountains of data in the Brown Lab. For this reason, their team uses AI to analyze chemical patterns and signatures that would otherwise be very difficult to detect. Over time, such computational approaches have become essential in the lab.

Innovation Without Incentive

Another team at McMaster, led by Dr. Gerard Wright, has recently discovered a new class of antibiotics, the first in nearly 40 years.[15] Unfortunately, discoveries like this are incredibly rare. Why? Because for most patients, our current antibiotics still work. Outside of critically ill ICU patients with a multi-drug-resistant infection, most patients are reliably able to recover with standard antibiotic options.[9] From a business perspective, this makes antibiotic development a hard sell: pharmaceutical companies are expected to invest millions into a drug that will only be used by a small number of patients, and even then, for short durations to avoid resistance[16].

It is not a profitable business model. In addition to poor investment, labs like Dr. Brown's face practical hurdles as well. His team uses human plasma to grow bacteria under infection-like conditions, an approach that is expensive, time consuming and difficult to scale.[9] Incentives, policies and funding must shift to encourage innovative antibiotic discovery.[16]

The Joy of the Discovery

When asked about a career moment he's most proud of, Dr. Brown recalled a memory from his early days as a student working in a lab at the University of Guelph. He described the thrill of looking at something under the microscope that no one had ever seen before and realizing he could build a career around that feeling.

Today, what brings him the most pride isn't a particular discovery or award, but the people he gets to work with. Watching his students grow – coming into the lab as wide-eyed students, unsure of their path, and leaving with confidence and clarity is what he finds most meaningful. Recently, Dr. Brown celebrated his 25th anniversary at McMaster University – a milestone that brought together former students and reminded him how meaningful mentorship can be.

Dr. Brown's work serves as a reminder that even in a stalled field like antibiotic development, a shift in perspective can reveal new possibilities – sometimes, simply by changing the plate. By recreating the nutrient limitations bacteria face within the human body, his lab is reframing old questions in more clinically relevant ways and moving closer to the answers that we really need.

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Interview with Dr. Catrina Loucks

Unravelling genomic factors behind opioid side effects in children

By Erika Scott

Dr. Catrina Loucks
University of British Columbia

The Human Genome Project began in 1990 and was a groundbreaking initiative to sequence the human genome, taking over a decade and approximately 3 billion USD to complete.[1] Since then, genomics technologies have advanced so rapidly that a human genome can be sequenced in as little as one day for approximately 200 USD.[2] Today, a variety of sequencing technologies are available, allowing researchers to analyze not only entire genomes but also exomes (protein-coding regions) and RNA. The impact of the Human Genome Project is long lasting, as it simultaneously revealed both the simplicity and complexity of the human genome. Remarkably, as humans we share 99.9% of our genetic makeup, yet it is the remaining 0.1% that gives rise to our individuality.[1] This tiny fraction accounts for a diverse array of traits, from varying hair and eye colours to differences in heights and personalities. It also plays a critical role in health, influencing susceptibility to certain diseases and the likelihood of experiencing adverse effects to medications.

The field of pharmacogenomics focuses on understanding how variability within the human genome influences individual responses to medications. It is well known that individuals can respond differently to the same medication doses, even something as simple as the caffeine in a cup of coffee. Some individuals can drink a cup of coffee and feel energized, while others may not notice any effect, and some may even feel anxious or jittery. This variability in response can be influenced by several factors, such as age and/or sex, but genetic factors also play a significant role.[3] Researchers in pharmacogenomics use a variety of genomics techniques to study this variability, enabling them to uncover genetic factors that influence individual responses to drugs and impact overall safety and effectiveness. As a result of this field of research, several drug labels now include warnings about the potential impacts of genetic factors on the metabolism or effect of a drug, and any recommended genetic testing to ensure its' safety and efficacy for a particular individual.[4]

Dr. Catrina Loucks is an Assistant Professor in the Division of Translational Therapeutics, Department of Pediatrics, and the Department of Anesthesiology, Pharmacology and Therapeutics at the University of British Columbia. Additionally, she is an Investigator at the British Columbia Children's Hospital Research Institute. In these roles, she leads a team of pharmacogenomics researchers that are using genotyping and sequencing techniques to delineate the factors underlying poor pain relief and side effects of opioids used to treat pain in children.

Dr. Loucks' interest in genetics research began during her Bachelor of Health Sciences (Honours) degree and subsequent Master's degree in Medical Sciences at the University of Calgary. As a doctoral student at Simon Fraser University, she uncovered novel biological roles for disease-related genes using the model organism *Caenorhabditis elegans*.[5,6] *C. elegans*, a microscopic worm whose genome was mapped shortly before the completion of the Human Genome Project[1], shares remarkable genetic similarities with humans, with over 50% of its genes having counterparts in the human genome.[7] This genetic connection makes *C. elegans* a valuable model in genetics research. By manipulating the *C. elegans* version of a gene, scientists can explore the effects of specific genetic markers identified in humans, providing valuable insights into their potential implication in human health and disease.

As genomics technologies continued to advance, Dr. Loucks became interested in pursuing research in the human genomics field, particularly in pharmacogenomics. She came to the University of British Columbia to work as a postdoctoral fellow at the

https://doi.org/10.29173/hsi492
Received 28 March 2025
Accepted 1 July 2025

Canadian Pharmacogenomics Network for Drug Safety led by Dr. Bruce Carleton, a Canada-wide network of clinicians and researchers focused on identifying genetic factors underlying adverse reactions to medications.[8] Now, as an Assistant Professor at the University of British Columbia, she combines her previous experiences of conducting genetics research in humans and *C. elegans* to improve the lives of children experiencing severe pain. According to Dr. Loucks, "every person carries genetic characteristics that influence their responses to medications, putting them at an unknown risk of drug-induced harm or ineffectiveness. It is an immense privilege to contribute to pharmacogenomic knowledge that can ultimately empower patients to help choose medications that are both safe and effective for them."

Children undergoing invasive medical procedures or who have severe cancer-related pain often receive opioids, such as morphine or fentanyl, as the first line of treatment.[9–11] However, treatment with opioids can have three different outcomes: good pain relief, poor pain relief, or side effects such as vomiting, breathing problems, or allergic reactions.[12] Poor pain relief and side effects are especially devastating in children as chronic pain can affect brain development, which can lead to behavioural problems as children grow older.[13,14] The opioid crisis has led to a hesitancy to prescribe opioids due to concerns about abuse and overdose[11,15,16], however, opioids are effective pain relievers for many children. "If we can balance the safety and effectiveness of opioids, such that only those who will benefit from them are treated with them, we can effectively treat pain without increasing the harmful effects of opioids," says Dr. Loucks. Dr. Loucks' research team at the University of British Columbia and British Columbia Children's Hospital Research Institute works closely with clinicians to identify and recruit opioid-treated children from hospitals across Canada. They use genomics technologies, such as genome-wide genotyping and exome sequencing, combined with advanced bioinformatic tools, to identify genetic markers that influence how children respond to opioids. As *C. elegans* have recently been shown to be ideal model organisms for opioid pharmacogenomics research[17], Dr. Loucks' team tests genetic markers in *C. elegans* models to better understand how they affect the body's opioid response. Ultimately, her team plans to develop genetic tests that could be administered before opioid use to better predict treatment outcomes. Patients who are expected to experience poor pain relief or side effects to opioids could then be offered alternative pain-relieving medication.

Similar genetic tests are already available for adults for codeine, an opioid that is metabolized to morphine by the enzyme *CYP2D6* to exert its pain-relieving effect. Depending on the genetic markers that an individual carries within the *CYP2D6* gene, they can be classified as a poor metabolizer (where reduced morphine formation leads to poor pain relief), a normal metabolizer (where expected morphine formation leads to good pain relief), or an ultrarapid metabolizer (where increased morphine formation leads to side effects).[18,19] Individuals classified as poor or ultrarapid metabolizers are then recommended other opioids that are not metabolized by the *CYP2D6* enzyme so that they can experience adequate pain relief with minimal side effects.[18,19] However, for opioids other than codeine, there may be other genetic markers that can interfere with pain-relieving abilities. For example, there are currently no genetic markers with strong evidence for affecting the pain-relieving abilities of morphine and fentanyl, and thus no such genetic tests to predict treatment outcomes in these cases. Dr. Loucks' work therefore aims to develop such tools that would ensure patients who require pain management with opioids receive sufficient pain relief while minimizing adverse effects.

Nevertheless, uptake of these genetic tests in the clinic can be challenging. Since genetic testing is a relatively recent addition to clinical practice, some clinicians may not have adequate training to know how or when to use it.[4,20] Some clinicians may also not fully understand, or have easy access to, the evidence for genetic testing in certain contexts.[4,20,21] Dr. Loucks' team hopes to overcome these barriers by creating clinical practice guidelines – essentially, a manual for clinicians.[4] These guidelines provide information about which genetic markers to test for, what the results of the test mean, and whether an alternative medication or dose should be used based on the test results.

Dr. Loucks is enthusiastic about the future of the pharmacogenomics field. In the few decades since the completion of the Human Genome Project, initiatives such as the publicly available genetic data in the 1000 Genomes Project[22], UK Biobank[23], and Genotype-Tissue Expression[24] databases have made it increasingly easier for researchers to investigate genomic variation in large

populations. However, these populations are typically comprised primarily of patients with European ancestry. In response, Genome Canada recently launched an initiative to sequence the genomes of at least 100,000 Canadians, with the aim to reflect Canada's diversity so that these data can be used to improve the health of all Canadians.[25] "Patients of diverse ancestries have historically been underrepresented in pharmacogenetics research, so I'm excited to see more genetic markers discovered in diverse populations," says Dr. Loucks. In addition, advanced machine learning techniques are making it easier to model and find genetic markers for complex drug reactions.[26] Dr. Loucks envisions a future where the insights gained from innovative technologies and diverse genomic data will empower patients and healthcare providers to make well-informed treatment decisions, shaping a future where pharmacogenomics can truly cater to the unique needs of every individual.

Erika Scott is a postdoctoral researcher at the University of British Columbia where she is working to identify genetic predictors of variable responses to morphine treatment in infants and children to better manage pain in these vulnerable patient populations.

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Cracking Cancer's Drug Resistance Code: How Omics is Shaping the Future of Precision Medicine

By Shannen Arviola

Cancer is one of the leading causes of death worldwide, responsible for nearly 10 million fatalities in 2020 – about one in six deaths, according to the WHO.[1] Cancer is a disease in which abnormal cells grow uncontrollably, usually spreading beyond their normal boundaries to invade other areas, even moving to other organs. It can originate in any organ or tissue of the body.[2] Despite billions of dollars invested in cancer research, the disease remains a profound mystery to the scientific community, with many aspects still not fully understood.[3]

In spite of the continuous development of cutting-edge cancer therapies, imagine a scenario where cancer cells become resistant to treatment–they simply do not respond to therapy, no matter how effective it is. In this battle against cancer, drug resistance is the silent enemy that undermines even our most potent therapeutics.[4] When cancer cells become less responsive or completely resistant to the effects of treatments, major challenges in cancer therapy arise, which often lead to treatment failure, disease progression, and ultimately poorer outcomes for patients.[2,3] Drug resistance, which can either exist before treatment or can occur after therapy, accounts for most relapses of cancer and is also responsible for 80-90% of cancer-related deaths.[5,6,7]

What if the key to understanding drug resistance in cancer lies in a much deeper understanding of cancer at a molecular level? Multi-omics is a holistic approach that combines data from multiple levels of biology, such as genomics (genome), metabolomics (metabolites), transcriptomics (RNA transcripts produced by the genome), epigenomics (heritable changes in gene expression that are not caused by DNA changes), proteomics (proteins), and other omics disciplines.[8,9] It is an integration of various omics fields, which presents enormous potential in advancing our understanding of drug resistance in cancer. Multi-omics offers a more comprehensive understanding of molecular changes that affect normal development, cellular responses, and diseases – including cancer.[8]

Challenge of Drug Resistance in Cancer

For many patients, a major challenge arises when a treatment that was once effective suddenly stops working. How is this possible? Some cancer cells are inherently resistant to treatment from the onset; others can adapt through various mechanisms, utilizing the body's own defenses to develop resistance.[10]

A notable barrier in understanding cancer is its complexity and heterogeneity. Cancer can originate in any organ, with the cell type involved varying according to the tissue of origin. Further complicating this is the fact that significant cellular heterogeneity is often exhibited within a single tumor, regardless of its origin. Aggravating the problem, patients with the same cancer diagnosis may have tumors with distinct molecular profiles. This heterogeneity complicates diagnosis, prognosis, and treatment, making the tumor more adaptable, aggressive, and resistant to therapy.[5,10]

Intrinsic resistance refers to the natural resistance cancer cells have to treatment before therapy even begins. This can arise from pre-existing genetic mutations that reduce responsiveness to therapy.[5,6] For instance, mutations like overexpression of cell growth proteins (e.g., *HER2*) in gastric cancer can make cells resistant to cisplatin therapy by promoting epithelial-mesenchymal transition.[6] That process increases cancer cell survival and drug resistance. Additionally, tumors are often heterogeneous with resistant subpopulations such as cancer stem cells that survive treatment and lead to relapse.[6] Intrinsic resistance can also be driven by activation of defense mechanisms like ATP-binding cassette (ABC) transporters or the glutathione system, which help cancer cells expel or detoxify drugs, further reducing the treatment's efficacy.[6]

Meanwhile, ***acquired resistance*** develops over time when cancer cells initially respond to treatment but gradually become resistant.[5,6] This can occur through mutations or changes in the expression of drug target genes, which reduce drug efficacy. For example, in

https://doi.org/10.29173/hsi491
Received 28 March 2025
Accepted 1 July 2025

chronic myelogenous leukemia, an alteration mutation in the *BCR-ABL* gene changes the drug-binding site, making imatinib less effective.[6] Another factor in acquired resistance is changes in the tumor microenvironment (TME), where interactions between cancer cells and stromal cells, through exosomes, can lead to resistance.[6] Importantly, acquired resistance can develop as cancer cells accumulate new mutations during therapy, allowing them to evade the effects of initially effective treatments.[5,6]

Cancer resistance to chemotherapy is commonly observed among nearly all medications used to treat the deadliest cancers.[7] Some of these include doxorubicin, paclitaxel, 5-fluorouracil, and carboplatin, wherein resistance is linked to cancer recurrence, poorer prognosis, and shorter survival in breast cancer patients.[7] Resistance to drugs such as cisplatin and oxaliplatin leads to similar outcomes in gastric cancer.[7]

While acquired resistance to therapy has long been recognized as a challenge to achieving fully effective cancer treatments, it is becoming an increasingly critical issue even for new molecular-targeted drugs.[11] With the rise of target chemotherapy, drugs are designed to block specific molecules and target metabolic pathways involved in cancer cell growth, such as imatinib (Gleevec) that targets *BCR-ABL* gene in chronic myeloid leukemia.[11] Targeted therapies aim to provide maximum efficacy with minimal toxicity compared to traditional cancer therapies. In theory, the more precise a drug is, the lower the likelihood of resistance. Since molecularly-targeted drugs focus specifically on particular cancer targets, they allow for effective treatment at much lower doses.[11] Despite their potential, both targeted and traditional therapies face challenges with intrinsic and acquired drug resistance.[5,6,7,11]

What if the key to overcoming cancer lies in leveraging existing technologies and combining their collective power to provide us with data, analyses, and insights that can help us unravel the code of resistance? In this fight against cancer, multi-omics approaches are emerging as a crucial tool in tackling this complex challenge.

Multi-Omics – A New Approach to Cancer

The Canadian Institutes for Health Research (CIHR) has been actively supporting multi-omics research through its various funding initiatives. Under its newly launched "Team Grants: Embracing Diversity to Achieve Precision and Increase Health Equity" program in 2024, the general omics pool is expected to take up to three grants, amounting to up to $2,000,000 per grant.[12] Additionally, in a collaboration with Genome Canada, CIHR co-funds projects under Genome Canada's "Canadian Precision Health Initiative," which aims to sequence genomes of at least 100,000 Canadians.[13] This funding supports cancer research by generating population-level genomic and multi-omics data.[13]

Why are we heavily investing in multi-omics, and what potential does it hold for cancer research? Using multiple biological data types from a single individual allows for a more complete picture of the molecular factors and cellular processes influencing their health and disease state. This approach uncovers both genetic and non-genetic contributions to overall health and disease.[15] For example, examining the genome, RNA transcripts, proteins, and metabolites involved in cellular functions, as well as changes in gene expression, gives us a holistic view of complex diseases like cancer – far beyond what a single data type could reveal.[14,15]

Significant advancements in high-throughput technologies allow detailed analyses at molecular, cellular, and tissue levels. Whole exome sequencing (WES) and whole genome sequencing (WGS) provide us with data on gene expression. Single-cell technologies provide us with insights into gene activity and cellular characteristics. Moreover, mass spectrometry enables accurate detection of proteins and metabolites.[15]

Cancer, being a complex disease, often involves the interaction of multiple molecular pathways. This includes not only genetic mutations but also changes in gene expression, DNA alterations, metabolic abnormalities, disrupted signaling pathways, and environmental factors – all of which require insights from various fields of omics.[15] Multi-omics helps us identify the key players involved in cancer development, progression, and treatment.[15,16] In summary, multi-omics provides a wealth of valuable information that offers new knowledge about cancer that we've never had before.

The Role of Multi-Omics in Overcoming Cancer Drug Resistance

Researchers from Peking University Cancer Hospital in Beijing used multi-omics to characterize the molecular

features of gastric cancer and its correlation with responses to neoadjuvant chemotherapy (chemotherapy before primary surgery).[16] They identified a critical research gap: neoadjuvant chemotherapy is often underutilized due to a limited understanding of the drug resistance mechanisms involved.[16] To address this, the team applied a multi-omics approach, combining WES, WGS, and RNA sequencing to identify various molecular aberrations. This integrated analysis of diverse biological data sets provided high-confidence results.[17] Their findings revealed that mutations in the *C10orf71* gene were linked to treatment resistance, with drug response data suggesting potential inhibition of the cell cycle.[16] Additionally, their research demonstrated that neoadjuvant chemotherapy alters tumor-immune signaling and reshapes the TME. This work offers valuable insights for developing precision neoadjuvant treatment regimens.[16]

Researchers from Samsung Medical Centre and Sungkyunkwan University School of Medicine in Korea used a multi-omics approach to investigate drug resistance in breast cancer, focusing on resistance to CDK4/6 inhibitor therapy combined with endocrine therapy.[17] Palbociclib, a CDK4/6 inhibitor, blocks cell cycle progression and reduces cell proliferation when combined with anti-estrogen agents.18 However, about 25% of patients show no response, and others eventually experience cancer progression.[19] The researchers aimed to identify patients most likely to benefit from treatment and uncover therapeutic targets to overcome resistance. By integrating genomics and transcriptomics, they identified molecular features linked to acquired resistance, including mutations in *TP53*, *BRCA1/2*, and other genes associated with homologous recombination deficiency (HRD).[17] Their study suggested that a combined TP53/HRD-high mutant cluster could serve as a new biomarker for identifying patients with poor responses to CDK4/6 inhibitors, who may benefit from PARP inhibitors or other DNA-targeting therapies. Additionally, tumors analyzed after progression were found to have mutations in ***ESR1***, *RB1*, and *KMT2C*, which contributed to resistance.[17] This multi-omics approach helps identify patients who would benefit most from treatment and uncovers potential targets to overcome resistance; ultimately it aims to improve breast cancer treatment and outcomes.[17]

Due to the complex nature of cancer, high-throughput analyses like multi-omics function as a powerful tool in combating the disease. By understanding drug resistance, we could identify new drug targets that could lead to the development of more effective treatments.[17,19]

The Future of Cancer Treatment with Multi-Omics

The full potential of multi-omics remains largely untapped. With the rapid evolution of emerging technologies and the integration of artificial intelligence (AI), we expect to make significant strides in cancer research. AI can accelerate data analysis, allowing for vast datasets to be processed in a fraction of the time, offering more generalizable results.[20] This faster analysis will hopefully enable the medical community to improve patient outcomes more quickly, which is a critical factor in cancer treatment.[20] By harnessing the power of multi-omics, we are unlocking new doors for precision medicine – a world where cancer treatments are tailored to the individual patient.

Multi-omics data can reveal how mutations and gene expression influence treatment responses, particularly in immunotherapy.[9,21] Current researchers are applying single-cell multi-omics to study patient responses to therapies like checkpoint inhibitors. This allows the identification of biomarkers that predict treatment efficacy and uncover mechanisms of resistance.[21] Machine learning also plays a crucial role in analyzing the vast multi-omic datasets, enabling the identification of relevant gene sets and pathways that can lead the way to personalized treatment strategies.[21] Despite these advances, the integration of diverse multi-omic data remains a challenge, where more sophisticated bioinformatics tools are needed to make sense of the data.[8,9,21]

This is an exciting time to leverage the power of multi-omics to crack the code of drug resistance and revolutionize the future of cancer care. Looking ahead, multi-omics could become a routine tool for cancer diagnosis, prognosis, and personalized treatment.[21] It would allow deeper understanding of tumor dynamics and could help align therapies with the optimal patient population.[21] As the cost of sequencing decreases and data integration improves, multi-omics will likely become integral to clinical cancer care, offering a holistic view of cancer and moving personalized treatment closer to reality.[8,9,21]

Shannen Arviola is an incoming third-year Doctor of Pharmacy student at The University of British Columbia. She has always been involved in research, across various fields like oncology, pharmacogenomics, and epidemiology.

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Unlocking the Secrets of the Gut: How Multi-Omics is Revolutionizing IBD Research

By Michael Hamilton

There is a certain irony in how the human gut, an organ so essential to our survival, can also be a source of immense suffering. As someone living with a gastrointestinal condition, I know firsthand how unpredictable and disruptive these diseases can be. Simple daily activities become a strategic game of managing symptoms. This personal struggle is what drew me toward the medical subfield of gastroenterology. Beyond my own experience, I have seen how more serious conditions like Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel diseases, or IBD) can take an even greater toll, limiting one's ability to live without the constant worry of an impending flare-up. In fact, it is estimated that over 1.5 million people in North America and 2 million people in Europe live with these diseases,[1] costing the average patient roughly $13,000 in annual expenses.[2] This economic burden underscores the urgency of advancing gastroenterological research. By improving diagnostic precision and enabling more targeted therapies, multi-omics has the potential to reduce costly and time-consuming trial-and-error treatment approaches, hospitalizations, and ineffective medication use, ultimately alleviating both personal and systemic healthcare costs.

While researchers have long searched for ways to better diagnose, treat, and even prevent these diseases, the complexity of the gut microbiome, home to trillions of microbes, has been a significant roadblock. The microbiome is an ecosystem that interacts with our immune system, our intestinal lining, and external factors like lifestyle. Historically, understanding this intricate interplay between the microbiome and its environment has been difficult, especially with conventional research methods that focused on simply one type of biological data at a time, such as genes, proteins, or metabolites. Multi-omics overcomes this limitation by integrating these diverse biological 'layers' into a unified, high-resolution view of the gut's biological landscape. By combining metagenomics (which identifies microbial species and the genes they carry that suggest their potential biological functions), transcriptomics (which tracks active gene expression), metabolomics (which measures biochemical byproducts of microbial activity), and proteomics (which catalogues proteins involved in inflammation and immune response), multi-omics allows researchers to see both the microbiome's composition and its functional impact on gut health. This comprehensive approach has already begun to yield novel biomarkers, which are biological molecules found in bodily fluids or tissues that can act as a sign of normal or abnormal processes.[3] With the advent of machine learning algorithms, researchers are now able to integrate these vast datasets to uncover previously hidden patterns, paving the way for precision medicine in IBD.

From Gut Feeling to Hard Science: What is Multi-Omics?

For decades, scientists have attempted to untangle the intricate relationship between the gut microbiome and IBD using individual research methods, such as genetic analysis or microbiome sequencing. However, these siloed approaches often fall short in capturing the full picture. Multi-omics, on the other hand, integrates multiple layers of biological data, including:

- **Genomics** – Investigating DNA sequences that may predispose individuals to IBD.
- **Metagenomics** – Sequencing microbial communities in the gut to understand which bacteria are present.
- **Transcriptomics** – Analyzing RNA to see which genes (both human and microbial) are actively being expressed.
- **Proteomics** – Examining proteins to identify inflammation markers or disease-related dysfunctions.
- **Metabolomics** – Measuring metabolites (small molecules involved in metabolism) to assess the gut's biochemical environment.

By layering these datasets together, researchers can pinpoint novel biomarkers. In simpler terms, multi-

https://doi.org/10.29173/hsi494
Received 28 March 2025
Accepted 1 July 2025

omics allows scientists to track not just which bacteria are in the gut, but also what they are doing and how it affects the host.

FeelingThe Power of Biomarkers: Predicting IBD Before it Strikes

Imagine a future where doctors can detect IBD before symptoms even appear, offering early interventions that prevent severe disease progression. Multi-omics is making this a real possibility. One groundbreaking study analyzed blood samples from individuals who later developed Crohn's disease, revealing a distinct pre-diagnostic protein signature up to five years before their official diagnosis.[4] This was achieved through proteomic analysis, where researchers examined thousands of proteins in the blood plasma of patients, comparing those who eventually developed Crohn's disease with healthy controls. They identified key inflammatory proteins and immune-related markers that were elevated long before any clinical symptoms appeared, indicating that systemic inflammation and immune activation may precede gut-specific symptoms by several years.

Another study utilized multi-omics by integrating metagenomics, metabolomics, and transcriptomics to assess the gut microbiome's role in predicting IBD flares.[5] By analyzing stool samples from patients over time, researchers discovered that subtle shifts in microbial gene expression and metabolite production correlated with upcoming disease activity. For example, a reduction in short-chain fatty acid-producing bacteria and an increase in pro-inflammatory microbial pathways were observed in patients who later experienced flares. These findings indicate that IBD isn't a sudden onset disease; rather, it follows a long, silent trajectory that multi-omics can help unveil, allowing for earlier intervention.

Adult IBD patients are not the only patients that can benefit from multi-omics research. In 2017, a study utilizing pediatric IBD patients revealed that distinct gene expression profiles at the time of diagnosis could predict whether they would develop complications like strictures or fistulas.[6] This study integrated transcriptomic, proteomic, and metagenomic data from intestinal biopsies and blood samples of newly diagnosed pediatric patients. By analyzing gene expression patterns within the intestinal mucosa, researchers identified upregulation of fibrosis-related pathways in children who later developed strictures, while inflammatory cytokine signalling was predominant in those who progressed to penetrating disease.

This insight is invaluable. High-risk patients might receive more aggressive therapy early on, such as biologics that target inflammatory pathways aligned with their predicted disease course. Meanwhile, low-risk individuals could potentially avoid unnecessary medications such as tricyclic antidepressants or chloride channel modifiers.[7] Tricyclics are often used off-label to manage gut-related pain but can cause side effects like excessive drowsiness and dry mouth. Chloride channel modifiers, typically prescribed for IBS-related constipation, may offer little benefit to IBD patients experiencing diarrhea-predominant symptoms. In parallel, multi-omics approaches have revealed microbial imbalances[8] that correlate with disease complications, suggesting that specific bacterial species may contribute to disease progression. These findings emphasize the power of multi-omics not only in identifying prognostic biomarkers but also in uncovering insights into the biological mechanisms by which IBD complications develop.

Moving Beyond Trial-and-Error Medicine

One of the biggest frustrations for IBD patients is the trial-and-error nature of current treatments. Some respond well to biologic therapies, while others endure months (or years) of failed treatments before finding relief. This unpredictability stems from the fact that IBD is not a singular disease but a spectrum of disorders with unique underlying biological mechanisms in each patient.[9] Traditional treatment approaches often fail to account for these individual differences, leading to prolonged suffering and unnecessary exposure to ineffective drugs.

Multi-omics is revolutionizing this approach by identifying biomarkers that predict drug response, enabling a more personalized treatment strategy. By integrating genomic, transcriptomic, and proteomic data, researchers can determine which patients are most likely to respond to specific therapies. For example, genomic sequencing has revealed that patients with specific NOD2 mutations have different responses to common anti-TNF agents such as infliximab and adalimumab.[10] Proteomic analysis has also shown that elevated levels of Oncostatin M, a secreted cytokine involved in chronic inflammation in intestinal tissues, correlate with poor response to biologics.[11,12] This means that before even

prescribing a medication, clinicians can now assess whether a patient has a molecular profile that suggests they will, or will not, respond to a given treatment.

Multi-omics also allows researchers to track real-time treatment responses by analyzing dynamic changes in gut microbial composition and host immune activation over time. Evidence from a recent metabolomic study suggests the presence of specific microbial metabolites, such as branched-chain amino acids, correlated with successful remission following biologic therapy.[13] These findings suggest that changes in microbial metabolite production may not only reflect treatment response but also influence it. As a result, therapies that directly target the gut microbiome – such as dietary interventions or probiotic supplementation – could potentially enhance the effectiveness of conventional drugs when used in combination.

The Future of Multi-Omics in IBD Research

Despite its immense promise, multi-omics still faces challenges. The technology is expensive, with one study indicating that it costs a staggering $12,743 for annual genomic and preliminary testing for pediatric oncology patients.[14] Additionally, while multi-omics has identified hundreds of potential IBD biomarkers, only a few have been clinically validated.[15] More large-scale, longitudinal studies are needed to translate these findings into everyday medical practice. However, the future is bright. Researchers are already exploring AI-driven multi-omics models that can integrate complex datasets and generate precise disease predictions.[16] Additionally, as sequencing costs decrease[17], multi-omic profiling may become a routine part of IBD diagnosis and treatment planning. For individuals living with IBD, this research represents something far greater than scientific progress; it offers hope. Hope for earlier diagnoses, personalized treatments, and perhaps one day, the ability to prevent these diseases altogether. The gut may still hold many secrets, but thanks to multi-omics, we are closer than ever to unlocking them.

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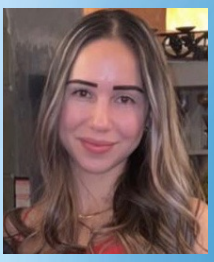
HSI 2025
MAIN SUBMISSION AWARDS

Best Submissions 2025 articles were judged by a panel of independent faculty experts. Want to read our top two submissions? These authors have the opportunity to publish in Lifestyle Genomics and Epigenomics as part of our journal's collaboration initiative.

Redefining Malignant Hyperthermia: Multiomic Insights into a Complex Anesthetic Disorder

Cassandra Thachuk, University of Limerick



FIRST PLACE AWARD

Cassandra Thachuk is a Canadian medical student studying in Ireland. Prior to medical school, she worked as a registered nurse for five years in labor and delivery and the neonatal ICU, and spent three years teaching neonatal resuscitation. Her interest in malignant hyperthermia was sparked after receiving specialized training to administer dantrolene for this rare and complex anesthetic disorder.

Integrating Gut Microbiome and Host Transcriptomics for the Personalized Management of Inflammatory Bowel Disease

Darragh Barry, University of Limerick

SECOND PLACE AWARD

Darragh Barry is a first-year Graduate Entry Medical Student at the University of Limerick, Ireland. He completed his undergraduate degree in Physiology at Trinity College Dublin, where he developed an interest in the molecular pathogenesis of gastrointestinal disorders.

Albumin as a Marker of Ascites: The Role of Proteomics in Uncovering Novel Diagnostic Biomarkers

THIRD PLACE AWARDS

Dr. Jasmine Momoh is an internal medical trainee at University Hospital Coventry and Warwick in the UK. Over the past few years she has been involved in the care of patients presenting with ascites. Her understanding and knowledge of the disease is very important as it helps with the discovery and the development of novel biomarkers which would in turn help further improve treatment pathways for the disease.

Ifeanyi Kennedy Nmecha is a final-year PhD candidate at McMaster University, Canada. His research focuses on uncovering the mechanisms and complications of diabetic kidney disease, with a particular emphasis on identifying novel biomarkers that can detect kidney decline at its earliest stages. This work is critical, as progressive kidney damage can lead to severe complications, including ascites. Beyond the lab, he is an avid food enthusiast who enjoys exploring diverse cuisines and culinary experiences.

Spruha Joshi is a nursing student at McMaster University, Canada. With an interest in applied research and primary health care, she has contributed to projects focused on improving community health and supporting diverse populations. As she completes her Bachelor of Science in Nursing, Spruha plans to continue contributing to health promotion and research initiatives while advancing her career in the medical field.

Exercise as an Adjunctive Treatment Modality for Major Depressive Disorder: A Multi-Omics Perspective

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Major Depressive Disorder (MDD) is characterized by genetic and environmental factors. Current interventions, including selective serotonin reuptake inhibitors and cognitive-behavioural therapy, are often effective yet prone to the development of treatment resistance. A major mechanism for MDD pathogenesis involves dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, which results in chronic elevation of cortisol. Cortisol has been linked to MDD symptomology through downstream cellular effects, which can be elucidated through multi-omics analyses such as genomics (NR3C1, FKBP5), proteomics (pro-inflammatory cytokines), and metabolomics (shifted kynurenine pathway). A systematic literature search of OVID Medline and similar databases was conducted using literature from the past 10 years to identify studies investigating exercise interventions targeting multi-omics markers in MDD. Inclusion criteria required independent MDD cohorts and included a minimum of two omics levels and their relationship to exercise as an intervention. Existing literature demonstrates that aerobic exercise can regulate cortisol levels: increasing NR3C1 and FKBP5 gene expression, reducing proinflammatory cytokines, and shifting tryptophan metabolism towards the neuroprotective kynurenic acid and away from neurotoxic metabolites. A change in these biomarkers suggests that regular physical activity can exert widespread biological and neurological effects by regulating molecular dysfunctions at a multi-omics level in MDD. Exercise, when prescribed as an adjunct to conventional MDD therapies, may improve clinical outcomes by modulating stress-responsive and inflammatory pathways at multiple omics levels. Further large-scale and longer-term randomized trials are required to validate specific biomarkers for personalized medicine, and additional work should investigate sex-based differences in exercise efficacy. Exercise offers significant promise for optimizing MDD management and promotes greater physiological resistance to depressive symptoms.

Introduction

Major depressive disorder (MDD) is a multifaceted mood disorder arising from a combination of genetic, biological, and psychological factors.[1] Manifestations include explicit changes in mood, pleasure, and cognition; the specific diagnostic criteria are outlined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision and International Classification of Diseases 11th Revision.[1,2] MDD is defined as an individual showing at least five depressive symptoms almost every day within a 2-week period; individuals must present a change from previous functioning, including depressed mood, anhedonia, sudden mood and sleep fluctuations, or fatigue.[3,4]

Globally, 5% of adults experience depression, with women at a nearly two-fold higher risk of developing MDD.[2,5] The economic burden of MDD is significant, with an estimated $210.5 billion USD in 2010, and a reported increase of 37.9% between 2010 and 2018 – which encompasses direct, workplace, and suicide-related costs.[6] Despite the rising burden, the Association of British Pharmaceutical Industry asserts that only 7% of global research and development is invested in central nervous system diseases – indicating an unmet need for more effective treatments for MDD.[7]

MDD is a highly prevalent psychiatric illness that can be managed, to some extent, through an integrated approach involving psychotherapy, pharmacotherapy, and somatic interventions. Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-line treatments due to their relatively favourable safety profile. For more resistant or severe cases, other options

https://doi.org/10.29173/hsi500
Received 28 March 2025
Accepted 2 July 2025

include serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, or even ketamine-based therapies.[8,9] Cognitive-behavioural therapy (CBT) and interpersonal therapy are also effective in reducing depressive symptoms and preventing relapse.[8] In refractory situations, electroconvulsive therapy and repetitive transcranial magnetic stimulation are considered[8,9] Additionally, emerging research suggests lifestyle modifications – such as improved sleep habits, dietary adjustments, exercise, and social support – as promising strategies to prevent and mitigate MDD.[9] Noetel et al. predict that various exercise modalities outperform independent SSRI use compared to active controls, and that exercise alone and in conjunction with standard treatments is significantly more efficacious in reducing depressive symptoms.[10]

Various hypotheses have been proposed to explain MDD pathogenesis, with many arising from chronic cortisol elevation due to hypothalamic-pituitary-adrenal (HPA) axis dysfunction.[1,8] Increased cortisol results in homeostatic deviations within multiple molecular pathways, contributing to disease progression and symptom severity (Figure 1).[11]

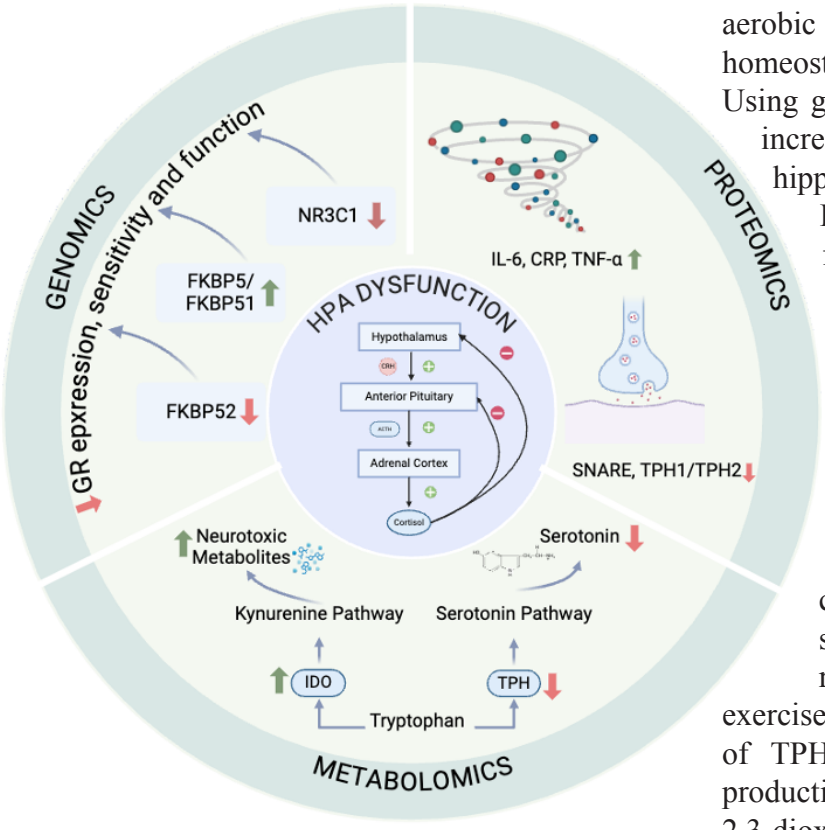

Figure 1. Endocrine and Multi-Omics Insights into Molecular Changes in MDD Patients.

At the genomic level, irregular DNA methylation and decreased expression of genes FKBP5 and NR3C1 reduce downstream glucocorticoid receptor (GR) protein expression, impairing the negative feedback system and subsequent HPA hyperactivity.[12,13] Dysfunctions at the proteomic level include increased expression of pro-inflammatory cytokines – such as interleukin-6 (IL-6) and C-reactive protein (CRP) – and downregulation of enzymes involved in serotonin synthesis–like tryptophan hydroxylase (TPH).[13,14] Metabolomic studies reveal a shift in tryptophan metabolism, favouring the kynurenine (KYN) pathway over serotonin production. In MDD patients, KYN metabolism yields increased neurotoxic metabolites – such as quinolinic acid – and decreased neuroprotective metabolites – such as kynurenic acid (KYNA).[15,16] Through a multi-omics analysis of MDD, it is evident that although standard therapeutic interventions—such as SSRIs, SNRIs, and CBT – target specific omics levels, they do not adequately address the relevance of cortisol dysfunction.[8]

Exercise presents a potential non-pharmacological intervention for MDD, with extensive literature supporting its regulatory effects on the HPA axis and widespread downstream signalling.[12-16] Chronic aerobic exercise has been shown to restore HPA axis homeostasis, regulating cortisol levels in MDD patients.[17] Using genomics analysis, exercise has been shown to increase NR3C1 and FKBP5 gene expression in the hippocampus and prefrontal cortex. Exercise reduces DNA methylation and activates transcription factors, which allows NR3C1 to effectively co-repress GR activity and FKBP5 to increase GR sensitivity.[18,19] Regarding proteomics, exercise has been shown to mitigate neuroinflammation by downregulating IL-6, tumour necrosis factor-alpha (TNF-α), and CRP.[20,21] Dysregulated immune function in chronic stress conditions leads to the upregulation of these pro-inflammatory cytokines. Exercise helps restore microglial structure and regulate its activation, ultimately reducing neuroinflammation.[22] Concurrently, exercise has been shown to increase the expression of TPH – the rate-limiting enzyme for serotonin production – and decrease the expression of indoleamine 2,3-dioxygenase – the rate-limiting enzyme for KYN production. At the metabolomic level, increases in the neuroprotective ratio following exercise indicate a

shift towards kynurenic acid production during KYN metabolism.[23,24] Collectively, these findings substantiate exercise as a systemic regulator to mediate multi-omics disruptions observed in MDD; given its accessibility and widespread benefits, exercise should be prescribed as an adjunctive first-line treatment for depression.

This paper proposes that structured exercise interventions can modulate multiple biological systems implicated in MDD, as captured through multi-omics analysis. By targeting shared pathways underlying depression, exercise offers a potent complementary approach alongside standard pharmacotherapies, while providing additional metabolic benefits.

Methods

A literary search was conducted in OVID Medline to examine the relationship between multi-omics biomarkers, MDD, and exercise modulations of cellular pathways. Studies that were published within the last 10 years in PubMed, ScienceDirect, and ResearchGate were included. Omics studies must have included either MDD patients as a subgroup or the distinct study population or included exercise and control groups. Exercise studies must have investigated MDD patients independently ofhealthy controls. Exclusion criteria included papers that did not examine the relationship between at least two of MDD, exercise, and omics analysis. Randomized-controlled trials and systematic reviews using in vivo models were prioritized in data extraction; however, some observational and narrative studies were used to supplement background information on the topic.[25]

The Role of Omics in the Development of Therapies Targeting MDD

Traditional healthcare has historically focused on disease treatment over prevention, often leading to high costs and limited effectiveness due to a 'one-size-fits-all' approach that ignores individual genetic, environmental, and lifestyle differences.[26] Omics technologies have revolutionized medicine by providing a more nuanced understanding of diseases through the integration of genomics, transcriptomics, proteomics, and metabolomics, enabling personalized treatment and early detection. MDD has a polygenic basis, with approximately 50% of cases linked to genes involved in the serotonergic system and HPA axis.[27] These genes serve as potential diagnostic markers and drug targets, but genetic risk alone insufficiently predicts MDD, underscoring the need for multi-omics integration. Biomarkers such as cortisol, serotonin, CRP and IL-6, and metabolic disruptions in tryptophan metabolism contribute to MDD pathophysiology.[28] In metabolomics, pro-inflammatory cytokines elevate kynurenine levels, which exacerbates symptoms.[29] This integrated omics approach enables the development of biomarker-driven therapies, including anti-inflammatory agents, metabolic modulators, and exercise, thus offering alternatives for patients unresponsive to SSRIs.[30] Exercise, which impacts inflammation and neuroplasticity, emerges as a key non-pharmacological therapy.[31] However, data complexity and validation remain a challenge when translating omics findings into clinical practice.[32]

Omics-Level Alterations in MDD and Their Modulation Through Exercise

MDD risk can be analyzed at the levels of the genome and transcriptome. The NR3C1 gene encodes GRs, which binds cortisol and regulates stress response through negative feedback on the HPA axis.[14] The gene FKBP5 modulates GR sensitivity, reducing its activity to prevent excessive stress responses.[33]

Thus, decreased expression of NR3C1 and FKBP5 influences HPA axis hyperactivity by reducing GR response to cortisol. The transcription of NR3C1 can be modulated on levels of decreased transcription through DNA methylation and modulation of mRNA expression by RNA silencing or translational repression by microRNAs (miRNAs).[34] NR3C1 is located on chromosome five and consists of 9 non-coding first exons, which are hypothesized to act as promoters. Many of these first exons occur on CpG islands, and thus DNA methylation of these areas significantly reduces the transcription of GRs. Consequently, higher levels of DNA methylation are observed in MDD patients, implicating it in MDD risk.[28] Micro-RNA (miR)-124, a small non-coding RNA molecule which downregulates GR activity in vivo, is highly expressed in the brain.[34-36] Zeng et al. found that all CpG islands were significantly hypomethylated in MDD when compared with healthy controls, thus implicating miR-124 dysregulation in MDD.[37] Specifically, the 1F promoter region methylation of the gene is associated with transcriptional silencing of GR and RNA via miR-124.[11,34-37]

Patients with FKBP5 polymorphisms also show higher MDD risk. The presence of the T-risk allele in single nucleotide polymorphism rs1360780 leads to elevated FKBP5 mRNA transcription and translation.[38-40] The T allele specifically forms the transcription start site on intron 2 and is associated with chromatin conformation that increases glucocorticoid response element binding.[40] However, due to the limitations of genetic research, there is significant heterogeneity in research for the rs1360780 T allele. Menke et al. found that depressed patients with the T allele showed reduced FKBP5 mRNA induction, and less cortisol and ACTH suppression post-dexamethasone stimulation compared to healthy T carriers because of GR resistance in MDD risk.[12] These results are in opposition to the research claiming that increased FKBP5 expression is associated with reduced GR sensitivity. Furthermore, Young et al. showed that across various brain regions – including the medial prefrontal cortex, hippocampus, and insular cortex – an increase in NR3C1 and FKBP5 was observed in rats that underwent exercise compared to the non-exercise groups.[41] Increased expression of these genes recalibrates the brain to adjust for stress resilience. Elevated GR enhances the HPA negative feedback loop, while FKBP5 modulates GR activity, preventing excessive cortisol effects. Thus, the discrepancies in the research indicate further need for investigation into the genetic influence on HPA axis regulation and MDD.

Proteomic changes in MDD provide insights into mood regulation. Key proteins play crucial roles: including neurotransmitter transporters, synaptic proteins, and inflammatory cytokines. MDD is characterized by significant changes in proteins including TPH and soluble NSF attachment protein receptors (SNARE); these are essential to neurotransmitter release and synaptic plasticity.[14,42] Elevated levels of inflammatory markers such as IL-6, TNF-α, and CRP have been observed in both brain and serum, establishing a link between inflammation and mood dysregulation.[28]

Exercise demonstrates therapeutic potential for modulating cortisol and pro-inflammatory cytokines.[43-45] After 4 weeks of aerobic training, Liu et al. observed that exercising mice had decreased hippocampal IL-6 and TNF-α expression.[22] A randomized control trial study conducted by Lavratti et al. demonstrated decreased serum IL-6 in patients with psychological disorders after exercise treatment.[20] Additionally, Kasapis et al. showed consistent decreases in CRP levels between various patient profiles after exercise treatment.[46] As these cytokines are linked to depressive symptoms like anhedonia, poor sleep, and poor appetite, exercise serves as a viable holistic supplement for MDD treatment.[13] However, chronic aerobic overtraining may elevate pro-inflammatory cytokine levels, emphasizing the need for individualized treatment plans.[47]

Preclinical and clinical omics data further support resistance training as an effective intervention. In rodents, ladder climbing reversed stress-induced depressive behavior by normalizing TRKB-Akt-mTOR signaling and dampening NLRP3-mediated neuroinflammation.[48] In older men, 12 weeks of high-load training upregulated PGC-1α/PPAR pathways and kynurenine-aminotransferase expression, promoting neuroprotective KYN metabolism.[49]

At the metabolomic level, MDD involves disruptions in amino acid, lipid, and energy metabolic pathways, including tryptophan metabolism which favours KYN over serotonin production. Acute exercise promotes beneficial shifts in tryptophan metabolism, favouring a neuroprotective profile.[23] Extending these findings, Javelle et al. showed that eight weeks of high-intensity interval training decreased neurotoxic quinolinic acid and increased KYNA levels, suggesting a sustained protective phenotype.50 In rodent models, Kim et al. reported that aerobic exercise reversed stress-induced deficits in dorsal raphe TPH expression, highlighting its capacity to restore serotonergic function.[24] Monitoring shifts in KYN–KYNA ratios, quinolinic acid levels, and TPH expression can guide personalized exercise interventions to optimize therapeutic outcomes. Alongside pharmacotherapies, these biomarker-driven interventions – including exercise – may improve remission rates in MDD minimizing adverse effects.[23,24,50]

Understanding the importance of exercise at multi-omics levels – including genomics, transcriptomics, proteomics, and metabolomics – provides a detailed analysis of specific biomarkers which exert an effect on exercise. Deciphering the connection between these levels and their relation to exercise elucidates how physical activity optimizes molecular pathways and promotes greater physiological resistance to depressive symptoms.

Conclusion

Undoubtedly, identifying biomarkers which enhance stress resilience is crucial for regulating mood in MDD patients. Future research should prioritize large-scale studies to validate multi-omics-based biomarkers as a tool for guiding personalized interventions. This underscores the necessity for precision medicine recognizing that patient care for mental disorders must be tailored to individual needs. Future studies would also investigate sex-related disparities in MDD and differences in treatment. Research should focus on strategies for integrating exercise as a therapeutic or adjunct intervention, while considering some individuals may face physical or mental barriers to exercise. Such advancements hold significant promise for improving mental health through specific, evidence-based approaches.

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Navigating Ethical Challenges of Multi-Omics and Electronic Health Records in Healthcare

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The integration of multi-omics approaches with Electronic Health Records (EHRs) has the potential to transform personalized medicine by offering deeper insights into disease mechanisms, treatment responses, and patient outcomes. Multi-omics enhances diagnostic accuracy, treatment, optimization, and predictive modelling through the like of genomics, proteomics, and other omic layers. However, this advancement also raises critical ethical concerns regarding privacy, confidentiality, autonomy, and justice. Multi-omics data serves as a distinct biological identifier, making it highly sensitive and vulnerable to misuse. Equity in multi-omics research is another significant challenge; genomic studies have historically been biased toward populations of European descent, limiting the generalizability of findings across diverse groups. While federal regulations such as the United States' Health Insurance Portability and Accountability Act (HIPAA) and the province of Ontario's Personal Health Information Protection Act (PHIPA) establish a baseline for legal protections, their effectiveness depends on robust digital infrastructure, public education, and the development of privacy frameworks. Robust security measures such as encryption, blockchain, and privacy-preserving algorithms are essential to mitigate risks. However, existing governance frameworks must extend beyond security protocols to establish clear regulations on data ownership, access rights, and ethical usage. Emerging challenges, including AI-driven data analysis and the commercialization of genetic information, further underscore the need for proactive governance to prevent misuse, discrimination, and bias in healthcare and insurance industries. To ensure ethical multi-omics integration into EHRs, continuous policy updates, interdisciplinary collaboration, and patient-centered approaches are essential. Balancing innovation with ethical integrity will be crucial in advancing precision medicine while safeguarding individual rights and promoting equitable healthcare access.

Keywords: Ethics, Electronic Medical Records, Multi-Omics, Precision Medicine, Blockchain Technology

Introduction

Integrating multi-omics approaches with Electronic Health Records (EHRs) offers a powerful opportunity to advance personalized medicine by delivering deeper insights into disease mechanisms, treatment responses, and patient outcomes. EHRs, which contain comprehensive clinical data on a patient's medical history, treatments, and outcomes, have significantly transformed the healthcare system since their introduction in the 1960s.[1] They have revolutionized the way patient information is recorded, stored, and accessed, which has enabled faster, more accurate documentation, and improved the coordination of care.[2] All healthcare providers who are involved in the patient's medical care can now access a patient's complete medical history in real time, leading to more informed decision-making, reduced medical errors, and enhanced patient safety. Multi-omics, which emerged in the early 2000s, further reshaped healthcare by integrating data from genomics, proteomics, metabolomics, and other omics layers.[2] Genomics focuses on the study of genomes, while proteomics investigates the structure, function, and interactions of proteins. Other omics layers, such as metabolomics, transcriptomics, and epigenomics, build on genomics and proteomics to offer a more comprehensive understanding of biological processes. While each discipline provides unique molecular insights, their integration enhances the precision and personalization of healthcare, enabling physicians to diagnose diseases more accurately, predict treatment responses, and identify novel therapeutic targets.[3]

https://doi.org/10.29173/hsi497
Received 28 March 2025
Accepted 1 July 2025

Multi-omics evolved from interdisciplinary research, particularly following the completion of the Human Genome Project in 2003, and gained significant traction in 2023-2024 for its potential to advance disease prevention and manage conditions like cancer, neurological disorders, and metabolic diseases.[4,5] Multi-omics data uncovers complex biological networks, revealing how genes, proteins, metabolites, and other molecules interact to influence health and disease.[6] This systems-level understanding provides a holistic approach, improving clinical decision-making by considering not only genetic information but also environmental influences, lifestyle choices, and molecular interactions. The combination of multi-omics and EHRs offers transformative potential for healthcare, but this integration also presents critical ethical dilemmas that must be addressed before it can be fully embraced. It should be noted that many of the findings and analysis are presented from an Ontarian perspective, rather than a global one. This commentary will explore some of the ethical issues including privacy, confidentiality, autonomy, and justice.

Privacy

Privacy in ethics pertains to the control over personal information, which requires careful collection, storage, and use to maintain ethical standards and patient trust. While multi-omics advances precision medicine by identifying inherited traits, disease risks, and treatment responses, it also introduces significant privacy risks if mismanaged.[5]

A major concern is that genomic data acts as a personalized "fingerprint", revealing extensive details about an individual's health deviations, disease risks, and lineage.[7,8] The interdisciplinary nature of multi-omics necessitates extensive data sharing, making it harder to track data destinations and increasing the risk of unauthorized access.[5] Furthermore, the extensive data demands of personalized medicine heighten the risk of exposing sensitive information through seemingly unrelated samples that may be pieced together with malicious intent by insurers or employers, for example, without the individuals consent.[7,9] This is particularly critical in genetic testing, where data shared with third parties raises privacy concerns. Such vulnerabilities (weaknesses or risks in systems and practices used to manage and protect sensitive data) underscore the need for clear data retention policies and secure disposal practices.[7,9] Without such measures, these disadvantages may undermine public trust and hinder the advancement of multi-omics in EHRs and precision medicine.

To address these concerns, the current literature recommends implementing activity traceability methods (systems that monitor and log the accessibility of data), blockchain technology, and adherence to General Data Protection Regulation (GDPR) standards.[5,7] The GDPR is a legal framework enacted by the European Union in 2018 that sets strict guidelines on how personal data is collected, stored, processed, and shared. Blockchain, in particular, provides a secure framework for data sharing and verification.[5] Molla et al. propose a multi-faceted strategy to mitigate potential risks which includes strong encryption, routine security audits, stringent access controls, and clearly defined data retention policies that outline specific storage timelines, deletion criteria, and secure disposal procedures.[7] Ultimately, the integration of multi-omics data into EHRs demands a careful balance between privacy protection and data accessibility to ensure ethical use and sustain public trust in precision medicine. This balance inevitably raises critical ethical considerations, particularly surrounding patient confidentiality and autonomy, as individuals must retain control over how their sensitive health information is accessed and used.

Confidentiality and Autonomy

While confidentiality and privacy are often used interchangeably in healthcare data security, confidentiality specifically refers to the duty of safeguarding sensitive information from unauthorized disclosure, particularly in EHRs, which consolidate long-term records from multiple providers.[10]

Incorporating multi-omics data into EHRs increases security risks, as even anonymized genetic information can potentially be reidentified when combined with phenotypic or clinical data, thereby heightening the risk of data breaches.[11] Genomic data predicts individual health outcomes and inherited conditions, creating an ethical dilemma between balancing patient confidentiality while being obligated to inform relatives of genetic risks.[12]

To safeguard confidentiality, Jamshed et al. emphasize restricting EHR access through role-based permissions and traceability measures, such as user identifications and passwords for accountability.[13] Another approach

in some countries is granting patients greater control over records and limiting third-party access.[10] While this enhances autonomy, it may also restrict providers' access to critical information, potentially affecting care quality.[10]

Autonomy in ethics refers to an individual's right to self-determination and informed decision-making.[14] In EHRs, clear consent frameworks are essential to ensure individuals understand how confidentiality is maintained.[8] Empowering patients to make informed choices about data sharing can bring tangible benefits, allowing healthcare to be more personalized, timely, and effective. For instance, sharing genomic information can help healthcare providers detect risks earlier and reduce trial-and-error in treatment plans. While poorly designed regulations may create a false sense of security and shift accountability away from data stewards, reducing transparency, overly rigid policies that discourage data sharing can deny patients these advancements.[15]

A well-balanced system is needed with the use of EHRs, and multi-omics to ensure sensitive information is used transparently, empowering patients to make autonomous healthcare decisions. While research on autonomy in multi-omics and EHRs remains limited, upholding individual choice is essential to maintaining ethical integrity in this advancing field.

Justice and Multi-Omics

In ethics, justice is the "fair, equitable and appropriate treatment of persons".[16] In the context of multi-omics and EHRs, justice ensures that advanced healthcare technologies benefit all populations equitably, without discrimination.[17] While multi-omics enables personalized treatments, concerns regarding access, representation, and health outcomes are persistent.

Williams and Anderson emphasize that equitable research selection is crucial, as underrepresentation limits certain groups from benefiting from scientific advancements.[17] Historically, genome-wide association studies have predominantly focused on individuals of European ancestry, creating disparities in genetic research. For instance, American biobank recruitment materials aimed at engaging Hispanic individuals were only available in English and exceeded recommended reading levels, creating barriers to participation.[17,18] This is not due to a lack of willingness but rather ineffective recruitment strategies that fail to promote inclusivity. Clarke and van El highlight that disadvantaged individuals must first receive adequate healthcare access before benefitting from genomic services.[19] Barriers such as poverty, disability, and limited internet access hinder engagement with genomic technologies.[19] Even when individuals access genomic services, they may struggle to stay informed due to changing personal circumstances or evolving genetic interpretations that impact their healthcare decisions.

Sustained access requires public initiatives and dedicated healthcare efforts to keep all patients, including those facing financial hardship, connected to the healthcare system. Achieving justice in multi-omics requires intentional efforts to improve inclusivity and equitable access. Without proactive measures, personalized medicine and EHR risks are deepening health disparities rather than reducing them.

Discussion

Researchers agree that while multi-omics and EHRs hold significant potential for precision medicine, critical issues must be addressed before integration into routine healthcare. EHRs improve healthcare quality at a relatively low cost, yet concerns persist around responsibility, data privacy, and ethical implications.[20] A key issue is ensuring clearer consent processes, so patients fully understand how their data is used. Strong security measures are crucial to protect patient data and prevent breaches. Alongside these measures, clear guidelines on data ownership and access are essential. In North America, federal laws like the Health Insurance Portability and Accountability Act (HIPAA) in the United States and provincial laws such as Ontario's Personal Health Information Protection Act (PHIPA) provide frameworks for EHR security through access controls, encryption, and audit trails.[21] Regulatory frameworks alone are not enough, and practical implementation requires investment in secure digital health infrastructure. In Canada, Health Infoway, a federally funded agency, plays a key role in advancing secure and interoperable EHR systems to align with privacy laws. Its' ACCESS 2022 initiative aims to expand digital health services and improve patient access to their medical records while promoting data security and interoperability.[22] However, challenges remain in balancing accessibility with privacy, particularly under Ontario's Freedom of Information and Protection of Privacy Act (FIPPA).[23] While PHIPA protects personal health information,

administrative and operational hospital records containing anonymized patient data, this information may still be accessible under FIPPA.[23] FIPPA's potential to permit access to such data creates uncertainty about unintended secondary usage, emphasizing the need for updated policies that account for the sensitivity of omics data.

To further mitigate these risks, advanced security measures are essential to protect EHRs from breaches and cyber threats. Literature shows that the most effective methods for securing EHRs include encryption, firewalls, blockchain, access controls, and audit logs. Cryptogenic techniques enable selective data removal from cloud servers while maintaining privacy through encryption monitoring, digital signatures, and robust authentication.[20,24] Users should regularly update passwords, avoid weak credentials, and log out after sessions.[20] Firewall technology plays a crucial role in blocking unauthorized intranet access, while innovative methods like privacy-preserving algorithms and machine learning anonymization strengthen security against cyberattacks.[25,26] As Canada continues to expand digital health initiatives, integrating these advanced security measures will be critical to ensuring patient data remains protected while enabling multi-omics integration into healthcare.

Clear governance is equally as important to security measures in defining who has access to sensitive patient data and under what circumstances. Ethical multi-omics use requires unity, collaboration, and accountability. While governments must establish and enforce clear regulations, the ultimate responsibility rests with hospitals and research institutions to apply ethical practices in real-world settings. A major challenge is ensuring all stakeholders understand privacy obligations.[24] Tardif notes that misinterpretations of privacy laws often lead to patient consent violations in EHR access, particularly when healthcare professionals assume broad access rights beyond their intended scope, highlighting the need for better education on privacy regulations.[27]

Beyond compliance, scientists and healthcare providers must advocate for ethical standards and educate patients about their rights. For instance, academic researchers must follow Tri-Council guidelines and require certification before conducting studies.[28] The Tri-Council refers to the Tri-Council Policy Statement (TCPS) in Canada, which is a set of ethical guidelines for research involving humans. The guidelines emphasize the importance of respecting the rights, dignity, and autonomy of research participants and ensuring informed consent, privacy protection, and proper ethics review processes. Similarly in Ontario, private-sector organizations like clinics, pharmacies, and insurers are governed by the Personal Information Protection and Electronic Documents Act (PIPEDA), which regulates the collection and disclosure of personal health information.[29] Ethical concerns grow with secondary multi-omics data use in population health research and historical studies.[24] Private vendors like Google and Microsoft offer personal health records services directly to patients, but the level of security and privacy vary.[24] Without consistent oversight, privacy risks increase. A standardized privacy framework is needed to promote collaboration while protecting individual rights.[24]

As multi-omics evolves, emerging challenges require attention, particularly in AI-driven data analysis, which raises concerns about bias, accuracy, and privacy. The commercialization of genetic information presents ethical risks, including potential misuse. AI systems may fail to fully anonymize health data, use information for unintended purposes, or enable cross-border transfers that bypass regulations.[30] Predictive health data could also be exploited by insurers or employers, leading to discrimination. McGraw and Mandl highlight how social determinants of health influence wellness, making multi-omics data particularly sensitive due to stigma and financial risks.[31] For example, insurers could use this data to deny coverage to high-risk populations.[31] However, if ethically managed, AI and commercialization can expand access to care by reducing diagnostic delays and identifying patterns across underrepresented populations. If AI is used responsibly, it can be beneficial in reducing the ongoing healthcare and economic burden. To prevent ethical breaches, organizations must comply with laws like PIPEDA and implement responsible data use strategies. Privacy Incident Management Processes can help detect, mitigate, and report ethical violations.[32] Addressing these challenges requires continuous policy updates, open discussions on ethics, and adaptable regulations. Prioritizing ethical considerations will ensure multi-omics advances equitably and responsibly. It is important to understand that ultimately the role of trust in healthcare, from both patient and provider perspectives is crucial for informed consent and responsible data use.

Conclusion

This paper examined the ethical challenges associated with integrating multi-omics into EHRs and precision medicine. It explored key strengths, limitations, and existing strategies for ensuring ethical and fair use of these technologies. However, the findings are not exhaustive, as the level of ethical integration varies across healthcare facilities. Future research should focus on how multi-omics can inform clinical practice across disciplines and assess its long-term impact on patient care. Additionally, clearer consent models are needed to empower patients in making informed decisions about data usage while ensuring healthcare providers have access to essential information for optimal care.

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Albumin as a Marker of Ascites: The Role of Proteomics in Uncovering Novel Diagnostic Biomarkers

This article received an annual HSI scholarship for **third best submission**. Articles were judged by a panel of independent faculty experts.

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Liver cirrhosis is a progressive and often irreversible condition that represents a leading cause of morbidity and mortality worldwide. One of the most common and severe complications is the development of ascites, a condition which not only signals hepatic decompensation, but also portends a poor prognosis and increased risk of hospitalization and mortality. Traditional diagnostic tools, such as the serum-ascites albumin gradient (SAAG), are widely used to differentiate between various causes of ascites (whether it is as a result of liver damage or other unknown causes). However, these albumin-based markers can be limited in sensitivity and may not fully capture the complexity of pathophysiological changes occurring in cirrhosis and its associated complications.

In recent years, advances in omics technologies, particularly proteomics, have opened new avenues for identifying disease-specific biomarkers that reflect underlying molecular dysfunction. Proteomics – the comprehensive study of protein expression, modifications, and interactions has emerged as a valuable tool for discovering novel biomarkers that may enable earlier and more accurate diagnosis, better prognostic stratification, and personalized therapeutic monitoring in cirrhotic patients. Biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have shown promise in detecting acute kidney injury in patients with cirrhosis, even before traditional clinical indicators become apparent. Their application in ascites-related pathophysiology could enhance clinical vigilance and facilitate pre-emptive interventions.

This review synthesizes current diagnostic approaches for ascites, evaluates their limitations, and explores the transformative potential of proteomics approaches in augmenting the clinical management of cirrhosis and its complications. We highlight key studies that support the use of proteomic profiling for identifying early renal dysfunction and systemic inflammatory responses in cirrhotic patients. Additionally, we propose a framework for integrating these emerging biomarkers into existing diagnostic algorithms, thereby improving accuracy and clinical relevance. Ultimately, combining proteomic insights with conventional diagnostics offers a powerful strategy to improve early detection, optimize therapeutic interventions, and reduce the overall burden of cirrhosis-related complications such as ascites.

Introduction

Liver diseases pose a major global health burden, accounting for nearly 2 million deaths each year.1 Liver cirrhosis is the eleventh leading cause of mortality worldwide, highlighting the critical need for improved prevention and treatment strategies.[1] Liver cirrhosis can be defined as irreversible liver scarring which can be caused by a number of factors such as excessive drinking, hepatitis B and C viruses, and fatty liver.[1] Liver cirrhosis can progress from an asymptomatic compensated stage where the body functions adequately even with liver scarring to a decompensated stage, where liver function is significantly impaired usually resulting in complications like ascites.[2] This progression of liver cirrhosis to the decompensated stage can lead to clinical portal hypertension (PHT), a condition characterized by increased blood pressure in the portal vein system[3] (Figure 1). The most common sign of decompensated cirrhosis is ascites, a condition marked by the accumulation of fluid in the peritoneal cavity.[3]

https://doi.org/10.29173/hsi496
Received 28 March 2025
Accepted 1 July 2025

Ascites signals a poor prognosis and significantly worsens patient outcomes. It is associated with symptoms such as abdominal discomfort, dyspnea, and loss of appetite, and increases the risk of severe complications like spontaneous bacterial peritonitis (SBP), a potentially life-threatening infection of ascitic fluid that develops in approximately 25% of individuals with cirrhosis and ascites.[3–5] Evaluating the burden of ascites is essential, as it contributes to frequent hospitalizations, prolonged stays, and a poor quality of life, while placing considerable strain on healthcare systems. However, the burden of ascites needs to be evaluated from the context of liver cirrhosis, which is the underlying cause.[6] It was reported by Hudson et al. that between 2013 and 2015, the cost of management of liver disease in England, UK in over thirteen thousand individuals in their final year of life was an average of £21,113 (CAD $39329.72) per patient.[7] Similarly, Fagan et al. found that 41 patients requiring paracentesis (a medical procedure used to relieve ascites) reported 127 hospital admissions, over 1000 bed-days, and 733 imaging procedures. Notably, 80.3% of admissions were for ascites management, with 41.2% being unplanned.[6] These findings underscore the limitations of current diagnostic and monitoring strategies, which rely heavily on albumin-based markers like the serum-ascites albumin gradient (SAAG). These markers may lack sensitivity for early disease detection, highlighting the need for more predictive approaches.

The objective of this article is to examine the clinical impact of ascites, to explore the potential of proteomic approaches to enhance early detection, and to discuss the use of novel biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). These markers could offer earlier insights into disease progression and therapeutic response with an aim to improve diagnostic precision and patient outcomes.

Clinical Relevance of Ascites

As noted above, ascites is a common and clinically significant complication of liver cirrhosis.[3,4] However, the symptoms of ascites are quite common and non-specific, necessitating a thorough differential diagnosis to rule out other systemic diseases such as peripheral edema in heart failure which presents similarly.[8,9] Therefore, it is imperative to have a structured diagnostic approach to determine its etiology in order to guide effective management. One of the most effective ways to achieve this is through a physical examination and percussion of the abdomen, with shifting dullness being a hallmark clinical sign of ascitic fluid buildup.[4] Ascitic fluid accumulation is a key manifestation of decompensated liver disease but may also arise from malignancy, infection, or nephrotic syndrome. Ascitic fluid analysis is essential to determine disease etiology and remains a cornerstone of diagnostic evaluation, with biomarkers offering promise for precision diagnostics.

The initial diagnostic workup for patients presenting with ascites includes a comprehensive biochemical assessment, comprising serum creatinine, albumin, and liver function tests to evaluate renal and hepatic status.[8,9] Once obtained, ascitic fluid is evaluated using parameters such as total protein concentration, cell counts, and albumin-creatinine ratio, to classify the fluid as either transudative (fluid buildup as a result of systemic conditions like hypertension) or exudative (fluid buildup as a result of conditions like inflammation).[8]

A reduction in serum albumin, a hepatic-synthesized protein crucial for maintaining oncotic pressure, is frequently observed in advanced cirrhosis, as reflected by its lowered concentration in ascitic fluid.4,10 This loss contributes significantly to fluid leakage into the peritoneal cavity and the development of ascites in up to 85% of cases, while the remaining 15% are attributable to non-hepatic causes such as nephrotic syndrome or congestive heart failure[4] (Figure 1). A pivotal diagnostic marker in the ascitic fluid is the serum-ascites albumin gradient (SAAG), calculated by subtracting the ascitic albumin concentration from serum albumin.[8] A SAAG ≥1.1 g/dL is indicative of portal hypertension and transudative ascites, most commonly associated with cirrhosis. In contrast, a SAAG <1.1 g/dL suggests exudative ascites, often linked to malignancy, infection, or peritoneal inflammation[4,8] (Figure 1).

Visual inspection of ascitic fluid can provide immediate diagnostic clues: clear or straw-colored fluid typically reflects cirrhotic ascites; cloudy fluid may indicate SBP; and chylous or bloody fluid suggests malignancy or tuberculosis.8 Biochemical analysis further aids differentiation through parameters such as glucose, lactate dehydrogenase, white cell count, and amylase.[4,8]

While ascites is not curable,[4] it is manageable through a tiered approach. Lifestyle modifications (e.g., sodium and fluid restriction), pharmacological therapies (e.g.,

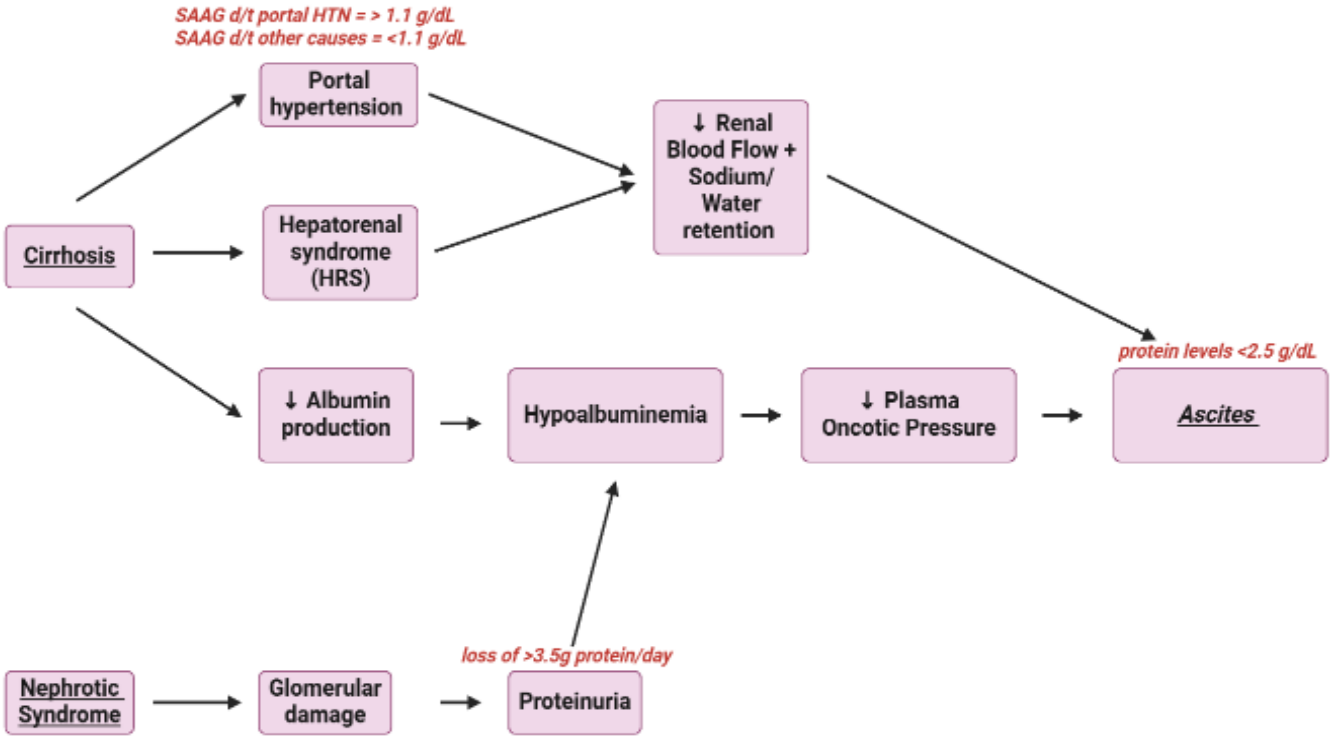

Figure 1. Pathophysiology showing the development of Ascites through Cirrhosis and Nephrotic Syndrome.

diuretics, albumin infusions, antibiotics for SBP), and interventional procedures such as large-volume paracentesis or trans-jugular intrahepatic portosystemic shunt may be employed.[4] Nevertheless, the need for more sensitive and specific molecular biomarkers remains a pressing clinical challenge to reduce diagnostic uncertainty and streamline management.

Despite their clinical utility, conventional methods for assessing ascites, including ultrasound imaging and SAAG calculations, have notable limitations. Ultrasonography, while non-invasive and widely accessible, is operator-dependent and cannot reliably differentiate between benign and malignant ascites.[11] Similarly, SAAG is primarily effective in distinguishing portal hypertension-related ascites but may yield inconclusive results in mixed etiologies or malignancy-associated ascites, where hypoalbuminemia due to systemic inflammation or cancer-related cachexia complicates interpretation.[5,9,12] Routine biochemical assays also lack specificity and fail to detect early molecular alterations that precede clinical symptoms or fluid accumulation, limiting their utility for timely and accurate diagnosis.[13] These diagnostic shortcomings can result in delayed interventions, inappropriate management strategies, and increased healthcare burden. Advances in multi-omics technologies, particularly proteomics can offer promising solutions to these diagnostic gaps. Proteomics plays a crucial role in understanding cellular processes, disease mechanisms, and treatment responses. By contrasting the protein expression profiles of healthy individuals with those afflicted by disease, or by comparing pre- and post-treatment states, proteomics can pinpoint proteins expressed differentially. Such proteins hold promise as potential biomarkers for disease diagnosis, prognosis, and therapeutic efficacy. Moreover, integrating these high-dimensional data sets with machine learning algorithms may significantly enhance diagnostic accuracy, enabling early detection, better risk stratification, and personalized treatment planning. As precision medicine continues to evolve, incorporating these novel diagnostic modalities could transform the clinical landscape of ascites management.

Omics: The next best thing in ascites care

During Mayo Clinic's Tenth Annual Individualized Medicine Conference, Dr. Farrugia, then president and CEO of Mayo Clinic, said *"The road ahead must be focused on expanding our genomic tools and further integrating individualized medicine. We've only just begun to glimpse what is possible."*[14] This quote has gone on to define a role of omics not only in health research but as an innovative tool to change our

approach to life's challenges. Simply put, omics refers to the comprehensive study of sets of biological molecules with aims to identify, quantify and characterize these molecules.[15,16]

Omics research is driven by various motivations, with one primary goal being to gain a comprehensive understanding of biological systems. For example, a proteomics study on normal human kidney tissues can provide valuable insights into protein to protein interactions, functional pathways, and molecular interactions. Another key objective is to link omics-derived molecular data to clinical outcomes, such as prostate cancer survival, breast cancer recurrence risk, or treatment response. By leveraging these detailed molecular measurements, researchers can develop more precise predictive or prognostic models, leading to omics-based tests that offer greater accuracy than conventional clinical approaches.[15] Many areas of research can be classified as a form of omics, such as genomics (the study of the entire genome of an organism)[16], transcriptomics (the study of the complete set of RNA transcript produced by the genome)[17], epigenomics (the study of reversible chemical modifications to DNA or to the histone proteins that package it, influencing gene expression without altering the underlying DNA sequence)[16], metabolomics (the study of the complete set of metabolites within an organism that are implicated in diverse cellular functions and metabolic pathways)[18], and proteomics (the study of the entire set of proteins expressed by an organism).[19]

Proteomics is an increasingly powerful tool in the identification of novel biomarkers and therapeutic targets, offering critical insights into disease mechanisms, treatment responses, and individual variability.[19] In the setting of cirrhosis and ascites, proteomic profiling holds transformative potential for enhancing diagnostic accuracy and guiding clinical decision-making. High-throughput mass spectrometry-based proteomic analyses have enabled the detection of previously unrecognized proteins in biological fluids, including ascitic fluid, which may not only clarify the etiology of fluid accumulation but also provide early indicators of systemic complications such as renal dysfunction.[19]

Historically, the SAAG has been the cornerstone for differentiating ascites due to portal hypertension from other causes such as malignancy or peritoneal infection.[5,8,9] A SAAG value equal to or greater than 1.1 g/dL is highly suggestive of portal hypertension and has long been the gold standard and employed as a first-line diagnostic criterion to distinguish transudative ascites from exudative causes in cirrhotic patients (Table 1).[10] However, despite its diagnostic utility, the accuracy of SAAG can be compromised in patients with coexisting etiologies or atypical presentations.[10] Several studies have highlighted its limited sensitivity and specificity, especially in populations with heterogeneous disease patterns or overlapping inflammatory and malignant processes.[10,13,20,21] These limitations underscore a critical need for improved biomarkers that offer higher diagnostic precision and prognostic value.

Proteomics has emerged as a leading approach in this regard, facilitating the identification of kidney injury biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), both of which have shown considerable promise in cirrhotic patients with ascites.[22–24] These biomarkers are upregulated in the setting of nephrotic-syndrome induced-ascites (Figure 1), and can be readily quantified in urine, providing a non-invasive method for early detection of renal complications. Importantly, acute kidney injury (AKI), particularly in the form of hepatorenal syndrome (HRS), represents a life-threatening complication of decompensated cirrhosis with ascites, making early recognition essential for timely intervention (Figure 1).[25,26] Allegretti et al. also demonstrated that urinary NGAL levels were significantly elevated in patients with HRS-AKI who developed ascites compared to those with other forms of AKI or no renal impairment, offering both a potential diagnostic and prognostic information.[27] Furthermore, NGAL not only differentiated between AKI subtypes but also improved mortality risk prediction, suggesting its potential role in patient stratification and individualized care.[27,28] Likewise, KIM-1, a transmembrane protein expressed in injured proximal tubular cells, was found to be elevated in patients with HRS, with strong sensitivity and specificity for AKI related to cirrhosis.[23,29] Supporting evidence from diverse clinical contexts reinforces the reliability of these biomarkers in HRS-AKI.[8,13,30] For example, in a study of preterm neonates, Hanna et al. found that urinary NGAL levels were significantly higher in those who developed AKI, underscoring the broader applicability of this biomarker across disease states and age groups.[31]

Incorporating NGAL and KIM-1 into the diagnostic landscape of cirrhotic ascites could offer substantial clinical benefit. While SAAG remains a valuable structural indicator of portal hypertension, NGAL and KIM-1 provide dynamic information about renal stress and injury. Together, these markers offer a more holistic view of disease pathophysiology, capturing both hemodynamic and inflammatory components, and identifying patients at higher risk for adverse outcomes.

Conclusion

The integration of proteomic biomarkers such as NGAL and KIM-1 into the clinical evaluation of ascitic patients represents a promising advancement in the management of cirrhosis. Although not yet adopted in standard practice guidelines, these markers have demonstrated strong potential for differentiating ascites etiology, predicting the onset of AKI, and stratifying mortality risk.[13,23–25] Future directions will focus on validating these biomarkers in larger, diverse cohorts and on embedding them within multi-omic frameworks incorporating genomic, transcriptomic, and metabolomic data to advance personalized medicine in liver disease. By bridging the gap between molecular insights and clinical outcomes, proteomics may redefine the diagnostic and therapeutic approach to cirrhotic ascites.

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Table 1. Comparison of Albumin, KIM-1, and NGAL as markers of Ascites.

Marker (Sample collected)	Albumin (Blood Test, SAAG)	Albumin (Urine Test)	Albumin (Ascitic Fluid, SAAG)	KIM-1	NGAL
Sample type	Venous blood sample	Spot urine sample or 24-hour urine collection	Paracentesis (ascitic fluid)	Urine or blood sample	Urine or blood sample
Normal and pathological reference ranges for liver	Normal: >3.4 g/dL - 5.4 g/dL Low: < 2.5 g/dL[32,33]	Normal UACR: <30 mg/g Elevated UACR: >300 mg/g [34]	Normal: SAAG > 1.1 g/dL = Portal HTN SAAG < 1.1 g/dL = Non-cirrhotic ascites [32]	Normal: <1ng/mL Elevated: >1 ng/mL[29]	Normal: <149 ng/mL Elevated: >150 ng/mL[35]
Patient populations with highest changes in these biomarkers	Cirrhosis, nephrotic syndrome, malnutrition, sepsis	Nephrotic syndrome, Chronic kidney disease (CKD), diabetic nephropathy, infections[36]	Cirrhosis, malignancy, infections, heart failure[32]	Acute kidney injury (AKI), CKD, sepsis-associated AKI, HRS-AKI[37]	AKI, CKD, hepatorenal syndrome, sepsis, heart failure[28]
Sensitivity and specificity for detecting ascites	Highly specific (~97%) for cirrhotic ascites[32]	Useful for assessing kidney function and detecting proteinuria, but low sensitivity for diagnosing ascites.	Highly sensitive and specific for ascites for cirrhotic ascites (~97%).[32]	Limited research on direct connection to ascites.	May predict worsening renal function in cirrhosis but not specific to ascites.
Biomarker that can distinguish between cirrhosis-related vs. nephrotic syndrome-related ascites?	Normal: SAAG > 1.1 g/dL = Portal HTN SAAG < 1.1 g/dL = Non-Cirrhotic Ascites.[32]	Helps diagnose nephrotic syndrome but does not classify ascites directly.	Gold standard for ascites classification (cirrhosis vs. nephrotic syndrome)[32]	KIM-1 is elevated in liver or kidney damage but has no direct role in ascites detection.	NGAL is elevated in AKI-related ascites caused by cirrhosis.
How do these biomarkers perform in predicting disease progression?	Low albumin indicates poor prognosis in cirrhosis and nephrotic syndrome or malnutrition.[32]	High proteinuria predicts worsening CKD and nephrotic syndrome.	SAAG levels differentiate between cause of ascites.	Strong early predictors in kidney disease, can predict progression.[29]	Strong early predictors of AKI and HRS in cirrhosis.[28]
Analysis time in clinical setting	Routine lab test/CBC (~hours)	Routine urine test (~hours)	Paracentesis lab analysis ~24 hours	Rapid tests available (~hours)	1 - 4 hours.[28]
External factors that affect their accuracy?	Malnutrition, infection, inflammation[32]	Dehydration, exercise, diabetes, fever or infection, heart failure, hypertension.	Fluid sample contamination and infection	Sepsis, ischemia, inflammation.[37]	Sepsis, systemic inflammation, nephrotoxic drugs.[28]
Costs and feasibility	Low-cost	Cost-effective	Invasive procedure, costly	Moderate costs (ELISA Kits)	Cost-effective[38]

A Multi-Omics Therapeutic Approach using SAHA, SP600125, and Exercise to Modulate BDNF levels in Major Depressive Disorder

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Major depressive disorder (MDD) is a leading cause of global disability, which is linked to reduced quality of life and comorbidities (e.g., diabetes, hypertension), and is burdened by a significant therapeutic knowledge gap. Brain-derived neurotrophic factor (BDNF), with its pro-apoptotic precursor (proBDNF) and neuroplasticity-promoting mature form (mBDNF), is dysregulated in MDD, where dysregulation of the proBDNF:mBDNF ratio serves as a biomarker and potential therapeutic target. Exercise has been documented to alleviate MDD symptoms partly by enhancing BDNF via epigenetic mechanisms. Inhibitors of the exercise metabolites β-hydroxybutyrate (BHB) and histone deacetylase 2 (HDAC2) (e.g., suberoylanilide hydroxamic acid (SAHA), a clinically approved drug) mimic this effect by suppressing BDNF-silencing HDAC2. However, excess proBDNF activates Jun N-terminal kinases (JNK)-p75 neurotrophin receptor apoptosis pathways, necessitating combinatorial therapies to optimize therapeutic effects. An example of combination therapy includes use of SAHA, a BHB mimic which upregulates BDNF transcription, with SP600125 which blocks JNK-mediated apoptosis.

In this review, we explore the use of multi-omics strategies aimed at restoring the proBDNF:mBDNF equilibrium, with some evidence supporting the combined use of BHB, SAHA, and SP600125 in polygenic models of major depressive disorder (MDD).We propose a series of multi-omics assays that can be used to validate this hypothesis: epigenomic via chromatin immunoprecipitation-sequence HDAC2 occupancy, transcriptomic via quantitative polymerase chain reaction for splice variants, proteomic via enzyme-linked immunosorbent assay for isoforms, and metabolomic via liquid chromatography-mass spectrometry for BHB. Moreover, assessing behavioural tests (e.g., forced swim) permits the further understanding of molecular changes that underlie symptom alleviation. This strategy bridges exercise-mimetic mechanisms (BHB/SAHA-driven HDAC2 inhibition) with precision medicine. We propose this scalable therapeutic blueprint by leveraging SAHA's clinical approval and SP600125's apoptotic mitigation. Future work must prioritize clinical trials to translate multi-omics insights into biomarker-guided human therapies.

Introduction

Major depressive disorder (MDD) is predicted to be the number one contributor to burden of disease worldwide by 2030.[1] In 2022, the prevalence of MDD among Canadians aged 15 years and older was estimated at 7.6%, equating to over 2.5 million people.[2] The annual economic burden of mental illness in Canada is estimated at over $50 billion, including healthcare costs and losses related to work absences, reduced productivity, and diminished quality of life.[2] MDD is characterised by feelings of guilt, worthlessness, loss of interest in pleasurable activities, and is associated with an increased risk of suicide. Furthermore, MDD's association with comorbidities such as diabetes and hypertension necessitates a need for deeper understanding of its mechanism of action.[3,4,5,6] Therefore, developing novel therapeutic targets and markers to help alleviate the burden of MDD on patient outcomes is crucial.

Current MDD-related therapies, including medications like fluoxetine, target various biomarkers such as cortisol, leptin, and interleukins.[2,7] One of the most promising proteomic markers is brain-derived neurotrophic factor

https://doi.org/10.29173/hsi502
Received 28 March 2025
Accepted 5 July 2025

(BDNF), with previous work supporting its ability to regulate neural plasticity and nervous system survival.[7,8,9] Importantly, BDNF comes in two forms; mature BDNF (mBDNF) and proBDNF, which play dichotomous roles in synaptic survival and plasticity. There is growing evidence highlighting the link between reduced serum mBDNF levels and a propensity for MDD progression, making it a promising biomarker for diagnosis and treatment.[6,10]

Intrinsically, mBDNF can be modulated through exercise, with evidence of it effectively ameliorating symptoms of MDD through its involvement in neural cellular functions, synaptic plasticity, and neurogenesis.[5,11,12,13] Additionally, prolonged exercise upregulates the production of β-hydroxybutyrate (BHB), a ketone body that can increase mBDNF expression by inhibiting histone deacetylases (HDACs).[5,11,12,13] Further research into mBDNF's potential as a therapeutic treatment may lead to more effective approaches for treating MDD.
Given the substantial evidence linking reduced levels of mBDNF with the pathophysiology of MDD, we propose that a multi-modal approach targeting key regulatory checkpoints of BDNF expression and function may offer a novel therapeutic avenue. Specifically, we hypothesize that concurrent modulation of BDNF transcription (via HDAC2 inhibition with suberoylanilide hydroxamic acid (SAHA)), translation (via Jun N-terminal kinases (JNK) inhibition with SP600125), and activity-dependent secretion (via BHB) will act synergistically to restore synaptic plasticity and reverse depression-like behavior in polygenic rodent models of MDD. This integrated strategy aims to overcome the limitations of single-target interventions and address the complex molecular deficits underpinning MDD.

Methods

To elucidate the molecular underpinnings of MDD and assess the therapeutic potential of modulating mBDNF, a targeted literature review was conducted across PubMed, Ovid, and ScienceDirect databases. The search prioritized primary research articles, systematic reviews, and meta-analyses published from 2015 onward, ensuring alignment with the rising global burden of MDD and advances in molecular research methodologies.

We included studies that examined the role of mBDNF in neuroplasticity and its modulation by interventions such as physical exercise, SAHA, SP600125, and BHB. Preference was given to studies employing omics-level analyses, specifically epigenomics, transcriptomics, proteomics, and metabolomics, to provide mechanistic depth and translational relevance.

Articles were screened for relevance based on their exploration of validated molecular markers of MDD and the integration of experimental or clinical data. We were especially interested in studies assessing exercise-induced modulation of BDNF, contextualized by evidence linking reduced serum BDNF levels to depressive phenotypes. This comprehensive synthesis facilitated a multi-dimensional understanding of BDNF pathway regulation in depression and identified potential nodes for therapeutic intervention.

Clinical Relevance of MDD

BDNF is a significant biomarker of MDD, with decreased mBDNF and increased proBDNF levels observed in affected patients.[8,14] Multiple studies have shown that exercise increases mBDNF levels through upregulation of protein synthesis via the inhibition of HDACs, garnering importance for HDAC inhibitors like SAHA in MDD treatment.[5,8,10,13]

mBDNF is known to promote neuronal survival and plasticity through the activation of several key signalling pathways by binding to the tropomyosin kinase receptor B (TrkB), an important receptor in MDD pathophysiology. Upon binding TrkB, mBDNF stimulates: the PI3K/mTOR pathway to enhance neuroplasticity, the mitogen-activated protein kinase-extracellular signal-regulated kinase pathway to support neurogenesis and cognitive resilience, and the phospholipase C-gamma (PLC-γ) pathway to regulate intracellular calcium for synaptic plasticity.15 Dysregulation of these pathways, particularly PLC-γ, has been linked to neuronal weakening and apoptosis, which contributes to the symptom presentation seen in MDD. Therefore, targeting these signalling cascades is essential for mBDNF-based MDD therapies.[16]

Conversely, upregulating the precursor proBDNF levels may increase neuronal cell apoptosis.[17] ProBDNF is known to bind to the p75 neurotrophin receptor (p75NTR) to induce apoptosis, growth cone retraction, and long-term depression.[18] This has critical implications for researchers and clinicians, as neural cell apoptosis compromises synaptic integrity by reducing

dendritic spine density and neurotransmitter signaling efficiency, mechanisms that have been implicated in the pathophysiology of neurodegenerative diseases like Alzheimer's disease and MDD.[19] Activation of the JNK pathway – a known promoter of oxidative stress and apoptosis – as a result of proBDNF binding to p75NTR can be inhibited with SP600125, negating the apoptotic side effects of proBDNF upregulation.[20] Interestingly, exercise plays a role in this approach by naturally enhancing mBDNF levels and priming neuroplastic pathways, thereby complementing the molecular effects of SAHA and SP600125. A combination therapy of SAHA, SP600125, and exercise presents a novel strategy for treating stress-related disorders and neurodegenerative diseases, including Alzheimer's disease.[19] Leveraging the benefits of exercise and pharmacological treatments while mitigating potential apoptotic side-effects could enhance neuroplasticity and cognitive resilience.[21] Further research to validate the evidence in clinical settings could offer a targeted and multifaceted intervention for conditions associated with BDNF dysregulation.

The role of Omics in the development of therapies targeting MDD

The link between exercise and BDNF inherently involves a multi-omics approach, emphasizing the value of various omics-level research. We see this at the epigenomic level, where BDNF transcription is tightly controlled by chromatin accessibility.[18] Among epigenomics studies, heritable gene expression changes have been identified that alter DNA expression, often via methylation or histone modification. Specifically, HDAC2 is an epigenetic silencer that binds to the promoter region of the BDNF gene and prevents the recruitment of certain transcriptional factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and cyclic adenosine monophosphate response element-binding protein (CREB).[22,23] Chromatin will bind more tightly due to the deacetylation of histones from HDAC, making transcription less accessible. Pharmacological tools altering the function of HDAC, such as SAHA, have been developed.[24] SAHA is a clinically approved HDAC2 inhibitor for cutaneous T-cell lymphoma that chelates zinc ion in the active site of HDAC2 and blocks its deacetylation function.[25] Therefore, SAHA maintains chromatin in a transcriptionally active state, enabling the genomic expression of BDNF.[26] While BHB levels fluctuate with metabolic activity, SAHA, a mimic of BHB, offers a more controlled means of promoting BDNF transcription, the impact of which can be measured with chromatin immunoprecipitation sequencing (ChIP-Seq) to quantify HDAC2 occupancy at BDNF promoter regions and track changes in acetylation patterns over time. Epigenomic regulation of BDNF through SAHA and exercise-induced BHB inhibiting HDAC2 presents a promising avenue for MDD treatment through BDNF upregulation.

Further, BHB connects BDNF in MDD at the level of metabolomics, the study of small-molecule metabolites representing the biochemical state of an organism or cell. BHB is a ketone body secreted from the liver and muscle tissue following exercise and can metabolically relieve HDAC-induced chromatin repression.[27] As a ketone body, it crosses the blood–brain barrier where it can act as a class I HDAC inhibitor, a group of enzymes primarily involved in altering gene expression in the brain, thereby increasing histone acetylation and access to BDNF promoter regions. Many other metabolites have been previously implicated in BDNF and exercise. El Hayek et al. showed lactate induces hippocampal BDNF expression via the sirtuin 1–peroxisome proliferator-activated receptor gamma coactivator 1-alpha signalling axis.[28] Additionally, Moon et al. linked elevated Cathepsin B levels in mice with increased hippocampal BDNF expression.[29] Though other metabolites have also been historically implicated (such as kynurenine and irisin), there are no recent studies to confirm such findings. Notably, among exercise-induced metabolites, BHB is particularly well-suited for experimental investigation due to its dual role in both metabolic and epigenetic regulation: as a metabolic intermediate of ketogenesis and as an endogenous inhibitor of class I HDACs. BHB directly influences chromatin accessibility at BDNF promoter regions, a clear link between metabolic shifts and epigenetic regulation.[30] Additionally, and quite importantly, lower circulating BHB levels and reduced mBDNF expression have been independently implicated in MDD. [9,31] BHB can be measured in both plasma and cerebrospinal fluid (CSF) using enzymatic assays or mass spectrometry, and its epigenetic effects can be evaluated through ChIP-Seq. Therefore, BHB represents a compelling metabolomic entry point for exploring the molecular basis of depression and potential exercise-mimetic therapies. BHB's bridge between metabolic and epigenetic BDNF regulation further strengthens its potential application as an MDD therapy.

At the transcriptomic level, MDD patients exhibit reduced pro/mature BDNF gene expression, leading to impaired neurogenesis, reduced hippocampal volume, and weakened synaptic plasticity. Exercise and antidepressants restore mBDNF mRNA levels, making it a potential transcriptional target.32 ProBDNF activation of the JNK pathway promotes pro-apoptotic gene transcription (e.g., BAX) while suppressing synaptic support genes (e.g., B-cell lymphoma 2 (BCL-2), postsynaptic density protein 95 (PSD-95)).[33] This JNK-mediated shift contributes to MDD's structural and functional deficits.[34] To counteract SAHA's potential upregulation of proBDNF transcription, SP600125 could be co-administered. This selective JNK inhibitor blocks JNK isoforms 1, 2, and 3, preventing the pro-apoptotic cascade from increased proBDNF-p75NTR signaling while retaining mBDNF's beneficial functions.

Proteomics, the large-scale study of proteins, captures BDNF's post-translational modifications, crucial for its function.[35] BDNF is translated as proBDNF, then cleaved into mBDNF by proteases like furin. In MDD, the proBDNF to mBDNF ratio shifts towards equality, promoting neurodegeneration,[36] unlike the healthy ratio.[37] This imbalance is measurable via Western blotting or enzyme-linked immunosorbent assays (ELISA) with isoform-specific antibodies, serving as a functional biomarker for disease progression and treatment efficacy. In neuropsychiatric disorders like MDD, proteomic alterations often involve downstream synaptic and apoptotic regulators: reduced PSD-95, essential for excitatory synapses38; downregulated BCL-2, promoting neuronal survival39; and increased caspase-3, activated downstream of proBDNF-p75NTR signaling, a common apoptosis biomarker and a critical readout of the consequences of an altered proBDNF:mBDNF ratio.[40] While epigenomic and transcriptomic findings suggest BDNF's pathological involvement, only proteomic analysis confirms its functional form. Measuring caspase-3 evaluates successful inhibition of proBDNF-induced apoptosis.

Proposed Multi-Omics Experiment in MDD Mouse Models

The current paper presents a synthesis of the extant literature that explores the mechanistic role of BDNF in MDD, with a particular focus on exercise and its molecular mediators. Particularly, evidence frames mBDNF as a central and tractable therapeutic target in MDD. While previous research has often treated these omics layers in isolation, our review highlights the need for integrative approaches that capture the interplay between metabolic signals like BHB, chromatin remodeling enzymes such as HDAC2, transcriptomic shifts in apoptotic regulators, and proteomic imbalances in proBDNF:mBDNF ratios. To move from theoretical integration to applied investigation, we propose a model experiment using polygenic mouse strains of MDD. These mice could be treated with BHB, SAHA, and SP600125, alone and in combination. Molecular outcomes would be measured as follows: BHB in plasma or CSF (metabolomics), HDAC2 promoter occupancy via ChIP-Seq (epigenomics), expression of BDNF and JNK-pathway genes via quantitative polymerase chain reaction (transcriptomics), and BDNF and caspase-3 via ELISA (proteomics). This approach would evaluate the efficacy of exercise-mimetic and pharmacological interventions combination as a potential novel treatment regimen for MDD patients.

This proposed experiment serves as one possible extension of this framework and, more importantly, outlines the role of multi-omics thinking in informing experimental design and clarifying the mechanisms underlying complex psychiatric conditions like MDD. By examining BDNF regulation across metabolomic, epigenomic, transcriptomic, and proteomic layers, this review highlights the importance of systems-level approaches in identifying precise therapeutic targets. As the field moves toward integrative, mechanism-based psychiatry, multi-omics research offers a powerful lens through which to untangle and leverage the molecular heterogeneity of depression.

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From Correlation to Causation: How Omics Technologies Illuminate the Role of INHBC in 2 Cardiometabolic Disease

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The integration of omics technologies such as genomics, proteomics, and metabolomics into clinical research has enabled discoveries of complex biological mechanisms underlying disease. In this commentary, we examine recently published data outlining the use of multi-omics to investigate the liver-derived protein inhibin-βC (INHBC) and its role in cardiometabolic health. Through bidirectional Mendelian Randomization and phenome-wide analysis, INHBC was identified as both a driver and consequence of metabolic dysfunction, including obesity, dyslipidemia, and inflammation.This review discusses the contribution of INHBC to coronary artery disease risk by altering lipid levels which was also associated with renal and liver traits. Further, how INHBC exerts is pathological effects- through its transformation into activin C and signaling via the ALK7 receptor which suppresses fat breakdown in adipose tissue- will be discussed. These findings position INHBC as a potential biomarker with translational therapeutic relevance in complex disease pathways, like cardiometabolic disease.

Introduction

In the post-genomic era, the convergence of omics technologies (i.e., genomics, proteomics, transcriptomics, and metabolomics) has revolutionized biomedical research.[1] Researchers are no longer limited to identifying associations between biomarkers and disease traits; instead, they can interrogate the causal architecture of complex diseases to identify therapeutic targets and develop system-level models of human physiology.

This commentary critically analyzes work by Loh et al., which exemplifies a paradigm shift in the role of inhibin-βC (INHBC), a member of the transforming growth factor (TGF)-β superfamily, in cardiometabolic disease.[2] INHBC is the precursor to the homodimer activin C, a protein typically viewed as a minor regulator of activin bioactivity due to its limited mRNA expression and lack of abnormality in INHBC-null mice.[3] Previous proteome-wide Mendelian randomization studies identified an association between INHBC and a greater progression of CKD.[4,5,6] However, there is no clear consensus on whether INHBC actively contributes to disease progression or rather reflects metabolic stress. This ambiguity is striking given the broader interest in the activin family, whose members (including activin A and B) are known to modulate cell growth, lipid metabolism, and inflammation through SMAD signalling pathways.[7]

A recent study used integrative omics technologies to test whether INHBC acts as a causal driver of metabolic dysfunction and cardiovascular disease risk or whether it simply reflects these conditions. Their study employed a powerful combination of genome-wide association studies (GWAS), protein quantitative trait loci (pQTL) mapping (where genetic variants near a gene influence its protein expression), bidirectional Mendelian Randomization (MR; a genetic method that uses inherited variants to infer the direction of causal relationships), phenome-wide association studies (PheWAS; screening a wide range of health traits for associations with a single genetic exposure), and functional assays in human adipocytes.[2] These methods provided a comprehensive view of INHBC's role in lipid metabolism, inflammation, and cardiovascular risk, clarifying both the directionality and underlying biological mechanisms.

The objective of this commentary is to critically evaluate how Loh et al.'s integrative omics approach determined the causal role of INHBC in metabolic disease, to situate their findings within the broader context of omics-driven discovery, and to highlight key challenges that arise when translating these insights into clinical and therapeutic applications.

https://doi.org/10.29173/hsi502
Received 28 March 2025
Accepted 5 July 2025

Omics at the Core: Multi-Layered Insight into Causality
Central to the study is the use of bidirectional MR, an approach that mimics a natural randomized trial by using inherited genetic variants as proxies for modifiable exposures.[8] Because genetic variants are randomly allocated at conception and remain fixed throughout life, MR minimizes the confounding and reverse causation seen in observational studies. Bidirectional MR strengthens causal inference by testing whether the relationship operates in both directions: from the exposure (INHBC) to disease traits and from disease traits back to the exposure.[6] In this study, the dual design revealed a self-reinforcing cycle: elevated INHBC levels causally increased low-density lipoprotein (LDL) cholesterol, triglycerides, inflammation, and coronary artery disease (CAD) risk, while central adiposity, hypertriglyceridemia, and inflammation themselves raised circulating INHBC.[2] These reciprocal effects underscore the power of MR to establish likely directions of causality.[8] Nonetheless, MR relies on assumptions such as the absence of pleiotropy which, while addressed through sensitivity analyses, can never be fully excluded.[8]

What makes this study particularly compelling is the depth of omics integration. The authors used cis-pQTL instruments from over 35 000 Icelandic participants to perform MR against outcomes from large European-ancestry GWAS cohorts.[2] This allowed for high-resolution mapping of INHBC's effects on lipid traits, systemic inflammation, and anthropometric indices, such as BMI-adjusted waist-to-hip ratio (WHRadjBMI). The reverse MR used similarly robust instruments to establish that metabolic traits also drive INHBC levels, reinforcing a feedback loop.[2]

Mechanisms, Mediation, and Metabolic Dysfunction

The study further incorporates multivariable MR and mediation analysis, advanced tools in the omics toolkit, to determine how much of the observed effects were direct versus mediated through intermediate traits. For example, 26% ($\beta \pm SE; 0.088 \pm 0.0034$) and 23% ($\beta \pm SE; 0.122 \pm 0.025$) of BMI's impact on INHBC was mediated by triglycerides and CRP, respectively.[2] Similarly, 35% ($\beta \pm SE; 0.062 \pm 0.031$) of the effect of WHRadjBMI was mediated through triglycerides.[2] These nuanced insights would not be possible without multi-layered omics data and modern causal inference methods. Still, mediation analysis can be sensitive to measurement error and unmeasured confounding variables, and these models depend heavily on the assumption of no residual confounding between mediators and outcomes.[7]

In terms of downstream outcomes, INHBC was found to modestly increase the risk of CAD and non-alcoholic fatty liver disease (NAFLD).[2] However, no effect was observed on type 2 diabetes (T2D).[2] Further mediation analysis revealed that 40% ($\beta \pm SE; 0.016 \pm 0.008$) of INHBC's effect on CAD was mediated through lipid traits, particularly high-density lipoprotein (HDL) cholesterol, highlighting the power of omics to pinpoint mechanistic intermediaries.[2]

PheWAS and the Broad Reach of Omics

Beyond MR, the study's PheWAS explored INHBC's associations across 367 traits, offering a panoramic view of its systemic impact. Significant associations emerged not only in lipid metabolism and statin use, but also in renal dysfunction (e.g., lower estimated glomerular filtration rate, higher serum urea, and creatinine), hyperuricemia, and calcium regulation.[2] Although some of these effect sizes were modest, their consistent directionality and colocalization with causal variants strengthen the argument for INHBC's involvement in diverse physiological systems.[2]

This PheWAS approach reflects the true power of omics: to take a candidate protein and rapidly map its influence across a wide array of biological outcomes, generating testable hypotheses that extend beyond traditional disease categories. For example, the study suggests that elevated INHBC may contribute to kidney stress, raising questions about its role in fibrosis and chronic kidney disease, areas of active investigation in related research.[4,5,6] Still, the PheWAS approach involves multiple testing which, even with stringent statistical corrections, raises the possibility of false-positive associations and highlights the need for further validation in independent cohorts.

Experimental Validation and Expanded Functional Insight: Connecting Omics to Function

One of the most compelling aspects of this study is how it bridges large-scale omics data with cellular biology. Using dedifferentiated human adipocytes from both abdominal and gluteal depots, the authors tested whether the omics-identified protein product of INHBC, recombinant activin C, could directly modulate metabolic

processes. Their experiments showed that activin C activates the ALK7 receptor, triggering SMAD2/3 phosphorylation and suppressing adrenaline-stimulated lipolysis.[2] These findings strongly support the omics predictions; however, translation to in vivo systems, where tissue-specific expression and physiology come into play, will be essential.

Notably, the signalling response to activin C was initially weak due to low baseline ALK7 expression, mirroring real-world variation in tissue responsiveness.[2] However, when ALK7 was induced using a doxycycline-inducible vector, activin C robustly triggered SMAD2/3 signaling.2 These results confirmed ALK7 as the receptor mediating INHBC's effects and validated the predicted liver–adipose signalling axis.

The ALK7-SMAD2/3 pathway is known to regulate metabolic, inflammatory, and fibrotic responses.[10] Its demonstration here adds functional weight to the causal claims of MR and pQTL analysis and raises questions about INHBC's possible role in kidney disease and fibrosis. Future studies using tissue-specific transcriptomics and single-cell proteomics will be crucial to map INHBC's systemic impact. Here, we highlighted the power of omics-driven research moving from high-dimensional data to specific, testable molecular hypotheses. It exemplifies how genomics and molecular biology can work together to unravel complex disease mechanisms.[2]

Omics Implications: Beyond This Study

The value of omics in this study lies not only in its methods but in its implications. First, it establishes INHBC as a hepatokine with pleiotropic effects across organ systems. Second, it demonstrates how omics frameworks, ranging from GWAS to pQTLs to MR to PheWAS, can be utilized to deconstruct both disease etiology and therapeutic opportunities. Third, it opens the door to pharmacogenomic precision: variants like rs2229357 (INHBC missense) and rs3741414 (3'UTR) were found to colocalize with CAD and lipid traits, providing targets for personalized intervention.[2] However, the modest effect sizes observed in many of these associations, while robust in directionality, suggest that INHBC is likely only one component in the multifaceted landscape of metabolic disease. For therapeutic applications, these small effect sizes indicate that INHBC-targeted interventions would likely have incremental impacts when used alone and may be best evaluated in the context of combination therapies or personalized risk profiles.

Perhaps most importantly, this paper suggests that omics approaches have the potential to shift the medical model from reactive to predictive. INHBC, which has been relatively underexplored, is now positioned as both a biomarker and a possible contributor to metabolic dysfunction, supported by genetic and functional data. In a clinical future that increasingly relies on proteomic and genomic profiling, such molecules could help inform more precise prevention strategies.[2]

Limitations and Caution in Omics Interpretation

Despite its strengths, the study underscores key limitations of omics interpretation. The reliance on European-ancestry datasets limits generalizability to global populations, underscoring the need for validation in more diverse genetic backgrounds. Another layer of complexity arises from the inherent challenges in integrating multi-omics data. Differences in sample sizes, data types, and measurement platforms can introduce heterogeneity and bias, requiring careful harmonization and validation to ensure that conclusions are robust and reproducible.[11] Harmonization issues across omics layers, such as aligning cis-pQTL data with GWAS/PheWAS results, are particularly critical when moving from discovery to translational applications.[11] This emphasizes the importance of standardized data collection, transparent data management, and rigorous cross-validation to minimize confounding factors.

Biological causation also depends on functional validation; although the study addresses this through in vitro adipocyte studies, several questions remain. Notably, while lipid traits mediated 40% of the increased CAD risk with upregulated INHBC, the remaining 60% remains unexplained, raising questions about other potential mediators, such as inflammation, endothelial dysfunction, or oxidative stress. Future research should incorporate dynamic and tissue-specific omics layers, such as metabolomics, to capture how INHBC's expression and function shifts with metabolic states and to better understand its complex roles in disease progression.[11]

Finally, while the study positions INHBC as a promising clinical biomarker and therapeutic target, several challenges warrant caution. As a hepatokine and member of the TGF-β superfamily, INHBC's circulating levels and downstream effects are likely influenced by broader metabolic and inflammatory processes.[7] This context-dependent regulation could limit its specificity as a clinical marker and raises questions about reproducibility across different populations and disease contexts. These considerations underscore the importance of integrating INHBC into multi-marker risk models or broader precision medicine frameworks rather than relying on it in isolation.

Moreover, translating these omics insights into clinical practice requires not only addressing statistical challenges but also grappling with ethical and logistical barriers, including patient data privacy and equitable access to omics-informed care. These considerations emphasize the need for both technical rigour and broader ethical frameworks to realize the promise of omics in translational precision medicine.

Conclusion

A Blueprint for Omics-Driven Discovery

Loh et al.'s study provides a compelling example of how omics technologies can illuminate disease biology in unprecedented detail. By integrating genomic, proteomic, and functional data, the authors move beyond correlation to suggest causality, uncover potential therapeutic pathways, and highlight promising avenues for clinical translation. The study's implications extend beyond INHBC itself, offering a methodological roadmap for future efforts to unravel complex biological networks and gain a deeper understanding of disease mechanisms.

Nevertheless, as this commentary emphasizes, caution remains warranted. Translating omics findings into clinical practice requires addressing modest effect sizes, harmonizing data across platforms, and validating functional relevance in diverse populations. INHBC, while implicated as both a biomarker and possible contributor to metabolic dysfunction, illustrates the broader challenges and promise of omics-informed discovery. In an era where medicine is gradually shifting from generalized treatment to more targeted interventions, omics technologies are poised to become essential tools in navigating the complexity of human health. Loh et al.'s study, with its comprehensive approach and integrative vision, lays the groundwork for future exploration in this exciting and evolving field.

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Proteomic Profiling of IGFBP2: Modulation and Biomarker Potential in Atherosclerotic Cardiovascular Disease Prevention

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Population aging and growth have led to a dramatic rise in atherosclerotic cardiovascular disease (ASCVD) prevalence, particularly in Canada over the past two decades. As the national ASCVD burden grows, accurately identifying high-risk individuals is essential. Drawing on existing proteomic research, we have highlighted Insulin-like Growth Factor Binding Protein 2 (IGFBP2) as a potential novel biomarker for ASCVD development. Past literature examined four protein groups related to ASCVD progression: (1) extracellular matrix proteins, (2) lipid-binding and metabolic proteins, (3) inflammatory proteins, and (4) phagocytic ligands and apoptotic cell receptors. IGFBP2 affects arterial vascular smooth muscle cells (VSMC) by modulating the bioavailability of insulin-like growth factor 1 (IGF1), causing VSMC hypertrophy. Individuals with pre-existing cardiomyopathies display elevated levels of IGFBP2 and subsequent higher rates of mortality. Counterintuitively, higher IGFBP2 levels in healthy individuals correlate with reduced arterial stiffness and lower low-density lipoprotein (LDL) cholesterol levels—indicators of ASCVD severity. Although the relationship between IGFBP2 and ASCVD remains unclear, IGFBP2 presents as a promising biomarker due to its association with ASCVD-related effects and bioavailability. We propose further exploration of IGFBP2 across stages of ASCVD and its evaluation as a potential therapeutic target.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a significant health concern in Canada, with cardiovascular disease being the second leading cause of death from 2019-2022.[1] The 5-year prevalence of ASCVD in Canada alarmingly increased from 43.7 to 69.1 per 1000 individuals between 2004-2008 and 2013-2017, reinforcing the severity of this growing epidemic.[2] This rise disproportionately affects specific demographics. In Ontario, Black individuals have the highest risk of cardiovascular disease, likely due to a higher prevalence of major cardiovascular risk factors (11.1%). Whereas South Asians have the highest rates of heart disease or stroke (6.6%), likely due to greater glucose intolerance, elevated LDL, and reduced high-density lipoprotein (HDL) levels[3,4] Sex-based differences were also observed, with Canadian females aged 40-44 having a 2.3-times higher ASCVD prevalence than males, suggesting a need for targeted therapeutic approaches.[5]

ASCVD diagnosis and disease management remain a substantial financial burden for the Canadian healthcare system. Adjusted for inflation, first-year healthcare costs for a newly diagnosed ASCVD patient are ~$41,000 CAD, up from ~$37,000 CAD in 2022.[5,6] Rogoza et al. identified $66.6 billion CAD in costs for incident adult ASCVD between April 2005 and March 2016, adjusted to ~$85.1 billion CAD today[7] Key drivers of these annual costs are three events that are consequences of ASCVD: myocardial infarction (MI), stroke, and peripheral artery disease (PAD).[7] Therefore, increasing public funding and awareness are critical factors in preventing and mitigating the burden of ASCVD.

Early ASCVD detection is imperative to prevent disease progression. As the second most bioavailable Insulin-like Growth Factor Binding Protein (IGFBP), IGFBP2 enables easier detection and more reliable measurements, supporting its potential as an ASCVD biomarker. IGFBP2 has also been associated with other

https://doi.org/10.29173/hsi501
Received 28 March 2025
Accepted 8 July 2025

cardiovascular risk factors. For instance, Arai et al. reported a correlation between IGFBP2 and thrombolysis in MI risk scores, highlighting its potential as a biomarker for patients with acute coronary syndrome, a disease closely related to ASCVD, as it often results from the rupture of atherosclerotic plaques.[8] ASCVD's chronic and progressive nature burdens patients and the healthcare system, rendering the discovery of novel biomarkers for early disease identification a valuable advancement.

Pathophysiology of ASCVD

ASCVD is a chronic, inflammatory condition triggered by endothelial damage from factors like smoking, hypertension, or hyperlipidemia.[9] Endothelial injury promotes specific adhesion molecule expression, which leads to monocyte recruitment to the area of injury where they differentiate into macrophages that engulf oxidized LDL, and form foam cells.[9] Foam cells accumulate into fatty streaks—the earliest visible signs of ASCVD.[9] Vascular smooth muscle cells (VSMCs) then proliferate and migrate from the tunica media to the tunica intima to form a fibrous cap over the plaque.[9] Over time, plaques can enlarge from cholesterol, calcium, and cellular debris buildup.[10] Plaque instability may cause the fibrous cap to rupture and expose thrombogenic contents, leading to obstructed blood flow and complications such as MI or stroke.[9]

Identification of ASCVD and Clinical Perspectives

ASCVD diagnosis is often delayed due to the disease's asymptomatic onset and progression, increasing the risk of serious cardiovascular events like plaque rupture and MI.[11] This underscores the need for a biomarker that can detect early plaque development. Existing ASCVD biomarkers yield notable limitations. LDL cholesterol accumulates on the walls of arteries, oxidizes, and promotes arterial stiffness and plaque formation, making it a useful biomarker.[12] However, LDL is typically measured by mass, a time-consuming process that delays diagnosis.[13] Alternatively, nuclear magnetic resonance (NMR) spectroscopy provides quicker results,[14] but the cost of traditional high-field NMR systems used for lipoprofiles preclude their routine clinical use, costing millions per instrument and up to $450 per patient.[15,16] Consequently, current LDL cholesterol measurement methods are time-intensive, not widely accessible, and may offer limited utility in comprehensive cardiovascular risk assessment.

Bødtker Mortensen et al. assessed the association between LDL cholesterol and ASCVD events over 5 years in individuals with and without coronary artery calcification (CAC).[17] LDL cholesterol was strongly associated with ASCVD events in middle-aged participants with pre-existing coronary atherosclerotic buildup. However, LDL cholesterol showed limited predictive value for ASCVD in individuals without previous CAC, further demonstrating its limitations for early ASCVD detection.[17]

Given the drawbacks of current assessments and the lack of early detection methods, serum IGFBP2 shows promise as an emerging biomarker. Its' high binding affinity to insulin growth factor 1 (IGF1) enables regulation of cardiac hypertrophy and protection.[18] Berry et al. previously identified IGFBP2 as a candidate diagnostic biomarker for heart failure (HF) through mass spectrometry-based proteomics analysis of urine and plasma, noting elevated levels in HF patients.[19] Elucidating the cellular pathways involving IGFBP2 in ASCVD pathogenesis is key to understanding its potential utility as a biomarker.

Pathway and Insights into IGFBP2's Role in ASCVD

The IGF1/Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (Akt) signaling pathway is a critical regulator of physiological cardiac hypertrophy and protection.[19] This pathway is initiated by binding IGF1 to the insulin-like growth factor 1 receptor (IGF1R). Binding leads to the activation of PI3K, which subsequently activates Akt, a serine/threonine kinase involved in cell growth, survival, and metabolism. In adaptive settings, such as exercise, the activation of this pathway leads to physiological hypertrophy, characterized by an increase in heart mass with normal or enhanced cardiac function, in contrast to the pathological hypertrophy seen in heart disease.[19] Furthermore, enhanced IGF1/PI3K/Akt signaling has demonstrated cardioprotective benefits in preclinical rodent models of various cardiac diseases, including pressure overload and MI.[19,20] The pathway also inhibits signaling cascades involved in pathological cardiac hypertrophy and HF.[19]

IGFBP2 is a secreted protein that primarily binds to IGF1 and IGF2, modulating their bioavailability and receptor interactions as the second most abundant IGFBP in circulation.[20,21] Depending on surrounding cell types,

IGFBP2 can inhibit or enhance IGF actions, prolonging the half-life of IGF1 and increasing its cardioprotective effects.[20] IGFBP2 also exerts IGF-independent effects by binding to cell surface receptors like α5β1 integrin, which is linked to cardioprotective effects in its active form.[25] This interaction can activate downstream signaling pathways, including focal adhesion kinase and integrin-linked kinase, which maintain myocardial structure and function.[20,22] Altered levels of IGFBP2 have been associated with various metabolic conditions, including metabolic syndrome and insulin resistance, known risk factors for cardiovascular diseases.[20]

The interplay between the IGF/PI3K/Akt pathway, IGFBP2, and atherosclerosis is multifaceted. IGF1 has antiatherogenic effects through its modulation of anti-inflammatory and pro-repair pathways, potentially reducing atherosclerotic plaque burden and increasing plaque stability.[22] These effects are often coupled with changes in vascular oxidative stress, with IGF1 enhancing antioxidant activity.[22] IGFBP2's role in atherosclerosis is increasingly recognized in current research. It has been shown to play a crucial part in regulating the mitogen-activated protein kinase (MAPK) pathway and the PI3K/Akt signaling pathway, both of which are implicated in the pathological processes of atherosclerosis. Furthermore, IGFBP2 can enhance the migration and proliferation of VSMCs, promoting atherosclerotic plaque formation.[23]

Studies have linked circulating IGFBP2 levels with atherogenic metabolic risk profiles.[23-25] For instance, higher IGFBP2 levels have been associated with a more favourable metabolic risk profile, characterized by lower fasting insulin and glucose.[24] Paradoxically, elevated IGFBP2 levels are also linked to higher mortality in elderly men, reflecting its potential role in age-related conditions such as bone loss and cancer progression.[23] Adiposity, a major risk factor for atherosclerosis, is inversely associated with IGFBP2 levels.[24] Lower IGFBP2 levels in the context of obesity and insulin resistance may impair cardioprotective signaling, potentially contributing to left ventricular remodeling and dysfunction seen in aortic stenosis (AS).[20,25]

Several hypotheses and confounders may help explain this paradox. The disease state and its severity are crucial determinants of IGFBP2's impact.[26,27] Reduced IGFBP2 in conditions like obesity or mild-to-moderate AS may impair cardioprotective signaling via integrin binding or disruption of the IGF1/PI3K/Akt pathway, contributing to adverse remodeling and dysfunction.[18,20,28] Conversely, high IGFBP2 in severe disease (e.g., advanced AS, PAD, or HF) may reflect disease severity or a maladaptive compensatory response, rather than a direct cause.[26-29] IGFBP2's impact may also depend on whether it acts through IGF-dependent mechanisms (modulating IGF1/IGF2) or IGF-independent pathways, such as integrin-mediated signaling involved in growth and angiogenesis.[30] In advanced disease, high IGFBP2 may inhibit IGF1's cardioprotective effects.[18,28] Additionally, IGFBP2 levels increase with age, and associations with mortality in older adults may reflect aging-related processes rather than metabolic dysfunction.[27,31] Interpretation is further complicated by its integration in the broader IGF system, which includes multiple IGFBPs and regulators such as growth hormone and estradiol.[30] Collectively, these findings suggest that IGFBP2 may be contextually pleiotropic, exerting protective metabolic effects in some settings while signaling disease severity or poor prognosis in others.

Modulation of IGFBP2 Through Exercise

Exercise is known to protect against atherosclerosis and can modulate the IGF1 system, although its specific effects on IGFBP2 require further investigation.[32,33] While studies have shown conflicting results on the optimal exercise mode, chronic exercise consistently demonstrates superior protective effects compared to acute exercise.[33-35] Chronic exercise improves insulin sensitivity and reduces adiposity, both correlated with increased IGFBP2 levels, suggesting a potential link.[36] We hypothesize that IGFBP2 mediates exercise's anti-atherosclerotic effects by modulating IGF-dependent and independent signaling pathways that support vascular homeostasis. Elucidating how exercise modulates IGFBP2 and downstream IGF/PI3K/Akt signaling may reveal mechanisms supporting chronic exercise as a targeted intervention for preventing ASCVD and related vascular diseases. Adopting a systems-level proteomic approach to investigating protein dynamics during exercise may uncover novel biological mechanisms.

Role of Proteomics in ASCVD Biomarker Identification

A greater understanding of these novel mechanisms can be achieved through omics. Omics refers broadly to the many scientific fields that aim at measuring large numbers

of molecules in a biological system to understand underlying functions and processes.[37] Proteomics is a widely applicable field that studies protein expression, modification, and interaction,[38] and can be applied to study disease mechanisms to help identify potential biomarkers for diagnosing and treating diseases.[36]

Proteomics has been used to study various cardiovascular conditions, leading to the discovery of several diagnostic biomarkers.[39] For example, research using proteomic techniques has led to cardiac troponin I being included in the diagnosis of MI.[40,41] Proteomics is used in the study of ASCVD by revealing proteins involved in the formation, progression, and rupture of atherosclerotic plaques.[39] It is especially applicable in the early diagnosis of ASCVD before the appearance of clinical symptoms. Analyzing blood proteins with proteomic technologies offers a promising approach to identifying biomarkers for ASCVD development.[39]

To detect IGFBP2 as a biomarker for conditions such as cardiovascular disease, researchers employ highly precise analytical techniques known as Selected Reaction Monitoring or Multiple Reaction Monitoring.[42] These methods are targeted molecular probes, identifying specific proteins within complex blood samples. The process begins with the automated preparation of plasma samples, followed by micro-scale liquid chromatography to separate proteins. Subsequently, mass spectrometry fragments IGFBP2 and measures its unique molecular signatures with exceptional sensitivity and specificity. This methodology enables the detection of even minute quantities of IGFBP2, facilitating comparative analyses between healthy individuals and patients with atherosclerosis.[42] Such comparisons can elucidate patterns that contribute to understanding disease risk and progression, thereby offering valuable insights into the precise relationship between ASCVD and IGFBP2 levels in the body.

Conclusion

ASCVD is a major global health concern. Measuring serum IGFBP2 levels may offer healthcare practitioners greater insight into atherosclerotic progression and support earlier diagnosis of ASCVD.[21,43] However, previous studies show that IGFBP2's relationship with ASCVD varies depending on the developmental stage, highlighting the need for further research. Proteomics targeting IGFBP2 expression may clarify this relationship, while examining protein function through biochemical and functional analyses could reveal molecular mechanisms that can be modulated as possible interventions for ASCVD and other cardiovascular diseases.

Plaque buildup contributes significantly to age-related cardiovascular mortality. Identifying early biomarkers like IGFBP2 brings us closer to preventing ASCVD, a major contributor to the world's leading cause of death, cardiovascular disease.

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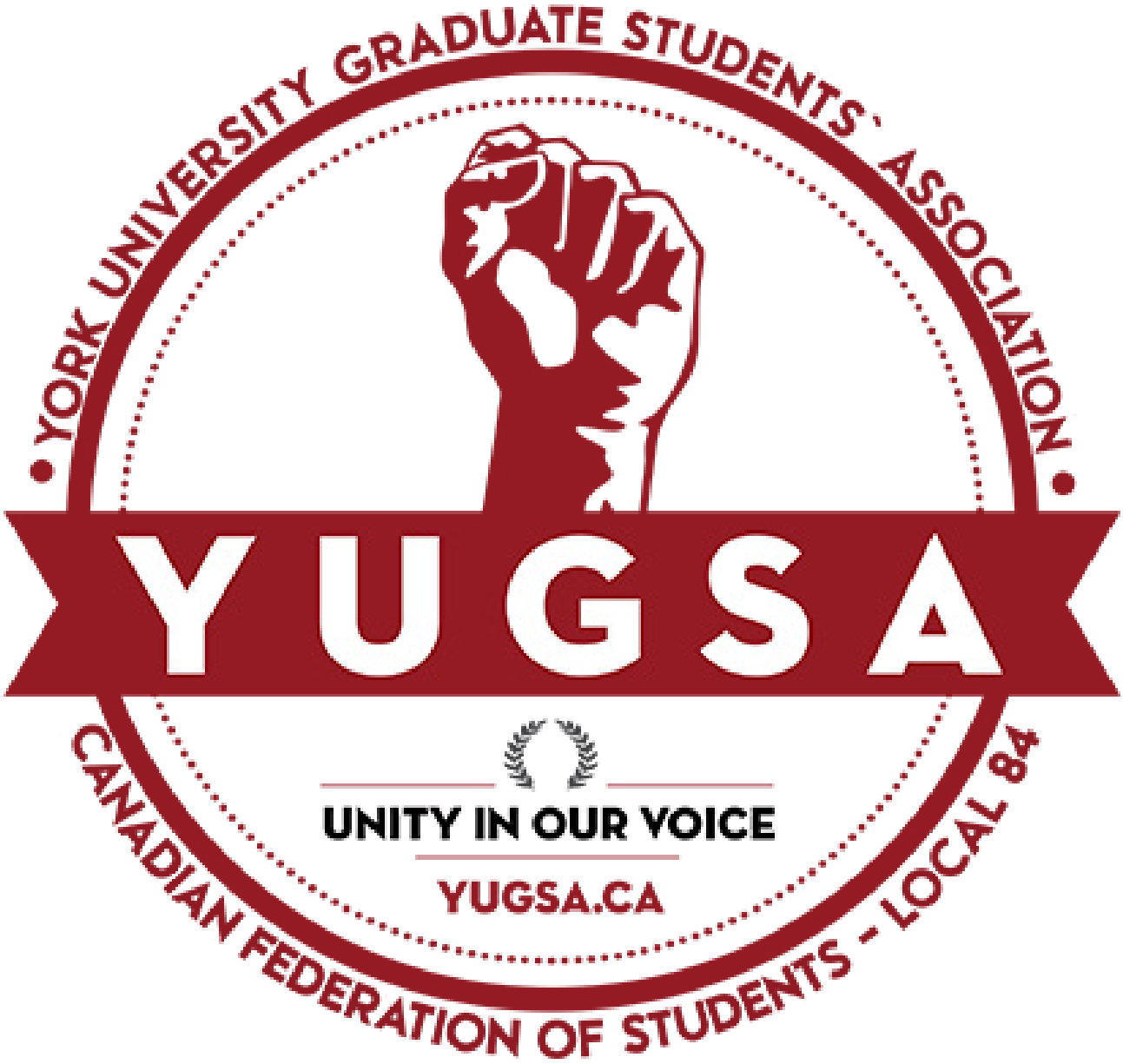

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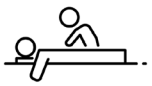

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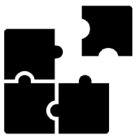

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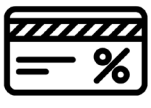

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