

Child Health & Wellness

Research Strategy:
Grand Challenges
JUNE 2020



UNIVERSITY OF
CALGARY



Children and families are the foundation of Canada's future. Research in child health and wellness is research in life trajectories. When researchers, health care providers, community organizations, children and families identify critical gaps in health and wellness, we can target our research to improve wellbeing, transform care and save lives.

Canada ranks 30th of 38 industrialized countries worldwide on child health and wellbeing.

Together, **we have superpowers** – when we conduct cutting edge research with innovative partners in Alberta Health Services, our community and around the world, we rapidly translate this new knowledge into better care, and improve child and family outcomes in our province and far beyond. An interdisciplinary community of scholars developed the five grand challenges for the emerging, cross-cutting Child Health and Wellness (CHW) strategy. These challenges represent the alignment of strengths, needs and opportunities in child health and wellness at the University of Calgary.

Building on UCalgary strengths, internal and external consultations, and where we can make the greatest impact, we have identified five grand challenges.

Each is viewed through two distinct lenses – the social determinants and biological determinants of child health and wellness. These five grand challenges are tied together by two cross-cutting, complementary approaches within the overarching framework of precision child health. Our precision health promise is to develop preventative measures, diagnoses and treatments targeted to the needs, characteristics and

circumstances of each child, or specific populations of children and families. Each of our challenges also benefits from big data and machine learning. Finally, as we apply what we learn, each challenge emphasizes the transformation of health care, education and community systems to benefit patients, children and families (Figure 1).

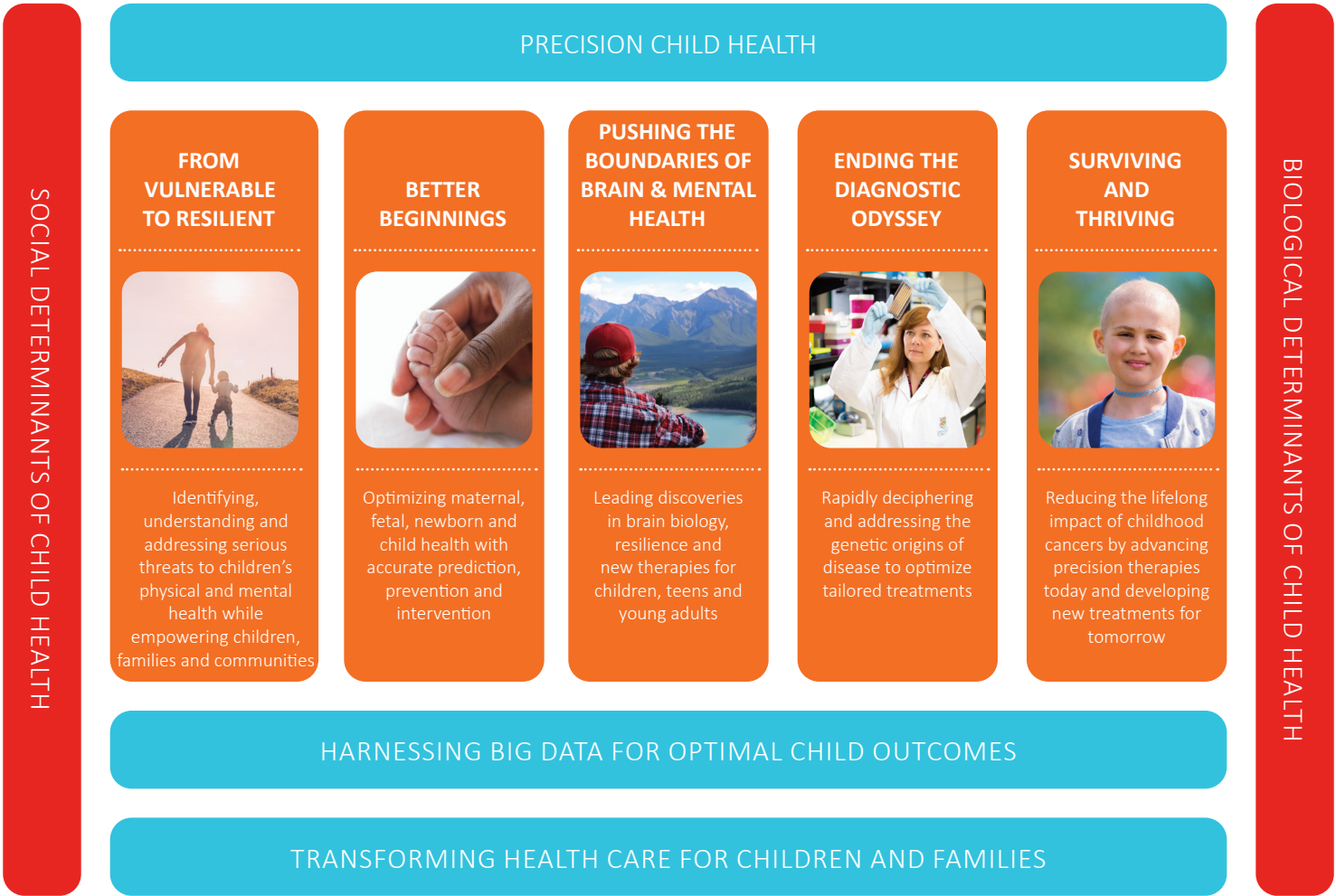


Figure 1: The CHW Grand Challenge conceptual framework.
Grand challenges (orange) are integrated by cross-cutting approaches (blue) and seen through the lenses of social and biological determinants.



CHILD HEALTH & WELLNESS

Principles & Grand Challenges

Our Grand Challenges are underpinned by a set of principles to ensure success.

Translational Impact

Data-driven with clear mechanisms to translate knowledge into improved health system delivery, diagnoses and treatments, evidence-based policies, and better outcomes for children, their families, our community and beyond.

Achievable

Bold aspirations enabled by coordinated research efforts and investments built upon our strengths and relevance to society.

Inclusive Partnerships

With children at the forefront, strong relationships with families, stakeholders, system partners, funders and community are essential.

Relevant

Reflect the needs of the community gathered through town halls, provincial and national trends and opportunities for partner funding.

Building Community


Ongoing, meaningful and strategic engagement, communication and planning with child researchers across campus and beyond.

Built upon Strengths

Focusing our efforts in established and emerging areas of research strength to maximize impact in child health and wellness.

Confirmed Programs and Priorities

Rooted in programs and priority areas identified through stakeholder consultation and data analysis.

A full-page background image showing a woman and a young child walking away from the camera on a paved path. The sun is low on the horizon, creating a strong backlight effect and long shadows. The woman is on the left, wearing a dark top and leggings, and the child is on the right, wearing a striped shirt and pants. The path is flanked by grassy fields.

GRAND CHALLENGE 1

From Vulnerable to Resilient

Identifying, understanding and addressing serious threats to children's physical and mental health while empowering children, adolescents, families and communities.

Decades of research have identified key threats to the well-being of children and families, including poverty, mental health, intentional (e.g. child abuse, suicide) and unintentional injuries, infant mortality, obesity, inactivity, food insecurity, vaccine-preventable illnesses, discrimination, and bullying. The COVID-19 global pandemic has amplified many of these issues for families in Canada and around the world – the effects of which we will see for years to come.

Although the global impact of threats to child and family well-being are well-documented, we need to better understand who is most impacted, how the impacts change with developmental stage, and which individual, familial and contextual factors confer a protective advantage. Further, evidence-based approaches for preventing and mitigating the effects of these threats and improving child health and well-being continues to challenge researchers around the world.

This grand challenge will identify the many factors that influence well-being in children and families, within the framework of the social determinants of health. We will identify modifiable and nonmodifiable factors as well as how these factors interact to impact child health and wellness. The ultimate goals are to develop evidence-based policies, prevention strategies, and interventions. We are uniquely positioned to address this grand challenge, given our multidisciplinary membership, expertise in longitudinal cohort family studies, and extensive experience in knowledge mobilization, health promotion, and policy analysis.

From Vulnerable to Resilient

Identifying, understanding and addressing serious threats to children's physical and mental health while empowering children, adolescents, families and communities.



This grand challenge focuses on contributing evidence-based health promotion and primary prevention strategies to enable children, families and communities to reach their full potential.



Key areas of investigation

Understanding healthy child trajectories and supporting at-risk children and families. The Alberta Births Common Data (ABCD) is the harmonization of two of the most comprehensive longitudinal studies of pregnant women and their babies in Canada, All our Babies (now All our Families) and APron (Alberta Pregnancy Outcomes and Nutrition). The All our Families study is a lifecourse analysis of the relationship between prenatal events and child development, taking into account many factors that influence child and family well-being (parental education, mental health, lifestyle, childcare, use of community services and availability of health services). The APron cohort examines the relationship between maternal nutrient status during pregnancy and maternal mental health, and child health and development. By collecting the same information from two separate cohorts, researchers are comparing variables in both datasets, increasing the sample size for research projects and enabling more complex, longitudinal analyses. Our researchers continue to follow these children and families to build the evidence picture around healthy child development and interventions that can put at-risk children back on track.

Improving the mental health of families at risk. Paramedics, police officers and firefighters have unique occupational stressors and often rely on their families as their first source of support. The Before Operational Stress: Evaluating Novel Psychosocial Interventions for Public Safety Personnel (PSP) and their Families study is evaluating a group-based peer support intervention. This is important work given the additional burden the COVID-19 pandemic has placed on first responders and their families.

Transformative improvement in the prevention, diagnosis and management of youth concussion and injury. Surveillance in High Schools to Reduce Concussions and Consequences of Concussions in Youth (SHRed) is a pan-Canadian high school surveillance program aimed at understanding the prevention, diagnosis,

management and rehabilitation of concussions in youth athletes. This major prospective cohort study, funded by the National Football League Scientific Advisory Board, brings together a multidisciplinary group of researchers working to ensure concussions and injuries are no longer barriers for adolescents participating safely in sports.

Working to Vision Zero: elimination of serious and fatal active transportation injuries in children and youth. The Child Active-Transportation Safety and the Environment Program (CHASE) is a 5-year research program that aims to understand factors in the built environment that make it safer for children and youth who are walking and biking. The program is identifying which features increase the likelihood of children and youth adopting active transportation. This team is working with community partners on an integrated knowledge translation approach to overcome barriers to safe active transportation at municipal, provincial and federal levels.

Maximizing the public health impact of vaccines. Alberta Children's Hospital Infectious Diseases Epidemiology and Vaccine Evaluation (ACHIEVE) researchers are investigating vaccine hesitancy, vaccine effectiveness and dosing schedules. The team is also studying the epidemiology and outcomes of infectious vaccine-preventable diseases. This group's work on prospective, population-based surveillance studies of infectious diseases spans three decades. New studies on the epidemiology,

diagnosis and management of children with COVID-19 represents the marshalling of enormous intellectual resources to protect children and their families from this pandemic. ACHIEVE researchers are sharing rapid, real-time data from across Alberta with national and international partners, contributing to the world-wide scientific effort.

Addressing critical social policy gaps. Canada lags behind other developed countries on measures of child health and wellness. Integrated social policy can address many of the key areas of vulnerability for children and families. Fragmentation in social policies creates barriers to children and families realizing their full potential and this is especially true for children with developmental challenges. The Neurodevelopmental Disability Policy Research Program seeks to address these issues through economic evaluation and policy analysis. This research program contributes timely and important information on social policies and interventions to address gaps with comprehensive evaluation including the use of longitudinal and administrative data.

Research in this program is highlighting evidence-based strategies for preventing serious threats to child and family well-being, and optimizing child health and development. A social determinants of health lens is driving program research activities and contributing to making Canada one of the best countries in the world to live.

DID YOU KNOW

that one in four children in Canada is vulnerable in one or more areas of development prior to entering grade one?

Early life experiences have a vital impact on learning skills, coping skills, resiliency and even our overall health as an adult. Dr. Nicole Letourneau's research provides evidence-based therapies to help families thrive.

Mothers like Lana Clyde understand how important intervention can be. For years, the Calgary mom suffered from post-partum depression. She recovered by enrolling in an intervention program, VIDKIDS,



designed by Dr. Letourneau, PhD, to help mothers fully engage with their children. Dr. Letourneau, along with Dr. Martha Hart, PhD, are also reaching mothers through their program ATTACH™, promoting healthy relationships in families affected by violence, addiction, and low income. The programs build on studies from a unique mother-baby longitudinal cohort at the Owerko Centre. Letourneau holds the ACHF Chair in Parent-Infant Mental Health.

GRAND CHALLENGE 2

Better Beginnings

Optimizing maternal, fetal, newborn
and child health with accurate
prediction, prevention
and intervention.



Pregnancy is a time of rapid physiologic and social change with long-lasting impacts on maternal and child health outcomes. It is well established that adverse pregnancy outcomes, such as preterm birth or intrauterine growth restriction, can lead to long-term health challenges for the mother and the child, yet collectively we have a limited understanding of why and how these conditions originate. This impedes our ability to predict who is likely to have adverse pregnancy outcomes or prevent them from happening. This grand challenge is focused on improving our understanding of critical developmental, physiological, and social processes and mechanisms leading to typical and atypical development. Ultimately, our knowledge will be applied in laboratory, clinical, and community settings to optimize maternal, fetal, newborn and child health through enhanced prediction and prevention of adverse outcomes.

Better Beginnings

Optimizing maternal, fetal, newborn and child health with accurate prediction, prevention and intervention.

Key areas of investigation

Characterize the mechanisms leading to typical and atypical development. Through fundamental biological studies using human cells and model organisms we aim to better characterize typical development of the placenta, the fetus, and mechanisms leading to childbirth. This fundamental discovery science serves as a platform to identify novel targets for clinical interventions designed to improve outcomes across the life course.

Reducing the burden of preterm birth. Preterm birth is common, affecting 8% of Canadian pregnancies. Children born preterm often suffer from short and long-term health challenges. Recent data also suggests that preterm birth may be an early sign of cardiovascular disease in women. Work in this area encompasses: epidemiologic studies to understand the natural history of spontaneous and iatrogenic

preterm birth and its long term impacts on children, mothers, and families; clinical trials of interventions aimed at improving short and long-term outcomes following preterm birth; and knowledge translation activities with AHS to ensure best practices are integrated into the health care system.

Dads make a difference. A father's contribution to healthy pregnancy and child outcomes is much more than DNA. There are sex and gendered responses to child development and child rearing, but most research tends to focus on mother-child interactions instead of mother-father interactions or father-child interactions. This area of investigation aims to help dads by providing education, support, and outreach that is optimized for how men communicate and learn.

DID YOU KNOW

that at 6%, Alberta has the second highest incidence of low birth weight in Canada?

Infants born small, relative to gestational age, face increased risk for health challenges, including sudden infant death, diabetes, and heart problems. Low birth weight can occur due to a variety of genetic and environmental factors. Understanding how this happens and why the condition is more prevalent in Alberta is critical to preventing and ameliorating the effects of low birth weight. When she was born at



680 grams, Bella deSouza Cook was one of Alberta's smallest surviving babies. Her doctors didn't think she would live. In neonatal intensive care, her mom enrolled in a ground-breaking maternal-infant study led by Dr. Suzanne Tough, PhD, at the Owerko Centre. Bella is now thriving in her teens and her mom credits her health to early interventions informed by research.


Improved maternal mental and physical health.

Pregnant women have been systematically excluded from randomized clinical trials for fears of teratogeneity, leading to a dearth of evidence of how to better manage pre-existing and pregnancy-associated conditions with pharmacological, psychological, and surgical techniques. Yet, in the presence of physical illness or mental health concerns, women often face difficult choices with little evidence to support treatment options. Leveraging Alberta's extensive administrative data resources, this work includes phase four surveillance activities examining pregnancy outcomes following medication exposure in pregnancy, as well as phase 1, 2, and 3 clinical trials examining the safety and efficacy of different treatments on pregnancy outcomes and disease control. This work will not only optimize pregnancy outcomes, but also ensure that mothers are healthier long-term.



This grand challenge will generate new knowledge and translate findings into improved mental and physical outcomes for mothers and their children at all stages of development. Researchers on this team conduct interdisciplinary research that spans fundamental science in fetal and placental development, understanding how events during pregnancy impact women and children's health, and strengthening health care systems and communities for improved health and well-being of mothers and children in Canada and abroad.



A person with blonde hair, wearing a red baseball cap and a red and black plaid shirt, is seen from the back, looking out over a vast mountain landscape. The landscape features a deep valley with a river, a forested area, and a lake in the foreground, all under a blue sky with scattered clouds. The mountains in the background are rugged and partially covered in snow.

GRAND CHALLENGE 3

Pushing the Boundaries of Brain & Mental Health

Leading discoveries in brain biology, resilience and new therapies for children, teens and young adults.

Neurodevelopmental and mental health disorders are some of the fastest-growing health problems in the world. More than 20% of school-aged children suffer from a diagnosable disorder, and often have more than one. Developmental, behavioural and emotional problems are now collectively the leading cause of disability affecting our youth. There is an urgent need to devote resources to uncover the developmental and neural origins of these disorders and to develop effective interventions for children, teens, young adults and their families.

The new Centre for Child and Adolescent Mental Health, set to open in 2021, promises to be one of the most research-intensive, community-based mental health care facilities for young people in the country. Our researchers will have access to a direct pipeline from discovery to care – all in one setting. With the addition of this new facility, in partnership with Alberta Health Services, and child and youth serving agencies, we will be able to conduct research that has never before been possible in our community.

Pushing the Boundaries of Brain & Mental Health

Leading discoveries in brain biology, resilience and new therapies for children, teens and young adults.



This grand challenge will generate new knowledge and translate into improved physical and mental health outcomes for children and youth. Our researchers study brain development, neurodevelopmental and neurological disorders, brain injury, cognition, behaviour, and mental health. This diverse interdisciplinary group spans the full range of translation from bench to backyard, including cutting-edge molecular, genetic, neuroimaging, assessment and intervention techniques, in both model organisms and humans.



Key areas of investigation

Stress and brain development. The fetal brain is sensitive to its environment throughout pregnancy; exposures to substances and stress can have long-term impacts on child development. Our teams are studying how prenatal stress influences child brain development across multiple domains, including physiological stress response (cortisol), brain structure and function (via neuroimaging), mental health, and interactions between the brain and the gut microbiome. This cross-disciplinary research is identifying mechanisms underlying the intergenerational transmission of maternal stress to infants/children. This work ultimately supports recommendations for policy changes to optimize child brain development.

Understanding and treating neurodevelopmental disorders. Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication challenges and restricted, repetitive behaviours. Our researchers study model organisms and research volunteers to identify effective treatments for ASD. Examples include testing the efficacy of the ketogenic diet in mouse models of ASD and in-person therapy to mitigate anxiety in teens with ASD. This research is already impacting young people with ASD and will continue improving their quality of life in the years to come.

The neurodevelopmental basis for mental health. The partnership between the Owerko Centre at ACHRI and the Mathison Centre at HBI provides unique opportunities to determine why a sizable proportion of individuals with neurodevelopmental disorders experience mental health disorders. The expertise of faculty at both Centres, coupled with our partnerships with AHS hospital clinics and community treatment centres, enable our examination of an integrated model to identify key biological, psychological and social mechanisms in mental health issues. Identifying these mechanisms will provide foundational knowledge to develop and implement evidence-based treatment

and prevention strategies, few of which currently exist.

Understanding circuitry defects of neurodevelopmental disorders.

Our researchers are studying the defects in circuitry that occur in neurodevelopmental disorders and therapeutic options to repair them. They are examining neural stem cells, errors driving the timing of neuronal birth and whether they move to an incorrect location, thereby setting up improper circuits at the earliest steps in development. Synaptic physiologists are investigating defects in electrophysiological properties of circuits and associated behavioral defects across a variety of neurodevelopmental disorders. Glial biologists are studying the role of glial cells (astrocytes, oligodendrocytes, microglia) in modulating circuits. Imaging scientists are determining the functional and/or structural changes in the improperly developing brain in both rodents (where mechanisms can be tested) and in children (where translation can be established). Our stimulation experts are using transcranial stimulation to awaken the plasticity of the developing brain to try to modulate these defective

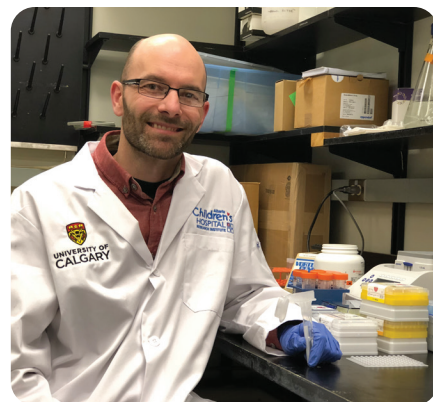
pathways. Finally, clinical researchers are exploring how alterations of these pathways improve behaviors and clinical outcomes in children. This work will clarify the underlying etiology of neurodevelopmental disorders and proposed treatment strategies, across a continuum from early embryogenesis through childhood.

Childhood brain injury. Millions of children experience a traumatic brain injury (TBI) each year, the majority of which are mild. While many children recover within a couple of weeks, up to 25% of children have persistent post-concussive symptoms for months, including somatic, cognitive, and affective complaints. Research is essential to better forecast, prevent, diagnose, and treat mild TBI to improve child outcomes. Our researchers are world leaders in pediatric concussion, covering the spectrum from epidemiology and prevention of mild TBI in children, to animal models of brain injury and large studies of children with mild TBI. This work is already changing policies and will continue to inform policy and practice across Canada and around the world.

DID YOU KNOW

that 1.2 million children and youth in Canada are affected by mental illness—yet, less than 20% will receive appropriate treatment?

Like so many others, Naomi Pearce struggled for months with finding the right medication and proper dosage to treat her depression and anxiety. She eventually needed hospitalization. Her journey reveals the urgent need to better understand the biology of young people and how each responds to anti-depressants. Dr. Chad Bousman, PhD, is



leading Canada's first evidence-based pharmacogenetics testing service aimed at accurately matching an individual's genome to the selection and dosing of medication. This work is tied to the new Centre for Child and Adolescent Mental Health. Today, Naomi is enjoying college life and is encouraged by Dr. Bousman's new research.

GRAND CHALLENGE 4

Ending the Diagnostic Odyssey

Rapidly deciphering and addressing the genetic origins
of disease to optimize tailored treatment.



Patients with undiagnosed disease often face a long diagnostic odyssey that causes significant emotional challenges for children and families, and substantial financial burdens to families and the health care system. Precision Health is driven by the belief that a deep knowledge of individuals and populations allows researchers to drive prevention, early diagnosis and better therapies. Yet despite our significant efforts, many patients remain inadequately or even undiagnosed, resulting in a trial-and-error-based approach to treatment options.

These unresolved cases are a function of two fundamental, inter-related shortfalls in our understanding of disease. Firstly, efforts to identify disease-causing gene mutations have focused almost exclusively on the gene sequence itself, but not its regulatory elements. Indeed, some 90% of genetic diseases are not the result of a mutation in a protein-coding sequence element, but in non-coding stretches of DNA that determine when and where a gene is switched on or off. Secondly, genetic mutations in any given protein commonly manifest in a wide spectrum of disease. As such, it is a challenge to diagnose these diseases as causally related. Inter-individual variation in gene regulatory DNA elements holds the key to this conundrum as it determines how severely a dysfunctional gene impacts health and wellbeing.

Ultimately, improving the health and wellness of patients with undiagnosed diseases requires innovative, multidisciplinary research programs. Diverse teams are essential to major advances in our understanding of early development and disease origin, and the timely translation of novel diagnostic and therapeutic approaches into clinical practice.

This mature program is establishing a basic science – clinical interface where advances built on fundamental research address unmet needs in prevention, patient diagnosis and ultimately treatment. This will be implemented through a precision health approach that integrates world-class biomedical sciences and patient-driven research.

Ending the Diagnostic Odyssey

Rapidly deciphering and addressing the genetic origins of disease to optimize tailored treatments.

Key areas of investigation

Modeling rare diseases. Individually rare, but collectively common, so called “rare diseases” represent a major proportion of the burden of disease in children. Developing effective treatments depends on understanding specific mechanisms of disease. Our MORPH program integrates medical genetics and developmental biology to model and investigate the mechanisms underlying genetic disease in individual patients with unknown genetic diseases.

Rare disease genomics. We partner with centres worldwide and lead initiatives within Canada to discover the genetic causes of rare disease. We are playing key roles in the international effort to reduce the number of children with unknown genetic disease from 50% of cases to zero. To this end, our KidOmics program combines cutting edge genomics with clinical informatics and patient imaging data to study the genetics of rare disease.

Unravelling the developmental origins of disease. Children with the same mutation often manifest a wide spectrum of disease. Understanding why this happens is important for precision medicine because genomic testing is often used to diagnose and predict disease outcomes. Frequently, however, we are unable to detect mutations in any of the disease-causing genes themselves, pointing to

mutations in genomic sequences that regulate these genes. To date, we know very little about the ‘regulome’ of the genome. To address this knowledge gap, we are integrating whole genome sequencing with analysis of the way DNA is packaged and interpreted (epigenomics and chromatin organization), developmental biology, and advanced imaging to investigate the developmental origins of disease in children.

Organoids for all. Understanding the cellular and molecular basis of disease and finding drugs to treat genetic diseases are extraordinarily difficult because of the myriad ways in which gene mutations can disrupt normal development and physiology. Recent advances in cell culture models allow recapitulation of some aspects of organ development in vitro, producing simplified versions of organs known as ‘organoids’. These novel methods will hugely accelerate research into developmental origins of disease. They can also help overcome the problem of finding an appropriate drug – as we are able to screen drug effects on cells cultured from patients with a genetic disease. We are developing organoid culture capacities for various organ systems (brain, heart, placenta, liver, gut), applying them to screen treatments for diseases such as epilepsy, and investigating how specific mutations disrupt normal function.

DID YOU KNOW

that nearly half of all children with a genetic disease never receive a definitive diagnosis?

While most genetic diseases are rare, they are collectively common, affecting 5% of all births and accounting for as much as a third of health care costs for children. A diagnosis is the key to treatment. It is also critical for children and families to access resources and support.



Madden Garraway was 2 years old when he suddenly became very ill. Dr. Micheil Innes, MD, and his team of clinical scientists sequenced Madden’s DNA and discovered a rare, fatal immune disorder. With the care and expertise of the Alberta Children’s Hospital blood and marrow transplant (BMT) team, Madden is happy, healthy and cured of his illness.



This grand challenge is applying advanced genetic, epigenetic, genomic, and other high-throughput technologies to decipher the molecular and cellular basis of normal development and childhood genetic disorders. Building on our diverse expertise, the overarching goal is a centre of excellence to apply precision medicine to genetic diseases of childhood. This is achieved through cutting edge research using model organisms, advanced cell culture methods, high-level imaging, and bioinformatics. Researchers are leveraging several intercalated initiatives, notably KidOmics and Model Organism Research for Pediatric Health (MORPH), to use fundamental basic research to advance progress across the childhood disease spectrum by rapid translation of lab findings into clinical care.



GRAND CHALLENGE 5

Surviving and Thriving

Reducing the lifelong impact of childhood cancers by advancing precision therapies today and developing new treatments for tomorrow.



Cancer is a leading disease-related cause of death in children and adolescents. About one in 285 children is diagnosed with cancer before their 18th birthday. Although our ability to treat cancer has improved with multi-modality combination therapies, much work remains to be done to improve outcomes for children.

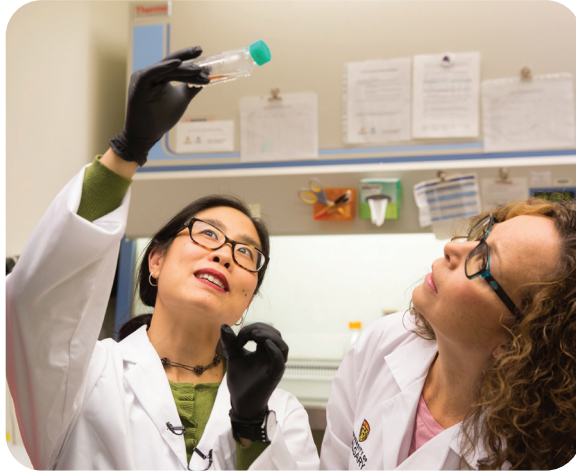
There are many different types of cancer, and they differ from one another. For some cancers, long term survival exceeds 90%. For others the prognosis is grim, with fewer than 1 in 10 surviving more than 5 years. Goals in this field are: to improve the survival of children for whom there is no known therapy, and to provide options for children whose cancers resist current therapies. This research resides at the intersection of fundamental cancer biology, precision oncology, medicinal chemistry, and experimental therapeutics.

Some children whose treatments are successful experience serious adverse effects. For some, the aftereffects are physical and include the development of additional cancers or other debilitating chronic medical conditions. Survivors are also impacted by cognitive, psychological, and social sequelae related to their disease, treatments, and experience. Thus, our research focuses on developing more effective and less toxic therapies, new tools for assessment and interventions focused on survivor health and well-being.

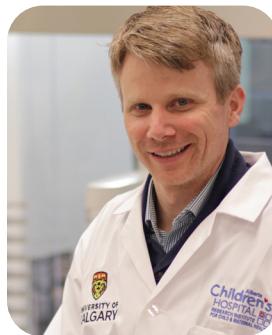
Improving the health and wellness of children and adolescents with cancer requires innovative, multidisciplinary research spanning basic science to clinical research and involving collaborative researchers and expert clinicians. It also requires advance molecular profiling, well-annotated clinical samples, robust experimental models of disease, synthetic biology and cellular engineering tools, detailed longitudinal patient data collection, and the ability to store and integrate complex data. Together, leveraging those resources, we will generate new knowledge and focus that knowledge on improving diagnosis, treatment, and care.

Surviving & Thriving

Reducing the lifelong impact of childhood cancers by advancing precision therapies today and developing new treatments for tomorrow.



This grand challenge aims to improve outcomes for children and adolescents with cancer by understanding the cellular and molecular basis for childhood cancer initiation and progression; matching potential treatments to patients using a precision molecular approach; innovating and testing new immune-based therapies; and measuring comprehensive cancer outcomes.



Key areas of investigation

Understanding the cellular and molecular basis of childhood cancer. Modern molecular profiling has revealed that childhood cancers frequently harbor DNA, RNA, and protein alterations distinct from alterations seen in adult cancers. Although the cataloguing of such differences is useful for classification, diagnosis, and prognostication, there is still a fundamental gap in our knowledge of what alterations do to drive cancer growth. In this area, we aim to understand the abnormal functions of cancer genes to determine which changes constitute new targets for therapy. We will also examine how multiple abnormalities work together within the cancer cells and how they influence neighboring cells (blood vessels and stromal cells), as well as inflammatory cells to sustain the cancer microenvironment.

Tailoring cancer therapy: The right treatments for the right patients. Cancer therapy involves a range of treatment modalities – from surgery to radiation to cytotoxic chemotherapy to targeted small molecules to cellular therapy. Currently, treatment is assigned according to broad disease types, with some cancers responding and others not. We seek to identify the alterations in childhood cancers that constitute novel targets. Our goal is also to determine whether matching certain drugs or drug combinations to cancers that carry specific molecular profiles can improve responses and decrease adverse effects for children.

Developing and testing the therapies of tomorrow: Harnessing the immune system.

One promising approach, still in its infancy, is engineering a patient's own immune system to seek out and attack the malignant cells. In this area, we are embarking on an ambitious initiative to develop and test new immune-based therapies for cancer patients. This focused program seeks to: identify novel targets for engineered T-cell therapies and vaccine therapies for high-fatality cancers; develop and test novel immune-based therapies in immune-competent preclinical models; elucidate fundamental interactions between engineered immune cells and host biology; and create a pipeline for clinical trials.

Measuring and improving long-term outcomes.

Survival is a key metric. As survival rates improve, our work also seeks to measure and improve upon the well-being of child survivors. This includes comprehensive and long-term follow-up beyond the 5-year mark to understand therapeutic efficacy and late-arising effects. Detailed, longitudinal, cancer cohort data will enable more robust biomarker development, improved risk stratification for late effects, and potential interventions or treatment modifications so that children can survive and thrive.

DID YOU KNOW

that up to 90% of children treated for cancer experience severe or life-threatening complications to their health?

Undergoing current cancer treatments during vulnerable stages of development often leave children with serious long-term side effects, including organ failure, hearing and vision loss, learning impairment, infertility and even secondary cancers. Dr. Faisal Khan, PhD, is leading the development of a prediction tool to reduce the risk of graft versus host



disease for children and adolescents requiring bone marrow transplants. A genetic test finds optimal matches between donors and recipients, and also identifies children who will require additional care post-transplant.



Precision Child Health

Precision child health is an overall approach that seeks to understand differences among children or populations of children to individualize diagnoses, treatments and interventions. All grand challenges are guided by precision health principles, whether it is genotyping tumours to individualize cancer treatments, developing organoids to screen drugs to treat a rare disease in a specific patient, or stratifying a community by relevant social determinants of health to pinpoint the most appropriate interventions in each setting. Precision health brings a focus to relevant differences among individuals and within populations. It is the opposite of “one-size-fits-all” and represents a transformative shift in child health and wellness world-wide.

Within this precision health framework, we have two cross-cutting approaches:

1. Harnessing big data for optimal child outcomes
2. Transforming health care for children and families

Harnessing big data for optimal child outcomes

In an increasingly data-driven world, data science and artificial intelligence are key tools for converting big data into tangible benefits. Health care is no exception. The wide-spread availability of diagnostic tools and techniques has dramatically increased the amount of medical data for single patients and populations. Deep phenotyping data, including genetics, metabolomics, imaging, and clinical assessments, is now available for many healthy and sick children. However, we are not yet making use of this wealth of information in medicine.

Enormous amounts of data are collected every day in the health care system. At the same time, data science and machine learning methods are increasingly important in all facets of our life. For data science and artificial intelligence to reach their true potential for children and their families, we need to find solutions for legal, ethical, and privacy challenges.

This cross-cutting approach will support the development and implementation of cutting-edge data science methods, including advanced big data machine learning and statistical methods, and foster high-end computational resources to enable precision health for children. Our researchers will collect, analyze, and integrate data from multiple sources to improve prevention, diagnosis, and treatment of pediatric diseases in direct collaboration with clinicians. This team will also enable innovative research to address gaps in knowledge for pediatric diseases.

Developing and evaluating dedicated data science and machine learning methods to mine big data is a grand challenge that will accelerate precision medicine for children. Harnessing big data will improve disease prevention, diagnosis, and treatment for children in Canada and beyond.

Demonstration Projects

Development of computer-aided diagnosis systems using multiomics data. Diagnosing diseases with high sensitivity and specificity remains a considerable challenge, and this is especially true for rare diseases. Advanced data science and machine learning methods offer the potential to support the diagnosis of diseases based on historical datasets of patients. Therefore, our developing and evaluating advanced diagnosis support systems using multiomics data is a major research aim. Since machine learning models are often considered ‘black boxes’, developing explainable artificial intelligence models is especially relevant in this context.

Identify disease-specific complex patterns in deep clinical and genomic phenotyping data. Advanced data science and machine learning methods play a major role in combining and analyzing complex multi-dimensional and multi-modal data sources, thereby overcoming traditional silos in medicine and connecting many specialties. Our

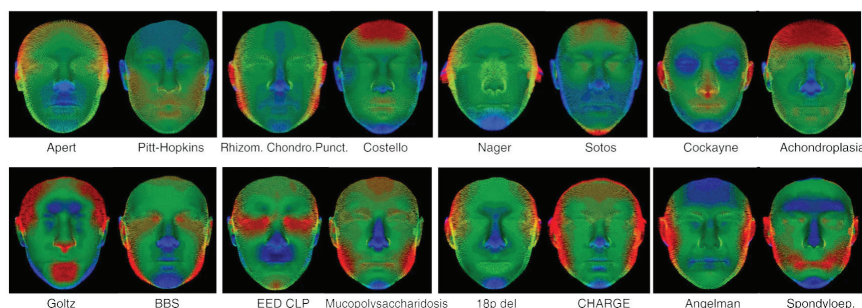
researchers will develop and apply dedicated data science and artificial intelligence solutions to analyze disease patterns in historical datasets. They will also incorporate future data acquired from children with various health statuses. This has huge potential to identify novel biomarkers and improve our systemic understanding of diseases.

Implementation of data-driven early warning systems to prevent diseases.

Enormous health care data is collected for most children in Canada and stored in a systematic and accessible way. Mining and analyzing this historical data offers the potential to prevent diseases at an early stage by developing dedicated warning systems to alert pediatricians based on individual patient data entered into the electronic health records. Alberta is the optimal place to develop such warning systems due to AHS’ centralized system.

DID YOU KNOW

that most children with rare genetic diseases spend years undergoing medical tests and waiting for a diagnosis?



To reduce the exhausting process that takes such a toll on children and families, Dr. Benedikt Hallgrímsson, PhD and teams from the University of California San Francisco and the University of Colorado have built a database of 3D facial images to identify most of today's genetic syndromes and speed up diagnoses. This transformational prototype will be particularly useful for telemedicine and in low-income countries where genetic testing is not available.

Improve algorithms for the analysis of pediatric imaging. Medical images are by far the largest data source in health care today. Due to the high volume and complexity, analyzing medical imaging data is challenging and time-consuming for radiologists and other clinical experts. Developing dedicated image processing and analysis methods, including machine learning models, is especially helpful to alleviate the burden of routine image analysis for physicians, allowing them to focus on complex patients and doctor-patient relationships. They also offer the potential to improve our understanding of diseases through clinical research. Advanced analytics driven by machine learning with medical imaging and other clinical data is expected to become a key tool for delivering precision medicine.

Advancing precision medicine through personalized treatment support by analyzing big data. For many diseases, we have multiple drugs and treatment approaches. Vast amounts of historical data are available from pediatric

patients treated with different drugs and treatment approaches, including treatment outcomes. Mining these datasets offers the potential to select case-specific treatments based on individually-acquired data including imaging, genetics, metabolomics, and clinical assessments.

Develop methods for the responsible and ethical mining of historical health care datasets. A special challenge when training machine learning models and especially deep learning models based on medical data relates to the fact that the training relies on highly private and sensitive patient data. The data used for training machine learning models can include: medical images such as x-rays or magnetic resonance imaging, metadata from electronic health records, clinical assessments, laboratory results, and other variables such as age, sex, and medical history. For this reason, it is imperative we develop dedicated methods to help overcome legal and ethical barriers to share datasets across institutions while protecting patient privacy.

Transforming health care for children and families

Alberta's children deserve comprehensive medical care tailored to their needs (Built4Kids). And yet, there is a lack of evidence specific to children, including limited understanding of disease mechanisms, uncertainty of medication dosing and interactions, few high-level interventional trials and inadequate health care policies for children.

This grand challenge will enable the generation of new knowledge into childhood diseases and translate evidence into action with our partners at AHS to improve outcomes for children and families. Researchers will build and empower multidisciplinary and multi-sectoral collaborations within AHS hospitals, clinics and community settings. We will contribute to the growth of an evolving health care system that engages children, families and health care practitioners- one in which research is embedded in care and connected to advancing evidence-based improvements in health care, health policy, and deeply integrated into Alberta's health system.

Demonstration Projects

Every Second Counts - Life Saving

Care. Trauma, infection, cancer and congenital abnormalities pose significant threats to the lives of Alberta children from birth through adolescence. Integrated acute-care clinical teams (emergency, neonatal- and pediatric- intensive care, neuro-critical care), precision diagnostics and evidence-based interventions significantly alter clinical trajectories during life-threatening illness. Multi-sectoral policy activities enhance our prevention of disease and injury through immunizations and building safe environments. Training our next generation (KidSIM and real-time) and advancing practice for our active clinicians through quality and patient safety initiatives at AHS will optimize patient outcomes when every second counts.

Fighting the Fire – Childhood inflammatory

diseases. Inflammation is a central feature of disease in children. Its effects, both acute and chronic, result in dysfunction across organ systems, impacting the quality and trajectory of life for millions of children globally. Building and empowering multidisciplinary collaborations we will expand and enhance biorepositories (ACHRI BioCore) and comprehensive clinical databases. Harnessing the power of a systems biology/precision medicine approach we will generate new knowledge and translate evidence into action, improving diagnostics and clinical interventions for children with inflammatory- and immune- mediated illnesses such as the COVID-related Multisystem Inflammatory

Syndrome of Childhood (MIS-C), Hemolytic Uremic Syndrome (HUS), Kawasaki, Crohn's & Colitis, neuro-vasculitis diseases and post-traumatic inflammation.

Stronger Together – Investing in our stakeholder teams.

Enhanced research partnerships with nursing and allied health (respiratory and orthopedic therapy, pharmacy, social work, psychology, child life) at AHS are essential to expand our cross-cutting impact on clinical care. Integrating our patients and families (ACH Family and Child Resource Centre, KidsCan) and cultural leaders (Indigenous and new Canadians) as key stakeholders in clinical research programs will establish innovative, family-centred research partnerships, ensuring what's important to children and families is important to us. Together, we are all building a better future for Alberta's children.

Evidence to Action – Driving clinical trials and translation to practice.

Interventional clinical trials generate high-level evidence to answer clinically relevant questions for optimal care. Supported by strong institute infrastructure, our teams will lead local and nationally (tri-council) funded clinical trials, generating new knowledge and transforming pediatric practice. Strong partnerships with quality improvement teams, educators and KT leaders will translate evidence onto the front lines and inform health systems policies.

Fostering the creation and implementation of evidence for childhood diseases will result in optimal child health outcomes. Building on our strengths and expanding our partnerships with our provincial health system, our care teams and state-of-the-art technologies, together we will build a bright future for the children of Alberta.

New models of child health care – harnessing technology for pediatric practice. Innovation through design. We will build and strengthen partnerships with biotech/medical engineering experts across campus, and establish industry partnerships for next-generation technologies. This will improve our capacity for diagnostics (point of care tests, bedside imaging), interventions and daily care for our most vulnerable populations, including children with medical complexity (CMC). Investment in robotics for

procedures and patient-provider interactions (Medicine and Engineering Designing Intelligence - MEDI) will transform how we provide care. We will pioneer high-quality, timely access to care through remote IT platforms.

Fostering the creation and implementation of evidence for childhood diseases will result in optimal child health outcomes. Building on our strengths and expanding our partnerships within AHS, our care teams and state-of-the-art technologies, together we will build a bright future for the children of Alberta.

DID YOU KNOW

that arthritis is one of the most common childhood diseases diagnosed in Canada?

Approximately three in 1,000 children live with arthritis, a condition that can too often be devastating. Bob required long-term steroid use to control his disease, leaving him with weight gain, bone loss, high blood pressure, diabetes and mobility issues that required the use of a wheelchair. Dr. Susa Benseler, MD, PhD, and an international network of researchers in childhood arthritis found

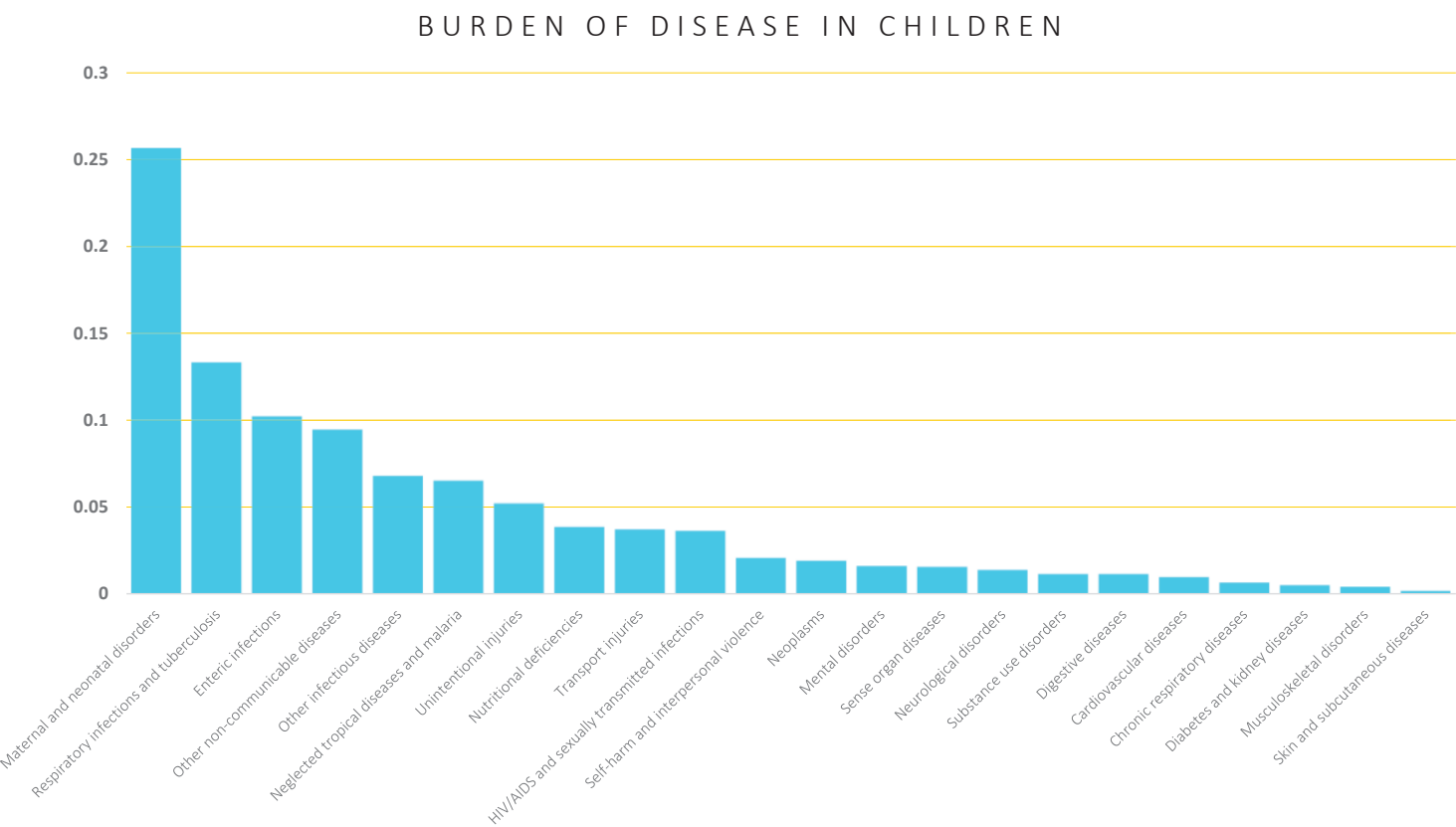


that he had elevated levels of IL-1b, a pro-inflammatory cytokine. With a precision medicine approach, Bob's treatment has been tailored to his biological profile. He is in remission, has recovered from the side effects of the steroids and is fully mobile.



Building the Evidence Base

We have identified and prioritized grand challenges to meet the needs of our communities, enable innovate cross-cutting partnerships and build on our research strengths. Our stakeholder consultation process yielded diverse ideas for grand challenges that coalesce into 45 distinct projects (Child Health and Wellness Strategy, Appendix pages 6-11). To ascertain the overlap between these grand challenges and Global Burden of Disease (GBD) categories, we scored each challenge by its intersection with the 22 level 2 categories in the GBD study for 2017.



These categories are shown in Figure 2, ranked by disease burden. We used the average of childhood mortality and disability-adjusted life years, expressed as proportions of the total burden. For example, maternal and neonatal disorders account for roughly 25% of the total disease burden by this measure.

Figure 2: Burden of childhood disease.
Source: Global Burden of Disease
<http://www.healthdata.org/gbd>

To help guide grand challenge areas, we determined the intersection of our research strengths, the strength and needs of our community and the importance of distinct child health areas. Our research strength is quantified as described in the CHW strategy, as the summary variable (PC1) that captures all available measures of productivity and impact. The ambitions and needs of our community were quantified by the intersections between the GBD level 2 categories and the grand challenges articulated through our year-long consultation process.

Many grand challenges overlap with multiple GBD categories and were scored accordingly. Figure 3 shows the results of this analysis. Here, GBD categories are plotted by disease burden and research strength while the points are colored by their intersection with the CHW grand challenges.

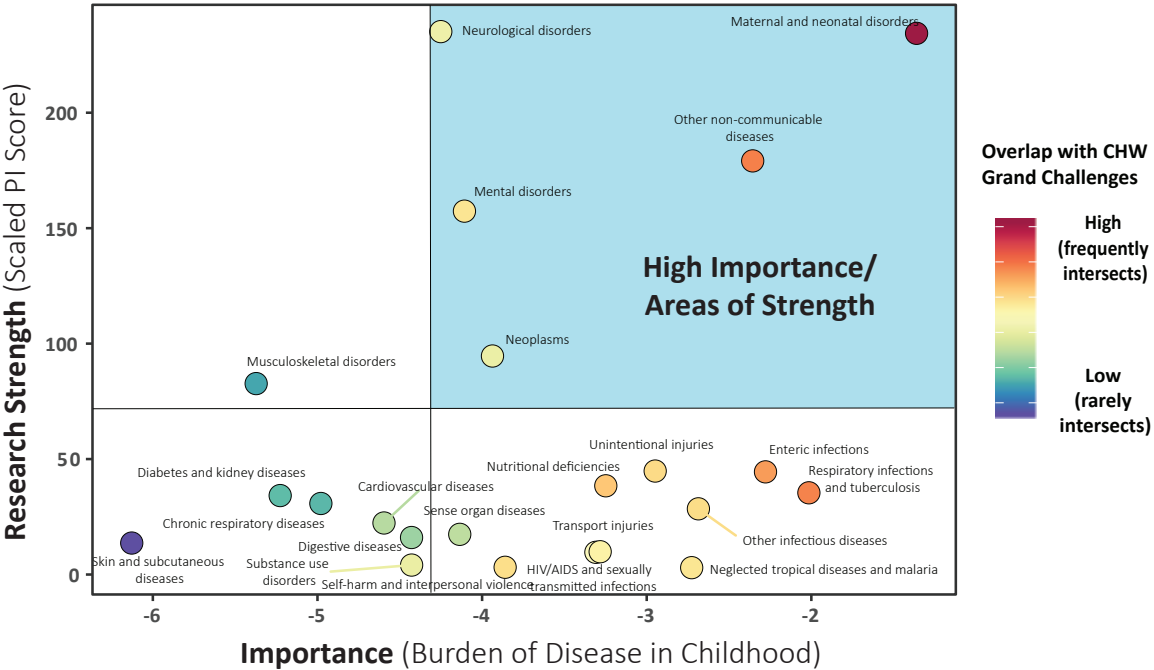
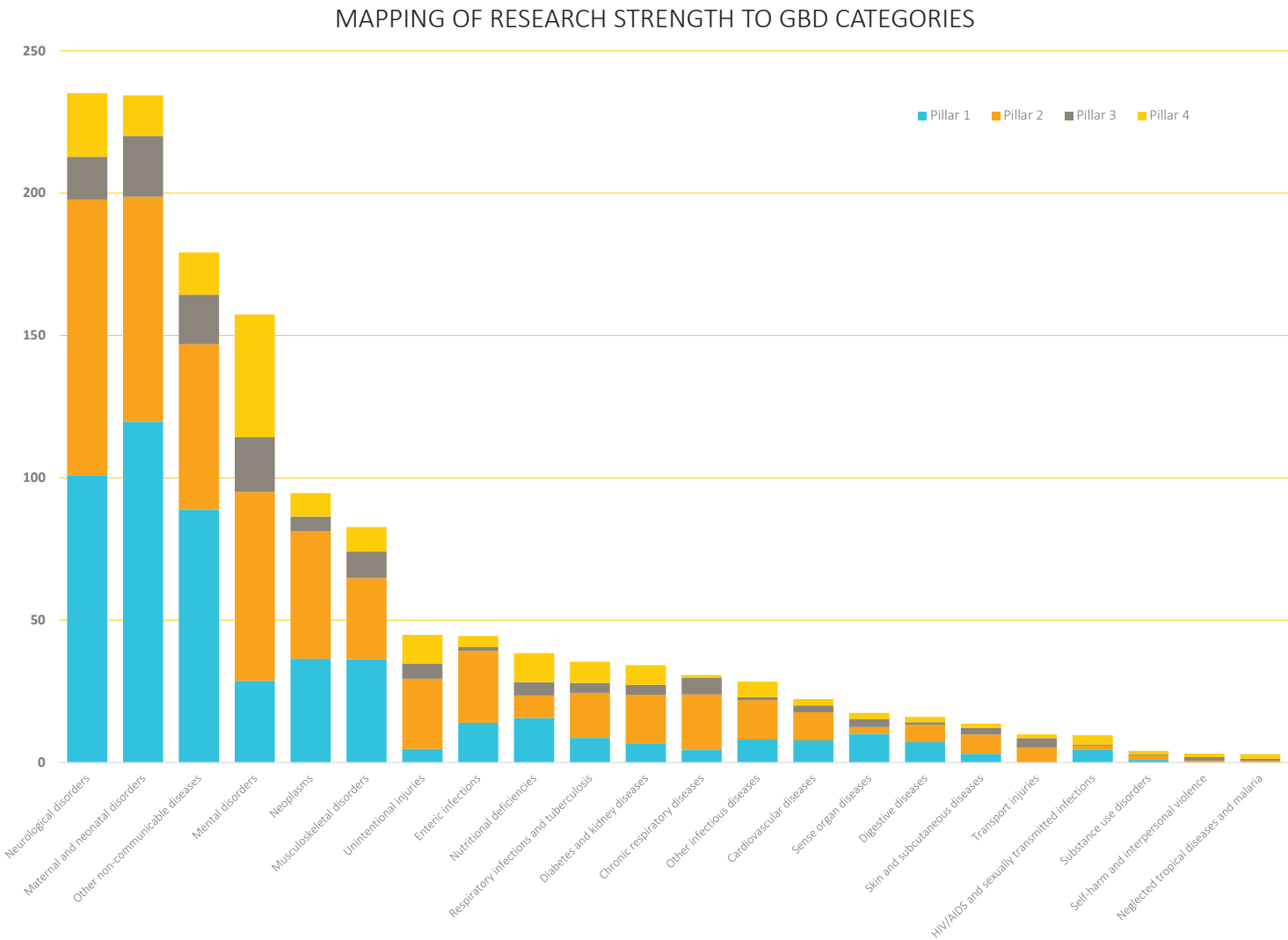


Figure 3: The intersection of importance and research strength. The X axis plots the GBD burden (on a log scale) for child health while the Y axis plots research strength measured as the number of PIs scaled by research impact and productivity. On this scale, a PI with a research score of 0, counts as 1, while a PI with a research score of 10 counts as 10. The research score is the first PC of publications per year, citations per year, first and senior authorships and journal impact factors.

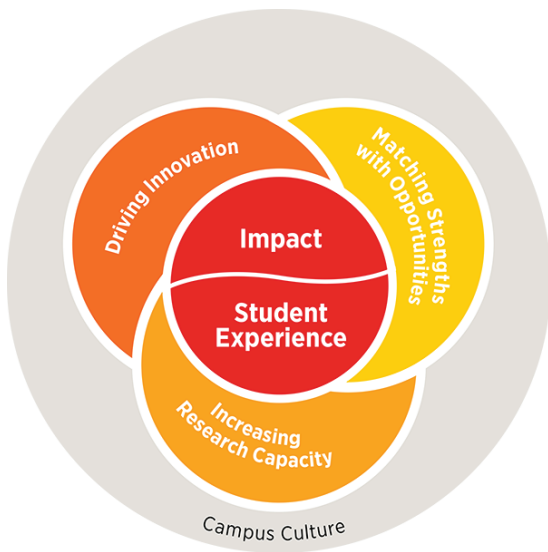
To further examine how areas of research strength coincide with areas of importance for child health, we scored 310 CHW investigators by CIHR pillar. Most of these data were self-reported from ACHRI forms, but some are inferred from publication histories. Many investigators work in more than one pillar and were scored accordingly.

Figure 4 illustrates the results of this analysis and demonstrates that CHW researchers are investigating virtually all GBD disease categories, with research ranging from molecular mechanisms to social determinants of health.



A limitation: CIHR pillars and GBD categories represent a disease-focused lens. This analytical approach does not substantively address wellness. However, the social determinants of health permeate the global burden of disease, impacting every one of these 22 categories. As such, it is reassuring that CHW investigators are pursuing understanding of these disease-issues through all four pillars of CIHR. That being said, this is a limitation we considered when formulating our overarching CHW strategy and our identified grand challenges. We will continue to address this limitation in consultation with researchers.

Figure 4: Research strength by GBD category broken down by CIHR Pillar.



The University of Calgary is one of Canada’s finest, most innovative universities founded upon and continuously inspired by our entrepreneurial, hard-working and deeply caring community.

The 2017-2022 University of Calgary Strategic Research Plan “Eyes High” identified six research themes that match Strengths with Opportunities, Increase Research Capacity, and Drive Innovation:

- Energy Innovations for Today and Tomorrow
- Engineering Solutions for Health: Biomedical Engineering
- Brain and Mental Health
- Infections, Inflammation and Chronic Diseases in the Changing Environment
- New Earth-Space Technologies
- Human Dynamics in a Changing World: Smart and Secure Cities, Societies, and Culture

We have established an innovative, interdisciplinary community of Child Health and Wellness Scholars across campus and far beyond. Together we will conduct cutting edge research and rapidly translate new knowledge into innovation, disease prevention, health promotion and transformational care initiatives to achieve optimal child and family outcomes in Alberta and beyond. We will embrace and foster partnerships with child and family health care providers of Alberta Health Services as well as child and youth serving organizations in our community - unified in our shared commitment to excellence, compassion and equality. Child Health and Wellness not only aligns well with the six Strategic Research Themes, it will build on those themes to foster unique cross-cutting efforts to match strengths with opportunities, increase research capacity and drive innovation at the University of Calgary.

Learn more about the University of Calgary's
Alberta Children's Hospital Research Institute at
research4kids.ucalgary.ca

