CIHR Institute of Genetics
IRSC Institut de génétique

STRATEGIC PLAN 2022–2027

SEQUENCING OUR FUTURE
CIHR INSTITUTE OF GENETICS STRATEGIC VISION

Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Canada

At the Canadian Institutes of Health Research (CIHR), we know that research has the power to change lives. As Canada's health research investment agency, we collaborate with partners and researchers to support the discoveries and innovations that improve our health and strengthen our healthcare system.

The CIHR Institute of Genetics supports research on the human and model genomes and on all aspects of genetics, basic biochemistry and cell biology related to health and disease, including the translation of knowledge into health policy and practice, and the societal implications of genetic discoveries.

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Executive Summary

The CIHR Institute of Genetics seeks to enable and empower researchers, healthcare providers, patients, policymakers, and the public to use genetics, genomics, and the numerous new 'omics' technologies to deliver better health and healthcare outcomes at a better value. We will deliver this by working to integrate research findings and their transition to care across all four CIHR research pillars: biomedical; clinical; health system services; and population health. The Institute of Genetics has adopted a "bedside to bench to bedside" approach to allow healthcare needs to inform research, and in turn, to integrate research findings into healthcare. This is meant to deliver a major goal of the Institute of Genetics: for genomics to enable the delivery of a learning health system that is continuously improving through increased knowledge creation and integration. Four major themes of commitment will be employed to deliver on this ambition.

Commitment A
Enabling Genomic Medicine

Genomic medicine, the analysis of the entirety of a person's gene set to determine what keeps a specific individual healthy and what contributes to making them sick, is increasingly being incorporated into clinical care. Ongoing research into genomics, and multiple other 'omics', (the analysis of an organism at a specific molecular level. E.g., transcriptomics covers the study of RNA transcripts; proteomics refers to the study of proteins, etc.) is providing the necessary information to inform why a person presents with a specific disease, with inherited disease and cancer currently at the forefront of this evolution. We are also on the verge of determining a person's predisposition to diseases – such as heart disease, stroke, diabetes, mental health conditions – that could affect their health in the near or long-term future. Other applications of genomic medicine include anticipating adverse drug events based on a person's specific genome, as well as using genomics to inform public health on infectious disease; SARS-CoV-2 tracking being an excellent example. The Institute of Genetics is committed to improving the health of people living in Canada by promoting and contributing to a learning health system, whereby patient health informs genomic research, which in turn informs healthcare. (See Figure 1.1)

Commitment B
Improving Genetic Disease Diagnosis and Therapies

Rare disease constitutes an under-appreciated global health issue. Rare diseases are actually not rare at all: 1 in 25 children born worldwide has a rare disease, and half of these children will not reach adulthood. Estimates are that 1 in 3 pediatric hospital beds in Canada is occupied by a child with a rare disease. Importantly, 85% of rare diseases are inherited, meaning they have a genetic origin. The genetic origin of most rare disease has enabled their identification and rapid diagnosis as the cost of sequencing human genomes has precipitously dropped over the past decade. It is now clear that inherited disease is a major cause of mortality and morbidity for many children. Unfortunately, children with a rare disease are not accounted for by the coding systems used in healthcare and hospitals. As such, it is very difficult to determine the necessary resources to enable the best level of care, research, and socioeconomic support for patients with a rare disease and their families if the costs, both direct and indirect, cannot be determined. The Institute of Genetics is determined to account for these kids, because if they are not counted, they do not count. Beyond support for diagnosis and care, we are committed to finding a path forward to enable accessible and affordable therapies for children with rare disease. Sadly, 95% of rare diseases do not have a treatment, and although some treatments are incredibly affordable (e.g. changes in nutrition), some are very high-cost therapies – as high as a single-dose gene therapy priced at over $2 million per child. We will leverage previous Institute of Genetics funding that connected clinicians with rare disease researchers to pioneer an open-science model to develop therapies for children with rare-disease that are affordable, and hence accessible to all.

Beyond rare disease, genetic predisposition for many chronic diseases (e.g. heart disease, diabetes, cancer, etc.) is becoming clearer as more genomes are sequenced and other omics technologies are overlaid. We will soon be in a position to accurately predict predisposition to a disease prior to its onset. This bridging of science with the clinic will result in yet another important tool in the toolkit of clinicians. This enables clinicians to inform patients of potential disease prior to onset to better monitor for disease risk, and for patients to make lifestyle changes to delay or prevent onset of disease.

Commitment C
Embracing Diversity, Inclusion, and Indigenous Rights

There is a bias in current genomic databases in Canada and around the world as the overwhelming majority of genomes and associated health data are from people of European descent. The Institute of Genetics is committed to increasing equity, diversity, and inclusion, and recognizing the role of Indigenous rights. This includes defining a responsible approach to include Indigenous Peoples (First Nations, Métis, and Inuit) who wish to include genomic medicine as part of health research and care in a manner that is purpose-oriented, and reflects the crucial role of data in advancing innovation, governance, and self-determination. Enabling genomic research and medicine requires a set of representative genomes from the various ancestries and diverse communities within Canada to accurately reflect any meaningful changes that could affect one's health status or predisposition to disease. This representation extends to making Canada an attractive destination for clinical trials. Data linkages that include genomics and healthcare data that capture a large and diverse population are much more useful when determining a drug's efficacy and safety. Without this knowledge, genomics and drug responses will only reflect the biased population currently captured in our genome libraries, which currently do not reflect Canada's rich diversity. The Institute of Genetics is committed to ensuring that the diversity of Canada is captured in genomics and other 'omics' research such that all people can benefit from advances in genomics, regardless of ancestry.

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Commitment D
Strengthening the Community

To implement genomic medicine in clinical pathways will require a healthcare workforce versed in genomic knowledge and literacy. Capacity building in the education of clinicians and trainees will be important to ensure genomic medicine is implemented appropriately. There is also an urgent need to increase access to genetic counsellors to better integrate genetic counselling into research and care. Health professionals need to be able to assess who would best benefit from genomic medicine and how to report genomic results. Training will be supported by the Institute of Genetics to ensure that Canadian healthcare providers have the required level of genomic literacy to enable genomic medicine.

Beyond the clinic, a major bottleneck in our implementation of genomic research into better care is the ability to properly analyze the wealth of genomic data that is being generated. These large data sets are growing at a near logarithmic rate and there is a paucity of computational personnel that can apply their expertise to the healthcare setting. Capacity building of a diverse computational biology workforce is an essential step to translate the knowledge of our genomes to the betterment of health for all.

Genetic and genomic literacy contributes to public attitudes, interest, and participation in genomic research, ultimately determining the impacts of genomic medicine. Increasing public genomic literacy is a major commitment of the Institute of Genetics. Beyond knowledge of the role of genomics in healthcare, there are rightful concerns about access to genomic data and if the data can be used to discriminate against individuals. Addressing concerns, and seeking advice from ethicists, patients, and the general population are paramount, and we are committed to ensuring these consultations take place and that concerns are meaningfully addressed with ecosystem partners.

The Institute of Genetics is committed to enabling a learning health system whereby the needs and care of patients and the population drive genomics research. The knowledge is returned in near real time to healthcare systems to improve the health and wellbeing of people who live in Canada and around the world.

Message from the Scientific Director

The Institute of Genetics is one of CIHR's thirteen virtual health research Institutes. Each Institute is headed by a Scientific Director who receives guidance and advice from its Institute Advisory Board. Institute Advisory Boards are composed of representatives of the public, private, and non-profit sectors including the research community, health practitioners, and patient representatives. The Institutes are formally accountable to both the President and Governing Council of CIHR, and through the Minister of Health to Parliament. Ultimately, according to the *Canadian Institutes of Health Research Act,* the mission of CIHR is "to excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its translation into improved health for those who live in Canada, more effective health services and products and a strengthened Canadian health care system."

The purpose of each CIHR Institute is to "support individuals, groups and communities of researchers for the purpose of implementing, within its mandate, the objective of the CIHR".

A major role for the Institutes is to forge relationships across disciplines to stimulate integrative, multifaceted research agendas that respond to the health needs of people who live in Canada while adhering to the highest ethical standards. Accelerating the use of health research findings for the benefit of those who live in Canada is another major mandate, with innovative knowledge mobilization strategies being the key to translating research into action.

The Institute of Genetics' strategic plan closely aligns with CIHR's Strategic Plan 2021-31, and is informed by a broad consultation process that included many bilateral conversations, and national and international meetings and workshops that included clinicians and healthcare providers, researchers, and policymakers from all disciplines, as well as patients and members of the general public. We held a far-reaching survey of these groups to learn about genomics research priorities in Canada, and have developed a vision for how the Institute of Genetics can benefit people in Canada and around the world by supporting collaborative research that is driven by patient needs.

Our core approach involves starting from patients and civil society, and working towards meeting research needs to improve health outcomes, and we look forward to working with researchers, healthcare providers, patients, and the public to foster this true learning health system in Canada. Moving forward, we will identify and monitor performance metrics to assess the outputs, outcomes, and impact of the Institute of Genetics' investments and partnerships, provide an evidence base to optimize initiatives, strengthen the integration of EDI (equity, diversity, and inclusion) principles, and evaluate our contribution to improving equitable health outcomes for all.

Sincerely,
Chris

Christopher McMaster, PhD, FCAHS
Scientific Director
CIHR Institute of Genetics

Danny Abriel

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Our Vision

To maximize equitable health outcomes for all, driven by world-class, interdisciplinary research in genetics.

Our Mandate

To support research in all aspects of genetics, genomics, molecular biosciences, and computational biology, including the development and translation of new knowledge to improve human health. To foster anticipatory, interdisciplinary research to inform ethical, equitable, and effective implementation and impact of evidence-based health policy and practice of genomic technologies. Promote and integrate the lived experiences of patients and families, including patient partnerships, in research endeavors.

Our Values and Principles

SCIENTIFIC APPROACH PROMOTING ETHICAL RESEARCH

- Responsible science
- Research ethics and research integrity
- Privacy and protected access to information when relevant
- Equitable and inclusive participation in research
- Open science

COLLABORATION

- Promote interdisciplinary translational research that links basic science, ethical, legal, social, economic, policy, health services and implementation research in genetics
- Strive to foster and sustain partnerships across Canada and worldwide
- Ensure *FAIR* (findability, accessibility, interoperability, and reusability) principles for data sharing are employed, encouraged, and valued
- Implement the *San Francisco Declaration on Research Assessment (DORA)* which seeks to improve how scholarly outputs are evaluated by acknowledging the importance of data sharing when evaluating research proposals and researchers themselves
- Promote the adoption of the *CARE* Principles (collective benefit, authority to control, responsibility, ethics) for Indigenous data governance

DIVERSITY AND INCLUSION

Ensure all people who live in Canada, regardless of citizenship, ancestry, ability, gender, geographic location, or socioeconomic status, are included and benefit from genetics research and its application to healthcare

- Include underrepresented populations with proper safeguards in study design and participation to ensure equitable health benefits for all
- Promote ethical, effective, and equitable access to genetic services, taking equity, diversity, and inclusion into consideration in regard to geographical access, patient communities' specific needs, and types of diseases

CAPACITY DEVELOPMENT

Continue to support and grow training and capacity building

- Support researchers at all career stages
- Address systemic barriers for researchers at all levels
- Address training needs and diversity of the workforce in genomics and its application to healthcare
- Promote the introduction and uptake of genetics beyond genetics specialists and to maximize the value obtained from genetic data across medical disciplines

ENGAGEMENT

Promote engagement and dialogue with the public, patients and our healthcare workforce, placing the patient and the diverse Canadian population at the heart of this journey

- Promote public trust in science and genetic literacy of the public and healthcare workers through science communication, implementation science, and knowledge mobilization
- Engage Indigenous communities to guarantee the culturally safe and effective use of genomics in health and healthcare while supporting governance models to ensure self-determination over data access and use for research
- Contribute to the development and adoption of transparent practices and governance policies in genetics research that promote trust in science
- Promote expertise in patient partnership and knowledge mobilization

QUALITY OF EVIDENCE

Promote rigorous research on the implementation of genetics and genomics technologies to guide decision-making while optimizing clinical utility and health service along the healthcare delivery continuum

- Promote rigorous research design that generates high-quality evidence
- Include premarket stage, clinical trials, and evaluations of technology before implementation
- Promote the rigorous evaluation of the implementation of genetic and genomic technologies in real-world settings
- Develop methods to assess process and outcomes along this continuum to inform health policy decisions
- Co-design/partner on the development of health outcomes/endpoints that are important for patients/users
- Promote implementation science into health service delivery

Our Support to CIHR's Strategic Plan Implementation

Following a thorough consultation process, and being sensitive to the evolving Canadian social context, CIHR recently launched its *2021-31 Strategic Plan* with the aspiration that in 10 years, "Canadian health research will be internationally recognized as inclusive, collaborative, transparent, culturally safe, and focused on real-world impact." This plan guided the development of the present document, ensuring that the Institute of Genetics' orientations, while firmly supporting the development of our research community, contribute as optimally as possible to the achievement of CIHR's overarching goals and objectives. Five priorities supporting those goals have been defined, and each of those guided the elaboration of our orientations.

- **PRIORITY A**
  Advance Research Excellence in All Its Diversity
- **PRIORITY B**
  Strengthen Canadian Health Research Capacity
- **PRIORITY C**
  Accelerate the Self-Determination of Indigenous Peoples in Health Research
- **PRIORITY D**
  Pursue Health Equity through Research
- **PRIORITY E**
  Integrate Evidence in Health Decisions

Integration of these priorities in CIHR Institute of Genetics commitments will be highlighted at the end of the coming sections.

Our Commitments

In order to achieve our mandate and vision while strongly supporting the implementation of CIHR's Strategic Plan 2021-2031 priorities, the Institute of Genetics is committing to working towards the development of four major themes. Woven with our values and principles, these commitments are the materialization of input from the broad genetics and genomics community, to patients and caregivers, to clinicians and clinician scientists, to basic biomedical researchers.

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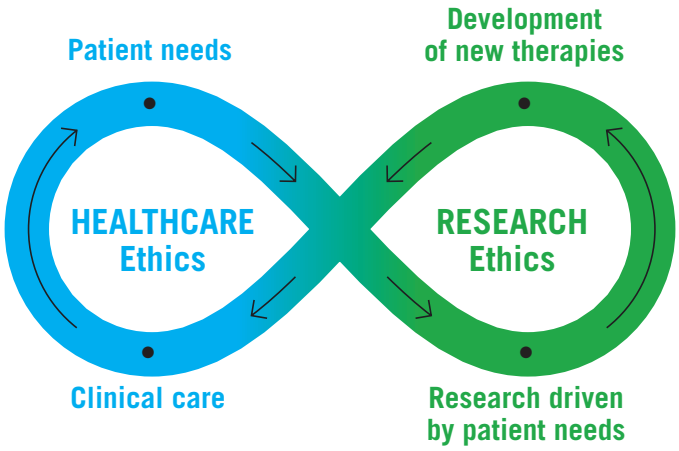
Commitment A

Enabling Genomic Medicine

Figure 1.1: Genomics Research to Health Care Infinity Loop



Genomic medicine is at the cusp of a learning health system wherein patient information informs research, which in turn drives clinical care. This genomic learning health system (see infinity loop, Figure 1.1) will increasingly accurately determine what within our genomes keeps us healthy, and what results in sickness or predisposition to disease. Using genomics to stratify inherited and acquired diseases is already a reality. Expanding the number of people living in Canada whose genomes are sequenced and analyzed will result in an increasingly impactful effect of genomics on healthcare.

A unified strategy to generate store, access, and share genomic information is a necessary and defining step to enable genomics to improve the health for people who live in Canada.

Early Steps

An essential early step for such a strategy is the creation of a single-entry point to all genomes sequenced in Canada. A governance structure will establish a common set of standards to ensure interoperability, manage access to data, and address ethical and legal aspects while managing the data infrastructure and computing power. Early engagement of the public and patients on issues such as privacy and security will be crucial to its success. This engagement will need to include research centered on the patient/community needs as well as their participation in all stages of studies, from co-design to execution to implementation.

Canadian Human Genome Library – a national asset

A responsibly governed Canadian Human Genome Library is a key research and clinical resource that will be designed to ensure that human genome sequencing efforts can unite in real time to enable a learning health system. This will also enable Canada to be better prepared to answer the challenges brought by any future viral or multi-drug-resistant bacteria outbreaks. The development of this library will represent a structuring initiative and will be empowered by combining strengths from the Health, and the Innovation, Science and Economic Development Portfolios.

Why genomics and why now? Simply put, the time and cost of sequencing a human genome has decreased over time, from taking over a decade to complete the first working draft of the human genome in 2001, to less than a day in 2021. The cost decreased from over $1 billion in 2001, to $50,000 in 2010, to $750 currently, and is still decreasing. Genomics research is increasingly being integrated into clinical care and is starting to be incorporated into medical records (personalized medicine). To further put this advance into perspective, a few hundred thousand human genomes have been sequenced worldwide thus far, and this will increase exponentially such that over 60 million human genomes are anticipated to be sequenced by 2026.

Towards Predictive and Personalized Medicine

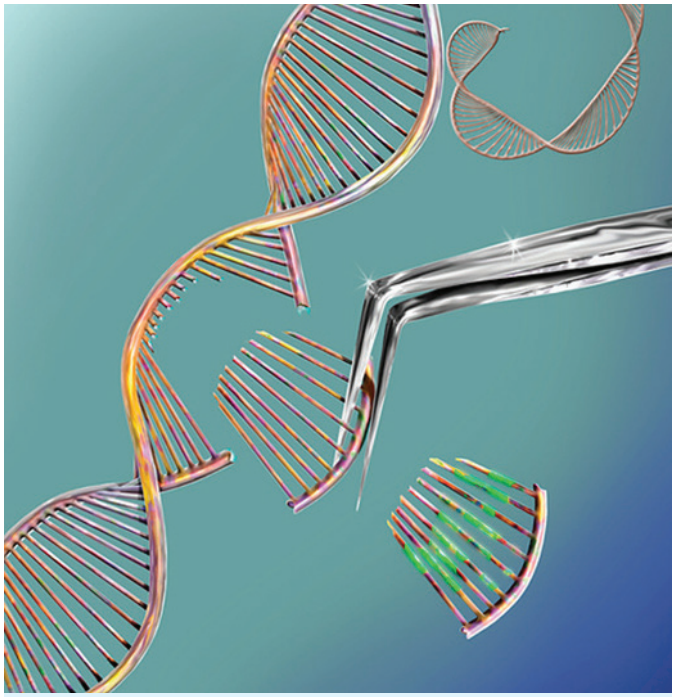
One major advantage of genomes versus many other tests is that a person's genome is normally static: it does not change over their lifespan. It is a test that is only done once (unlike blood pressure, cholesterol levels, heart/brain/liver function, etc.) and can be analyzed and reanalyzed over a person's lifespan. Our knowledge of what is within our genomes that keeps us healthy and makes us sick is becoming increasingly accurate. This new knowledge can be integrated throughout a person's life, including reanalysis of genomes, health records,and other data sources, thereby increasing the value of a learning health system.

As your once-in-a-lifetime genome sequence becomes increasingly incorporated into healthcare data and its analysis, this will enable a major goal of genomic medicine: preventing disease before its onset. As more genomic data sets become available, polygenic risk scores will enable predictions for the potential for common diseases (e.g. heart disease and stroke, cancer, diabetes, and many others) to be made at an individual level. Ever-expanding genomics and health data sets will enable Artificial Intelligence (AI) to be used to determine what combination of genes predisposes a person toward a specific disease(s). As other omics technologies come online (that can indicate acute changes in levels of proteins, metabolites, and other biological reporters) even more accurate predictors of disease risk will be enabled. This information can guide more preventative medicine, resulting in delay or prevention of the onset of a chronic disease or of the occurrence of an acute event (e.g. heart attack, stroke, or diabetes, cancer, mental illness, etc.)

Establishing accurate polygenic risk scores to improve risk prediction can be used for common diseases. These can be incorporated into the clinic in ways that will decrease healthcare burden and increase quality of life for the people who live in Canada. As this knowledge changes healthcare, these advancements need to be instituted in a manner that involves patients and the public in its implementation. This demands clarity in how data will be employed, meeting necessary ethical, legal, and regulatory requirements to ensure public trust. The infinity loop driving the genomic learning health system will be an example of the responsible use of health data for the benefit of patients, and for society at large.

Preventing Adverse Events

Beyond disease prediction, genomics can improve drug safety. Genetics can predict if a particular drug will be effective and/or cause harm to a particular patient. Adverse drug reactions to medicines account for ~10% of Canadian hospital admissions with an average stay of one week. Cross-referencing genomics with prescribing of medicines (known as pharmacogenomics) can decrease adverse events, decrease hospital admissions and associated costs, and ensure only patients that are most likely to benefit from a therapy will receive it.



Science Photo Library

CRISPR is now entering the clinic! In a world first, successful treatment of a rare and fatal inherited disease called transthyretin amyloidosis was achieved by treatment with a CRISPR-Cas9 gene-editing therapy.

New England Journal of Medicine.
Published online, Aug. 5, 2021.
DOI: 10.1056/NEJMoa2107454

Response to Emerging Health Threats

Genomics extends beyond human genomes to other organisms, the most relevant currently being the SARS-CoV-2 coronavirus that causes COVID-19. The critical role of genomics in the COVID-19 response is the sequencing of viral genomes in patients. Viral genome sequencing also enables tracking of the global and national spread of COVID-19 variants and helps determine which of those is of concern; essentially which versions of the virus are more virulent and/or more deadly. Tracking emerging variants of concern imported into Canada is an essential part of the contact tracing to detect, and thus decrease the spread of these more virulent strains.

In addition, genome sequencing of the SARS-CoV-2 coronavirus in infected patients is essential to rapidly identify and characterize any potential 'made in Canada' variants of concern. Once identified, variants

of concern can then be analyzed to determine how they spread more quickly, why they are more deadly, or if they can evade current vaccines.

On the human (host) side, there are varied responses to COVID-19 infection, even among healthy people infected with the same COVID-19 strain. Some people have mild to no symptoms, while others die. Sequencing the genomes of infected patients will increase our understanding of the biology that results in differences in disease severity among individuals. These could range from the ability of COVID-19 to infect cells, to its ability to replicate and spread within a person's body, to its ability to initiate a cytokine storm and lead to more severe disease or death, or to the development of long COVID in some patients. To maximize the impact of genomics in the international efforts against COVID-19, there is a pressing need to streamline, accelerate and facilitate data sharing of genomic and associated clinical and large metadata sets, both at the national and at the international levels.

International Genomic Data Sharing

Enabling genomics in medicine requires the sharing of large and diverse data sets, validated tools for data quality, access, and analysis, and high-end computational power. Over the past decade, the Global Alliance for Genomics in Health (GA4GH) has emerged as the international leader to establish standards and a common framework to enable large-scale international genomic and healthcare data sharing. These past efforts have been a major driver behind the global response to sharing of COVID-19 variant genomes by many nations, including Canada. Rapid sharing of high-quality data is critical for the scientific understanding that underpins an effective and timely response to any pandemic.

Now officially established in Canada, GA4GH continues to develop and promote the creation of real-world genomic data initiatives. This is done through the adoption of tools and standards for sharing of genomic data, including regulatory and ethical aspects. Among others, they address issues pertaining to the return of results to patients, data security, data access, and data sharing.

The GA4GH framework for responsible sharing of data is based on the idea that science and society are partners in determining data sharing principles. This framework is founded on the premise that everyone benefits from science and its applications as stated in the Universal Declaration for Human Rights, 1948, Article 27. Now being internationally recognized as a core resource, international data projects are incorporating GA4GH standards and policies.

The CIHR Institute of Genetics is committed to ensuring GA4GH standards and principles will be used to enable national and international data sharing to advance the capacity of genomics to increase the health and welfare of the people who live in Canada as well as all peoples worldwide. This aligns with Canada's Research Data Management Framework which is aiming to enable open science and data sharing. Indeed, to ensure an equitable access and participation in both the scientific process and its benefits, Canada must rigorously maintain technical and ethical standards that support the open sharing of data and knowledge – now and always.

Enabling Genomic Medicine – Supporting CIHR's Priorities

Our commitment towards the development and implementation of genomic medicine aligns with and supports all five of CIHR's priorities. Through the promotion of open science, implementation of FAIR principles, and the support of national cross-cutting initiatives and international collaboration, this initiative is all about "advancing research excellence in all of its diversity" (Priority A). By providing an essential structure to responses to emerging health threats, it will also "strengthen Canadian health research capacity" (Priority B). By creating an ecosystem that supports Indigenous (First Nations, Métis, Inuit) self-determination and governance, this commitment aims to reduce the "genomic divide" and improve the well-being of Indigenous people (Priority C). Also, by strongly supporting the identification of determinants of health, this commitment will pave the way to more predictive medicine (Priority D). Ultimately, the core of this commitment is to contribute to the establishment of a true learning health system (Priority E).

Disability Images

Commitment B

Improving Genetic Disease Diagnosis and Therapies

Rare Diseases (RD) constitute an under-recognized global health issue. In fact, notwithstanding their name, RDs are far from rare. Importantly, 85% of rare diseases are single-gene disorders, meaning that only one gene in a person is malfunctioning and is causing their disease. What is truly alarming is that 1 in 25 children is born with an inherited disease, and recent studies have shown that over half of these children will not reach adulthood. In addition, it is estimated that 1 in 3 pediatric hospital beds is occupied by a child with an inherited disease, and 5-10% of all hospitalization costs (adult plus pediatric) are caused by a so-called rare disease. It is becoming clear that inherited diseases are the major cause of mortality and morbidity in children in Canada.

In the 2020 *Speech from the Throne*, the Canadian government stated it remains committed to a rare-disease strategy to help families in Canada save money on high-cost drugs. In response to the burden of RDs, as well as the fundamental inequities faced by RD patients and their caregiver families, the UN High Commissioner for Human Rights designated RDs as a priority for the conceptualization and enactment of Universal Health Coverage. There is a medical, economic, and human rights obligation to address the current unmet needs of patients with RD.

If Kids are not Counted they Do not Count

What is unfortunate is that children with rare diseases are currently not counted by our healthcare system as they do not appear in hospital, provincial, or national records. It is next to impossible to determine the appropriate level of resources to be apportioned for care/medicines/research for patients with rare diseases without knowledge of both the direct and indirect costs to the healthcare system, and the socioeconomic and mental health burden to patients and their families. Fundamentally, if these children are not counted, they do not count. Implementation research towards a system that captures this information is essential to adequately address this critical health problem and ensure equitable distribution of healthcare resources.

The diagnostic odyssey is a multidimensional burden that affects RD patients. Using clinical diagnostic pathways, a rare disease takes on average five years to diagnose at an average cost of $25,000, with 2-3 misdiagnoses made prior to the final diagnosis. This diagnostic odyssey, along with social isolation, an absence of care coordination, and resultant mental health burden on the affected children and their caregiver families, are too often the norm for those affected by RDs. Fortunately, genomics is now enabling this diagnostic odyssey to be shorter, more accurate, and less expensive.

If the genetic change that causes a rare inherited disease is known, then a diagnosis can be made in weeks at a fraction of the cost of the current clinical diagnostic pathway. Indeed, recent genomics discoveries have uncovered the defective gene for 5,500 of the predicted 7,000 inherited disease-causing genes. An accurate genomic diagnosis can immediately inform treatment decisions for a patient while also providing information to the parents regarding the risk of future children inheriting the same disease.

Using genomics is not only the most efficient way to achieve a genetic-disease diagnosis, but also the most economical, allowing patients – and the healthcare system – to modernize and bypass years of traditional clinical tests. The use of implementation science to determine if digital delivery of healthcare (such as virtual/digital care, telemedicine, and electronic consultations) will additionally improve access to care, quality of care, equity in diagnosis, economical delivery of medicine, and overall improvement in patient and societal outcomes.

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Accessible and Affordable Therapies

We can now diagnose rare inherited diseases in children, for the first time, with unprecedented accuracy at an unprecedented success rate. This achievement has been made possible in part by previous CIHR Institute of Genetics programs, jointly led with Genome Canada, that brought advances in genomics that transformed our ability to identify the genetic causes of rare diseases. However, our ability to identify genetic causes of inherited disease dramatically outperforms our ability to act on this information. Indeed, as many inherited-disease causing genes were discovered in the past five years, over 90% of inherited diseases are awaiting a treatment.

To address this gap, the Institute of Genetics will leverage previous funding that connected clinicians discovering new inherited-disease genes with scientists in Canada that were able to study equivalent genes and pathways in model organisms. This network now comprises more than 85 medical and clinical geneticists and 623 scientists working with and conducting experiments on model organisms. This network approach has proven to be an incredibly powerful paradigm in the discovery and functional analysis of rare-disease genes, and was adopted by funders in Europe, the United Kingdom, and Australia. This (now international) network provides functional evidence that a suspected disease gene variation causes a disease, provides a molecular understanding of what drives the disease, and delivers an experimental model organism for further study.

The establishment of such models immediately enables the use of the plethora of cutting-edge omics research technologies ranging from transcriptomics (the study of RNA transcripts), to proteomics (the study of proteins in an organism), to metabolomics (the study of metabolites in an organism), and extends into other basic science research areas such as protein structure and function. This allows us to understand how genetic changes cause diseases, paving the way to determine how best to diagnose, treat, or prevent disease from happening altogether. Rare/inherited-disease research and the movement towards therapies are on the leading edge of the precision medicine transformation of healthcare in Canada.

Many treatments for inherited diseases, including lifesaving and life-transforming treatments, can be quite affordable. Indeed a simple change to a newborn child's diet can be sufficient. One example is phenylketonuria (PKU), where specific variants in the *PAH* gene cause the disease, resulting in intellectual disability, seizures, behavioural problems, and mental disorders. If diagnosed at birth, PKU can be prevented by a diet low in the amino acid phenylalanine. Another example is children with rare variants in the *BTD* gene which results in a defect in the metabolism of biotin (also referred to as vitamin H). If undetected, these children will develop seizures, be developmentally delayed, and will die at a very young age. Detection of this condition at birth enables a diet supplemented with biotin to be implemented resulting in these children growing up to lead a normal, healthy life.

However, some genetic diseases cannot be treated by alterations to diet and require either a new drug or gene therapy to be developed. These drugs, often called orphan drugs, are high-cost drugs that can cost $300,000 per drug per year, or, $2 million for a single-dose gene therapy. These costs are unsustainable for Canada's publicly funded healthcare system over the long term. In addition, using the current RD therapy development paradigm treatment for many of the rarest of the rare diseases would be unprofitable as there is not a large enough patient base to justify investment in therapy development.

> "Almost 1 in 5 patients who die from unexplained sudden cardiac death have a suspicious gene whose early detection would have substantially prevented these deaths."
>
> (*JAMA Cardiology.* Published online, June 2, 2021)
> *DOI:10.1001/jamacardio.2021.1573*

The Institute of Genetics will seek to pioneer an open-science model to move medicines into the clinic using primarily academia and research hospitals. As pivotal clinical trials for most rare diseases are a combined phase 1-2 trial on 10-12 patients, after which drug approval can be granted, these can be done in a research hospital setting. As these medicines will be developed primarily within academic settings using an open-source model (i) the total cost of drug development will be reduced and will be known, and (ii) the price point can be controlled as all work will be performed by the not-for-profit sector. Small molecules (drug), stem cell, and gene therapy approaches such as AAV, mRNA, and CRISPR, will be pursued in collaboration with not-for-profit partners and Government of Canada agencies including the National Research Council for the development of gene therapies, and Health Canada for the implementation of their enabling legislation for innovative health products and clinical trials.

The CIHR Institute of Genetics is committed to the development of comprehensive genomic solutions for the diagnosis of inherited (rare) diseases, and the development of affordable medicines for their treatment, to ensure ethical, efficient, cost-effective, and equitable access.

Improving Genetic Disease Diagnosis and Therapies – Supporting CIHR's Priorities

This commitment supports many priorities of CIHR. Efforts supporting the development of accessible and affordable therapies through the establishment of innovative open-science drug development models will advance research excellence (Priority A). The work aiming to reduce regulatory barriers to enable the introduction of innovative therapies will strengthen investigator-initiated research, making it more accessible to develop therapies in an academic setting (Priority B). By allowing the generation of strong evidence regarding the burden of rare diseases for people who live in Canada, this will both improve evidence-informed decision making, allowing better allocation of resources (Priority E), and improve health equity and access to health care (Priority D). Both priorities will also be supported by the creation of an alternative to traditional for-profit drug and therapy development, addressing inequities through the development of accessible therapies (Priority D) while strengthening the Canadian health system (Priority E).

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A 5-week-old, previously healthy male child was admitted to hospital after hours of atypical crying and irritability. The child's genome was sequenced and returned within hours, flagging a defect in a single gene--SLC19A3. The diagnosis: Thiamine Metabolism Dysfunction Syndrome. It is known that thiamine and biotin administration can treat this genetic disease, and this was started 37.5 hours after admission. Six hours later, the patient was calm and feeding. After a further 24 hours passed without seizures, the patient was discharged. He is now thriving at 7 months of age.

New England Journal of Medicine. Published online, June 3, 2021. *DOI: 10.1056/NEJMc2100365*

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Commitment C

Embracing Diversity, Inclusion, and Indigenous Rights

The Value of Canadian Genomic Diversity

There is a racial bias in current research and clinical genomics databases in Canada and around the world. The overwhelming majority of sequenced genomes are from people of European descent. There is a pressing need to more accurately reflect the actual diversity of the people who live in Canada in genomic databases so that advances in research and their translation in clinical care provide accurate and equal healthcare information to all who live in Canada.

For minority groups with very small numbers, it means that a larger proportion of their population needs to be included than their total population might suggest in order to generate an accurate genomic reference – a process termed "oversampling". This is because a discrete number of genomes are required to obtain an accurate reference genome for any population. Without an accurate reference genome, personalized medicine for groups, regardless of ancestry, will not be enabled unless they are adequately represented in population data. The CIHR Institute of Genetics will work to ensure that the entirety of Canada's diversity will have the opportunity to benefit from advances in genomics to better their health in a culturally safe manner that respects principles including self-determination and data sovereignty.

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Diversity Fueling Clinical Trials

It is important that patients, and the population in general, are offered the opportunity to participate in clinical trials for new medicines as they become available. Data linkages, that include genomics and healthcare records, especially in the areas of inherited diseases and cancer (the two major diseases of DNA), are essential to apply personalized medicine approaches for treatment and disease management. As an example, for an inherited disease where a variation in a single gene causes the disease, gene therapy can replace the defective gene with a normal gene to treat (and potentially cure) the disease. Lack of knowledge about genomic variation in underrepresented populations brings challenges in differentiating normal gene variants from those causing the disease. Without knowing the precise gene defect for every patient with an inherited disease, people in Canada will not be able to participate in gene therapy clinical trials. Enabling clinical trials not only ensures that all people who live in Canada have first access to leading edge therapies, but also ensures engagement of industry with the healthcare system in Canada. In this context, capturing a broader population diversity will represent an advantage for Canada in attracting investments, while contributing to improving the health of all people who live in Canada and around the world.

Increasing the diversity and number of sequenced genomes in Canada will also drive more clinical trials to our country as many drug responders versus non-responders, or those who experience serious side effects or very few side effects can be parsed based on their genome. If the genome of patients participating in a trial is known up front, the genomic data can be deconstructed to determine which patients will respond well to a drug while also having the fewest side effects. This will both increase drug approval rates and simultaneously ensure that moving forward, the drug will only be prescribed to patients with the highest likelihood of benefiting from the drug. As ~10% of all hospitalizations in Canada are due to adverse drug reactions, these advances will also decrease patient morbidity and mortality while simultaneously decreasing hospitalizations; capturing the diversity of people living in Canada will be essential to ensure that everyone can benefit from this decrease.

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Diversity for Equitable Algorithms

As more genomes are sequenced and analyzed, polygenic risk scores for more common diseases, such as heart disease and stroke, diabetes, mental health conditions, cancer, and others, will become accurate predictors of disease onset. Simply put, data within your individual genome will be able to predict the likelihood of you being predisposed to a common/chronic disease prior to disease onset. This is incredibly important information for both the patients and the clinical team that cares for a person as (i) the patient can initiate lifestyle changes to prevent disease occurrence, and (ii) the clinicians can monitor the patient more closely for a particular disease for which the person is predisposed. In essence, this is a more accurate version of the question commonly asked during a doctor's visit: "do any diseases run in your family?" However, without the inclusion of genomic diversity in the development of the algorithms used in these polygenic risk scores, the outcome will be increased health inequities resulting from the reduced performance of the predictions for underrepresented populations.

All of the aformentioned benefit and advances, which will be coming online within the next five years, require the entirety of all of Canada's populations be adequately represented in available sequenced genomes. The CIHR Institute of Genetics is committed to helping to achieve this goal.

Embracing Diversity, Inclusion, and Indigenous Rights – Supporting CIHR's Priorities

The commitment to increase diversity and inclusion is embedded in all of our other commitments and also represents a central aspect of CIHR's priorities. Working closely with provinces, territories, Indigenous people and other communities will be essential to capture the genomic diversity of Canada (Priority A). Going beyond the promotion of diversity, this commitment recognizes and embraces diversity as an exceptional asset required for the success of personalized healthcare in Canada, and promotes inclusion in all of its aspects (Priority B). As previously described, the proposed approach supports the necessity of Indigenous self-determination and opportunities to advance health and well-being (Priority C). Overall, the inclusion of all of Canada's diversity will contribute to reducing health inequities that cause representation biases (Priority D).

Next page: DNA Double Helix Turns Fifty: A visitor views a digital representation of the human genome, August 15, 2001, at the American Museum of Natural History in New York City. Fifty years before, James Watson and Francis Crick published an account of the DNA double helix in the science journal *Nature*. Photo: Mario Tama/Getty Images.

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Commitment D

Strengthening the Community

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Healthcare Professional Education

Adoption of genomics into routine care will require a clinical workforce that possesses a level of genomics knowledge and literacy to understand and best implement genomic testing and personalized medicines into current clinical pathways. Capacity building in both the education of clinicians, and the development of adequate interfaces providing "on-demand training" will be important. Also, the training of medical and clinical geneticists and genetic counsellors will be a major need for Canada in the very near term, as genomic medicine rapidly becomes a reality for day-to-day care. The Institute of Genetics is committed to increasing capacity through research on optimal training and educational outreach programs to ensure that genomic research and genomic medicine advances can be appropriately and ethically implemented into our healthcare system.

Health professional teams need to be enabled and supported when deciding which patients require genomic testing, and how best to convey the results of genomic medicine into current clinical practice. This requires appropriate referral pathways to be identified and instituted – supported by strong evidence and the alignment of genomic clinical findings across disciplines – to ensure information is shared and efforts are not duplicated. To achieve the infinity loop of a genomic learning health system (Fig. 1.1), interdisciplinary teams of healthcare professionals, scientists, decision makers, and patients will need to be assembled to ultimately improve the health and well-being of people who live in Canada.

Defining solutions to optimize the training of healthcare professionals will be an important component of preparing healthcare communities for the genomic medicine revolution. The CIHR Institute of Genetics will embark on developing training programs to empower genomic literacy. We envision genomics training programs across numerous disciplines in our healthcare system, including medical doctors, nurses, allied healthcare professionals, and non-clinical staff to bring about a level of knowledge and awareness such that patients and society can benefit from genomic medicine. Research towards workforce modeling to inform determinations for training numbers across all medical professions, needs to be supported.

Computational Biology and Bioinformatics Training

A major bottleneck for the understanding and incorporating of genomic information into medicine and healthcare is our inability to analyze the large data sets that currently exist, and the exponential growth in the size of these databases that will occur over the next decade. There is a paucity of bioinformaticians, computational biology and health data scientists that can employ advanced methods such as AI and machine learning research for their application to improve human health and healthcare. Capacity building in this workforce is essential for Canada to take advantage of the logarithmic increases in genomic information that will occur over the near and long term. These computational aspects of modern science are crucial for the future of basic, translational, and clinical research.

The efficiency at which the computational biology and health data science communities need to be expanded has to occur rapidly and at scale. This expansion needs to ensure equity, diversity, and inclusion in the training of this class of researchers by incorporating outreach to underrepresented groups for inclusion in education, training, and career development. Research into current disparities in training, and the barriers that need to be overcome will inform optimal programs designs. Training and education programs can serve as a basis for establishing good open science practices, ensuring the use of FAIR principles for the use in, and the evaluation of, research impact.

Sustainability for scientific software deployment, use, and updating will need to be addressed as large databases are increasingly incorporated into both health research and health care.

General Literacy and Public Acceptability

Public genetic and genomic literacy is an essential and important aspect of genomic research and genomic medicine. Understanding public attitudes can assist in integrating genomics into research and care, as well as inform the development of public outreach and education strategies and platforms.

Research into perceived genomic knowledge versus actual knowledge, the sources used by the public to obtain this knowledge, and enabling uptake of accurate and meaningful knowledge will play an important role in ensuring people can make appropriate and informed decisions on the use of genomics in their own health, and the health of their dependents. Efforts will be required to ensure that all people who live in Canada have equal understanding of genomics in order to promote self-determination and reduce health inequities.

There currently exists a high level of public interest, as well as a concomitant high level of expectation, for genomics and its application to personalized medicine. There is great interest in understanding the family history of disease and personal risk for the future development of disease(s). As more members of the public become exposed to genomics in a healthcare setting, they will need to make decisions about their genomic data and its use.

The public has rightful concerns about who will have access to a person's genomic information and whether it can be used to discriminate against them. Much of the public is unaware that people living in Canada are protected by the Genetic Non-Discrimination Act which essentially prohibits anyone (or company) to require an individual to disclose the results of a genetic test without their consent, thereby protecting people who live in Canada from discrimination (e.g. insurance, employment) based on results of a genetic test. Concerns, and the solutions and governance, regarding data storage and security, data sharing and use for research, and the level of control and consent over access, are paramount. The use of genomics in medicine will be driven by both clinical utility and public uptake. Research to further our understanding of the public's views and attitudes will shape genomics research and the provision of genomic medicine.

Strengthening the Community – Supporting CIHR's Priorities

This commitment aligns naturally with the aim to strengthen Canadian health research capacity through training and career support (Priority B). But by doing so, it will also contribute to developing research excellence by ensuring that expertise in genomics and computational biology can be fully integrated in multidisciplinary research teams, increasing their strength (Priority A). Multidisciplinary teams are crucial in order to continue to push the boundaries of our evolving genomic landscape, as genomics increasingly contributes to the implementation of a learning health system (Priority E). Finally, through specific actions established in collaboration with Indigenous populations across the country, this commitment will also allow Indigenous people to make informed decisions about embarking in this era of computational medicine driven by genomics (Priority C).

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Looking Forward

Aspirations for genomics in 10 years

1. Every inherited-disease gene will be known
2. Genomic literacy will prevail amongst clinicians and the general public, enabling more informed decisions to be made concerning personalized health
3. Over 100 million human genomes will have been sequenced, adding unprecedented accuracy to prognostic health and disease predictors at an individual level
4. The values of people who live in Canada will be incorporated into genomic medicine delivery, contributing to the establishment of a learning health system
5. A Canadian Human Genome Library will enable artificial intelligence to determine what keeps people healthy and makes them sick
6. Your genome will be part of your healthcare record, accessible on your smartphone or laptop to better enable personalized, patient-informed care
7. Pharmacogenomics will be standard procedure, determining specific drug dosing and preventing undesirable drug-drug interactions at a personalized, individual level
8. Therapies for the treatment of inherited (rare) diseases will be increasingly accessible and affordable
9. Combining other omics (proteomics, transcriptomics, metabolomics, and others) with genomics will improve disease diagnosis and health outcomes
10. Genomics will be a primary vehicle for health equity

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- Our colleagues at CIHR in Ottawa, including our Integrated Institute Team members, and fellow CIHR Institutes across Canada.

Cover photo: DNA Double Helix Turns Fifty: A visitor views a digital representation of the human genome, August 15, 2001, at the American Museum of Natural History in New York City. Fifty years before, James Watson and Francis Crick published an account of the DNA double helix in the science journal *Nature*. Photo: Mario Tama/Getty Images.

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