Canada's Drug Agency
L'Agence des médicaments du Canada

Discussion Paper for Engaging With Collaborators

# Pan-Canadian Guidance for Newborn Screening: Building the Foundations for Early Detection and Diagnosis of Conditions

In Support of the National Strategy for Drugs for Rare Diseases

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## About the Panel Members

The advisory panel is composed of 2 co-chairs and 11 members who come from across Canada and represent dimensions of difference, including women, Indigenous Peoples, and persons of all races, places of origin, religions, abilities, sexual orientations, and gender identities and expressions. The advisory panel brings together a range of expertise and experience, including health care providers (e.g., clinicians, program administrators, researchers), persons with lived and living experience, and individuals with backgrounds in ethics, law, and/or health administration. The names, biographies, and conflict of interest declarations of the 13 members on the panel are available on the Canada's Drug Agency website.

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## About the Consultation

Canada's Drug Agency, on behalf of its ad hoc multidisciplinary newborn screening advisory panel (the advisory panel), is inviting interested parties to provide input on a proposed approach to foster greater consistency on the types of conditions tested for during newborn screening to support earlier diagnoses, timelier access to treatments, and the opportunity for better health outcomes. Your input is both needed and highly valuable. Your comments will be used to inform a final report that will be submitted to Health Canada, shared with provincial and territorial governments, and made publicly available. The advisory panel prepared this discussion paper to contribute to the dialogue around this work.

This discussion paper sets out key principles for a proposed coordinated model for newborn screening in Canada, and builds on existing work to develop a proposed approach for the addition or removal of conditions, and to recommend a path forward to consider proposed criteria to evaluate conditions that could be added or removed from a proposed pan-Canadian newborn screening list. Questions for input are included throughout this document, located within the related sections.

Please submit your responses and comments using the online form available at the following links:

- English form
- French form.

You are welcome to respond to all or some of the questions. The consultation period will close on September 11, 2024. If you have any questions about this consultation, please email us.

## Public Posting for Input

To encourage conversation on this topic and ensure transparency, Canada's Drug Agency will publish the comments we receive through this consultation. By submitting your written comments to Canada's Drug Agency, you or the organization you represent agree to the full disclosure of the information. We will not edit or validate your feedback or review any references or links you include for accuracy or with respect to content.

Canada's Drug Agency will collect your personal information at the time of your submission. You will be asked to provide us with certain personal information, including your name, contact information, and affiliation. While we encourage respondents to self-identify in their submission, you are not required to do so. However, if you choose to make an anonymous submission, we will be unable to follow-up with you on any issues you raise.

Canada's Drug Agency reserves the right to refuse to post feedback, in whole or in part, that, in our sole discretion, is deemed to be unrelated to the issue under consultation; contains complaints and/or compliments about identifiable individuals; contains personal identifiers and/or other information that may identify a third party; is abusive, obscene, harassing, threatening, or otherwise inappropriate; includes defamatory or libellous comments; and/or does not comply with the Canada's Drug Agency Terms of Use and/or Privacy Policy.

## Setting the Context

Newborn screening refers to testing done shortly after birth to check for serious but treatable diseases. It helps to identify certain conditions as early as possible to prevent serious health problems. In particular, the early identification of rare diseases through newborn screening can lead to more timely diagnosis and appropriate access to treatments and supports early in life.

Newborn screening policies, practices, and processes across Canada are not uniform as there are currently no standards at the national level. This variation includes differences in the governance of, and use of, advisory committees; the number of conditions screened and the procedures used to review them; the technologies used; legal frameworks and consent; and treatment and follow-up practices, including funding and access to treatments. Some of these differences may be attributable to the policies, priorities, and economic capacity, including resourcing supports, of the province or territory. Other reasons for the variation have a scientific basis, such as variations in ethnicity within a province or territory and the prevalence of specific genetic isolates.

There is a recognition that much progress has been accomplished in this area at the provincial and territorial level. In 2016, when an Intergovernmental Newborn Screening Working Group explored areas of pan-Canadian **cooperation** for newborn screening and made recommendations for a Canadian newborn screening list, which consisted of 22 conditions, to inform and provide guidance to provincial and territorial newborn screening programs.[1]

As part of setting the foundation for supporting the National Strategy for Drugs for Rare Diseases, there is an opportunity to further enhance systems coordination and equity of access for newborn screening. An advisory panel was established to build on existing work by:

- developing guidance around issues relating to newborn screening including a common set of guiding principles for newborn screening in Canada
- exploring a proposed process and criteria for the addition or removal of conditions, and a recommendation for conditions for which newborn screening programs in Canada could screen
- when appropriate, identifying the potential need for additional evidence on emerging newborn screening tests through the existing health technology assessment infrastructure at Canada's Drug Agency.

The issues that are considered out of scope for the advisory panel include an assessment of:

- individual newborn screening program processes
- funding for implementing recommendations (e.g., funding allocation, financial contributions, individual program budgets or projected estimates for those budgets)
- laboratory service agreements and processes
- sharing records, including patient-level data
- matters relating to private insurance coverage
- drugs and/or treatments for rare diseases
- the negotiation or review of commercial test prices
- prenatal genetic testing.

## Background

The Government of Canada, through its National Strategy for Drugs for Rare Diseases, is supporting a range of activities to increase access to, and affordability of, promising and effective drugs for rare diseases.[2] Some of this work includes funding to support the advancement of rare disease screening and diagnosis.

Early identification through screening for rare diseases is an important means of assisting with timely and appropriate access to patient supports and treatments. In Canada, newborn screening programs are established and funded by the individual provinces and territories; each program has its own decision-making processes, policies, and approaches. Newborn screening has existed across Canada since the 1960s with screening for phenylketonuria (PKU), a rare inherited and/or genetic metabolic disorder.[3] As new technologies emerged, newborn screening programs across provinces and territories expanded to include screening for other rare diseases. It is anticipated that an estimated 60 new transformative cell and gene therapies are predicted to come to market in the next 10 years.[4] Newborn screening is therefore a critical component that supports improvements in care for treatable rare diseases in newborns by enabling the early diagnosis of rare diseases[3] and thereby facilitating access to timely treatment.

As a result, there is an opportunity to provide support to newborn screening decision-makers, through convening experts and building on existing work, to provide the best available advice across Canada.

# Proposed Guiding Principles That Anchor the Advisory Panel's Approach

To set the foundation, the advisory panel established a set of draft guiding principles to inform and shape decision-making when developing processes, criteria, and a proposed list of conditions to screen for in newborns. These draft guiding principles are a core set of aspirational values that serve to guide the advisory panel's exploratory vision for a potential coordinated newborn screening system and its associated activities.

To support the advisory panel's discussion on selecting a set of draft guiding principles, a limited literature search, grey literature search, and focused internet search were conducted. Identified sources included Canadian and international publications (e.g., the Canadian Organization for Rare Disorders' Rare Disease Strategy, newborn screening program documents, the US Recommended Uniform Screening Panel, among others). For additional details about the methodology, please refer to Appendix 1.

## Proposed Guiding Principles

The advisory panel proposes 6 draft guiding principles (refer to Table 1 and Figure 1). These draft guiding principles include the health rights of the newborn; equity; effectiveness, safety, and quality; transparency; collaboration; and sustainability. These draft guiding principles are guideposts and are not listed in any order or intended to be ranked, except for the health rights of the newborn, a principle that is central to the activities and decision-making considerations.

The advisory panel members acknowledged that they are proposing draft guiding principles that may be adopted and used to inform newborn screening policies, processes, and procedures across Canada. While the advisory panel representation is diverse and the members undertook careful deliberations, the perspectives offered by this advisory panel were inevitably limited. Therefore, the proposed guiding principles require thoughtful feedback and inclusive public engagement.

**Question 1: Do you agree with the proposed guiding principles and definitions? Please provide your reason(s) and suggested changes, if any.**

## Figure 1: Proposed Guiding Principles and Definitions

## Table 1: Proposed Guiding Principles, Proposed Definitions, and Advisory Panel Rationale

| Proposed guiding principle | Proposed definition | Rationale |
|---|---|---|
| Health rights of the newborn | Policies, processes, and procedures relating to newborn screening should prioritize the health of the newborn. When considering what conditions to screen for in newborns, the focus should be on reaching the highest attainable state of health for newborns. | Given the goal of newborn screening is to improve the health of newborns, the advisory panel agreed that the right of the newborn to achieve the highest attainable state of health should be granted primacy and viewed as an overarching principle for all newborn screening activities. The advisory panel suggested that each of the proposed guiding principles should therefore be linked to and executed with a focus on the health rights of the newborn. |
| Equity | Policies, processes, and procedures relating to newborn screening should ensure access for all newborns to quality screening, and to diagnosis, treatment, and follow-up where appropriate. When considering what conditions to screen for in newborns, their diverse needs, circumstances, and best interests need to be considered. | The advisory panel discussed equity issues relating to access to newborn screening and to the entire care pathway that includes screening and the diagnosis, treatment, and follow-up of a positive screening result. There was consensus that equitable access is critical from screening through to follow-up for all newborns in Canada across geographical and cultural contexts. When decisions regarding newborn screening are made, the newborn's diverse needs, circumstances, and best interests need to be considered. |
| Effectiveness, safety, and quality | Policies, processes, and procedures relating to newborn screening should be actionable, regularly reviewed, evaluated, modernized, and updated for continuous improvements. Newborn screening pathways should be effective, safe, evidence-informed, and of high quality. | The advisory panel acknowledged that prioritizing the health of the newborn within the newborn screening landscape will require consideration of the available evidence on the harms and benefits of screening. The advisory panel noted the importance of criteria and the evidence review for understanding test performance to characterize potential harms, such as false-positive results. The advisory panel indicated that newborn screening is a pathway that includes screening, follow-up on positive screening results, |

| Proposed guiding principle | Proposed definition | Rationale |
|---|---|---|
| | | diagnosis, and treatment and that this continuum needs to be effective, safe, evidence-informed, and of high quality. They also described quality measures for newborn screening processes, policies, and procedures and how they will require regular review, evaluation, modernization, and updating for continuous improvement and adaptation to changes, developments, and advances in health systems to ensure the highest quality. |
| Transparency | Policies, processes, and procedures relating to newborn screening, as well as the work of the advisory panel, should be explicit, impartial, clear, and accessible to all people in Canada. Information about newborn screening should be accessible, accurate, and easy to understand. | To support trust and foster accountability, the advisory panel indicated that their work and future decisions and processes relating to newborn screening need to be transparent. When sharing information on newborn screening, it should be explicit, clear, impartial, and accessible to all. |
| Collaboration | Policies, processes, and procedures relating to newborn screening should be developed in collaboration with partners and with diverse perspectives. | The advisory panel indicated that newborn screening policies, processes, and procedures should be developed through a collaborative approach and be informed by multiple perspectives respecting regional differences. They identified the need for effective collaboration, which will require early, inclusive, and meaningful engagement with interested parties to ensure the values and diverse perspectives of those from across Canada are embedded in newborn screening activities. |
| Sustainability | Policies, processes, and procedures relating to newborn screening should focus not only on creating value to support a sustainable health system in the present, but should also include considerations for future generations, such as | The advisory panel considered sustainability as a driver for newborn screening, which included balancing the current needs of health care systems with the needs and rights of future generations. To support the long-term vision of improving the health systems in Canada, it will be important to |

| Proposed guiding principle | Proposed definition | Rationale |
|---|---|---|
| | environmental, economic, and social factors. They should also support a holistic, long-term vision of improving health systems and the public's health. | consider the environmental, economic, and societal factors that could impact, positively or negatively, the newborn screening ecosystem. |

# Exploring a Future Coordinated Model for Newborn Screening in Canada

## Part 1: Working Toward a Pan-Canadian Coordinated Approach for Newborn Screening

There is currently no coordinated approach to newborn screening in Canada. Each province and territory has its own approach and processes to review and add conditions to their respective newborn screening lists. This has led to differences in the conditions screened and access to screening across the country. A strategy to align processes and criteria may enhance uniformity of newborn screening practices in Canada. A coordinated approach may enable efficiency in processes and resources, mitigate risks, facilitate quality improvement, and support anticipating and responding to new challenges across the newborn screening ecosystem.

As part of the advisory panel's discussions, different examples of governance structures for newborn screening programs were reviewed and summarized. The programs were identified through a scan of publicly available sources. Identified sources included information from 2 national programs (the US and Australia), and 2 programs in Canada that operate at the provincial level (Ontario and British Columbia).

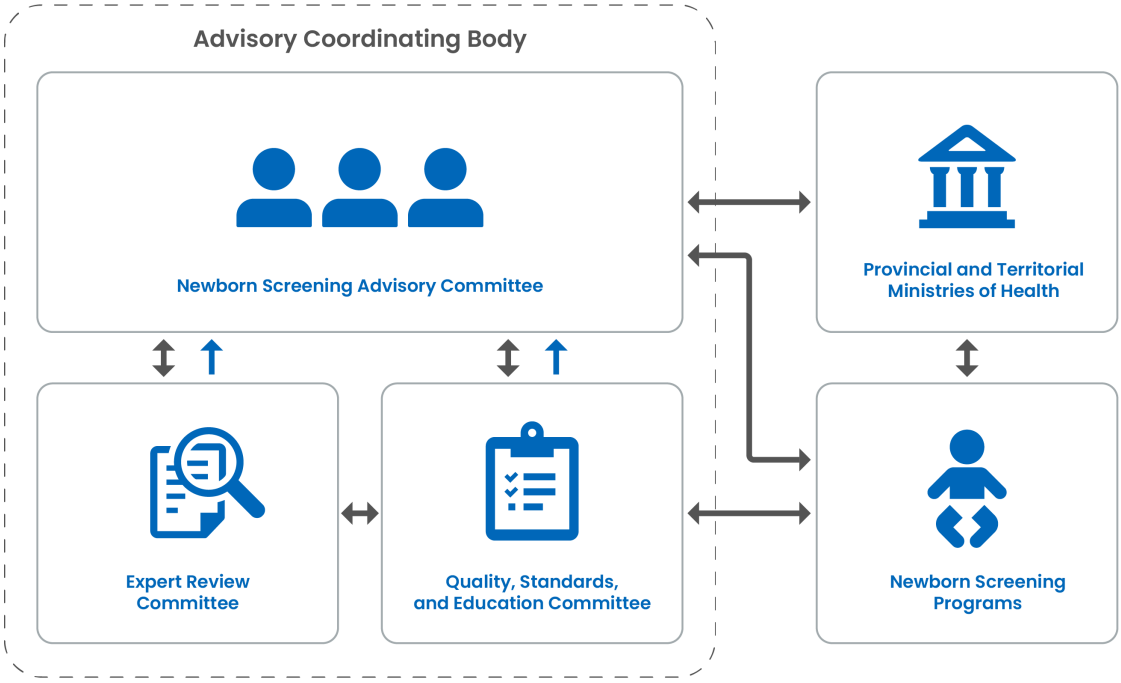
### A Proposed Exploratory Coordinated Model for Newborn Screening

The advisory panel developed a high-level vision for a potential coordinated newborn screening ecosystem. Through discussions, they proposed an exploratory and potential coordinated system (an illustrative example is represented in Figure 2). The intent of the proposed coordinated model is to complement jurisdictional newborn screening programs by supporting the alignment of processes and criteria across Canada, with the provinces and territories retaining autonomy to deliver and tailor newborn screening programs to their local needs.

**Question 2: Do you have any specific changes that you would recommend for the proposed approach to the potential coordinated structures for newborn screening?**

When discussing the proposed exploratory coordinated model for newborn screening to enhance the consistency of conditions screened, the advisory panel described the importance of setting clear mandates and functions for the different committees. Setting clear mandates ensures clarity in the purpose and scope of responsibilities, sets accountability, and provides transparency of the approach and processes to interested parties. Collaboration, communication, and information sharing across all potential committees was also identified as an important component to enable the successful implementation of the newborn screening work across Canada. While each potential committee may have distinct functions, some activities will build on and use information provided by other committees.

## Figure 2: Illustrative Example of a Potential Coordinated Model for Newborn Screening




Note: A thick grey line indicates communication and information sharing; a blue line indicates accountability.

The overall vision for the proposed coordinated model considers using an advisory coordinating body to house and support the integration of the proposed structure into our health systems. The advisory panel recommended that a coordinated structure be housed within 1 organization to ensure continuity, collaboration, and unification of goals and objectives. Examples of organizations identified by the advisory panel that could serve this role were Canada's Drug Agency, based on its health technology assessment capabilities and convening functions, or the Public Health Agency of Canada, based on its public health mandate.

### Opportunity to Leverage Existing Processes and Structures to Support a Proposed Coordinated Model for Newborn Screening

Different committees may be considered to support the vision of the proposed coordinated model for newborn screening. The proposed committees' composition and functions are not meant to be prescriptive or exhaustive but to represent ideas and considerations made by the advisory panel to enable the overall vision and align with the draft guiding principles (Table 2 and Table 3).

## Table 2: Proposed Coordinated Model for Newborn Screening — Linkages to Draft Guiding Principles

| Proposed newborn screening coordinated model and linkage to draft guiding principles |
|---|
| • The **health rights of the newborn** will be the top priority in decision-making and activities executed by the committees, newborn screening programs, and the provincial and territorial ministries of health.<br>• **Equity** considerations will be included when carrying out committee activities. Committees will work to ensure equal access to quality screening and will consider the newborn's diverse needs, circumstances, and best interests.<br>• **Effectiveness, safety, and quality** of newborn screening will be a part of different committee activities (e.g., the evidence review will consider the benefits and harms to the newborn, guidance will be provided on key performance indicators to support testing quality).<br>• **Transparency** will be achieved through publication of the committees' work, including, but not limited to, the recommendations and their rationale, nominations, evidence reviews, quality standards and definitions, best practices, and educational materials.<br>• **Collaboration** will occur across and within the different committees, newborn screening programs, and the provincial and territorial ministries of health. There may be opportunities for different committees to collaborate and engage with the public.<br>• **Sustainability** considerations will be incorporated into committee activities (e.g., evidence reviews, best practices, program guidance). |

## Table 3: Potential Committee Composition and Functions of a Proposed Coordinated Model for Newborn Screening

| Proposed committee | Potential composition | Potential functions |
|---|---|---|
| **Newborn Screening Advisory Committee** | The committee may be composed of 5 to 15 multidisciplinary members. Such a committee would be required to have diverse representations, perspectives, and expertise (e.g., laboratory experts, clinical experts, people with lived and living experience, allied health care providers, ethicists). | The advisory panel explored the following potential responsibilities of this committee:<br>• providing oversight and advising committees<br>• providing strategy and intelligence in the newborn screening policy landscape<br>• maintaining records of newborn screening adoption |

| Proposed committee | Potential composition | Potential functions |
|---|---|---|
| | | • reviewing and deliberating draft recommendations<br>• making and communicating recommendations<br>• providing a coordinated forum for communication with newborn screening programs and provincial and territorial ministries of health<br>• building relations within the broader drugs for rare diseases space<br>• conducting consultations with the public. |
| **Expert Review Committee** | The committee may be composed of 5 to 8 multidisciplinary members with the potential need for additional smaller expert subcommittees or working groups of 3 to 4 members.<br><br>The membership of the Expert Review Committee could include, but is not limited to, clinician experts, laboratory scientists, health economists, ethicists, experts in health technology assessment, experts in public health, members of the general public, and people with lived and living experience. | The advisory panel explored the following potential responsibilities of this committee:<br>• reviewing information from the nomination form<br>• conducting horizon scans to detect emerging newborn screening conditions<br>• completing evidence reviews of the nominated conditions or new screening technologies<br>• conducting public engagement<br>• drafting recommendations. |
| **Quality, Standards, and Education Committee** | The committee may be composed of 5 to 8 multidisciplinary members with the potential need for additional smaller expert subcommittees or working groups of 3 to 4 members.<br><br>The membership of the Quality, Standards, and Education Committee could include, but is not limited to, knowledge translation and communication experts, data management administrators, newborn screening laboratory and clinical experts, health care policy and standards administrators, population and public health experts, ethicists, and people with lived and living experience. | The advisory panel explored the following potential responsibilities of this committee:<br>• providing guidance on best practices, standards, definitions, key performance indicators, and follow-up for newborn screening programs<br>• providing support for developing protocols or proposals for newborn screening programs<br>• coordinating and supporting a pan-Canadian newborn screening data repository<br>• developing educational materials and providing learning opportunities for health care providers and the public. |
| **Newborn screening programs** | This includes representatives from the newborn screening programs. | The advisory panel considered the following potential roles for newborn screening programs: |

| Proposed committee | Potential composition | Potential functions |
|---|---|---|
| | | • communicating program needs (e.g., bring forward issues and discuss key areas of interest)<br>• sharing information about their program data<br>• providing input on newborn screening nominations and recommendations. |
| **Provincial and territorial ministries of health** | This includes representatives responsible for newborn screening funding decisions within the provincial and territorial ministries of health. | The advisory panel considered the following potential roles for the provincial and territorial ministries of health:<br>• communicating priorities related to newborn screening<br>• reviewing screening recommendations to make funding decisions for their respective jurisdictions. |

When recruiting members for various committees, the advisory panel indicated that it is important to include a diversity of perspectives and represent dimensions of diversity, including, but not limited to, women, Indigenous people, and persons of all races, places of origin, religions, abilities, sexual orientations, and gender identities and expressions. There also may be specific jurisdictional considerations relating to equity that should be considered when identifying potential committee members.

The advisory panel recommended that, for specific committees, there may be a need for specialized subcommittees, either standing or ad hoc or time-limited, to address specific tasks; this will ensure the required activity is executed with the appropriate expertise. While noting the need for a variety of experts, the advisory panel also recognized the need to manage recruitment on different committees because of the limited number of experts in newborn screening, which may result in experts having to serve on multiple committees at a pan-Canadian and local level. If such a model is explored in future, there could be opportunities to further consider the operations and processes to leverage existing expertise without putting undue burden on these experts; as an example, by examining and reducing any potential duplication of efforts within these processes and ensuring that people are engaged at times and in ways that add value.

## Part 2: Opportunities to Enhance Newborn Screening Processes to Evaluate the Appropriateness of Adding, Removing, or Reassessing Conditions

The advisory panel explored processes that are in current use among newborn screening programs for adding, removing, or reassessing conditions. Relevant Canadian and international sources were identified using a scan of publicly available information.

The advisory panel proposed 4 key sequential and dependent processes that could inform the addition and removal of a condition to or from a proposed pan-Canadian newborn screening list:

1. a process to nominate conditions for review
2. an evidence review process
3. a process to inform deliberation and the development of recommendations
4. a process to inform communication and engagement with interested parties.

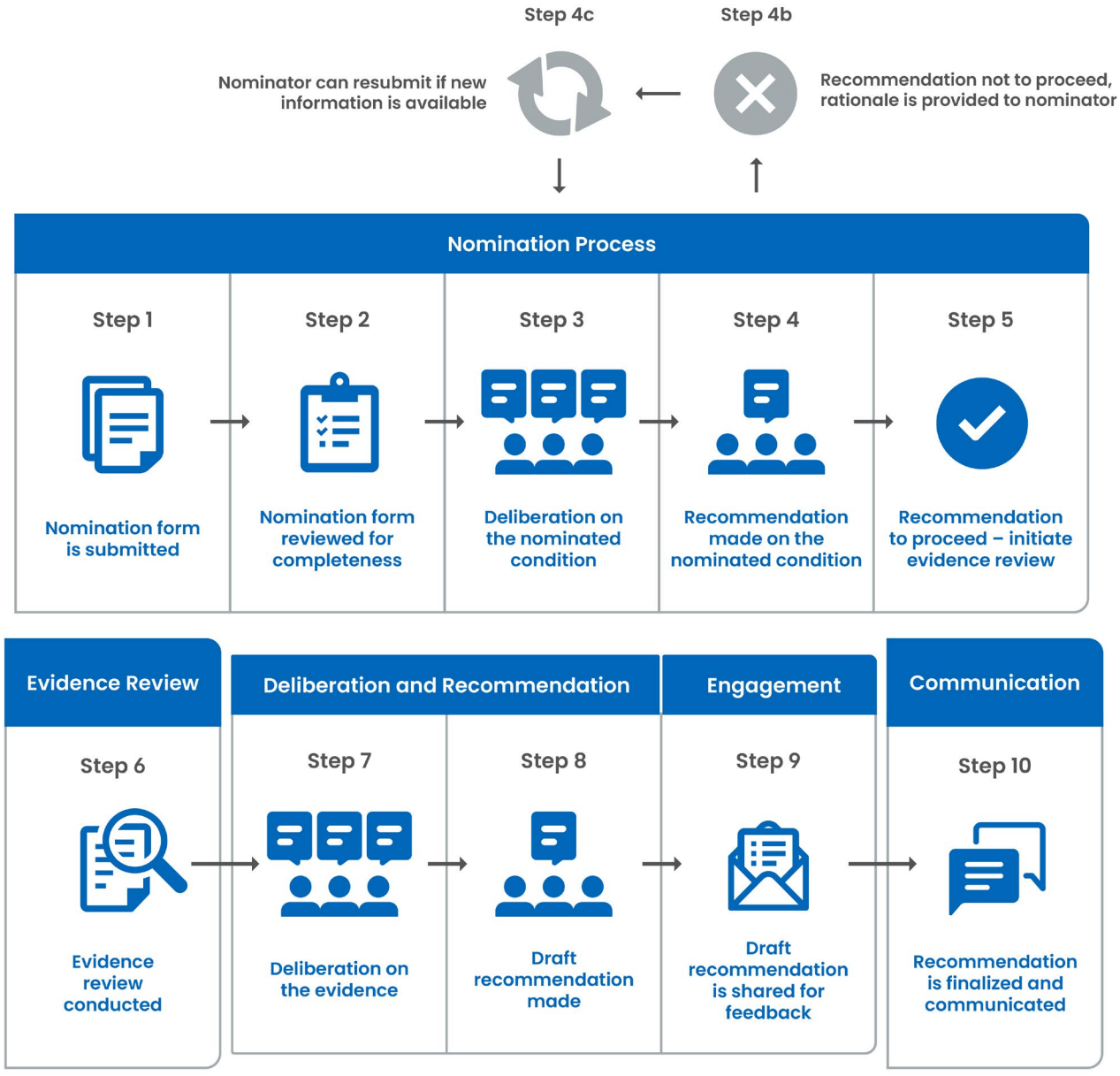
### Proposed Processes for Adding or Removing Conditions From a Pan-Canadian Newborn Screening List

Figure 3 illustrates and describes the 4 proposed key processes and their alignment with the draft guiding principles.

#### *Nomination Process for a Newborn Screening Condition*

The process for adding or removing a condition would begin with nomination. Each nomination would propose a target condition for addition or removal to or from a proposed pan-Canadian newborn screening list and would include supportive information and/or evidence to justify the nomination, describing why the condition should be added or removed. The proposed nomination process would demonstrate the proposed guiding principles, ensuring that due consideration be afforded to all nominations that are complete and meet prespecified criteria (refer to the Table 4).

## Figure 3: Proposed Process for Adding or Removing a Condition From a Proposed Pan-Canadian Newborn Screening List



**Question 3: Do you agree with the proposed process for nominating a condition? Please provide your reason(s) and suggested changes, if any.**

The steps in the nomination process and their linkages to the proposed guiding principles are described in Table 4.

### Table 4: Steps in the Proposed Nomination Process for Adding or Removing a Condition to or From the Proposed Pan-Canadian Newborn Screening List

| Steps | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| **Step 1: Nomination submitted** | The advisory panel explored the following considerations:<br>• Nominations can be submitted by:<br>  ○ individuals (including patients, caregivers, member of the public, clinicians, and others)<br>  ○ groups or organizations (including patient and advocacy groups, industry, ministries of health, and others).<br>• The nomination form is designed to be accessible.<br>• The nomination form is designed to ensure that appropriate and sufficient information, evidence, and sources are available to support the rationale for the nomination, describing the:<br>  ○ condition<br>  ○ target population for screening<br>  ○ availability of an appropriate screening test<br>  ○ availability of effective treatment.<br>• Support for developing the nomination may be made available to accommodate nominators, depending on the complexity of the information requirements.<br>• Nomination forms, excluding the nominator's personal information, will be made publicly available. | • The nomination process should be available and accessible to all people living in Canada (health rights of the newborn; equity; collaboration).<br>• Nominations should be supported by appropriate and sufficient evidence and/or information (effectiveness, safety, and quality).<br>• Nominations should be made public to reduce duplication of effort (transparency; collaboration). |
| **Step 2: Nomination form reviewed** | • The nomination is reviewed for completeness.<br>• Nominations with missing information and/or evidence may be | • Nominations are complete and align with the criteria (effectiveness, safety, and quality). |

| Steps | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| | returned to the nominator for completion.<br>• Nominations that are deemed to be complete are advanced to the next step. | • Decisions concerning whether a nomination proceeds to evidence review are justified and communicated (collaboration; transparency). |
| **Step 3: Nomination form discussed and deliberated** | • The nomination form is reviewed for alignment with the criteria and deliberations take place. | |
| **Step 4 and step 5: Recommendation for or against an evidence review** | • The outcome of the nomination review is communicated to the nominator and made public, including a rationale for the decision.<br>• Nominations deemed to align with the criteria proceed to evidence review.<br>• Nominations that do not proceed to evidence review may be resubmitted within a prespecified time frame if new information becomes available. | |

### *Evidence Review*

Once a decision to review the evidence has been made, an evidence review is initiated to ensure that a comprehensive review of available evidence for the nominated condition is summarized and reported. The completed evidence review then informs the steps that follow (i.e., deliberation and recommendations concerning whether to add or remove the condition from a proposed pan-Canadian newborn screening list).

**Question 4: Do you agree with the proposed process for evidence review? Please provide your reason(s) and suggested changes, if any.**

The proposed evidence review process and its c linkages to the proposed guiding principles are described in Table 5.

## Table 5: Proposed Evidence Review Process for Adding or Removing a Condition From the Proposed Pan-Canadian Newborn Screening List

| Step | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| **Step 6: Evidence review conducted** | • The approach to the evidence review should be informed by the proposed guiding principles, and will consider the potential benefits and harms of | • The evidence review is designed to identify and summarize potential benefits and harms to newborns (health rights of the newborn). |

| Step | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| | screening for the nominated condition in newborns.<br>• Additional information may be included as part of this step where there is, for example, uncertainty in the availability of evidence to support eligibility or a full evidence review.<br>• The evidence review may be conducted by a time-limited or commissioned working group, including potential ad hoc members with clinical or other expertise and/or experience with the condition (e.g., clinicians, researchers, and people with lived and living experience).<br>• The scope, detail, and timeline for completion of the evidence review will be contingent upon practical, technical, and methodological considerations.<br>• The evidence review will identify, assess, and summarize the available information and evidence describing the condition, available screening tests, treatment, and societal and other considerations.<br>• There may be opportunities to engage members of the public and people with lived and living experiences during the review process.<br>• The evidence review working group will use the criteria to consider the evidence and the net benefit of screening for the condition to make a draft recommendation whether to add the condition. | • The evidence review is informed by the criteria for adding and removing conditions (effectiveness, safety, and quality).<br>• The evidence review process is inclusive of experts, those with lived and living experience, and the public (equity; collaboration). |

### *Deliberation and Recommendation Process*

Once the evidence review is complete, the process for deliberating the evidence and developing recommendations to add or remove a condition is initiated.

This process is intended to provide an opportunity for the proposed Newborn Screening Advisory Committee to consider the draft recommendations and available evidence and its relevance to the criteria, engage in discussion, and develop recommendations to inform the addition or removal of a condition to or from a proposed pan-Canadian newborn screening list.

**Question 5: Do you agree with the proposed processes for deliberating and developing recommendations? Please provide your reason(s) and suggested changes, if any.**

The steps in the deliberation and recommendation process and their linkages to the proposed guiding principles are described in Table 6.

### Table 6: Steps in the Proposed Deliberation and Recommendation Process for Adding or Removing a Condition to the Proposed Pan-Canadian Newborn Screening List

| Steps | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| **Step 7: Deliberation** | • The proposed Newborn Screening Advisory Committee will review the proposed recommendation made by the evidence review group and the evidence review package.<br>• The proposed Newborn Screening Advisory Committee will deliberate on the net benefit of screening for a condition and consider the proposed recommendation using the criteria for adding or removing a condition.<br>• The deliberations will include diverse perspectives and will be structured to ensure that all criteria and relevant considerations are contemplated.<br>• The approach to making a recommendation may include:<br>  ○ a decision matrix (e.g., rates the magnitude and/or impact across domains such as benefits, harms, and readiness and/or feasibility)<br>  ○ a consensus-style voting process.<br>• The deliberations may be made public with meeting minutes being publicly available. | • The deliberations will be informed by the criteria and a structured approach (health rights of the newborn; effectiveness, safety, and quality; collaboration).<br>• The deliberations will be publicly available (transparency).<br>• The recommendations will consider variations in populations, capacities, and resources within and across health jurisdictions (equity, collaboration, sustainability). |
| **Step 8: Recommendations** | • The proposed Newborn Screening Advisory Committee will refine and propose recommendations.<br>• The recommendations will generally focus on whether to add or remove the nominated condition to or from a proposed pan-Canadian newborn screening list. | |

| Steps | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| | • Conditional recommendations may be issued (and may outline what is needed to satisfy the conditions for an unconditional recommendation).<br>• Recommendations may also address:<br>  ○ the need for generating additional evidence (i.e., where the net benefits to the newborn for a condition remain unclear, optimal types of screening tests)<br>  ○ the need for developing clinical guidelines for the diagnosis and treatment of a condition when it is not recommended for addition<br>  ○ the need to consider screening and/or diagnostic testing that may have implications beyond newborn screening. | |

### *Engagement and Communication Process*

The process for engagement and communication follows the development of the recommendations and is intended to provide an opportunity for broad engagement with interested parties and members of the public.

**Question 6: Do you agree with the proposed process for engagement and communication? Please provide your reason(s) and suggested changes, if any.**

The steps in the proposed engagement and communication process and their linkages to the proposed guiding principles, are described in Table 7.

## Table 7: Steps in the Proposed Engagement and Communication Process for Adding or Removing a Condition to or From the Proposed Pan-Canadian List

| Steps | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| **Step 9: Draft recommendation published for feedback** | • Draft recommendations will be made publicly available and eligible parties will be able to provide feedback. | • Draft recommendations are made publicly available to ensure all relevant feedback is solicited, considered, and incorporated (health rights of the newborn, transparency; equity; collaboration). |
| **Step 10: Recommendation finalized and communicated** | • Input and feedback will be publicly accessible, collated, and incorporated into the recommendations, as appropriate. | |

| Steps | Description and features | Linkage to proposed guiding principles |
|---|---|---|
| | • A final recommendation will be issued by the proposed Newborn Screening Advisory Committee, made publicly available, and communicated to health decision-makers across Canada's provinces and territories. | |

### Consideration for Reassessment of Conditions on a Proposed Pan-Canadian Newborn Screening List

As part of discussing the process for addition and removal of a condition from a proposed pan-Canadian newborn screening list, the advisory panel also considered the potential for reassessment of a condition that is already on such a proposed list.

A condition may undergo reassessment for numerous reasons, such as a new test or target becoming available, new evidence on the harms and benefits of screening or new or emerging therapies, or as part of quality improvement initiatives that identify the need for further investigation. A reassessment could result in a recommendation to change current screening practices, including the removal of a condition from a newborn screening list, or the opportunity for the development and implementation of quality improvements.

The advisory panel reviewed available information describing reassessment processes used by newborn screening programs in other jurisdictions. The members agreed that integrating reassessment within the processes for the addition and removal of conditions was likely to be the most pragmatic approach. In support of the proposed guiding principle of effectiveness, safety, and quality, the reassessment of a condition may be initiated by a nomination or at regular intervals, which would not require a nomination process. The decision to triage a reassessment to evidence review would be dependent on the reason for considering reassessment, as would any resulting review of the evidence. The deliberation and development of recommendations would follow a similar process to that proposed for the addition or removal of conditions from a proposed pan-Canadian newborn screening list.

## Part 3: Developing Canadian-Specific Criteria for Adding and Removing Conditions to a Proposed Pan-Canadian Newborn Screening List

### Using Criteria to Add and Remove Conditions to or From Newborn Screening Lists

Many jurisdictions in Canada and internationally use explicit predefined criteria as part of deliberations and making recommendations to add or remove a condition from a newborn screening list. Typically, the criteria cover several domains, including the condition, test, treatments, and societal and other considerations, and are often tailored to the specific condition under review. While these criteria are

intended to be used in the deliberations and recommendations process, they may also be adapted and used to guide the nomination process and evidence reviews.

Criteria are part of a deliberative framework and are used to enable the systematic consideration of a range of benefits, harms, and perspectives when recommending to add or remove a condition from a newborn screening list. They are not intended to be prescriptive in how information or methods ought to be used for gathering information to support deliberations. Using the criteria in deliberations is inherently an ethical endeavour and is based on value judgments; a key component would be to consider ethical implications as part of the deliberative process.

Criteria can enhance deliberations and recommendations by serving as transparent standards that can be applied consistently and can help ensure recommendations to add or remove a condition are legitimate, impartial, and inclusive.[5] Furthermore, criteria support consistency in deliberative reasoning and decisions and advance transparency by making the rationale for recommendations to add or remove a condition explicit.

To support future decision-making on expanding a proposed pan-Canadian newborn screening list, the advisory panel developed proposed criteria for adding and removing conditions. These criteria are intended to be used in the deliberations and recommendations process. It is important to note that these criteria will likely need to be refined over time and should be revisited to ensure their continued relevance and appropriateness.

### Developing the Proposed Criteria for Adding and Removing Conditions

To develop the proposed criteria for adding or removing conditions from a proposed pan-Canadian newborn screening list, the advisory panel reviewed the criteria from several key screening programs, including criteria from newborn screening programs in Canada and internationally (refer to Table 15 in the Appendix 1). The advisory panel discussed opportunities to modify several existing criteria, including collapsing some criteria for operational feasibility, and identified ways to embed the draft guiding principles into the criteria to add a condition on a proposed pan-Canadian newborn screening list. For removing a condition, the advisory panel drew on the considerations for removing a condition in Australia's Newborn Screening Framework[6] as it covered the key relevant considerations and could be adapted for Canada.

### Proposed Criteria for Adding a Condition

The advisory panel considered that Wilson and Jungner's[7] 1968 criteria for screening programs developed for the WHO continue to be relevant and foundational for adding conditions to newborn screening programs. However, they recognized that these criteria need to be tailored to be specific for newborn screening, adapted for relevance in Canada, and modernized in light of changes in the newborn screening space.

The advisory panel proposed adopting the 8 of the 10 criteria from Wilson and Jungner with modifications, including being more specific in the articulation and interpretation of the criteria, drawing on how the criteria are interpreted and expressed by other newborn screening programs in Canada and internationally. Specifically, the panel identified the need to modify the criteria in the following ways:

- Create additional clarification that eligible conditions are those that manifest in early life (i.e., neonatal period, infancy, or early childhood) as opposed to those later in life (e.g., adolescence or adulthood) or carrier status.
- Account for having a benefit of screening in newborns and not just convenience of bloodspot screening.
- Consider regional and jurisdictional variability in populations and condition incidence, particularly in frequently underserved populations and equity-deserving groups, as this is an important consideration that needs to be incorporated. The advisory panel recognized the population of Canada is increasingly diverse[8] and that there is often limited evidence about the incidence of many conditions and/or screening targets within cultural or ethnic subpopulations, which is an important consideration when making recommendations about conditions.
- Be explicit about equitable access to screening, diagnosis, and treatment as this is an important addition that links clearly with the draft guiding principles.
- Recognize the importance of acceptance of the screening test, diagnosis, and treatment. There was discussion about the role of health care providers and public acceptance and recognition of the need to keep the health rights of the newborn at the fore.
- Add a criterion adapted from Newborn Screening Ontario to reflect the explicit need for net benefit of screening (i.e., weighing harms and benefits to newborns and society).

**Question 7: Do you agree with the proposed criteria for adding a condition to a proposed pan-Canadian newborn screening list? Please provide your reason(s) and suggested changes, if any.**

Throughout the development of the proposed criteria, the advisory panel adhered to the draft guiding principles and considered how they connect with and are reflected within the proposed criteria. Key linkages to the draft guiding principles are described in Table 8.

### Table 8: Proposed Criteria to Add a Condition to a Proposed Pan-Canadian Newborn Screening List — Linkages to Draft Guiding Principles

| Guiding principle | Linkages to draft guiding principles |
|---|---|
| **Health rights of the newborn** | The criteria prioritizes assessing the benefits and harms of newborn screening for newborns' health. |
| **Transparency** | The criteria enable consistency and transparency in what considerations are used to decide to add a condition from a proposed pan-Canadian newborn screening list. |

| Guiding principle | Linkages to draft guiding principles |
|---|---|
| **Equity** | Facilities for screening, diagnosis, and treatment should be available across Canada; this is directly considered as a criterion. |
| **Effectiveness, safety, and quality** | Several criteria address issues related to the effectiveness of screening on improving a newborn's health, the safety of screening for newborns, and the quality of newborn screening programs. |
| **Collaboration** | A criterion emphasizes collaboration across health care systems from screening to diagnosis to treatment. |
| **Sustainability** | A criterion includes considerations of the impact of adding a condition on health systems. |

The draft modified Wilson and Jungner's criteria with the additional criterion from Newborn Screening Ontario are outlined in Table 9.

## Table 9: Proposed Criteria for Adding Conditions to the Proposed Pan-Canadian Newborn Screening List

| Wilson and Jungner's criteria[a] | Proposed modification to criteria |
|---|---|
| **The condition** | |
| 1. The condition is an important public health problem. | The condition should be serious and 1 that arises in children and/or leads to morbidity and mortality in childhood. |
| 2. There should be a recognizable latent or early symptomatic stage. | Removed. The advisory panel indicated that this criterion is not relevant to newborn screening and elements (e.g., natural history) are captured by criterion 3. |
| 3. The natural history of the condition, including development from latent to declared disease, should be adequately understood. | The epidemiology (including incidence and variation across regions and jurisdictions) and natural history of the condition should be adequately understood. Differences in the incidence and variation in test performance in subpopulations, particularly in equity-deserving groups, should be characterized and adequately understood. |
| **The test** | |
| 4. There should be a suitable test or examination. | There should be a robust, scalable, safe, precise, and validated screening test.[b] |
| 5. The test should be acceptable to the population. | The screening test, diagnosis, and treatment, should, on balance, be socially and ethically acceptable to health professionals and the public. |
| This is an additional criterion adapted from Newborn Screening Ontario. | The benefits of screening should outweigh the physical and psychological harms caused by the screening test (including the sample collection), diagnostic procedures, and treatment. |

| Wilson and Jungner's criteria[a] | Proposed modification to criteria |
|---|---|
| **The treatment** | |
| 6. There is an agreed policy on whom to treat as patients. | There is an agreed policy on the further diagnostic investigation of newborns with a positive screening test result.<br>There should be agreed evidence-based policies covering which newborns should be offered treatment and the appropriate treatment to be offered. |
| 7. There should be an accepted treatment for patients with recognized disease. | There should be an effective treatment or intervention for newborns identified through early detection, with evidence of early treatment leading to better health outcomes and reduced morbidity and/or mortality than late treatment. |
| **Societal and other considerations** | |
| 8. Facilities for diagnosis and treatment should be available. | Services and facilities for screening, diagnosis, and treatment should be available across Canada. |
| 9. Case finding should be a continuing process and not a "once and for all" project. | Removed. The advisory panel indicated that this criterion is not relevant to adding a condition to a pan-Canadian newborn screening list. |
| 10. The cost of case finding (including diagnosis and treatment of patients who are diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. | The budgetary impact of case finding (including screening, diagnosis, and treatment) should be considered in relation to not screening. |

[a] The term *treatment* is used in this table to refer to health care (including pharmaceuticals, medical devices, and clinical interventions) that is intended to alter the course of and/or improve a person's health.

[b] The additional consideration for this can include the distribution of test values in the target population should be known and a suitable cut-off level defined and agreed, and, if the screening test includes a test for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

### Considerations For Removing a Condition

The advisory panel proposed adopting the modified questions for removing a condition established by Australia's Newborn Bloodspot Screening Framework,[6] which outlines 1 of the few public processes for removing a condition from a newborn screening list. These 13 questions cover similar domains to those in Wilson and Jungner's criteria. They align with the proposed guiding principles in the following manner:

- they put the health rights of the newborn at the forefront in light of effectiveness, safety, and quality by ensuring screening is effective and safe
- they consider harms such as unnecessary testing
- they encourage further sustainability by supporting appropriate uses of resources and effective care.

The advisory panel made modifications to these considerations by adding whether the condition, if reassessed, would meet the criteria for adding a condition. They also considered how a condition might not be explicitly listed as a primary target, but in some cases could still be identified through the screening test results for another condition.

**Question 8: Do you agree with the proposed considerations for removing conditions from a proposed pan-Canadian newborn screening list? Please provide your reason(s) and suggested changes, if any.**

## Table 10: Proposed Considerations for Removing a Condition From a Pan-Canadian Newborn Screening List

| Considerations for removing a condition |
|---|
| When was screening initiated for this condition and why? |
| What is the rationale for removing the condition from screening? Provide relevant information that draws on current screening experience and a review of literature to support removal. |
| Would the condition meet the criteria for adding a condition on the list at this time? |
| What is the incidence in Canada? Is this determined clinically or through screening studies in Canada or other countries? |
| What positive and negative impacts would removing this condition have on the screening program (e.g., in terms of the impact on families, on the laboratory, on maternity service providers)? |
| What would be the clinical implications of removing the condition from screening? Include reference to the burden of disease associated with the condition, including morbidity and mortality, and the spectrum of disease. |
| Are there other risks of removing this condition from screening (e.g., impact on the ability to detect other conditions; impact on the family, including future reproductive risk; community concern)? |
| Is the condition screened internationally? |
| Would removal of this condition from screening have any other implications for the quality of the program? |
| Are there any alternatives to removal (e.g., alterations to cut-offs, further follow-up testing)? |
| For the current testing protocol, comment on the clinical and analytic validity, sensitivity, specificity, false-positive rate, false-negative rate, positive predictive value, and negative predictive value. |
| Is the test part of an assay that tests for multiple targets simultaneously (i.e., multiplexed)? Does its removal affect the detection of other treatable (i.e., secondary) conditions? Will it continue to be identified as a secondary target by screening of another primary condition? |
| Does testing identify other conditions (clinical or of unknown significance)? |
| What would be the cost implications of removing the test? |

Source: Adapted from Australia's Newborn Bloodspot Screening Framework.

## Part 4: A Proposed Pan-Canadian Newborn Screening List

### Addressing Challenges With Counting and Defining Newborn Screening Conditions

Comparing the number of screening conditions across newborn screening programs can be challenging because of differences in how newborn screening conditions are reported and defined. Typically, a primary or core condition is a condition that has a newborn screening test that is specifically designed to assess whether a newborn may be at risk for having the condition. A secondary finding typically includes identifying a condition where newborn screening is not specifically designed to identify it, but the condition is identified through screening for a primary condition. It can be difficult to compare the number of primary screening conditions across newborn screening programs in Canada because some programs consider conditions as primary findings while other programs consider the same conditions as secondary findings. Discrepancies in terminology can also add complexity to comparing screening across programs, as different jurisdictions refer to and define disorders, deficiencies, or conditions screened in different ways. Given the issues with counting and defining conditions, it is important to be clear about the types of conditions that will be included on a proposed pan-Canadian newborn screening list. To support consistency with the condition counts, the advisory panel recommended focusing on primary conditions and acknowledged that future work should include the development of a pan-Canadian secondary findings list and case definitions, which would include laboratory screening parameters, for each condition.

### Building Toward a Proposed Pan-Canadian Newborn Screening List

To identify potential candidate conditions that could be considered for a proposed pan-Canadian newborn screening list, the advisory panel first considered what conditions are being screened for in Canada. A table outlining the newborn screening conditions and which jurisdictions provide screening can be found in Appendix 2.

The advisory panel also considered previous newborn screening work that was done at the pan-Canadian level in 2016. At that time, an Intergovernmental Working Group made recommendations for a pan-Canadian list for newborn screening and prepared a report for the ministers of health. The Intergovernmental Working Group developed a newborn screening list through a consensus-based approach. During their deliberations, the members drew upon Wilson and Jungner's criteria and considered test performance, treatment options, benefits of care on newborn health, and information from the different newborn screening programs. The principle of fairness of access to newborn screening across Canada was an overarching theme in their discussions. The list of 22 conditions that were recommended for the Canadian list by the Intergovernmental Working Group in 2016 can be found in Table 11.[1] While the list was proposed to the ministers of health, there was no official adoption of the list at a pan-Canadian level.

## Table 11: The 2016 Recommended Canadian Newborn Screening List of Conditions

| Identified condition |
| --- |
| • Congenital adrenal hyperplasia<br>• Congenital hypothyroidism<br>• Cystic fibrosis<br>• Sickle cell disease (which includes hemoglobin SS, hemoglobin SC, and hemoglobin Sb-thalassemia)<br>• Severe combined immunodeficiency<br>• Biotinidase deficiency<br>• Classic galactosemia<br>• Medium-chain acyl-coenzyme A dehydrogenase deficiency<br>• Very long-chain acyl-coenzyme A dehydrogenase deficiency<br>• Long-chain hydroxyacyl-coenzyme A dehydrogenase deficiency<br>• Trifunctional protein deficiency<br>• Carnitine uptake deficiency<br>• Classic phenylketonuria<br>• Tyrosinemia, type I<br>• Maple syrup urine disease<br>• Citrullinemia, type I<br>• Argininosuccinic aciduria<br>• Glutaric acidemia, type I<br>• Isovaleric acidemia<br>• Propionic acidemia<br>• Methylmalonic acidemia (methylmalonyl-coenzyme A mutase)<br>• Methylmalonic acidemia (cobalamin A and B disorders) |

**Question 9: Do you agree with the proposed pan-Canadian newborn screening list? Please provide your reason(s) and suggested changes, if any.**

### A Proposed Pan-Canadian Newborn Screening List

The advisory panel identified an opportunity to build on the work of the Intergovernmental Working Group, as the conditions that were proposed in 2016 have been adopted, or are in the process of being adopted, by most newborn screening programs in Canada. The advisory panel is proposing that the list of 22 conditions from 2016 be adopted as a part of the proposed pan-Canadian newborn screening list with a few modifications.

The first modification is to separate out sickle cell disease and count each of the 3 different subtypes of this condition. Different newborn screening programs have different approaches for counting sickle cell

disease, and some programs include sickle cell conditions within the broader group of conditions known as hemoglobinopathies. On the 2016 recommended Canadian newborn screening list, sickle cell disease was counted as 1 condition, but there are different subtypes of the condition that were identified through the newborn screening process. In the US, they separate and count each subtype of sickle cell disease.[9] To provide clarity and align with international standards, it was recommended to split out this condition into the 3 subtypes for a proposed pan-Canadian newborn screening list.

The second modification that the advisory panel made to the proposed newborn screening list was to expand the list to include uniformly screened conditions that have been added to newborn screening programs across Canada after the original 2016 list was proposed. One new condition, spinal muscular atrophy, was identified as in the process of being screened for across all jurisdictions in Canada and may be included on a proposed pan-Canadian newborn screening list.

The proposed pan-Canadian newborn screening list can be found in Table 12 and includes 25 conditions. While the advisory panel agreed that the proposed list of conditions is a starting point, the advisory panel wants to emphasize that the conditions on the proposed list will require further review to support the development of case definitions and guidance on best screening practices. In addition, the advisory panel noted that even if a condition is currently being proposed for the pan-Canadian newborn screening list, this will not preclude it from being reviewed or reassessed in the future.

### Table 12: The Proposed Pan-Canadian Newborn Screening List

| Conditions on the proposed pan-Canadian newborn screening list |
|---|
| • Congenital adrenal hyperplasia<br>• Primary congenital hypothyroidism<br>• Cystic fibrosis<br>• Hemoglobin SS disease (sickle cell anemia)<br>• Hemoglobin SC disease<br>• Sickle cell beta-thalassemia<br>• Severe combined immunodeficiencies<br>• Biotinidase deficiency<br>• Classic galactosemia<br>• Medium-chain Acyl-coenzyme A dehydrogenase deficiency<br>• Very long-chain Acyl-coenzyme A dehydrogenase deficiency<br>• Long-chain hydroxyacyl-coenzyme A dehydrogenase deficiency<br>• Trifunctional protein deficiency<br>• Carnitine uptake deficiency<br>• Classic phenylketonuria<br>• Tyrosinemia, type I<br>• Maple syrup urine disease |

| Conditions on the proposed pan-Canadian newborn screening list |
| --- |
| • Citrullinemia, type I<br>• Argininosuccinic aciduria<br>• Glutaric acidemia, type I<br>• Isovaleric acidemia<br>• Propionic acidemia<br>• Methylmalonic acidemia (methylmalonyl-coenzyme A mutase deficiency)<br>• Methylmalonic acidemia (cobalamin disorders)<br>• Spinal muscular atrophy |

During the advisory panel's review of conditions that are screened for across Canada, 9 conditions were identified as not being uniformly screened. The advisory panel discussed these 9 conditions to explore if they should be added to a proposed pan-Canadian newborn screening list or if additional information was required to make a recommendation. Because of the variation in screening practices, and the rarity of some of the conditions, the advisory panel recommended that all 9 conditions undergo a full evidence review to determine if they could be added to a proposed pan-Canadian newborn screening list. The advisory panel identified that future evidence reviews should be guided by the proposed guiding principles and the proposed criteria that are outlined in this report. Table 13 includes the list of conditions that would require further evidence review.

### Table 13: List of Conditions That Require Further Evidence Review

| Conditions identified that require further evidence review |
| --- |
| • Guanidinoacetate methyltransferase deficiency<br>• Homocystinuria<br>• 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency<br>• Carnitine palmitoyltransferase I deficiency<br>• Carnitine palmitoyltransferase II deficiency<br>• Carnitine acylcarnitine translocase deficiency<br>• Mucopolysaccharidosis, type I<br>• Congenital cytomegalovirus (hearing loss risk factor)<br>• X-linked adrenoleukodystrophy |

## Part 5: Anticipating Emerging Conditions for Newborn Screening in Canada

With new and emerging health technologies, it becomes imperative to anticipate the emerging newborn screening conditions on the horizon. Anticipating the need to review conditions enables more strategic and proactive decision-making, supports the appropriate allocation of resources, and helps to prioritize and manage potential condition review requests. By anticipating and monitoring emerging conditions,

when new information becomes available or a new treatment comes to market, the system may be ready and primed to support efficient and timely decision-making.

**Question 10: Are there other emerging conditions that you would recommend the advisory panel consider in its final report?**

The advisory panel discussed some of the potential emerging newborn screening conditions that are not yet available in Canada. An emerging condition may be a condition that has been added to or is under review by a newborn screening program in another country. It also can include conditions that have treatments in the pipeline that should be monitored. Table 14, in no particular order, outlines examples of emerging conditions that were identified for further monitoring and may be considered in the future for addition to a proposed pan-Canadian newborn screening list. This list is not meant to be exhaustive; rather, it is intended to capture key conditions that would benefit monitoring for early awareness to support health systems readiness.

### Table 14: List of Emerging Conditions for Consideration for Newborn Screening in Canada

| Emerging conditions identified for consideration |
|---|
| • Pompe disease<br>• Fabry disease<br>• Mucopolysaccharidosis, type 2<br>• Mucopolysaccharidosis, type 3<br>• Batten's disease<br>• Niemann-Pick disease, type A and B<br>• Gaucher disease<br>• Duchenne muscular dystrophy<br>• Krabbe disease<br>• X-linked agammaglobulinemia<br>• Metachromatic leukodystrophy |

## Next Steps

After the end of this first engagement period, comments will be shared with the advisory panel for deliberation. A second session will be organized in early 2025 to discuss the comments and key changes that helped refine the report with nonbinding recommendations. The final report will be submitted to Health Canada, shared with provincial and territorial newborn screening decision-makers, and made publicly available.

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# Appendix 1: Approach, Assumptions, and Limitations

Note that this appendix has not been copy-edited.

## Approach

- To support the development of the guiding principles, the process to add or remove a condition, and the criteria for deliberations and recommendations on adding or removing a condition, Canada's Drug Agency supported the advisory panel with relevant publicly available information and published literature.
- An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy.
    - The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were newborn screening programs and equity, evidence-based medicine, decision-making, or principles. The search was completed on September 19, 2023, and limited to English-language documents published since January 1, 2018.
    - Search results were screened by one reviewer experienced in citation screening in Endnote. Citations selected for potential full-text retrieval were those that were relevant to newborn screening program policy and decision-making. The focus was on selecting citations that were described in the title and/or abstract a focus on principles for newborn screening criteria and decision-making for newborn screening, including ethical, legal or social issues, emerging conditions, and perspectives and experiences from collaborators.
- For the guiding principles, we drew on 5 key sources: the Canadian Organization for Rare Disorders: Canada's Rare Disease Strategy,[10], Quebec's newborn screening program reference framework,[10] Australia's National Policy Framework for Newborn Screening,[10] the US ACHDNC's decision matrix,[10] and the key principles for newborn screening from EURORDIS.[10]
- We developed potential opportunities for a coordinated model of newborn screening using key sources including the composition, terms of reference, and reporting structures of newborn screening advisory committees in British Columbia, Ontario, the US, and Australia, and the process of adding or removing conditions in those same jurisdictions. Information was supplemented with relevant published literature as appropriate.
- For the criteria for adding or removing a condition, we relied on published literature and 3 key examples of publicly available criteria for advisory committees in Ontario, the US, and Australia (Table 1).

## Table 15: Canadian and International Sources of Decision-Making Criteria for Adding Conditions to a Proposed Newborn Screening List

| Source | Purpose |
|---|---|
| Wilson and Jungner's criteria | Wilson and Jungner's criteria, first published in 1968, are cited as the foundational criteria for many public health screening programs, including newborn screening programs. |
| Dobrow, 2018[11] | Dobrow and team aimed to build on Wilson and Jungner's initial criteria and conducted a systematic review of principles used in public health screening, then used a consensus-based approach to develop a consolidated set of criteria. |
| Newborn Screening Ontario, High-level criteria from Form 3 | These criteria are used to guide the evidence review and the committee deliberations on the evidence when making recommendations on a condition for screening in Ontario. |
| Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) | The ACHDNC uses Key Questions and Topics to guide the evidence review. A different set of questions is used in deliberations on recommendations which evaluate net benefit, certainty of those benefits, system readiness, and feasibility. |
| Australia's Newborn Bloodspot Screening Framework | Australia uses these criteria to guide their evidence review and the deliberations on the evidence when making recommendations on a condition for screening in Australia. |

## Assumptions

- The draft guiding principles, proposed criteria, and process approach will be presented for engagement with interested parties for further refinement to support the recommendations that will be made by the advisory panel.
- The draft guiding principles, exploratory outline of a coordinated model for newborn screening, proposed processes and criteria to add or remove a condition, and the proposed pan-Canadian approach are being advanced as a first step with recognition that there will be a need for modification should they be considered and adopted in future for implementation.
- Inequities in outcomes can be affected by inequities in access to screening but can also affect those who do access newborn screening. This can be for several reasons, including difficulties accessing diagnostic services, delays in accessing care, challenges accessing treatment. Inequalities can also arise where the benefits of newborn screening are not realized by a population. This can include scenarios where the clinical and analytic validity of a particular screening target differs for a specific population, for example where the genetic variants that contribute to a condition differ in type or distribution by population. Where appropriate, activities outlined in this will incorporate the use of the Equity Checklist for HTA (ECHTA).[12]. Efforts will be made to ensure there is inclusive, diverse, and equitable representation among experts and interested persons engaged in this project (demonstrated through experience/representation of equity-deserving populations) aligned with our commitment to IDEA.[13]

- Additionally, Canada's Drug Agency acknowledges the critical need for Indigenous perspectives in Canadian health care systems. In both historical and ongoing ways, Indigenous Peoples and communities in Canada have been excluded from and/or harmed by medical research and have faced systemic racism and prejudice within health care systems. We commit to reconciliation,[14] and as part of our journey toward reconciliation, we will work toward  will be made to creating space and committing resources within Canada's Drug Agency to ensure Indigenous voices are heard and have an influence in this work.
- Coordination of efforts including having a proposed common list of conditions to screen in future would not infringe upon the authority and the responsibilities of respective parties, including newborn screening programs and provincial and territorial ministries of health decision-makers.

## Limitations

- The identification of guiding principles, their definitions and existing processes and criteria for adding or removing conditions for newborn screening relied on a limited literature search and iterative selection process that were done at a point in time, and any updates since the search period were not included in the discussion by the advisory panel.
- While the advisory panel was composed with considerations of diversity, the perspectives of the advisory panel members are not reflective of all perspectives and opinions relevant to newborn screening in Canada. Engaging with members of the public and interested parties to elicit their perspectives on the advisory panel's proposals is intended to address this limitation.
- These limitations are being addressed by prioritizing transparency of, and collaboration on, the final outputs of the work i.e., consulting broadly and soliciting public input to ensure there is opportunity for identifying as broad a set of inputs and perspectives as is possible.
- Other limitations include the difficulties accounting for variation in newborn screening programs across Canada.

# Appendix 2: Primary Conditions for Newborn Screening Across Canada (Updated June 2024)

Note that this appendix has not been copy-edited.

## Table 16: Conditions Screened Through Dried Bloodspot Newborn Screening Across Canada

| Condition | BC | AB | SK | MB | ON | QC | NB | PE | NS | NL | NU (Qikiqt-ani) | NU (Kitik-meot) | NU (Kivill-iq) | YT | NT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Congenital adrenal hyperplasia | + | + | + | + | + | * | * | * | * | ** | + | + | + | + | + |
| Primary congenital hypothyroidism | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystic fibrosis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemoglobin SS (sickle cell anemia) | + | + | * | + | + | + | + | + | + | ** | + | + | + | + | + |
| Hemoglobin SC disease | + | + | * | + | + | + | + | + | + | ** | + | + | + | + | + |
| Sickle cell beta-thalassemia | + | + | * | + | + | + | + | + | + | ** | + | + | + | + | + |
| Severe combined immunodeficiencies | + | + | + | + | + | + | + | + | + | ** | + | + | + | + | + |
| Biotinidase deficiency | + | + | + | + | + | ‡ | + | + | + | ** | + | + | + | + | + |
| Classic galactosemia | + | + | + | + | + | ‡ | + | + | + | ** | + | + | + | + | + |
| Medium-chain acyl-coenzyme A dehydrogenase deficiency | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Very long-chain acyl-coenzyme A dehydrogenase deficiency | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Long-chain hydroxyacyl-coenzyme A dehydrogenase deficiency | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

| Condition | BC | AB | SK | MB | ON | QC | NB | PE | NS | NL | NU (Qikiqt-ani) | NU (Kitik-meot) | NU (Kivill-iq) | YT | NT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trifunctional protein deficiency | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carnitine uptake deficiency | + | + | + | + | + | * | | | | | + | + | + | + | + |
| Classic phenylketonuria | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tyrosinemia, type I | + | + | + | + | + | + | * | * | * | + | + | + | + | + | + |
| Maple syrup urine disease | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + |
| Citrullinemia, type I | + | + | + | + | + | † | + | + | + | + | + | + | + | + | + |
| Argininosuccinic aciduria | + | * | + | + | + | + | + | + | + | + | + | * | + | + | * |
| Glutaric acidemia, type I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Isovaleric acidemia | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + |
| Propionic acidemia | + | + | + | + | + | * | + | + | + | + | + | + | + | + | + |
| Methylmalonic acidemia (methylmalonyl-coenzyme A mutase deficiency) | + | + | + | + | + | * | + | + | + | + | + | + | + | + | + |
| Methylmalonic acidemia (cobalamin disorders) | + | + | + | + | + | * | + | + | + | + | + | + | + | + | + |
| Spinal muscular atrophy | + | + | + | + | + | + | * | * | * | + | + | + | + | + | + |
| Guanidinoacetate methyltransferase deficiency | + | * | – | – | + | – | – | – | – | + | – | * | – | + | * |
| Homocystinuria | + | – | – | + | + | * | – | – | – | + | + | – | + | + | - |
| 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency | – | + | – | – | – | – | – | – | – | – | – | * | - | – | * |
| Carnitine palmitoyltransferase I deficiency | – | – | + | + | † | † | + | + | + | + | + | – | + | – | – |
| Carnitine palmitoyltransferase II deficiency | † | – | + | + | † | + | + | + | + | + | + | – | + | – | – |

| Condition | BC | AB | SK | MB | ON | QC | NB | PE | NS | NL | NU (Qikiqt-ani) | NU (Kitik-meot) | NU (Kivill-iq) | YT | NT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carnitine acylcarnitine translocase deficiency | † | – | + | + | † | † | + | + | + | + | + | – | + | – | – |
| Mucopolysaccharidosis, type I | – | * | – | – | + | – | – | – | – | ** | + | * | – | – | * |
| Congenital cytomegalovirus: hearing loss risk factor | – | * | + | – | + | – | – | – | – | – | – | * | – | – | * |
| X-linked adrenoleukodystrophy | – | – | – | – | * | – | – | – | – | – | – | – | – | – | – |

Notes: + (dark green) denotes a primary screened condition (i.e., a stated target of the screening program); † (light green) denotes a secondary screened condition (i.e., not a stated target, but is anticipated to be detected as a result of screening); ‡ (yellow) denotes a condition targeted to a specific population (i.e., the screening is provided to a specified subset of the population or by request); * (blue) denoted a condition that is in development (i.e., the condition has been approved and screening is in development); ** (grey) denotes a condition that is under review (i.e., the condition is formally being reviewed for inclusion); and – (pink) denotes not screened (i.e., the condition has not been formally considered or has been reviewed and declined as a target).