# Environments, Genes and Chronic Disease

# National Workshop Report

February 7-8, 2012

## Canadian Institutes of Health Research

Institute of Nutrition, Metabolism and Diabetes
Institute of Genetics

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

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**Institute of Human Development, Child and Youth Health**
**Institute of Population and Public Health**

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## CIHR Institute of Nutrition, Metabolism and Diabetes

The mandate of the CIHR Institute of Nutrition, Metabolism and Diabetes is to support research to enhance health in relation to diet, digestion, excretion and metabolism and to address the causes, prevention, screening, diagnosis, treatment, support systems and palliation for a wide range of conditions and problems associated with hormone, digestive system, kidney and liver function.

## CIHR Institute of Genetics

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

# Executive Summary

In February, 2012 the Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes and Institute of Genetics convened a workshop in Ottawa attended by 35 health research leaders from across the country. The **objectives** of the workshop were (1) to define strengths, gaps and opportunities for targeted research in environments, genes and chronic, non-communicable disease in Canada, (2) to identify strengths, gaps and opportunities for increasing research capacity in Canada in this research area, and (3) to articulate research priorities for a proposed environment, genes and chronic disease targeted research initiative.

Six plenary speakers from Canada and the United States were invited to share recent research advances related to this topic area in their respective fields. Their presentations provided important context to the breakout group deliberations which followed.

Several **key themes** emerged throughout the workshop deliberations: the need for data standardization, better metrics and data sharing; the importance of enhanced networking among researchers including new and innovative models to bring like-minded people together across disciplines; the urgency of addressing barriers to the current research ethics approvals process; the need for more centralized support for cohort study development and enhanced collaboration and sharing among cohorts; and, the importance of interagency collaboration and national and international partnerships for moving large scale research projects and programs forward.

After identifying gaps, strengths and opportunities for moving this important field of research forward, participants focused on the research questions that were seen to hold the most promise in advancing research in Canada in environments, genes and chronic disease. Questions arising from the breakout groups were subsequently prioritized by the participants in plenary. The **top three goals** identified were:

- Addressing the effects of genes and environmental factors, including exposures during critical periods of development, on chronic disease in Canadians, recent Canadian immigrants and those living in developing countries.

- Defining signature molecular pathways of environment-gene interactions for the purposes of phenotyping chronic diseases and identifying biomarkers of environmental exposure.

- Developing novel study designs, including bioinformatics and statistics approaches, to delineate environment-gene interactions and characterize key environmental factors in the development of chronic disease.

The workshop ended with a summary by the co-hosts of the key assets and challenges for environments, genes and chronic disease research in Canada.

## Key assets:

- Canada's ethnic diversity with specific, well-defined populations including First Nations, Inuit, and Métis communities and other culturally and geographically isolated groups;
- a strong cadre of scientists across all pillars and good networking among researchers;
- a strong research capacity in the "omic" sciences; and,
- the existence of numerous cohort studies, many already well phenotyped, but also presenting challenges related to restrictions on access, variable quality of curation, visibility and sustainability issues.

## Key challenges:

- high-throughput technologies being cheaper and more advanced for obtaining genetic data than for obtaining environmental data;
- limited standard operating procedures for measuring environmental exposures;
- deficits in theoretical and methodological tools for integrating genetic and environmental data;
- suboptimal integration, utilization and coordination of cohort studies;
- limited investment in Environment-Wide Association Studies;
- complex research ethics board processes, especially impacting large consortia;
- complications concerning data harmonization and data sharing across provinces; and,
- past difficulties that have eroded trust and still impact cooperation between researchers and Aboriginal populations.

# 1. Workshop Objectives

The Environments, Genes and Chronic Disease Workshop brought together health research leaders from across the country to determine strengths, gaps and opportunities for environments, genes and chronic disease research in Canada.

The workshop was co-hosted by the Canadian Institutes of Health Research (CIHR) Institute of Nutrition, Metabolism and Diabetes (INMD) and the Institute of Genetics (IG). While there have been major advances in understanding the role of genetics in the pathobiology of chronic diseases, there is increasing evidence that the environment also contributes substantially to the development and severity of many chronic diseases.

Moreover, there are critical knowledge gaps on the role of gene-environment interactions in the development of chronic disease. Seeking answers to such research questions has the potential to improve prevention strategies and improve the quality-of-life for patients with both common and rare chronic diseases. Improved prevention and treatment of chronic disease will also reduce health care inequities for populations of increased vulnerability, who are more likely to develop chronic disease[1].

Pre-workshop consultations undertaken by INMD indicated strong support for a focus on this topic, which is seen as an important emerging area of health research that crosses basic science, clinical and population health research themes.

Participants were asked to address the following **objectives**:

1. Define strengths, gaps and opportunities for targeted research that will identify the interactions and roles of natural and built environments, human behaviour and genes on the pathogenesis and pathobiology of chronic non-communicable diseases.

2. Identify strengths, gaps and opportunities for increasing research capacity in Canada for the area of natural and built environments and their impacts on genes and chronic disease.

3. Develop Canadian research priorities for an environment, genes and chronic disease targeted research initiative.

During the workshop, six speakers from a range of disciplines were invited to discuss recent research advances related to the topic of environments, genes and chronic disease. These presentations provided the context for breakout group deliberations, which followed each of the three plenary sessions.

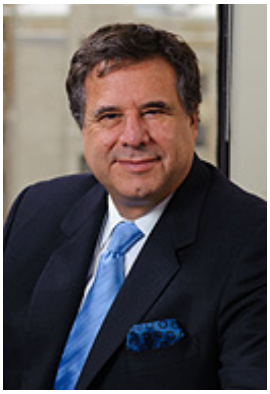
Participants were assigned to breakout groups, each with a mix of participants from different institutions and varying research foci so as to ensure that each group had access to broad range of perspectives. At the end of each breakout session, the groups summarized and

shared insights and ideas with colleagues in a plenary session that was followed by a discussion to clarify key recommendations and determine areas of convergence between groups.

An additional plenary presentation on partnerships emphasized the potential synergies in addressing environments, genes and chronic disease through strategic partnerships across institutes, fields and sectors.

In total, 35 researchers with backgrounds in biomedical, clinical and population health research themes actively participated in the workshop, as did representatives from government and potential partner organizations.

# 2. Opening Remarks



**Dr. Alain Beaudet**, President of CIHR, provided his personal welcome to workshop participants. He noted that workshops are powerful tools that provide the research community and stakeholders with insight into the current state of health research in Canada and that they play a key role in assisting CIHR and partners with planning for the future.

Chronic non-communicable diseases constitute a significant social and economic burden both in Canada and around the world. Chronic disease impacts many of Canada's most vulnerable populations, including the very young, the elderly and First Nations, Inuit and Métis populations, who are disproportionately affected by chronic disease.

Dr. Beaudet stated that great strides have been made in understanding how genes contribute to chronic disease, and that the interplay between genes and environmental factors plays a role in the etiology of many chronic diseases. There is great potential for an improved understanding of chronic disease through addressing the interplay between environments and genes. Discussions at this workshop are an important step in assisting CIHR in targeting support for research in the area of environments, genes and chronic disease and in forging strategic partnerships with other institutes and organizations to extend the reach of this research and, ultimately, improve the health of Canadians and the health care system.

**Dr. Philip Sherman**, Scientific Director of the CIHR Institute of Nutrition, Metabolism and Diabetes (INMD), welcomed the participants on behalf of INMD and workshop co-host, Dr. Paul Lasko, Scientific Director of the Institute of Genetics (IG). He thanked participants for taking the time to provide their expertise and insights into this important undertaking. He underscored the importance of this workshop for both host institutes and placed the purpose and objectives of the workshop in the context of the INMD 2010-2014 Strategic Plan, in which Environments, Genes and Chronic Disease is one of four strategic priorities. He noted that the aim over the course of the workshop was to generate the basis for a targeted research initiative.

Dr. Sherman introduced four CIHR Scientific Director colleagues who were present at the workshop: Drs. Nancy Edwards, Institute of Population and Public Health; Malcolm King, Institute of Aboriginal People's Health; Shoo Lee, Institute of Human Development, Child and Youth Health, and Marc Ouellette, Institute of Infection and Immunity. He then introduced Dr. Jane Aubin, Chief Scientific Officer and Vice-President Research at CIHR. The active engagement of CIHR leadership at this workshop underscores the importance of this emerging research area, and the relevance it has to the mandates of multiple institutes.

Dr. Sherman encouraged all participants to actively engage in discussions, as the differences of perspectives and opinions serve to enrich the deliberations and subsequent report. He noted that it was not the intent to come to consensus on all issues, but, rather, to have a comprehensive range of ideas brought forward in order to be able to develop emerging areas of research priority. He then introduced the workshop facilitator, Ms. Sally Brown, who outlined how the workshop would unfold.

# 3. Presentations

## Keynote Presentation

### *Gene-Environment Interactions in Cardiometabolic Disease*

**Dr. Robert Hegele**
Distinguished University Professor of Medicine and Biochemistry
Western University

Dr. Hegele discussed three studies on the impacts of environment and genes on cardiometabolic disease. The first study described the high prevalence of type 2 diabetes (T2DM) among Ojibwa-Cree peoples of Sandy Lake, an isolated reserve in Northwestern Ontario[2]. The study was initiated by the Band Council in the 1990s to address their concerns about the rate of T2DM, which was found to be the third-highest in the world. The researchers identified a novel genetic mutation in Sandy Lake residents that tripled the risk of T2DM in non-smoking carriers and increased the risk 7-fold in carriers who smoked. However, many diabetic individuals were not carriers of the mutation and many carriers were not yet diabetic. These results refuted an earlier theory that a single gene accounts for the high incidence of T2DM in Canadian First Nations. Furthermore, the impact of the genetic variant on diabetes risk is about one-third of non-genetic factors, such as diet and activity level. These results support the view that, at least in some cases, environmental factors can have a much greater influence on chronic disease than does genetic propensity.

Dr. Hegele noted that the Band Council recently approved an intervention study promoting the reintroduction of traditional foods three times a week and has built a boardwalk around the reserve to encourage residents to take up walking and increase physical activity. In a second example, Dr. Hegele showed that 10 genetic variants explain roughly 30% of the susceptibility to hypertriglyceridemia in non-Aboriginal patients[3]. Bundling variants to create a genetic risk score shows clear differences between patients and controls. However, these genetic risk scores overlap considerably, so that the genetic profile for an individual does not reliably predict the development of hypertriglyceridemia.

Dr. Hegele then shared the results of a genotyping scan performed on himself, to show how environmental changes, including diet adjustments and lifestyle modifications to include increase physical activity, could counteract the effects of susceptibility genes predisposing an individual to obesity and heart disease.

In the ensuing discussion, Dr. Hegele acknowledged the importance of obtaining sufficient sample sizes in order to obtain statistical significance in environmental health research. He also stressed the need for detailed and rigorous methods to collect environmental

information, and the importance of improved methodologies to tackle the complex inter-relationships between environments, genes and chronic disease. He emphasized that while viewed separately, environmental and genetic factors may have a small impact on chronic disease, but when combined, environment-gene interactions could potentially have a much greater impact.

## Plenary Presentations

### *Measuring Environmental Exposure: Workshop Report*[4]

**Dr. Laurie Chan**
Professor and Canada Research Chair in Toxicology and Environmental Health
University of Ottawa

Dr. Chan noted that the number of chemical compounds in commercial use has increased from approximately 200,000 to 88 million over the last 40 years. This enormous increase has led researchers to question the long-term effects of these chemicals on human health, resulting in a need for improved measures of chemical exposure. Despite this increased demand, the measurement techniques for both acute and chronic chemical exposures remain poorly developed.

The Measuring Environmental Exposures Workshop, held in Montreal in November 2011, and co-hosted by the CIHR Institute of Human Development, Child and Youth Health (IHDCYH) and the British High Commission, highlighted a number of measurement issues and challenges:

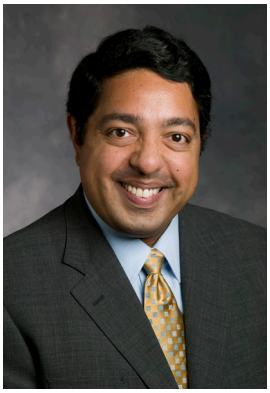
- environmental regulators control and monitor chemical concentrations, but effects are determined by exposures;
- the relationship between environmental exposure and biomarkers of exposure is often not well understood;
- characterization of the effects of environmental exposure generally lags behind an understanding of genetic influences;
- measurement of acute environmental exposures is challenging, as is monitoring and documenting exposures to chemicals with a short half-life;
- certain environmental exposures, such as indoor air pollution, remain poorly studied;
- while it is possible to measure known and expected chemicals, it can be more challenging to detect unexpected new chemicals or byproducts.

Challenges also exist with respect to the development of non-invasive techniques for the measurement of biomarkers, numerous age and sex differences, as well as ethical and technical issues related to sharing samples and data between studies.

Dr. Chan then outlined research methodology issues associated with gene-environment interactions, including sample size considerations and study design. While cohorts are still the preferred method, strong support is also needed for multi-generational studies, as well as the capacity to measure epigenetic effects. He spoke to the importance of using information from current cohorts more efficiently, and the need for enhanced coordination in the planning of future cohorts.

In the discussion that followed, it was noted that the field of exposure measurement would benefit from better integration with the field of experimental toxicology, and that the methodologies for integrating protocols and data from multidisciplinary studies are still lacking. Participants raised concerns over the risk of bias when pooling or sharing existing cohorts with different methodologies. Dr. Chan suggested that there is a need to develop a set of common indicators that can be included in future cohort studies.

## *Environment-Wide Association Study on Type 2 Diabetes*



**Dr. Atul Butte**
Chief of the Division of Systems Medicine
Associate Professor of Pediatrics and Medicine
Stanford University

Dr. Butte started his presentation by commenting on the modern revolution in genetics and molecular biology which has focused attention on the genetic component of disease at the expense of the environmental component. While genetic factors clearly play a major role in chronic disease, T2DM, and other chronic diseases such as atherosclerosis, inflammatory bowel diseases, cancers and obesity, are likely to be caused by a more complex combination of multiple genetic and environmental factors. To study the interplay of genetic and environmental factors, there is a pressing need to develop research methodologies that can better establish the role of various environmental factors as a risk for the development of chronic disease.

Genome Wide Association Studies (GWAS) is a method that correlates genetic factors with disease phenotype[5]. GWAS have clearly shown that genetic variants contribute to disease. However, the effect of genetic variants on polygenic disease is unexpectedly weak. For example, for T2DM, only 6% of heritable risk is explained by genetic variants[6]. To better understand the role of the factors predisposing to chronic disease, environmental factors and environment-gene interactions must also be assessed.

Dr. Butte discussed the Environment-Wide Association Study (EWAS) related to T2DM in which environmental exposure data, which was obtained from National Health and Nutrition

Examination Survey (NHANES)* cohorts, were systematically interpreted in a manner analogous to a GWAS. This study showed that certain environmental exposures had as large of an impact on the development of T2DM as the most influential genes identified by GWAS. This finding suggests that the EWAS technique could be useful for identifying environmental factors associated with other chronic non-communicable diseases.

Dr. Butte also spoke to the importance of the preservation of original research data. While the data from many biological investigations are published either as summary tables or in a graph format, the original biometric data on which the results are based are often withheld. Yet these data can contain information that has not been extracted by the author and could well stimulate other researchers to develop new and valuable statistical applications. Dr. Butte stressed the need for continued development of methodologies to better study the impacts of environment and genes on chronic disease.

Summary points included:

- studying environmental and genetic risk factors together may be more difficult, yet it may hold the key to future advances in unravelling the etiology and course of many chronic diseases.
- clinical and environmental measures, as well as DNA, should be considered in future initiatives related to personalized medicine.
- interdisciplinary research collaboration is necessary to unravel the effects of the environment and genes on chronic disease.
- future research studies should be designed to assess the impacts of multiple environmental exposures, rather than individual exposures.

* The National Health and Nutrition Examination Survey (NHANES) is program of the Centers for Disease Control and Prevention (CDC) designed to assess the health and nutritional status of adults and children to determine the prevalence of major diseases and risk factors for diseases in the U.S. The survey combines interviews and physical examinations and includes demographic, socioeconomic, dietary and health-related questions along with an examination component.

## *Assessing Environment-Gene Interactions*

**Dr. Daniel Krewski**
Scientific Director
McLaughlin Centre for Population Health Risk Assessment
University of Ottawa

Dr. Krewski presented a draft framework for advancing the next generation of risk assessment. The NexGen Risk Assessment Framework is comprised of three building blocks:

1. National Research Council's *Toxicity Testing in the 21st Century*[7] that focuses on using computational tools in biology to predict chemical properties and characteristics,

2. McLaughlin Centre Population Health Approach to Risk Assessment[8], a multidisciplinary approach to the assessment of human health risks within populations that integrates traditional human health risk assessment with a comprehensive assessment of health risks in the general population based on multiple determinants of health, and

3. *Science and Decisions: Advancing Risk Assessment*[9], which is a report on risk assessment methodologies, such as how to tailor a risk assessment effort to risk management decisions.

Dr. Krewski noted that each of these building blocks independently advances the field of risk assessment. However, when taken together these three approaches produce a next generation framework (NexGen) that could shape the future of health risk science. Once risk is comprehensively assessed, multiple interventions are then possible including regulatory, economic, advisory, community-based and technological interventions.

New directions in toxicity testing were then considered. Advances in molecular biology, biotechnology and other fields are paving the way for major improvements in how scientists can evaluate health risks posed by potentially toxic chemicals that are found at low levels in the environment. These advances should make toxicity testing quicker, less expensive, and more directly relevant to human exposures. They could also reduce the need for animal testing by substituting more laboratory tests based on human cells.

In the discussion that followed, Dr. Krewski noted that human toxicity pathways are not well described. However, a consortium to study these pathways is being established. It is felt that this consortium will, ultimately, identify several thousand human toxicity pathways.

## *The Environment and Inflammatory Bowel Diseases: Challenges and Future Directions*

**Dr. Gilaad Kaplan**
Assistant Professor, Faculty of Medicine
University of Calgary

Dr. Kaplan noted that the incidence of chronic inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, is increasing globally, but remains highest in developed countries, including Canada. While over 100 genes have been reported to increase susceptibility to IBD, it is clear that important environmental exposures interplay with genetic susceptibility and, thereby, result in disease development[10]. These exposures include: environmental pollutants, allergic responses and smoking, with the latter increasing the risk of developing Crohn's disease in adults roughly two-fold.

The ability of researchers to study the effects of multiple environmental exposures has been constrained by a number of methodological challenges including: misclassification bias, lack of identification of confounding factors and the challenge of separating true phenomenon from background noise. Going forward, there is a need to integrate population-based research with person-level data so as to be able to better inform translational research efforts. The Michael J. Howorth Inflammatory Bowel Disease Genetic, Environmental and Microbial (GEM) Study, which is currently recruiting and then following individuals with at high risk of developing Crohn's disease, is a Canadian research effort aimed at dissecting the role of various risk factors in disease susceptibility.

Future directions at the strategic level include:

- developing appropriately designed, large population-based, prospective cohorts of IBD patients and controls,
- characterizing environment-microbial-gene interactions stratified by disease phenotype,
- evaluating mechanisms of interactions through complementary in vitro and in vivo studies, and
- delineating IBD phenotypes in both emerging nations and migrant communities.

## *Environment-Gene Interactions in Asthma*

**Dr. Catherine Laprise**
Professor
Université du Québec à Chicoutimi

Dr. Laprise noted that since 2007 there have been more than 30 GWAS studies on asthma with over 30 associated genes identified[11]. She outlined a number of environmental triggers that contribute to phenotypic diversity in asthma including: respiratory infections, allergens, temperature change, stress, medications, tobacco, food additives and pollutants. In response to a query about the link between air pollution and asthma, Dr. Laprise noted that while there was a considerable decrease in air pollution in eastern Europe in the 1990s, there has been no decrease in the prevalence of asthma in these countries.

A review of several recent Canadian asthma studies was then presented:

- Saguenay-Lac-St-Jean (SLSJ) Asthma Familial Collection of 254 extended families of French-Canadian origin identified five novel asthma gene determinants[12].
- Canadian Asthma Primary Prevention Study (CAPPS), which included 549 children at high risk for developing asthma and their parents, illustrated the benefit of multi-faceted interventions such as indoor allergen and tobacco smoke avoidance and breastfeeding coupled with delayed introduction of complementary foods[13].
- Study of Asthma Genes and the Environment (SAGE), a nested case-control study of 723 children from Manitoba, demonstrated the associations between (1) obesity, depression and asthma, (2) maternal postnatal distress, cortisol levels and asthma and (3) early life antibiotic use and asthma[14].

Dr. Laprise next discussed a large GWAS undertaken by the GABRIEL Consortium, which included 23 independent studies. This analysis identified a number of genes associated with asthma as well as a number of disease markers. However, due to the variability in environmental factors, none of the identified genetic markers were found to be useful as predictors of disease[15].

Dr. Laprise concluded by reviewing the Canadian Healthy Infant Longitudinal Development (CHILD) cohort of 5,000 infants from four cities across Canada, co-funded by CIHR and the Allergy, Genes and Environment Network (AllerGen)†. The cohort was established to determine the role of environmental factors and their interaction with genetic and other host factors in the development of allergy and asthma. While the CHILD study originally focused on asthma, it could potentially be opened for the study of other chronic diseases.

† AllerGen is one of five health-related networks currently funded under the federal Networks of Centres of Excellence (NCE) Program.

# 4. Key Insights from Breakout Groups

Breakout groups were asked to respond to questions about the knowledge and infrastructure challenges and gaps in environments, genes and chronic disease research in Canada, as well as the strengths and opportunities in Canada to overcome these gaps.

Participants were asked to consider technological, methodological, ethical, social and legal infrastructure gaps, as well as resource-related challenges.

Groups were then asked to identify how Canada can best improve research capacity in the area of genes, environments and chronic disease.

## A. Gaps and Challenges in Environments, Genes and Chronic Disease Research

**Collection and Analysis of Complex Data:**

Analytical Tools and Methods: The complexity of quantifying relationships between genes, environments and chronic disease was recognized. Concerns were expressed about the need for: (1) statistical, analytical and data management tools, (2) conceptual frameworks for examining these relationships and (3) standardized, precise, scalable and reproducible metrics in this research area.

Participants recognized that environmental exposures change over the course of life, and that the need to capture both chronic and acute exposures adds to the complexity of measuring environmental exposures.

Beyond identifying the environmental and genetic factors that cause chronic disease, participants also indicated a need to develop and implement effective public health interventions.

A lack of standardized and reproducible metrics makes it difficult to measure dose and time effects for environmental exposures in a reliable and cost-effective manner. Moreover, while high-quality genetic data is currently available, researchers often find themselves using poor quality environmental exposure data sets. In addition, population-based data are limited and different metrics are often used in different studies. The need for Canadian researchers to develop consensus measures for studies on environmental exposures was highlighted. For example, the PhenX Toolkit, which arose from the Phenotypes and eXposures project provides the United States research community with a core set of high-quality and well-established consensus measures for use in studies involving phenotypes and environmental exposures, with the goal of facilitating cross study comparisons and data analyses.

Expertise and Research Capacity: Limited systems biology expertise in Canada was noted, particularly compared to capacity in the United States. A systems biology approach was seen

as essential to characterizing environment-gene and environment-environment interactions. The need for additional Canadian expertise in the areas of environmental epidemiology, bioinformatics, biostatistics, and computational biology was highlighted. The need for additional clinician scientists in Canada with sufficient protected time for a focus on research was also emphasized.

**Cohort Studies and Biobanks:**

Research capacity in the study of environment-gene interactions could be massively enhanced with shared access to biological samples and cohort data. Technical issues, including the lack of standardized technology platforms and the lack of a central repository for data, were noted as shortcomings that inhibit the sharing of samples and cohort data between researchers. Different privacy regulations in various provinces were also noted as a barrier to sharing of data and samples.

Cohort Studies: Prospective cohort studies, in which large groups of individuals are followed over long periods of time, were seen as central to identifying environmental, lifestyle and socio-economic factors that predispose an individual to chronic disease.

Workshop participants noted that, despite Canada's diverse population, there are challenges with enrolling suitably representative populations, which may limit the interpretation of cohort studies. While there are several important national and provincial cohort studies in Canada, the need for large cohort studies was emphasized.

The limited number and breadth of cohort studies in Canada and coordination of cohorts was identified as a common theme. Existing cohorts are not linked, so it was suggested that incentives are needed to encourage networking and data sharing. The lack of centralized support for cohort development, including a central repository to store cohort data, was also noted.

Sustained funding of existing cohorts was pointed out as a concern. Opportunities for long term funding for cohorts are few, so that cohorts may not be extended beyond the life of the initial grant.

Biobanks: It was noted that numerous biobanks currently exist across Canada, but that these are costly to develop and to maintain. A centralized list of biobanks should be developed so that interested researchers can be made aware of the various biobanks that exist. It was noted that researchers may have difficulty in accessing existing samples, because the ownership of the samples is not explicitly stated or because they cannot obtain ethics approval for use of the stored sample.

**Biomarkers, Tissue-Expression, and Phenotyping:**

Biomarkers: Biomarkers can be used to provide an index of chronic or acute environmental exposure, and to evaluate responses to therapeutic interventions. Presently, some biomarkers

provide a good index of environmental exposure, disease state or genetic susceptibility. However, in many cases, there is a lack of consensus on whether the available biomarker has been adequately validated. It was noted that many available biomarkers require invasive sampling techniques, rendering them unsuitable for widespread clinical use.

Tissue Expression: Newly discovered biomarkers are not necessarily superior to existing tools. Investigating genetic and environmental determinants of a given disease may, ultimately, hold more promise. In Canada, there is a paucity of tissue expression studies comparing gene expression across tissues obtained from different individuals. Tissue expression studies, such as those supported by NIH Genotype-Tissue Expression (GTEx) program, allow researchers to determine the mechanisms of gene regulation and disease-related perturbations.

Phenotyping: Phenotyping is used to identify sub-populations within the same disease or condition. By defining and studying these sub-populations, researchers can reduce heterogeneity in the populations under study, thereby leading to an improved understanding of the role of environmental exposures and specific genes in disease causality. Significant challenges were identified in defining phenotypes of particular chronic diseases. The presence of genetic variants, which may influence the gene penetrance of an allele, can further complicate clear phenotyping for a given chronic disease.

**Research Ethics:**

Multiple barriers to study inception and integrity associated with the current process for obtaining research ethics board (REB) approval were emphasized. Difficulties include privacy concerns that prevent linking across institutional and provincial jurisdictions, and enormous time lags in obtaining REB approvals. On the other hand, the need to address the legitimate privacy concerns that arise while expediting REB approvals was acknowledged. The REB approval process is seen as a challenge and frustration across all fields.

**Intervention Research:**

The relatively small amount of intervention research currently performed in Canada was also identified as an important gap. It was noted that defining risk factors, may not provide an indication as to whether a particular intervention will be successful in either preventing or ameliorating disease.

**Research on both Rare and Common, Non-Life-Threatening Diseases:**

Rare and common but non-life-threatening chronic diseases (e.g., gastroesophageal reflux, irritable bowel syndrome) pose a high burden and immense cost to individuals, their families and the health care system. Despite these high costs, there is very little funding support for research on these types of diseases and conditions.

**Equipment:**

Funding for research equipment is also an important part of building capacity for research in environments, genes and chronic disease. It was noted that partnerships with the Canadian Foundation for Innovation (CFI), Genome Canada and universities can potentially fill this gap.

## B. Strengths and Opportunities in Environments, Genes and Chronic Disease Research

While major gaps in environment, genes and chronic disease research were identified, it was also observed that the Canadian health research community has core strengths that can help to overcome these challenges:

**Discipline-Specific Scientific Expertise:**

There is a solid community of scientists in specific, well-established research fields, including several disease-specific fields such as diabetes, gastrointestinal diseases, cardiovascular disease, cancers and lung diseases. There is a huge potential in Canada for research focused on groups of diseases with shared risk determinants, including both environmental and genetic factors.

**Scientific Expertise in Inflammation:**

Canada has considerable strength in inflammation, which is a common factor among a number of chronic non-communicable diseases including, for example, inflammatory bowel diseases, obesity, atherosclerosis and asthma. One CIHR Signature Initiative, Inflammation in Chronic Disease, builds on this strength and will support additional research in this area. It is anticipated, therefore, that an environmental research initiative would complement such a funding opportunity.

**Expertise in "Omics":**

Canada has good research capacity in molecular biology and the "omic" sciences, including genomics, proteomics and metabolomics. These fields will play an important role in identifying the role of environment and genes in chronic disease, not only through the production of new experimental data, but also through the development of new and emerging techniques and technologies.

**Openness to Collaboration:**

There is a strong tradition of networking among researchers in Canada, with growing support for multidisciplinary research teams. For example, the CIHR Strategy for Patient-Oriented Research (SPOR) will develop multidisciplinary Support Units of trial methodologists and other experts to assist investigators with research study design and project management, conducting biostatistical analyses, managing large data sets and biobanks and ensuring studies meet relevant regulatory standards.

**Established Cohort Studies:**

Despite considerable concerns and gaps with respect to cohort studies, there is the potential to build on numerous existing cohorts in Canada‡. Many of the cohorts are well phenotyped, and there may be opportunities to link these existing cohorts. Developing approaches to educate primary health care providers, so that they may encourage patients to participate in cohorts was also emphasized. Such an approach could include ways to enhance understanding by patients and by the general public of the potential benefits of enrolling in cohort studies.

It was agreed that collaboration between cohorts is a high priority for improvement, and careful consideration be given to how best to galvanize such change in the research community. CIHR is currently undertaking an inventory of existing CIHR-funded cohorts, which represents an initial step towards improving cooperation. In the future, maintaining an inventory of cohorts could well be done through a process similar to that currently used to register clinical trials.

**Partnerships with Health Charities and Federal and Provincial Agencies:**

Although there is the potential for improvements in developing partnerships with the private sector, long-standing and productive partnerships between CIHR, Rx&D and health charities in Canada were emphasized. The importance of Genome Canada and the health-related Networks of Centres of Excellence (NCE) to the research community were highlighted. The availability of toolkits, such as Health Canada's measurement tools, was also noted. The potential to either build on or adapt the PhenX kit developed in the US is also an important opportunity worth pursuing.

Provincial research organizations were viewed as important potential partners going forward. The publicly funded nature of the Canadian health care system is also a major strength that could allow researchers to access data from increasingly representative population-based sample sets. The Canadian Community Health Survey (CCHS) and the Canadian Health Measures Survey (CHMS) were cited as examples.

**Diverse Populations:**

Canada's ethnic diversity, coupled with defined and special populations including First Nations, Métis, and Inuit populations, restricted cultural and geographical populations and special high risk populations (e.g., South Asians with respect to diabetes and cardiovascular disease) present an opportunity for well-designed intervention studies. The ethnic diversity of Canada serves as an opportunity for studies that determine how changes in environmental exposures and lifestyle changes stimulated by migration impact on disease risk in the next generation of family members.

‡ Key cohorts that currently exist in Canada include: Canadian Longitudinal Study on Aging; Genetic, Environmental and Microbial (GEM) Project; Canadian Healthy Infant Longitudinal Development (CHILD) Study; and the Tomorrow Project.

## C. Supporting Environments, Genes and Chronic Disease Research through Capacity-Building

The groups were asked how Canada can best improve research capacity in the area of environments, genes and chronic disease given the identified strengths and gaps. Research capacity includes people (researcher training, mentoring, recruitment and retention) and research culture (research environment and infrastructure).

**People:**

Continued support for trainees by CIHR was noted as a key element of research capacity development. Participants indicated that training opportunities should provide an intellectual framework for researchers to identify appropriate study designs for environments, genes and chronic disease research. Postdoctoral fellowships within multidisciplinary teams could encourage collaborations across themes. There was strong support for the training of clinician scientists.

Networking activities, such as multidisciplinary "boot camps", could bring researchers together across disciplines to promote interdisciplinary collaboration and to encourage more systems biology approaches. Significant support was expressed for new, innovative approaches and funding models that could bring like-minded people together across disciplines in a truly integrated manner, building on CIHR experience with Team Grants and the Strategic Training Initiative in Health Research (STIHR).

There was also a strong sense that there are opportunities to build Canadian research capacity by fostering interagency collaboration with the Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council of Canada (SSHRC), Genome Canada, Canada Foundation for Innovation (CFI) and the Canada Research Chairs (CRC) program. Research capacity may also be built by increasing international exposure, enhancing international partnerships and integrating efforts with international funding agencies, including the US National Institutes for Health (NIH).

**Research Culture:**

Numerous improvements to research infrastructure and environment were identified that could improve research capacity in environments, genes and chronic disease research. For example, research capacity could be enhanced with improved availability of appropriate blood and tissue samples through biobanks. The importance of more centralized support for cohort study development was also emphasized, including data harmonization, improved REB processes (with a preference for a collective approvals process) and a network of recruiting centres to enhance and expedite the recruitment of individuals into cohorts and trials. There was support for collaborative, multidisciplinary teams and population health level sources of data, such as NHANES, CCHS and CHMS.

The CIHR Open Access Policy, introduced in 2008, was referenced with respect to helping build research capacity in Canada. The underlying premise is that widespread and barrier-free access to cutting-edge research and knowledge enables scientists, clinicians, policymakers and the public to use and build on this knowledge.

# 5. Opportunities for Partnerships

Following the first two breakout group discussions, **Dr. Jane Aubin** led a discussion on the importance of partnerships for large scale research projects and programs. She emphasized the central role that partnerships play at CIHR and how important it is for partners to be involved at the early planning stages of a research initiative.

CIHR partnerships are critically important in six areas: improving health research funding; improving health research capacity; translating research knowledge into outcomes; setting research priorities; using resources effectively; and sharing best practices. She challenged participants to think creatively to develop innovative approaches to partnership.

Dr. Aubin highlighted two CIHR Signature Initiatives, and the approaches that CIHR is taking to promote international partnerships and collaborations between Canadian researchers. As part of the Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) Initiative, CIHR became a full member of the International Human Epigenome Consortium, with the aim of stimulating international partnerships. In contrast, in the Community Based Primary Health Care Initiative (CBPHC) Initiative, researchers partnered with community physicians to advance disease prevention and health services delivery at a community level. Going forward, CIHR will aim to marry aspects of both of these partnership approaches in other research initiatives.

Dr. Aubin noted that it is important at the outset for partnerships to develop common metrics to evaluate the success of the project. With respect to data harmonization, Dr. Aubin noted that a large number of working groups in multiple government agencies are currently examining ways to improve sharing of electronic records and biobank data. Dr. Aubin also observed that while current economic conditions have left funders of health research financially challenged, by partnering research funders increase the amount of research conducted for every research dollar spent.

Ensuing discussion focused on CIHR partnerships with provinces, the pharmaceutical industry and issues related to data harmonization and sharing. In response to comments, Dr. Aubin acknowledged that CIHR is well aware of the need to partner with federal and provincial research funding agencies. She also noted that the International Review Panel recommended increased collaboration between CIHR and the other federal funding agencies, and acknowledged the important role health charities continue to play in partnering with CIHR.

It was noted that future meetings should include the users of information, as they are the ultimate partners in health research and have much to offer.

# 6. Prioritization

A summary of the most promising research questions is presented in **Table 1**. The topic of environmental factors on early life development, genetic and common origins (e.g., inflammation) of chronic disease in Canada and in recent Canadian immigrants compared to those living in developing countries drew considerable support from workshop participants. Similar studies of Aboriginal people and their migration to urban setting were also noted as a priority. There was also strong support for defining signature molecular pathways of environment-genome-epigenome interactions for the purpose of phenotyping chronic disease. Investing in bioinformatics, statistics and improved methodologies for studying the roles of environments and genes in chronic disease was also highlighted.

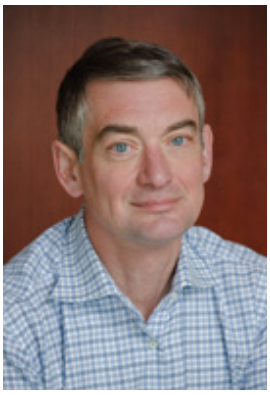
**Table 1. Most Promising Research Questions in Environments, Genes and Chronic Disease**

| Overall Goal |
| --- |
| Determine the roles and mechanisms of interaction of the environment and the genome on the development of chronic non-communicable disease. |
| **Specific Goals** |
| • Address the effects of genes and environmental factors, including exposures during critical periods of development, on chronic disease in Canadians, recent Canadian immigrants and those living in developing countries<br>• Define signature molecular pathways of environment-gene interactions for the purposes of phenotyping chronic diseases and identifying biomarkers of environmental exposure<br>• Develop novel study designs, including bioinformatics and statistics approaches, to delineate environment-gene interactions and characterize key environmental factors in the development of chronic disease<br>• Investigate how the environment modulates chronic disease severity in genetically susceptible populations, including expression of varying disease phenotypes<br>• Assess how environment-gene interactions modify responses to therapeutic interventions for chronic disease<br>• Determine the roles of environments and genes in chronic functional disorders ("neglected" but common conditions) |

In the considerable discussion that followed, support for basic science research and research related to vulnerable populations was strong. In contrast, intervention research, which was frequently mentioned during the workshop, was not frequently mentioned. Dr. Malcolm King commented that this could be the result of uncertainty about whether current scientific understanding provides sufficient basis for intervention research. Participants suggested that the study of environmental and genetic determinants of biomarkers is useful, and that discovery of biomarkers is closely related to discovery of new disease-related molecular pathways.

Cohort data and biobank information sharing were identified as clear needs, as well as increased capacity in bioinformatics, systems biology and related emerging fields. The need for additional communication across agencies in order to improve investment in research infrastructure was also highlighted.

# 7. Workshop Summary



**Dr. Paul Lasko** offered reflections on the workshop. He summarized key assets identified for Canadian research in environment-gene interactions:

- Canada's ethnic diversity with specific well-defined populations, including First Nations, Inuit and Métis communities as well as other culturally and geographically isolated groups;
- a strong cadre of scientists across all pillars
- a strong history of productive networking among researchers;
- a strong research capacity in the "omic" sciences; and,
- the existence of numerous cohorts, many already well phenotyped, but also presenting challenges related to restrictions on access, variable quality of curation, visibility and sustainability issues.

Dr. Lasko then recapped several of the overall challenges for research in environment-gene interactions:

- high-throughput technologies are cheaper and more advanced for obtaining genetic data than is currently available for obtaining environmental data;
- lack of standard operating procedures for measuring environmental exposures; and,
- deficits in theoretical and methodological tools for integrating genetic and environmental data.

Additional Canadian challenges for work in this area include:

- sub-optimal integration, utilization and coordination of cohorts;
- limited investment in EWAS-type studies;
- complex REB processes, especially impacting large consortia;
- complications concerning data harmonization and data sharing across provinces; and,
- past difficulties that have eroded trust and still impact cooperation between researchers and Aboriginal populations.

Dr. Lasko noted that it is imperative to ensure that a new Canadian initiative in Environments, Genes, and Chronic Disease is well integrated with international efforts to take full advantage of emerging technologies and potentially access larger cohorts. He suggested that this initiative might best seek to address an issue of particular importance to Canada. Finally, he spoke about the need to ensure that the new Canadian initiative complements CIHR Signature Initiatives in epigenetics and personalized medicine that are already being launched.

In the discussions that followed, Dr. Shoo Lee indicated that it is imperative to make cohorts sustainable, including those not funded by CIHR, such as the GEM project. He indicated the importance of assigning control to cohort samples and data. As an example, he described the Canadian Neonatal Network, a birth cohort of close to 500,000 births, which involves the collection of data from all high risk pregnancies in the country. This is a tremendous resource for the country and is now open to community access, at the discretion of the Science Advisory Board.

# 8. Conclusions

It is now widely recognized that many non-communicable chronic diseases arise as a result of a complex interaction of environmental and genetic risk factors. This workshop reinforced that there remain critical gaps in knowledge related to the role of environment-gene interactions in chronic disease, as well as numerous infrastructure challenges and gaps particular to Canada. Filling these knowledge gaps and collectively addressing the identified infrastructure challenges is seen as imperative to reducing the burden of illness of both common and rare chronic diseases, to improving the quality of life of affected patients and to reduce health care inequities for vulnerable populations across Canada.

**Key themes** that emerged throughout the workshop deliberations included:

- the need for data standardization, better metrics and data sharing;
- the importance of enhanced networking among researchers, including new and innovative models to bring like-minded people together across disciplines;
- the urgency of addressing barriers to the current research ethics approvals process;
- the need for more centralized support for cohort study development and enhanced collaboration and sharing among cohorts; and,
- the importance of interagency collaboration and national and international partnerships for moving large scale research projects and programs forward.

**Key research goals** identified at this workshop included:

- Addressing the effects of genes and environmental factors, including exposures during critical periods of development, on chronic disease in Canadians, recent Canadian immigrants and those living in developing countries.
- Defining signature molecular pathways of environment-gene interactions for the purposes of phenotyping chronic diseases and identifying biomarkers of environmental exposure.
- Developing novel study designs, including bioinformatics and statistics approaches, to delineate environment-gene interactions and characterize key environmental factors in the development of chronic disease.

INMD and IG partnered on this national workshop in order to better understand the nature and extent of the gaps and challenges in Canada in undertaking research into environments, genes, and chronic disease. The comprehensive and thoughtful deliberations and insights gained will facilitate ongoing discussions with respect to how to best move forward in this important research area. Environments, Genes and Chronic Disease is a topic of international

interest, as demonstrated by a number of recent workshops[16, 17]. It is imperative that a new Canadian initiative is well integrated with international efforts in order to leverage emerging technologies and to access large cohort studies.

# Appendix I - Participants

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