CIHR IRSC | Institute of Nutrition, Metabolism and Diabetes
Institut de la nutrition, du métabolisme et du diabète

JDRF

Opportunities for T1D Screening & Prevention in Canada

VIRTUAL WORKSHOP REPORT

FEBRUARY 15TH, 2022 | 11:00-2:30 PM (EDT)

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Welcome & Opening Comments: JDRF Canada / CIHR INMD

Dave Prowten – *President & CEO of JDRF Canada*
On behalf of JDRF Canada, Dave Prowten welcomed participants and thanked CIHR's Institute of Nutrition, Metabolism and Diabetes (INMD) for co-hosting this virtual workshop, and for collaborating in the ongoing Partnership to Defeat Diabetes, through which JDRF and CIHR have been jointly funding type 1 diabetes (T1D) research since 2018. Canada has a long history of excellence in diabetes research, and he said he was looking forward to the upcoming discussions about opportunities for Canadian research that can continue to advance this field.

Sarah Linklater – *Chief Scientific Officer, JDRF Canada*
Sarah Linklater provided a brief background of JDRF's perspective on screening. In the past few years, screening for T1D has become a key pillar of the organization's global research strategy. JDRF has learned a great deal from research programs that focused on screening in family members, and several efforts are now underway in different countries to determine how to advance universal population screening. There is strong evidence that if people are identified in the early stages of T1D, before the onset of insulin dependence, outcomes may be improved around the time of clinical diagnosis, particularly through the reduction in the incidence of Diabetic Ketoacidosis (DKA) and by supporting families in adapting to a diagnosis. In addition, multiple therapies with the potential to prevent progression of T1D to insulin dependence are being explored. Canada has been pivotal in many of the earlier studies involving family-based T1D screening, and this workshop will focus on opportunities in research in the area for T1D screening in Canada.

Dr. Norm Rosenblum – *Scientific Director, Canadian Institutes of Health Research (CIHR) Institute of Nutrition, Metabolism and Diabetes (INMD)*
Dr. Norm Rosenblum began by thanking participants of the workshop, and noting that in 2021, Canada celebrated 100 years since the discovery of insulin. In 2018, CIHR held a workshop and then launched the strategic research initiative, 100 Years of Insulin: Accelerating Canadian Discoveries to Defeat Diabetes, together with JDRF Canada and other partners. This five-component initiative is the largest strategic investment in diabetes research in the history of the CIHR. Today, 19 new Canadian research teams have been funded to pursue diverse research topics, and more will be funded through competitions that are in progress. CIHR is very appreciative of the partnership and collaboration efforts of JDRF Canada.

The topic of this workshop is timely. Advances in genetics, biomarkers and prevention are beckoning us to imagine how screening can be configured for T1D and what roles it can play in improving the lives of individuals. The first set of presentations will provide an overview of the global state of the science and a glimpse at some of the initiatives that are ongoing in different jurisdictions. After the break, the focus will be on screening in Canada more generally and some key considerations that are relevant to T1D screening.

Workshop Objectives

- To review the state of the science and key research gaps/questions in the field of T1D screening and prevention, globally and in Canada
- To determine Canada's readiness for T1D screening and prevention (capacity, infrastructure, etc.)
- To identify the potential risks or challenges (including ethical, economic, legal and social) and benefits of T1D screening in Canada, and potential research questions related to identifying and quantifying these risks and benefits
- To identify Canada's particular strengths that can help to accelerate research efforts to advance T1D screening and prevention
- To consider the international context for Canada in the field of T1D screening and prevention

T1D Screening in the International Landscape

T1D Screening and Prevention: Global Landscape & State of the Science

Frank Martin - Senior Director, Research, JDRF International

Frank Martin provided a brief overview of the state of the science in universal T1D screening around the world. He started by outlining the current barriers of universal T1D screening including lack of awareness of T1D stages, limited access to screening, and lack of insurance coverage for screening. Currently, there are no approved guidelines for T1D screening and there are no FDA approved treatments to slow or prevent T1D progression.

Data from the IDF Diabetes Atlas 2021 shows that Canada is among the top five countries with the highest incidence rates of T1D in children under 14 years of age. Globally, the T1D Index project aims to quantify the true global burden of T1D across the world (number of people who have T1D vs number of people who would be alive today with access to appropriate therapies).

The American Diabetes Association (ADA) recommends T1D screening for first degree family members of a proband with type 1 diabetes with a panel of islet autoantibodies as the presence and type of islet autoantibodies can be used to predict T1D risk. By and large, current research-

based screening programs are focused on only screening those people with family history of T1D. However, up to 90% of people diagnosed with T1D do not have any history of T1D in their family. Today, more and more countries have started to pilot general T1D screening programs recognizing the limitation in only screening at-risk communities. Recent efforts have indicated the optimal ages in childhood at which to screen to capture the majority of the at-risk community. Accurate staging of disease and identification of the at-risk community is critical to determine who would benefit from interventions and when best to apply them. Without screening efforts, the risk of mortality and complications of DKA can go up to 40-60%, whereas with screening, this risk goes down to 3-5%.

The future of T1D staging/risk stratification goes beyond the use of an oral glucose tolerance test (OGTT) and measurement of autoantibodies. While OGTT is accurate in determining progression from stage 2 to 3 of the disease, it is limited in its accuracy in determining when this progression will occur. The use of CGM may be able to predict progression between stage 2-3 better (from 1 year compared to 5 years via OGTT, recent publication from Steck, et al.). There is also a need to consider feasibility and the optimal timepoint for screening T1D. In TIDI, a recent study that aggregated data from 5 international cohorts using AI analysis, researchers found that screening at ages 2 and 6 have the most optimal sensitivity in identifying T1D.

Before screening can be implemented in the population, consideration must be given to its potential limitations. Screening will not tell when and if someone will develop T1D for certainty. Therefore, the results of screening can increase anxiety and distress which may be alleviated with education and counselling.

Topic #2: Case Study – Launching a Pilot Trial of General Population T1D Screening in Australia

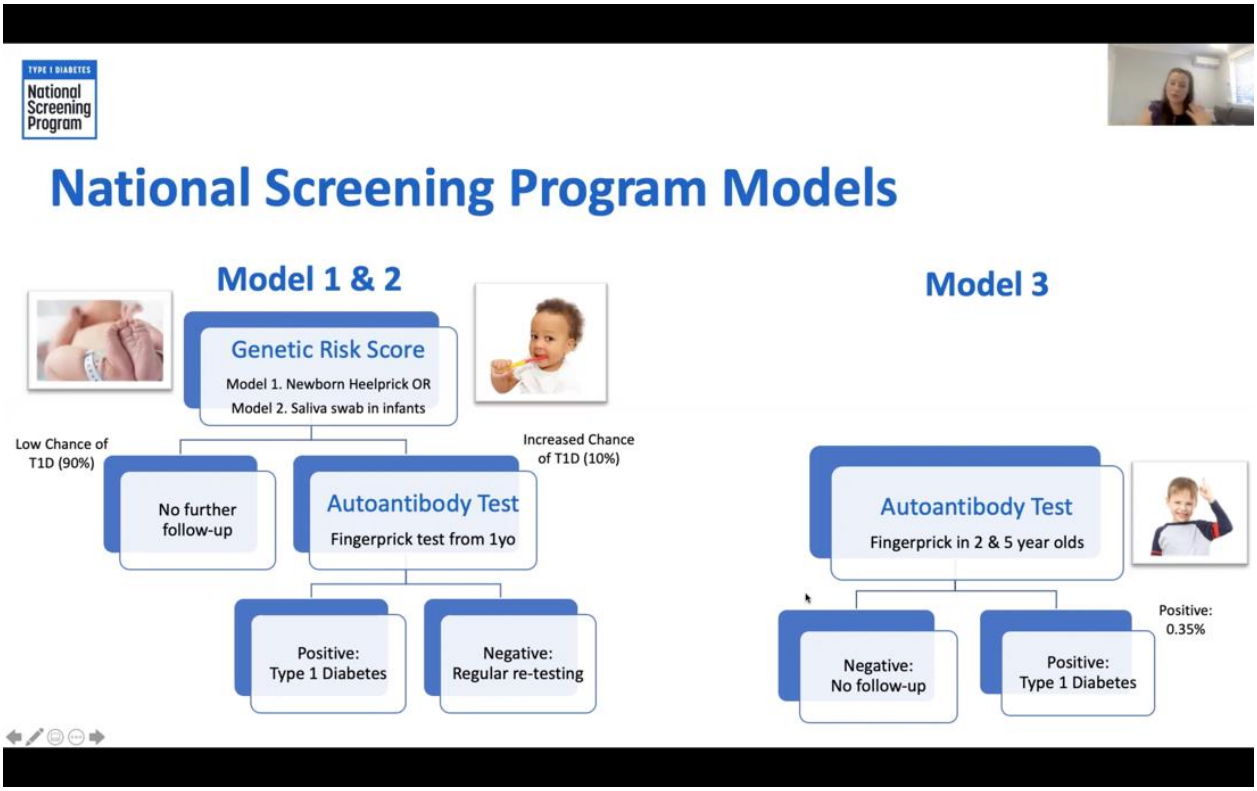
Dr. Kirstine Bell - Principal Research Fellow – Australian Type 1 Diabetes National Screening Program Pilot, The University of Sydney

Kirstine Bell spoke about the Australian Type 1 Diabetes National Screening Pilot Program which she is leading. The vision for this pilot is to establish a national general population screening program for T1D in Australia to reduce burden of DKA and multiple sequelae. Prior to starting the pilot, certain requirements were outlined and considered to ensure the success of the program. The program should be public health and policy-focused, embedded in the health system, consistent nationally, scalable and sustainable, future-focused, and adaptable.

In designing such a screening program, the group embarked in an in-depth planning and design process. They evaluated and assessed the current evidence within the context of the Australian landscape, created a stakeholder map and engagement plan, and are building the screening infrastructure. A large-scale screening program such as this requires the involvement and engagement of many stakeholders and collaborators, such as clinical care, research domains, government, professional bodies, and families.

With this screening pilot, the overarching objective is to find an optimal model for routine screening in Australia. There are three aims in total:

- Feasibility and acceptability of three screening models
- Health technology assessment and economic modelling
- Stakeholder mapping and engagement



In terms of the three screening models, models 1-2 use a genetic risk stratified approach (via newborn heelprick or infant saliva swab) to follow-up with participants who have an increased risk of developing T1D via autoantibody testing. Model 3 skips the first step of establishing a genetic risk score and goes directly to the autoantibody testing at 2 and 5 years of age[1]. Each model was carefully rolled out in at least two Australian States to make sure that feasibility and acceptability is not State-specific, with the intention of keeping the catchment area narrow and the goal of screening the majority of the population in that catchment area.

The Australian Type 1 Diabetes National Screening Pilot Program is expected to run for three years, and recruitment is due to commence in 2022.

[1] Note from Dr. Bell: they have subsequently updated their model to screen 2-, 6-, and 10-year-old children, in line with recent evidence regarding optimal ages for screening. She noted that this may be population-specific, and they would like to capture feasibility and acceptability data on children in the 10-year old age group (in addition to the 2- and 6-year old children).

Topic #3: Clinical Trial Networks to Enable T1D Screening & Early Intervention Research: The INNODIA Experience

Prof. Chantal Mathieu - Professor of Medicine at the Katholieke Universiteit and Chair of Endocrinology at the University Hospital Gasthuisberg Leuven, Belgium

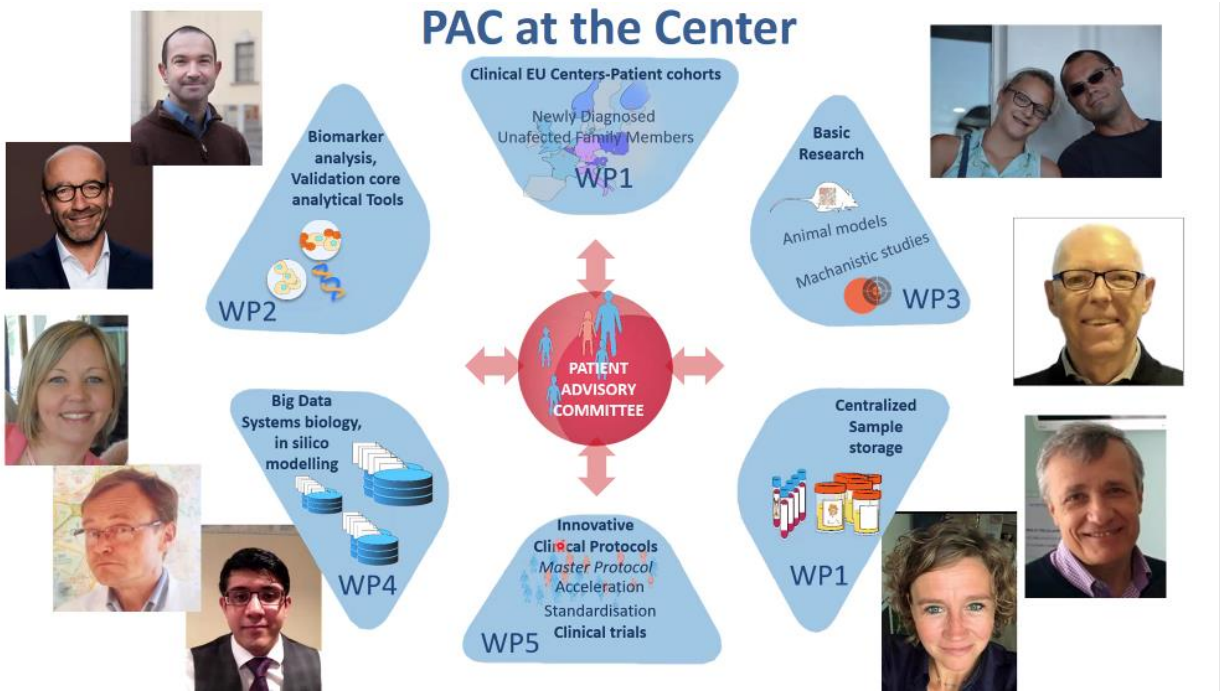
Dr. Chantal Mathieu is a physician-scientist who coordinates the European Innovative Medicines Initiative (IMI)-funded project 'INNODIA' on biomarker discovery and intervention studies in type 1 diabetes. INNODIA is a global partnership between 31 academic institutions, 6 industrial partners, a small sized enterprise and 2 foundations, bringing their knowledge and experience together with one common goal: "To fight Type 1 Diabetes". INNODIA examines samples and data from newly diagnosed patients with type 1 diabetes and unaffected first-degree relatives throughout Europe to better understand the relationship between changes in β-cell function, immune profiles, genetic and environmental factors, and their role in the onset of the disease. From the start, another major goal of INNODIA, was to undertake clinical intervention studies in an attempt to halt the further decline in beta cell functionality in people with newly diagnosed T1D, addressing the immune system or the beta cells by different treatment modalities.

Dr. Mathieu shared some insights from INNODIA in Europe. Both INNODIA and INNODIA HARVEST are a public-private-partnership funded by the European Commission within the framework of the Innovative Medicines Initiative in collaboration with JDRF, the Helmsley Charitable Trust, and private companies. INNODIA has two aims:

1. Establish a logistic network in Europe – Given that Europe consists of many different countries, cultures and languages, it is not a simple feat to establish a logistic network. The importance of setting up this network was instrumental in standardizing and accrediting centers and satellites for intervention trials.
2. Discovery of T1D biomarkers – Although there are already biomarkers being used today, such as genetic markers and autoantibodies, there is a dire need to discover more T1D biomarkers relevant to the general population that will allow more accurate T1D risk prediction.

One of the biggest hurdles in establishing INNODIA was getting the clinicians on board as the lack of current treatment to prevent T1D creates hesitancy. With the many different countries

in Europe, there was a need to provide regional context through adequate translation and adaptions to the materials. There were also logistic issues with transferring samples and data from one country to another.



In terms of what makes INNODIA work, there are funds that strategically support the network, which provided the momentum to collaborate with academic institutions, industry partners, and foundations. Other key factors included standardization at each site and logistical support within the network. At the heart of INNODIA is the Patient Advisory Committee (PAC), which consists of people living with the disease and their families. The PAC was instrumental in designing the studies by providing advice on the protocol and methodology, specifically which parts are feasible and acceptable from the perspective of the participants. They continue to play a key role in knowledge mobilization, by helping create information brochures, newsletter, recruitment video, etc.

Currently, INNODIA has recruited over 6000 participants and reached its target sample size. The next steps are to continue working with different studies that work on general population screening and share knowledge globally to further INNODIA's mission.

Panel Discussion:

- **How do you ensure that the PAC is diverse for INNODIA?**
    - JDRF was crucial in helping to establish the PAC for INNODIA. Diversity in Europe takes into account different countries and cultures. The PAC members are volunteers and so continual recruitment is needed. Also PAC members are "trained" to understand scientific concepts (e.g., understand biomarkers, screening, risk).
- **What genetic risk scores are being used in Australia and how might they be applied to Indigenous populations in Australia?**
    - They are using GRS2 methodology from Richard Oram and his team. They are looking to see if it is also relevant to the Australian population. In terms of studying the disease in the Indigenous community, it is a complex issue and a challenge as Indigenous Peoples often don't present traditionally.
    - To study Indigenous population a large enough sample size is needed, and a good understanding of diabetes classification, to study genetics directly.
    - Ownership and guardianship of data (e.g., genetics / epigenetics / other) in relation to Indigenous Peoples is a very important issue and must be dealt with appropriately.
- **How essential would it be to follow single autoantibody (AA)+ individuals?**
    - In INNODIA, there are about 300 individuals with single AA+ and some of them jumped immediately to T1D (i.e. they did not follow the stages). The primary reason for including single AA+ individuals was to investigate if there might be some biomarkers that might help identify how single AA+ individuals progress in terms of T1D. The decision to include them or not depends on the study, for example, if it is an intervention study specific to the timepoint around dysglycemia, then it might be easier to include only double AA+ individuals. If the study is attempts to capture everyone, then including single AA+ would be good.
    - For Australia, single AA+ individuals were not included because the pilot was designed to be public health focused and there is a need to weigh cost-effectiveness and capturing the most people.
    - Single AA+ cases should be looked at relevant to the timepoint. If single AA are detected very early in life, then it is high risk and should be followed-up very carefully. If it is detected in an 8–10-year-old and it seems relatively stable over a period of time, then the risk is much lower.
    - Any comprehensive system has to be able to deal with single AA+ individuals. We need to confront this, especially in screening studies.
- **What do we actually need? Is it population screening in the general population or is it the infrastructure to screen so we can treat the disease?**
    - We need both. In terms of public health, we are not treating T1D as early as we should be. We need to work on implementation science to get T1D risk screening into newborn screening panels, and/or primary care, as well as monitoring. We

also need the screening infrastructure to support development of trials and therapies.

- Funding is what is needed to advance the field -- but we also need people to work well with each other

T1D Screening in Canada

Topic #4: Newborn Screening

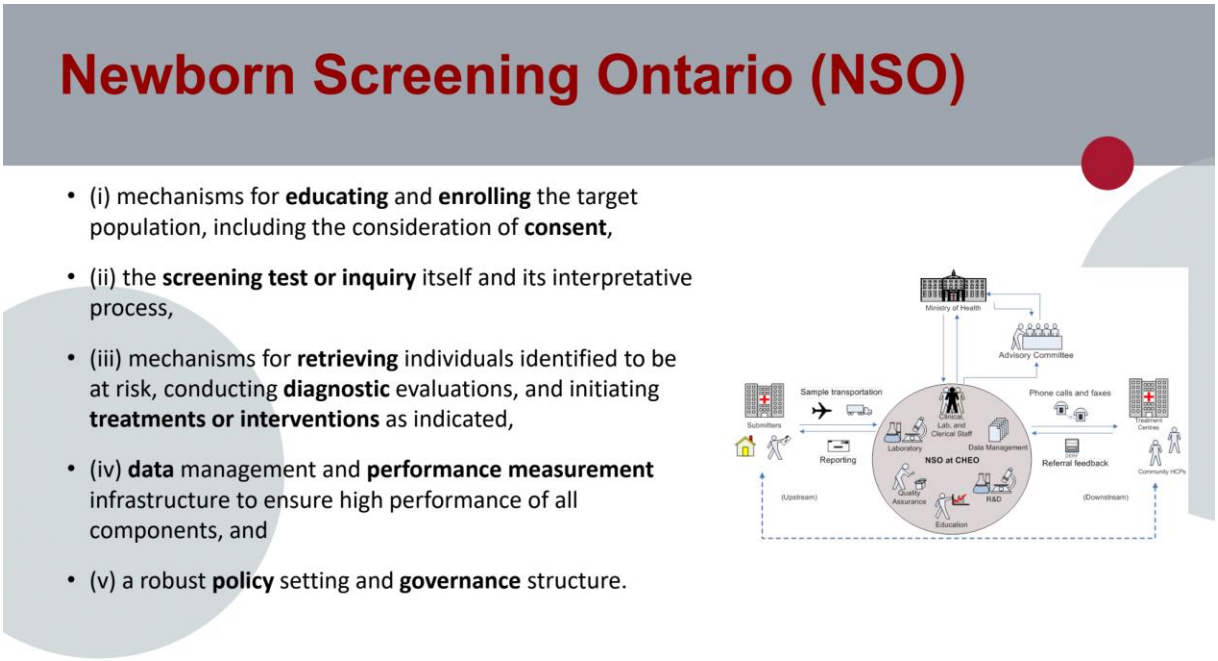
Dr. Pranesh Chakraborty

Dr. Chakraborty is a physician certified by the Royal College in Medical Biochemistry and Pediatrics, with a subspecialty in Biochemical Genetics. He joined CHEO in 2003 as a clinician seeing patients with Inherited Metabolic Diseases, and now serves as Division Head. In 2006 he led the transition of Ontario's newborn screening program to Ottawa establishing the Newborn Screening Ontario (NSO). NSO has grown substantially over the ensuing years now performing a wide variety of genetic and biochemical tests, and Dr. Chakraborty continues to lead this internationally-recognized screening program as Medical and Laboratory Director. He served on an expert advisory panel reviewing the American federal recommended universal screening panel decision process and is a co-Principal Investigator and co-lead of the CIHR-funded Canadian Inherited Metabolic Disease Research Network and INFORM-RARE projects.

Dr. Chakraborty spoke about his experience with introducing screening programs in Ontario as well as Ontario's framework for nominating a new screening program. Dr. Chakraborty began his talk by distinguishing between screening (aimed at better outcomes by initiating treatment early in disease progression in an asymptomatic population), and diagnosis (used to establish pathology in a symptomatic population). The main task when evaluating potential screening targets is to appraise the relative benefits and harms, including societal and health economic implications. Newborn Screening Ontario (NSO) provides screening education, analysis, research, and development while considering caregiver consent, policy setting, and governance structure. Next, he addressed the 1968 Principles and Practice of Screening for Disease by Wilson and Jungner, which provides relevant information for broad population and primary care screening practices. As with other possible targets, the main considerations for T1D screening based on these principles would be the public health burden of disease, existence of a treatment and suitable test, detailed knowledge of the natural history of the condition, and the acceptability to the population.

Dr. Chakraborty acknowledged that Canada does not have a unified process for considering whether a condition should be considered for newborn screening panels. Ultimately, a national

newborn screening program would have to consider 13 different jurisdictions. In Ontario, the framework follows Wilson and Jungner's Principles and organizes committee recommendations by the conditions, test, treatment, and societal considerations. Concerns in any of these domains by scientific, societal, or political bodies would prevent the consideration and implementation of screening.



He also showcased the decision matrix used in the United States by the [Advisory Committee on Heritable Disorders in Newborns and Children]. To investigate the implementation of newborn screening, this matrix focuses on a dimension of net benefit and grading of certainty, readiness, and likely feasibility across all 50 states from a federal perspective.

Dr. Chakraborty shared his experience with the screening for risk-based programs currently offered in Ontario, which include MCAD deficiency and permanent hearing loss (PHL). He noted that from his history working with people who screened positive for MCAD deficiency risk, the system of care that follows a positive screening can place significant mental and physical burden on an individual. He ended his presentation by providing an overview of the work Ontario has been doing on PHL through a universal newborn hearing screening program for early PHL risk factors. He asked the group to consider how high of a risk is needed to justify population screening and if Canada has the system of care in place to facilitate the needed next steps. Specifically, for T1D, consideration around surveillance and interventions (primary and secondary, including psychosocial) for screen positive individuals is important.

Topic #5: Genetic Risk Scores to direct screening in type 1 diabetes

Dr. Richard Oram

Richard Oram, Associate Professor at the University of Exeter, has developed an inexpensive, simple method to assess genetic risk in type 1 diabetes – a T1D genetic risk score (T1D GRS). He has shown this can be used as a diagnostic test to differentiate type 1, type 2 and monogenic diabetes and he is working on uses of the T1D GRS in an ethnically diverse population. Richard is testing the utility of the T1D GRS for prediction of type 1 diabetes by combining genetic information with longitudinal biomarkers to better predict type 1 diabetes and other autoimmune diseases from birth in the NIH-funded TEDDY study and Trialnet Pathway to Prevention study.

Dr. Oram began his presentation by highlighting the nuances within T1D as the genetic risk score is strongly discriminative for T1D compared to T2D, and this relates to the fact that the majority of T1D risk is captured by a small number of SNPs in the HLA region. Dr. Oram proposed investigating the proportion of infants at risk of developing T1D that would be captured by a population screening program and suggested that genetically directed early life follow-up efficiently identifies most early life T1D.

Dr. Oram explained that genetics are becoming increasingly cheap and simple to measure and could be used as a new biomarker, alongside autoantibody screening, to better predict T1D. Studies have shown that peak islet autoantibody immunity occurs around 1 year of age and those who convert to islet autoantibody positive at age 1 are at risk of progressing to T1D by age 1-3. In some cases, these individuals are most vulnerable to presenting with severe DKA and other major health complications. It is difficult to identify these patients on a cross-sectional screen, but the majority of them could be picked up by genetic risk score screening from birth.

An important consideration for all studies of genetic risk, is the impact of ancestry. For any T1D screening programme that includes a genetic risk score it will be important to assess whether there is an impact of ancestry on the discriminative power of a T1D GRS, and baseline genetic risk. Given the majority of heritable risk in T1D is strongly associated with HLA class II, the population frequency of T1D risk and protection HLA class II alleles is likely to determine the

impact of ancestry. He recommended that future studies of T1D genetic risk and epidemiology in Canada may want to include the full diversity of ancestry in the Canadian population.

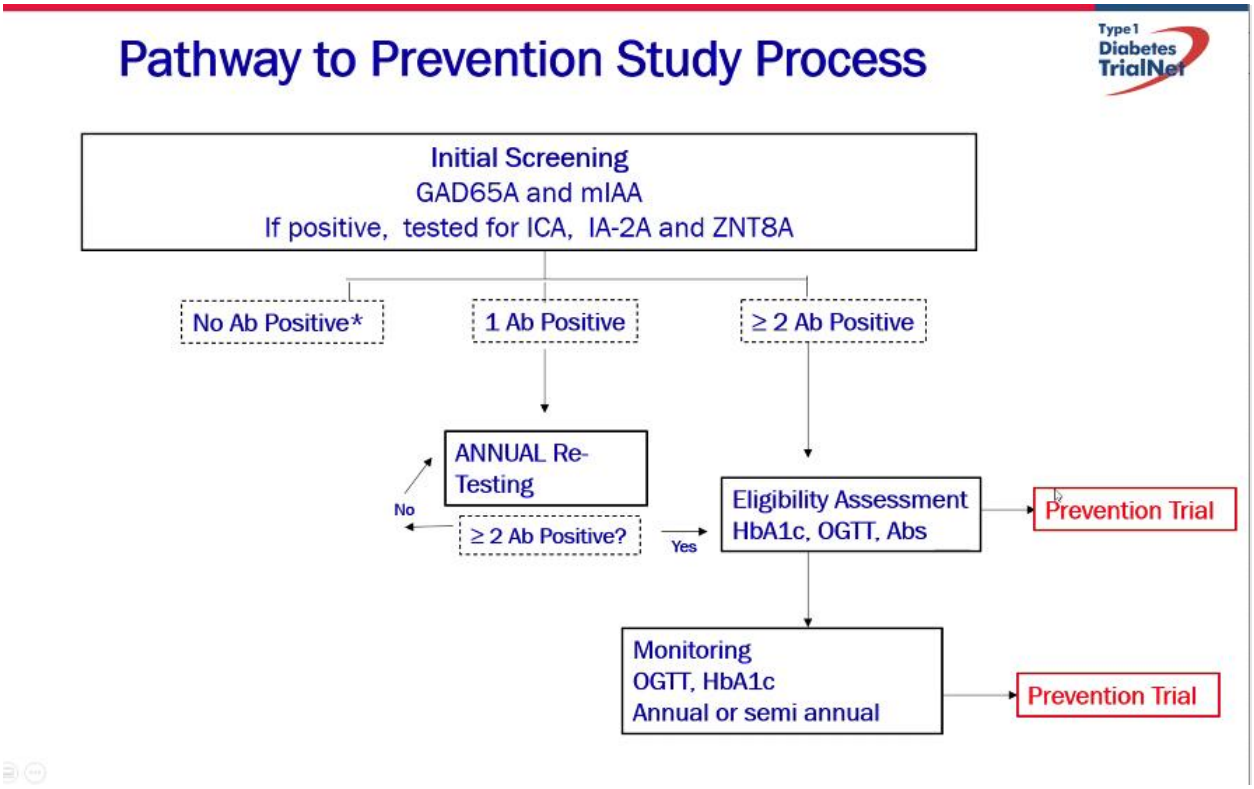
Finally, he highlighted important considerations for any screening programme such as the consequences of screening, including adverse effects of identifying high-risk individuals, the impact on health insurance, and the cost-effectiveness of infant screening relative to its benefit (i.e., DKA prevention, intervention, practical issues, and long-term benefits).

Topic #6: T1D Screening in Canada: The TrialNet Experience and Perspectives on General Population Screening

Dr. Diane Wherrett

Dr. Diane Wherrett is a pediatric endocrinologist at the Hospital for Sick Children and Professor, Department of Pediatrics, University of Toronto. Her major research focus is in interventions to prevent beta cell loss in type 1 diabetes. She is a member of the Steering Committee of the NIH-sponsored multi-centre clinical trials group, Type 1 Diabetes TrialNet, chairs its largest study and is the director for the Canadian Clinical Centre for this study group.

Dr. Wherrett spoke on the history of Canada in T1D screening, particularly with TrialNet. Canada has a long history of family-member screening in clinical trials as it has participated in various projects such as the European Nicotinamide Diabetes Intervention Trial (CANENDIT), Diabetes Prevention Trial – Type 1, and the Trial to Reduce Insulin-Dependent Diabetes in the Genetically at Risk (TRIGR). Additionally, Canada contributed to the T1D TrialNet study, beginning in 2001, whose main goal was to assess therapy to preserve beta-cell function. The Pathway to Prevention study associated with TrialNet has made efforts to characterize T1D development risk, elucidate the pathogenic factors of T1D development with biobank accumulation, and uncover the natural history of T1D. Gold-standard central antibody screening for TrialNet targets children at 2.5 years of age or relatives of individuals with T1D using on-site or at-home capillary kits. This program also provides surveillance and prevention trials for those who test positive, especially those who present 2+ autoantibodies.



In Canada, TrialNet sites are represented nationally with participants self-identifying as White (78%), Asian (5.5%), and Black and Hispanic (~2%). These categories are based on the American context, which might explain the 12% of participants who did not report a race/ethnicity.

Dr. Wherrett went on to share some of the main lessons and considerations learned from TrialNet, such as the importance of surveillance, research teams with an understanding of T1D risk, capacity in clinics and remote areas, public acceptance, education for those at increased risk, and a uniform national Research Ethics Review framework. To expand screening in Canada, the research community must optimize autoantibody testing, implement recruitment and education strategies for health care professionals, develop general-population surveillance for individuals who screen positive, and address inequities by identifying those most at risk.

Break Out Groups

All participants were invited to take part in 30-minute breakout groups to discuss questions aligned with the workshop objectives. Each breakout room was assigned a specific question and asked to appoint a facilitator and a note-taker. The facilitator guided the discussion and ensured all members of the group had an opportunity to contribute. The note-taker captured what was discussed and provided a 2–3-minute summary upon return to the main room.

Breakout #1: Knowledge Gaps and Research Questions

Question: What are the priority knowledge gaps and research questions that you would like to see the Canadian research community prioritize in the area of T1D screening during the next 3-5 years?

Discussion:

- Knowledge Gaps:
    - Basic epidemiology and rate of progression/incidence of T1D in different populations across various geographic regions within Canada
    - Metabolic monitoring, especially in remote areas
    - Feasibility of a national screening program requires basic logistics of population screening – who to screen, how to screen, and when to screen
    - The use of newborn genetics and autoantibody screening as a prognosticator of specific risk for patients
    - The health economics of a population-wide T1D screening policy in the Canadian context – consider costs relating to an individual's follow-up after a positive first screening and education (both influenced by the individual's age at initial screening)
    - Unique considerations regarding screening implementation, health economics, and basic science in the Canadian Indigenous population
    - Evidence required for insurance companies/other payers to reimburse screening tests
    - Evidence required for professional associations to create guidance around screening recommendations
    - Considerations for national vs local screening approaches
- Research Questions:
    - What is the cost effectiveness of continuous glucose monitoring tools and how do they compare to other at home/remote metabolic monitoring techniques?
    - How to garner trust and acceptance from patients, families, primary care providers, professional communities (ex. endocrinologists), and payers (ex. insurance companies) regarding screening?
    - Does DKA prevention provide sufficient rationale to merit continued work on a screening approach in the absence of an intervention to delay or prevent T1D?

- What is the cost effectiveness of newborn genetics vs auto-antibody screening for determining young childhood T1D development? Which method would be best suited for trial recruitment?
- What data from other countries can be repurposed in the Canadian context and what needs to be generated anew? (i.e., data from TrialNet, Fr1DA, and Innodia)
- The natural history/DKA prevention studies will require sufficient cohort sizes – How to overcome challenges regarding informed consent from parents?

Breakout #2: Strengths and Barriers

Question: What are Canada's particular strengths and barriers that can help or challenge efforts to accelerate research to advance T1D screening and prevention?

Discussion:

- Strengths:
  - Canada offers a public health care system, therefore, access is not a barrier
  - Organizations such as JDRF and Diabetes Canada (DC) have made significant efforts in connecting with the diabetes community, patients, and caregivers – they have established populations who are willing to participate in a screening program
  - Canada has a history of undertaking clinical trials for those with T1D and their families - previous trials have used antibodies to stratify risk
  - Canada has a history of using capillary tests for screening, therefore, in-person patient screening may not be necessary (especially beneficial for remote populations)
  - The Canadian Pediatric Endocrine Group has a history of physicians collaborating on long-term studies – would be required to advance T1D screening and prevention
- Barriers:
  - Patchy network for screening programs and clinical studies
  - Canada's research ethics boards are complicated to navigate – provinces are not all harmonized
  - Creating a national approach is challenging because Canada's health care is provincial - each provincial jurisdiction has their own regulatory structure for assessing screening and there is often a lack of formal communication between provinces to support decision-making (need to create a unified road map early)
  - Canada lacks capacity for autoantibody assessment – currently shipped to the US for all studies
  - There are unique challenges within the Indigenous community, including building trust, gaining acceptance, providing education, and elucidating genetic risk score without publicly available data
  - Previous T1D clinical trials lack data on stratifying risk based on genetics

    - Genetic risk testing is complicated in terms of who owns the data and how the data is used
    - Navigating stigmatization of those identified as having T1D risk

Breakout #3: Potential Risks and Benefits

Question: How can research be used to identify the potential risks and benefits (which may include ethical, economic, legal, or social) of T1D screening in Canada?

Discussion:

- Utilize the science of patient-preference research to better understand what is needed for consent and what can be done to support families going through the process (elements to consider include cost, location, potential for follow-up, etc.)
    - Can engage with Canada's established SPOR Networks
- Understand the logistical context of the research – need to clearly define PICO (population, intervention, comparator, and outcome), which will alter the risks/benefits
- Determine what research projects would need a screening approach to identify the research subjects for a primary prevention trial
- Need to establish the infrastructure for screening and applying interventions – basis for recruitment, managing psychosocial burden on patients/caregivers, etc.
- Elucidate the phenotype of T1D across ethnic groups to apply genetic risk scores – could start by performing validation research on the genetic risk scores of adults with T1D in the Canadian context (easier to get consent in this group as they are more knowledgeable on the topic compared to the general public)
- The need for this screening is not fully understood by the unaffected population so it would be a hard sell – research into public relations and marketing campaigns is needed
- Research to understand the psychological burden from a positive screening with the goal of implementing systems that will minimize harm to maximize benefit
    - How useful would screening results be in the real world and how much of a burden would it actually present/relieve in a general population vs those with a family history of T1D
- Determine if it is better to have a targeted intervention or a general population-based intervention for acceptability and feasibility
- Research to elucidate the relative risk over time and mitigate the duration that families will be living with uncertainty – consider how much risk are families willing to tolerate (idea of "ignorance is bliss")
- Need to better understand the support that individuals and families need after screening – learn from past studies that have provided emotional and psychological support to see what has/has not worked (ex. Genetic counsellors)
- How to best follow and monitor positively screened patients from a clinical perspective
- What are the benefits for an individual to get tested without a current disease modifying therapy?

- How much more likely would people be to get screened if there were multiple trial opportunities – does this work need to be linked with the other efforts to create trial opportunities to be accepted by the public?

Breakout #4: Key Ethnocultural Considerations

Question: What are some of the key ethnocultural considerations that must be incorporated into new research as part of an approach for equitable T1D screening in Canada?

Discussion:

- Ethnocultural considerations:
  - We need to distinguish between ancestry and genetics (test performances, etc.)
  - We need to consider differences in behaviours, beliefs, cultures, practices, and experiences
  - We need to consider equity and the groups historically excluded (how do we ensure that populations excluded from the past are part of the research process?)
  - We need to bring people to the table at the earliest stage as they can help design and shape the research themselves, not just further downstream or solely as data points
  - We need to invest in the messiness of authentically collecting ethnocultural data as it is time-consuming, expensive and resource intensive
  - We need to collect data on ethnicity and ancestry as they are critical in registries, interventions studies, etc.
  - We need to re-evaluate our measures of risk (are they actually good at identifying those at risk across all populations?)
- Stakeholder engagement:
  - Ask stakeholders what it means for them to be participating in research
  - Patients / Participants
    - Patient voice is incredibly important
    - Establishing trust is critical - we need to learn how much distrust there is in some communities (specifically on how their data will be used) and create opportunities to discuss and address their concerns
    - Reaching out to the hard-to-reach populations that are least likely to engage in interventions via authentic community engagement to optimize their opportunities for participation
    - Distribution of educational materials and engagement strategies require dissemination in multiple languages and sensitivity of the different cultural contexts. This is important to improve trust in the security of data

    - Healthcare practitioners
        - Education of clinicians in how to be part of the infrastructure that supports those who are identified as positive on screening
- Health System Perspective – need to understand how screening itself may increase/undermine equity?
    - Consider that those who are better able to handle the impacts of a condition are more likely to benefit from interventions that are designed to reduce morbidity or prevent disease
    - If screening is positive, how will equitable access to care (primary care or specialty) be ensured?
    - What is the impact of 'knowing' your child is at risk in terms of family/patient experience and what infrastructure needs to be built to ensure all patients/families are supported (no matter what their ethnic background is, where are they located, etc.)?
- Other Considerations
    - In the CHILD study, over 50% self-identify as Caucasian but when you use the Statistics Canada definition, the next largest group is "Mixed".
        - Consider if we need to re-define the paradigm of ethnicity - should it be defined by genetics, behaviours (i.e., exercise, diet)

Breakout #5: Knowledge Gaps and Research Questions

Question: What are the priority knowledge gaps and research questions you would like to see the Canadian research community prioritize in the area of T1D screening during the next 3-5 years?

Discussion

- **Uniqueness of Canadian research**
    - ⊄ Heterogeneity
        - Since Canada is a multi-cultural country, we may be able to use this to our advantage (i.e., what do HLA haplotypes look like in a far more genetically diverse country?). This will advance our understanding of GRS in diabetes.
        - There is still a lot to understand in terms of disease progression (why some eventually get the disease and others do not; why some progress faster and others slower)
        - Will need to consider genetics (genetic phenotyping, genetic load, etc.), environmental factors, stages of the disease at which treatment can be targeted
    - ⊄ Collaboration

        - Would like to see coordination of the Canadian effort specifically in some kind of a consortium where biobanking and subsequently biomarker analyses will be possible
        - Can potentially emulate large scale networks like INNODIA where there is ability to apply for research funding as independent centres / investigators
- **Research Questions**
    - How to increase uptake of screening between the many different stakeholders?
        - Will need to consider what parents would say and if they actually want this
        - Currently, very little uptake on governments and healthcare providers to do genetic testing on any diseases or conditions
        - It is extremely difficult to get healthcare providers onboard with the idea of screening
        - Having an approved treatment might change approach of thinking which might make screening more acceptable
        - Genetics is important but complex, as there is still a lot of hesitancy in the use of genetics in terms of screening (preconceptions and beliefs)
        - Might need CIHR and other public agencies to play a leadership role in this and start the process before governments will take a closer look
    - How would a screening program look in Canada?
        - Will need to consider who will be paying, how it could be implemented, and what is acceptable to all stakeholders
        - Will need to develop better communication strategies for parents / individuals screened
        - In terms of economics, would need to consider how to balance between costs and feasibility of screening and effects on healthcare costs in the future
        - It would be beneficial to work with a screening body like Newborn Screening Ontario and incorporate it into the system

Conclusions and Closing Remarks

Sarah Linklater

Sarah thanked everybody for their participation from across different time zones and countries. She said that JDRF is very grateful that participants took the time to be part of this discussion and provide their perspectives. She welcomed feedback in a short 5-question survey that was circulated to meeting participants.

Norm Rosenblum

Norm added that, based on CIHR-INMD's 2018 experience where the ground was prepared for new strategic research funding in diabetes, and this discussion will feed into the way he thinks about the future. He is confident that he will find new ways to explore this through collaboration. Finally, he thanked all participants tremendously for putting the time aside and adding their terrific comments.

Contact Us

For more information about the Virtual Workshop on Opportunities for T1D Screening & Prevention in Canada, please visit contact us at: inmd.comms@sickkids.ca or research@jdrf.ca

Appendix 1: Agenda

Start – End (All times EST)		Presenter(s)
10:50-11:05am	**Sign-In Period**	
11:05-11:10am	**Welcome & opening comments: JDRF Canada**	**Dave Prowten**, President & CEO of JDRF Canada Sarah Linklater, PhD, Chief Scientific Officer, JDRF Canada
11:10-11:15am	**Welcome & opening comments: CIHR-INMD**	**Norman Rosenblum**, MD, FRCPC, FCAHS, Scientific Director, CIHR Institute of Nutrition, Metabolism & Diabetes
11:15-11:30am	**Introductions**	Participants
11:30-11:40am	**Topic # 1:** T1D screening and prevention: Global Landscape & state of the science	**Frank Martin**, PhD, Senior Director, Research, JDRF International, USA
11:40-11:50am	**Topic # 2:** Case study – launching a pilot trial of general population T1D screening in Australia (pre-recorded)	**Kirstine Bell**, APD, CDE, PhD, Principal Research Fellow – Australian Type 1 Diabetes National Screening Program Pilot, U of Sydney, Australia
11:50am-12:00pm	**Topic # 3:** Clinical trial networks to enable T1D screening & early intervention research: the INNODIA experience	**Chantal Mathieu**, MD PhD, Professor of Medicine, Katholieke Universiteit Leuven, Belgium
12:00-12:30pm	**Discussion**	
12:30-12:45pm	**Break**	
12:45-12:55pm	**Topic # 4:** Introducing childhood screening for risk of genetically determined hearing loss in Ontario	**Pranesh Chakraborty**, MD, FRCPC, FCCMG, Executive Director & CMO of Newborn Screening Ontario
12:55-1.05pm	**Topic #5:** Polygenic risk scores and autoantibody screening: considerations for the diverse Canadian population	**Richard Oram**, PhD, Associate Professor, University of Exeter, UK
1:05-1:15pm	**Topic # 6:** T1D screening in Canada: the TrialNet experience and perspectives on general population screening	**Dianne Wherrett**, MD, FRCPC, Professor, Division of Endocrinology, SickKids Hospital
1:15-1:30pm	**Discussion and Q and A**	
1:30-2:00pm	**Break Out Rooms**	
2:00-2:15pm	**Summarize Break-Out Discussions**	
2:15-2:30pm	**Wrap-Up**	

Appendix 2: Meeting Participants

Andrew Paterson	Co-director of Statistical Analysis Facility at The Centre for Applied Genomics; Professor, Divisions of Epidemiology & Biostatistics, Dalla Lana School of Public Health, University of Toronto
Anne Koralova	Program Officer for the Helmsley Charitable Trust's Type 1 Diabetes (T1D) Program
Ashish Marwaha	Medical Genetics Staff Physician, Alberta Children's Hospital, University of Calgary
Brandy Wicklow	Associate Professor, Department of Pediatrics and Child Health; Clinical Investigator, Children's Hospital Research Institute of Manitoba
Brenda Wilson	Professor & Associate Dean, Community Health and Humanities
Bruce Verchere	Professor, Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of British Columbia; Professor, Department of Surgery, Faculty of Medicine, University of British Columbia; BC Children's Hospital
Campbell Hutton	Vice President, Regulatory and Health Policy at JDRF International
Carol Huang	Associate Professor, Departments of Endocrinology, Medical Science, Pediatrics; Associate Professor, Department of Biochemistry & Molecular Biology
Chantal Mathieu	Professor of Medicine at the Katholieke Universiteit and Chair of Endocrinology at the University Hospital Gasthuisberg Leuven, Belgium
Cheril Clarson	Section Head of Pediatric Endocrinology at the Children's Hospital, London Health Sciences Centre, Associate Professor at the University of Western Ontario, and an Associate Scientist at the Lawson Health Research Institute
Colin Dayan	Professor of Clinical Diabetes and Metabolism, Cardiff University School of Medicine.
Diane Wherret	Hospital for Sick Children and Professor, Department of Pediatrics, University of Toronto
Elizabeth Rosolowsky	Pediatric Endocrinologist, Department of Pediatrics, University of Alberta
Ellen Leschek	Pediatric Endocrinologist & Program Director at the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health

Frank Martin	Senior Director, Research, JDRF International
Grant Kealey	Scientific Evaluator, Health Canada
Jan Dutz	Head, Department of Dermatology and Skin Science, UBC
Jayne Danska	Anne and Max Tanenbaum Chair in Molecular Medicine; Senior Scientist, Associate Chief, Faculty Development and Diversity; Hospital for Sick Children Research Institute; Professor, Faculty of Medicine, University of Toronto
Kevan Herold	Long Professor of Immunology and professor of medicine (endocrinology), Yale School of Medicine
Kirstine Bell	Principal Research Fellow – Australian Type 1 Diabetes National Screening Program Pilot, The University of Sydney
Kurt Griffin	Todd and Linda Broin Chair for Diabetes Research, Director of Clinical Trials, The Sanford Project
Lisa Spain	NIDDK
Marian Rewers	Professor, Pediatric Endocrinologist, Pediatrics-Barbara Davis Center
Megan Levings	Professor, Department of Surgery, Faculty of Medicine, University of British Columbia and Investigator at BC Children's Hospital
Padmaja Subbarao	Clinician-Scientist in Paediatric Respiratory Medicine, SickKids Hospital, Toronto, Canada
Peter Senior	Director of the Alberta Diabetes Institute
Pranesh Chakraborty	Associate Professor, Physician, Division of Metabolics and Director, Newborn Screening Ontario
Richard Oram	Associate Professor, University of Exeter
Sarah Lawrence	Associate Professor and Chief, Division of Endocrinology, CHEO, Ottawa, Ontario
Seema Nagpal	Vice President, Science & Policy, Diabetes Canada
Shayne Taback	Director, Clinician Investigator Program, Faculty of Medicine; Associate Professor, Departments of Pediatrics and Child Health; Community Health Sciences; Obstetrics, Gynecology and Reproductive Sciences, University of Manitoba; Scientist, Manitoba Institute of Child Health; Adjunct Scientist, Children's Hospital of Eastern Ontario Research Institute
Shazhan Amed	Head of the Division of Endocrinology at BC Children's Hospital
Tamara Spaic	Medical Director, Diabetes Education Center · St. Joseph's Health Care London, Ontario
Vincent Xie	Medical Devices Directorate, In-Vitro Diagnostic Devices, Health Canada
Will Cefalu	Director of the Division of Diabetes, Endocrinology and Metabolic Disease; National Institute of Diabetes and Digestive and Kidney Diseases

William Hagopian	Clinical Professor, Pacific Northwest Diabetes Research Institute

Appendix 3: JDRF Canada and CIHR Staff

Abidah Shamji	National Director of Government Relations and Advocacy, JDRF Canada
Anne-Marie MacDonald	National Manager, Research Programs and Communication, JDRF Canada
Britney Marbain	Program Analyst, CIHR Institute of Nutrition, Metabolism and Diabetes
Christine Dhara	Business Analyst and Event Planner, CIHR-INMD
Dave Prowten	President & CEO, JDRF Canada
Frank Ong	Project Manager, CIHR Institute of Nutrition, Metabolism and Diabetes
Heather Salema	Program Coordinator, JDRF Canada
Joey Wong	Government Relations and Advocacy, JDRF Canada
Mary-Jo Makarchuk	Assistant Director, CIHR Institute of Nutrition, Metabolism and Diabetes
Norm Rosenblum	Scientific Director, CIHR Institute of Nutrition, Metabolism and Diabetes
Renee Lafleur	Acting Advisor, CIHR
Sarah Linklater	Chief Scientific Officer, JDRF Canada