Genome Canada – Strategic Research Themes

Child Health Genomics: An Investment in Canada's Future

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Executive Summary

Many of the most complex and devastating diseases of childhood have a strong genetic basis. The Canadian genomics community is poised to make substantial contributions in the understanding, prediction, and treatment of these illnesses, enabling better long term health outcomes for children in five key areas of impact:

1. Childhood cancer
2. Neurodevelopmental diseases (autism, mental retardation, schizophrenia, ADHD)
3. Auto-immune, inflammatory and allergic disease (type 1 diabetes, asthma)
4. Obesity and type 2 diabetes
5. Birth defects

New genomic technologies are changing the way we analyze diseases from one gene and one patient at a time, to population-wide analysis of entire genomes. These evolving tools are transforming how we do genetics and genomics, and have the potential to dramatically impact our understanding of a broad spectrum of diseases. While Canada has made significant investments in health genomics, the vast majority of these efforts have been focused on adult diseases. The time has come to deploy Canada's considerable health genomics capacity to address the issues associated with disease in children and to identify preventive interventions aimed at avoiding/delaying the onset of many common adult diseases.

This world-class health genomics capacity has been developed through significant investments by Genome Canada, the regional genome centres and Canada's paediatric centres. Other core Canadian assets of relevance include: A) a national child research community that features an unparalleled degree of networking and cooperation (with all 17 of Canada's paediatric centres integrated into a common research network), B) unique cohorts and distinct founder populations, and C) strengths in related fields including stem cell research, developmental biology, reproductive technologies, cancer, mental illness and metabolic disorders. In addition, Canada has world leading strengths in the legal and ethical components of GE^{3}LS research which can be deployed to address the significant GE^{3}LS challenges associated with child health genomics research, such as the need for informed consent and the shifting nature of this consent as children grow older. Combined, these assets form the foundation for a distinct Canadian competitive advantage in the field of child health genomics.

The economic and social costs of childhood disease are enormous. The costs of treating Canadian children afflicted with the diseases targeted in the five areas of impact run into the billions of dollars annually, not taking into account a myriad of additional factors such as the personal costs to families dealing with a sick child. In addition, with so many of the serious diseases of adulthood having their origin in childhood and youth, the potential benefits of an investment in child health genomics are broad indeed. Socio-economic benefits of a Canadian investment in child health genomics include:

- Improved quality of life for our children and families
- Reduced health costs through early detection and intervention
- Improved long-term health outcomes, with children transitioning to healthy and productive adults
- Potential commercial impacts, including diagnostics, genetic screening, and the development of new therapeutics for childhood as well as adult disorders.

Even incremental contributions to realizing improved health outcomes will deliver substantial social and economic benefits. When the funding request of $100 million for Canadian child health genomics research is compared to the short and long term benefits, it clearly delivers significant returns on investment. However, it must not be forgotten that it is fundamentally the lives of children that are at issue. In the words of a distinguished contributor to the development of this position paper who works in the field of childhood cancer: "there is a unique agony, a wrongness to the death of a child."

The importance of the health of Canadian children cannot be overemphasized. In a literal sense, the future of Canada depends on their well being. The medical community and the Government of Canada have made child health a national priority. The field of child health genomics represents a unique opportunity to deploy Canadian strengths in genomics and child health to make a profound and lasting contribution to the health of our children, and to children around the world.

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Three supporting documents have been provided with this position paper:

Supporting Document A — **Canadian Child Health Research Institutions and their Current Involvement in Child Health Genomics**

Supporting Document B — **Participating Stakeholders in the Development of the Child Health Genomics Position Paper**

Supporting Document C — **Compendium of Letters of Support from:**

- The Royal College of Physicians and Surgeons of Canada
- The Canadian Cancer Society
- Stem Cell Network
- Canadian Cystic Fibrosis Foundation
- Michael Smith Foundation for Health Research
- Juvenile Diabetes Research Foundation
- Spina Bifida and Hydrocephalus Association of Canada
- Allergen (Allergy, Genes and Environment Network)
- Labco Diagnostics (one of the largest diagnostics companies in Europe, which has expressed an interest in expanding into Canada)
- Dr. Simon Davidson (Chair of the Child and Youth Advisory Committee, Mental Health Commission of Canada, among other positions)
- Dr. Thomas J. Hudson (President and Scientific Director, Ontario Institute for Cancer Research)
- Canadian Child and Youth Health Coalition
- Council for Canadian Child Health Research, on behalf of its 17 member Child Health Research Institutions.
- Genome Quebec
- BIOTECanada

A. Introduction

"We all need to work together to improve the health of Canada's children and youth." [1]

This recent statement from Tony Clement, Minister of Health captures a fundamental truth. The continued success of our society is dependent on the health of our children and their successful transition to robust and productive adults. With the health of children clearly identified as a priority by the Canadian public, politicians and the medical community, the time is *now* to make child health a strategic priority in the Canadian genomics community.

The considerable investments made to date by Genome Canada in developing Canada's genomics capacity have set the stage for major new initiatives in child health genomics. Rapid advances in the field of genomics and related disciplines have unlocked extremely promising areas of pursuit in children's health. Canada has significant strengths in all aspects of genome research and a strong cadre of child health researchers ready to exploit these resources to deliver world-leading outcomes.

This position paper on *Child Health Genomics* looks at the critical role that genomics research can play in predicting, identifying and enabling better long term health outcomes for children in five key areas of impact:

1. Childhood cancer
2. Neurodevelopmental Diseases
3. Auto-immune, inflammatory and allergic disease (type 1 diabetes, asthma)
4. Obesity and Type 2 diabetes
5. Birth defects

Working Definition of Child Health Genomics

For this Strategic Research Theme (SRT) 'child health genomics' denotes the continuum from prenatal stages through infancy, childhood and youth, with outcomes impacting on adult health and productivity. It includes the study of single gene diseases, gene-gene and gene-environmental interactions as they impact on disease prevalence and outcomes.

B. The Relevance of Genomics to Child Health

Many of the most complex and devastating childhood illnesses have a strong genetic involvement. For example:

- Childhood cancers often involve both germline and somatic mutations with specific chromosomal/molecular signatures.
- There is increasing evidence for genetic involvement in virtually all psychiatric disorders of both childhood and adulthood.
- Genetic and epigenetic changes underlie congenital anomalies, that are responsible for 38% of perinatal and childhood mortality and morbidity in Canada.[2]
- Gene-environment interaction is responsible for the growing obesity epidemic in North America which may be, in part, programmed during fetal life by maternal factors, resulting in early childhood obesity that has lifelong health, social and economic impacts.
- Immune system disorders including type 1 diabetes, asthma, and allergies all have strong genetic components.

Historically, genetic and genomic techniques in paediatrics have been most intensively applied to the study of single gene disorders. New technologies in genomics are providing us with the ability to obtain vast amounts of data which is revolutionizing the potential for unravelling the complexity of multi-gene as well as complex diseases, with direct and significant impacts on child and adult health across Canada.

Differences in Physiology

Child health genomics must be regarded as a distinct form of health genomics, as the physiology of children is inherently different than that of adults. Attempting to treat childhood diseases with therapies designed for adults is not straightforward, and can trigger dangerous and unexpected side effects. As such, the genomic aspects of childhood illness and disease must be addressed as a discrete endeavour within the overall contribution of genomics to the health of Canadians. Nevertheless, work in child health genomics has consistently led to discoveries with relevance to related adult conditions, multiplying the benefits of this work.

C. Canada's Commitment to Child Health

A Call to Action

Canada is among the most prosperous nations in the world. We boast a universally accessible health care system, and a large number of generous social programs, many of which were conceived to help children and youth stay healthy. Yet, Canada's standing when it comes to the health and wellness of children and youth is remarkably poor. Among 29 industrialized nations, Canada ranks:

- 22nd when it comes to preventable childhood injuries and deaths
- 27th in terms of the absence of childhood obesity
- 21st in child well-being, including mental health[3]

Overall, Canada only ranked 12th out of 21 wealthy countries in the United Nations' rankings of child well-being.[4] Health outcomes are particularly poor in vulnerable populations such as our First Nations.

We Can Do Better

A recent report[5] by Dr. K. Kellie Leitch to the Minister of Health highlighted three major areas of focus to improve child health. Genomics will play a critical role in addressing two of these areas: obesity and healthy lifestyles, and mental health and chronic illness.

Improving child health through genomics directly aligns with the goals of the National Science and Technology strategy, focusing our S&T investment in the high priority area of *health and related life sciences and technologies,* which is identified as one of four areas of focus for investment.[6]

Canadian health organizations including the Canadian Medical Association, the Canadian Paediatric Society and the College of Family Physicians of Canada, have already articulated a clear five-year goal: *to make Canada one of the top five nations with the healthiest children.*[7] A research initiative in Child Health Genomics can be a critical tool toward achieving this goal.

D. The Canadian Opportunity in Child Health Genomics

Canada is well placed to have a major impact on child health through genomics due to its strengths in genomics, proteomics, systems biology, fundamental developmental biology in model organisms and access to clinical material.

State of the Science

There have been great strides in using positional cloning to successfully identify the underlying basis of many Mendelian disorders of children. The severity of even these disorders, however, is greatly affected by genetic modifiers and gene-environment interactions. The molecular pathogenesis of many more complex disorders remains unexplained due to the often complex genetic, epigenetic and environmental interactions involved in their etiology. However, there is reason for optimism. New genomic technologies – single nucleotide polymorphism (SNP) and copy number variant (CNV) arrays, comparative genomic hybridization (CGH) arrays, and next generation sequencing – increasingly allow genome-wide analyses at a reasonable cost. They are changing the way we analyze diseases from one gene and one patient at a time, to population-wide analysis of entire genomes. Combined with genome-wide epigenetic analysis and new tools for detailed phenotypic stratification, the outlook for understanding and treating complex diseases is rapidly improving.

While Canada has made significant investments in health genomics, the vast majority of these efforts have been focused on adult diseases. This is mirrored in the international context. For example, the International Cancer Genome Consortium (ICGC) has been launched to perform comprehensive genomics studies of over 50 cancer subtypes. Of the first 21 projects, all but one target adult cancers. Clearly there is a need for genomic research directed specifically at child health issues.

Canadian Strengths in Child Health Genomics

Given the unique combination of assets outlined below, combined with the rapidly evolving genomic technologies, it is clear that Canada has unique opportunities to make a globally significant contribution in the field of child health genomics.

Extensive Canadian Health Genomics Infrastructure

Canada has made significant investments in health-related genomics infrastructure through Genome Canada, the regional genome centres and our country's unmatched national network of paediatric centres. Table 1 provides an overview of current and near-term capabilities. To date, however, these platforms have been applied only to a limited extent to childhood diseases. Incremental investment would allow advances in the lab to be translated into knowledge that would have direct application for children.

Canada's Health Genomics Researchers

Canadian genomics researchers and consortia are:

- Developing genomic platforms at the cutting edge of new technologies (Table 2)
- Leading the analysis of the genetic basis of diseases like autism and diabetes, and are active in international child health genomics projects and processes (Table 3)
- Canadian regional genome centres (BC, Ontario, Quebec) are acquiring and implementing the newest sequencing technologies (Solexa, 454, etc) and CGH methodologies.

Canada's Capacity for Child Health Research

Canada's child health research community runs both deep and broad. There are 15 primary research institutions across Canada, with close to 1500 researchers, with total funding of $420 million. Approximately 270 workers have a child genomics focus (see Supporting Document A). Some of Canada's best-known and most active human genomics researchers undertake their research in Child Health Research Institutes (e.g., Michael Hayden, BC Women's and Children's; Steve Scherer, SickKids: Guy Rouleau, Ste Justine; and Constantin Polychronakos, Montreal Children's), ensuring a wealth of expertise to take on this expanded initiative.

Collaborative Research Networks

The degree to which the Canadian child health research community is networked is unparalleled on the international stage. Unique to Canada, all 17 paediatric research hospitals are linked in a research coalition, the Maternal, Infant, Child and Youth Research Network (MICYRN).[8] MICYRN enables collaboration and the sharing of expertise, patient data and clinical material on a national scale and links with over 20 established discipline/disease-specific networks and working groups in Canada.

Canada's universal health coverage assures that virtually all children with significant chronic health problems are followed in centralized academic centres participating in these networks, a very significant advantage over other jurisdictions such as the U.S.A., where care is much more fragmented. In addition, a host of networks such as the Canadian molecular cytogenetics platform provide a national link between researchers, projects and research institutions.[9]

Unique Cohorts

Through MICYRN, a pan-Canadian collaboration linking databases for 13 existing pregnancy/birth cohort studies has been established. Three additional birth cohort studies - the Canadian Healthy Infant Longitudinal Development (CHILD) asthma and allergy birth cohort, the Integrated Research Network in Perinatology of Quebec and Eastern Ontario and the Interdisciplinary Team in Childhood Obesity - have recently been funded as the first components of the MICYRN birth cohort coalition. Together, these 16 existing independent cohort studies form the MICYRN birth cohort coalition that collectively represents over 79,000 mother-baby pairs, 47,000 of which were or are being studied prospectively and longitudinally up to five years of age. This innovative approach to linking existing pregnancy/birth cohort databases is an acknowledged Canadian strength, and provides a multitude of unique opportunities for world-leading child health genomics research.

Another distinct Canadian asset is our founder populations, including First Nations, French-Canadians and Newfoundlanders, all of which possess unique genomic traits, providing significant future opportunities.

Strengths in Related Fields

Canada has deep expertise in a number of related fields, including stem cell research, developmental biology, reproductive technologies, cancer, mental illness and metabolic disorders. Canada is a world-leader in the ethical and legal components of GE^{3}LS research, providing Canadian researchers with significantly broader license to operate in areas such as embryonic stem cell research and prenatal and perinatal health, than many of their international counterparts.

E. Key Areas of Impact

Although the opportunities for Canada in child health genomics are broad, it is critical to identify specific areas of impact in which Canada has:

- World-leading science capacity, and
- The potential to generate significant returns on investment in terms of improvements in the quality of life of our children.

The Child Health Genomics working group and the broad range of stakeholders that were consulted in developing this working paper have identified five key areas of impact that meet these criteria:

1. Childhood Cancer

Opportunity: Cancer is the leading cause of death in Canadian children beyond the neonatal period. One in 400 Canadian adults are survivors of childhood cancer, and more than two-thirds experience chronic and/or late-occurring health problems, that often are not clinically apparent until decades after treatment.[10] Non-random molecular or cytogenetic events are found in > 50% of childhood cancers, and many types of childhood cancers are associated with congenital anomalies, or family cancer history, suggesting a strong genetic basis for the etiology of cancer in children.

All Canadian children with cancer are treated in 17 networked paediatric centres, offering a unique opportunity to conduct population-based studies. Canada's C17 Childhood Cancer network links all 17 centres with a common collaborative, inter-disciplinary infrastructure to harmonize childhood cancer care nationally, and facilitate multi-institutional, inclusive, population-based research studies. Canada also has leadership in the new paradigm of cancer stem cells, first identified in childhood leukemias by John Dick and childhood brain tumours by Peter Dirks.

Strategic Approach: 1) Utilize high throughput genomic/genetic platforms to characterize genetic susceptibility biomarkers of childhood cancer/cancer stem cells and to identify targets for novel tumour stem cell-directed molecular therapeutics, 2) develop advanced mechanisms and ethical/regulatory guidelines to conduct population-based genetic/genomic studies in children, 3) link biobanks to high-throughput functional analysis of individual tumours to assess responses to drugs and growth factors, adverse reactions to treatment, long-term side effects of treatment, and genome-wide expression of coding and non-coding RNA.

Global Context: While 78% of childhood cancers are curable, this number drops to <50% in the developing world. Less than 30% of children with metastatic disease at diagnosis and <50% of children with brain tumours are successfully cured in Canada. The population of patients in Canada reflects the global population and, as such, work done here (particularly genetics and cancer) would have obvious application beyond Canada. Canada is strong in pharmacogenomics in children (Hayden), long term outcomes after treatment (Sinnett) and cancer susceptibility (Malkin).

Outcomes: 1) Identify the molecular basis of common and rare childhood cancers, 2) identify environmental modifiers, 3) define the molecular basis of susceptibility to short- and long-term therapeutic toxicities, including hearing loss, infection risk, growth delay, skeletal morbidities, cardiac, metabolic and cognitive dysfunction, 4) develop novel therapeutic interventions or more effective anti-cancer drugs for children, and 5) improve long term morbidities of treatment.

Impacts: Reducing the morbidity of therapy by tailoring it to the child's 'molecular' signature reduces the financial burden of long-term care, and increases the survivor's productivity over a lifetime. One estimate has Canada spending upwards of a quarter billion dollars per year for the treatment of childhood metastatic cancer alone, so the economic benefits that accompany long term improved health outcomes are clear.[11] Long term goals would be to improve the overall survival rate for children with cancer from 78% (current) to 90%, improve overall survival for children with metastatic cancer from 35% (current) to 70%, and decrease the prevalence and severity of long-term effects.

2. Neurodevelopmental Diseases (autism, mental retardation, schizophrenia, ADHD)

Opportunity: Over 70% of mental health problems have their onset in childhood or early adolescence. 20% of all children have a significant mental health problem that causes impairment. 10% of all children have a chronic psychiatric disorder with a significant genetic aetiology. Neurodevelopmental disorders such as mental retardation and autism are lifelong debilitating diseases which affect 2-3% of children.[12] Schizophrenia affects 1% of the population and is likely also a developmental disorder. Violent behaviours are thought to result largely from gene-environment interactions during development.[13]

Identifying at-risk youth and intervening as close to onset as possible is of paramount importance in order to improve their life trajectories and productivity as Canadians, and to reduce the prevalence of mental health problems in adulthood.[14] There is significant opportunity for the application of genomics to identify risk factors for these diseases, develop diagnostic screens to identify at-risk individuals, and develop effective treatments.

Canada has been at the forefront in the establishment and study of longitudinal cohorts aimed at defining behavioural traits, all of which continue to be studied (e.g. ELEM 1037 boys ascertained in kindergarten in 1984; ELEMQ 3018 children ascertained in kindergarten in 1986; ELDEQ 2872 births ascertained in 1997; and 600 pairs of twins born and ascertained in 1996, ELNEJ 30,000 children aged 0-11 followed every 2 years since 1994). DNA and extensive longitudinal phenotypic information is already available for all cohorts except ELNEJ.

Canada has a strong neuroscience research community whose ability to perform detailed neurophenotyping and attack the complexity of brain function when linked with application of new genomic technologies to brain diseases, will ensure major new inroads into neurodevelopmental and psychiatric disorders. These strengths, combined with Canada's large well-defined cohorts, provides Canada with a distinct global advantage.

Strategic Approach: 1) Identify genetic risk factors for neurocognitive and psychiatric illnesses through high throughput genotyping, proteomics or next generation sequencing platforms, 2) leverage Canada's unique populations and cohorts for the genetic analysis, 3) develop new phenotyping modalities to stratify populations for analysis.

Global Context: All neurocognitive and psychiatric disorders of childhood seen in Canada occur worldwide. In autism, mental retardation, and other diseases, it is becoming clear that rare genomic variants account for a significant proportion of illness. Currently about 10% of autism cases can be accounted for by rare and frequently *de novo* CNV's. This proportion is likely to increase with enhanced knowledge of this condition. Canada has significant expertise in this methodology (Scherer).

Canada has excellence in the phenotyping of complex behavioural traits, with several examples of genetic isolates (the provinces of Newfoundland and Prince Edward Island, and the Saguenay region of Quebec) that are of interest for many diseases, including autism (Szatmari, etc), behavioural abnormalities (Tremblay), mental retardation (Friedman, Michaud), schizophrenia (Basset, Maziade, etc) and bipolar disease (Maziade, etc). Canada has invested upwards of $11M over the last five years through competitive funding grants for research into mental retardation and $35M in autism.

Outcomes: 1) Identify genes predisposing to neurodevelopmental and psychiatric disorders, 2) develop molecular diagnostic tools for predictive testing and early diagnosis, 3) allow genetic stratification according to the specific molecular defect, to help target a small percentage of the population for intensive (and genotype-specific) early intervention, and 4) identify key disease pathways for the development of novel therapeutics.

Impacts: The economic burden of mental illness in Canada in 1998 was estimated at $4.7B in direct costs (hospital & institutional care, physician care, and prescription medications) and $3.2B in indirect costs (short-term sick days, long-term disability, and premature death).[15] People with mental retardation have a life-long handicap that produces an enormous social, emotional and financial burden on the families and communities in which they live. The lifetime cost in 2003 dollars for a person with MR in the USA was estimated to be more than $1M greater than that of an unaffected person.[16]

It has been established that with neurocognitive and psychiatric disorders in children, early intervention has a large impact on outcome; even recovery in many cases. For example, without effective intervention, most people with autism and other pervasive developmental disorders (PDD) require lifelong specialized educational, family, and adult services, at a total cost that is estimated at upwards of $4 million per person. The overall average savings from implementation of Early Intensive Behavioural Intervention (EIBI) are estimated at $1M-2M per individual across their lifespan, without taking into account the human benefits.[17]

3. Auto-immune, Inflammatory and Allergic Disease (Type 1 Diabetes, Asthma)

Opportunity: Asthma and type 1 diabetes (T1D) are major causes of chronic morbidity in childhood. Canada has the sixth highest occurrence rate of T1D in children 14 years or younger in the world, and the incidence is rising. In the next 10 years, approximately 36,000 Canadians will be diagnosed with T1D and 5,800 will die of complications from the disease. Persons with T1D have a shortened life expectancy (by as much as 15 years), a reduced quality of life and an increased likelihood of complications such as coronary artery disease, stroke, kidney disease, blindness, and peripheral vascular disease leading to amputation.

Asthma is the most common chronic disease and the most common reason for hospitalization in children in North America. In the province of Ontario, the lifetime risk of a newborn developing asthma is 42%.[18] The interaction of genetic, allergenic, environmental and lifestyle factors likely all play a role in the development of asthma.

Genome wide association studies, including a Canadian-led study, have shown that common genetic variants explain only part of the genetics of T1D. New tools for re-sequencing offer the opportunity to detect additional rare genetic T1D-associated variants. Canada can play a leading role in identifying genetic risk factors, and developing molecular diagnostics tools to predict the most effective interventions in preventing and treating these conditions.

Strategic Approach: 1) Family-based and case-control designed studies to detect CNV and re-sequencing studies to detect SNP variants that predispose to T1D, 2) functional analysis of genetic variants associated with T1D using cell line and rodent models to identify pathways that can be targeted by new therapies, 3) identify important environmental factors, including early childhood exposures to commensal and pathogenic microbes, that influence the risk of T1D, 4) determine the role of environmental factors and their interactions with genetic and host factors in the development of allergy and asthma in children through multidisciplinary, longitudinal, population-based birth-cohort studies, 5) utilize high output genomic/genetic platforms to characterize genetic susceptibility biomarkers of childhood asthma, and 6) identify targets for novel immune-directed molecular therapeutics.

Global Context: Childhood asthma is a major global health problem that exerts a substantial burden not only on the child, but also on the family, on healthcare systems, and on society as a whole. Under the universal health care system in Canada, all children with asthma and T1D are accessible for longitudinal follow-up through linkages amongst population-based health administrative databases to examine the burden of asthma over time. Family-based studies of autoimmune diseases and asthma are a Canadian strength that will be important in identifying rare causative CNVs associated with these diseases. Canada also has well established multi-disciplinary, collaborative research programmes linking genetic epidemiology, genome-wide analysis approaches, and mechanistic disease studies in rodent models.

Outcomes: 1) Identify genetic risk factors for these disorders using whole genome/proteome approaches, 2) develop molecular diagnostic and predictive tests for primary prevention (before the appearance of antibodies), 3) develop secondary prevention tests to drastically narrow down the number of children to be followed by yearly antibody testing, and 3) develop T1D-preventive interventions.

Impacts: The costs of T1D interventions have already been reduced by 80% due to the ability to genetically identify the 20% of the population that includes 90% of future cases. Nevertheless, in the next 10 years, the health care costs of T1D in Canada will be $7B and the total economic burden, including lost tax revenue and years lost to disability will be ~$13.5B. Similarly, asthma represents a significant ongoing cost to Canada's health care system. In Ontario alone, approximately $100M is spent per year on medical interventions. Beyond these numbers, are the tens of thousands of children and their families whose lives will be burdened by caring for a child with a chronic, progressive and ultimately debilitating disease.

With investment in collaborative, multi-disciplinary teams, Canada can identify children before disease onset using genetic and immune markers, and can develop strategies to modify risk factors that contribute to disease incidence. With asthma, improved understanding of gene-environment effects will reduce hospitalizations and other costly medical interventions.

4. Obesity and Type 2 Diabetes

Opportunity: Obesity is a major cause of morbidity in children and adults. In the US, in 2000, it was responsible for approximately 400,000 deaths and accounted for about 7% of health care expenditures. Obesity, particularly abdominal obesity, is a significant risk factor for cardiovascular disease and type 2 diabetes (T2D). Furthermore, obesity results in many other adverse conditions and disorders such as rheumatoid arthritis, various forms of cancer and chronic respiratory diseases. It augments mortality rate and may truncate lifespan by as much as 5–20 years. It is also economically costly to society and reduces quality of life and productivity.

Family and twin studies have shown that genetic factors contribute 40–70% to the variation in common obesity. Gene discovery efforts for obesity have had only limited success and progress in the field has been slow. Thus, identification and subsequent intervention with many potentially modifiable factors that influence obesity development may be required to make profound and enduring changes to the population levels of obesity.

It is also known that environmental influences in foetal and early postnatal life can have life-long health consequences, in many cases through biological changes that persist after the causative factor is no longer present (programming). Well established animal models for such effects (e.g. foetal nutrition, early-life maternal care) can be leveraged with emerging new genome-wide epigenomics technologies to elucidate these important events.

Gene-gene and gene-environment interactions remain poorly characterized in relation to obesity and T2D. The progressive nature of obesity and T2D in which one stage depends on the previous, strongly indicates that gene-gene interactions are important. T2D has its origins in genetic predisposition, perinatal exposures, childhood obesity and lifestyle habits. Early prediction and intervention to modify lifestyle is crucial to reduce incidence and lessen morbidity. Use of the large longitudinal birth cohorts that include significant environmental data and biological samples combined with emerging genomic technologies constitutes a key strategic advantage for Canadian researchers. Canadian scientists are at the forefront of T2D research in aboriginal populations.[19]

Strategic Approach: 1) Identify genetic risk factors using massively parallel whole-genome technologies on well-defined patient and control cohorts, 2) improve characterization of the obesogenic environment, and 3) better understand the determinants and consequences of obesity in potentially vulnerable subpopulations.

Global Context: The Westernized and developing world are experiencing a steady increase in the prevalence of obesity. More than one billion people around the globe are overweight or obese. With childhood rates of obesity in the area of 15%, obesity has been recognized as a serious public health risk by the World Health Organization and a host of national governments and health agencies.

In Canada, childhood obesity rates rose 3-fold over the last 25 years, with more than 1 in 4 Canadian children being overweight or obese. [20] Alarmingly, obese children develop early signs of pre-diabetes, hypertension, and abnormal blood lipid profiles, all risk factors for cardiovascular disease. Aboriginal people in Canada have a rate of T2D diabetes that is three to five times higher than the general Canadian population; a condition now being diagnosed in Aboriginal children and not just older persons.

Outcomes: 1) Advance the ability to genetically stratify at-risk individuals according to specific molecular defects, in order to help target a small percentage of the population for intensive (and genotype-specific) early intervention, 2) develop new pharmacotherapies to support safe and effective treatment, 3) develop intelligent combination therapies (nutrients and drugs) tailored for individuals based on genetic predisposition, and 4) improve public health surveillance and interventional research.

Impacts: Globally, ~150 million adults suffered from diabetes in 2000. By 2025, the number of people suffering from diabetes is projected to reach 300 million. The global market for diabetes therapeutics and diagnostics is estimated at US$214B in 2008. This is expected to increase to more than $242B by 2013. Aging populations in the western world, greater incidence of diabetes, population growth, growing disposable income, changes in lifestyle and diet, and genetic predisposition are some of the key factors influencing the market for diabetes diagnostics, therapeutics and devices.

Approximately 20-30% of obese children will develop diabetes.[21] If this subpopulation can be genetically defined, it will be possible to target intensive early lifestyle interventions to this subset, to decrease the incidence or lessen morbidity. This could have a large impact in Canada as throughout the world, on therapeutic costs as well quality of life of affected individuals.

5. Birth Defects

Opportunity: Major structural anomalies affect 3-5% of all infants.[22] Additional anomalies detected after birth raise the incidence to 8% by the age 5 years. These anomalies are the most common cause of infant death and life-long disability. It has been estimated that around 15% of birth defects are explained by monogenic transmission and chromosomal aberrations, 10% are due to environmental exposures (drugs, viruses and others), 25% are thought to be caused by multifactorial inheritance involving both genetic and environmental factors and 50% remain of unknown aetiology.[23]

Counselling families who have a child with birth defects of unknown cause about recurrence risks is problematic and not knowing the etiology often results in many costly medical tests aimed at establishing a diagnosis. Canadian researchers have been instrumental in identifying genetic and epigenetic factors for a number of important genetic diseases and this expertise has extended to many dysmorphological syndromes including hypophosphatasia, Bowen Conradi, Cat-Eye and Beckwitch-Weidemann.

The Canadian Congenital Anomalies Surveillance Network supported by the Public Health Agency Canada has a mandate to improve the evaluation of birth defects in Canada for both public health and research purposes. The recent announcement of additional federal funding of $1M per annum to enhance surveillance and further assess environmental factors in birth defects, including possible gene-environmental interactions, is very timely.

Strategic Approach: Birth defects that lead to early mortality or significant morbidity have historically been difficult to study. Potentially, a significant fraction of these will result from *de novo* mutations of important genes that, when disrupted, lead to dramatic phenotypes and decreased reproductive fitness. This disease mechanism has been difficult to study using classic genetic methodologies or even whole genome association studies. The recent and imminent emergence of whole genome analysis, be it CNV or whole genome resequencing, provides a viable strategy to study this group of diseases. In addition, genomic approaches may be the only way to identify the genetic basis behind birth defects that are, to date, less amenable to environmental modification, such as folate-resistant neural tube defects.

Global Context: Via MICYRN and other networks, Canada has an extensive collection of well-characterized biological samples from subjects with a wide variety of birth defects. Canada has an exceptionally strong research community in the biology of birth defects, primarily based on model organisms. Such expertise is critical for validation and understanding of the role of any gene in the development of birth defects. Phenomics of dysmorphic conditions is a strength (Evans) and Canadians are routinely overrepresented at the international David W. Smith Malformations and Morphogenesis annual workshops (>10% of platform presentations for the upcoming 2008 meeting). Canada has also been a key player in the evaluation of new modalities in prenatal diagnosis and screening. Finally, Canada is at the forefront of the development of emerging whole genome technologies, such as CNVs (e.g. Scherer) and whole genome resequencing (e.g. Hudson, Rouleau). The combination of these strengths provides a competitive edge in this field.

Outcomes: 1) Identify genomic causes and developmental pathways for a number of important birth defects, 2) identify environmental or nutritional factors that play a key role in the development of birth defects, 3) reduce or prevent birth defects by modifying environment or diet, and 4) develop inexpensive, accurate and rapid early prenatal screening tests for many birth defects.

Impacts: The introduction of food fortification with folate led to a 42% reduction in neural tube defects in Canada, with major economic and societal impact[24]. Identification of other gene-environmental interactions may allow additional simple cost-effective interventions. Additional innovative methodologies, such as those developed by Dr. Alain Moreau (CHU Ste.-Justine, Montreal) who has developed innovative genomic screens using functional assays to detect children at risk of developing scoliosis and those at risk of severe progression, recently licensed by Paradigm Spine Inc., is an example of the private sector's interest in developing tests and therapies for these types of common conditions.

Reducing the incidence of birth defects will have many significant impacts. The first is reduced reproductive wastage via prevention. The second is less human and medical care costs, as well as increased productivity by having fewer children with debilitating birth defects. Positive economic outcomes will result from the development of novel screening methodologies based on the emerging technologies.

F. Socio-Economic Benefits

An investment in Child Health Genomics would produce a number of key socio-economic benefits, which include:

1. Improved Quality of Life

The first and overriding benefit realized through investments in child health genomics will be the significant positive impact on the quality of life of children in Canada. In the absence of any other incentive, this capacity to improve the lives of Canadian children would still be extremely compelling. That being said, there are a number of economic indicators that suggest that investments in child health genomics can have profound economic as well as health benefits for Canada.

2. Reduced Health Costs through Early Detection and Intervention

Ralph Synderman has demonstrated that health costs increase exponentially as treatment moves into the later chronic stage and, conversely, that there are real opportunities for healthcare savings in early risk identification and lifestyle modification to mediate these risk factors (see Figure 1). Genomics provides the tools necessary to identify genetic risk factors much earlier than would otherwise be possible, allowing for earlier and more efficacious interventions focused on prediction and prevention rather than treatment for chronic illness.

The economic benefits of early intervention are increasingly well understood. A recent study by Cleveland and Krashinsky on childcare suggests that: "For every $1 spent on child care there is a $2 economic benefit. The benefit comes back through increased tax revenues, and decreased social, education and health costs."[25] Heckman and Carneiro, have found that the return on investment for dollars spent on early intervention is as high as 15% to 17% per annum.[26] Haddad has suggested that every dollar invested during childhood is worth 3 to 18 dollars later in life in savings to society.[27]

3. Improved Long-Term Health Outcomes

Child health genomics promises to make substantial impacts on the treatment of diseases with lifelong health and economic consequences. To put the lifetime burden of disease in perspective, a recent study by RiskAnalytica for the Juvenile Diabetes Research Foundation put the cost of T1D over the next ten years at $6.4B in lost wages, $1.4B in lost Federal Income Tax, $0.79B in lost Provincial Income Tax and $7B in healthcare costs, amounting to over $1.4B per year for Canada. Similarly, the annual cost of obesity in Canada has been estimated at between $1.6 - 1.8B in direct costs and $2.7B in indirect costs.[28]

4. Potential Commercial Impacts

There is a significant untapped commercial potential for genomics discoveries relating to child health. We are more likely to be able to understand the genes involved in predisposition to childhood onset diseases, where the proportionate role of genetics is likely to be larger, than for adult diseases where the individual impact of single genes is likely to be smaller. Pathways identified in childhood diseases, however, are likely to be potential candidates for adult onset diseases too e.g., genes that are active in childhood cancer will also have applications in therapies for adult cancer, opening up possible commercial applications, as has already been demonstrated.[29]

Diagnostics represents another significant commercial opportunity. As genomics identifies disease predisposing genes, and genomic technologies such as whole genome resequencing become available and affordable, they will revolutionize the field of molecular diagnostics. A Frost & Sullivan Report[30] identified three major areas with economic growth potential: 1) Pharmacogenomic testing: forecast US$468M annual market by 2011, 2) Prenatal & newborn testing: forecast US$796M annual market by 2011, and 3) Predisposition and diagnostic testing: forecast US$268M annual market by 2011.

In the longer term, investments in child health genomics also have the potential to identify new therapeutic targets for childhood asthma, cancer, diabetes, cognitive and emotional disorders and to develop new diagnostic and prognostic markers that could be commercialized. Childhood asthma, obesity, diabetes and mental illness affect a significant and rapidly growing number of young Canadians. Strong genomics research in these areas will encourage new commercial investment as new innovations emerge and new targets are identified.

G. GE^{3}LS

There are fundamental GE^{3}LS issues that are specific to child health research. Canada is uniquely suited to tackle these challenges, and this could be a primary component of Canada's overall contribution in child health. Canada has world leading strengths in the ethical and legal components of GE^{3}LS research. Further, this GE^{3}LS capacity is integrated with the research community that is undertaking cutting edge genomics research.

Addressing GE^{3}LS issues is of special importance in the field of child health. Medical researchers often specifically avoid working with children due to real and perceived ethical, legal and privacy issues with these activities.

The Ethics of Predictive Genomics

While predictive genomic data may enable a family to make informed choices around the treatment and prevention of some genetic conditions, there is also a very real danger that genetic typing could lead to stigmatization, with identified pre-dispositions serving to negatively impact the individuals involved.

Another critical issue is how we present complex genomic data effectively to families. Identification of pre-dispositions to conditions and diseases with negative outcomes is of questionable value unless accompanied by information, support, and access to effective interventions. The use of new genomics platforms and technologies coming online will require a significant GE^{3}Ls framework, and this is an area in which Canada can take a leading role.

Security, Privacy and Informed Consent

The rapid physical and emotional development of children, their vulnerability as patients and the potential for conflict of interests with their parents together with the probabilistic nature of genetic information constitute fertile ground for unique ethical dilemmas. Complex diseases and the participation of children in population health, biobanks and cohorts have important privacy and consent implications for children and their families.

A perceived barrier to working on issues of child health for many researchers is the issue of informed consent with children. The shifting nature of this consent as children age can also be problematic. Significant concerns can also arise around the use of DNA analysis on samples that were not collected initially for genetic studies, such as newborn blood spots. The use of stem cells for therapy and innovative reproductive technologies in the prenatal-perinatal contexts are new targets of interest for the prevention of a variety of diseases. A myriad of related ethical issues have entered the public debate, especially in the US. Canada has leadership in this area through the Stem Cell Network and StemGen, led by Dr Bartha Knoppers.[31]

H. Funding Request

One of the real strengths of the Child Health Genomics SRT is its ability to extensively leverage existing Canadian genomics and health infrastructure. However, to take these studies to the next level with real world applications for children will require major investments in biobanking of fetal, maternal and children's DNA, tissues and cells, including stem cells, associated clinical informatic databases, and integrated data access and data handling to ensure cross-compatibility of resources across the country. Free and open access to these resources will enable major new initiatives in the key impact areas described and also in areas yet to be identified. We envisage a need for an investment of around $20M in biobank/database resources and around $180M to fund 12 large and 6 smaller projects over the course of 3-4 years. Given Genome Canada's co-funding policy, the estimated request from Genome Canada would be in the range of $100M.

I. Key Partners and Stakeholders

An investment in Child Health Genomics would mobilize a national network of public and not-for-profit organizations as well as a broad spectrum of potential commercial partners. Consultation with representatives from each of these stakeholder groups was central to the development and formation of this Position Paper. Representatives were asked for their input into the Position Paper as it was being developed and had the opportunity to comment on drafts as they were finalized. They were also asked to consult more broadly amongst their peers to ensure that this SRT is representative of as broad a range of views as possible. A list of participants who attended the workshop, and other who contributed thereafter, has been provided as a supporting document to this position paper (see Supporting Document B).

Tables and Figures

Table 1: Canadian Health Genomics Capabilities

Current capabilities	• High throughput sequence analysis of multiple candidate genes, genome-wide SNP association studies and array-based approaches to copy number variations in the genome. • Large-scale model organism genetic platforms (such as GC-funded yeast and mouse projects and the Regulome Consortium) ensure that Canadian researchers have the ability to mechanistically analyze genetic components of complex disorders.
Near term capabilities	• Implementation of new and emerging sequencing technologies (454, Solexa, and others) will soon allow cheap and rapid whole genome sequencing of large patient sample sets. • Proteomic and mass spectrometric technologies are moving forward to prognostic biomarkers of complex disease.

Table 2: Selected Canadian Genomic Platforms

Lead Researcher	Organization
Marco Marra	BC Genome Sequencing Centre
Christoph Borchers	UVic Genome BC Proteomics Centre
Colleen Nelson	Vancouver General Hospital's Microarray Facility
Steve Scherer	Toronto Centre for Applied Genomics (TCAG)
Katherine Siminovitch	Analytical Genetics Technology Centre (University Health Network Research) (Toronto)
Shoshana Wodak	Centre for Computational Biology (Sick Kids)
Eric Brown	McMaster High Throughput Screening Laboratory
Michael Rudnicki	StemCore High-Throughput Genomics Facility (Ottawa Health Research Institute)
Marjorie Brand	Ontario Genomics Innovation Centre –Proteomics Services (Ottawa Health Research Institute)
Ken Dewar	Genome Quebec Innovation Centre
Benoit Coulombe	Proteomic platform - Montreal Clinical Research Institute
Pierre Thibault	Proteomic platform – Institute de Recherche en Immunologie et en Cancerologie, University of Montreal
Michael Phillips	Genome Quebec Pharmacogenomics Centre
Geoff Hicks, Janet Rossant	NorCOMM (North American Conditional Mouse Mutagenesis project) (Genome Prairie)

Table 3: Selected health and child health genomic research consortia and initiatives in which Canadian researchers are playing a primary role

Name of Consortia	Lead Researcher(s)
Autism Genome Project	Peter Szatmari (McMaster University), Steve Scherer (SickKids / University of Toronto)
Type 1 Diabetes Initiative	Constantin Polychronakos (McGill University), Hakon Hakonarson (Children's Hospital of Philadelphia 1,500 Canadian families with one or more children with type 1 diabetes
Multiple Sclerosis	George Ebers (University of Western Ontario), Dessa Sadovnik (University of British Columbia) Paediatric set: Brenda Banwell (University of Toronto)
NET on adult vs. child autoimmune disease	Amit Bar-Or (McGill University)
Québec Child and Adolescent Health and Social Survey	Marie Lambert and Emile Levy (University of Montreal), 1,600 children and adolescents with DNA and metabolic samples as well as environmental info
Genome –Environment Interactions in Type 1 Diabetes	Jayne Danska (SickKids / University of Toronto), Andrew Macpherson (McMaster University), Ake Lernmark (Malmo, Sweden)
Gene Approaches to Child Therapy	Hayden and Carleton (University of British Columbia)
Canadian Molecular Cytogenetics Platform	Partnership of 13 major research institutions
Database of Genomic Variants (the "Toronto Database")	The Centre for Applied Genomics (TCAG) at The Hospital for Sick Children (SickKids)
The North American network of the T1D Genetics Consortium	The only use to-date of this DNA collection for a genome-wide study has been by Canadian researchers.
The Childhood Leukemia International Consortium (CLIC)	Involving 14 countries, and including Canadian scientists Sinnett (Unviersity de Montreal) and Infante-Rivard (McGill University)
The Environmental Determinants of Diabetes in the Young (TEDDY	Multi-centre, prospective, nested case-control study epidemiological study to identify environmental factors that modulate diabetes risk
Genome Project for Common Diseases at the Children's Hospital of Philadelphia	Various Canadian researchers are active

International research consortium for the development of new technologies and useful pharmacological agents to prevent scoliosis or to stop its progression	Led by Dr. Moreau at St. Justine Research Hospital
Human and Malaria Genomic Sequencing and Interactions	Philip Awadalla (University of Montreal), Xinshuan Su (NIAID-NIH)
AllerGen CHILD birth cohort study	led by Peter Paré, Denise Daley, Michael Kobor and others at UBC/iCAPTURE, with collaborations in Quebec with Catherine Laprise (Chicoutimi) and Tom Hudson, at OICR.

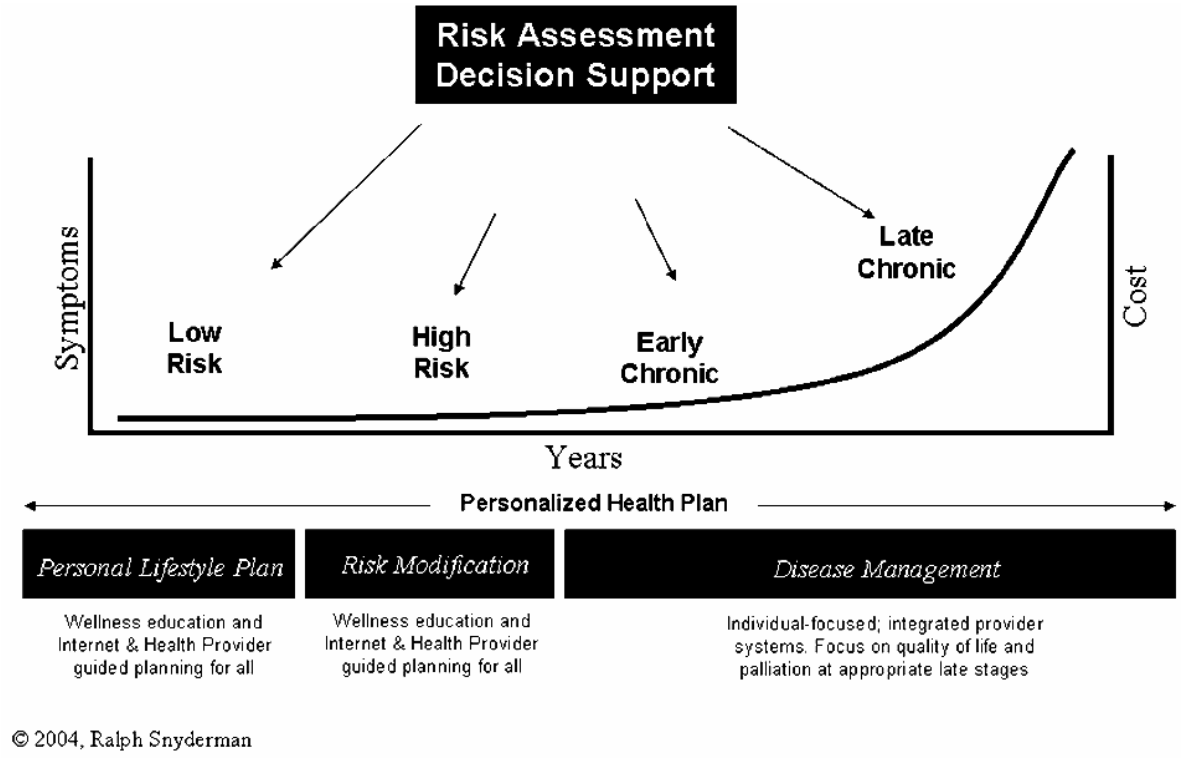

Figure 1: Risk Assessment and Health Care Costs

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