Timing is Everything

Toward a national newborn screening program for rare disorders.

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NRBDO RAVTSR

Network of Rare Blood Disorder Organizations

Réseau des Associations Vouées aux Troubles Sanguins Rares

A 2023 report and recommendations for federal and provincial/territorial policymakers, prepared by ImmUnity Canada and the NRBDO.

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About This Project

ImmUnity Canada and the Network for Rare Blood Disorder Organizations (NRBDO) have collaborated to create a report for the Federal Ministry of Health and Health Canada on the current landscape of rare disease newborn screening in Canada, and recommended considerations for the establishment of a national newborn screening program for Canada.

From October to December 2022, we consulted with various stakeholders, including provincial newborn screening program leads, patient advocacy groups, Health Canada, the Canadian Public Health Laboratory Network, and others. We conducted an environmental scan of the current state of newborn screening in Canada, as well as a literature review.

As sometimes happens, we feel the value of the project lies more in the process than in the final report itself. Through these interviews, we began many meaningful conversations at what seems to be an ideal time, which we hope will lead to the creation of a national newborn screening program.

Introduction

Newborn Screening

Newborn screening is considered to be one of the greatest public health achievements of our time. With just a tiny sample of blood drawn via a heel prick shortly after birth, we can screen for a variety of conditions that can hinder a baby's healthy development. Early detection and treatment can help prevent intellectual and physical disabilities and life-threatening illnesses.

The journey to treatment with rare disease drugs begins at diagnosis. There is no way of knowing if a treatment (or drug) will be successful in the absence of a diagnosis. Many of the screened diseases are rare individually, but when considered together, they are a leading cause of pediatric morbidity and mortality.

The benefits of early diagnosis from screening are monumental. Many rare conditions and diseases are progressive. If detected at birth, families can start taking measures right away to prevent illness or infection and develop a treatment plan with their doctor.

Newborn Screening Across Canada

In Canada, newborn screening programs are established and funded by the provincial and territorial Ministries of Health. Currently, national newborn screening guidelines and standards do not exist. This results in a nationwide patchwork of testing programs that leaves some newborns with rare diseases and conditions going undetected simply because of where they are born. This can cause delayed diagnosis, delayed treatment, even non-diagnosis and in some cases death.

For years, experts (including patient advocates) have been calling for a national strategy to establish guidelines and standards for newborn screening programs.[1,2,3] The development of a National Drugs for Rare Disease Strategy, with funding of $500 million/year from the federal government, presents an opportunity to address this gap.

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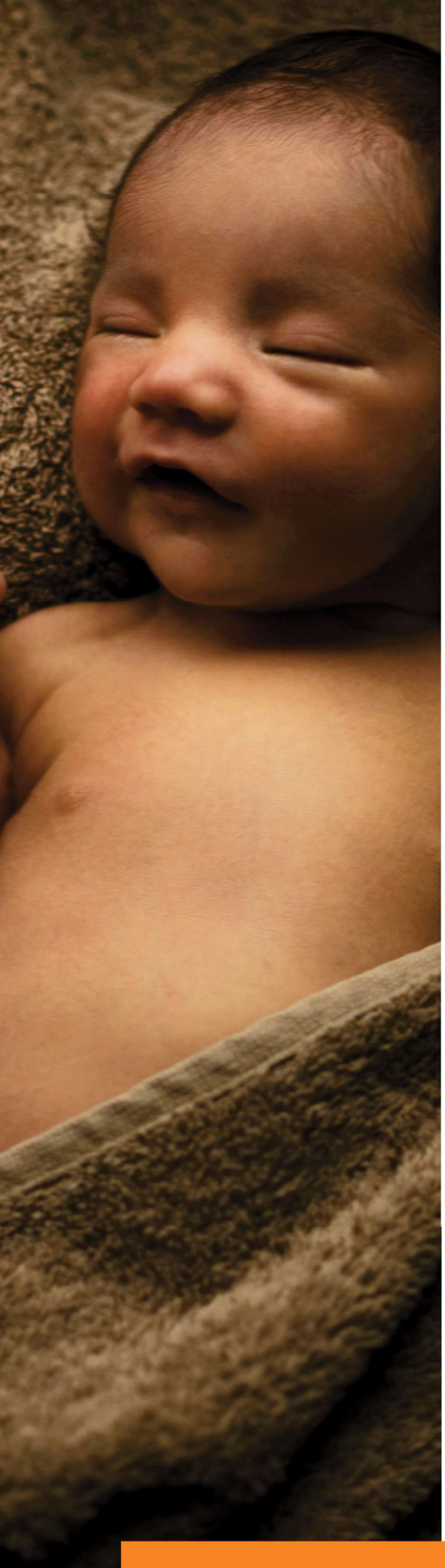
> "Because in the end, we're trying to save a child. Who are we if we fund basic science, basic science moves to translational science, then moves to clinical trials, INDs, IRBs, and approved therapies...and we cannot figure out a way to deliver the therapy to a baby? We have just spent a billion dollars to develop the therapy ... but we're going to let the newborn screening be the hiccup? That doesn't even make any sense to me."[4]

- Study Participant, "Preparing newborn screening for the future: a collaborative stakeholder engagement exploring challenges and opportunities to modernizing the newborn screening system."



Why Newborn Screening?

400,000,000

people are living with

10,867

life-threatening rare diseases[5]

92%

of rare diseases are suspected[5]
to have a genetic basis

5-7 years

is the average time to
accurate diagnosis[6]

According to Dr. Christopher McMaster, Scientific Director, CIHR Institute of Genetics, new research has determined that **1 in 40 children are born with an inherited disease**, and half of those will not reach adulthood.[6]

"It is becoming apparent that so-called 'rare' inherited diseases are the **most prevalent cause of mortality and morbidity in children**. Indeed, it is estimated that **1 in 3 pediatric hospital beds in Canada is occupied by a child with an inherited disease**. Without genomics, rare diseases take an **average of 5-7 years to diagnose**, presenting myriad symptoms that have patients trekking from specialist to specialist and undergoing countless tests in hopes of receiving a diagnosis." [6]

A Brief History

Universal newborn screening started in the 1960s with PKU screening by bacterial inhibition assay. Congenital hypothyroid (CH) screening followed in the late 1970s. The incidence of PKU in Canada is 1:15,000 births, and that of CH is 1:2500 births. Newborn screening for these two diseases is now universal across North America, Europe, and in many other countries. As new technology became available in the 1980s and 1990s, newborn screening programs were expanded.[7]

Economics of Screening For Disorders With High Benefit-Risk Ratios

Delivering effective treatments to people living with rare diseases is a challenge globally. Newborn screening saves lives and prevents severe disabilities through early diagnosis and pre-symptomatic treatment. Tens of thousands of babies have been diagnosed with PKU and other potentially disabling or fatal diseases through newborn screening.[7] For these patients and their families, the benefit of newborn screening is immeasurable. The societal benefits are also significant: early diagnosis and treatment through newborn screening help avoid high costs to the health system, and the economy benefits as patients and their caregivers are more likely to be able to be part of the workforce.[7] Many rare diseases and disorders are progressive, meaning earlier diagnosis and intervention, whether it be dietary, surgical, or medicinal, can make all the difference.

Newborn screening and a pre-symptomatic diagnosis also prevent the years of anxiety and expense that mark the typical rare disease diagnostic odyssey.[7]

Why now? Looking Ahead

Many newborn screening programs mandate that there must be a known treatment in order for a condition or disease to be added to the provincial screen. Up until now, the availability of effective treatments has been a limiting factor in the number of conditions screened for.

However, with projections that as many as 60 transformative cell and gene therapies could be approved in the next decade, there is an added urgency for newborn screening systems to be modernized and have the capacity to evaluate and add to the screening panels as warranted.

The United States has had a federal newborn screening program since 2005 to address inequities of care from state to state.[3,8] This program includes a system for reviewing new conditions to be added to the Recommended Uniform Screening Panel (RUSP), their original core panel of 29 diseases. Since it was established, they have added just six new disorders to the RUSP, and are currently considering how their system can be modernized to accommodate the additions that will be needed in the next decade.[4]

Systems for updating guidelines and standards equitably across Canada at scale and with the capacity to review and add many new conditions to the core list are needed.

Current State

With no national guidelines, working group, or advisory committee on newborn screening, each province works independently, and there are no set standardized criteria for labs or procedure to review conditions, or even standardized *names* for the conditions. Currently, each province establishes their own decision-making processes for adding a condition to its screening panel. This lack of uniformity is a detriment to newborn health and creates inequality across the provinces.

CASE STUDY: SCID
The Shirley Family (BC) and The Drayton Family (ON)

To highlight the current inequities, one need look no further than the case of Severe Combined Immune Deficiency (SCID) screening across Canada. Ontario was the first province to add SCID to its provincial newborn screening program in 2013. BC and Quebec both recently added it in late 2022. Newfoundland is now the only province not screening for SCID.

Dawn & Quinn Shirley (BC)

When Quinn was born at Victoria General Hospital, we thought everything about her was perfect. She acted like any other newborn, but as her mother, I soon noticed something was wrong. Her condition continued to worsen, and early on, she was admitted to the pediatric ICU with failure to thrive. Fortunately, an experienced immunologist who happened to be visiting the hospital observed her symptoms and suspected she had SCID. This saved her life. Her road has been difficult (failed gene therapy, bone marrow transplant, transfusions and ongoing treatments for life, unable to eat solid foods), but Quinn is now six years old and alive and well. If she had been diagnosed at birth, she would have started treatment immediately. Sadly, other babies born with SCID in BC were not as fortunate since there was no newborn screening for SCID until September 2022.

Barbara & Isaiah Drayton (ON)

Isaiah was one week old when we received a phone call from SickKids Toronto that he had tested positive for a rare disease they had tested for following his birth. Within days, our family received the news that our baby suffered from SCID and without treatment, he would unlikely survive past the age of two years.

At three weeks old, Isaiah was placed in isolation at SickKids. At ten months, he was treated with gene therapy at UCLA. At 20 months, Isaiah began making his own antibodies and no longer required any treatment. Today, Isaiah is a happy, healthy, and energetic 8-year-old!

Table 1. Rare Diseases and Conditions Included in Newborn Screening Programs by Jurisdiction

Primary Target	Primary Target abbreviation	AB	BC	MB	NL	NS	NB	NT	NU - Qikiqtin	NU - Kitikmeot	NU - Kivilliq	ON	PE	QC	SK	YT
Congenital Adrenal Hyperplasia	CAH															
Congenital Hypothyroidism	CH															
Cystic Fibrosis	CF															
Sickle Cell Disease	SCD															
Severe Combined Immunodeficiency	SCID															
Biotinidase Deficiency	BIOT															
Galactosemia	GALT															
Medium Chain Acyl-CoA Dehydrogenase Deficiency	MCAD															
Very long-chain acyl-CoA dehydrogenase Deficiency	VLCAD															
Long Chain L-3-OH Acyl-CoA Dehydrogenase Deficiency	LCHAD															
Mitochondrial Trifunctional protein deficiency	MTP															
Carnitine Uptake Deficiency	CUD															
Phenylketonuria	PKU															
Tyrosinemia type I	TYR															
Maple syrup urine disease	MSUD															
Citrullinemia	CIT															
Argininosuccinic acidemia	ASA															
Glutaric Acidemia Type 1	GA1															
Isovaleric Acidemia	IVA															
Propionic acidemia	PA															
Methylmalonic acidemia: mutase deficiency	MUT															
Cobalamin A Disease	CblA															
Cobalamin B Disease	CblB															
Homocystinuria	HCY															
Beta-ketothiolase Deficiency	BKT															
HMG-CoA Lyase Deficiency	HMG															
3-methylcrotonyl carboxylase Deficiency	3-MCC															
Spinal Muscular Atrophy	SMA															
Mupolysaccharidosis Type 1	MPS1-H															
X-linked Adrenoleukodystrophy	XALD															
Pompe Disease	IOPD															
CPT I Deficiency	CPT1															
CPT II Deficiency	CPT2															
CACT Deficiency	CACT															
GAMT Deficiency	GAMT															

Purple = conditions on the consensus list approved in 2016 by the P/T Ministers of Health
Green = currently a screening target
Blue = being implemented or considered
Red = not a screening target

Credit and thanks to Dr. Pranesh Chakraborty for sharing this summary of ongoing work to create a consistent and comparable communication framework for the screening targets in programs across Canada, with input from colleagues in each jurisdiction. This work will provide more clarity about the number and exact set of conditions for which babies in Canada are screened.

This table differs significantly from a table of the conditions each jurisdiction lists on their governmental websites for their newborn screening programs, and does not include a number of additional conditions that only a small number of provinces have listed.

Challenges & Opportunities

DECISION-MAKING PROCESSES

In Ontario, any member of the public is able to recommend a condition to be reviewed and added to the screening panel. By contrast, only Alberta Health recommends new conditions for review in Alberta. Each province is different. When the decision-making process is unclear, it can cause frustration for clinicians, patient advocacy groups, and families and delay a condition being reviewed. It can also lead to increased political involvement.

Some provinces choose to screen for conditions based on universality (standard practice), and others because they have the ability and capacity to do so, such as Saskatchewan's decision to be the only jurisdiction we could identify globally screening for XLA.

LEVELS OF CAPACITY

Some smaller provincial labs struggle for capacity and resources. This has led to a wide disparity in test quality which can lead to unnecessarily high rates of false positives and the risk of missing diagnoses in babies affected with one of the treatable conditions.

Multiple stakeholders noted that robust standard operating procedures and knowledge sharing between labs would assist smaller labs in overcoming these deficits. There is also the possibility of having some tests done in specialized labs rather than all labs running tests for all conditions and diseases.

LEAD ROLES

Some provinces run their newborn screening programs through public health labs. Others are based in hospitals and/or universities. Clinician-led programs are more likely to make sure follow-ups for positives are in place before adding a condition to the screening panel, ensuring patient support is ready. Regardless of the setting, newborn screening programs require established algorithms to ensure cases are referred to appropriate healthcare practitioners and receive appropriate care.

> "The cornerstone of the proposed Canadian Rare Disease Strategy and Drug Strategy is nation-wide newborn screening. We cannot assure patient-and-family-centred, efficient, and value-based care and treatment unless we can assure universal early screening, testing and diagnosis, initially for a core group of rare diseases but expanded as new conditions and new opportunities for intervention emerge.

-Durhane Wong-Rieger, President & CEO, CORD

> Our system of provincialized newborn screening leads to significant inequities province to province. It is unjust that infants receive different care from one province to the next with this system. In SCID alone we have seen the inequity as patients died during the years screening was not available in their province, while babies just across the provincial border might be receiving treatment. Canada needs a national strategy for newborn screening to work toward eliminating this significant inequity.

-Dr. Nicola Wright, co-Chair of the Alberta Newborn Metabolic Screening Program Advisory Committee

INDIVIDUAL CHAMPIONS

The current system is built on collaboration and goodwill shared among a small group of dedicated clinicians and lab directors. These individuals have made great progress building their provincial programs but currently lack the mandate and the administrative infrastructure to create a national program. The current inter-provincial collaboration is overly reliant on individual champions who could be pulled away for a number of personal or professional reasons and lacks a system to maintain momentum in their absence.

FULL PIPELINE OF TREATMENTS FOR RARE DISEASES

An estimated 60 novel treatments for rare diseases are ready to come to market in the next decade, many for conditions that could be screened for at birth.[4] This presents a great opportunity for patients but also threatens the capacity of our current system of newborn screening without a national mechanism for evaluating and implementing new conditions and diseases to the screening panel.

NEXT-GENERATION SEQUENCING

Efforts to apply genetic methods to newborn screening using next-generation sequencing (NGS) have been underway for several years, but there are currently a number of large studies launching around the world to generate evidence on whether and how genomics can be used in screening. Similar to the advent of tandem mass spectrometry (MS/MS), next-generation sequencing offers the promise of screening for more disorders at a lower overall cost per disease one day. The potential for scalability of NGS offers an unprecedented opportunity to address the global health issue of diagnosing and managing rare diseases.[9]

> MPS-1 is a progressive disease, so early diagnosis is extremely important. Matteo was diagnosed at 7 months, and I always wonder what would have happened if he had been diagnosed at one month. Would we have avoided some of those surgeries? Would he maybe not have some of the challenges that he has today?
>
> *-Angie Lombardo, mother of Matteo, who lives with MPS-1, also known as Hurler Disease.*

DATA TO INFORM RARE DISEASE RESPONSES

Currently, pediatric hospitalizations and deaths related to undiagnosed rare diseases are not properly recorded or accounted for in hospital records.[6] These patients are usually reported and recorded based on their symptoms (neurological, metabolic, cardiac, etc.) instead of the condition causing the symptoms. This makes it difficult to determine the exact number of Canadians with a rare disease, and consequently, the appropriate level of resources to allocate for care, medicines, and research.

CANADIAN PUBLIC HEALTH LABORATORY NETWORK (CPHLN)

The CPHLN is a federal/provincial network of public health labs across Canada. The National Microbiology Lab (NML) is funded by the federal government through the Public Health Agency of Canada to act as the network's secretariat. In meeting with the co-chairs (one federal, one provincial), we learned that there is the capacity and the willingness to explore the provision of backbone administrative support to the current inter-provincial efforts among clinicians to establish a national newborn screening program committee or working group.

THE NATIONAL DRUGS FOR RARE DISEASES STRATEGY

A national newborn screening program aligns with the federal government's Drugs for Rare Disease Strategy. The strategy consulted stakeholders across Canada, and many of the objectives of the strategy are consistent with—and point to the need for—a newborn screening program. For example, the report states 'a single framework would make the system fairer, avoid political influence, reduce the burden on smaller provinces and get more consistent information to the public.'[10] There is also agreement among stakeholders on the need for government leadership and support as administrator and facilitator.

Recommendations

1. Provide the funding and mandate to a Secretariat organization, such as the CPHLN or a provincial newborn screening program, to act as the administrative support for a National Newborn Screening Advisory Committee, which would have a transparent mechanism for reviewing conditions, and meet regularly to consider additions to the core list.

2. Adopt an agreed-upon set of principles, such as Dobrow et al., which builds on the Wilson and Jungner principles of screening, to use when considering new additions to the national screening panel.[11]

3. Continue to allow provinces to review additional conditions on a regional and demographic basis.[3]

4. Leverage the network of provincial programs and labs to work with the National Newborn Screening Advisory Committee for the development of standard operating procedures and for conducting specialized rare tests as needed.

5. Consider methods of improving and centralizing reporting to facilitate an improved understanding of rare disease prevalence and a more accurate allocation of resources for care, medicine, and research. This could include leveraging already existing frameworks, such as SPOR (Strategy for Patient Oriented Research, CIHR) and/or developing a registry to monitor follow-up and long-term care nationally.

6. Request the National Newborn Screening Advisory Committee to also provide guidance and best practices for uniformity on the various ethical, communication, data management and sharing, legal, and social implications of newborn screening programs.[3,9]

> Now is the time to establish a focus, process, and budget to harmonize newborn screening in Canada so every baby has the benefit of these wonders of modern science and medicine.
>
> *-John Adams, President & CEO, Canadian PKU and Allied Disorders Inc.*

The Federal Role

According to the Health Canada report, *Building a National Strategy for Drugs for Rare Diseases: What We Heard from Canadians*, next steps include considering 'how best to support patients more holistically, including diagnostics, screening and genetic testing.'[10]

We believe that a national newborn screening program delivers on the drugs for rare diseases strategy objectives, and that the offer from CPHLN to provide administrative support is an elegant and efficient solution that should be explored further for inclusion in the strategy.

Through increased collaboration, knowledge exchange, and federal support, Canada's national newborn screening program can be robust and sustainable, and provide equitable access to all newborns across the country, regardless of where they are born.

Acronyms

CH - Congenital hypothyroid

CIHR - Canadian Institutes of Health Research

CPHLN - Canadian Public Health Laboratory Network

MPS - Mucopolysaccharidosis

MS/MS - Tandem Mass Spectrometry

NBS - Newborn Screening

NGS - Next-Generation Sequencing

NML - National Microbiology Lab

PKU - Phenylketonuria

RUSP - Recommended Uniform Screening Panel

SCID - Severe Combined Immune Deficiency

XLA - X-linked agammaglobulinemia

"Newborn Screening for MPS I-H in Canada is imperative to ensuring those diagnosed have the best prognosis, health outcomes, and quality of life in their future. Not only will early detection for MPS I-H allow for life-altering interventions, it will also prevent the diagnostic odyssey and allow for informed reproductive decisions for the family going forward. The improved performance of screening tests and improved health outcomes with early diagnosis and intervention call attention to the responsibility that Health Canada and Provincial Health Ministers have in ensuring young Canadians are protected, and healthcare as a human right is realized.

-Kim Angel, Executive Director, The Canadian MPS Society

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