Canadian Organization for Rare Disorders

Recommendations for Implementing a World-Class State-of-the-Art Canadian Newborn Screening Programme

Submitted by:
Canadian Organization for Rare Disorders
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Introduction

The Canadian Organization for Rare Disorders (CORD) is pleased to respond to the invitation to provide input to the pan-Canadian initiative on newborn screening and specifically recommendations on a national list of primary conditions for screening and other issues to assure best health outcomes and quality of life for Canadians. We wholeheartedly endorse the mandate of the working group addressing this initiative and urge the Health Ministers to act as expeditiously as possible to begin implementation.

As the national umbrella organization for rare disease organizations, patients, and other stakeholders in Canada, CORD has developed, in consultation with diverse stakeholders over the past three and-a-half years, Canada's Rare Disease Strategy. Launched in May 2015, the RD Strategy identifies five over-arching goals, the first of which is Improving Early Detection and Prevention, under which a national program for newborn screening (NBS) is one of the priority action items.

In this brief, CORD will provide recommendation and commentary on five issues:

1. Adoption of a national Canadian Uniform Screening Panel (CUSP) that will list mandatory primary core conditions and secondary targets for testing and as corollaries, provisions for updating the list to match international best practices as appropriate to Canada's population demographics and optimization of the number and location of NBS sites to assure efficiency and expertise
2. Process for nomination and review of new conditions for inclusion in the CUSP, which also includes definition of criteria for inclusion and recommended timelines for implementation
3. Standards and guidelines for timeliness of NBS, including testing and reporting of findings to healthcare providers and families to assure that conditions requiring urgent intervention as well as appropriate care and treatment, whether from professionals or families, may be implemented to avoid unnecessary harm and distress
4. Provision of follow-up education, care and support, including genetic counselling, access to appropriate specialists and/or Centres of Expertise/Reference, and referral to community services

5. DNA testing for newborns, namely consideration of genome and exome screening for newborns, as a clinical service, implementation based on feasibility, cost-effectiveness, and potential benefit to families and society

To address these issues comprehensively and efficiently, we call upon leadership from both the federal level and the provincial/territorial levels.

CORD Data: Need for Early Diagnosis

Newborn screening is the cornerstone to early detection, diagnosis and (primary and secondary) prevention for rare diseases. The needs for screening and early diagnosis were amply demonstrated in an extensive survey conducted by the Canadian Organization for Rare Disorders in early 2015. More than 550 Canadians took part in the bilingual survey, about two-thirds patients themselves and one-third parents or caregivers. The findings were revealing:

More than one in five (21%) persons with rare diseases took more than six years to be correctly diagnosed, with 30% of patients receiving three or more incorrect diagnoses before the right one was made. As a result, more than 61% required visits to three or more specialists; one in four (25%) required six or more specialists.

The survey lent support to the proposed goals and priority actions identified in Canada's Rare Disease Strategy, the first of which is Early Detection and Prevention.

Under this goal, the first action is to adopt a national approach to newborn screening. This tactic is a very good illustration of how quickly Canada could succeed in addressing rare disease challenges, if there is the political will. About 80% of rare diseases are genetic, and we have seen success with newborn screening using the heel-prick dried blood spot sample taken immediately upon birth. For example, since the 1960s, NBS for phenylketonuria has saved thousands of lives and/or prevented serious physical and developmental disabilities.

Today, it is possible to screen for about 50 rare conditions at birth; however, Canada has never adopted a national standard or program for NBS. Until 2006, provincial programs screened for two to 11 conditions; with the exception of Saskatchewan, which screened for 29. Thanks primarily to strident advocacy, provincial standards have improved but are still highly disparate, ranging from five to 30 conditions, with only two conditions included in every provincial program. We have many examples of children who could have been spared devastating outcomes if they had been born in the adjacent province.

Canada's Rare Disease Strategy calls for two clear and simple actions to address this gap: development by all provinces and territories of a national approach to newborn screening and collaboration to implement early detection and preventive services to allow detection of rare diseases as early as possible. There are many reasons why a national approach is beneficial, not only to assure equitable access for all families regardless of where they live, but nationally coordinated programs promote

efficiencies, expertise in diagnosing, and development of cost-effective solutions across jurisdictions.

The outcomes of the Ontario-led Provincial/Territorial (P/T) initiative could make this action an "early win" leading to achievement of many other aspects of the strategy.

Recommendation 1: Canadian Uniform Screening Panel

A 2007 comparison of the status of newborn screening internationally reported that the USA and Canada were similar in having no national programs; there are 51 state/territorial programs in the USA and 13 provincial/territorial programs in Canada. In both countries, they found major differences across programs, not based on evidence, standards, or demography, resulting in huge disparities in patient outcomes and public health impact. Since then, federal initiatives adopted in the USA have significantly improved the possibility and the actuality of consistent best practices across the American states.

In 2008, the U.S. Congress passed *The Newborn Screening Saves Lives Act* (recently reauthorized), which provides, among other things; grant programs for various activities, including education, training in newborn screening technologies, and follow-up care. The act addresses consumer awareness of services, laboratory quality standards, an emergency contingency plan, and a central online clearinghouse. As importantly, it created the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) to provide national leadership.

Since adoption of the initial 29 core conditions and 25 recommended secondary targets, four additional core conditions [severe combined immunodeficiency disease (SCID), critical congenital heart disease (CCHD), Pompé's disease, and Mucopolysaccharidosis type I (MPS I)] along with one secondary target, T-cell lymphocyte deficiencies, have now been recommended for inclusion and all except one (MPS I) have been recommended by the Secretary, increasing the RUSP to 32 conditions.

In Canada, Ontario currently leads the provinces in screening for 29 conditions but, frankly, given the similarities between the USA and Canada, we should be keeping pace in terms of core primary conditions, both in terms of numbers of conditions and the implementation. The evidence will be the same. At the same time, it is important that local demographics are used to identify targeted conditions based on historic heritages represented or emerging trends based on migration or other factors, including environment or observed emerging incidences.

An important support to a national NBS list is a strategy to optimize the number and location of NBS laboratory sites. We are not apprised of the criteria for establishing laboratories but we do know that a province-by-province approach is neither cost-effective nor likely to result in the appropriate expertise for accurate diagnosis,

especially in cases where the number of positive cases may be very small, the results not conclusive, or the need for confirmatory testing. Like the Canadian Blood Services, a national advisory board should be established to recommend the most effective and cost-effective number and location of sites.

Recommendation 2: Nomination and Review Process for Adding Conditions

An important function of the SACHDNC in the USA has been the implementation of a process for nominating and reviewing proposed conditions for including in the RUSP. In particular, The SACHDNC has outlined a process, with clear guidelines, that starts with nomination by, ideally, a multidisciplinary team providing the supporting scientific/clinical data, review by an internal Nomination and Prioritization Workgroup, systematic evidence-based external Condition Review Workgroup, and the evidence considered by the SACHDNC using a decision matrix to arrive at a recommendation for the Secretary of Health and Human Services, who makes the final decision.

The decision matrix is based on three criteria, namely, net benefit/certainty, readiness, and feasibility, with varying levels from low to high, allowing for the classification of the nominated condition from "low benefit/certainty" to "high benefit/certainty, high-to-moderate feasibility, and high readiness to implement." The process provides clear criteria and transparency in the decision-making, which increases acceptance of the recommendation as well as possibility for quick uptake.

We recommend that Canada adopt a similar process managed by a national committee, with support for teams to propose conditions for inclusion. We also recommend that patients be included in all phases of the process, not only as consultees but also as partners, especially on the nominating teams and the national review committee.

Such a process would have assured that screening for Pompé's disease, recently recommended in the USA for their Uniform Screening Program, would have had a similar pathway in Canada and could have been included in Canada at the same time as in the USA. Instead, the Canadian Association of Pompé, (CAP) which has put together an evidence-based proposal, has been writing to and/or meeting with the various provincial NBS programs with no clear pathway or assurance of a consistent response for families across the countries. We strongly urge this committee to give careful consideration to the CAP process, which we have included as an appendix. We are hopeful, with this pan-Canadian initiative, Pompé's disease will be included in a forthcoming Uniform Screening list. Similarly, we urge the committee to look at the US recommendation for MPS I.

We also recommend funding to support the implementation and follow-up on new conditions to improve the timeliness of implementation across all provinces and territories.

Recommendation 3: Timeliness in newborn screening

A key challenge for NBS programs is the timely receipt of the blood spots, timely testing and interpretation, timely notification of healthcare providers, and finally timely information (with education and support) to families. There are newborn conditions that require urgent intervention, modifications of diet or other care, and introduction of therapies or immunization to prevent progression, disability, or even death. The Toronto Star earlier this year published data showing that "16,800 blood samples, representing about 11 per cent of 142,500 babies born in Ontario in 2014, took five days or longer to reach the lab" compared to the benchmark of three days or less. The consequences of delayed testing and notification meant that, in one case, a child born with galactosemia, a rare condition in which the body can't break down galactose, was literally being "poisoned" by her mother's breast milk. In fact, galactosemia can be "easily" treated through changes in diet, but the consequences are so serious that Newborn Screening Ontario has classified it as one of "eight aggressive diseases" in which diagnosis within the first week of life is considered crucial. There are other stories of serious or near-serious impacts due to delayed diagnosis and/or notification. Thus, the Canadian Newborn Screening Program needs to establish standards and guidelines for timeliness and to support the provincial programs to meet these targets.

We may consider emulating, for example, another very important initiative in the USA, whereby funding opportunities are being made available to support states to improve timeliness, specifically in the following categories.

1. Presumptive positive results for time-critical conditions should be communicated immediately to the child's healthcare provider but no later than the fifth day of life.
2. All presumptive positive results for all other conditions should be communicated to the child's healthcare provider as soon as possible but no later than seven (7) days of life.
3. All NBS results should be reported within seven (7) days of life.
4. Initial NBS specimens should be collected in the appropriate time frame for the baby's condition but no later than 48 hours after birth.
5. NBS specimens should be received at the Laboratory as soon as possible, ideally within 24 hours of collection.

We propose learning from agencies like the Canadian Blood Services where timely delivery of fragile materials (including blood samples) has been much studied to develop a "fail-safe" network based on best practices, quality assurance tracking and evaluation, contingency pathways, and emergency rescue plans.

Recommendation 4: Follow-up Care and Support

The survey conducted by CORD found that there was a general lack of follow-up even after a diagnosis was made. About 40% (English) to 80% (French) of rare

disease respondents who had received a diagnosis (not just on the basis of NBS) said they did not receive good post-natal support and about 75% to 80% said they did not receive counselling with the diagnosis. Four out of five of the surveyed patients and family members felt their general practitioners were not adequately informed about rare diseases and half felt that their paediatricians and other specialists did not have adequate knowledge about rare diseases.

Many families with these conditions do not have access to patient support groups, in part because the numbers are so small. Often parents may set up an information and support exchange but these may not be sustainable because of the tremendous needs for family care, or if the patient does not survive, the families may eventually drift away. Newly diagnosed families are not always aware of the community resources that do exist; our patients also said that the rehabilitation, social and financial support services, workplace programs and even insurance benefits are often not available because their rare disease is not specified. Many may lack advocacy skills or access to social worker or other advocate. A few of the children's hospitals are offering volunteer parent support programs, and these offer emotional support as well as practical assistance.

The Canadian Organization for Rare Disorders is an umbrella organization that comprises more than 100 rare disease patient organizations. We offer regular training and develop programs as well as assistance to many of the patient groups ranging from administrative and fundraising assistance to advocacy and system navigation. However, CORD receives no assistance from any of the healthcare services neither to provide this support nor to maintain a national network. We strongly recommend a provision of the pan-Canadian NBS program includes resources for patient organizations and patient networks to education, support, and empower patients and families, from the pre-screening to diagnosis and post-natal engagement. These resources may be provided through grants, program development funds, or sustaining support

Recommendation 5: DNA Testing for Newborns

In our collaborations with genetic researchers and clinicians toward the development of Canada's Rare Disease Strategy, CORD has engaged with state-of-the-art genomics screening programs, primarily used in research but also available for selective clinical care cases. Canada has world-calibre laboratories and expertise in genome and exome sequencing. We believe the provision for consideration of a national program on DNA testing for newborns should be included for further development within this pan-Canadian Newborn Screening initiative.

As noted by one expert, "with the evolving research in the 'omic' sector in health care, which encompasses genomics, proteomics, metabolomics and epigenetics, the time for whole genome sequencing/ exome sequencing at newborn screening has arrived." Another said, "Previously, [NBS] was done by metabolite (initially for PKU) by heelstick blood, and now the possibility for DNA testing with a totally

different platform exists. It may allow us to detect hundreds of diseases, ideally diseases that present in the newborn period, need early treatment, and have treatment available."

Obviously, there are many challenges, including financing, disclosure, and ethics, as well as practical needs for genetic counselling with each test and follow-up care. But there are likely many more advantages, including the ability to prevention some conditions, reduce the burden of others, and target therapies for still others.

An important exploratory step is offered in a proposal for a pilot project to examine how *"whole genome sequencing (WGS) and other emerging 'omics technologies [could be] best leveraged towards the needs of undiagnosed rare disease patients and families?"* The proposed project capitalizes on existing networks and centres with WGS experience and resources and the pilot work done by Children's Hospital for Sick Children (Ottawa) CARE4RARE. The aim, as they state, is to "refine a WGS methodology specifically designed to address the objective of obtaining a diagnosis for every patient."

Canada has the innovation, technology, and now political will to implement a world-class state-of-the-art Newborn Screening Program. It is a priority action toward the implementation of Canada's Rare Disease Strategy. The Canadian Organization for Rare Disorders is committed to working in partnership to realize Canada's Newborn Screening Program and Canada's Rare Disease Strategy.

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Appendices:

Now is the Time: A Strategy for Rare Diseases is A Strategy for All Canadians, Canadian Organization for Rare Disorders, May 2015

Submission to the Provincial-Territorial Working Group on Newborn Screening, Canadian Association of Pompé