Citizen Brief

Accessing Precision Therapies for Children and Youth in Canada

7 May 2021

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On behalf of The Hospital for Sick Children and the McMaster Health Forum we would like to THANK YOU for taking the time to review this document in preparation for our Citizen Panel. Access to precision therapies for Canadian children and youth is a complex issue. This document aims to summarize key components of the problem, potential solutions, and other important considerations. Throughout the document there are questions and case studies to help stimulate your thinking and set the stage for discussion together. The public's voice – your voice – is crucial when discussing how to sustainably improve health outcomes of children and youth in Canada. We look forward to hearing your perspective at our Citizen Panel. Once again, thank you!

The McMaster Health Forum

The McMaster Health Forum's goal is to generate action on the pressing health-system issues of our time, based on the best available research evidence and systematically elicited citizen values and stakeholder insights. We aim to strengthen health systems – locally, nationally, and internationally – and get the right programs, services and drugs to the people who need them.

The Hospital for Sick Children (SickKids), Child Health Evaluative Services

The Hospital for Sick Children (SickKids) Research Institute, affiliated with the University of Toronto, is Canada's largest, hospital-based child-health research institute dedicated to improving the health of children. Its research programs range from basic discovery research to clinical care and health policy, supported by state-of-the-art expertise, technologies and facilities. Child Health Evaluative Sciences (CHES) is the Research Institute's largest research program. Its multidisciplinary researchers seek to conduct cutting-edge research and translate their findings into clinical practices, systems and policies to improve the health and well-being of children and their families in Canada and around the world.

About citizen panels

A citizen panel is an innovative way to seek public input on high-priority issues. Each panel brings together 14-16 citizens from all walks of life. Panel members share their ideas and experiences on an issue, and learn from research evidence and from the views of others. A citizen panel can be used to elicit the values that citizens feel should inform future decisions about an issue, as well as to reveal new understandings about an issue and spark insights about how it should be addressed.

About this brief

This brief was produced by the Hospital for Sick Children and the McMaster Health Forum to serve as the basis for discussions by the citizen panel on how to improve access to precision therapies for children and youth in Canada. This brief includes information on this topic, including what is known about:

- the underlying problem;
- three possible elements of an approach to addressing the problem; and
- potential barriers and facilitators to implement these elements.

This brief does not contain recommendations, which would have required the authors to make judgments based on their personal values and preferences.

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Purpose of this citizen panel

Precision medicine is an evolving field of medicine that aims to tailor treatment to individual patients by using new technologies to identify and treat specific causes of their disease, often genetic in nature (see Figure 1). These changes may be different for each person. Once the change has been identified, a **precision therapy** can sometimes be used to fix or fight the underlying disease-causing genetic change.

Precision therapies are increasingly important to improving patients' health outcomes. However, they also have a growing impact on public budgets. This has prompted discussion in societies around the world about the scientific, social and financial implications of the widespread use of precision therapies. This citizen panel will generate discussion and input from members of the public about improving access to precision therapies for children and youth. The primary focus of this citizen panel is to understand what **values and principles** Canadians think should be used to inform **decisions** about which precision therapies to publicly fund for children and youth in Canada.

Figure 1: Overview of precision therapies (figure from Dana-Farber Cancer Institute)

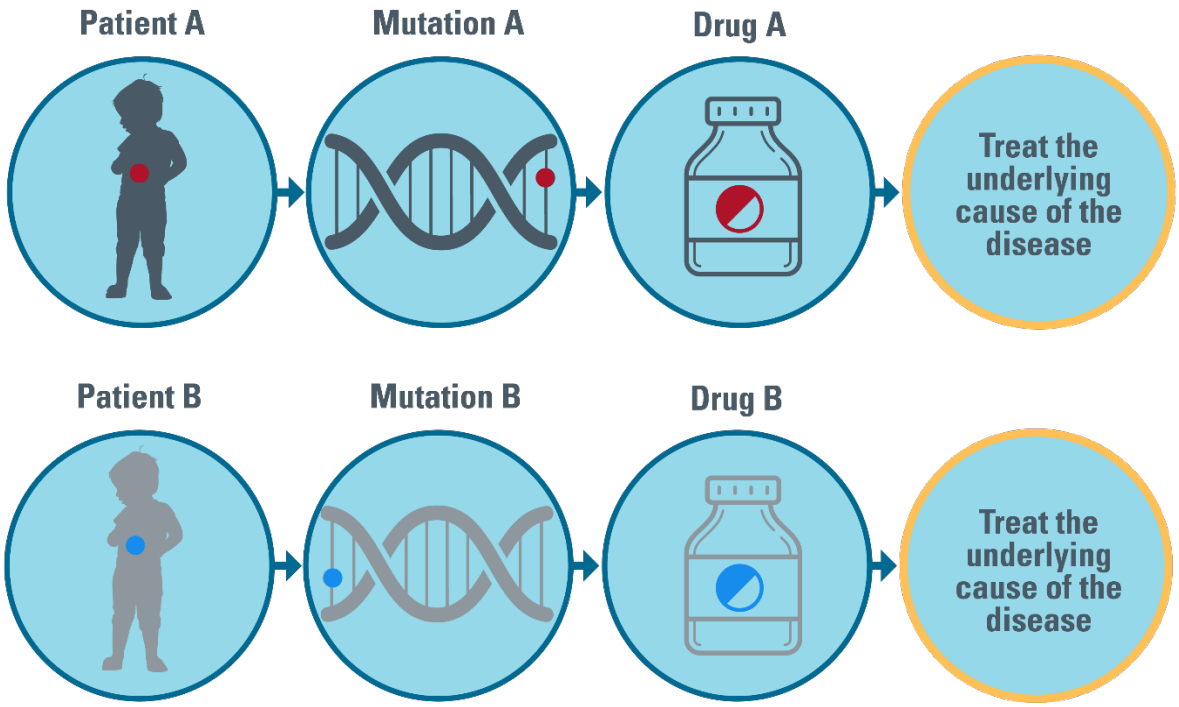


Figure 1 Permission: "Adapted with permission from Dana-Farber/Boston Children's Cancer and Blood Disorders Center, "Infographic: What Is Precision Cancer Medicine?" (https://www.danafarberbostonchildrens.org/innovative-approaches/precision-medicine/what-is-precision-medicine.aspx). © 2015-2021 Dana-Farber Cancer Institute, Inc. and Boston Children's Hospital. All rights reserved."

Key messages

What's the problem?

Precision therapies have the potential to substantially improve the health and quality of life of children and youth with hard-to-treat or rare diseases. However, Canadian children and youth often have limited and unequal access to these therapies. Key reasons for this are that:

- few innovative therapies for children and youth are being developed;
- few innovative therapies for use in children and youth are being submitted for sale and funding consideration in Canada;
- high-cost but potentially high-benefit drugs, including precision therapies, are putting pressure on health-system budgets;
- incomplete assessments of value specific to child health are being made in health technology assessment; and
- there is a patchwork of funding coverage for precision therapies across Canada, creating potential for inequities in access by children and youth.

What is a potential solution to the problem?

The problem of limited and unequal access to innovative therapies for children and youth needs a comprehensive solution. We have identified three elements that could enhance opportunities and address problems within Canada.

- **Element 1**: Reform federal drug regulations to address key challenges in access to precision therapies for children and youth
  - This element could include: 1) creating regulations to require and incentivize submission of data to Health Canada from research on precision therapies conducted with children and youth; and 2) creating opportunities to engage citizens in creating new regulations and polices on precision therapies for children and youth.
- **Element 2**: Develop a health technology assessment (HTA) framework that is tailored to child health
  - This could include understanding how values and principles are used in HTA to: 1) determine how they may be used differently for children and youth; and 2) identify new values and principles that are important for children and youth.
- **Element 3**: Improve generation, collection and management of information about precision therapies for children and youth

- This could include changes such as: 1) developing a pan-Canadian platform to share evidence on the use of precision therapies for children and youth; 2) developing research funding mechanisms to ensure data from children and youth are collected in clinical trials; and 3) developing new approaches to studying precision therapies in children and youth.

What are some implementation considerations?

- **The biggest challenges** to implementing these elements are likely legislative, institutional and technological barriers for accessing precision therapies.
- **Key opportunities** for implementing these elements could be: 1) the increasing importance placed on incorporating patient and family values into policy decisions about health systems in Canada; and 2) the relevance of this topic to important national policy discussions, including universal pharmacare and strategies for funding high-cost drugs for rare diseases.

Questions for the citizen panel

>> The primary focus of this citizen panel is to understand what values and principles Canadians think should be used to inform decisions about which precision therapies to publicly fund for children and youth in Canada.

We want to hear your views about the problem, three elements of a potential approach to addressing it, and how to address barriers to moving forward.

The views and experiences of citizens can make a significant contribution to finding the best ways to meet their healthcare needs. This panel will provide an opportunity to explore the questions outlined at the beginning of each section. Although we will look for common ground during these discussions, the goal of the panel is not to reach consensus, but to gather a range of perspectives, including areas of agreement and divergence on the topic.

Below, Box 1 provides some questions for you to consider when reading this brief. We provide additional questions for you to consider in each section of the brief, particularly about the elements of a potential approach to addressing the problem. In Box 2, we provide a glossary of some important terms and concepts used in this brief.

Box 1: Questions to consider

Questions about the problem

- What do you see as the biggest challenges in access to medicines for children and youth in Canada?
- What do you think are the biggest challenges in access to precision therapies by children and youth, in particular?

Focus question for panel discussion

- What do you think are the most important values and principles to consider when determining which precision drugs to publicly fund for children and youth in Canada?

Box 2: Glossary

Children and youth
For the purpose of this brief, children and youth are those aged 0-19; occasionally the term "childhood" or "pediatric" is used to refer to the same group, when appropriate.

Personalized/precision medicine
Identifies the unique aspects of an individual or their disease, which are utilized to select an appropriate and targeted treatment plan.

Precision therapy
A therapy that enables individualized treatment by targeting the specific characteristic (often genetic) that is causing a disease in a given person. Patients who have this characteristic may be eligible for the corresponding precision therapy.

"High-cost" drug
A drug whose cost is many times more than the average price of drugs currently funded by public health-insurance plans. While there is no standard definition of a high-cost drug, the Canadian Institute for Health Information and the Patented Medicine Prices Review Board use a threshold of $10,000 per patient per year for its analyses on health expenditures, and Health Canada references $200,000 per patient per year in high-cost drugs for rare diseases.

Clinical trials
An important source of clinical evidence about a drug or intervention, used to determine if it is a safe and effective treatment for a disease. Clinical trials also determine the types and frequency of any tolerable or serious adverse events, like fatigue, fever, hospitalization, disability or death.(1)

Health Technology Assessment (HTA)
HTA is a multidisciplinary process that systematically integrates medical evidence, economic data, and social values to support decision-making on the adoption and funding of a health technology by a health system.(2; 3) Precision medicine technologies include drugs, diagnostics, devices and services.

Canada's children and youth have limited and unequal access to precision therapies

The context: Why does the issue of access to precision therapies for children and youth in Canada require your input?

As diseases are better understood, precision therapies may be developed to more accurately and effectively target their causes. Such therapies might hold especial promise for children and youth who have hard-to-treat or rare diseases. Yet, there are few available precision therapies for children and youth in Canada. Those that are available in Canada can be difficult to access because of their high cost, where they are administered, and how they are administered. Certain drugs are available in some provinces, but not in others.

Researchers at the Hospital for Sick Children in Ontario are examining how the evaluation of precision therapies for children and youth can be improved. The goal is to guide fair and sustainable decision-making about which therapies to publicly fund in Canada. To reach that goal, the researchers are working with a broad representation of Canadians to deliberately include their views on the values and principles that should be included in an improved evaluation approach. In an earlier study, the researchers interviewed patients/caregivers, clinicians and policymakers.(4) Currently, a series of citizen panels, including this one you are a part of, is being held to capture the views of the general public.

In this section of the brief, we provide some information about the diseases that may be treated with precision therapies, how drugs are approved in Canada, and how

recommendations are made for funding through provincial drug plans. We also provide information about some of the initiatives underway to help health systems deal with the problem of limited access to precision therapies for children and youth.

Who might benefit from the use of child health precision therapies?

Precision therapies can be effective in diseases where the specific genetic changes that cause the underlying problem are known.(5-7) We provide two examples below where there are clear needs and reasonable expectations for achieving benefits from precision therapies.

Example 1 – Childhood cancer (also see Box 3)

Every year about 1,000 children and youth are newly diagnosed with cancer in Canada.(8) In the last 50 years, there have been significant improvements in both survival and quality of life of children and youth with cancer.(9) This has been achieved through the introduction of new therapies and improvements in how existing therapies are used.(10) However, some of these therapies – including chemotherapy and radiation therapy – cause unwanted short- and long-term side effects. These can include impairments in cognitive function, mobility challenges, hearing loss, stunted growth, infertility, and organ damage. They can also increase the likelihood of developing other cancers.(11)

In contrast to many traditional cancer therapies, precision therapies are more targeted to the disease-causing change in the body. It is hoped that precision therapies will therefore have fewer immediate and long-term side effects. Also, some pediatric cancers remain extremely hard to treat with conventional treatments such as chemotherapy, radiation and surgery. For example, one-third of children and youth with cancer will have their cancer aggressively spread throughout the body, return after treatment, or do not respond to therapy at all. Only a small minority of these children and youth will survive – a situation unchanged over the past three decades, despite efforts to improve treatment for these 'hard-to-treat' cancers.(9)

Box 3: Spotlight on childhood cancer: the difference precision therapies can make for 'hard-to-treat' cancers in children and youth

Acute lymphoblastic leukemia: New therapies, new hope

Acute lymphoblastic leukemia (ALL) is the most common cancer in children. While cure rates for ALL now exceed 85%, a substantial number of children with ALL still suffer from disease relapse.(12) When ALL comes back (or does not go away) despite treatment, it is hard to cure and many children die from relapsed or refractory disease. Until recently, few options existed to treat ALL in relapse – particularly in cases where the disease has come back more than once. Intensive chemotherapy and bone marrow transplant have remained the main treatment options for relapsed ALL for decades; these options cure a minority of children. Over the past few years, however, a number of promising precision therapies for childhood ALL have been developed, tested and approved for use in children. The most promising among them include chimeric antigen receptor T-cell (CAR-T) therapy and blinatumomab, both of which direct a patient's own immune cells to attack the leukemia.(13)

These therapies have begun to change the game for relapsed ALL, offering cures for children whose disease has resisted all other attempts to eradicate it. In addition, some of them have fewer and less severe side effects than traditional chemotherapy or bone marrow transplant. Most of these new treatments are very expensive and the best ways to use them are still being studied. But children are now surviving who never did before.

Rhabdomyosarcoma: Still searching

In Canada from 2012 to 2016, 210 children were diagnosed with a soft tissue sarcoma – a cancer of the tissues that connect, support and surround other body structures.(14) The most common type of childhood soft tissue sarcoma is rhabdomyosarcoma (RMS). RMS generally affects muscle cells and requires multiple approaches to treatment, including chemotherapy, surgery and radiation therapy. Use of these treatment techniques has increased the chance of survival of low- and intermediate-risk RMS, so that roughly 70% of children in these categories are alive at least five years after diagnosis.(15) However, outcomes for high-risk RMS – where the cancer is widespread and its cells have a specific genetic mutation – have not improved much, and only a minority of these children survive. There are currently no approved precision or other innovative therapies in Canada for the treatment of advanced RMS. Clinical trials are ongoing.

Example 2 - Spinal muscular atrophy (SMA) (see Box 6 for new drugs and their cost for SMA)

SMA is a group of rare genetic diseases caused by a mutation in a gene important for muscle movement and development.(16) It is most commonly detected in childhood, often showing up in infancy. Over time, SMA causes a loss of muscle function, including those needed for crawling, walking, eating and breathing. Less than 1% of children in Canada are born each year with SMA. Without therapies to directly treat the gene change causing the disease, the treatment of patients with SMA has focused on reducing the burden of

symptoms and improving the quality of life for children and their families. However, recently there have been innovative precision therapies developed that are more effective in treating the underlying cause of the disease.(17; 18)

How are precision therapies for children and youth currently regulated and funded in Canada?

Precision therapies for children and youth are regulated and funded through the same pathway as other drugs and technologies in Canada (Box 4). The national and provincial organizations involved in these processes interact closely (Figure 2). At the national level:

- Health Canada regulates what drugs are safe, effective and of good quality to sell in Canada;
- the Canadian Agency for Drugs and Technology in Health (CADTH)
  - assesses the value of drugs in terms of clinical benefit, cost-effectiveness, alignment with patient values and feasibility of health-system adoption, and
  - makes recommendations to guide funding by provincial health insurance plans;
- the Patented Medicine Prices Review Board (PMPRB) regulates prices to ensure that they are not excessive; and
- on behalf of member provinces, the pan-Canadian Pharmaceutical Alliance (pCPA) negotiates with manufacturers to establish the reimbursement price under the public drug programs.

At the provincial and territorial level, each health ministry makes its own decision on whether to fund the new drug under the public drug plan. It may gather more local data and evidence, including how the drug may be incorporated within its own health system. Provinces that opt out of pCPA negotiations may directly negotiate prices with manufacturers.

Quebec is not a member of CADTH and has its own HTA agency, Institut national d'excellence en santé et services sociaux (INESSS). However, it works closely with CADTH and has similar criteria for assessing drugs. It also works very closely with the national regulatory and pricing agencies.

Precision therapies may also be accessed through private drug plans, through direct purchase by individuals (out-of-pocket payment), or though compassionate access provided by the manufacturers. The federal government also directly provides access to drugs through programs for certain groups of Canadians, including First Nation, Inuit and Métis communities. While all these pathways are important, this panel will focus on the pathway through public funding by provinces and territories.

Box 4: The drug approval and funding process in Canada

Stage 1: Authorize for Sale

- Preclinical – Manufacturers conduct non-human studies to determine if a drug is safe and shows promise as a treatment. This evidence is presented in an application to Health Canada requesting to run a clinical trial with human participants to test the drug.
- Clinical – Manufacturers submit all the data from the clinical trials to Health Canada for examination. If safety, efficacy and quality criteria are met, a Notice of Compliance is issued for the drug. This permits the licensing and marketing of the drug in Canada.

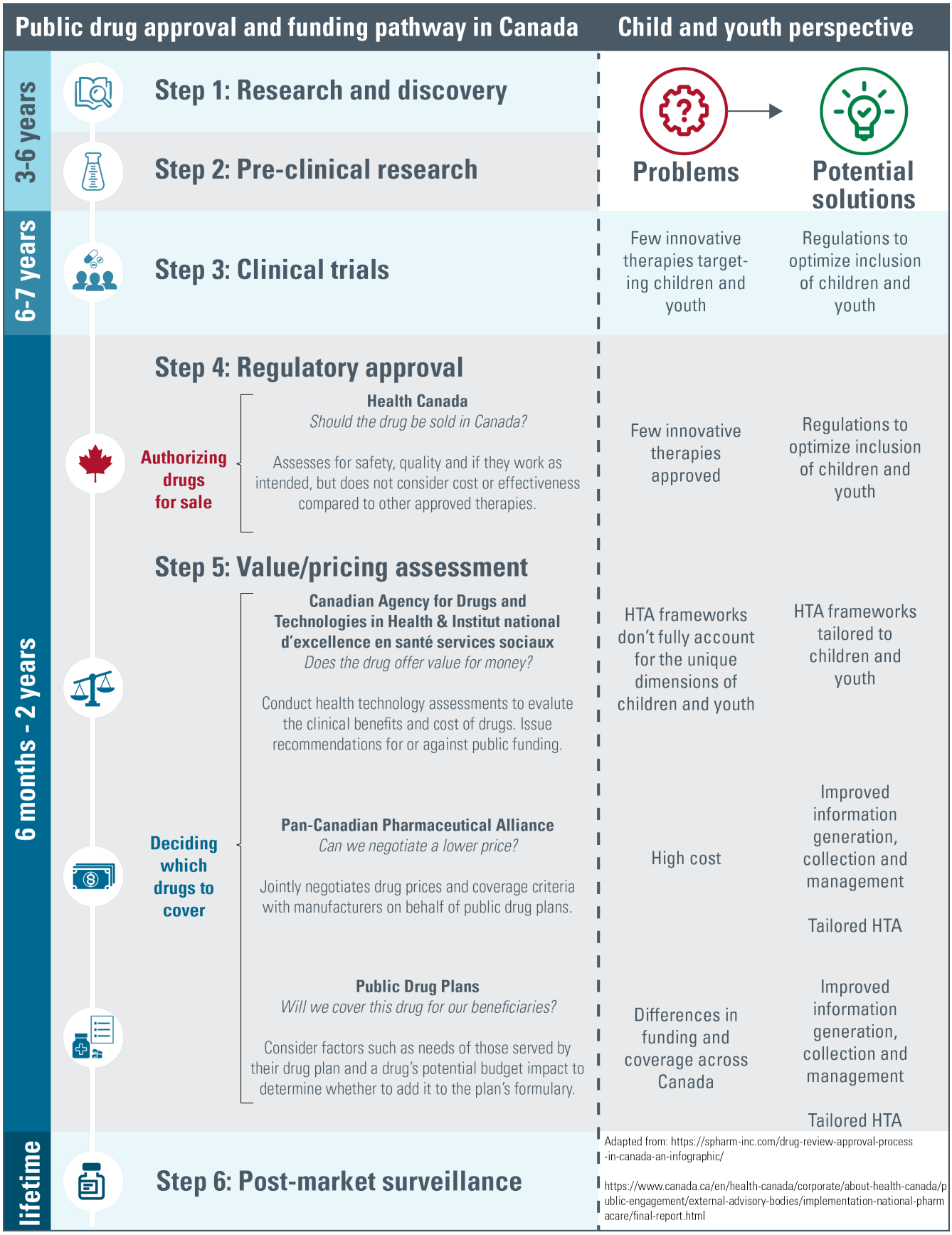
Stage 2: Recommend to Fund or Not

- CADTH undertakes a comprehensive review that includes evidence about the drug's effectiveness compared to other available treatments, its potential budget impact, its cost-effectiveness, its implementation factors, and legal, social, equity, patient and provider considerations. Under CADTH, expert advisory committees in the pan-Canadian Oncology Drug Review (pCODR) examine cancer drugs and the Common Drug Review (CDR) examines all other drugs. A recommendation is made to fund (sometimes with conditions) or to not fund, but the final decision for public funding is made by the provinces.
- The Patented Medicines Prices Review Board (PMPRB) ensures that drugs are sold at a reasonable price given their benefits and compared to other drugs. It sets the "ceiling" price for Canada based on how much the same drug costs in other relevant countries.

Stage 3: Decision to Fund – Provincial and Territorial Ministries of Health

- Provinces make their own assessment of precision therapies based on their local situation. Provinces may rely on their own expert committees and may conduct an HTA that is more specific to their circumstances. There is no single standard way that all provinces use to decide on funding a drug.
- Some large hospitals also have hospital-based HTA units or drug review committees, and access to a drug may be decided on a drug-by-drug or case-by-case basis.

Figure 2 – Public drug approval and funding pathway in Canada



Precision therapies have the potential to substantially improve the health and quality of life of children and youth with hard-to-treat or rare diseases

The problem: What challenges exist in access to precision therapies for children and youth in Canada?

Canadian children and youth have limited and unequal access to precision therapies. Key reasons for this are that:

- as for pediatric medicines in general, few innovative precision therapies for children and youth are being developed and consequently approved for sale and for funding consideration in Canada;
- high-cost but potentially high-benefit drugs, including precision therapies, are putting pressure on health-system budgets;
- incomplete assessments of value specific to child health are being made in health technology assessment; and
- there is a patchwork of public funding coverage for precision therapies across Canada, resulting in inequities in access by children and youth.

We provide a summary of key data and evidence in relation to each of these challenges below.

Few innovative therapies for children and youth are being developed and approved for sale and funding consideration in Canada

There are few precision therapies being developed and approved for children and youth in Canada. Many of the reasons for this overlap with more general challenges related to the development and approval of drugs for children and youth.

Differences in the nature and prevalence of adult and childhood diseases and ethical considerations limit pediatric drug research and development (R&D).(19) This then affects regulatory processes, which in turn limits the number of innovative therapies being submitted for federal approval and provincial funding recommendations.(20) As a result, fewer drug therapies are available for children and youth.

Compared to adults, children and youth have fewer severe diseases, but this does not mean that such diseases are not a serious problem. For example, even though childhood cancers only account for 1% of total cancer cases in Canada, they are the main cause of death by disease for children and youth.(8) Children also make up about two-thirds of all individuals with rare diseases in Canada.(21)

Some of the differences between adult and childhood diseases are poorly understood. For example, environmental factors usually play a much smaller role in childhood diseases.(22) Specific genetic changes that cause disease in children and youth are starting to be better understood. However, much more is still known about adult diseases.

Drug manufacturers can have less interest in creating new drugs, including precision therapies, for children and youth than for adults. It is expensive to develop new drugs. If there are relatively few potential users, the investment in precision-drug development may not be considered worthwhile. Clinical trials are also expensive to run and can also be challenging given that few children are eligible as participants, and/or that families may not be willing to participate.(23) Yet, strong evidence for how well a drug works and how safe it is can only be established by testing it in enough people. Often, a clinical trial must run in multiple hospitals/institutions in different provinces or different countries to enroll enough children to gather data. In general, the smaller number of potential participants for

precision therapies has forced researchers to design new types of clinical trials to collect enough evidence about a drug's safety and efficacy.(24)

As a result, children and youth are often treated with drugs originally developed for adults. To do so, doctors must try to adapt the dose or the method of administration (e.g., crushing a pill to add to liquids) to suit a child. Also, doctors sometimes use drugs that were meant for another disease or condition because a drug is not available for a child's particular disease.

At this time, Health Canada has few regulatory requirements to encourage better rates of submissions, and therefore approvals, for pediatric therapies in general or for precision therapies for children and youth in particular.

Box 5: Case Study – Precision Therapy for Cystic Fibrosis in Adults versus Children and Youth

Cystic fibrosis (CF) is a genetic disorder that affects many organs but is commonly associated with progressively worsening lung function. If therapy is initiated before structural damage in the lung occurs, then outcomes for people with CF are much better. Since the disease becomes progressively worse with time, earlier initiation of therapy is ideal. However, CF treatments can be very costly. For example, Kalydeco®, a new drug to treat a specific gene change that causes CF, costs more than $300,000 annually and is required lifelong.

It can be difficult to measure if a new CF treatment is better for children and youth compared to adults with CF, because the baseline for each group could be different. For example, adults may have already sustained lung damage so an improvement is measurable. However, young children with normal lung function that is sustained by other treatment may not show improvement in lung function when given the new treatment.

These issues raise difficult questions about, for example, who should have access to such expensive therapies, when patient therapy should start in the course of the disease or a child's development, how long access to the therapies should be provided, and how to measure their impact.

Source of images: https://consultqd.clevelandclinic.org/new-cystic-fibrosis-medication-may-be-a-game-changer/ www.vcuhealth.org/news/new-drug-for-cystic-fibrosis-patients-could-be-life-changing

High-cost but potentially high-benefit drugs, including precision therapies, are putting pressure on health-system budgets

The high cost of many new drugs in Canada, including precision therapies, has created difficult decisions about which drugs should be added to public drug programs and who should be eligible to receive them. High-cost drugs account for an increasing share of public spending on drugs. In 2018 high-cost drugs that were $10,000 or more per patient accounted for 21.6% of spending by public plans. In 2019, that proportion increased to 28.8%, and in 2020, to 29.7%. Also, the spending is concentrated on a small number of individuals, about 2% of beneficiaries in 2019.(25) The threshold of what is considered to be high cost is creeping up as new drugs become more expensive. For example, the proportion of drugs that cost more than $50,000 per year has risen from 0.4% in 2007 to 5.3% in 2017.(26)

Drugs for rare diseases, many of which are precision therapies, are particularly high cost, ranging from $200,000 to $2 million per patient per year in Canada.(27) Three-quarters of the drugs approved in 2019 for rare diseases cost $200,000 or more per year.(28) Box 6 shows how the advent of new therapies for SMA are posing difficult questions to patients and the health system.

Because public funds are not unlimited, responsible management means trade-offs have to be made between what is and what is not funded in health systems. This requires careful, valid assessment of the value of new drugs to Canadian patients and healthcare systems. With each additional expenditure on a new drug, a reduction in expenditure must be made elsewhere in the health system. This could ultimately result in health benefits being reduced for some patients. This issue is complicated by the lack of direct association between drug price and value: high prices do not consistently translate into substantial benefits to patients.

Box 6: Case Study – High-Cost Precision Therapies

Spinal muscle atrophy (SMA) is a genetic disorder where a gene involved in the maintenance of nerves for muscle movement is faulty, causing the degeneration of muscles over time. Up until five years ago, this disorder was incurable. Now, there are three breakthrough medications approved for the treatment of SMA in the United States. Two of them are approved in Canada (Spinraza™ and Zolgnesma®) and the third (Evrysdi™) is currently under review. Below are the estimated costs of the drugs in the United States.

Approved SMA Products

Product	Patient population	Therapy	Annual cost
Evrysdi (risdiplam)	All SMA types, children greater than 2 months of age	Oral medication	Up to $340,000
Spinraza (nusinersen)	All SMA types, all ages	Intrathecal injection	$750,000 in first year, then $375,000
Zolgensma (onasemnogene abeparvovec-xioi)	All SMA types, children younger than two years	Intravenous (IV) infusion	$2.1m one time only

Source: www.gillettechildrens.org/khm/gillette-helps-with-new-treatments-and-choices-for-sma-patients

Zolgensma® is a one-time medication that aims to fix the underlying faulty gene, whereas Evrysdi™ and Spinraza™ are lifetime medications that aim to fix the gene products made from the faulty gene. The major difference between Evrysdi™ and Spinraza™ is that Evrysdi™ is an oral medication while Spinraza™ requires a lumbar puncture injection. While these medications bring new-found hope to a brutal disease, there are also new issues with regards to clinical decision-making, funding, access and more. For example:

- For a child younger than two years old, how do policymakers and clinicians decide which therapy is the ideal choice?
- Clinical trials cannot readily be performed to assess how patients' health changes over their life course once the medications are stopped – as a result, no long-term data exist for health outcomes of patients on these therapies.
- Older patients have much less gene activity, so is it "worth" the cost to treat them, especially without clinical trial data?

If the HTA does not recommend funding of these treatments through the public system, what role do other funding sources, e.g., hospitals and special drug programs, have in paying for them?

Incomplete assessments of value specific to child health are being made in health technology assessment

After Health Canada has approved a new drug, the public funding of that drug depends on an evaluation of its worth or value to society. The evaluation is based on a system called health technology assessment (HTA). The national body responsible for this evaluation is the Canadian Agency for Drugs and Technology in Health (CADTH). In Quebec, the responsible body for HTA is the Institut national d'excellence en santé et services sociaux (INESSS).

The recommendations from the HTA process help to guide policymakers and decision-makers in each province and territory to allocate healthcare resources. These recommendations are based on detailed reviews by an expert committee assessing the clinical and economic evidence. To ensure all relevant perspectives are captured, the process also gathers input from patients, doctors, pharmaceutical companies, and representatives from provincial and territorial governments. These recommendations provide guidance on ensuring clinical benefit and achieving 'value-for-money' from recommendations that are made to the public drug programs. This requires using a structure of values and principles that integrate considerations about the diseases the drugs are meant to treat, personal preferences of patients and family members, the health systems that get the drugs to those who need them, and additional societal considerations.

HTA also often includes an ethical analysis. For example, all HTAs performed by Ontario Health are carefully reviewed for equity considerations. This process identifies all segments of the population that may face inequities in accessing the technology. This is guided by the PROGRESS framework(29), which considers:

- place of residence;
- race/ethnicity/culture/language;
- occupation;
- gender/sex;
- religion;
- education;
- socio-economic status; and
- social capital.

Age group is another important consideration for all technologies aimed at the population as a whole. For technologies geared towards children, the PROGRESS framework is used to identify inequities among children and youth.

CADTH, like all HTA agencies in the world, faces difficulties in assessing the value of drugs for children and youth in general, and for precision therapies for children and youth in particular. A key reason for this challenge is the lack of clinical data for children and youth as well as the lack of approval by Health Canada for drugs in this patient population. Also, established HTA methods do not specifically consider the unique situation of biology, health and illness in children and youth, whether in pediatric drugs in general or in precision therapies.(30-32) There are no dedicated evaluation methods for children and youth.

Some of the difficulties faced by the current system of evaluation relate to the nature of clinical evidence and the techniques that are used in the economic evaluation. With respect to clinical evidence:

- because precision therapies often target rare diseases, or divides patients with the same disease into smaller groups based on the specific genetic cause of their disease, it can be challenging to design clinical trials with enough participants to demonstrate how well a given therapy works as compared to existing therapies;
- new ways of conducting clinical trials for precision therapies provide evidence that may be hard to assess, creating uncertainty about the benefit provided by the therapy; and
- long-term data on clinical outcomes of patients taking new precision therapies are not available, creating uncertainty about the real-world impacts (both benefits and harms) of these therapies on children and youth over their life-course.

In terms of economic evaluation techniques:

- little data on how well precision therapies work in children or for specific age groups may be available for assessing cost-effectiveness;
- although many of the conditions treated by precision therapies are lifelong, the long-term cost-related data is also limited and creates uncertainty;
- one of the hoped-for benefits of precision therapies are fewer or less severe side effects, but very little data are available for children and youth because precision therapies for children are so new and there has been so little use of them in the real world;
- the many uncertainties make economic analyses difficult to complete, and economic models may have to rely on adult data or make assumptions based on adult data; and

- the measurement of benefits rarely includes an evaluation of the preferences children have for certain stages of sickness and wellness; parents' preferences, where incorporated as proxies, may not accurately represent children's preferences.

There is a patchwork of coverage for precision therapies across Canada, resulting in inequities in access by children and youth

Provinces and territories decide how to organize and administer their public drug plans according to their own resources and local realities.(33) There is no standard unified pan-Canadian system of evaluating precision therapies for children and youth. Unlike provincial and territorial HTA agencies, CADTH makes its recommendations without consideration of jurisdictional budgets, population demographics and priorities. Therefore, drugs that are recommended for public funding by CADTH are not necessarily added to provincial plans. Some provinces may adopt special programs to fund treatment for specific pediatric conditions, such as CF. As a result, children who rely on public drug plans in some parts of Canada do not have access to certain drugs, including precision therapies, while others do.(34) Indigenous children and youth in particular may face additional barriers in access to precision therapies. Their care is administered through federal health plans, which are governed distinctly from provincial and territorial ones, and often make different decisions about which drugs to cover.

Another issue is that precision therapies for children and youth may need to be delivered in large, well-equipped hospitals in urban centres. They often require specialized equipment, companion diagnostic tests, and highly skilled healthcare workers to administer them and manage adverse effects. For the 20% of families who live in rural areas, accessing those services may be difficult and costly.(35) Related to this, if growing experience with precision therapies enables gradual shifts in their delivery from hospital-based to outpatient services, financial barriers to accessing these therapies may worsen, as some of the costs that would have been paid through public plans are transferred to families.

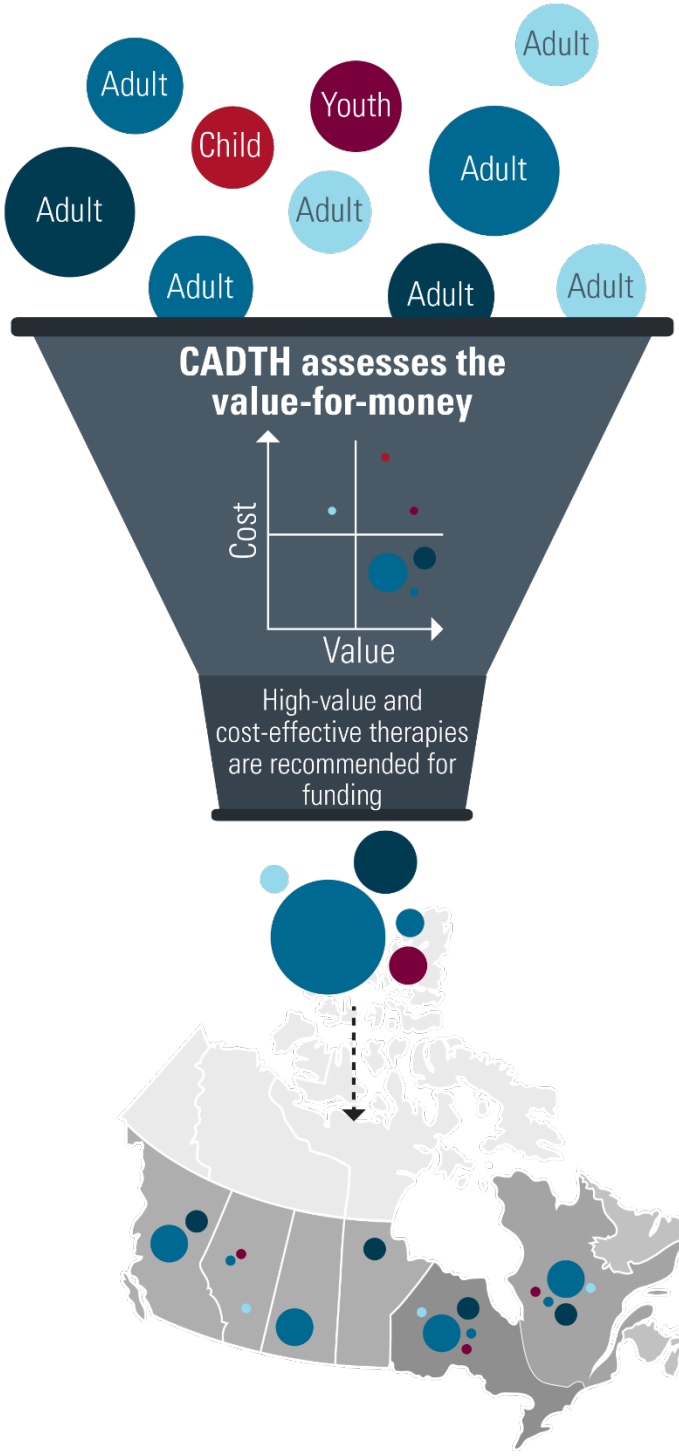
In addition, precision therapies often require extra education about what they are, the pros and cons of using them, and how they are best used. Some groups in Canada may have limited access to that information and to the therapies. Also, doctors sometimes do not

know how to determine whether new precision therapies are the right choice for their patients and their families. They can be unsure whether the drug would improve the child's health or about how to obtain or pay for it.(36)

The problems of differences between adults and children, high-cost drugs, an incomplete system to evaluate precision therapies for children and youth, and challenges to equitable health-system implementation are not separate. They are linked to each other and result in some Canadian children having limited access to pediatric precision therapies.

Figure 3 below provides an illustration of how all these problems come together.

Figure 3: Four factors leading to limited and unequal access to precision therapies for children and youth in Canada



Few innovative therapies

Few innovative therapies for children and youth are being developed and approved for sale and funding consideration in Canada.

High cost

High-cost but potentially high-benefit drugs, including precision therapies, are putting pressure on health-system budgets.

Incomplete health technology assesssment

Processes to determine whether a new drug is worth funding do not fully account for unique dimensions of child and youth health.

Unequal access

There is a patchwork of funding coverage for precision therapies across Canada, creating potential for inequities in access by children and youth.

We have identified three elements of an approach to address the problem for which we are seeking public input

Elements of a comprehensive approach to address the problem

>> To promote discussion about the pros and cons of potential solutions, we have selected three elements of an approach to improving access to precision therapies for children and youth in Canada

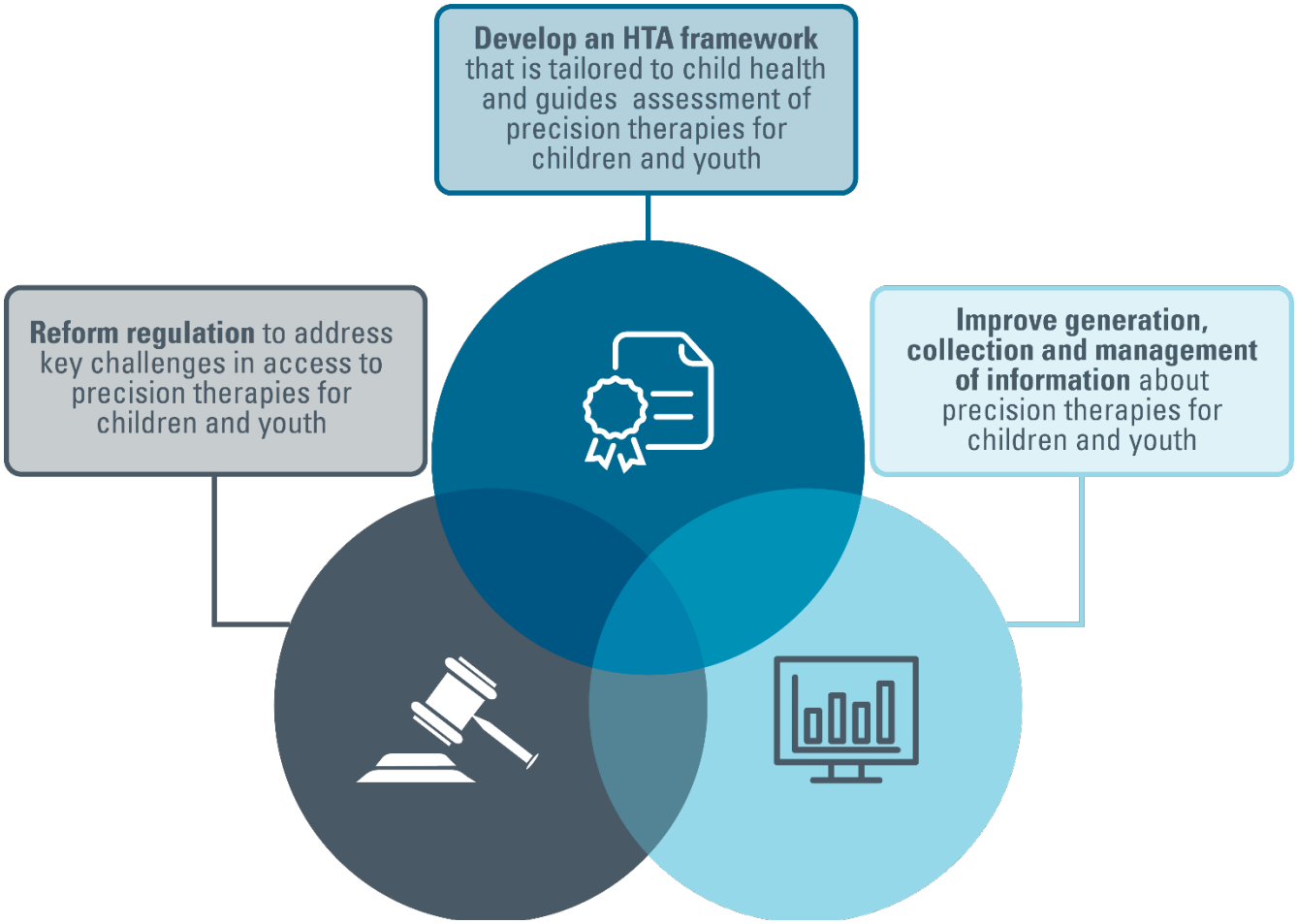
It is important that Canadians should have a voice in decisions about the healthcare that children and youth receive, now and in the future. This requires careful consideration of citizens' values and preferences. Many approaches could be selected as a starting point for discussion. We have selected the following three elements of an approach for which we are seeking public input:

- reform federal drug regulations to address key challenges in access to precision therapies for children and youth;
- develop a health technology assessment (HTA) framework that is tailored to child health; and

- improve generation, collection and management of information about precision therapies for children and youth.

These elements should not be considered separately. Instead, each should be considered as contributing to a potentially comprehensive approach to addressing the problem (Figure 4). New elements, different combination or sequencing of the elements could also emerge during the discussions.

Figure 4 – Integrated elements of an approach for increasing access to precision therapies by children and youth



Element 1 – Reform federal drug regulations to address key challenges in access to precision therapies for children and youth

Overview

The focus of this element is on identifying what citizens think of changing regulations and related policies to support increasing the availability of precision therapies for children and youth. The activities that could be included as part of this element are outlined in Table 1. Information and questions to consider during your deliberations are provided below.

Table 1. Types of activities that could be included in Element 1

Area of focus	Types of activities
Creating legislation to incentivize and compel submission of data about children and youth to Health Canada for precision therapies that could benefit them	• Analyzing and comparing the drug-approval and regulatory practices for precision therapies in the context of Canada and in other countries • Identifying key areas of concern in promoting and regulating drug development for children and youth, including precision-drug development, through: 1) conducting of surveys with expert and lay audiences; and 2) convening cross-institutional symposia that integrate academic evidence with decision-maker perspectives • Undertaking knowledge translation efforts with key decision-makers at national regulatory, HTA, and pricing bodies, and provincial/territorial government funders, to share tools and data to inform evidence-based pediatric precision-therapy approvals and assessment
Creating opportunities to engage citizens in creating new regulations and polices on precision therapies for children and youth	• Exploring approaches to patient and public engagement on drug policy across Canadian provinces and internationally, to create evidence-informed and citizen-engaged models for formulary decisions • Engaging clinicians, policymakers, patients and families, and members of the public in interdisciplinary pan-Canadian working groups on reform for precision pediatric therapies, to leverage and inform Health Canada-led pediatric and rare-disease drug strategies, respectively. • Conducting co-design processes with citizens, patients and their families to identify and implement priority reforms of existing regulatory processes that draw on their values and preferences as well as the views and experiences of clinical experts and system leaders

Understanding current laws and regulations

Outside Canada, policies and legislation have been implemented to address the gap in the number of approvals made for drugs targeting children and youth and those for adults, including precision therapies. These legislative measures are designed/implemented to

increase the numbers of clinical trials for children's drugs. They attempt to do this by incentivizing or compelling industry submission of drug use and data specific to children and youth when applying for regulatory approval of drugs that have adults as the primary target, but are considered potentially suitable for children and youth too. Key examples are outlined below.

- Under the US Food and Drug Agency, important pieces of legislation have been enacted over several years.
  - Currently, the Pediatric Research Equity Act of 2003 requires companies to conduct pediatric trials unless it can be shown conclusively that they are not needed.
  - The complementary Best Pharmaceuticals for Children Act of 2002 encourages trials through the provision of funding and extended market exclusivity.(37)
- In line with the development of precision medicine, the new Research to Accelerate Cure and Equity (RACE) for Children Act (2020) in the United States requires new precision and innovative therapies that are intended for adult diseases to be evaluated for and extended to children and youth if the genetic target is relevant to them.(38; 39)
- In the European Union, the European Medicines Agency enacted the Pediatric Regulation in 2007 to provide both obligations and incentives for research and development of medicines for children.(40; 41)
  - A provision of the legislation was a child-specific committee set up to oversee all scientific matters related to children's medicinal products.(42)

In contrast, there are no current equivalent pieces of legislation or regulatory provisions in Canada. Health Canada does not have regulations to increase clinical trials for new drugs specific to children. Nor does it oblige pharmaceutical manufacturers to submit child-specific data to support regulatory approval of novel drugs for children and youth. However, it does offer an incentive by providing a six-month data protection of an approved adult-targeted drug if companies can submit child-and-youth specific trial data within five years of the approval of the adult drug. Nevertheless, fewer medical products specifically for children and youth are approved in Canada compared to in the United States and Europe. Similar legislation to those in the United States and Europe might therefore be proposed, with due consideration for the Canadian context.

In response to recognized issues in access of drugs for Canadians, including for children and youth, Health Canada has started several initiatives within its strategic direction to modernize regulatory processes.(43)

Other countries have used a co-design process with multidisciplinary and multi-stakeholder groups to address the deficiencies in current legislation and to speed up the public response to legislation or policy.(44) Similarly, there is a potential for Canadian citizens to participate in reforming legislation aimed at increasing access to precision therapies for children and youth.

Questions to consider

Focus question

- How might Canada use legislation and regulations to increase the number and quality of submissions for pediatric precision therapies?

Probing questions

- What types of information are important to guide regulations about which precision therapies are approved for use in children and youth in Canada?
- What role, if any, do you think citizens, patients and families, and/or pediatric experts could play in co-design processes for Canadian regulations on pediatric drugs, including precision therapies?

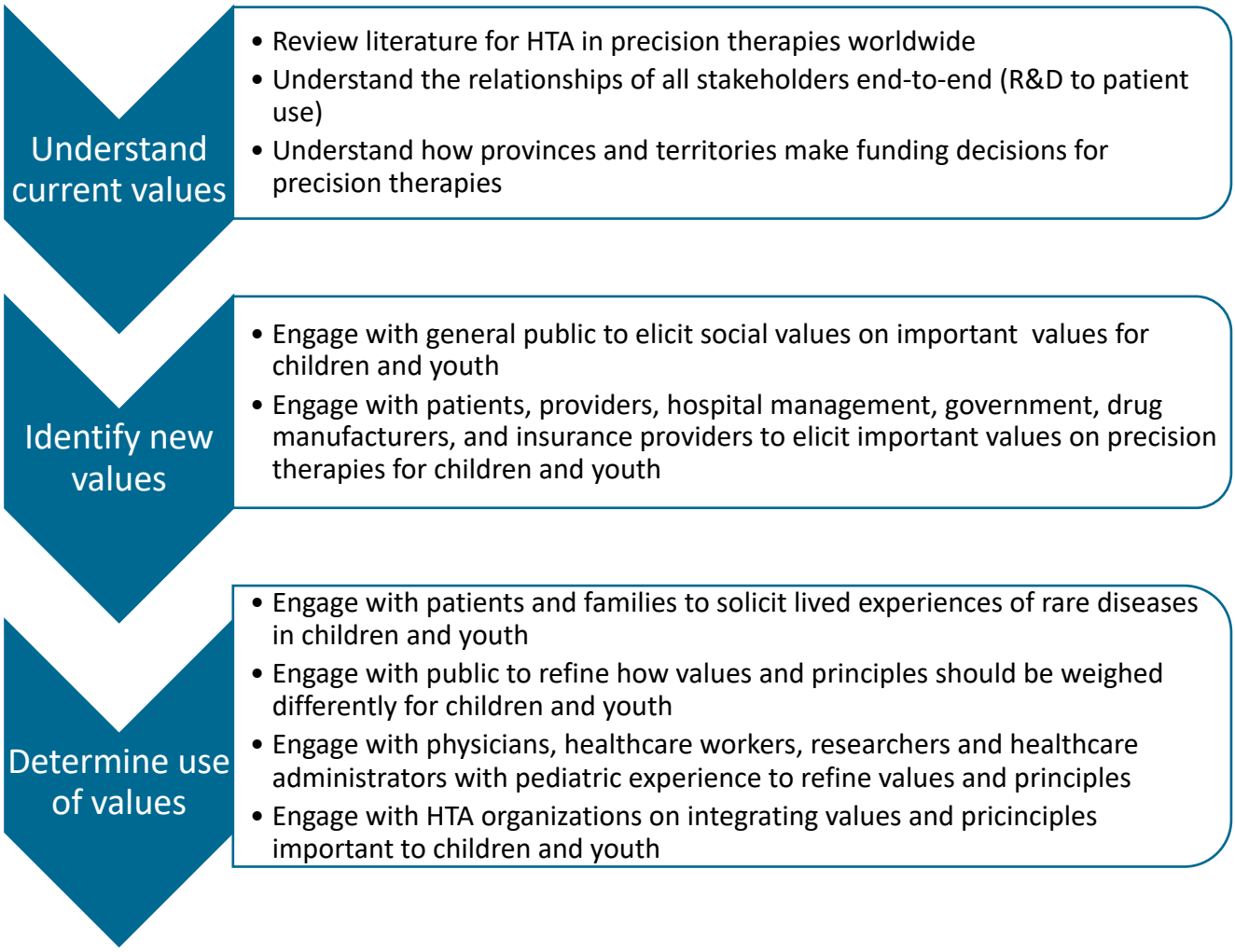
Element 2 – Develop a health technology assessment (HTA) framework that is tailored to child health

Overview

The focus of this section – and the primary focus of this panel – is to understand what citizens think about the current values, principles and processes used in HTA for precision therapies, and whether they require any amendments or additions to account for the needs and lived realities of children and youth.

HTA is a key step in determining access to new therapies in Canada. Clinical and economic evidence, important societal factors such as equity, and a wide range of views are used as inputs and deliberated upon by multi-stakeholder committees to guide recommendations for public coverage by provincial and territorial drug plans. The activities that could be included as part of this element are outlined in Figure 5. Information and questions to consider during your deliberations are provided below.

Figure 5. Types of activities that could be included in Element 2



Understanding the current HTA framework

When CADTH and INESSS expert panels review new drugs, they follow clear guidelines based on internationally accepted principles for health technology assessment.(45-47) Within these guidelines, judgments about the worth of a new technology are based on values and principles considered important to Canadian society. These are summarized below.

Clinical evidence: One factor is whether a new drug provides clinical benefits in treating a specific disease. Medical experts review information related to the drug's safety and effectiveness. They also consider the impact of the disease and the overall need for the treatment.

Patient values: Assessment of the drug in question also takes into account alignment with patient values. In addition to detailed review of the available published evidence on patient

preferences and quality of life, patient advocacy groups are invited to provide input to inform the review. They seek to highlight the values held by patients for their treatment, and may comment on how the drug does or does not meet patients' needs, ease of use, cost of a treatment, and acceptability of possible side effects.

Economic evaluation: The cost-effectiveness of the new drug compared to other drugs or alternative treatments is also an important part of HTA. Economic considerations such as the overall cost of the drug and its efficiency in producing desired outcomes (e.g., incremental cost per life-year gained) are reviewed. Because some of the economic assessment relies on projections into the future and/or on incomplete information, the uncertainty of the results must also be carefully reviewed.

Ethical analysis: The ethical and socio-cultural issues presented by a new technology are critically reviewed. These include equity considerations – specifically, attention to the impacts of funding decisions on different groups of people in various circumstances to strive for fairness in decision-making.

Implementation feasibility: The feasibility of adopting the new drug into the health system is also reviewed. The practical requirements for introducing the drug into existing healthcare programs are reviewed, as are the impacts on provincial drug-plan budgets.

These components – clinical and economic evidence, patients' values, ethical analysis, and implementation considerations – are integrated to guide deliberation by HTA committees on the overall value of a new drug to patients and the health system. However, as discussed above, a number of unique considerations related to child health and illness complicate standard approaches to HTA. Neither CADTH nor INESSS has separate criteria or methods to assess the value of a new drug for children and youth, and they are limited by sparse data specific to children and youth. More fundamentally, whether or not children and youth should be regarded differently than other vulnerable segments of the population when valuing health technologies remains an open question.

Questions to consider

Focus questions

- What do you think are the **most important values and principles** to consider when determining which precision drugs to publicly fund for children and youth in Canada?

Probing questions

- In what ways do you think these values or principles should differ from those that are used to assess precision therapies for adults?
- What additional factors should be measured to assess value in drugs for children and youth?
- When trade-offs have to be made in decisions about whether to fund new precision therapies for children and youth or to continue funding for existing drugs, how much weight should be given to:
  - potential benefits (e.g., whether the drug can save a life, lengthen life or help improve quality of life);
  - potential harms that could happen as a result of taking the precision drug (e.g., pain and adverse effects from a lumbar puncture);
  - costs that have to be paid by public and private drug coverage or by patients and their families;
  - availability of alternative medical treatments;
  - citizens' values and preferences (e.g., as identified through citizen panels or other mechanisms); and
  - equity (fairness)?
- Should other factors matter, and how much should they matter? For example:
  - differences between children and youth and adult diseases (burden, causes, types of treatment, availability of treatment);
  - the impact of the benefits and harms on the family and family life;
  - severity of a health condition (e.g., whether it is curable or not);
  - unmet need (e.g., lack of treatment);
  - disease rarity;
  - vulnerability (e.g., dependence);
  - quality of life of children and youth;
  - children's and youth's own views on their health and treatment;
  - disadvantaged families (e.g., remote residents, certain ethnic-cultural groups, marginalized families); and
  - other ethical and social concerns particularly related to children and youth.

Element 3 – Improving generation, collection and management of information about precision therapies for children and youth

Overview

This focus of this element is on identifying what citizens think are important considerations in generating, collecting and managing information about precision therapies for children and youth. The activities that could be included as part of this element are outlined in Table 2. Evidence and questions to consider during your deliberations are provided below.

Table 2. Types of activities that could be included in Element 3

Area of focus	Types of activities
Develop a pan-Canadian platform to share: • **real-world evidence** • **processes that incorporate therapeutic indications and value considerations for children and youth**	• Develop an understanding of how real-word evidence (RWE) is currently gathered at different institutions, at both provincial and national levels in Canada • Integrate experiences and expertise from children and youth in major RWE initiatives involving key national institutions (Health Canada, CADTH)
Develop coordinated funding models to support the enrolment of children and youth into multi-centre clinical trials	• Engage international and Canadian researchers who lead multi-jurisdictional trials to identify best practices and 'lessons learned' • Engage with provincial/territorial health ministries and scientific bodies to identify potential funding opportunities to develop coordinated multi-centre trial infrastructures

Understanding health information

Real-World Evidence (RWE) is health information generated outside of clinical trials, such as patient treatment records at hospitals, reimbursement information at provincial insurance plans or numbers of deaths in disease registries. Currently the main use of RWE in the regulatory process is the collection of information by drug manufacturers about any adverse effects of their drug once it is in use. However, RWE is fast becoming recognized as a key source of information for the effectiveness of healthcare interventions for patients, and for impacts on health systems.(48; 49) Health Canada and CADTH have developed initiatives aimed at making it easier to use RWE to support approval and funding decision-making.(50)

Although Canadian researchers and the medical community are starting to use RWE to extend the limited knowledge from clinical trials, there are still problems to solve when trying to use existing information in the health system or to collect and store new

information. For example, the electronic systems that collect and store information can be quite different. This makes it difficult for institutions or provinces to share or combine information.(51) The management of data to ensure patient information is stored securely is also an important consideration.

In childhood diseases, information is scarce, so it is ideal to combine or link information from as many different sources as possible to make well-informed decisions. An example that might be helpful to increasing RWE for precision therapies for children and youth is the Marathon of Hope Cancer Centres Network pilot projects. One of the aims of the projects is to develop a common platform among the top cancer hospitals across Canada to allow sharing of patients' genomic, treatment and outcomes information.(52)

Questions to consider

Focus question

- What kinds of 'real-world' data are important to guide funding decisions for pediatric precision therapies?

Probing questions

- How should the perspectives of children/youth and families be incorporated into real-world evidence collection?
- Should real-world evidence from other jurisdictions guide drug funding decisions for children and youth in Canada?

Implementation considerations

It is important to consider what barriers may be encountered when implementing the proposed elements of a potential approach to address the problem. These barriers may affect different groups (for example, patients, citizens, healthcare providers), different healthcare organizations or the health system. Some potential barriers to implementing the

elements are included below and are summarized below in relation to the elements of the proposed approach.

Challenges to creating regulations to increase availability of and access to precision therapies for children and youth could include:

- limited opportunities for formal incorporation of patient and public perspectives;
- not enough engagement by patients and citizens in citizen engagement and co-design processes;
- lack of windows of opportunity to influence governmental policymaking on pharmaceutical regulation; and
- resistance to regulatory reforms by pharmaceutical companies.

Challenges to implementing an HTA framework that incorporates specific considerations for children and youth could include:

- it may be difficult to agree on the values and principles that should govern assessments of precision therapies for children and youth;
- the general public and/or specific groups may be concerned about why children and youth are treated differently than other vulnerable segments of society in decisions about which precision therapies to publicly fund; and
- certain stakeholders may deem the problems with HTA for pediatric precision therapies too fundamental and question the legitimate role of HTA in determining public funding recommendations for precision therapies for children and youth.

Challenges to improving generation, collection and management of information about precision therapies for children and youth could include:

- complexity and cost of the infrastructure required to collect and manage sensitive information from multiple institutions;
- difficulties associated with cross-provincial coordination of health data governance and management; and
- patient and family privacy concerns with data-sharing.

The implementation of each of the three elements could also be influenced by the ability to take advantage of potential windows of opportunity. A window of opportunity could be, for example, a recent event that was highly publicized in the media, a crisis, a change in public opinion, or an upcoming election. A window of opportunity can facilitate the implementation of an option.

In the wider medical field and in national policymaking there are recent developments that could aid the improvement of access to precision child-health therapies. These include the examples below.

- **Increasing relevance of precision medicine**
  - Precision therapies have captured the imagination and interest of the public and many healthcare sectors, with more and more research evidence demonstrating potentially high-value therapies targeting difficult-to-treat or rare diseases, including in pediatrics.
  - As a result, HTA organizations worldwide have been grappling with how to evaluate the new forms of evidence coming from these trials.
- **Increased incorporation of patient and family values**
  - There is wide acknowledgment of the importance of patient and family values to define priorities and guide the allocation of resources in health systems, including in drug funding.
- **Debate on a national pharma-care program**
  - There have been recent public, high-profile discussions about a national pharmacare program in Canada, and about the foundational principles and provisions of such a program.
- **Technological advances in data storage and management**
  - Technology platforms to handle large volumes of data being created by research and healthcare systems are improving.
  - Health data and other socio-economic and demographic data are increasingly linked, which may allow a more fine-tuned and equitable delivery of healthcare services, including precision therapies for children and youth.
- **National initiatives at the federal level**
  - Health Canada is leading the development of a strategy to address the high cost of drugs for rare diseases, which opens up avenues to address issues of access to precision child-health therapies, given the many areas in which these two topics intersect.

Acknowledgments

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Conflict of interest

The authors declare that they have no professional or commercial interests relevant to the citizen brief. The funder played no role in the identification, selection, assessment, synthesis, or presentation of the research evidence profiled in the citizen brief.

Merit review

The citizen brief was reviewed by a small number of citizens, other stakeholders, policymakers and researchers in order to ensure its relevance and rigour.

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