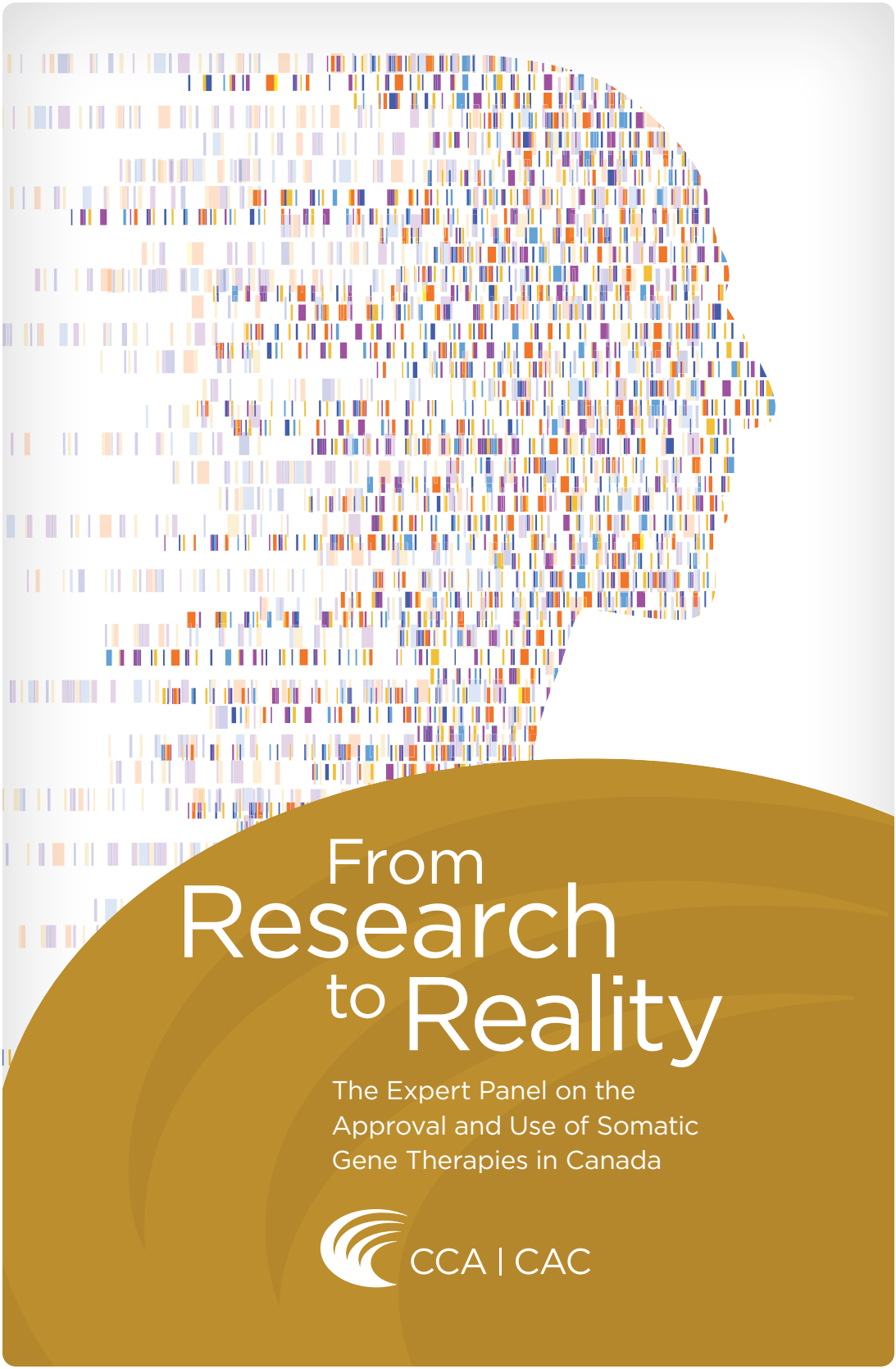

From Research to Reality

The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada

CCA | CAC

From Research to Reality

The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada

The Council of Canadian Academies
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This report was prepared in response to a request from the National Research Council of Canada (NRC). Any opinions, findings, or conclusions expressed in this publication are those of the authors, The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada and do not necessarily represent the views of their organizations of affiliation or employment, or the sponsoring organization, NRC.

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The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada

Under the guidance of its Scientific Advisory Committee, Board of Directors, and founding Academies, the CCA assembled The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada to undertake this project. Each expert was selected for their expertise, experience, and demonstrated leadership in fields relevant to this project.

Janet Rossant, PhD, C.C., FRSC (Chair), President, Gairdner Foundation; SickKids Chief of Research Emeritus, SickKids Research Institute; and Senior Scientist, Developmental and Stem Cell Biology Program, the Hospital for Sick Children (Toronto, ON)

Harold Atkins, MD, Physician, The Ottawa Hospital; Scientist, Ottawa Hospital Research Institute (Ottawa, ON)

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The CCA also recognizes the important contribution of **Joanne Castonguay,** Economist, Former Associate Professor, Pôle Santé, HEC Montréal (Montréal, QC).

Workshop Participants

As part of the evidence-gathering process, the Expert Panel convened a workshop, which brought together its own members and an additional 12 experts.

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Fabien Touzot, MD, PhD, Associate Professor, Centre hospitalier universitaire (CHU) Sainte-Justine (Montréal, QC)

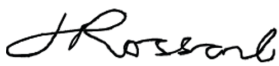
Message from the Chair

After decades of discovery and clinical research, gene therapies are beginning to enter the clinic. As of September 2020, three such therapies have been approved in Canada, and the rapidly advancing science of somatic engineered cell and gene therapy will bring more potential treatments into the pipeline. These new therapies, however, pose a number of challenges in terms of their introduction into the Canadian healthcare system and ensuring access to those who would most benefit.

Challenges include issues of safety, access, and affordability of prospective therapies. Due to the high cost of currently available gene therapies, the practical realities of commercial feasibility and affordability may impede future access to these treatments. However, certain proposed approaches may help resolve some of these issues. Canada's manufacturing sector and universal healthcare system are assets that could be leveraged. Canada also has an opportunity to share in the global efforts of translating gene therapy discoveries into clinical treatments, while ensuring equitable access for all those who could benefit from them.

There was a diversity of expertise and perspectives on this Panel, whose members are at the forefront of discovery research, clinical medicine, healthcare innovation, and health law. Collectively, they identified and focussed on key gene therapy accessibility and affordability challenges. Panel discussions were supplemented by a complementary workshop with additional experts. The resulting report identifies ethical, legal, and social challenges associated with access to affordable gene therapies, and explores promising approaches that may help to overcome some of these issues.

I would like to express my gratitude to all members of the Panel for their focused work and commitment to this project. I would also like to extend my thanks to the workshop participants for sharing their expertise and engaging in active debate. Their efforts helped to steer the Panel in its deliberations for the final report. On behalf of the Panel, I would also like to thank the staff members of the Council of Canadian Academies for their hard work and support in translating Panel and workshop discussions into this report.



Janet Rossant, PhD, C.C., FRSC
Chair, The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada

Message from the President and CEO

Ever since the discoveries that genetic changes underlie many diseases and cancers, developing safe and effective gene therapies has been a long-sought goal, especially for rare diseases. Those discoveries were aided by research involving human participants, where the primary ethical considerations focused on informed consent and assessment of risk and potential benefits. As therapies move from the bench to the bedside, that focus is now shifting to broader issues related to access and affordability. The challenges raised by the approval and use of gene therapies apply to patients and families, but extend to industry, payers, and federal, provincial, and territorial regulators.

The National Research Council of Canada, which has a broad interest in the Canadian ecosystem for developing, regulating, commercializing, and delivering gene and engineered cell therapies, asked the CCA to undertake an assessment of the legal, ethical, regulatory, and social challenges associated with their use. The final report, *From Research to Reality,* covers many of these challenges as well as possible paths forward. Recognizing the pace of science and other social issues, this is not the last word on the subject.

I would like to thank Janet Rossant, PhD, C.C., FRSC, her fellow expert panellists, and the workshop participants, for contributing their time and expertise. The CCA Board of Directors, Scientific Advisory Committee, and the CCA's three founding Academies — the Royal Society of Canada, the Canadian Academy of Engineering, and the Canadian Academy of Health Sciences — all provided guidance and input throughout the assessment process. I thank them for their support. Finally, I would like to thank the Sponsor, the National Research Council of Canada, for referring this important topic to the CCA.

Eric M. Meslin, PhD, FCAHS
President and CEO, Council of Canadian Academies

Acknowledgements

Over the course of its deliberations, the Panel reached out to a number of individuals and organizations who shared their experiences and knowledge. The Panel wishes to thank the following people for their participation:

Cindy Bell, Executive Vice-President, Corporate Development, Genome Canada

Ronald Cohn, President and CEO, SickKids

Karen Dewar, Director, Genomics Program, Genome Canada

Brent Fraser, Vice-President of Pharmaceutical Reviews, CADTH

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Peer Review

This report was reviewed in draft form by reviewers selected by the CCA for their diverse perspectives and areas of expertise. The reviewers assessed the objectivity and quality of the report. Their confidential submissions were considered in full by the Panel, and many of their suggestions were incorporated into the report. They were not asked to endorse the conclusions, nor did they see the final draft of the report before its release. Responsibility for the final content of this report rests entirely with the authoring Panel and the CCA.

The CCA wishes to thank the following individuals for their review of this report:

Mohamed Abou El-Enein, MD, PhD, Professor of Regenerative Medicine and Head of Clinical Development Platform, BIH Center for Regenerative Therapies (BCRT), Charité – Universitätsmedizin Berlin (Berlin, Germany)

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The peer review process was monitored on behalf of the CCA's Board of Directors and Scientific Advisory Committee by **Malcolm King, PhD, FCAHS,** Scientific Director, Saskatchewan Centre for Patient-Oriented Research, University of Saskatchewan. The role of the peer review monitor is to ensure that the Panel gives full and fair consideration to the submissions of the peer reviewers. The Board of the CCA authorizes public release of an expert panel report only after the peer review monitor confirms that the CCA's report review requirements have been satisfied. The CCA thanks Dr. King for his diligent contribution as peer review monitor.

Main Findings

The diversity of gene therapies requires a flexible and tailored approach to addressing access and affordability challenges

There is substantial diversity among gene therapies — in diseases treated, ways that genetic material is altered, ways therapies are administered, and ways genetic material is delivered to a cell. Each gene therapy will have its own profile across these four dimensions, with implications for safety, effectiveness, cost, and complexity of manufacturing and provision. Availability of treatment alternatives, patient population size, and potential complications add to the complexity of gene therapies.

This diversity necessitates a flexible approach to decision-making as gene therapies move through regulatory approval, funding decisions, manufacturing, and ultimately use in clinics. Clinical trials may be difficult to design, access may be complicated by advanced manufacturing and provision requirements, and value may be enhanced when therapies apply to severe diseases that lack alternative treatments. When regulation, provision, and reimbursement approaches are flexible, decision-makers can accommodate these potential challenges, and ultimately enhance affordability and access. This growing flexibility can be seen in Health Canada's new pathway for reviewing advanced therapeutic products, the emergence of collaborative patient registries, and adjustments to health technology assessment (HTA) processes.

Risk-based purchasing agreements and post-market surveillance could mitigate the significant clinical and economic uncertainties associated with approved gene therapies

The long-term safety and durability of gene therapies are uncertain by virtue of their recent introduction in the market and the short length of clinical trials relative to the anticipated long-term impacts of therapies. This uncertainty is a challenge for regulators, HTA bodies, and public drug plans that must proceed with decision-making despite limited information. Performance-based agreements between payers and manufacturers could be used to share the risks associated with funding gene therapies. Additionally, ongoing monitoring of the performance of approved therapies could help to reduce uncertainty over time. Post-market surveillance could be used to inform regulatory and economic reassessments of approved gene therapies as the evidence base grows.

High prices, complex provision, and the nature of diseases treated by gene therapies exacerbate existing inequities in healthcare access

To date, approved gene therapies have generally been priced in the hundreds of thousands of dollars, and these prices do not include any additional costs of hospital care. This necessitates careful scrutiny of the value and affordability of gene therapies by public drug plans. Jurisdictions may reach different funding decisions based on their own valuations, leading to unequal access across regions. Further compounding access challenges, complex gene therapies will likely only be available in large urban hospitals that have the advanced infrastructure and personnel required to administer them and manage adverse reactions. Patients with rare diseases may confront additional difficulties receiving accurate diagnoses and accessing high-cost treatments in public healthcare systems.

Different conceptions of value may lead to disagreement over the merits of publicly funding individual gene therapies

Inevitably, public payers face trade-offs. On the one hand, they wish to maximize health gains at the population level by funding drugs that offer the greatest improvement in life expectancy and quality of life at the lowest cost. On the other, they also consider funding more expensive drugs based on additional values such as severity, rarity, and novelty of illness, as well as lack of treatment alternatives. These trade-offs have long been debated, with well-established ethical arguments underpinning different conceptions of value. Based on existing research in Canada and Europe, society appears to broadly support spending on those drugs that offer the greatest improvements at the least cost, but favours spending on relatively high-cost drugs in cases where diseases are severe and lack alternative treatments. Enhanced transparency in value assessments could improve consistency and help manage patient and sponsor expectations.

Pan-Canadian coordination could control spending and improve access to gene therapies

Coordinated efforts to manage drug prices are well established. The pan-Canadian Pharmaceutical Alliance (pCPA) negotiates drug prices on behalf of numerous public drug plans to help contain and equalize costs, while the Patented Medicine Prices Review Board (PMPRB) provides federal oversight on the prices of patented medicines, ensuring they are not excessive. Further coordination could be achieved through national pharmacare, which could bring regulatory reviews, HTAs, and price negotiations under a joint approach, potentially reducing overall review time and equalizing access across jurisdictions. Even in the absence of a national program, provinces, territories, and the federal government could work

together to establish common principles and approaches to accessing high-cost therapies. Further areas for collaboration include the development and maintenance of registries, training of highly qualified personnel, and manufacturing capacity.

Stewardship of public investments in gene therapy research could alleviate challenges associated with commercialization and high drug prices

Despite early public investments in research, technologies are usually transferred to the private sector as new gene therapies move toward commercialization. In this process, the public sector loses its claims over the intellectual property it helped develop. Patent leasing has been proposed as one mechanism to enhance the value of public research investments. Or, if patents are sold to the private sector, there may be opportunities to build in favourable drug pricing clauses that could enhance public benefit. Public manufacture and commercialization of gene therapies offer additional options for protecting public investments. With these controls, the public could potentially exert greater influence over the price and accessibility of new gene therapies.

List of Acronyms and Abbreviations

ALL	acute lymphoblastic leukemia
ATP	advanced therapeutic product
ATTC	Advanced Therapies Treatment Centres
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	chimeric antigen receptor
CCRM	Centre for Commercialization of Regenerative Medicine
CDR	common drug review
CFDI	Canadian Fabry Disease Initiative
CORD	Canadian Organization for Rare Disorders
CRISPR	clustered regularly interspaced short palindromic repeats
EHR	electronic health record
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HTA	health technology assessment
HQP	highly qualified personnel
INESSS	Institut national d'excellence en santé et en services sociaux
IP	intellectual property
NIH	National Institutes of Health
NRC	National Research Council Canada
OTCD	ornithine transcarbamylase deficiency
pCPA	pan-Canadian Pharmaceutical Alliance
PMPRB	Patented Medicine Prices Review Board
P3	public-private partnership
QALY	quality-adjusted life year
RCT	randomized controlled trial
RWE	real-world evidence
SME	small and medium-sized enterprise
TALEN	transcription activator-like effector nuclease

Contents

1

Introduction

The concept for gene therapies emerged several decades ago following discoveries illustrating the fundamental role played by DNA in biology and genetics. Many diseases were by then understood to be linked to inherited genetic anomalies or to the abnormal behaviour of genes (Tatum, 1966). Indeed, in remarks made in 1966 regarding new directions for medicine, Nobel laureate Edward Tatum already offered an outline for the basic mechanism of gene therapy, writing: "[w]e can even be somewhat optimistic on the long-range possibility of therapy by the isolation or design, synthesis, and introduction of new genes into defective cells of particular organs" (Tatum, 1966). This mechanism would offer the possibility of restoring the function of these cells, raising the prospect of cures for certain diseases. Research then showed that the introduction of foreign genes into cells could be performed in a stable manner, paving the way for genetic-level modifications of human cells to treat diseases (Friedmann, 1992).

Despite this optimism, scientific, clinical, policy, and ethical challenges had to be addressed over four decades, and only recently have some therapies been approved for use (Fletcher, 1990; Friedmann, 1992; Addison, 2017). The prospect of directly acting on the genetic sources of diseases was appealing, but, as an unexplored medical intervention, the genetic modification of human cells for therapeutic purposes presented unknown and potentially great risks. What would the guidelines be for attempting gene therapy in patients, and under which conditions could these interventions cross the boundary from research to treatment (Anderson & Fletcher, 1980; Churchill *et al.*, 1998)? Discussions surrounding these challenges would be heightened in the 1990s and 2000s, as major scientific advances were accompanied by rare tragic outcomes (Sibbald, 2001; Cavazzana-Calvo *et al.*, 2004). Those incidents highlighted multiple issues that would need to be resolved in order to bring somatic gene therapies to the clinic, resulting in increased oversight in many jurisdictions, and continued research towards safer protocols for gene therapy and the underlying biology of targeted diseases (Addison, 2017).

With recent advances addressing some of these issues, a handful of gene therapies have now received market authorization.[1] The first authorized gene therapies in Canada target somatic cells which, unlike germline cells, are not involved in sexual reproduction and do not pass genetic material to future generations (NIH, n.d.). Two gene therapies for cancer treatment (Novartis's Kymriah and Gilead's Yescarta) and one for the treatment of a rare neuromuscular disease (Biogen's Spinraza) have received market authorization in Canada, with more

1 This report uses the term *gene therapy* to encompass both engineered cell and gene therapies. See Chapter 2 for definition of terms.

being investigated in clinical trials[2,3] (HC, 2019m, 2019n). The arrival of somatic gene therapies in markets around the world has prompted an active global discussion about the numerous legal, ethical, social, and policy issues arising from their approval and use. The present discussion differs from earlier debates about gene therapy which focused on challenges arising from the design and conduct of research in human participants, the distinction between somatic and germline gene therapy, and the potential for genetic enhancement.

Contemporary challenges and questions raised by the approval and use of gene therapies are significant — for patients, for regulators, for industry, and for payers. How can regulatory review and funding decisions be made in cases where the evidence base on the durability[4] of the therapies is limited? Does the capacity exist to manufacture and deploy these therapies at scale? Which therapies should be funded and, given their price, under what circumstances?

Recognizing these challenges and the implications they have for different stakeholders, the National Research Council of Canada (NRC) asked the Council of Canadian Academies (CCA) to convene an expert panel to provide an evidence-based and authoritative assessment of the legal, ethical, social, and policy implications specific to the approval and use of somatic gene therapies in Canada.

1.1 The Charge

The CCA was asked to answer the following question and sub-questions:

What are the key legal/regulatory, ethical, social, and policy challenges specific to the approval and use of somatic gene and engineered cell therapies in Canada?

- In particular, what are the affordability and accessibility challenges specific to the approval and use of somatic gene and engineered cell therapies in Canada?
- Drawing from Canadian and international examples, particularly those with healthcare systems similar to Canada, what are some of the promising approaches for overcoming these main challenges?

2 The generic names for these therapies are, respectively, tisagenlecleucel, axicabtagene ciloleucel, and nusinersen. This report uses brand names throughout for accessibility and ease of reading.

3 On October 14, 2020, Health Canada approved a fourth gene therapy, Luxturna (voretigene neparvovec), for the treatment of some individuals with inherited retinal dystrophy. The approval was issued after this report was finalized and thus is not reflected in the discussion.

4 *Durability* in this report refers to the long-lasting efficacy of a treatment.

In order to answer the charge provided by the NRC, the CCA assembled an experienced and multidisciplinary panel of experts (The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada, hereafter *the Panel*). Each member served on the Panel as an informed individual rather than as a representative of a specific discipline, organization, region, or set of values.

1.2 The Panel's Approach

The Panel focused on the legal, ethical, social, and policy challenges related to the approval and use of gene therapies, as well as interventions that may overcome these challenges, using the following approach:

Focus on challenges specific to somatic gene therapies. Recognizing that Canada's healthcare systems face a range of challenges, this report only assesses issues that are in some way distinctly connected to or exacerbated by gene therapies. The Panel members acknowledged that many of the issues introduced may nonetheless be applicable to other contexts, such as other high-priced therapies, other treatments for diseases with small patient populations, and some forms of regenerative medicine. They also recognized that, while identified challenges are specific to gene therapies, potential solutions may be broadly applicable.

Consider legal, ethical, social, and policy issues simultaneously. Given that these issues are often intertwined, the Panel built from earlier work that assessed legal, ethical, social, and policy issues jointly alongside scientific developments, and on approaches first applied to the Human Genome Project (Langfelder & Juengst, 1993), and then to other scientific developments (Kosseim & Chapman, 2011).

Emphasize access and affordability. The NRC expressed particular interest in affordability and accessibility challenges. This set the focus for the Panel's work, but other legal, ethical, social, and policy challenges associated with the approval and use of gene therapies are highlighted throughout.

Recognize the spectrum of somatic gene therapies. The Panel members recognized significant diversity across somatic gene therapies, particularly in terms of their complexity and delivery methods. They sought to identify challenges and promising approaches that reflect the full spectrum of somatic gene therapies.

Address multiple report audiences. The issues raised throughout this assessment involve a wide range of interested parties beyond the NRC. The Panel expects that regulators, payers, patient groups, and industry are

among the actors in the gene therapy ecosystem that have roles to play in addressing these challenges.

Aim for breadth over depth. In light of the NRC's charge and the assessment's workshop approach, the Panel members identified issues that may arise throughout the process of approval and use of gene therapies. They endeavoured to introduce a wide range of issues and present ideas on possible paths forward. Since few therapies have gone through the process of approval and use, some of the approaches raised in this report are proposed as concepts without evidence on their effectiveness at overcoming challenges in real-world settings. This report is not intended to be an exhaustive literature review, nor an evaluation of specific promising approaches. As the evidence base expands and Canadian policies governing the introduction of gene therapies develop, more detailed examination will be warranted for the challenges and promising approaches discussed in this report.

1.2.1 Scoping Decisions

As stated in the charge, the Panel was tasked with identifying challenges related primarily with the approval and use of somatic gene therapies, specifically throughout the period from market authorization through use and post-market surveillance. The challenges that arise during market authorization, health technology assessment (HTA) review, inclusion in public drug plans, manufacture, provision, and post-market surveillance are all examined in this report.

The focus of the report is the use of gene therapies in human somatic cells. Importantly, the legal, ethical, social, and policy issues as applied to reproductive (germline) cells are out of the scope of this report. The Panel also focused on gene therapies used to treat diseases, and not applications used for any known enhancement purposes. Therapies involving transplantation of non-engineered cells, or transplantation of genetically engineered organs, are also out of scope. Upstream challenges encountered during discovery research and clinical trials were excluded for the most part, but were introduced when they had significant bearing on downstream affordability and access. This scoping issue was particularly blurred for the development of gene therapies for rare diseases.

1.2.2 Sources of Evidence

The Panel met eight times over the course of eight months (twice in person and six times by videoconference) to review evidence and deliberate on its charge. The Panel's assessment is based on a review of diverse sources of evidence, including peer-reviewed publications, publicly available government information and statistics, and other grey literature related to the challenges of the adoption

and use of gene therapies in Canada. The Panel used a structured literature review to survey the landscape of published material on the legal, ethical, social, and policy issues related to gene therapies, which identified 150 references. Gene therapy implementation is a rapidly evolving field. While gene therapies have been under development for several decades, it is only recently that they have become available to patients around the world. As such, available evidence surrounding implementation in healthcare systems is limited. The Panel identified these evidence gaps, drew from a broader literature base as appropriate (e.g., rare disease literature), and supplemented the literature review with an expert workshop and interviews to partially address these gaps.

The Role of the Expert Workshop

As part of the evidence-gathering process, the Panel convened an expert workshop in November 2019, which brought together its own members and an additional 12 experts from across Canada and the United States. Participants from various sectors and academic disciplines were selected based on their knowledge of healthcare policy and economics, healthcare innovation, commercialization of therapies, the ethical and social dimensions of gene therapy adoption and use, and gene therapy science. A facilitator aided analysis, discussion, and debate using a group decision support software platform that allows for rapid idea generation and consensus-building. This process assisted in gathering evidence from a wider group of experts and in synthesizing insights on the relative severity of the challenges related to the adoption and use of gene therapies. The Panel's conclusions incorporate insights gained during this workshop.

Other Sources of Evidence

The Panel was also informed by interviews with experts in the field of ethics and who work with patient groups. The broad questions posed in the workshop were also used to guide the interview discussions. This report underwent a comprehensive peer review, whereby an additional six experts from Canada and abroad provided further evidence and expertise. The CCA's review process occurs relatively early in the assessment and is designed to inform report development and revisions.

International Examples

In addition to the above, the Panel reviewed evidence from the United States and Europe to identify promising approaches that may be applicable to Canadian healthcare systems. These regions were thought to be particularly relevant given that Canada represents a mix of European-style public insurance for drugs administered in hospital settings and U.S.-style private insurance

(or out-of-pocket payment) for other drugs. However, the Panel notes that any approach adopted from abroad would need to be adjusted to suit the Canadian context.

1.3 Overview of Report

Chapter 2 of this report defines gene therapy and provides historical context. It subsequently describes the complexity of, and variability in, different therapies, and outlines the existing phases of gene therapy approval and use. The Panel analyzed challenges associated with access and affordability across each of these chronological phases, and grouped challenges by key focal areas. The report first examines challenges associated with regulatory oversight (Chapter 3), then identifies those particular to the supply of and access to gene therapies (Chapter 4), and finally examines downstream issues related to value and affordability (Chapter 5). In each chapter, challenges that may impede access to gene therapies or undermine affordability are presented followed by promising approaches to addressing these challenges. Finally, Chapter 6 concludes by presenting the Panel's key findings alongside several Panel reflections.

2

Gene Therapy Foundations

Gene therapies modify genetic material in a patient to treat disease. A gene therapy can be both a medicine and a procedure. In this case, the *medicine* is genetic material that is introduced or modified with the purpose of alleviating disease symptoms. The *procedure* is the means used to deliver the genetic material, which could be through the injection of vectors to modify genes in cells inside the body (*in vivo*) or the reinfusion of patient cells that were modified outside the body (*ex vivo*).

For the purpose of this assessment, the term gene therapy will be used to encompass both gene therapy and engineered cell therapy.

- Gene therapy is the "introduction, removal or change in genetic material — specifically DNA or RNA — into the cells of a patient to treat a specific disease" (ASGCT, 2019a).
- Engineered cell therapy "involves [the] transplantation of autologous or allogeneic cells that have been engineered to introduce desired properties" (Wilson & Carroll, 2019).

In the literature, other commonly used terms include gene therapy products, engineered cell and gene therapy, and cell and gene therapy.

To inform the Panel's analysis presented in Chapters 3 to 5, Chapter 2 (i) provides historical context of the development of gene therapies; (ii) presents a framework to understand the diversity of gene therapies; and (iii) outlines six stages of approval and use of gene therapies.

2.1 Discovery and Development of Gene Therapies

The basic mechanisms underpinning rare genetic diseases, and the prospect of treating these using gene therapies, were proposed in the 1960s (Friedmann & Roblin, 1972; Friedmann, 1992). By the late 1970s, the scientific community had the tools required for attempting gene therapies in humans (Friedmann, 1992). One such attempt culminated in an early setback, in the form of unsuccessful experiments on human patients wherein the genetically modified bone marrow cells did not produce enough of the functional protein (Wade, 1980). The studies drew widespread criticism on scientific and ethical grounds: the investigator had not received permission for human studies, and tests on animal models suggested that the likelihood of success in humans was "vanishingly small" (Beutler, 2001).

Though the patients were unharmed, they were exposed to what was an unknowable risk at the time.

This unsuccessful trial galvanized members of the scientific community and beyond to discuss and define the necessary parameters for overseeing gene therapy (Friedmann, 1992). Importantly, these discussions also drew the boundary between somatic cell gene therapy and germline interventions, which are therapies that pass on genetic changes to future generations (Addison, 2017). In 1974, a National Institutes of Health (NIH) subcommittee on gene therapy research was established to oversee research in the field (O'Reilly *et al.*, 2012).[5] From 1988 onwards, all human gene therapy trials required approval by the subcommittee, following the extensive discussions raised by unsuccessful experiments and failed trials (O'Reilly *et al.*, 2012; Collins & Gottlieb, 2018). By the 1990s, gene therapies appeared poised for implementation, though it remained unclear whether they constituted research or treatment or both (Allan & Dubé, 1996; Churchill *et al.*, 1998). Early studies investigating a gene therapy for a rare immune disorder reported that the therapy appeared to not only be safe, but that patients had also shown improvement in their condition (Blaese *et al.*, 1995). However, the subsequent enthusiasm would be quickly muted, following the widely reported case of Jesse Gelsinger (Box 2.1) and other clinical trials where patients developed cancers (Cavazzana-Calvo *et al.*, 2004; Wirth *et al.*, 2013).

Public confidence in gene therapies diminished in part because of these poor trial outcomes (Cavazzana-Calvo *et al.*, 2004; Yarborough & Sharp, 2009; O'Reilly *et al.*, 2012); however, changes brought about due to those outcomes improved clinical research in the field and contributed to later successes. Developments in the research of disease biology and the improved safety of viral vectors for delivery also contributed to new breakthroughs.

A decade after Gelsinger's death, the aforementioned improvements contributed to new therapies showing clinical promise. For example, a new *in vivo* therapy launched on the commercial market, and a novel form of engineered cell therapy showed tremendous potential in treating an aggressive form of blood cancer that resisted chemotherapy (Grady, 2012; Kastelein *et al.*, 2013). This promising form of engineered cell therapy used chimeric antigen receptor (CAR) T-cells, and showed positive clinical results, successfully treating acute lymphoblastic leukemia (ALL) in children (Box 2.2). The same technology was developed to treat similar blood cancers, such as diffuse B-cell non-Hodgkin's lymphoma (Kochenderfer *et al.*, 2015; Rosenbaum, 2017).

5 The Recombinant DNA Advisory Committee (RAC) of the NIH is responsible for developing NIH guidelines for the safe handling and use of recombinant DNA (O'Reilly *et al.*, 2012).

Box 2.1 Jesse Gelsinger

In 1999, 18-year-old Jesse Gelsinger volunteered in a Phase I gene therapy trial treating ornithine transcarbamylase deficiency (OTCD), a rare metabolic disorder with a high fatality rate (Sibbald, 2001). Gelsinger suffered from partial OTCD, allowing him to manage his symptoms through a combination of dietary restrictions and drugs. He was administered the therapy, and subsequently developed a severe inflammatory response to the viral vector used to deliver the treatment, dying four days later (Wilson, 2009).

The aftermath of his death revealed numerous errors and violations in clinical trial operating procedures (Yarborough & Sharp, 2009). Neither Gelsinger, the University of Pennsylvania Institutional Review Board, nor the Food and Drug Administration (FDA) had been made aware of the side effects experienced by other patients, or deaths among primates in animal-model studies (Sibbald, 2001; Wilson, 2009). Upon further investigation, Gelsinger's eligibility to participate in the trial was called into question (Wilson, 2009).

As a result of Gelsinger's death and other poor trial outcomes, the FDA and NIH implemented additional oversight and monitoring of gene therapy clinical trials (O'Reilly *et al.,* 2012). This brought a diversity of ethical and scientific issues to light, highlighting the inherent risks and the potential vulnerability of research subjects (Cavazzana-Calvo *et al.,* 2004; Yarborough & Sharp, 2009).

Clinical trials for other types of gene therapies were also completed in the early 2000s, in some cases paving the way for market authorization. E.U. market authorization of Glybera (alipogene tiparpovec), for instance, was granted in 2012 (EMA, 2015). Among the first approved gene therapies worldwide, Glybera was fast to draw attention due to its high price and questions surrounding its efficacy (Regalado, 2016a; Crowe, 2019). Discovered in Canadian academic laboratories, marketed in the E.U., and ultimately only used by a handful of patients, the development and subsequent challenges of this therapy reflect many of the central issues explored in this report: uncertain efficacy and durability, high prices, and the global nature of this field.

Box 2.2 Emily Whitehead

In 2010, five-year-old Emily Whitehead was diagnosed with ALL (Rosenbaum, 2017). Multiple rounds of chemotherapy over several years did not result in long-term remission. Hoping to find an alternative treatment, her parents enrolled Emily in a gene therapy research study at the University of Pennsylvania, and she became the first child to receive CART-19, a form of CAR T-cell therapy. After three doses of CART-19, Emily developed high fevers, respiratory failure, and shock — what is now known to be cytokine-release syndrome, a side effect that occurred in 78% of patients in the later Phase II trial. Additional treatment with a drug developed for juvenile rheumatoid arthritis was able to eliminate these effects, and Emily has been in remission ever since (Rosenbaum, 2017).

In the Phase II trial for CART-19, 83% of the 63 children who received the therapy had complete elimination of malignant cells at three months (Buechner *et al.,* 2017; Kuehn, 2017). The technology used to treat Emily is now approved in both Canada and the United States as Novartis's Kymriah (tisagenlecleucel) (Rosenbaum, 2017).

As one of the first patients to receive CAR T-cell therapy, Emily Whitehead continues to be monitored. To date she continues to be in remission, and is a model success story for this type of therapy (Rosenbaum, 2017). However, as with all gene therapies, the long-term durability and possible complications associated with CAR T-cell therapy are yet to be determined.

While only a handful of gene therapies have been approved for use in jurisdictions worldwide, hundreds are being tested in clinical trials (Ginn *et al.*, 2018). By 2025, the FDA anticipates that it will be approving between 10 and 20 gene therapy products annually (FDA, 2019). These treatments are approaching the clinic at an accelerating pace, and decision-makers are faced with difficult choices in managing uncertainties, and weighing the promise and value of gene therapy.

2.2 Complexity and Diversity of Gene Therapies

The Panel identified four dimensions that capture the diversity of gene therapies: disease treated, mechanism of action (i.e., how it works), route of administration, and delivery tool (Figure 2.1). Each of these dimensions has implications for cost, regulation, complexity of manufacturing and provision, and for safety and efficacy.

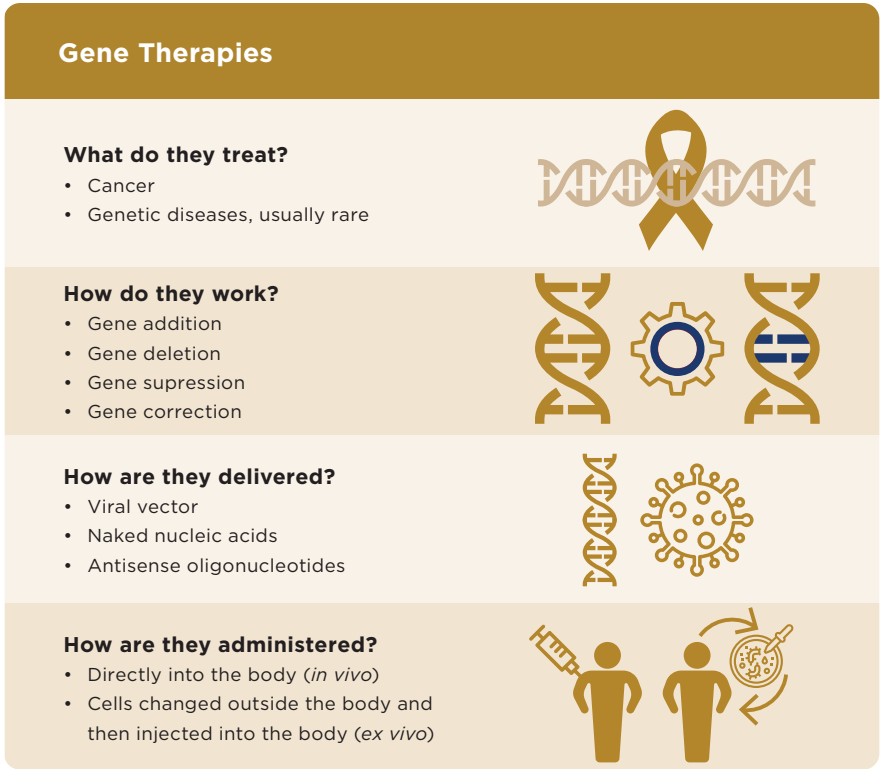


Figure 2.1 Four Dimensions of Gene Therapies

Under the umbrella of gene therapies, diverse treatments exist or are under development, with characteristics spanning four dimensions: disease treated, mechanism of action (i.e., how it works), route of administration, and delivery tool (viral or non-viral vector). The heterogeneity of gene therapies within and across these different dimensions impacts the ease with which they can be adopted and used in Canada.

Table 2.1 shows how a selection of gene therapies vary according to these four dimensions. Spinraza (nusinersen), for example, is administered *in vivo* and uses naked antisense oligonucleotides, which results in modified gene action and an increase in the amount of functional protein, restoring nerve function (Vukovic *et al.*, 2019). By restoring nerve function, the symptoms of a rare genetic disease, spinal muscular atrophy, are reduced (Vukovic *et al.*, 2019). In contrast, the more

complex therapy Kymriah involves modifying genetic material with a viral vector outside of the body and then administering *ex vivo*, delivering a gene that makes CAR T-cell therapy to treat blood cancer (HC, 2019m).

Table 2.1 Examples of Gene Therapies Spanning Different Dimensions

	Glybera (alipogene tiparvovec)	Kymriah (tisagenlecleucel)	Spinraza (nusinersen)	Strimvelis
What does it treat?	Lipoprotein lipase deficiency (rare genetic disease)	B-cell acute lymphoblastic leukemia (blood cancer)	Spinal muscular atrophy (rare genetic disease)	Adenosine deaminase deficiency-severe combined immunodeficiency (rare genetic disease)
How does it work?	Gene addition to produce functional protein	Synthetic gene addition to make CAR T-cells	Gene suppression via antisense oligonucleotide to improve production efficiency of functional protein	Gene addition to make functional protein
How is it administered?	*In vivo*	*Ex vivo*	*In vivo*	*Ex vivo*
How is it delivered?	Viral vector (adeno-associated virus serotype 1)	Viral vector (lentiviral vector)	Naked DNA	Viral vector (gammaretrovirus)
Source	Kastelein *et al.* (2013)	HC (2019m)	Vukovic *et al.* (2019)	Aiuti *et al.* (2017)

Four examples of gene therapies that vary in their disease treated, mechanism of action, mode of administration, and delivery tool.

2.2.1 What Do Gene Therapies Treat?

Between 1989 and 2015, most gene therapy clinical trials were to treat various types of cancers (64%) with the second most popular target being monogenic diseases (10%) (Hanna *et al.*, 2016). Monogenic diseases are caused by a single genetic change, and examples include sickle cell disease or severe combined

immunodeficiency disease (SCID) (Boudes, 2014). Indeed, in Canada, the gene therapies approved to date treat these two categories of diseases exclusively. Clinical trials are, however, underway for gene therapies treating infectious, cardiovascular, neurological, and ocular diseases (Ginn *et al.*, 2018).

The motivation and investment in gene therapies for cancer treatment can be explained by the increasing prevalence of the disease within the population (Hanna *et al.*, 2016). The promising early results of CAR T-cell therapy are another reason for the focus on cancers (Geyer, 2019). Two of the three gene therapies approved to date in Canada are CAR T-cell therapies, indicated for use in blood cancers where other forms of treatment are no longer effective (HC, 2019m, 2019n).

Monogenic diseases are targeted for gene therapy because the alteration of DNA at only a single location in the genome allows for a single target for treatment (Boudes, 2014). Many monogenic diseases can be classified as *rare* (Boycott & Ardigó, 2018). A rare disease is a "life-threatening, seriously debilitating, or serious and chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons)" (HC, 2015). Many of the challenges that may arise through the adoption and use of gene therapies relate to challenges encountered during the treatment of rare diseases more broadly, including limited data to assess safety and efficacy (Section 3.2.1), and variable treatment access across Canada (Section 4.1.1) (CORD, 2015). Some of these issues are exacerbated by the novelty and price of gene therapies.

2.2.2 How Do Gene Therapies Work?

Gene therapies alter the genetic material of a patient through gene addition, deletion, or correction, or by suppressing gene expression in a patient. Added genes may include functional copies of naturally existing genes, as occurs in most gene therapies for genetic diseases. Some therapies, including those that treat cancer, add a gene that produces a synthetic (i.e., non-naturally occurring) CAR on the patient's T-cells to target and destroy cancer cells (NCI, 2019).

Gene editing, a specific type of gene therapy, uses technologies such as CRISPR (clustered regularly interspaced short palindromic repeats) or TALEN (transcription activator-like effector nuclease) enzymes to make genetic modifications (Shim *et al.*, 2017). In gene editing, the "goal … is to remove, disrupt or correct faulty elements of DNA within the gene rather than replace the gene as regular gene therapy would" (ASGCT, 2019b).

The way gene therapy works — its mechanism of action — has implications for affordability when it is subject to a patent. For example, if a manufacturer holds exclusive rights to a patent and the related technology necessary for a particular

therapy, they are in a position to increase the price to what they believe the market will bear, without any competition. The challenges arising from overly broad patents and technology ownership, which ultimately impact gene therapy affordability, are discussed in Section 4.3.1.

2.2.3 How Are Gene Therapies Administered?

Gene therapies are administered through one of two routes. Some are delivered by injection, and involve the direct delivery of genetic material into the tissue surrounding the targeted cells (*in vivo*) (High & Roncarolo, 2019). Others use *ex vivo* administration, whereby cells are removed from the body in a hospital or clinic, genetically modified, and then introduced back into the patient's body (High & Roncarolo, 2019).

While the degree of invasiveness for *in vivo* therapy will vary based on the disease treated, overall *in vivo* administration tends to be more straightforward than *ex vivo* therapies (High & Roncarolo, 2019). For example, a patient using Spinraza, an *in vivo* therapy, has synthetic DNA injected directly into their cerebrospinal fluid in order to reach the target motor neuron cells (Prakash, 2017). In contrast, *ex vivo* therapies require hospital admission and multiple treatment steps (including, for example, chemotherapy in some cases), with patient cells shipped to specialized facilities at some distance from the point of care, where they undergo modification.

This distinction between routes of administration has implications for the manufacture and provision of gene therapies; an *ex vivo* route involves a greater number of steps, and therefore demands a wider variety of expertise and more complex manufacturing logistics (Section 4.2.1). It may also carry a greater degree of risk of complications and longer recovery times for patients (Buechner *et al.*, 2018).

2.2.4 How Are Gene Therapies Delivered?

Gene therapies vary in the way genetic material is delivered to a cell; much depends on the biology of the disease being treated and the desired effect of the treatment. Vectors are often used to protect the therapeutic genetic material from degradation in the body and to allow it to enter target cells. Two main types of vectors exist: viral and non-viral (Hanna *et al.*, 2016). Viral vectors use viruses, which have been modified so they do not cause disease, to carry and introduce genetic material (usually a copy of a functional gene) into the patient's cells (NIH, 2019b). Non-viral vectors use a variety of delivery methods, including naked DNA (of both naturally occurring or synthetic sequences) or encapsulated DNA (Mali, 2013; Hanna *et al.*, 2016).

Viral vectors were the most common type of vector used in gene therapies undergoing clinical trials in 2017, due to their efficiency in delivering genetic material into target cells (Ginn *et al.*, 2018; Vormittag *et al.*, 2018). The type of vector used has implications for adverse reaction potential. While serious adverse reactions, such as inflammatory immune reactions and tumour generation, have been associated with viral vectors, there have been increased efforts in recent years to characterize and improve their safety through advances in vector engineering (Dunbar *et al.*, 2018; Lundstrom, 2018). The use of viral vectors can also increase the cost and time required to produce a gene therapy relative to other gene therapies that do not use viral vectors (Tarnowski *et al.*, 2017) (Section 4.2.1).

2.3 Stages of Gene Therapy Approval and Use in Canada

The Panel identified six stages of approval and use for any new drug in Canada, including gene therapies. The process starts with market authorization by Health Canada based on a review of clinical trial results, and continues through HTA, funding and pricing decisions, manufacture, provisioning, and post-market surveillance (Figure 2.2). As of September 2020, only three gene therapies have completed this process (HC, 2019m, 2019n). The stages outlined below are the same for all drugs in Canada, and are thus familiar to drug manufacturers (or sponsors), regulators, and administrators working in health ministries or institutions.

These stages of approval and use involve numerous actors, and seek to ensure the safe provision of drugs, as well as the responsible allocation of resources in healthcare. Nevertheless, there exist points of tension along this pathway where gene therapies might struggle to meet the criteria required to move on to the next stage. Some of these points of tension arise due to economic, clinical, and other legal, ethical, social, and policy considerations, which are discussed in Chapters 3 to 5.

2.3.1 Market Authorization

Market authorization grants approval for a drug to be made available for sale in Canada. Health Canada has the authority to grant market authorization based on its evaluation of the drug's quality, safety, and efficacy, and whether the risks are offset by the benefits (HC, 2019a).

The regulatory pathways for approval in Canada can vary depending on several factors, some of which are particularly salient for gene therapies due to the nature of conditions they target. For instance, alternate regulatory pathways have been developed for drugs treating a life-threatening illness, for which no approved

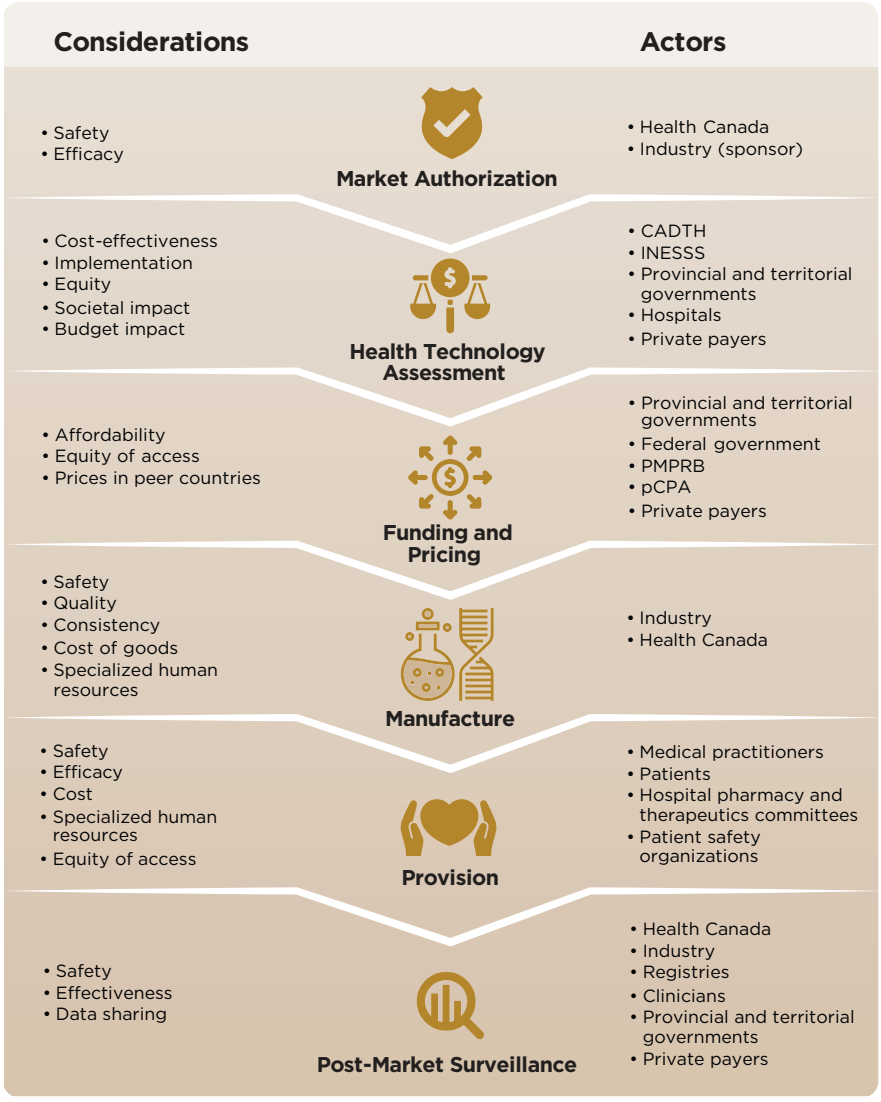


Figure 2.2 Stages of Approval and Use of Drugs in Canada

There are six stages in the approval and use of drugs (including gene therapies) in Canada. Each of these steps has distinct considerations and involves different actors, including government agencies, various levels of government, industry, and healthcare providers.

CADTH – Canadian Agency for Drug and Technologies in Health;
INESSS – Institut national d'excellence en santé et en services sociaux;
pCPA – pan-Canadian Pharmaceutical Alliance;
PMPRB – Patented Medicine Prices Review Board.

treatment exists in Canada, or which show promise for increased efficacy relative to alternatives (HC, 2009). In other cases, market authorization may be granted with limited clinical evidence if the drug demonstrates clinical benefit, has a suitable safety profile, and is of high quality (HC, 2016). In these cases, the drug sponsor must agree to conduct post-market studies to verify the long-term safety and durability of its product (HC, 2016) (Sections 2.3.6 and 3.2.1). For two of the three gene therapies that have received market authorization in Canada to date, the sponsors have been required to conduct long-term post-market surveillance in the form of patient registries and post-market studies (HC, 2019m, 2019n).

2.3.2 Health Technology Assessment

Once a drug has received market authorization, a decision has to be made about whether it will be eligible for reimbursement by public drug plans. Through a process called the common drug review (CDR), the Canadian Agency for Drugs and Technologies in Health (CADTH) conducts an HTA based on clinical evidence, economic assessment, and patient perspectives, before recommending that any drug be added to public drug plans (CADTH, n.d.). A similar system exists in Quebec, where the Institut national d'excellence en santé et en services sociaux (INESSS) assesses whether a drug should be added to the provincial public plan — with the additional step of considering societal perspectives, such as impacts on caregivers or general population health (INESSS, 2018a).

Accelerated market authorization processes may have implications on HTAs for gene therapies, as the uncertainties with respect to safety and efficacy are carried forward along the lifecycle. In 2020, CADTH launched a new review process for gene therapies (CADTH, 2020b). This new process is based on the CDR process but includes additional requirements. For instance, issues related to ethics and implementation are considered during the evaluation, and sponsors are required to submit a plan for implementation in Canada (CADTH, 2020b). The requirements for HTA applications by INESSS do not differ for gene therapies. However, in describing its 2016 evaluation framework, INESSS acknowledges certain challenges posed by innovative therapies, along with a desire to develop tools to better evaluate associated uncertainties and weigh collective health needs versus individual patients' interests (INESSS, 2018a).

2.3.3 Funding and Pricing

For the cost of a therapy to be reimbursed publicly, or by private health insurance plans, it must be listed in a formulary. The CDR process and associated economic evaluations (as part of the HTA) provide guidance to potential payers (public or private) on whether or not to list drug products in formularies, thereby funding

their use. Provincial and territorial health ministries independently decide whether to list drugs on their respective formularies. Private insurance plans develop their own formularies.[6] Services rendered in hospitals must be reimbursed, and so consequently hospitals manage their own formularies.[7] For each of these payers, the decision-making process is informed by non-binding CDR recommendations. The considerations taken into account during these deliberations are further discussed in Section 5.1.1.

The cost of procuring and administering gene therapies could place a significant strain on public healthcare budgets as the number of gene therapies increases and as gene therapies become available for more common diseases. For example, CAR T-cell therapy is being tested for solid tumour cancers (Yeku *et al.*, 2017; Ma *et al.*, 2019); if found to be clinically effective, a much larger number of patients would be eligible for the treatment.

Drug pricing is influenced by two additional players: the pan-Canadian Pharmaceutical Alliance (pCPA) and the Patented Medicine Prices Review Board (PMPRB). The pCPA was established in 2010 by the provinces and territories in order to combine negotiating power to decrease drug prices for participating jurisdictions (pCPA, 2019). The PMPRB is an independent quasi-judicial body established under the *Patent Act* in order to ensure patented medicine prices in Canada are not excessive; it has the authority to order reductions in drug prices and require excess revenues be returned to the crown (PMPRB, 2018).

2.3.4 Manufacture

Regulatory oversight also applies to the production of therapies to ensure that they are safe and of high quality. Manufacturing facilities must possess an establishment licence from Health Canada and comply with the Good Manufacturing Practices (GMPs) outlined in the *Food and Drug Regulations* (HC, 2013, 2019a). GMPs are a standardized system of practice that ensures pharmaceuticals are produced and controlled according to quality standards. The production of gene therapies in a GMP-compliant process is more complex than that of conventional drugs, as they involve the use of living material (e.g., viral vectors, donor or patient cells) (HC, 2019a). This complexity may limit the number of manufacturing facilities able to produce the therapies, which in turn may be an important determinant of geographical access (Section 4.1.1).

6 Private payers may also play a role in funding gene therapies in the future, but to date there is no evidence about these payers funding gene therapies in the Canadian context.

7 Formulary decisions within hospitals also include other factors, such as the hospital's budget and model of care.

2.3.5 Provision

Guidelines for the dosage and administration of drugs are submitted to Health Canada by manufacturers for assessment, and are typically made available in the Drug Product Database following approval (HC, 2019b). In Canadian hospitals, pharmacy and therapeutics committees oversee the cost-effective, appropriate, and safe use of drugs for patients. Certain gene therapies will require extended stays in hospitals, while others may not. The nature of the disease treated, and therefore the type of gene therapy provided, will dictate requirements for infrastructure and human resources (Buechner *et al.*, 2018). Depending on the nature of the treatment, there may be additional costs associated with provision of care not included in the direct (approved) cost of the therapy, such as the prolonged hospital stay or additional procedures (e.g., chemotherapy). Even if the therapy itself is included in the formulary, hospitals may or may not cover these additional care costs, impacting access.

2.3.6 Post-Market Surveillance

Health Canada continues to monitor drugs for safety and quality after they are granted market authorization. Post-market surveillance includes: investigation of complaints, reporting of adverse events, monitoring compliance with GMPs, and recalls (HC, 2019a).

Post-market surveillance can be especially important in cases where therapies have used accelerated approval processes (Section 2.3.1), and when they are novel, leading to higher uncertainty with respect to long-term safety and durability. Post-market surveillance can be used to help address a lack of data and provide additional evidence to inform clinical practice (Fritsche *et al.*, 2019). The use of post-market surveillance as a means to address this dearth of evidence is discussed further in Chapter 3.

While gene therapies approved for use will demonstrate short-term benefits in patients, it remains unclear whether these benefits are durable, or if there are any long-term complications. While this caveat is true of all new classes of drugs, the potentially permanent nature of genetic change associated with gene therapies, along with unknown long-term impacts of genetic changes and disease manifestation in patients, make post-market surveillance of particular importance for these therapies.

3

Regulatory Oversight and Decision-Making

Chapter Findings

- There are multiple actors and many steps involved in a gene therapy's pathway from market authorization to funding decisions. This contributes to the length of the process, which could be shortened through proactive and enhanced domestic and international cooperation.
- Regulators are challenged with making market authorization decisions for gene therapies that have demonstrated short-term efficacy but that lack long-term safety and durability evidence.
- Post-market surveillance offers the opportunity to continue to assess the long-term safety and durability of gene therapies after market authorization is granted.
- Efforts to adapt regulatory oversight for innovative drugs, including some gene therapies, present an opportunity to remove barriers to innovation in this emerging therapeutic field.

This chapter explores the stages involved in getting a new drug listed in a public formulary, and how the coordination of these stages affects the roll-out of gene therapies. It also examines how regulatory decisions in two of these stages — market authorization and post-market surveillance — may impact patient access to gene therapies.

3.1 Coordination of Decision-Making Stages in Approval and Use

The first step in the process of getting a drug listed in a public formulary is receipt of market authorization, which allows for the sale of a gene therapy in Canada. Once drugs receive market authorization, some patients may be able to access treatment via private health insurance plans, or by paying out of pocket if they have the means to do so. However, patients who rely on public health payers must wait until a drug has been included in a public formulary to gain access. In this instance, three additional stages are involved: HTA, price negotiations, and inclusion in public formularies. The length of time it may take to complete these additional stages for some drugs may delay access to treatment, resulting in progressive health deterioration.

3.1.1 Challenges

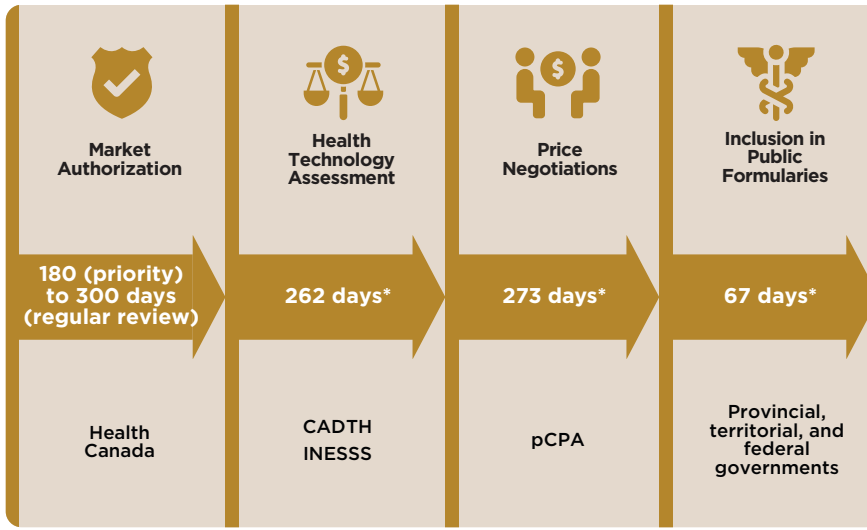
In Canada, the process of taking a drug from market authorization through to inclusion in public formularies often takes years to complete (Salek *et al.*, 2019). The Panel and Workshop Participants observed that a lack of coordination among actors involved in different stages may prolong the process from market authorization to public reimbursement, thereby lengthening the time until a drug is included in public formularies and, by extension, patient access. While this issue is not unique to gene therapies, the nature of the diseases they treat can exacerbate the challenge, as described below.

Multiple reviews in a predominantly sequential decision-making process lengthens the time it takes for approved gene therapies to be included in public formularies

In one study that measured the time it takes for market-authorized drugs to qualify for public reimbursement, Canada was ranked 15th out of 20 OECD jurisdictions (Milson *et al.*, 2016). In Canada, the average time taken for drugs to be listed in public formularies after market authorization was received was 27% greater than the average among these 20 jurisdictions (Milson *et al.*, 2016). While speed is an important consideration for patient access to therapies, the Panel underscores that it is also important to ensure adequate time is taken to provide a thorough review of the evidence and to make informed decisions. Further, ensuring access to drugs, including gene therapies, is not the primary role of the bodies that carry out these stages. Potential efficiencies in the process are secondary to performing their primary roles, including reviewing safety and efficacy.

The steps towards deciding whether or not to publicly reimburse a drug in Canada involve multiple, mostly sequential, reviews (Figure 3.1). This prolongs the process of getting drugs included in public formularies and thus accessible to patients (Salek *et al.*, 2019). Health Canada's market authorization review normally takes 300 days, but sponsors can apply for Priority Review,[8] which shortens review time to 180 days (HC, 2009, 2019c), as was done for two of the three approved gene therapies (Kymriah and Yescarta) (HC, 2019m, 2019n). The time it takes for a drug to complete the remaining steps in the pathway (HTA, price negotiations, and inclusion in public formularies) is less clear, although one study determined that the average length is approximately 600 days (Salek *et al.*, 2019). Based on these timelines, a drug could be submitted for market authorization and included in a public formulary in just over two years with Priority Review, or just under two and a half years with the standard review process.

8 New drugs for serious diseases for which there are currently no treatments in Canada, or that show an increase in efficacy and/or reduction in risk relative to existing drugs, are eligible for Priority Review (HC, 2009). Substantial clinical evidence is required upon submission to support these claims (HC, 2009).



Data Source: HC (2009, 2019c), Salek *et al.* (2019)

Figure 3.1 Pathway from Market Authorization to Inclusion in Public Formularies

Prior to inclusion in public formularies, drugs must first receive market authorization, then undergo HTA and price negotiations.

*Denotes the average time found by Salek *et al.* (2019) in their review of approvals in Canada (excluding Quebec) between 2012 and 2016. The 262-day average for HTA includes 236 days for HTA and 26 days between market authorization and the start of the HTA.

CADTH – Canadian Agency for Drugs and Technologies in Health;
INESSS – Institut national d'excellence en santé et services sociaux;
HTA – health technology assessment;
pCPA – pan-Canadian Pharmaceutical Alliance.

The challenges associated with the length of the decision-making process are exacerbated for gene therapies due to the nature of the diseases they target

Some approved gene therapies treat diseases that can be fatal (e.g., spinal muscular atrophy, adenosine deaminase deficiency–severe combined immunodeficiency, relapsed or refractory diffuse large B-cell lymphoma) (Prakash, 2017; Stirnadel-Farrant *et al.*, 2018; CADTH, 2019e). The time it takes to review, approve, and include a therapy in public formularies might "exceed the time frame of a life-threatening disease" (Fountzilas *et al.*, 2018). Thus, while waiting for approval and possible inclusion in formularies, a patient's symptoms may progress to such an extent that gene therapy is no longer effective, and in severe cases, patients may die. This is a risk for gene therapies used to halt or slow

the progression of a disease, such as Spinraza for spinal muscular atrophy, where early intervention is thought to produce better results (Prakash, 2017). Similarly, in cases of Leber congenital amaurosis, which affects eyesight, the disease may progress to a point where gene therapy is "futile" (Lee *et al.*, 2019).

Some approved gene therapies have age eligibility criteria. Therefore, delaying their inclusion in public formularies may result in patients becoming ineligible for the treatment if they surpass an age restriction for coverage or if their symptoms worsen. For example, the eligibility criteria for access to CAR T-cell therapies for relapsed/refractory B-cell ALL in Ontario require that the "patient is between the ages of 3 to 25 years inclusive" and that the "patient is clinically stable, and expected to remain so through to the planned CAR T-cell infusion date" (CCO, 2019). Therefore, patients may age out or become unstable and no longer eligible for treatment while waiting for market authorization and possible inclusion in formularies.

3.1.2 Promising Approaches

A coordinated pan-Canadian approach to reviews and funding decisions could shorten the time required to include gene therapies in public formularies

The Panel and Workshop Participants agreed that a coordinated pan-Canadian approach to market authorization, HTA, and funding decisions could decrease the time needed to reach a listing decision for gene therapies in public formularies. Improving coordination would also allow industry to better predict the processes and related timelines (Salek *et al.*, 2019). The Panel noted parallels with the national approach to pharmacare recommended by the Advisory Council on the Implementation of National Pharmacare and endorsed by the federal government in Budget 2019, which suggested a Canadian drug agency be created to evaluate the effectiveness of drugs and negotiate prices (GC, 2019c, 2019d). This coordination is consistent with Health Canada's 2019 commitment to implement a plan for improved collaboration with HTA organizations by 2021, with the goal of decreasing time between market authorization and reimbursement recommendations (HC, 2019d).

Other Canadian initiatives support clinical trial designs that produce endpoints satisfying both regulatory reviews and HTA, which could help increase speed of access to gene therapies by reducing the likelihood of rejection and need for resubmission (EXCITE International, 2020). Incorporated as a not-for-profit in 2015, EXCITE International brings industry, regulators, payers, and other key stakeholders together to inform the design of clinical trials by identifying the evidence needed by decision-makers and ensuring it is collected (EXCITE International, 2020).

A supplemental process for highly specialized/complex drugs could make oversight more efficient by allowing parallel reviews by multiple actors

A working group established by provincial and territorial health ministers has proposed the creation of a supplemental approval process for expensive drugs for rare diseases. This could reduce patient wait times for access to qualifying drugs by providing greater alignment and coordination between the regulatory and decision-making steps leading to listing decisions (CORD, 2018; pCPA, 2018). For example, sponsors of eligible drugs could submit applications for concurrent reviews to multiple agencies (e.g., Health Canada, CADTH). Stakeholders were consulted about the proposed process in 2018 (CADTH, 2018b; pCPA, 2018), but next steps have yet to be announced.

Regulatory collaboration with other international jurisdictions could reduce market authorization review times

Two Health Canada initiatives present an opportunity to reduce the time required for market authorization reviews: work-sharing with other international agencies, and consideration of foreign reviews (HC, 2018b, 2019d). The work-sharing initiative aims to increase collaboration between Health Canada and regulators in other jurisdictions through a streamlined joint review process (HC, 2018b). This initiative will build on the partnerships Canada has already established through the Australia-Canada-Singapore-Switzerland (ACSS) Consortium, which was founded, in part, to help individual regulatory agencies overcome challenges in providing "timely access to safe therapeutic products" (HC, 2020). New partnerships will be explored as interest arises from other regulatory authorities, with implementation expected to begin in 2020 (HC, 2018b).

The second initiative involves the use of foreign regulators' market authorization reviews by Health Canada. These reviews would support Health Canada's market authorization decisions and be limited to drugs that meet a medical need where there are currently no alternatives available in Canada (HC, 2019e). This initiative would also involve standardizing how Health Canada reviews regulatory approvals from other jurisdictions, with the goal of increased efficiency in Health Canada's own reviews. A policy analysis of this initiative was completed in April 2018, and the publication of draft regulations will be the next step in its development (HC, 2019e).

However, as noted by Coppens *et al.* (2018), "regulatory authorities accept varying levels of uncertainty and safety risks for approval [of gene therapies], taking different combinations of non-evidentiary factors into consideration." For example, in Japan, the *Act on Pharmaceuticals and Medical Devices* (PMD Act,

November 2013) allows gene therapies to be approved after Phase II trials with a small sample if they are shown to be safe and likely efficacious, and with the requirement that Phase III trials be conducted after market authorization (Halioua-Haubold *et al.*, 2017). In addition, the example of Exondys 51 (eteplirsen) illustrates how jurisdictions may make controversial decisions related to market authorization, and that approval decisions may vary among jurisdictions (Box 3.1). Thus, the Panel notes that differences in regulatory requirements for safety and efficacy may limit the feasibility of relying on foreign reviews and developing joint processes. Harmonization or standardization of regulatory frameworks for gene therapies among jurisdictions could help alleviate this issue through increased alignment of market authorization decisions (Shukla *et al.*, 2019).

Box 3.1 Exondys 51

Exondys 51, a gene therapy for Duchenne muscular dystrophy, was approved by the FDA in 2016 despite a recommendation by its advisory committee to reject the drug due to "concerns about the quality of the evidence" (Editorial, 2016). These concerns were related to the small sample size used in the clinical trial, as well as the uncertain relationship between the small gains observed in the surrogate endpoint measures and the clinical benefit observed in patients (Kesselheim & Avorn, 2016). The Director of the FDA's Center for Drug Evaluation and Research made the final decision to approve the gene therapy based on its potential clinical benefit — an important consideration since the life-threatening disease lacked other treatments at the time (FDA, 2016b). Approval was contingent upon the completion of a randomized trial to confirm clinical benefit, with the submission of results required by May 2021, at which time Exondys 51 could be withdrawn if a benefit is not demonstrated (FDA, 2016a). However, the same gene therapy was denied market authorization by the European Medicines Agency (EMA) in 2018 based on concerns related to the efficacy and durability of the treatment. The differences in these market authorization decisions demonstrate the variability in benefit-risk uncertainty that regulators are willing to accept (EMA, 2018).

3.2 Market Authorization and Post-Market Surveillance

Two stages in the approval and use of drugs, market authorization and post-market surveillance, are linked. Under a lifecycle approach, regulators consider requirements for post-market surveillance when making market authorization decisions, then monitor and act upon the information that is collected post-approval (IOM, 2012). While this approach is important for all drugs, it is especially relevant for gene therapies due to the limited evidence available at the time of market authorization (Fritsche *et al.*, 2019). To date, decisions to approve gene therapies are often accompanied by explicit requirements for the manufacturer to conduct post-market surveillance in the form of studies or registries (Fritsche *et al.*, 2019). In addition, post-market surveillance can be used to determine whether market authorization should be maintained or revoked (Dhruva *et al.*, 2018). For these reasons, market authorization and post-market surveillance are considered together in the following section.

3.2.1 Challenges

The novelty of some gene therapies may call for regulatory flexibility and new approaches (Halioua-Haubold *et al.*, 2017). The Workshop Participants noted that regulators will be challenged to establish suitable review mechanisms for new therapies while providing sufficient clarity to sponsors. Proceeding with regulatory reviews in the face of considerable uncertainty about the durability and long-term safety of the drugs also creates challenges (Abou-El-Enein & Hey, 2019).

Existing regulatory pathways may pose a barrier to innovation for some gene therapies

To date, gene therapies have been listed as drugs under the *Food and Drug Regulations* (HC, 2019f). However, in its 2019 regulatory review, Health Canada acknowledged that some emerging and innovative technologies, including some gene therapies, may not be suited to this existing regulatory pathway due to their novelty, complexity, and personalized nature (HC, 2019g). As basic and applied clinical research on gene therapies continues to expand, new discoveries will facilitate the development of innovative treatments, which may increase the number of gene therapies that do not fit within the existing regulatory pathway (High & Roncarolo, 2019; Mukherjee, 2019).

Incremental improvements in approved gene therapies present an additional regulatory challenge. For example, improvements could be made to delivery tools (e.g., viral vectors) and mechanisms of action (e.g., gene editing using CRISPR) (Mukherjee, 2019). Under current drug regulations, any changes made to a gene therapy by the sponsor, including those related to manufacturing or adding new

indications, may trigger additional regulatory requirements (HC, 2018c). Depending on the potential impact of these changes to an approved therapy's safety and efficacy, Health Canada may require additional studies and review before the changes can be implemented (HC, 2018c). However, the additional time and money required to go through this process may present a barrier to such improvements (Mukherjee, 2019).

The novelty and features of gene therapies increase uncertainty in the evidence needed for market authorization and long-term safety and durability

Clinical trial design challenges may reduce certainty in the efficacy estimates for some gene therapies submitted for market authorization (Abou-El-Enein & Hey, 2019). Gene therapies may involve invasive modes of administration, target small patient populations, and lack available comparator treatments, which makes it difficult to conduct randomized control trials (RCTs) (Hampson *et al.*, 2017). For example, many gene therapies are being developed to treat rare diseases, and small patient populations may limit the number of participants in a clinical trial (Bubela *et al.*, 2015). Furthermore, for many diseases targeted by gene therapies, there may be no other available treatment, so it may not be possible to choose a comparator against which to assess safety and efficacy (Hampson *et al.*, 2017). When RCTs are possible, the follow-up time is usually short and surrogate endpoints[9] are used (Hampson *et al.*, 2017). However, the relationship between a surrogate endpoint (e.g., reduction in tumour size) and the desired outcome (e.g., length of survival) may be weak or unknown, making surrogates poor predictors of actual benefit (Kemp & Prasad, 2017). Thus, as noted by Abou-El-Enein and Grainger (2018), "cell and gene therapies generally have small, single-arm, short-term trials likely yielding biased, imprecise clinical results." While none of these issues are unique to gene therapies, combined with the novelty of altering a patient's genetic material as treatment, they cause some to question whether there is adequate evidence to determine durability (e.g., Hampson *et al.*, 2017; King & Bishop, 2017; Abou-El-Enein & Hey, 2019).

Many gene therapies are designed to provide long-term, or even lifetime improvements, however clinical trials are relatively short (Sinclair *et al.*, 2018). A clinical trial may show a therapy slowing or halting the progression of disease, but it cannot demonstrate whether these benefits will continue through time (King & Bishop, 2017). Additionally, some safety concerns may take years to emerge; there is evidence that patients may be at risk for tumour development or

9 Surrogate endpoints are indicators thought to correlate with desired outcomes, such as reduction in tumour size in the case of some cancers. They may be used because the ideal indicator, such as length of survival, could make clinical trials very long or difficult to measure (Kimmelman, 2009; Hampson *et al.*, 2017).

other impacts from genetic manipulation, which would only occur years after treatment (Schule *et al.*, 2010; Psaty *et al.*, 2012; Lee *et al.*, 2019). Gene therapies are unique in that many lead to irreversible modification of somatic cells, the effects of which can persist for as long as the cells are alive (Baylis, 2019). Due to the novelty of the field, no gene therapy has yet been used and observed over long periods of time (Sinclair *et al.*, 2018).

The uncertainty of the evidence, as well as the lack of long-term safety and durability data, may make it difficult for regulators to determine whether market authorization should be granted. While uncertainty at the time of market authorization occurs for other drugs, it is often heightened for gene therapies due to the limited data available, which impacts the ability of clinicians to reliably determine their benefits (Abou-El-Enein & Hey, 2019). As such, regulators in different jurisdictions may make different, sometimes controversial, decisions about market authorization (Box 3.1).

The lack of long-term safety and durability evidence for gene therapies, combined with the lack of alternative treatment options for some serious diseases, makes it difficult to decide whether to offer or choose a gene therapy as treatment

Because there may be limited safety and durability evidence for innovative gene therapies at the time of market authorization, it can be difficult for doctors, payers, patients, and families to fully understand the risks and benefits of treatment (Stafinski *et al.*, 2010; Fountzilas *et al.*, 2018). Indeed, for some therapies, such as Kymriah, this lack of evidence has prevented clinicians from agreeing on the balance of risks and benefits that are ethically justifiable (CADTH, 2019e). Further, the public discussion of gene therapies frequently focuses on success stories, which "often overestimates beneficial effects and underestimates potential harms" (King & Bishop, 2017).

Patients face additional challenges in deciding whether to pursue such treatment. Gene therapies have been developed and approved to treat rare diseases, which are serious and sometimes fatal (e.g., spinal muscular atrophy), and cancer, where conventional treatment has been unsuccessful (e.g., diffuse large B-cell lymphoma) (HC, 2019h, 2019m, 2019n). In these contexts, gene therapies may be the only treatment option available (High & Roncarolo, 2019). The lack of evidence, combined with the severity of disease and lack of alternative treatment options, may make patients vulnerable to making decisions based on what they anticipate to be the best outcome (Cossu *et al.*, 2018; Fountzilas *et al.*, 2018). As a result, a tense interplay exists among limiting harm, enabling patient choice, and providing access to a therapy that could offer significant benefits (Beauchamp & Childress, 2009; CADTH, 2019e).

Mechanisms that trigger post-market reassessments for drugs with uncertain long-term efficacy are lacking

All drugs that receive market authorization in Canada are subject to post-market surveillance by Health Canada and the Public Health Agency of Canada, with a focus on the quality and safety of the drug (e.g., investigating reports of adverse reactions, instituting recalls) (HC, 2019a). Health Canada can also stipulate additional post-market requirements related to efficacy. In these cases, the manufacturer is responsible for collecting and analyzing data, and submitting reports to the regulator for review and analysis of risks and benefits.

Given the challenges in designing robust clinical trials for some gene therapies and uncertainty about long-term safety and durability, many jurisdictions, including Canada, have approved these therapies with requirements for post-market surveillance that aim to fill the evidentiary gap (Fritsche *et al.*, 2019). For example, Health Canada's market authorization of Kymriah requires that a registry of patients receiving the therapy be established, while Novartis, the manufacturer, is required to monitor and analyze the data gathered (HC, 2019m). However, additional post-market monitoring has not been a market authorization requirement for all gene therapies. For example, Spinraza was approved for use in Canada with no additional post-market requirements listed on the regulatory decision summary (HC, 2019h).

Reliance on post-market surveillance studies to evaluate the long-term safety and durability of gene therapies raises some concerns. As noted by Herder (2019), post-market requirements "frequently lack transparency, are subject to delays, and fail to answer the questions of greatest clinical importance." In addition, some drugs that initially received conditional approval were ultimately granted full approval despite a lack of evidence demonstrating efficacy in post-market studies. For example, a review of cancer drug approvals in the United States by Gyawali (2019) found that post-market studies for three drugs granted conditional approval using surrogate outcomes did not show improvements in overall patient survival, yet one of these drugs was granted full approval.

Further, when therapies or indications have been withdrawn due to limited efficacy demonstrated by post-market data, the decisions have been contested by patients, manufacturers, and even clinicians (Vitry *et al.*, 2015). Avastin (bevacizumab), a drug for advanced breast cancer, was approved in the United States in 2008 with the requirement to conduct further studies to confirm efficacy (FDA, 2011). These studies showed no increase in survival and, in 2011, the FDA removed metastatic breast cancer as an indication for Avastin (FDA, 2011). The manufacturer, Genentech, contested the FDA's decision and requested a hearing to appeal it (Carpenter *et al.*, 2011). At the FDA hearing, many breast cancer patients voiced their concern about the withdrawal of Avastin, attributing their survival to

the drug despite clinical evidence to the contrary (Vitry *et al.*, 2015). This example illustrates the challenges that regulators face in withdrawing a drug once it has already been approved — regulators face pressure from patients and manufacturers to provide access to drugs, while at the same time ensuring that the drugs that are available are safe and effective throughout their lifecycle (Herder, 2019).

3.2.2 Promising Approaches

Ongoing regulatory reform presents an opportunity to address barriers to gene therapies

Amendments to the *Food and Drugs Act*, approved in June 2019, include the addition of a regulatory framework for advanced therapeutic products (ATPs). These are defined as "drugs or devices that are so novel, complex, and distinct that current regulations are not equipped to handle them" (GC, 2019c, 2020; HC, 2019i). Under this framework, ATPs identified by the Minister of Health will be listed in Schedule G of the Act, at which time they will be subject to review for safety, efficacy, and quality before a licence to sell or manufacture is granted (GC, 2020). Some gene therapies, including those that use gene editing, may be considered ATPs (HC, 2019i), while others may continue to be regulated as drugs.

Health Canada's proposed review pathway for ATPs includes a regulatory sandbox[10] where mechanisms for regulating innovative products, including some gene therapies, can be tested (HC, 2019i). However, this approach is not meant to be a permanent solution; as more information becomes known about specific therapies, regulatory pathways are intended to be developed and related therapies would be removed from the regulatory sandbox (HC, 2019g).

While the regulatory sandbox provides flexibility in how reviews are conducted, the same standards for patient safety used in the typical pathway would be applied by Health Canada (HC, 2019i). Market authorization would be accompanied by terms and conditions specific to the ATP, which could be amended over time as real-world evidence (RWE) from registries or electronic health records (EHRs) is gathered and analyzed (HC, 2019i). If evidence reveals that a therapy is unsafe or ineffective, the market authorization could be revoked (HC, 2019i). In this regard, the process may be similar to accelerated approval pathways. Under these pathways (e.g., Notice of Compliance with Conditions in Canada, Priority Medicines (PRIME) in the E.U.), market authorization may be granted with limited efficacy data to provide patients with more timely access to promising drugs that treat serious or life-threatening diseases (Fritsche *et al.*, 2019).

10 Sandboxes are "controlled 'safe spaces' in which innovative products, services, business models and delivery mechanisms can be tested without immediately being subject to all of the regulatory requirements" (EBA, 2017).

These authorizations are normally contingent upon the completion of post-market studies, which aim to fill the evidentiary gap present at the time of approval (Hampson *et al.*, 2017). In Canada, none of the gene therapies have been approved under Health Canada's accelerated pathway (i.e., regulatory sandbox), although two of the three were approved using the Priority Review pathway, see Section 3.1.1. But similar approaches to the regulatory sandbox have been used in the E.U. and United States.

The Panel notes that Health Canada could use this sandbox as an opportunity to learn more about the frequency and nature of requests from sponsors to make incremental improvements to gene therapies after market authorization and, if needed, revise existing or add new regulations that can respond to these innovations. This could include reconsidering the classification of some gene therapies, since they may be better regulated in a manner similar to medical transplants, for which Health Canada regulates product safety and quality assurance but not the transplant procedure, which falls under provincial or territorial jurisdiction (HC, 2018a).

Registries could address issues related to uncertainty over long-term safety and durability of gene therapies by providing a mechanism to track and gather evidence

The Workshop Participants identified the creation of registries as a promising approach to help address the uncertain long-term safety and durability of gene therapies. Registries are currently used in Canada and other jurisdictions to monitor the long-term safety of some gene therapies (e.g., Kymriah in the E.U. and Canada, Strimvelis in the E.U.) and have been identified as a way to track safety and efficacy across a class of therapies to allow for shared learning (Detela & Lodge, 2019; Elverum & Whitman, 2019; HC, 2019m). However, some question whether the current use of registries for post-market regulatory decisions falls short of their potential due to challenges with data quality, consistency of data among registries, and data sharing (McGettigan *et al.*, 2019).

There are opportunities to improve the ways registries collect and use data to facilitate post-approval regulatory decisions, especially for gene therapies. Stirnadel-Farrant (2018) points to the E.U. Strimvelis registry as a model for monitoring the long-term safety and durability of gene therapies, especially for those that treat rare diseases. The registry's unique design "streamline[s] data collection and . . . optimise[s] patient engagement," with the goal of following patients over a 15-year period. Olmo (2019) has noted growing interest in shifting from individual product registries to patient registries that focus on the type of disease treated. Progress is already being made on this front, with the manufacturers of the two approved CAR T-cell therapies in Canada (Yescarta and

Kymriah) participating in registries hosted by the U.S. Center for International Blood and Marrow Transplant Research and the European Society for Blood and Bone Marrow Transplantation (CADTH, 2019e, 2019j).

Inclusion in registries will inevitably raise concerns about access to information and related risks to privacy. Patients may be reluctant to participate in registries due to concerns about the security and privacy of their medical information (Korngut *et al.*, 2013). Registries can address this ethical issue by ensuring patients understand what data are recorded and with whom they are shared by providing informed consent (Olmo *et al.*, 2019). Research in the area of privacy and healthcare data is an active field in Canada and internationally, providing an opportunity for lessons to be learned and shared with others. For example, both the ICES (formerly known as the Institute for Clinical Evaluative Sciences) in Canada and the Patient-Centered Outcomes Research Institute (PCORI) in the United States have identified ways to protect privacy while conducting research activities (PCORI, 2019; ICES, n.d.-a, n.d.-b).

Ethical issues may also arise if treatment is contingent upon enrolment in a registry, as has been observed in the United States (Wadman, 2005; Carnahan, 2007). This requirement led to an ethical debate — some defended it as necessary to inform safety and efficacy data, especially in light of the high price of new drugs and devices, while others said this amounted to coercion (Wadman, 2005). While this requirement has not been applied to gene therapies to date, the Panel notes that there is evidence of such contingencies being associated with treatments elsewhere, and that high prices and limited safety and efficacy data may lead to such requirements.

RWE may help address gaps in safety and durability evidence

Post-market surveillance can use RWE, which is "clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of [real-world data] RWD"[11] (FDA, 2017). The use of RWE is increasing as data sources, such as EHRs, and the ability to interpret these data, are rapidly advancing (Hampson *et al.*, 2018). At the same time, the use of RCTs for market authorization is declining, often placing an increased reliance on post-market surveillance (Fritsche *et al.*, 2019). In these cases, RWE has been suggested as a means to fill this evidence gap as it can increase the robustness of the therapeutic evidence (Abou-El-Enein *et al.*, 2018).

11 Real-world data are "observational data collected not under clinical trial conditions (RCTs), but rather from post-approval clinical use, and are usually recorded in registries, electronic health records, and insurance and home use data" (Abou-El-Enein *et al.*, 2018).

With the increasing use of RWE, questions have emerged about its quality and whether the methods and designs employed are suitable (Pearson *et al.*, 2018). RWE used in post-market surveillance often has a greater risk of selection and reporting biases, and lacks transparency (Hampson *et al.*, 2018; Pearson *et al.*, 2018). In addition, some study designs reflect those used in pre-market trials, which may not provide the evidence that regulators and payers need to make informed decisions (Fritsche *et al.*, 2019). Thus, as noted by Hampson *et al.* (2017), "[t]he design of post-launch evidence collection is likely to be crucial for establishing medium-to-long-term evidence of effectiveness and comparative effectiveness." Issues related to bias could be addressed by developing a mandatory national registry, similar to that available for RCTs, and that buy-in from stakeholders on a common set of standards could address design issues (Hampson *et al.*, 2018). Health Canada has acknowledged that quality issues related to RWE exist, and is working on several initiatives to address this. For example, it has published a guidance document that includes "overarching principles to guide the generation of RWE," and is working collaboratively with CADTH, INESSS, and industry to "establish an approach to using RWE across the drug life cycle that is both systematic and transparent" (HC, 2019j).

The data used in RWE also have challenges related to availability, compatibility, and completeness (Dhruva *et al.*, 2018; Hampson *et al.*, 2018). Many of these challenges stem from the fact that data are often collected via mechanisms that pre-date the study and were thus not designed to generate data for this use (Pearson *et al.*, 2018). For example, EHRs are often sources of data for RWE but collected for other clinical purposes, such as records of doctor's visits. As a result, they are frequently missing information, incompatible with data from other organizations, or difficult to access due to privacy issues (Hampson *et al.*, 2018). However, EHRs have been noted to be one of the best sources for RWE due to their ability to provide longitudinal data, as well as a wealth of detailed clinical data (Dhruva *et al.*, 2018), and are thus often used in post-market observational studies (Pacurariu *et al.*, 2018).

EHRs are currently being used for post-market surveillance monitoring in countries worldwide, including many European countries (Pacurariu *et al.*, 2018). For example, Italy has used EHRs in post-market surveillance registries of innovative therapies for rare diseases for over a decade (Valent *et al.*, 2019). Due to the popularity of EHRs for post-market surveillance studies, it is important that limitations are addressed, as regulatory decisions may be based on these studies (Valent *et al.*, 2019). Many have proposed solutions to address data limitations, including the development of national data repositories and guidelines for reporting in the repositories (e.g., White, 2016; Hampson *et al.*, 2018; Pearson *et al.*, 2018).

A post-market authorization renewal policy could manage uncertainty relating to long-term safety and durability

The creation and implementation of a post-approval renewal policy was identified by the Panel and Workshop Participants as an option that could help address issues related to the uncertainty of long-term safety and durability, especially in cases where no post-market requirements are included as part of market authorization. At least one other regulatory body already uses this type of policy: the EMA requires manufacturers to submit an application for renewal five years after the original market authorization is granted (EMA, 2016). While not specific to gene therapies, this renewal provides regulators with an opportunity to re-evaluate the safety and efficacy of previously authorized drugs (EMA, 2016). The Panel, Workshop Participants, and the literature note that the utility of this type of policy, as well as post-market surveillance, rests on the ability of the regulator to analyze and act on the evidence, if needed (Herder, 2019).

The evidence generated through post-market surveillance, which can include RWE, is relevant not only to regulators, but also to HTAs and payers, as uncertainties over safety and efficacy are carried forward along a therapy's lifecycle. In these contexts, RWE can be used to "assess the economic value of a therapy and adjust pricing and reimbursement recommendations and decisions as appropriate" (CADTH *et al.*, 2018). CADTH has acknowledged the importance of RWE for HTA and is currently developing a reassessment framework, as well as considering its use for comparative safety and effectiveness over the long term (CADTH *et al.*, 2019). In Quebec, the recommendation by INESSS to include Spinraza in the provincial formulary was issued on the condition of clinical monitoring, and INESSS highlighted the role of RWE in assessing the value of the therapy without compromising access. INESSS further noted that, if the results of this ongoing monitoring indicated that Spinraza was not meeting expectations, reimbursement may be discontinued (INESSS, 2018b).

4

Access and Supply

Chapter Findings

- Inconsistent access to specialized healthcare across Canada is a challenge, and is exacerbated for gene therapies. Their cost, the nature of the diseases treated, and the requirements on infrastructure and personnel, restrict the locations where these therapies can be administered.
- Increased coordination among jurisdictions in Canada can minimize existing difficulties faced by patients with rare diseases in obtaining access to diagnoses and to gene therapies.
- Canada is well positioned to scale up the commercial manufacture of key components necessary for the administration of gene therapies, but more highly qualified personnel (HQP) will be needed to maintain a strong competitive position internationally.
- The intellectual property (IP) landscape for gene therapies is complex. It acts as a potential barrier in the development and commercialization, and therefore availability, of new therapies.

This chapter explores challenges in delivering gene therapies in Canada through an access and manufacturing lens. Additionally, the Panel considered IP protections as they affect Canadian innovation in this globally significant sector. Though IP issues occur upstream from market authorization, the Panel believes they warrant highlighting given their potential to affect Canadian capacity to develop a domestic supply of gene therapies.

4.1 Patient Access

4.1.1 Challenges

While accessibility is one of the five cornerstones of Canada's public healthcare system (GC, 1985), providing equitable access to health interventions remains a challenge. Access to care may be undermined by (i) unique considerations for rare diseases; (ii) remoteness of some communities relative to specialized medical care; and, (iii) discrepancies in treatment availability across provinces and territories. In some instances, patients may face all three barriers due to the requirements for gene therapy provision and the nature of the diseases they treat.

Access to advanced diagnostics is uneven

While genetic testing and counselling can support diagnoses for patients with rare diseases, access to sequencing and the ability to interpret these data are not widely available across Canada (Boycott *et al.*, 2015; Carroll *et al.*, 2016). Many patients, particularly those living outside large urban centres, rely on primary care physicians, most of whom would not have the training or access to resources required to offer these diagnostics (Carroll *et al.*, 2016).

Further, even when access to advanced diagnostics exists, these may not provide a clear diagnosis. The genetic causes of numerous rare diseases are currently unknown and subject to ongoing research, including several large-scale initiatives through Genome Canada's Precision Health Strategy (Boycott & Ardigó, 2018; Genome Canada, 2019). This leads to difficulties in making accurate diagnoses, a major problem in a patient's journey, as identified by the Canadian Organization for Rare Disorders (CORD) (CORD, 2015; Boycott & Ardigó, 2018). Additionally, the lack of diversity in current genetic databases has been criticized as impeding the comprehensive identification of rare diseases and compromising the understanding of patient responses to therapies among certain population groups due to biases towards individuals of European descent (Popejoy & Fullerton, 2016; Sirugo *et al.*, 2019).

Access to gene therapies will be concentrated in large urban centres

Procedures required to administer gene therapies vary in complexity, from a series of injections (e.g., Spinraza) to sophisticated interventions requiring multiple interactions, a diversity of expertise, and advanced supportive infrastructure (e.g., CAR T-cell therapy). Currently approved gene therapies are all administered in hospitals. The eligibility for sites to administer CAR T-cell therapy is restrictive due to the expertise and infrastructure required, and is contingent on training and certification by manufacturers (CADTH, 2019e, 2019j). Eligible treatment centres for Kymriah must, for example, receive accreditation from the Foundation for the Accreditation of Cellular Therapy. As of May 2020, accreditation has been given to 17 Canadian sites, located in 5 provinces (Novartis, 2019b; FACT, 2020). Hospitals meeting the eligibility criteria are not guaranteed to offer these therapies, as they manage their own formularies and therefore decide whether to adopt new treatments, given the required resources (Mittmann & Knowles, 2009). Even if they are offered, treatments may span several weeks, as patient cells are transported to centralized facilities[12] for genetic modification

12 Decentralized production models have also been proposed, with multiple facilities distributed regionally and responsible for specific steps in the therapy manufacture. This model offers the possibility for manufacture closer to the point of care, but also brings its own challenges from the standpoint of implementation (Harrison *et al.*, 2017).

(Novartis, 2018; Kite Pharma Inc., 2019). As such, many patients (and potentially their caregivers) may need to travel in order to receive treatment and remain at the site for an extended period of time (CADTH, 2018a).

These provisioning challenges may be less pronounced for *in vivo* gene therapies (Section 2.2.3), as they do not involve the collection and manipulation of patient cells. The reduced complexity of these procedures may facilitate more treatment locations. However, even for the *in vivo* therapy Spinraza, healthcare professionals with specific experience and training in injections into spinal fluid are required (BioGen Canada, 2018).

Patient access to therapies will depend on their province or territory of residence, raising questions of equity at the federal level

Equitable access to therapies, including gene therapies, may be further complicated as each province and territory determines which therapies to fund through their public formulary. Therefore, a therapy may be funded in one province or territory but not another (PMPRB, 2017). While these discrepancies are not unique to gene therapies, such barriers to access may be exacerbated due to the high prices of these therapies. For example, as of May 2020 only Ontario and Quebec provide reimbursement for Kymriah (CMSSS, 2019; Novartis, 2019a, 2019b). It is possible for a patient residing outside of these provinces to request access to this therapy through applicable out-of-province programs (CHUSJ, 2019; CCO, n.d.). In this respect, constraints based on the availability of infrastructure needed for provisioning become compounded by the fragmented multi-payer landscape of reimbursement mechanisms across Canada.

The combination of limited manufacturing capacity, treatment centre certification requirements, and formulary misalignment ultimately affects supply or availability of CAR T-cell therapy. In its assessments of both approved CAR T-cell therapies in Canada, CADTH points to the likelihood of insufficient supply due to restrictions on manufacturing capacity and limited geographic availability of the therapies (CADTH, 2019e, 2019k). In the event of scarcity, frameworks for allocation of health resources, such as gene therapies, can help prioritize access based on fairness and transparency. Jecker *et al.* (2017) provide one example of a potential framework that could be used to determine fair allocation of CAR T-cell therapy, which is based on the ethical principles of beneficence, equity, and procedural fairness. A review of the suitability of this and other frameworks proposed for allocating potentially scarce gene therapies is, however, beyond the scope of this report.

4.1.2 Promising Approaches

Deliberate research strategies can be implemented to enhance diversity in genetic databases and ultimately support more equitable access to effective diagnosis and treatment

As costs of genetic sequencing decrease and the ability to sequence whole genomes expands, new research initiatives tend to include more diverse study groups (Popejoy & Fullerton, 2016). Collecting more representative and diverse genomic data can improve the ability of researchers to identify new rare genetic variations, potentially providing targets for gene therapy. Raising researchers' awareness of the importance of studying underrepresented populations, and using the diversity of study participants as a grant evaluation criterion, are encouraging research on the genomes of non-European descendants. Diverse genomic data may also enable more accurate genetic testing results for diverse populations (Popejoy & Fullerton, 2016).

As gene therapies — and personalized medicine more broadly — become more widespread, the lack of diverse genomic data may exacerbate existing health inequalities experienced by Indigenous people (PHAC, 2018). But one initiative in Canada, Genome BC's Silent Genomes project, aims to "reduc[e] access barriers to diagnosis of genetic diseases in Indigenous children" (BCCRHI, n.d.). This project includes collecting genomic data, establishing governance processes for biological samples, conducting genomic testing, and assessing the economic and healthcare impacts of the program (BCCRHI, n.d.). Similar initiatives will increase the diversity of the genomic data pool in Canada, which ultimately may support more equitable access to diagnoses and treatment.

Rare disease patients can use registries to help them access gene therapies, and to identify themselves to payers

Patient registries may allow the distribution of rare disorders to be geographically mapped (Ng *et al.*, 2018). This information could assist the planning of healthcare provision or guide drug developers towards potential candidates for clinical trials or new products (Cavero-Carbonell *et al.*, 2015; Lacaze *et al.*, 2017). The Canadian Clinical Trials Coordinating Centre is developing a central listing for active patient registries for the purpose of supporting patient recruitment for clinical trials (CCTCC, 2019a, 2019b).

Small patient pools can limit the reliability of conclusions from clinical data, and may complicate long-term monitoring if retention rates for patients are low during follow-up (Stirnadel-Farrant *et al.*, 2018). Multinational collaborations, such as the International Rare Diseases Research Consortium and the TREAT-NMD Network and related registries, can mitigate some concerns relating to small sample sizes by coordinating clinical research efforts among countries, increasing

the data pool and thereby providing greater confidence in trial outcomes (Bladen *et al.*, 2013; Boycott *et al.*, 2017). Registries operating on international scales will present similar implementation challenges to those described in Section 3.2.2, and will require guidelines and frameworks to ensure privacy and maximize patient retention, particularly as patients age or change jurisdictions (Baker *et al.*, 2018; Stirnadel-Farrant *et al.*, 2018).

Support for medical travel can alleviate access challenges for patients in rural and remote regions

The need to travel for specialized medical care is a reality for people living in rural and remote regions in Canada, and government, private, and charitable funding programs for medical travel can help overcome some barriers (Mathews & Ryan, 2017). There are well-established funding programs in Canada that could be used by patients who need gene therapies, especially if treatment requires a prolonged hospital stay. All provinces and territories except Alberta and New Brunswick offer some form of medical travel assistance to residents. However, government travel programs vary in availability and resourcing across Canada, which, in turn, can contribute to uneven access (Mathews & Ryan, 2017). The Government of Canada administers the Non-Insured Health Benefits Program for First Nations and Inuit patients; travel costs, as well as living expenses incurred by a patient (and an escort for minors under some circumstances) when travelling for medical care unavailable locally, are included in the coverage (GC, 2019b). In addition to financial costs, however, medical travel can also remove patients from their cultural or community supports.

Pan-Canadian programs and frameworks can mitigate uneven access to therapies

The Workshop Participants suggested that a pan-Canadian approach could be considered to resolve challenges relating to differences in the outcome and timing of reimbursement decisions across provinces and territories, which negatively affect the ability for patients to access therapies. In 2000, two expensive therapies for Fabry disease, a rare genetic disease, received market authorization but were not included in public formularies, and were therefore only accessible through clinical trials or compassionate care programs (CCOHTA, 2005; Embrett & Mackinnon, 2012). The provincial and federal governments created the Canadian Fabry Disease Initiative (CFDI) as a means of collecting data to compare the outcomes of the two therapies through a longitudinal clinical research study (Sirrs *et al.*, 2010). The launch of the CFDI was accompanied by the introduction of a three-year cost-sharing agreement between the manufacturers, and the federal and provincial governments. Embrett and Mackinnon (2012) found that the CFDI

suffered from a number of flaws, notably in attempting to solve a public reimbursement challenge under the guise of a research study.

The Panel does not endorse the specific design of the initiative as such, but points to the fact that the CFDI produced a national database and tested a cost-sharing agreement between the federal government and the provinces for the treatment of a rare disease, marking the first implementation of a coordinated provincial-federal framework for granting access to an expensive rare disease therapy in Canada (Embrett & Mackinnon, 2012). Revisiting the lessons learned from CFDI could better prepare decision-makers for a near future where expensive gene therapies for rare diseases become more common, requiring difficult choices and innovative approaches for reimbursement (Chapter 5).

4.2 Manufacturing and Provisioning Capacity

4.2.1 Challenges

The provision of many gene therapies is more complex than that of typical drugs, often requiring the manufacture of components for both the drug and its delivery, as well as skilled personnel for its administration. Therapies that involve direct injection of a therapeutic agent (*in vivo*) will generally have fewer manufacturing challenges, as compared to more logistically complex (*ex vivo*) engineered-cell therapies (Bak *et al.*, 2019). For example, *in vivo* antisense oligonucleotide-based therapies are manufactured similarly to traditional drugs, whereas *ex vivo* CAR T-cell therapies require cell collection, selection, modification, expansion, and harvesting (Iyer *et al.*, 2018; Bak *et al.*, 2019). The manufacturing complexity of gene therapies is accompanied by regulatory oversight for safety. Different jurisdictions have different regulatory frameworks for manufacturing, and actors seeking to commercialize gene therapies must manage uncertainty and risk vis-à-vis the regulatory environment, particularly for *ex vivo* therapies (Galli & Serabian, 2015; Isasi *et al.*, 2016).

Viral vector production is a key bottleneck in the provision of gene therapies at scale

Gene therapies relying on the use of viral vectors comprise a large proportion of therapies in the current development pipeline (Ginn *et al.*, 2018). Among the many components that comprise gene therapies, the Panel, Workshop Participants, and supporting literature have identified the cost and inefficiencies of large-scale production of viral vectors as a bottleneck impacting the capacity to manufacture gene therapy components at scale (Merten *et al.*, 2016; Masri *et al.*, 2019). Viral vectors must be expressed in sufficient quantity to deliver a dose of the

therapeutic agent to patient cells; required quantities can vary drastically depending on the disease being treated (Masri *et al.*, 2019). For instance, the necessary amount of viral vector required for treating retinal diseases may be as much as eight orders of magnitude smaller than what is needed to treat neuromuscular disorders (e.g., Duchenne muscular dystrophy) due to vast differences in the amount and nature of tissue affected by the disease (Masri *et al.*, 2019).

Canada requires more HQP to scale up the provision of gene therapies

The Workshop Participants identified a lack of HQP capacity in Canada for the manufacturing and administration of gene therapies. CAR T-cell therapies in particular require HQP trained in a number of specialized skills (Buechner *et al.*, 2018). At present, specialized staff who possess the necessary expertise to manipulate and handle gene therapies are trained in academic research laboratory environments with small-scale manufacturing capabilities (Digiusto *et al.*, 2018). Based on their experience developing a GMP facility in an Italian public hospital, Vigano *et al.* (2017) argue that personnel with academic backgrounds possess biomedical expertise, but require additional training to take on important roles such as quality control specialists in a production setting. Hospital-based manufacturing of *ex vivo* gene therapies will require GMP-trained staff in sufficient quantity, and will also demand new roles within the hospital and strong coordination among healthcare professionals (Vigano *et al.*, 2017; Elverum & Whitman, 2019).

There is no available evidence to quantify the current number of HQP in Canada who are suitably trained to manufacture gene therapies. However, a 2019 survey of 55 U.K. companies active in gene therapy found that these companies anticipate a substantial need for people skilled in process development and quality-related roles by 2024, and that academic training is not producing industry-ready graduates (CGT Catapult, 2019a). This signals a need for professionals specifically trained in GMP to support the growth of a gene therapy industry.

4.2.2 Promising Approaches

Growth in manufacturing capacity will be essential as the range and application of gene therapies expand

An increasing number of manufacturing facilities suitable for the large-scale production of viral vectors and other gene therapy components, which follow GMP processes, exist in the Canadian academic, non-profit, and private domains. For example, in 2018 the Toronto-based Centre for Commercialization of Regenerative Medicine (CCRM) launched a 1,900 m^2 manufacturing facility for research and

early-phase clinical trials in cell and gene therapies (CCRM, 2018). A consortium between CCRM and private partners is set to further increase capacity for producing viral vectors at commercial scales, with support from the Next Generation Manufacturing Canada (NGen) Supercluster (CCRM, 2020). CellCAN is a knowledge mobilization network for regenerative medicine with several participating universities and research hospitals across the country (CellCAN, n.d.). Overall, this network represents 4,500 m^2 of additional cleanroom capacity that could be applied to the production of viral vectors (CellCAN, 2015, n.d.). The Cell Culture Pilot Plant at the NRC provides an additional 175 m^2 footprint of laboratory facilities that can be used for viral vector production (NRC, 2016).

The infrastructure listed above is not used exclusively for viral vector production at present, and is dedicated to other activities in the regenerative medicine sector. However, the total capacity in Canada (approximately 7,000 m^2) compares favourably to that which can be found in other jurisdictions active in the development of gene therapy. For example, the U.K. Cell and Gene Therapy Catapult initiative (a large-scale public-private partnership, P3) lists approximately 8,000 m^2 of manufacturing space available at its partner institutions, of which nearly half is located in the public or non-profit domain and therefore comparable to the Canadian examples above[13] (CGT Catapult, 2019b). The Panel emphasizes that manufacturing capacity is an area of strength for Canada, but could benefit from increased coordination among actors (explored below). Doing so could lay a path towards commercial-scale manufacture, providing reliable viral vector supply for the development and clinical use of gene therapies.

Networks of stakeholders can enhance capacity by taking advantage of shared priorities and complementary strengths

Opportunities for greater coordination among existing stakeholders was a recurring theme during the workshop. In other jurisdictions, innovation clusters focusing on technologies such as gene therapies have emerged, enabling partnerships that take advantage of existing infrastructure to address barriers associated with commercialization and clinical adoption. In addition to the Catapult program, the United Kingdom has also developed a network of Advanced Therapies Treatment Centres (ATTC). The ATTC network brings together partners from the public, educational, and private sectors to take on issues associated with the research, development, and adoption of advanced therapies (ATTC, 2020a). The centres are based in three locations with expertise offered by local partners, allowing each ATTC to focus on different solutions in manufacturing, scale-up,

13 Canadian manufacturing capacity in the private sector is not well described in publicly available literature, and was therefore not examined by the Panel for this report.

and delivery for gene therapies and other advanced therapy products (ATTC, 2020b, 2020c, 2020d).

In France, a geographically consolidated approach has been taken in the form of a large biocluster, Genopole. Genopole groups healthcare, educational, and manufacturing facilities together to form an innovation centre for biotechnology and genomics (Genopole, n.d.-a). Development and production of gene therapies is one of the focus areas for this cluster, which hosts a manufacturing centre for gene therapies that will offer 13,000 m^2 (or twice the existing capacity in Canada) of space by 2021 for clinical trials and commercial production (Généthon, 2016). These international examples provide manufacturing space to promote supply, and environments where universities, hospitals, start-ups, and industry can partner together to solve problems along the development pathway for gene therapies.

Training programs can address the deficit of HQP

Training initiatives outside of academic research environments are multiplying. In Canada, participating institutions in the CellCAN network have trained 250 people in GMP since 2014; CCRM hosts a range of workshops and conferences; BioCanRx offers an HQP training program consisting of several initiatives targeting individuals at all experience levels; and the Stem Cell Network offers training programs geared towards training over 3,000 additional HQP (SCN, 2019b; CCRM, 2020; CellCAN, 2020; BioCanRx, n.d.).

Internationally, the Advanced Therapies Apprenticeship Community was founded to foster skills development within the Cell and Gene Therapy Catapult and its partners across the United Kingdom (ATAC, n.d.). This program places participants in immersive traineeships ranging from one to five years in length, geared towards different levels of experience, in order to meet the industry-reported demand for HQP (CGT Catapult, 2019a, n.d.). In France, Genopole has partnered with a technical college to offer a training program for HQP (Genopole, n.d.-b). In addition to training HQP to industry-readiness levels in GMP, both of these international examples also act to strengthen existing partnerships nationally within the gene therapy ecosystem, which was identified during the workshop as crucial for ensuring continued Canadian success in this field.

4.3 Innovation and Intellectual Property

4.3.1 Challenges

Many opportunities exist for Canadian companies to advance innovation along the value chain of gene therapy development, with the promise of (i) economic benefits associated with selling a novel therapy in a global market; and, (ii) improved domestic supply and production of gene therapies. Canadian innovators face challenges such as scale-up, access to capital, and the potential for foreign acquisition, which diverts domestic IP outside of Canada (CCA, 2018). The IP landscape is an additional challenge for gene therapy development. For example, international players control critical gene therapy IP in areas of R&D and manufacturing, which can directly affect the viability of commercializing new therapies in Canada.

Broad patents on gene therapy technologies pose barriers to market entry

There is an extensive history surrounding patenting in genetic research. The question of patenting a gene was raised in the 1970s in the United States, concerning (among other candidates) the gene that encodes insulin (Cook-Deegan, 2008). It was recognized early on that patents on genes and genetic technologies impact the development of therapeutics, diagnostics, and scientific research (Cook-Deegan, 2008). These significant ramifications have resulted in ongoing debates and developments surrounding the patentability of genes to this day (Nicol *et al.*, 2019).

This history, combined with recent technological advances, has implications for gene therapies; IP that is important for the future development of gene therapies may be protected by numerous existing patents, or patents possessing a broad scope, both of which can limit competition and create commercialization barriers (Contreras & Sherkow, 2017; Sherkow, 2017b). For example, the CRISPR gene editing tool is not yet the basis of any commercial gene therapies, but it has the potential to target a broad number of diseases (Ledford, 2020). CRISPR was originally investigated by multiple distinct groups of researchers, some of whom filed patents and have since become embroiled in a protracted conflict regarding ownership of the IP and the ability to negotiate licensing agreements for commercial applications (Cohen, 2019). Despite this ongoing high-stakes IP dispute, the institutions holding the patents have entered into licensing agreements with commercial entities, for instance Editas Medicine was granted the exclusive right to develop human therapeutics using CRISPR from one of these institutions (UC Berkeley, 2013; President and Fellows of Harvard College *et al.*, 2014). CRISPR, moreover, is also a tool that can be combined with other technology

used in gene therapy, such that other prominent actors in the field may also wish to benefit from exclusivity to develop specific types of human therapeutics. For example, by entering into a partnership with Editas Medicine, Juno Therapeutics has obtained the exclusive rights to develop the subset of therapies where CRISPR is used to modify immune cells for CAR T-cell therapy, itself a broadly applicable technique due to the number of cancers it can target (Editas Medicine Inc., 2015; Picanco-Castro *et al.*, 2019).

Similar attempts at broad IP protection have recently occurred with CAR T-cell therapy in the E.U. A patent, held by Novartis, entitled "Use of chimeric antigen receptor modified T-cells to treat cancer," was challenged by Public Eye and Doctors of the World for promoting a monopoly over the use of CAR T-cell therapies to treat cancer (Doctors of the World, 2019a). The case against Novartis stated that the patent was overly broad, lacking in novelty, and effectively acted to extend the protection afforded to Kymriah through earlier patents (Doctors of the World, 2019a; Vial, 2019). In December 2019, Novartis retracted the patent before the legal proceedings of the opposition began (Doctors of the World, 2019a; Public Eye, 2019). While Kymriah remains protected by other patents in the E.U., the retraction clears the way for public hospitals to manufacture their own off-patent form of CAR T-cell therapy (Public Eye, 2019).

Broad patents may have additional problematic implications for access and affordability of gene therapies. Contreras and Sherkow (2017) argue that, from a practical standpoint, it is not realistic to think that either the patent owners or their surrogates would possess the resources to investigate all possible therapeutic applications of a technology. Moreover, given the numerous targets for CAR T-cell therapy, it is also unrealistic to expect one entity to develop all possible CRISPR-based CAR T-cell therapies.

IP complexity discourages new entrants in the gene therapy industry

Several components of gene therapies are subject to patents, including manufacturing processes, delivery methods, and aspects of research and development such as clinical trial data (Lexchin, 2019; Picanco-Castro *et al.*, 2019, 2020). This contributes to a complex IP landscape, and it may be challenging to identify which IP might be involved in a new therapy, as well as who owns it (Kaemmerer, 2018). Jurisdictional differences further contribute to this complexity for elements linked to gene therapies, as patent-granting decisions and the delineation of what is patentable can vary across borders (Garden & Winickoff, 2018; Nicol *et al.*, 2019).

In addition to CRISPR and CAR T-cell therapy, patents have been filed or issued for more specific elements of gene therapy, such as the genetic material contained in

therapeutic products, mechanisms of action, as well as methods and vectors for delivery (Kaemmerer, 2018; Jürgens & Clarke, 2019). Derivative patents act to cover small modifications to inventions or uses of techniques (Collier, 2013). These allow for the patenting of improvements on the original technology, thus extending market exclusivity to reinforce commercial advantage, but also delaying the emergence of unpatented versions of therapies (Cloney, 2016; Sherkow, 2017a). As with generic drugs, unpatented therapies could exert downwards pressure on costs through increased competition, provided they reach the Canadian market (PMPRB, 2019a).

The breadth and growing number of patents within the gene therapy IP domain are accompanied by licensing and cooperation agreements among patent owners; these define which entities are permitted to exploit given pieces of IP (Contreras & Sherkow, 2017; Sherkow, 2017a; Picanco-Castro *et al.*, 2019). Disentangling the resulting network of patents to identify the owners of IP and negotiate licence agreements demands time, but is necessary for the deployment of new gene therapies (Kaemmerer, 2018); should new players ignore or be unaware of existing IP, they face the risk of litigation over patent infringement (Gallini & Hollis, 2019). This acts as a potential barrier in developing new products, particularly for researchers at small and medium-sized enterprises (SMEs) and academics in Canada, who may have less familiarity with — and fewer resources to devote to dealing with — IP issues and litigation (Isasi *et al.*, 2016; Gallini & Hollis, 2019). Smaller entities or researchers in Canada may instead be incentivized to sell the ownership of their IP rather than securing partners, investors, and managers in response to the complex and dynamic IP landscape (Gallini & Hollis, 2019).

4.3.2 Promising Approaches

The Panel and Workshop Participants concurred that the IP capacity in Canada required to navigate the gene therapy landscape is insufficient within academic and research institutions, and pointed to the growth of IP capacity as an important area of future development. To increase Canadian IP capacity, the federal government recently launched an initiative to provide education and legal advice to innovators, including researchers and SMEs (GC, 2019a). A federal IP strategy of this type has not previously been attempted, and while not directly related to gene therapy, it could mitigate the challenges outlined above by building capacity to define IP strategy, negotiate licensing contracts, obtain access to patents, and defend IP in lawsuits (Gallini & Hollis, 2019).

Including reasonable-pricing clauses in technology transfer agreements between public laboratories and the private sector could reduce prices

Public funds play an important role in the discovery and development of gene therapies (e.g., CRISPR, CAR T-cell). However, the public may not benefit from the resulting IP once it has been acquired by private interests. In 1989, the NIH attempted to address this issue for all types of technology transfer, including drug development, mandating that reasonable-pricing clauses be required in all agreements. This requirement was removed in 1995 as a result of lobbying by industry groups (Brody, 1996). Reasonable-pricing clauses have, nevertheless, recently been applied to the marketing of gene therapies in France, where a charity focused on gene therapy development for rare diseases (Généthon) owns patents for Zolgensma (onasemnogene abeparvovec), which is needed to commercialize a gene therapy for spinal muscular atrophy (Love, 2019). Généthon included a reasonable-pricing clause in the licensing agreement with its commercial partner. The resulting effect on the price of the therapy in that jurisdiction is not yet known, but in principle the clause could provide leverage toward lowering the current list price of US$2.1M (Love, 2019).

Facing the IP challenge will require creative approaches to managing patents, and the creation of partnerships

Several strategies have been proposed to address bottlenecks in the development of new gene therapies resulting from broad patents. Contreras and Sherkow (2017) argue that IP pertaining to CRISPR should be assigned on the basis of specific areas of the genome, and that the entities currently disputing the ownership of the original IP should accept cross-licensing agreements with other institutions. In contrast to exclusive licensing, these agreements allow owners and licensees to share and exchange IP.

Horn (2017), meanwhile, suggests the creation of *patent pools*, whereby multiple pieces of IP are combined, such that a licensee may obtain access to a greater share of IP through a single licensing agreement, rather than require multiple licensing agreements with (potentially) multiple entities. This approach has been adopted by one of the two innovators of CRISPR for research applications outside of human therapeutics (e.g., plants, animals), and represents an approach for addressing CRISPR's complex IP networks, as well as other areas where access to multiple patents may be challenging (Gallini & Hollis, 2019; Langreth, 2019).

P3s between industry and the academic or public sectors have also been identified as a means to establish mutually beneficial IP sharing agreements and to overcome barriers associated with IP, particularly at precompetitive stages while research and development are ongoing (Garden & Winickoff, 2018). Several

examples of P3s geared towards fair access to vaccines for infectious diseases already exist (OECD, 2015). At present, examples of P3s do exist in the CAR T-cell therapy sphere, namely identifying therapy targets and making innovations in manufacturing (Bubela *et al.*, 2017).

Open-science approaches would circumvent the IP process entirely. Current open-science initiatives in Canada include non-profit organizations such as M4K Pharma and the Structural Genomics Consortium, which are investigating therapeutics for rare childhood diseases and drug discovery, respectively (M4K Pharma, n.d.; SGC, n.d.).

On a more fundamental level, some have questioned whether it is appropriate to patent foundational pieces of gene therapy, or to grant unrestricted exclusivity in IP development (Cook-Deegan, 2018; Feeney *et al.*, 2018). For example, a central criticism in the patent opposition to Kymriah in the E.U. was that it represented a *medical procedure* and not a *product* (Doctors of the World, 2019b). Similar questions have been raised regarding the patentability of CAR T-cell therapies overall, also representing them as medical procedures (Abinader & Contreras, 2019).

5

Value and Affordability

Chapter Findings

- Assessing the economic value of gene therapies is key to informed decision-making, owing to their high cost, uncertainty about long-term safety and durability, and patient demand.
- The stark trade-offs inherent in allocating finite healthcare budgets have led to debate on the circumstances under which resources should be directed toward gene therapies and other relatively high-cost treatments. This debate underscores the conflicting ethical values that inform public decision-making about which drugs to fund.
- Even when gene therapies are deemed to be of sufficient value, public payers may have difficulties covering the costs. Innovative payment arrangements and alternative provision models could alleviate these challenges.

This chapter considers current challenges and promising approaches to assessing the economic value of gene therapies and to funding them sustainably in Canada's public healthcare systems, where resources are limited. It also explores the ethical and moral principles, or values, that are implicated in economic value assessment.

5.1 Value Assessment

5.1.1 Challenges

The prices of gene therapies approved in Canada, the United States, and Europe to date often run in the hundreds of thousands of dollars, and can be significantly higher factoring in the additional costs of administering treatment, hospital stays, travel, prolonged accommodation near a hospital, and aftercare (Cowling & Jones, 2018; HC, 2019k, 2019l). Unmet patient needs combined with the hype and promise surrounding gene therapies can create considerable public pressure to fund these treatments despite the high prices (Kaemmerer, 2018; Mukherjee, 2019; The Guardian, 2019). Value assessment can provide clarity for public payers in this context.

The value of a drug is generally understood on a comparative basis. As Claxton *et al.* (2008) describe it, "[e]stablishing the value of a drug requires an assessment of whether the additional health expected to be gained from its use exceeds the health forgone as other . . . treatments are displaced by its additional cost." The

estimated cost of achieving a gain in one year of perfect health through the intervention (termed the *cost per QALY*, or quality-adjusted life year) is a common metric used to compare the cost-effectiveness of different drugs[14] (Jaswal, 2013). The QALY captures the extent to which a drug reduces suffering and illness, and postpones death (Claxton & Culyer, 2008).

The valuation of drugs in Canada is complex, involving multiple decision factors and several actors

In Canada, the value of new drugs, including gene therapies, is assessed first as part of the HTAs conducted by CADTH and INESSS, and second by public payers (often jointly through the pCPA (Section 2.3.3)). In both instances, the cost-effectiveness (represented by the cost per QALY) forms the basis of this valuation and is then supplemented by many other considerations. In the case of CADTH,[15] the CDR expert review committee's recommendations are supported by the following information:

> *Input from patients and caregivers; clinical and economic evidence; input from clinical experts; existing treatment options (e.g., what is or is not reimbursed and who is covered for reimbursement); the submitted price of the drug under review and the publicly available prices of comparators; the sponsor's requested reimbursement conditions (if any) and the evidence supporting those conditions; and, implementation considerations at the jurisdictional level.*
>
> CADTH, 2020a

A reimbursement recommendation is issued in cases where the drug offers "comparable or added clinical benefit and acceptable cost/cost-effectiveness relative to one or more appropriate comparators;" when the cost/cost-effectiveness is not acceptable but the clinical benefit is, then a recommendation for reimbursement under the condition of a lower price could be issued (CADTH, 2020a).

The pCPA uses the results of the HTA in its confidential price negotiations, and may consider additional elements of value such as international pricing, availability of treatment alternatives, and jurisdictional needs (pCPA, 2019). Budgetary impacts and affordability are also considered by the pCPA in its analysis (pCPA, 2019). Ultimately, each payer decides on its own listing decision based on the CADTH recommendations, the prices negotiated by the pCPA, and the drug plan's mandate, budget, and priorities (CADTH, 2020a). There is substantial

14 This approach is not without controversy. Reliance on QALYs and the ethical implications of this approach have been the topic of extensive debate (e.g., Harris, 2005; Quigley, 2007; Claxton and Culyer, 2008).

15 This discussion focuses on CADTH, but the process and considerations applied by INESSS are similar (see Section 2.3.2 for a discussion of the two HTA bodies).

alignment between CADTH's recommendations and final listing decisions (Allen *et al.*, 2016; CADTH, 2019a).

In Canada, on an ongoing basis, the PMPRB exercises an additional layer of scrutiny, reviewing prices charged for patented drugs to ensure they are not excessive (PMPRB, 2019b). Recent amendments to the *Patented Medicines Regulations* are expected to put more attention on the value for new drugs with a high cost per patient or that are expected to occupy a large market size (PMPRB, 2020c).[16] As part of these amendments, the PMPRB will list an explicit cost per QALY threshold. Cost per QALY thresholds can be used to indicate the opportunity cost of displacing existing spending (essentially, the point at which money could achieve greater health gains if spent elsewhere in the system) (McCabe *et al.*, 2008). Final guidelines will be established by January 1, 2021 when the amendments are expected to come into force (PMPRB, 2020b). These changes are already the subject of two court challenges, therefore time is needed to understand the full impact of these new rules (Grant, 2019b).

The complexity of gene therapies calls for some tailoring of the existing approach to valuation

Gene therapies will be subject to the analyses and reviews described above, but there is some tailoring already taking place in recognition of uncertainty, budgetary impacts, and the potential for higher costs of rare disease therapies. Gene therapies are still new and questions remain about the durability of treatment as well as long-term health risks relating to late side-effects of the treatment and disease itself. These uncertainties stem from the recent market introduction of gene therapies and the design of clinical trials (Section 3.2.1). As such, the cost per QALY estimates that form the basis of value assessment can be highly uncertain, with this uncertainty growing in later years (Marsden *et al.*, 2017).

CADTH has provisions for issuing recommendations for reimbursement with conditions when the new therapy addresses a "significant unmet need" (e.g., a rare condition for which there is no alternative treatment). In these instances, recommendations can be issued despite uncertainty surrounding clinical benefit, due to smaller sample sizes available for clinical trials, shorter study durations, or other factors (CADTH, 2020a). CADTH's new tailored review process for gene therapies aligns with the CDR's approach to economic analysis, with additional consideration given to budgetary impacts on a pan-Canadian scale (CADTH, 2020b).

16 In practice, value is expected to be further scrutinized when the 12-month treatment cost for a drug exceeds 150% of Canada's GDP per capita or when the estimated or actual revenues exceed a threshold (proposed at $50M) (PMPRB, 2020c). See GC (2019g) and PMPRB (2020c) for more details.

The PMPRB's threshold for high cost and/or large market-size therapies is proposed at $150,000 per QALY for most drugs, but up to $200,000 per QALY for therapies that are the first effective treatment for an illness (PMPRB, 2020c).[17] Beyond cost-effectiveness, the PMPRB considers other elements in its assessment of value, including list prices in comparator countries (PMPRB, 2020c). This may justify higher prices for gene therapies given the demonstrated willingness of payers to cover rare disease therapies elsewhere (Garrison *et al.*, 2019).

Differing value conceptions can yield conflicting assessments of the merits of publicly funding particular gene therapies

Patients, payers, clinicians, and industry may have varying concepts of value, underpinned by different ethical principles. Procedural justice in the allocation of resources is an important element of ethical decision-making; transparency, articulation of rationales, appeals mechanisms, and oversight are key elements for ensuring fairness and legitimacy (Daniels & Sabin, 1997; Stafinski *et al.*, 2011). Issues of distributive justice are particularly salient, as additional spending on one group of patients may take resources away from another group of patients. Orphan drugs illustrate differing value principles in public funding discussions especially well (Box 5.1). Beyond the life expectancy and quality of life offered by a drug, many other elements of value have been proposed, including rarity of the condition treated, availability of alternative therapies, closeness to end of life, novelty, curative nature of treatment, societal impacts, and severity of illness (Paulden *et al.*, 2015). Many of these additional factors are relevant to the gene therapies approved to date (Sinclair *et al.*, 2018).

Box 5.1 Ethical Values at Stake with Orphan Drugs

Orphan drugs are designed to treat serious rare conditions and, as such, may be perceived to have less market potential, which can reduce research support and spending for these treatments in the absence of additional incentives (McCormick *et al.*, 2018). Paulden *et al.* (2015) identify three ethical values that are often invoked in discussions about orphan drug funding: the rule of rescue, the equity principle, and the rights-based approach. Each has different implications for decision-making.

(Continues)

17 For a discussion of factors used in setting, adjusting, and applying thresholds, see Paulden *et al.* (2016).

(Continued)

- The rule of rescue favours spending on drugs to treat identifiable patients with more severe illnesses.
- The equity principle treats all units of health gain equally across the population, assesses drugs based on their opportunity costs, and chooses whether or not to fund them on the basis of cost-effectiveness analysis.
- The rights-based approach encourages decision-makers to work to provide a minimum level of healthcare across the population; thus, drugs that treat a condition for which few alternatives exist would be more highly valued.

These three approaches may conflict, illustrating the complex and longstanding debates that underlie healthcare resource distribution decisions generally, and high-cost technologies in particular (Mooney, 1989; Rawles, 1989; Beauchamp & Childress, 2009).

Current debates about amendments to the PMPRB's process exemplify these tensions. The positions advanced by various groups illustrate differing priorities and conflicting notions of value. Payers have voiced general support for PMPRB reforms, although Ontario and Quebec have expressed concerns about potential impacts beyond their respective healthcare budgets (e.g., delays in access) (GC, 2019g; Martell & Lampert, 2019). Patentees and patient groups have voiced significant opposition to these changes, with some suggesting these developments marginalize rare disease treatments and may even deter high-cost drugs (including gene therapies) from entering the Canadian market (Crowe, 2018; GC, 2019g; CORD, 2020). Some evidence shows that companies tend to pursue earlier launches in countries with higher pricing norms (Kyle, 2007; Danzon & Epstein, 2012; Vogler *et al.*, 2018). However, pricing is not the sole determining factor: PMPRB analysis shows that several comparator countries saw a greater share of new approved medicines on the market than Canada did, despite lower average list prices (PMPRB, 2018, 2020a).

Inevitably, decision-makers face trade-offs between maximizing total health gains and recognizing additional considerations such as severity of illness and availability of treatment alternatives. Choices about how to balance these ethical trade-offs can be informed by societal values (Paulden *et al.*, 2015). Some empirical evidence suggests there is public support for funding more expensive treatments for severe illnesses and those lacking alternative treatments (Mentzakis *et al.*, 2011; Pandey *et al.*, 2018). However, studies in multiple jurisdictions find little widespread support for funding more expensive treatments based on disease

prevalence or closeness to end of life, and only conditional support for funding in order to encourage innovation (Desser *et al.*, 2010; Mentzakis *et al.*, 2011; Linley & Hughes, 2013). McCabe *et al.* (2008) caution that, within fixed budgets, decision-makers should not lose sight of the "character of the claims of the anonymous bearers of the opportunity cost" when funding treatments with lower cost-effectiveness. In other words, while it is conceptually easier to grasp the potential gains for those who access these treatments, the losses incurred by other patients who do not have access to these healthcare resources should be considered.

Decisions about gene therapies to date indicate that public payers in Canada do assign additional worth to these drugs. CADTH's reviews of Kymriah, Yescarta, and Spinraza recommended coverage on the condition of price reductions (CADTH, 2019g, 2019h, 2019i). Based on CADTH's analysis, even if the price of Spinraza were reduced by 95%, it would not reach a threshold of $150,000 per QALY, or the approximate threshold proposed in the new PMPRB guidelines for most high-cost medicines (CADTH, 2019f). For the approved CAR T-cell therapies, CADTH found that price reductions of roughly 35% and 25% would be required for Yescarta and Kymriah respectively to reach a $150,000 per QALY threshold[18] (CADTH, 2019b, 2019d). While the final negotiated prices are unknown, Kymriah and Spinraza have subsequently received funding by multiple Canadian public payers (Grant, 2019a; Novartis, 2019a).

The PMPRB's updated review process includes grandfathering provisions and thus will not immediately impact the three gene therapies approved in Canada to date (PMPRB, 2020c). However, this updated process is likely to be important for gene therapies going forward. In its analysis of the likely impact of these regulatory changes, the Government of Canada notes that gene therapies are among the treatments most susceptible to the risk of excessive pricing "since they have few, if any, competitive substitutes and demand for new and better treatments among the more severely affected population is very high" (GC, 2019g).

5.1.2 Promising Approaches

Structured value assessments can be designed to reflect societal values, aid decision-making, and enhance transparency on reimbursement decisions

While many elements of value are considered in HTA and payer assessments, there is no public consensus on the weight that should be applied to various considerations. The Panel notes that transparency on how various factors are weighted could improve the consistency of drug reviews and support greater reliance on value-based healthcare decision-making. Additionally, transparency

18 For treatment of diffuse large B-cell lymphoma. The costs for Kymriah when used to treat ALL are already in line with accepted thresholds (CADTH, 2019c).

could offer greater clarity on how funding decisions are made and thereby help manage patient and sponsor expectations about future public funding of therapies under development.

Ideally, a more systematic approach to weighting various factors would be underpinned by enhanced understanding of Canadian societal values as they relate to healthcare decision-making (Drummond & Towse, 2014). Paulden *et al.* (2015) propose a framework where value is expressed as a weighted function of the decision factors deemed to be relevant to a given decision-maker. Decision-makers could use this framework to compare the value of a new drug with the value of other drug spending that would be displaced. The authors further suggest that such a framework could be used to support policy discussions and enhance transparency on reimbursement decisions (Paulden *et al.*, 2015).

The PMPRB's measures to establish cost per QALY thresholds for drugs could improve transparency and consistency, but its actual results will only be visible after some years of implementation.

Performance-based agreements between public payers and manufacturers can share risks associated with the uncertainties inherent in gene therapy valuations

Risk-sharing agreements like those reviewed by Adamski *et al.* (2010) have been developed to address the relatively high uncertainty about the value and long-term safety risks associated with gene therapies, and were identified by Workshop Participants as a promising model. Outcomes contracting could be established wherein payment for a drug is based on its effectiveness (GC, 2019d). Annuity payments would see a manufacturer receive a yearly payment for each year that the patient remains free of the disease, allowing that manufacturer to carry the risk while preserving the ability to be compensated for the full value (Jørgensen & Kefalas, 2017). Performance-based agreements generally cover the cost of acquiring a gene therapy, but the considerable costs of care (e.g., pre-treatment preparation, post-treatment interventions, hospital stays) are still incurred by the payer (Jørgensen *et al.*, 2020).

Challenges associated with such risk-sharing proposals include collecting evidence on outcomes, reaching agreement on contractual terms defining "success" in the treatment, and reluctance on the part of manufacturers to take on this additional liability without control over prescribing and use (Garrison *et al.*, 2015; Hampson *et al.*, 2017). These arrangements may be effective when the following conditions are met: clinical data are trusted and can be collected and made available to participating parties; outcomes can be attributed to the gene therapy rather than a broader group of treatment approaches; patients are advocating for access; few alternatives exist; therapies are costly; and the manufacturer and payer view the

value of the intervention differently and/or have different risk tolerances (McCabe *et al.*, 2009; Garrison *et al.*, 2013, 2015).

These models are already being deployed for some gene therapies, and recent experiences in Europe suggest interest is growing (Jørgensen *et al.*, 2020). Outcomes-based reimbursements were negotiated for Kymriah and Yescarta in Germany, Italy, and Spain (Jørgensen *et al.*, 2020). In the United States, Novartis is withholding billing for Kymriah until one month following treatment and is only charging for successful treatments (Salzman *et al.*, 2018). Italy reimburses Strimvelis but the government is entitled to a full refund when the treatment is not successful (Regalado, 2016b). Outcomes contracting addresses uncertainties surrounding the early effectiveness of a therapy but, unlike annuity payments, does not mitigate risks associated with durability of treatment (Jørgensen & Kefalas, 2017).

5.2 Affordability

5.2.1 Challenges

Despite high prices, some gene therapies may be more cost-effective than current treatments due to their large therapeutic potential. Or, even with a high cost per QALY, they may be deemed to be of sufficient value based on other considerations. This raises the question of how to pay for gene therapies.

Public payers may struggle to secure the resources required to fund gene therapies

A combination of high costs and the large number of gene therapies in the approval pipeline could place a significant financial burden on Canadian public payers in years to come. Concerns about the sustainability of financing new gene therapies are particularly salient when they are used as a last line of treatment (e.g., Kymriah, Yescarta) and thus represent additional spending. CADTH's economic appraisals of Kymriah and Yescarta (both CAR T-cell therapies) suggest a cumulative budget impact of over $500M over the first three years of deployment of these two therapies across Canada (CADTH, 2019b, 2019c, 2019d). For perspective, on an annual basis this would represent about 1% of the 2019 overall public prescribed drug spending of $15B (CIHI, 2019). Based on the list prices of current CAR T-cell therapies, should such a therapy emerge for a more prevalent form of cancer, the cost implications would be significant.

The one-time payment that is characteristic of some gene therapies accentuates affordability challenges. When a drug is prescribed over time, there is a built-in connection between payments and outcomes, and an option for a prescription to be terminated if it ceases to be effective. This is the case for Spinraza (BioGen

Canada, 2018). However, other gene therapies, including Kymriah and Yescarta, are administered in a single dose or for a short period of time (Novartis, 2018; Kite Pharma Inc., 2019). When gene therapies are administered in this manner, a one-time payment is made up front despite uncertainty about the duration of the drug's effect and potential long-term safety risks (and associated additional healthcare spending).

Patients may turn to private means when gene therapies are not publicly funded, potentially heightening inequalities in access

There is a history of gene therapies receiving regulatory approval only to be denied coverage in public drug plans. Four gene therapies approved for the E.U. market were all subsequently withdrawn due to lack of funding (see Section 5.2.2 for a discussion of one such therapy, Glybera) (Shukla *et al.*, 2019). When drugs are not covered, patients may turn to private means, or appeal to government or the manufacturer for exceptional access.

The prospect of unfunded gene therapies could contribute to disparities in health outcomes. It would favour groups with the resources to fund research and buy access to high-priced therapies not available in the public payer system (Levin, 2016). Beyond individual out-of-pocket purchases, crowd-funding platforms such as GoFundMe are raising resources to develop or purchase access to expensive medical treatments (White, 2019). In Canada, this has included two campaigns for infants with spinal muscular atrophy to access Zolgensma (White, 2019). Reliance on crowdsourcing raises its own set of ethical questions (Snyder, 2017). Does it exacerbate existing inequalities by favouring campaigns conducted by those with wider networks, better marketing skills, or fluency in the dominant language, for example? And does it obscure issues of justice in public healthcare coverage?

Many manufacturers offer patient assistance programs to help with payment for therapies. AveXis, the producer of Zolgensma, is administering a lottery to provide up to 100 doses free of charge. This initiative has been criticized by patient groups for pitting patients against one another, sensationalizing the issue, and failing to allocate the therapy based on clinical criteria (Murphy, 2020; TreatSMA, 2020). Reliance on random decision processes that ignore principles of justice have been criticized as "capricious and unfair" (Beauchamp & Childress, 2009). However, in the face of scarcity, and when medical gains are expected to be the same across patients, fairness considerations may favour a lottery or other random selection (Waring, 2004; Beauchamp & Childress, 2009). To date, lotteries have not been used widely to guide healthcare resource allocation by policy-makers in Canada or abroad.

Initial listing decisions may be overturned by advocacy and political involvement. Some recent experiences suggest that the risk of decision reversal may be

particularly relevant for high-cost gene therapies. CADTH has recommended reimbursement of Spinraza for a subset of spinal muscular atrophy patients, but patient groups have asked provinces to expand coverage (CADTH, 2019g; Grant, 2019a). These requests have met with variable success, resulting in significant differences in treatment access across Canada (Grant, 2019a). When gene therapies are not included in Canadian public payer plans, patients can often apply to these plans to consider requests for funding treatments on a case-by-case basis. In some instances, these programs can facilitate access to high-cost therapies for rare and life-threatening conditions. However, they typically provide funding on a temporary basis, and the procedural transparency is variable (Menon *et al.*, 2015). Prior to CAR T-cell therapy being made available in Canada, the Nova Scotia provincial health authority first denied a resident funding to access that therapy in the United States, but later reversed the decision following extensive media coverage and a social media campaign (Fraser, 2019; The Guardian, 2019). By further codifying decision criteria, the new PMPRB rules may go some way to reduce political involvement in these contentious decisions.

5.2.2 Promising Approaches

The PMPRB amendments (Section 5.1.1) are expected to constrain the costs of drugs and result in $8.8B in savings to payers (GC, 2019g). Additional cost-containment measures can be applied to individual high-cost drugs to help address the affordability challenge.

Additional controls can protect healthcare budgets as high-cost therapies are funded

One option for managing healthcare budgets is to include an additional layer of review for new drugs that are expected to exceed some spending threshold. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has introduced a rule wherein new therapies expected to exceed a threshold of £20M in annual spending in any of the first three years would trigger enhanced scrutiny, price negotiations, and the potential for restricted access (NICE, 2017). However, this kind of approach requires careful design, as it can disadvantage one-off treatments with high up-front costs and lead to sub-optimal access (Jørgensen & Kefalas, 2017).

Payers may also choose to explore innovative purchase agreements to constrain spending. Price caps and volume caps limit expenditures to an agreed upon total number of annual payments or treatment courses — after that point, additional treatments are cost-free (Hanna *et al.*, 2018). Price-volume agreements ratchet down prices in a step-wise manner at various purchase thresholds (Hanna *et al.*, 2018). Subscription models are another option, where a plan pays a fixed annual

fee for unlimited access to a drug. In the United States, subscriptions have already been established for hepatitis C medication (where insurers have struggled to absorb costs) and have been proposed as an option for gene therapies (Gottlieb, 2019; Trusheim & Bach, 2019).

Special criteria and dedicated funds can carve out resources for supporting high-cost therapies

The need for special policies for rare disease therapies is contingent on social support for considering these cases as *special* (Drummond & Towse, 2014). Existing research carried out in Canada, as well as other jurisdictions, suggests there is public support for special treatment in cases where there is severe illness and a lack of treatment options, but not for special treatment only on the basis of rarity (Mentzakis *et al.*, 2011; Pandey *et al.*, 2018). In practice, characteristics of rarity, genetic bases of disease, high-cost therapies, severity of disease, and a lack of alternative therapies may overlap (Boycott & Ardigó, 2018).

The Government of Canada is developing a strategy for improving access to therapies for rare diseases as it works towards implementation of national pharmacare (GC, 2019e). Budget 2019 announced the federal government would provide funding, starting in 2022-2023, of up to $1B over two years to improve access to high-cost drugs for rare diseases, with the potential for ongoing annual $500M funding after that time (GC, 2019f).

Any policy to provide special funding consideration to a subset of therapies requires careful design. International experiences with orphan drug[19] policies illustrate some of the challenges that can arise. Drummond and Towse (2014) summarize the frustration on all sides:

> *The payers for health care find that, because of their high prices, most orphan drugs do not justify funding based on cost-effectiveness, but payers often face political problems if they fail to give approval for funding. Manufacturers, having responded to the incentives for research embodied in orphan drug legislation, find that reimbursement is sometimes not approved for the therapies once developed. Consequently, patients find that, even if therapy is available for their rare condition, access to care is sometimes restricted.*

In some instances, the incentives created by such policies may allow producers to drive up prices to rates incommensurate with development costs, making orphan drugs more profitable than drugs being used more widely (Drummond & Towse, 2014; Hollis, 2019). Alternatively, orphan designation may be sought as a first step

19 See Box 5.1 for a definition of *orphan drugs*.

before wider indications may be added, potentially at the established (high) price (Côté & Keating, 2012). Workshop Participants cautioned against a direct legislative equivalent to the model used in the United States, the *Orphan Drug Act*. That Act has favoured advancements in oncology drugs and drugs for the least rare diseases, while some common diseases have been subdivided in order for drugs to qualify as orphan (Herder, 2013). Workshop Participants suggested that national guidelines or programs relating to funding and HTA present a more favourable strategy.

Orphan drugs could potentially be evaluated based on a set of criteria including rarity, severity of disease, and alternative treatment options, alongside business considerations such as the number of potential indications, extent of research investment, and complexity of production (Hughes-Wilson *et al.*, 2012). Nicod *et al.* (2019) underscore the need to recognize the specific circumstances associated with each drug, and that drugs used for multiple indications or repurposed drugs may not warrant the same level of special treatment.

Alternative provision models are emerging in response to market conditions

The federal government funds a significant share of upstream research. By one estimate, public funding for medical research in Canada in 2011 was $2.5B, representing 58% of overall medical research funding (Moses *et al.*, 2015). The Canadian Institutes of Health Research alone invests roughly $1B in health research annually (CIHR, 2019). Greater stewardship of public research investments is one means to reduce costs of therapies. The case of Généthon, described in Section 4.3.2, shows a similar approach, albeit from a not-for-profit perspective rather than government. AveXis, which markets Zolgensma for spinal muscular atrophy, licenses essential patents from a French charity and agreed to a clause stipulating the therapy would be made available in France at a price that would not pose an obstacle to access (Love, 2019). Rather than selling patents developed in government or government-funded academic contexts, licensing agreements could extend public influence over pricing for made-in-Canada therapies.

The merits of stewardship of public investments has been raised in the context of Glybera, a gene therapy to treat lipoprotein lipase deficiency (LPLD) first developed by researchers at the University of British Columbia (Crowe, 2019). In 2012, the gene therapy (by then licensed to uniQure) was given a five-year market authorization by the E.U. for the treatment of monogenic LPLD (EMA, 2017). With a US$1.4M price tag, it was only paid for in one instance by German private health insurer DAK-Gesundheit, which payed roughly US$1M (Regalado, 2016a). UniQure chose not to reapply for market authorization in 2017 for commercial reasons

(Hampson *et al.*, 2017). In 2019, the NRC announced plans to re-engineer Glybera, motivated in part by the relatively high prevalence of LPLD in Quebec's Saguenay region (Crowe, 2019). The re-engineered gene therapy being developed by NRC will rely on different viral vectors, so existing patents are not expected to be a barrier. The aim is to establish manufacturing capacity in the public sector to improve the affordability of this new therapy and other potential gene therapies (Crowe, 2019).

Moving to not-for-profit development and provision models for gene therapies was identified as a potential strategy to increase affordability by Workshop Participants. Canada's history with Connaught Laboratories shows a precedent for this enhanced non-profit role. Originating at the University of Toronto, Connaught was founded in 1917 in an effort to make an affordable diphtheria vaccine widely available (Callwood, 1955). The laboratory was funded through research grants and revenues that were then reinvested in further research. The lab played an important domestic and global role in vaccine development, insulin development, and the eradication of smallpox, and had a track record for bringing products to market at relatively low prices (Callwood, 1955; Rutty, n.d.).

Social entrepreneurship models are also emerging, wherein companies seek to deliver social rather than private returns (Dees, 2001). Gene therapies for rare diseases may not be developed by commercial interests if they are not seen as profitable. This was the case for a prospective therapy developed for Usher syndrome, a rare disease with a prevalence estimated to be as high as 1 in 6,000 individuals in the United States (Kimberling *et al.*, 2010). The therapy was not seen as commercially viable, and spurred the creation of U.S.-based Odylia Therapeutics, a non-profit biotech company that works to bring therapies to the clinic without commercial consideration (Odylia Therapeutics, 2018). Odylia Therapeutics is focused on treatments for rare retinal diseases and is looking to establish economies of scale in the resources, expertise, and clinical trials required to bring these therapies to the clinic (Savage, 2018).

Philanthropic undertakings could also play a role in providing affordable access to gene therapies. The Bill & Melinda Gates Foundation recently announced a US$100M investment in research to develop inexpensive gene therapies for sickle-cell anemia and HIV for global deployment as part of a collaboration with the NIH, which plans to invest the same amount (NIH, 2019a). The research will focus on "the development of curative therapies that can be delivered safely, effectively and affordably in low-resource settings" (NIH, 2019a).

6

Findings and Reflections

Three gene therapies are currently approved for use in Canada, and many more are in the pipeline. The complexity, variability, uncertainty, and promise surrounding gene therapies are considerable, and these factors complicate efforts to manage access and affordability. This report situates current and potential future therapies within the context of Canadian healthcare, identifying the ways in which gene therapies either pose unique problems, or exacerbate existing problems, in the approval and use of drugs. It additionally describes promising approaches for addressing these challenges. Because gene therapies are in the early stage of deployment, there is less evidence on the adoption and use of these promising approaches than for other drugs and therapies. Examples, however, are emerging as various jurisdictions explore ways to ensure timely market authorization decisions, and fair and affordable access.

6.1 Main Findings

The diversity of gene therapies requires a flexible and tailored approach to addressing access and affordability challenges

Gene therapies can be understood across a number of dimensions, including disease treated, mechanism of action, mode of administration, and delivery tool, each of which has implications for regulatory review, pricing, manufacturing, and provision. Therapies may have different profiles in terms of manufacturing complexity, risks of complications, availability of treatment alternatives, and so forth.

The current process for drug approval and reimbursement is challenged by some gene therapies. The nature of some therapies and diseases may make clinical trials difficult; existing regulatory pathways may discourage innovation in approved gene therapies; and some gene therapies apply to severe diseases that lack alternative treatments, potentially calling for special consideration in their valuation. Flexibility in policies relating to regulation, administration, and reimbursement can help accommodate this variability and facilitate the commercialization and adoption of gene therapies. New regulatory pathways, patient registries, and rare disease funds are emerging to manage these issues.

Risk-based purchasing agreements and post-market surveillance could mitigate the significant clinical and economic uncertainties associated with approved gene therapies

There is uncertainty about the durability and long-term safety of gene therapies owing to their novelty and the short length of clinical trials. Regulators, HTA bodies, and public drug plans will need to make decisions in the absence of

information on the long-term safety and durability of gene therapies. Performance-based agreements can be used to reduce risks borne by drug purchasers by tying payments to patient outcomes. Post-market surveillance, including RWE, can be used to gather and analyze data on safety and efficacy over time and, with the appropriate reassessment mechanisms in place, can allow for regulators, HTA bodies, and public drug plans to update their decisions as lessons emerge.

High prices, complex provision, and the nature of diseases treated by gene therapies exacerbate existing inequities in healthcare access

The prices of gene therapies in Canada, the United States, and Europe generally run in the hundreds of thousands of dollars, and can be significantly higher when factoring in additional costs such as travel, hospital stays, and aftercare. Within Canada, public coverage may vary across provinces and territories based on considerations of affordability and jurisdictional priorities. Gene therapies tend to be made available at large hospitals in urban centres owing to the expertise and infrastructure needed to administer some treatments, as well as the potential for complex adverse reactions. Patients outside of these areas will face barriers to access; they will need to travel for care, and sometimes be away from home or work for extended periods. Additionally, patients with rare diseases may face further access challenges relating to the diagnoses and funding of high-cost therapies.

Different conceptions of value may lead to disagreement over the merits of publicly funding individual gene therapies

Public drug plans may be forced to choose between maximizing health gains at the population level and funding relatively high-cost gene therapies based on additional considerations such as severity of illness and availability of treatment alternatives. The trade-offs inherent in allocating scarce healthcare resources are the subject of longstanding and extensive ethical debates. Research into societal values suggests that there is support for funding more expensive therapies for severe illnesses or in the absence of alternative treatments. Transparent value assessments could shed light on how public drug plans balance these considerations, improving consistency and managing patient and industry expectations.

Pan-Canadian coordination could control spending and improve access to gene therapies

The pCPA and PMPRB both play roles in managing drug prices in Canada. The former negotiates drug prices on behalf of multiple public payers, while the latter ensures the prices of patented medicines are not excessive. The development of national pharmacare could consolidate regulatory reviews, HTA, and negotiations. This has the potential to reduce the time required for drugs to move through the review process, and support equal access across provinces and territories through a national formulary. Even in the absence of national pharmacare, provinces, territories, and the federal government could coordinate access to expensive drugs through common principles and approaches. Collaborative efforts that pool capacity and expertise can be used to build evidence, share lessons, develop talent, and ultimately scale up manufacturing and delivery.

Stewardship of public investments in gene therapy research could alleviate challenges associated with commercialization and high drug prices

Public spending on health research is considerable, but commercial players tend to take ownership of innovations as new drugs advance toward the market. The intellectual property associated with publicly funded research is typically transferred at this point. Leasing rather than selling patents and negotiating reasonable-pricing clauses have been suggested as ways to create additional public benefit from research investments. Public manufacture and commercialization of gene therapies have also been proposed as a way to manage prices and protect public investments. This could allow for greater public influence over the prices of new gene therapies.

6.2 Panel Reflections

The Panel notes that there are two types of challenges to the deployment of gene therapies: those intrinsic to the Canadian context, and those that arise through the global development of gene therapies. Many of the intrinsic challenges involved in getting novel drugs to patients — complex, multi-actor decision-making processes, budgetary pressures, commercialization challenges — are exacerbated for gene therapies due to their high cost and complexity, but are not unique. As such, confronting the access and affordability challenges posed by gene therapies can serve as a valuable test case for other challenges in Canada's healthcare systems. Extrinsic challenges — which include evolving global research and intellectual property regimes, and the changing regulatory landscape of gene therapies — arise when decisions made outside Canada impact the accessibility and affordability of gene therapies within Canada.

Other countries are grappling with many of the same challenges, and much can be learned from approaches being tested and implemented abroad.

Emerging solutions can draw on existing Canadian strengths. The capacity to manufacture gene therapy components can be built on and improved as production ramps up to support provision across Canada. Additionally, the principle of universal accessibility set out in the *Canada Health Act* could help motivate the development of novel models that aim to provide these life-changing therapies to patients at reasonable prices. However, as pan-Canadian principles and approaches are contemplated, jurisdictions should be mindful of the potential for access to be inadvertently constrained through the adoption of lowered common standards. Broad-scale solutions will require participation from all stakeholders, from the bench to the bedside and beyond. This can be supported through the translation of existing strengths in Canadian discovery research into sustainable global companies based in Canada with sufficient access to capital and local manufacturing capabilities.

From an economic perspective, successfully overcoming the challenges outlined in this report could allow Canada to position itself at the forefront of gene therapy commercialization. By building a landscape in which public laboratories, SMEs, and larger commercial players can develop novel and affordable therapies within an effective regulatory framework, Canada will be well positioned to compete globally in this market. Skills development is an important component of success; in addition to training HQP in the manufacture and provision of gene therapies, complementary skills in the domain of IP law and drug price negotiations could enhance Canada's position.

Gene therapies are just beginning to be available in Canada, and the evidence on how best to overcome access and affordability challenges is limited. It will be important to document lessons as new models and emerging solutions are applied in various contexts. The Panel would like to emphasize that discoveries in this field continue to multiply. What constitutes the technological state-of-the-art is in rapid evolution, and may advance through developments in, for example, non-viral vector delivery or improvements in automated manufacturing solutions. This rapidly shifting landscape further justifies the importance of ongoing proactive approaches to tailoring research, oversight, and funding.

References

Abinader, L. G. & Contreras, J. L. (2019). The patentability of genetic therapies: CAR-T and medical treatment exclusions around the world. *American University International Law Review, 34*(4), 705-762.

Abou-El-Enein, M., Grainger, D. W., & Kili, S. (2018). Registry contributions to strengthen cell and gene therapeutic evidence. *Molecular Therapy, 26*(5), 1172-1176.

Abou-El-Enein, M. & Hey, S. P. (2019). Cell and gene therapy trials: Are we facing an 'evidence crisis'? *EClinicalMedicine, 7*, 13-14.

Adamski, J., Godman, B., Ofierska-Sujkowska, G., Osińska, B., Herholz, H., Wendykowska, K., . . . Gustafsson, L. L. (2010). Risk sharing arrangements for pharmaceuticals: Potential considerations and recommendations for European payers. *BMC Health Services Research, 10*(1), 153.

Addison, C. (2017). Spliced: Boundary-work and the establishment of human gene therapy. *BioSocieties, 12*(2), 257-281.

Aiuti, A., Roncarolo, M. G., & Naldini, L. (2017). Gene therapy for ADA-SCID, the first marketing approval of an ex vivo gene therapy in Europe: Paving the road for the next generation of advanced therapy medicinal products. *EMBO Molecular Medicine, 9*(6), 737-740.

Allan, D. S. & Dubé, I. D. (1996). Symposium highlights: Future prospects for gene therapy. *Transfusion Science, 17*(1), 203-205.

Allen, N., Walker, S., Liberti, L., Sehgal, C., & Salek, S. (2016). Evaluating alignment between Canadian Common Drug Review reimbursement recommendations and provincial drug plan listing decisions: An exploratory study. *CMAJ Open, 4*, E674-E678.

Anderson, W. F. & Fletcher, J. C. (1980). Gene therapy in human beings: When is it ethical to begin? *New England Journal of Medicine, 303*(22), 1293-1297.

ASGCT (American Society of Gene & Cell Therapy). (2019a). Gene Therapy Basics. Retrieved April 2019, from https://www.asgct.org/education/gene-therapy-basics.

ASGCT (American Society of Gene & Cell Therapy). (2019b). Different Approaches. Retrieved April 2019, from https://www.asgct.org/education/different-approaches.

ATAC (Advanced Therapies Apprenticeship Community). (n.d.). Upskilling: The Key to Scaling-Up. Retrieved March 2020, from https://www.advancedtherapiesapprenticeships.co.uk/about/.

ATTC (Advanced Therapy Treatment Centres). (2020a). About us. Retrieved January 2020, from https://www.theattcnetwork.co.uk/about.

ATTC (Advanced Therapy Treatment Centres). (2020b). Midlands and Wales Advanced Therapies Treatment Centre – Activity. Retrieved January 2020, from https://www.theattcnetwork.co.uk/centres/midlands-wales/activity.

ATTC (Advanced Therapy Treatment Centres). (2020c). Northern Alliance Advanced Therapies Treatment Centre – Activity. Retrieved January 2020, from https://www.theattcnetwork.co.uk/centres/northern-alliance/activity.

ATTC (Advanced Therapy Treatment Centres). (2020d). iMATCH (Innovate Manchester Advanced Therapy Centre Hub) – Activity. Retrieved January 2020, from https://www.theattcnetwork.co.uk/centres/imatch/activity.

Bak, A., Friis, K. P., Wu, Y., & Ho, R. J. (2019). Translating cell and gene biopharmaceutical products for health and market impact. Product scaling from clinical to marketplace: Lessons learned and future outlook. *Journal of Pharmaceutical Sciences, 108*(10), 3169-3175.

Baker, D. B., Knoppers, B. M., Phillips, M., van Enckevort, D., Kaufmann, P., Lochmuller, H., & Taruscio, D. (2018). Privacy-preserving linkage of genomic and clinical data sets. *IEEE/ACM Transactions on Computational Biology and Bioinformatics, 16*(4), 1342-1348.

Baylis, F. (2019). *Altered Inheritance: CRISPR and the Ethics of Human Genome Editing*. Cambridge (MA): Harvard University Press.

BCCRHI (British Columbia Children's Hospital Research Institute). (n.d.). Silent Genomes Project. Retrieved February 2020, from https://www.bcchr.ca/silent-genomes-project.

Beauchamp, T. L. & Childress, J. F. (2009). *Principles of Biomedical Ethics. Sixth Edition*. New York (NY): Oxford University Press.

Beutler, E. (2001). The Cline affair. *Molecular Therapy, 4*(5), 396-397.

BioCanRx. (n.d.). HQP Training Program. Retrieved June 2020, from https://biocanrx.com/training/hqp-training-program.

BioGen Canada. (2018). *Product Monograph Including Patient Medication Information: Spinraza*. Mississauga (ON): Biogen Canada Inc.

Bladen, C. L., Rafferty, K., Straub, V., Monges, S., Moresco, A., Dawkins, H., . . . Lochmüller, H. (2013). The TREAT-NMD Duchenne Muscular Dystrophy registries: Conception, design, and utilization by industry and academia. *Human Mutation, 34*(11), 1449-1457.

Blaese, R. M., Culver, K. W., Miller, A. D., Carter, C. S., Fleisher, T., Clerici, M., . . . Anderson, W. F. (1995). T lymphocyte-directed gene therapy for ADA- SCID: Initial trial results after 4 years. *Science, 270*(5235), 475-480.

Boudes, P. F. (2014). Gene therapy as a new treatment option for inherited monogenic diseases. *European Journal of Internal Medicine, 25*(1), 31-36.

Boycott, K., Hartley, T., Adam, S., Bernier, F., Chong, K., Fernandez, B. A., . . . Armour, C. M. (2015). The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. *Journal of Medical Genetics, 52*(7), 431-437.

Boycott, K. M., Rath, A., Chong, J. X., Hartley, T., Alkuraya, F. S., Baynam, G., . . . Lochmüller, H. (2017). International cooperation to enable the diagnosis of all rare genetic diseases. *The American Journal of Human Genetics, 100*(5), 695-705.

Boycott, K. M. & Ardigó, D. (2018). Addressing challenges in the diagnosis and treatment of rare genetic diseases. *Nature Reviews Drug Discovery, 17*(3), 151-152.

Brody, B. (1996). Public good and fair prices: Balancing technological innovation with social well-being. *Hastings Center Report, 26*(2), 5–12.

Bubela, T., McCabe, C., Archibald, P., Atkins, H., Bradshaw, S. E., Kefalas, P., . . . Viswanathan, S. (2015). Bringing regenerative medicines to the clinic: The future for regulation and reimbursement. *Regenerative Medicine, 10*(7), 897-911.

Bubela, T., Bonter, K., Lachance, S., Delisle, J.-S., & Gold, E. R. (2017). More haste, less speed: Could public-private partnerships advance cellular immunotherapies? *Frontiers in medicine, 4*, 1-10.

Buechner, J., Grupp, S. A., Maude, S. L., Boyer, M., Bittencourt, H., Laetsch, T. W., . . . Rives, S. (2017). Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with Relapsed/Refractory (R/R) Acute Lymphoblastic Leukemia (ALL): Update to the interim analysis. *Clinical Lymphoma Myeloma and Leukemia, 17*, S263-S264.

Buechner, J., Kersten, M. J., Fuchs, M., Salmon, F., & Jäger, U. (2018). Chimeric antigen receptor-T Cell therapy: Practical considerations for implementation in Europe. *HemaSphere, 2*(1), e18.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2018a). *Gene Therapy: An Overview of Approved and Pipeline Technologies*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2018b). CADTH Drug Portfolio Information Session. Retrieved April 2020, from https://www.cadth.ca/sites/default/files/pdf/Drug%20Portfolio%20Info%20Sess%20FINAL%20-%20Nov%201%202018.pdf.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019a). *2018-2019 at a Glance*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019b). *Tisagenlecleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019c). *Tisagenlecleucel for Acute Lymphoblastic Leukemia: Economic Review Report*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019d). *Axicabtagene Ciloleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019e). *Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma: Ethics and Implementation Report*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019f). *CADTH Common Drug Review Pharmacoeconomic Review Report (Resubmission) Nusinersen (Spinraza)*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019g). *CADTH Common Drug Review - CADTH Canadian Drug Expert Committee Recommendation - Nusinersen (Spinraza - Biogen Canada Inc.)*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019h). *Optimal Use Report. Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Clinical Report*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019i). *Optimal Use Report. Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma: Recommendations*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019j). *Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Ethics and Implementation Report*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2019k). *Axicabtagene Ciloleucel for Non-Hodgkin Lymphoma: Implementation and Ethics Project Protocol*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2020a). *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (2020b). *CADTH Review Process for Cell and Gene Therapies*. Ottawa (ON): CADTH.

CADTH (Canadian Agency for Drugs and Technologies in Health). (n.d.). Process in Brief. Retrieved January 2020, from https://www.cadth.ca/about-cadth/what-we-do/products-services/cdr/common-drug-review-submissions/process-in-brief.

CADTH, CAPT, HC, & IHE (Canadian Agency for Drugs and Technologies in Health, Canadian Association for Population Therapeutics, Health Canada, & Institute of Health Economics). (2018). *Defining Decision-Grade Real-World Evidence and its Role in the Canadian Context: A Design Sprint. Summary Report of a Workshop*. Edmonton (AB): IHE.

CADTH, HC, INESSS, & ARCC (Canadian Agency for Drugs and Technologies in Health, Health Canada, Institut national d'excellence en santé et services sociaux, & Canadian Centre for Applied Research in Cancer Control). (2019). *Building the RWE Blueprint: A Coordinated Approach to RWE Use in Pharmaceutical Regulatory and Reimbursement Decisions in Canada*. Paper presented at CADTH Symposium, Edmonton (AB).

Callwood, J. (1955, October 1). The Miracle Factory that Began in a Stable, *Maclean's*.

Carnahan, S. J. (2007). Medicare's coverage with study participation policy: Clinical trials or tribulations? *Yale Journal of Health Policy, Law, and Ethics*, 7(2), 229-272.

Carpenter, D., Kesselheim, A. S., & Joffe, S. (2011). Reputation and precedent in the bevacizumab decision. *New England Journal of Medicine, 365*(2), e3.

Carroll, J. C., Makuwaza, T., Manca, D. P., Sopcak, N., Permaul, J. A., O'Brien, M. A., . . . Grunfeld, E. (2016). Primary care providers' experiences with and perceptions of personalized genomic medicine. *Canadian Family Physician, 62*(10), e626.

Cavazzana-Calvo, M., Thrasher, A., & Mavilio, F. (2004). The future of gene therapy. *Nature, 427*(6977), 779-781.

Cavero-Carbonell, C., Gras-Colomer, E., Guaita-Calatrava, R., López-Briones, C., Amorós, R., Abaitua, I., . . . Zurriaga, O. (2015). Consensus on the criteria needed for creating a rare-disease patient registry. A Delphi study. *Journal of Public Health, 38*(2), e178-e186.

CCA (Council of Canadian Academies). (2018). *Competing in a Global Innovation Economy: The Current State of R&D in Canada*. Ottawa (ON): The Expert Panel on the State of S&T and IR&D in Canada, CCA.

CCO (Cancer Care Ontario). (2019). CAR T-cell Therapy for Pediatric and Young Adults with Relapsed/Refractory B-cell ALL. Retrieved January 2020, from https://www.cancercareontario.ca/sites/ccocancercare/files/assets/FINAL-CAR-T-cell_Therapy_for_Pediatric_and_Young_Adults_with_Relapsed_or_RefractoryB-cell_ALL_Version_1.0-2Dec2019.pdf.

CCO (Cancer Care Ontario). (n.d.). Chimeric Antigen Receptor (CAR) T-cell Therapy Enrolment Process and Forms. Retrieved December 2019, from https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/hematologic/car-t-cell-therapy-enrolment.

CCOHTA (Canadian Coordinating Office for Health Technology Assessment). (2005). *CEDAC Final Recommendation and Reasons for Recommendation: Agalsidase Beta Resubmission*. Ottawa (ON): CCOHTA.

CCRM (Centre for Commercialization of Regenerative Medicine). (2018). Leading-edge Centre for Cell and Vector Production Open for Business. Retrieved December 2019, from https://www.ccrm.ca/sites/default/files/media_room/Media%20Release_CCVP%20launch%20event%20Final_0.pdf.

CCRM (Centre for Commercialization of Regenerative Medicine). (2020). *From Lab to Life – 2019 Annual Report*. Toronto (ON): CCRM.

CCTCC (Canadian Clinical Trials Coordinating Centre). (2019a). Patient Registries Listing. Retrieved October 2019, from http://www.cctcc.ca/our-initiatives/patient-registries-listing/.

CCTCC (Canadian Clinical Trials Coordinating Centre). (2019b). Patient Registries. Retrieved March 2020, from http://www.cctcc.ca/wp-content/uploads/2018/02/CCTAM_Patient-Registries.pdf.

CellCAN (Regenerative Medicine and Cell Therapy Network). (2015). *Going Further - Together. CellCAN Strategic Plan 2015–2020*. Montréal (QC): CellCAN.

CellCAN. (2020). Our Training Offer. Retrieved January 2020, from https://cellcan.com/195/Our_Training____Networking_Offer.cellcan.

CellCAN. (n.d.). *Network Centres and Associated Expertise*. Montréal (QC): CellCAN.

CGT Catapult (Cell and Gene Therapy Catapult). (2019a). *UK Cell and Gene Therapy Skills Demand Report 2019*. London, United Kingdom: CGT Catapult.

CGT Catapult (Cell and Gene Therapy Catapult). (2019b). *Cell and Gene Therapy GMP Manufacturing in the UK – Capability and Capacity Analysis*. London, United Kingdom: CGT Catapult.

CGT Catapult (Cell and Gene Therapy Catapult). (n.d.). *Apprenticeships in Advanced Therapies – Guidance Booklet*. London, United Kingdom: CGT Catapult.

Churchill, L. R., Collins, M. L., King, N. M. R., Pemberton, S. G., & Wailoo, K. A. (1998). Genetic research as therapy: Implications of "gene therapy" for informed consent. *The Journal of Law, Medicine & Ethics, 26*(1), 38-47.

CHUSJ (Centre hospitalier universitaire Sainte-Justine). (2019). Thérapie « CAR T-cell » Hématologie - Oncologie. Retrieved December 2019, from https://www.chusj.org/fr/soins-services/H/Hematologie/therapie-car-t-cell.

CIHI (Canadian Institute for Health Information). (2019). *Prescribed Drug Spending in Canada 2019. A Focus on Public Drug Programs*. Ottawa (ON): CIHI.

CIHR (Canadian Institutes of Health Research). (2019). Funding Overview. Retrieved January 2020, from https://cihr-irsc.gc.ca/e/37788.html.

Claxton, K., Briggs, A., Buxton, M. J., Culyer, A. J., McCabe, C., Walker, S., & Sculpher, M. J. (2008). Value based pricing for NHS drugs: An opportunity not to be missed? *BMJ, 336*(7638), 251.

Claxton, K. & Culyer, A. J. (2008). Not a NICE fallacy: A reply to Dr. Quigley. *Journal of Medical Ethics, 34*(8), 598.

Cloney, R. (2016). Patent law and genome engineering: A short guide to a rapidly changing landscape. *Molecular Therapy, 24*(3), 419-421.

CMSSS (Cabinet de la ministre de la Santé et des Services sociaux). (2019). La Thérapie CAR T-Cell Maintenant Disponible au Québec. Retrieved October 2019, from http://www.fil-information.gouv.qc.ca/Pages/Article.aspx?motsCles=lymphocytes&listeThe=&listeReg=&listeDiff=&type=&dateDebut=2019-06-17&dateFin=2019-12-17&afficherResultats=oui&idArticle=2710082893.

Cohen, J. (2019). CRISPR patent fight revived. *Science, 365*(6448), 15-16.

Collier, R. (2013). Drug patents: The evergreening problem. *Canadian Medical Association Journal 185*(9), E385-E386.

Collins, F. S. & Gottlieb, S. (2018). The next phase of human gene-therapy oversight. *New England Journal of Medicine, 379*(15), 1393-1395.

Contreras, J. L. & Sherkow, J. S. (2017). CRISPR, surrogate licensing, and scientific discovery. *Science, 355*(6326), 698-700.

Cook-Deegan, R. (2008). Gene Patents. In M. Crowley (Ed.), *From Dirth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*. New York (NY): Garrison.

Cook-Deegan, R. (2018). CRISPR patents: Aspiring to coherent patent policy. *The American Journal of Bioethics, 18*(12), 51-54.

Coppens, D. G. M., de Wilde, S., Guchelaar, H. J., De Bruin, M. L., Leufkens, H. G. M., Meij, P., & Hoekman, J. (2018). A decade of marketing approval of gene and cell-based therapies in the United States, European Union and Japan: An evaluation of regulatory decision-making. *Cytotherapy, 20*(6), 769-778.

CORD (Canadian Organization for Rare Disorders). (2015). *Now is the Time: A Strategy for Rare Diseases is a Strategy for all Canadians*. Toronto (ON): CORD.

CORD (Canadian Organization for Rare Disorders). (2018). *Stakeholder Consultation: Supplemental Process for Complex/Specialized Drugs Background Document*. Toronto (ON): CORD.

CORD (Canadian Organization for Rare Disorders). (2020). *CORD Response to the PMPRB Guidelines*. Toronto (ON): CORD.

Cossu, G., Birchall, M., Brown, T., De Coppi, P., Culme-Seymour, E., Gibbon, S., . . . Wilson, J. (2018). Lancet Commission: Stem cells and regenerative medicine. *Lancet, 391*(10123), 883-910.

Côté, A. & Keating, B. (2012). What is wrong with orphan drug policies? *Value in Health, 15*(8), 1185-1191.

Cowling, T. & Jones, S. (Canadian Agency for Drugs and Technologies in Health). (2018). *Gene Therapy: International Regulatory and Health Technology Assessment (HTA) Activities and Reimbursement Status*. Ottawa (ON): CADTH.

Crowe, K. (2018, November 24). Canada has Found the Key to Lowering Drug Prices, but it Won't be Used any Time Soon, *CBC News*.

Crowe, K. (2019, October 17). Canadian Breakthrough that Became the World's Most Expensive Drug, then Vanished, Gets Second Chance, *CBC News*.

Daniels, N. & Sabin, J. (1997). Limits to health care: Fair procedures, democratic deliberation, and the legitimacy problem for insurers. *Philosophy & Public Affairs, 26*(4), 303-350.

Danzon, P. & Epstein, A. (2012). Effects of regulation on drug launch and pricing in interdependent markets. *Advances in Health Economics and Health Services Research, 23*, 35-71.

Dees, J. G. (2001). The Meaning of "Social Entrepreneurship". Retrieved February 2020, from https://entrepreneurship.duke.edu/news-item/the-meaning-of-social-entrepreneurship/.

Desser, A. S., Gyrd-Hansen, D., Olsen, J. A., Grepperud, S., & Kristiansen, I. S. (2010). Societal views on orphan drugs: Cross sectional survey of Norwegians aged 40 to 67. *BMJ, 341*, c4715.

Detela, G. & Lodge, A. (2019). EU regulatory pathways for ATMPs: Standard, accelerated and adaptive pathways to marketing authorisation. *Molecular Therapy - Methods & Clinical Development, 13*, 205-232.

Dhruva, S. S., Ross, J. S., & Desai, N. R. (2018). Real-world evidence: Promise and peril for medical product evaluation. *Pharmacy and Therapeutics, 43*(8), 464-472.

Digiusto, D. L., Melsop, K., Srivastava, R., & Tran, C.-A. T. (2018). Proceedings of the first academic symposium on developing, qualifying and operating a cell and gene therapy manufacturing facility. *Cytotherapy, 20*(12), 1486-1494.

Doctors of the World. (2019a). Novartis Withdraws an Abusive Patent for an Over-Priced Cancer Medication. Retrieved January 2020, from https://www.medecinsdumonde.org/en/news/nos-combats/2019/12/16/novartis-withdraws-abusive-patent-over-priced-cancer-medication.

Doctors of the World. (2019b). *Press Kit – Opposition Against the European Patent Covering Kymriah*. Paris, France: Doctors of the World.

Drummond, M. & Towse, A. (2014). Orphan drugs policies: a suitable case for treatment. *The European Journal of Health Economics, 15*(4), 335-340.

Dunbar, C. E., High, K. A., Joung, J. K., Kohn, D. B., Ozawa, K., & Sadelain, M. (2018). Gene therapy comes of age. *Science, 359*(6372), 1-10.

EBA (European Banking Authority). (2017). *Regulatory Sandboxes: A proposal to EBA by the Banking Stakeholders Group*. London, United Kingdom: European Banking Authority.

Editas Medicine Inc. (2015). Juno Therapeutics and Editas Medicine Announce Exclusive Collaboration to Create Next-Generation CAR T and TCR Cell Therapies. Retrieved May 2020, from https://ir.editasmedicine.com/news-releases/news-release-details/juno-therapeutics-and-editas-medicine-announce-exclusive.

Editorial. (2016). Patient need versus evidence: A balancing act. *Lancet, 388*(10052), 1350.

Elverum, K. & Whitman, M. (2019). Delivering cellular and gene therapies to patients: Solutions for realizing the potential of the next generation of medicine. *Gene Therapy*.

EMA (European Medicines Agency). (2015). *EPAR Summary for the Public: Glybera*. London, United Kingdom: EMA.

EMA (European Medicines Agency). (2016). *Guideline on the Processing of Renewals in the Centralised Procedure*. London, United Kingdom: EMA.

EMA (European Medicines Agency). (2017). *Public Statement: Glybera - Expiry of the Marketing Authorisation in the European Union*. London, United Kingdom: EMA.

EMA (European Medicines Agency). (2018). Exondys (eteplirsen). Retrieved May 2020, from https://www.ema.europa.eu/en/medicines/human/EPAR/exondys.

Embrett, M. & Mackinnon, N. J. (2012). Qualitative evaluation of the Canadian Fabry Disease Initiative. *Canadian Pharmacists Journal, 145*(3), 136-141.e133.

EXCITE International. (2020). What is EXCITE International? Retrieved May 2020, from http://www.exciteinternational.com/site/what-is-excite-international.

FACT (Foundation for the Accreditation of Cellular Therapy). (2020). Search for a FACT Accredited Organization. Retrieved November 2019, from http://accredited.factwebsite.org/?_sft_country=canada.

FDA (Food and Drug Administration). (2011). Proposal to Withdraw Approval for the Breast Cancer Indication for AVASTIN (Bevacizumab). Retrieved May 2020, from https://www.fda.gov/media/82467/download.

FDA (Food and Drug Administration). (2016a). Drug Approval Letter for Eteplirsen. Retrieved May 2020, from https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy.

FDA (Food and Drug Administration). (2016b). FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy. Retrieved May 2020, from https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy.

FDA (Food and Drug Administration). (2017). *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food and Drug Administration Staff*. Silver Spring, MD: US FDA.

FDA (Food and Drug Administration). (2019). Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on New Policies to Advance Development of Safe and Effective Cell and Gene Therapies. Retrieved January 2020, from https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics.

Feeney, O., Cockbain, J., Morrison, M., Diependaele, L., Van Assche, K., & Sterckx, S. (2018). Patenting foundational technologies: Lessons from CRISPR and other core biotechnologies. *The American Journal of Bioethics*, *18*(12), 36-48.

Fletcher, J. C. (1990). Evolution of ethical debate about human gene therapy. *Human Gene Therapy*, *1*(1), 55-68.

Fountzilas, E., Said, R., & Tsimberidou, A. M. (2018). Expanded access to investigational drugs: Balancing patient safety with potential therapeutic benefits. *Expert Opinion on Investigational Drugs*, 27(2), 155-162.

Fraser, L. (2019, May 3). N.S. Man's Stage 4 Cancer is in Remission After $900K Treatment in Boston, *CBC News*.

Friedmann, T. & Roblin, R. (1972). Gene therapy for human genetic disease? *Science*, 175(4025), 949.

Friedmann, T. (1992). A brief history of gene therapy. *Nature Genetics*, 2(2), 93-98.

Fritsche, E., Elsallab, M., Schaden, M., Hey, S. P., & Abou-El-Enein, M. (2019). Post-marketing safety and efficacy surveillance of cell and gene therapies in the EU: A critical review. *Cell & Gene Therapy Insights*, 5(11), 1505–1521.

Galli, M. C. & Serabian, M. (2015). *Regulatory Aspects of Gene Therapy and Cell Therapy Products: A Global Perspective*. Cham, Switzerland: Springer International Publishing.

Gallini, N. & Hollis, A. (2019). *To Sell or Scale Up: Canada's Patent Strategy in a Knowledge Economy*. Montréal (QC): Institute for Research on Public Policy.

Garden, H. & Winickoff, D. (2018). *Gene Editing for Advanced Therapies: Governance, Policy and Society*. Paris, France: Organisation for Economic Co-operation and Development (OECD) Publishing.

Garrison, L. P., Jackson, T., Paul, D., & Kenston, M. (2019). Value-based pricing for emerging gene therapies: The economic case for a higher cost-effectiveness threshold. *Journal of Managed Care and Specialty Pharmacy, 25*(7), 793-799.

Garrison, L. P., Jr., Towse, A., Briggs, A., de Pouvourville, G., Grueger, J., Mohr, P. E., . . . Sleeper, M. (2013). Performance-based risk-sharing arrangements-good practices for design, implementation, and evaluation: Report of the ISPOR good practices for performance-based risk-sharing arrangements task force. *Value Health, 16*(5), 703-719.

Garrison, L. P., Jr., Carlson, J. J., Bajaj, P. S., Towse, A., Neumann, P. J., Sullivan, S. D., . . . Dubois, R. W. (2015). Private sector risk-sharing agreements in the United States: Trends, barriers, and prospects. *American Journal of Managed Care, 21*(9), 632-640.

GC (Government of Canada). (1985). *Canada Health Act*. Ottawa (ON): Minister of Justice.

GC (Government of Canada). (2019a). Intellectual Property Strategy. Retrieved March 2020, from https://www.ic.gc.ca/eic/site/108.nsf/eng/home.

GC (Government of Canada). (2019b). Non-Insured Health Benefits (NIHB) Medical Transportation Policy Framework (Interim). Retrieved February 2020, from https://www.sac-isc.gc.ca/eng/1579891130443/1579891286837#a6.

GC (Government of Canada). (2019c). *Bill C-97 An Act to Implement Certain Provisions of the Budget Tabled in Parliament on March 19, 2019 and Other Measures*. Ottawa (ON): GC.

GC (Government of Canada). (2019d). *A Prescription for Canada: Achieving Pharmacare for All. Final Report of the Advisory Council on the Implementation of National Pharmacare*. Ottawa (ON): GC.

GC (Government of Canada). (2019e). Moving Forward on Implementing National Pharmacare. Retrieved December 2019, from https://www.budget.gc.ca/2019/docs/themes/pharmacare-assurance-medicaments-en.html.

GC (Government of Canada). (2019f). *Investing in the Middle Class: Budget 2019*. Ottawa (ON): GC.

GC. (2019g). Regulations amending the patented medicines regulations (Additional factors and information reporting requirements): SOR/2019-298. *Canada Gazette, 153*(17).

GC (Government of Canada). (2020). *Food and Drugs Act*. Ottawa (ON): GC.

Généthon. (2016). YposKesi. Retrieved January 2020, from https://www.genethon.fr/en/partnerships/yposkesi/.

Genome Canada. (2019). *Bringing Innovation to Life – Strategic Vision*. Ottawa (ON): Genome Canada.

Genopole. (n.d.-a). The Biocluster. Retrieved March 2020, from https://www.genopole.fr/France-s-leading-biotech-and-biotherapy-cluster.html#.Xl1Ww6hKiUl.

Genopole. (n.d.-b). A Training Facility for Careers in Biotech – The IMT. Retrieved January 2020, from https://www.genopole.fr/A-training-facility-for-careers-in-biotech.html#.Xg90EWRKjIU.

Geyer, M. B. (2019). First CAR to Pass the Road Test: Tisagenlecleucel's Drive to FDA Approval. *Clinical Cancer Research, 25*(4), 1133-1135.

Ginn, S. L., Amaya, A. K., Alexander, I. E., Edelstein, M., & Abedi, M. R. (2018). Gene therapy clinical trials worldwide to 2017: An update. *The Journal of Gene Medicine, 20*(5), e3015.

Gottlieb, S. (2019, May 21). Commentary: We Need to Make Sure New Drug Cures Don't Widen Income Gap for the Poor, *CNBC*.

Grady, D. (2012, December 9). In Girl's Last Hope, Altered Immune Cells Beat Leukemia, *New York Times*.

Grant, K. (2019a, June 13). Ontario Expands Coverage for Spinraza, *The Globe and Mail*.

Grant, K. (2019b, August 23). Pharmaceutical Companies File Constitutional Challenge to Canada's New Drug Price Regulations, *The Globe and Mail*.

Gyawali, B., Hey, S. P., & Kesselheim, A. S. (2019). Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Internal Medicine, 179*(7), 906-913.

Halioua-Haubold, C.-L., Peyer, J. G., Smith, J. A., Arshad, Z., Scholz, M., Brindley, D. A., & MacLaren, R. E. (2017). Regulatory considerations for gene therapy products in the US, EU, and Japan. *The Yale Journal of Biology and Medicine, 90*(4), 683-693.

Hampson, G., Towse, A., Pearson, S. D., Dreitlein, W. B., & Henshall, C. (2017). Gene therapy: Evidence, value and affordability in the US health care system. *Journal of Comparative Effectiveness Research, 7*(1), 15-28.

Hampson, G., Towse, A., Dreitlein, W. B., Henshall, C., & Pearson, S. D. (2018). Real-world evidence for coverage decisions: Opportunities and challenges. *Journal of Comparative Effectiveness Research, 7*(12), 1133-1143.

Hanna, E., Remuzat, C., Auquier, P., & Toumi, M. (2016). Gene therapies development: Slow progress and promising prospect. *Journal of Market Access & Health Policy, 5*(1), 1265293.

Hanna, E., Toumi, M., Dussart, C., Borissov, B., Dabbous, O., Badora, K., & Auquier, P. (2018). Funding breakthrough therapies: A systematic review and recommendation. *Health Policy, 122*(3), 217-229.

Harris, J. (2005). It's not NICE to discriminate. *Journal of Medical Ethics, 31*(7), 373-375.

Harrison, R. P., Ruck, S., Medcalf, N., & Rafiq, Q. A. (2017). Decentralized manufacturing of cell and gene therapies: Overcoming challenges and identifying opportunities. *Cytotherapy, 19*(10), 1140-1151.

HC (Health Canada). (2009). *Priority Review of Drug Submissions Policy*. Ottawa (ON): HC.

HC (Health Canada). (2013). *Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs)*. Ottawa (ON): HC.

HC (Health Canada). (2015). Regulatory Initiative Orphan Drugs for Rare Diseases - Forward Regulatory Plan 2015-2017. Retrieved January 2020, from https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/2015-2017/regulatory-initiative-orphan-drugs-rare-diseases.html.

HC (Health Canada). (2016). *Guidance Document: Notice of Compliance with Conditions (NOC/c)*. Ottawa (ON): HC.

HC (Health Canada). (2018a). *Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation*. Ottawa (ON): HC.

HC (Health Canada). (2018b). Worksharing with Other International Regulatory Agencies. Retrieved April 2020, from https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/worksharing-international-regulatory-authorities.html.

HC (Health Canada). (2018c). *Post-Notice of Compliance (NOC) Changes: Framework Document*. Ottawa (ON): HC.

HC (Health Canada). (2019a). Regulatory Road Map for Biologic (Schedule D) Drugs in Canada. Retrieved June 2019, from https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/regulatory-roadmap-for-biologic-drugs.html.

HC (Health Canada). (2019b). Drug Product Database Online Query. Retrieved November 2019, from https://health-products.canada.ca/dpd-bdpp/index-eng.jsp.

HC (Health Canada). (2019c). Service Standards for Drug Submission Evaluations (Pharmaceuticals and Biologic Products) under the Food and Drug Regulations - Health Canada. Retrieved August 2019, from https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/service-standards-high-volume-regulatory-authorizations/service-standards-drug-submission-evaluations-pharmaceuticals-biologic-products-under-food-drug-regulations.html.

HC (Health Canada). (2019d). Improving the Regulatory Review of Drugs and Devices. Retrieved June 2019, from https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html.

HC (Health Canada). (2019e). Use of Foreign Reviews and Decisions. Retrieved May 2020, from https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/use-of-foreign-reviews-and-decisions.html.

HC (Health Canada). (2019f). *What We Heard: A Summary of Scanning and Consultations on What's Next for Health Product Regulation*. Ottawa (ON): Health Canada.

HC (Health Canada). (2019g). Policy and Program Initiatives and Novel Regulatory Approaches. Retrieved November 2019, from https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/targeted-regulatory-reviews/policy-program-initiatives-novel-regulatory-approaches.html.

HC (Health Canada). (2019h). Regulatory Decision Summary - Spinraza - Health Canada. Retrieved October 2019, from https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00268.

HC (Health Canada). (2019i). *Agile Regulations for Advanced Therapeutic Products and Clinical Trials*. Ottawa (ON): HC.

HC (Health Canada). (2019j). Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making. Retrieved July 2019, from https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html.

HC (Health Canada). (2019k). Regulatory Decision Summary - Kymriah - Health Canada. Retrieved July 2019, from https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00422.

HC (Health Canada). (2019l). Regulatory Decision Summary - Yescarta - Health Canada. Retrieved July 2019, from https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00486.

HC (Health Canada). (2019m). Summary Basis of Decision - Kymriah - Health Canada. Retrieved September 2019, from https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?lang=en&linkID=SBD00416.

HC (Health Canada). (2019n). Summary Basis of Decision - Yescarta - Health Canada. Retrieved September 2019, from https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00442.

HC (Health Canada). (2020). Australia, Canada, Singapore, Switzerland (ACSS) Consortium. Retrieved May 2020, from https://www.canada.ca/en/health-canada/services/drugs-health-products/international-activities/australia-canada-singapore-switzerland-consortium.html.

Herder, M. (2013). When everyone is an orphan: Against adopting a U.S.-styled orphan drug policy in Canada. *Accountability in Research, 20*(4), 227-269.

Herder, M. (2019). Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *The Milbank Quarterly, 97*(3), 820-857.

High, K. A. & Roncarolo, M. G. (2019). Gene therapy. *New England Journal of Medicine, 381*(5), 455-464.

Hollis, A. (2019). Orphan drug pricing and costs: A case study of kalydeco and orkambi. *Healthcare Policy, 15*(1), 70-80.

Horn, L. (2017). Patent pools for CRISPR technology. *Science, 355*(6331), 1274.

Hughes-Wilson, W., Palma, A., Schuurman, A., & Simoens, S. (2012). Paying for the orphan drug system: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? *Orphanet Journal of Rare Diseases*, 7(1), 74.

ICES (formerly known as the Institute for Clinical Evaluative Sciences). (n.d.-a). Privacy at ICES. Retrieved May 2020, from https://www.ices.on.ca/Data-and-Privacy/ICES-data.

ICES (formerly known as the Institute for Clinical Evaluative Sciences). (n.d.-b). ICES Data. Retrieved May 2020, from https://www.ices.on.ca/Data-and-Privacy/ICES-data.

INESSS (Institut national d'excellence en santé et services sociaux). (2018a). *Evaluation of Drugs for Listing Purposes: A Change of Approach*. Québec City (QC): INESSS.

INESSS (Institut national d'excellence en santé et services sociaux). (2018b). *Spinraza - Spinal Muscular Atrophy 5q Type II, Type III and Presymptomatic - Notice Sent to the Minister in December 2018*. Québec City (QC): INESSS.

IOM (Institute of Medicine). (2012). *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*. Washington (DC): The National Academies of Sciences, Engineering, and Medicine.

Isasi, R., Rahimzadeh, V., & Charlebois, K. (2016). Uncertainty and innovation: Understanding the role of cell-based manufacturing facilities in shaping regulatory and commercialization environments. *Applied and Translational Genomics*, *11*, 27-39.

Iyer, R. K., Bowles, P. A., Kim, H., & Dulgar-Tulloch, A. (2018). Industrializing autologous adoptive immunotherapies: Manufacturing advances and challenges. *Frontiers in Medicine*, *5*, 150-150.

Jaswal, A. (2013). *Valuing Health in Canada: Who, How, and How Much?* Ottawa (ON): Canada 2020.

Jecker, N. S., Wightman, A. G., Rosenberg, A. R., & Diekema, D. S. (2017). From protection to entitlement: Selecting research subjects for early phase clinical trials involving breakthrough therapies. *Journal of Medical Ethics*, *43*(6), 391-400.

Jørgensen, J. & Kefalas, P. (2017). Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *Journal of Market Access & Health Policy*, *5*(1), 1355203.

Jørgensen, J., Hanna, E., & Kefalas, P. (2020). Outcomes-based reimbursement for gene therapies in practice: The experience of recently launched CAR-T cell therapies in major European countries. *Journal of Market Access & Health Policy*, *8*(1), 1715536.

Jürgens, B. & Clarke, N. S. (2019). Evolution of CAR T-cell immunotherapy in terms of patenting activity. *Nature Biotechnology*, *37*(4), 370-375.

Kaemmerer, W. F. (2018). How will the field of gene therapy survive its success? *Bioengineering and Translational Medicine*, *3*(2), 166-177.

Kastelein, J. J., Ross, C. J., & Hayden, M. R. (2013). From mutation identification to therapy: Discovery and origins of the first approved gene therapy in the Western world. *Human Gene Therapy*, *24*(5), 472-478.

Kemp, R. & Prasad, V. (2017). Surrogate endpoints in oncology: When are they acceptable for regulatory and clinical decisions, and are they currently overused? *BMC Medicine, 15*(1), 134.

Kesselheim, A. S. & Avorn, J. (2016). Approving a problematic muscular dystrophy drug: Implications for FDA policy. *JAMA, 316*(22), 2357-2358.

Kimberling, W. J., Hildebrand, M. S., Shearer, A. E., Jensen, M. L., Halder, J. A., Trzupek, K., . . . Smith, R. J. H. (2010). Frequency of Usher syndrome in two pediatric populations: Implications for genetic screening of deaf and hard of hearing children. *Genetics in Medicine: Official journal of the American College of Medical Genetics, 12*(8), 512-516.

Kimmelman, J. (2009). *Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation*. Cambridge (MA): Cambridge University Press.

King, N. M. P. & Bishop, C. E. (2017). New treatments for serious conditions: Ethical implications. *Gene Therapy, 24*(9), 534-538.

Kite Pharma Inc. (2019). *Product Monograph Including Patient Medication Information: Yescarta*. Santa Monica (CA): Kite Pharma Inc.

Kochenderfer, J. N., Dudley, M. E., Kassim, S. H., Somerville, R. P. T., Carpenter, R. O., Stetler-Stevenson, M., . . . Rosenberg, S. A. (2015). Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD 19 chimeric antigen receptor. *Journal of Clinical Oncology, 33*(6), 540-549.

Korngut, L., MacKean, G., Casselman, L., Johnston, M., Day, L., Lam, D., . . . Pringsheim, T. (2013). Perspectives on neurological patient registries: A literature review and focus group study. *BMC Medical Research Methodology, 13*, 135.

Kosseim, P. & Chapman, S. (2011). Science and society: Some "made-in-Canada" options for improving integration. *Accountability in Research, 18*(3), 194-216.

Kuehn, B. M. (2017). The Promise and Challenges of CAR-T Gene Therapy. *JAMA, 318*(22), 2167-2169.

Kyle, M. K. (2007). Pharmaceutical price controls and entry strategies. *The Review of Economics and Statistics, 89*(1), 88-99.

Lacaze, P., Millis, N., Fookes, M., Zurynski, Y., Jaffe, A., Bellgard, M., . . . Bittles, A. H. (2017). Rare disease registries: A call to action. *Internal Medicine Journal, 47*(9), 1075-1079.

Langfelder, E. J. & Juengst, E. T. (1993). Ethical, Legal, and Social Implications (ELSI) Program, National Center for Human Genome Research, National Institutes of Health. *Politics and the Life Sciences, 12*(2), 273-275.

Langreth, R. (2019). CRISPR Innovators Make it Easier to Use Their Gene-editing Technology. Retrieved January 2020, from https://www.bloomberg.com/news/articles/2019-07-18/crispr-innovators-create-patent-pool-to-spur-genetic-innovation.

Ledford, H. (2020). Quest to use CRISPR against disease gains ground. *Nature, 577*(7789), 156.

Lee, J. H., Wang, J.-H., Chen, J., Li, F., Edwards, T. L., Hewitt, A. W., & Liu, G.-S. (2019). Gene therapy for visual loss: Opportunities and concerns. *Progress in Retinal and Eye Research, 68*, 31-53.

Levin, A. V. (2016). Ethical considerations in gene therapy. *Ophthalmic Genetics, 37*(3), 249-251.

Lexchin, J. (2019). Increase in drug spending in Canada due to extension of data protection for biologics: A descriptive study. *Health Policy, 14*(3), 10-18.

Linley, W. G. & Hughes, D. A. (2013). Societal views on NICE, Cancer Drugs Fund and value-based pricing criteria for prioritising medicines: A cross-sectional survey of 4118 adults in Great Britain. *Health Economics, 22*(8), 948-964.

Love, J. (2019, September 18). Why Didn't Nonprofits and the NIH Require 'Reasonable' Pricing for Zolgensma? That May Happen in France, *STAT*.

Lundstrom, K. (2018). Viral vectors in gene therapy. *Diseases, 6*(2), 42.

M4K Pharma. (n.d.). About M4K Pharma. Retrieved May 2020, from https://m4kpharma.com/about/.

Ma, S., Li, X., Wang, X., Cheng, L., Li, Z., Zhang, C., . . . Qian, Q. (2019). Current Progress in CAR-T Cell Therapy for Solid Tumors. *International journal of biological sciences, 15*(12), 2548-2560.

Mali, S. (2013). Delivery systems for gene therapy. *Indian Journal of Human Genetics, 19*(1), 3-8.

Marsden, G., Towse, A., Pearson, S. D., Dreitlein, W. B., & Henshall, C. (2017). *Gene Therapy: Understanding the Science, Assessing the Evidence, and Paying for Value*. Boston (MA): Institute for Clinical and Economic Review and Office of Health Economics.

Martell, A. & Lampert, A. (2019, July 30). Exclusive: Two powerful Canadian provinces argued against federal drug price crackdown, *Reuters*.

Masri, F., Cheeseman, E., & Ansorge, S. (2019). Viral vector manufacturing: How to address current and future demands. *Cell and Gene Therapy Insights, 5*(Supplement S[5]), 949-970.

Mathews, M. & Ryan, D. (2017). Publicly funded medical travel subsidy programs in Canada. *Canadian Social Work Review, 34*(1), 123-139.

McCabe, C., Claxton, K., & Culyer, A. (2008). The NICE cost-effectiveness threshold: What it is and what that means. *PharmacoEconomics, 26*, 733-744.

McCabe, C., Bergmann, L., Bosanquet, N., Ellis, M., Enzmann, H., von Euler, M., . . . Zwierzina, H. (2009). Market and patient access to new oncology products in Europe: A current, multidisciplinary perspective. *Annals of Oncology, 20*(3), 403-412.

McCormick, J. I., Berescu, L. D., & Tadros, N. (2018). Common drug review recommendations for orphan drugs in Canada: Basis of recommendations and comparison with similar reviews in Quebec, Australia, Scotland and New Zealand. *Orphanet Journal of Rare Diseases, 13*(1), 27.

McGettigan, P., Alonso Olmo, C., Plueschke, K., Castillon, M., Nogueras Zondag, D., Bahri, P., . . . Mol, P. G. M. (2019). Patient registries: An underused resource for medicines evaluation. *Drug Safety, 42*(11), 1343-1351.

Menon, D., Clark, D., & Stafinski, T. (2015). Reimbursement of drugs for rare diseases through the public healthcare system in Canada: Where are we now? *Healthcare Policy, 11*(1), 15-32.

Mentzakis, E., Stefanowska, P., & Hurley, J. (2011). A discrete choice experiment investigating preferences for funding drugs used to treat orphan diseases: An exploratory study. *Health Economics, Policy and Law, 6*(3), 405-433.

Merten, O.-W., Hebben, M., & Bovolenta, C. (2016). Production of lentiviral vectors. *Molecular Therapy - Methods & Clinical Development, 3*, 1-14.

Milson, B., Thiele, S., Zhang, Y., Dobson-Belaire, W., & Skinner, B. (2016). *Access to New Medicines in Public Drug Plans: Canada and Comparable Countries*. Ottawa (ON): Innovative Medicines Canada.

Mittmann, N. & Knowles, S. (2009). A survey of Pharmacy and Therapeutic committees across Canada: Scope and responsibilities. *Canadian Journal of Clinical Pharmacology, 16*(1), e171-177.

Mooney, G. (1989). QALYs: Are they enough? A health economist's prespective. *Journal of Medical Ethics, 15*, 148-152.

Moses, H., III, Matheson, D. H. M., Cairns-Smith, S., George, B. P., Palisch, C., & Dorsey, E. R. (2015). The anatomy of medical research: US and international comparisons. *Journal of the American Medical Association, 313*(2), 174-189.

Mukherjee, S. (2019, July 15). The Promise and Price of Cellular Therapies, *The New Yorker.*

Murphy, J. (2020, January 30). When a Lottery 'Wins' Sick Babies Life-Saving Drugs, *BBC News*.

NCI (National Cancer Institute). (2019). CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. Retrieved November 2019, from https://www.cancer.gov/about-cancer/treatment/research/car-t-cells.

Ng, D. M., Hooper, A. J., Bellgard, M. I., & Burnett, J. R. (2018). The role of patient registries for rare genetic lipid disorders. *Current Opinion in Lipidology, 29*(2), 156-162.

NICE (National Institute for Health and Care Excellence). (2017). *Technology Appraisal and Highly Specialised Technologies Programmes*. London, United Kingdom: NICE.

Nicod, E., Annemans, L., Bucsics, A., Lee, A., Upadhyaya, S., & Facey, K. (2019). HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries. *Health Policy, 123*(2), 140-151.

Nicol, D., Dreyfuss, R. C., Gold, E. R., Li, W., Liddicoat, J., & Van Overwalle, G. (2019). International divergence in gene patenting. *Annual Review of Genomics and Human Genetics, 20*, 519-541.

NIH (National Institutes of Health). (2019a). NIH Launches new Collaboration to Develop Gene-based Cures for Sickle Cell Disease and HIV on Global Scale. Retrieved December 2019, from https://www.nih.gov/news-events/news-releases/nih-launches-new-collaboration-develop-gene-based-cures-sickle-cell-disease-hiv-global-scale.

NIH (National Institutes of Health). (2019b). How Does Gene Therapy Work? Retrieved November 2019, from https://ghr.nlm.nih.gov/primer/therapy/procedures.

NIH (National Institutes of Health). (n.d.). Somatic Cells. Retrieved September 2019, from https://www.genome.gov/genetics-glossary/Somatic-Cells.

Novartis (Novartis Pharmaceuticals Canada Inc). (2018). *Product Monograph Including Patient Medication Information: Kymriah*. Dorval (QC): Novartis.

Novartis (Novartis Pharmaceuticals Canada Inc.). (2019a). Novartis Completes Certification of Initial Sites in Ontario for First Approved Canadian CAR-T Therapy, Kymriah® (tisagenlecleucel). Retrieved December 2019, from https://www.novartis.ca/en/news/media-releases/novartis-completes-certification-initial-sites-ontario-first-approved-canadian.

Novartis (Novartis Pharmaceuticals Canada Inc.). (2019b). Novartis Completes Certification of Initial Sites in Quebec for First Approved Canadian CAR-T Therapy, Kymriah® (tisagenlecleucel)(i). Retrieved October 2019, from https://www.novartis.ca/en/news/media-releases/novartis-completes-certification-initial-sites-quebec-first-approved-canadian.

NRC (National Research Council). (2016). Cell Culture Pilot Plant. Retrieved March 2020, from https://www.nrc-cnrc.gc.ca/obj/doc/solutions-solutions/facilities-installations/cellculture_pilot_plant_fs_e.pdf.

O'Reilly, M., Shipp, A., Rosenthal, E., Jambou, R., Shih, T., Montgomery, M., . . . Corrigan-Curay, J. (2012). NIH oversight of human gene transfer research involving retroviral, lentiviral, and adeno-associated virus vectors and the role of the NIH recombinant DNA advisory committee. *Methods in Enzymology, 507*, 313-335.

Odylia Therapeutics. (2018). Our Story. Retrieved December 2019, from https://odylia.org/about-odylia/our-story/.

OECD (Organisation for Economic Co-operation and Development). (2015). *Public-private Partnerships in Biomedical Research and Health Innovation for Alzheimer's Disease and other Dementias*. Paris, France: OECD Publishing.

Olmo, C. A., McGettigan, P., & Kurz, X. (2019). Barriers and opportunities for use of patient registries in medicines regulation. *Clinical Pharmacology & Therapeutics, 106*(1), 39-42.

Pacurariu, A., Plueschke, K., McGettigan, P., Morales, D. R., Slattery, J., Vogl, D., . . . Cave, A. (2018). Electronic healthcare databases in Europe: Descriptive analysis of characteristics and potential for use in medicines regulation. *BMJ Open, 8*(9), e023090.

Pandey, H., Paulden, M., & McCabe, C. (2018). *Theoretical Models of the Cost-Effectiveness Threshold, Value Assessment, and Health Care System Sustainability*. Edmonton (AB): Institute of Health Economics.

Paulden, M., Stafinski, T., Menon, D., & McCabe, C. (2015). Value-based reimbursement decisions for orphan drugs: A scoping review and decision framework. *PharmacoEconomics, 33*(3), 255-269.

Paulden, M., O'Mahony, J., & McCabe, C. (2016). Determinants of Change in the Cost-effectiveness Threshold. *Medical Decision Making, 37*(2), 264-276.

PCORI (Patient-Centered Outcomes Research Institute). (2019). Building Data Registries with Privacy and Confidentiality for PCOR. Retrieved May 2020, from https://www.pcori.org/research-results/2014/building-data-registries-privacy-and-confidentiality-pcor.

pCPA (pan-Canadian Pharmaceutical Alliance). (2018). *Brief to House of Commons' Standing Committee on Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders*. Toronto (ON): pCPA.

pCPA (pan-Canadian Pharmaceutical Alliance). (2019). *pCPA Brand Process Guidelines*. Toronto (ON): pCPA.

Pearson, S. D., Dreitlein, W. B., Towse, A., Hampson, G., & Henshall, C. (2018). A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions. *Journal of Comparative Effectiveness Research, 7*(12), 1145-1152.

PHAC (Public Health Agency of Canada). (2018). *Key Health Inequalities in Canada – A National Portrait*. Ottawa (ON): PHAC.

Picanco-Castro, V., Gonçalves Pereira, C., Swiech, K., Ribeiro Malmegrim, K. C., Tadeu Covas, D., & Silveira Porto, G. (2019). Emerging CAR T cell therapies: Clinical landscape and patent technological routes. *Human Vaccines & Immunotherapeutics*, 1-10.

Picanco-Castro, V., Pereira, C. G., Covas, D. T., Porto, G. S., Athanassiadou, A., & Figueiredo, M. L. (2020). Emerging patent landscape for non-viral vectors used for gene therapy. *Nature Biotechnology, 38*(2), 151-157.

PMPRB (Patented Medicine Prices Review Board). (2017). *Alignment Among Public Formularies in Canada*. Ottawa (ON): PMPRB.

PMPRB (Patented Medicine Prices Review Board). (2018). *Patented Medicine Prices Review Board Annual Report 2017*. Ottawa (ON): PMPRB.

PMPRB (Patented Medicine Prices Review Board). (2019a). Biosimilars in Canada - Current Environment and Future Opportunities. Retrieved May 2020, from http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1456&lang=en.

PMPRB (Patented Medicine Prices Review Board). (2019b). About the PMPRB. Retrieved November 2019, from http://pmprb-cepmb.gc.ca/home.

PMPRB (Patented Medicine Prices Review Board). (2020a). *Meds Entry Watch 2018*. Ottawa (ON): PMPRB.

PMPRB (Patented Medicine Prices Review Board). (2020b). Message from the Chairperson – New coming into force date for the Patented Medicines Regulations. Retrieved June 2020, from https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html#cnews.

PMPRB (Patented Medicine Prices Review Board). (2020c). *PMPRB Guidelines 2020*. Ottawa (ON): PMPRB.

Popejoy, A. B. & Fullerton, S. M. (2016). Genomics is failing on diversity. *Nature, 538*, 161-164.

Prakash, V. (2017). Spinraza - a rare disease success story. *Gene Therapy, 24*(497).

President and Fellows of Harvard College, The Broad Institute Inc., & Editas Medicine Inc. (2014). *License Agreement by and Between President and Fellows of Harvard College, the Broad Institute Inc., and Editas Medicine Inc.* Cambridge (MA): President and Fellows of Harvard College, the Broad Institute Inc., and Editas Medicine Inc.

Psaty, B. M., Meslin, E. M., & Breckenridge, A. (2012). A lifecycle approach to the evaluation of FDA approval methods and regulatory actions: Opportunities provided by a new IOM report. *Journal of the American Medical Association, 307*(23), 2491-2492.

Public Eye. (2019). Novartis Drops the Kymriah Patent that was Opposed by Public Eye. Retrieved January 2020, from https://www.publiceye.ch/en/media-corner/press-releases/detail/novartis-drops-the-kymriah-patent-that-was-opposed-by-public-eye.

Quigley, M. (2007). A NICE fallacy. *Journal of Medical Ethics, 33*(8), 465.

Rawles, J. (1989). Castigating QALYs. *Journal of Medical Ethics, 15*, 143-147.

Regalado, A. (2016a, May 4). The World's Most Expensive Medicine Is a Bust, *MIT Technology Review.*

Regalado, A. (2016b, August 9). Gene-Therapy Cure Has Money-Back Guarantee, *MIT Technology Review.*

Rosenbaum, L. (2017). Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy. *New England Journal of Medicine, 377*(14), 1313-1315.

Rutty, C. (n.d.). *Connaught Labs, Smallpox & Stopping "The Speckled Monster".* Toronto (ON): University of Toronto.

Salek, S., Lussier Hoskyn, S., Johns, J. R., Allen, N., & Sehgal, C. (2019). Factors influencing delays in patient access to new medicines in Canada: A retrospective study of reimbursement processes in public drug plans. *Frontiers in Pharmacology, 10*(196).

Salzman, R., Cook, F., Hunt, T., Malech, H. L., Reilly, P., Foss-Campbell, B., & Barrett, D. (2018). Addressing the value of gene therapy and enhancing patient access to transformative treatments. *Molecular Therapy: The Journal of the American Society of Gene Therapy, 26*(12), 2717-2726.

Savage, N. (2018). Special delivery. *Nature, 564*, 518-519.

Schule, S., Renner, M., Longhurst, S., & Narayanan, G. (2010). Regulatory requirements for clinical trial and marketing authorisation application for gene therapy medicinal products. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz, 53*(1), 30-37.

SCN (Stem Cell Network). (2019a). Training. Retrieved December 2019, from https://stemcellnetwork.ca/training/.

SCN (Stem Cell Network). (2019b). Graduate Course in Regenerative Medicine. Retrieved December 2019, from https://stemcellnetwork.ca/training/workshops/graduate-course-in-regenerative-medicine/.

SGC (Structural Genomics Consortium). (n.d.). Mission and Philosophy. Retrieved May 2020, from https://www.thesgc.org/about/what_is_the_sgc.

Sherkow, J. S. (2017a). CRISPR, patents, and the public health. *The Yale Journal of Biology and Medicine, 90*(4), 667-672.

Sherkow, J. S. (2017b). Patent protection for microbial technologies. *FEMS Microbiology Letters, 364*(20).

Shim, G., Kim, D., Park, G. T., Jin, H., Suh, S. K., & Oh, Y. K. (2017). Therapeutic gene editing: Delivery and regulatory perspectives. *Acta Pharmacologica Sinica, 38*(6), 738-753.

Shukla, V., Seoane-Vazquez, E., Fawaz, S., Brown, L., & Rodriguez-Monguio, R. (2019). The landscape of cellular and gene therapy products: Authorization, discontinuations, and cost. *Human Gene Therapy. Clinical Development, 30*(3), 102-113.

Sibbald, B. (2001). Death but one unintended consequence of gene-therapy trial. *Canadian Medical Association Journal, 164*(11), 1612-1612.

Sinclair, A., Islam, S., & Jones, S. (2018). Gene therapy: An overview of approved and pipeline technologies. *CADTH Issues in Emerging Health Technologies*(171), 1-23.

Sirrs, S., Clarke, J. T. R., Bichet, D. G., Casey, R., Lemoine, K., Flowerdew, G., . . . West, M. L. (2010). Baseline characteristics of patients enrolled in the Canadian Fabry Disease Initiative. *Molecular Genetics and Metabolism, 99*(4), 367-373.

Sirugo, G., Williams, S. M., & Tishkoff, S. A. (2019). The missing diversity in human genetic studies. *Cell, 177*(1), 26-31.

Snyder, J. (2017). Appealing to the crowd: Ethical justifications in Canadian medical crowdfunding campaigns. *Journal of Medical Ethics, 43*, 364-367.

Stafinski, T., McCabe, C. J., & Menon, D. (2010). Funding the unfundable: Mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems. *Pharmacoeconomics, 28*(2), 113-142.

Stafinski, T., Menon, D., Marshall, D., & Caulfield, T. (2011). Societal values in the allocation of healthcare resources. *The Patient: Patient-Centered Outcomes Research, 4*(4), 207-225.

Stirnadel-Farrant, H., Kudari, M., Garman, N., Imrie, J., Chopra, B., Giannelli, S., . . . Ng, P. (2018). Gene therapy in rare diseases: The benefits and challenges of developing a patient-centric registry for Strimvelis in ADA-SCID. *Orphanet Journal of Rare Diseases, 13*(1), 49.

Tarnowski, J., Krishna, D., Jespers, L., Ketkar, A., Haddock, R., Imrie, J., & Kili, S. (2017). Delivering advanced therapies: The big pharma approach. *Gene Therapy, 24*(9), 593-598.

Tatum, E. L. (1966). Molecular biology, nucleic acids, and the future of medicine. *Perspectives in Biology and Medicine, 10*(1), 19-32.

The Guardian. (2019, April 2). Family of Nova Scotia Man Would Like to See CAR-T Cell Therapy Used More Often, *The Guardian*.

TreatSMA. (2020). Update on AveXis's global Managed Access Programme for Zolgensma. Retrieved May 2020, from https://www.treatsma.uk/2020/03/update-on-avexiss-global-managed-access-programme-for-zolgensma/.

Trusheim, M. R. & Bach, P. B. (2019, September 25). Next Steps for Netflix: Can 'All You Can Treat' Contracts Work Beyond Hepatitis C?, *Health Affairs*.

UC Berkeley (University of California, Berkeley). (2013). *Exclusive License Between Caribou Biosciences Inc., and The University of Vienna, and The Regents of the University of California for Methods and Compositions for RNA-Directed Target DNA Modification and for RNA-Directed Modulation of Transcriptio.* Berkeley (CA): UC Berkeley Office of Technology Licensing.

Valent, F., Deroma, L., Moro, A., Ciana, G., Martina, P., De Martin, F., . . . Bembi, B. (2019). Value of the rare disease registry of the Italian region Friuli Venezia Giulia. *Value Health, 22*(9), 1003-1011.

Vial, L. (2019). *Opposition Against European Patent n°3214091 (Application Number 17153799.6).* Gif-sur-Yvette, France: Cabinet Lionel Vial.

Vigano, M., Giordano, R., & Lazzari, L. (2017). Challenges of running a GMP facility for regenerative medicine in a public hospital. *Regenerative Medicine, 12*(7), 803-813.

Vitry, A., Nguyen, T., Entwistle, V., & Roughead, E. (2015). Regulatory withdrawal of medicines marketed with uncertain benefits: The bevacizumab case study. *Journal of Pharmaceutical Policy and Practice, 8*(1), 25.

Vogler, S., Paris, V., & Panteli, D. (2018). *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* Copenhagen, Denmark: World Health Organization Regional Office for Europe.

Vormittag, P., Gunn, R., Ghorashian, S., & Veraitch, F. S. (2018). A guide to manufacturing CAR T cell therapies. *Current Opinion in Biotechnology, 53*, 164-181.

Vukovic, S., McAdam, L., Zlotnik-Shaul, R., & Amin, R. (2019). Putting our best foot forward: Clinical, treatment-based and ethical considerations of nusinersen therapy in Canada for spinal muscular atrophy. *Journal of Paediatrics and Child Health, 55*, 18-24.

Wade, N. (1980). UCLA Gene Therapy Racked by Friendly Fire. *Science, 210*(4469), 509-511.

Wadman, M. (2005). Medicare compels heart patients to enlist in follow-up research. *Nature, 433*(7024), 341.

Waring, D. R. (2004). *Medical Benefit and the Human Lottery: An Egalitarian Approach to Patient Selection*. New York (NY): Springer.

White, P. (2019, December 27). In 2019, Canadians Directed most GoFundMe Donations to Children in Desperate need of Expensive Medical Treatments, *Globe and Mail*.

White, R. (2016). Building trust in real-world evidence and comparative effectiveness research: The need for transparency. *Journal of Comparative Effectiveness Research, 6*(1), 5-7.

Wilson, J. M. (2009). Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. *Molecular Genetics and Metabolism, 96*(4), 151-157.

Wilson, R. C. & Carroll, D. (2019). The daunting economics of therapeutic genome editing. *The CRISPR Journal, 2*(5), 280-284.

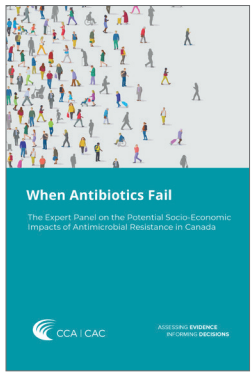
Wirth, T., Parker, N., & Yla-Herttuala, S. (2013). History of gene therapy. *Gene, 525*(2), 162-169.

Yarborough, M. & Sharp, R. R. (2009). Public trust and research a decade later: What have we learned since Jesse Gelsinger's death? *Molecular Genetics and Metabolism, 97*(1), 4-5.

Yeku, O., Li, X., & Brentjens, R. J. (2017). Adoptive T-Cell therapy for solid tumors. *American Society of Clinical Oncology Educational Book, 37*, 193-204.

CCA Reports of Interest

The assessment reports listed below are accessible through the CCA's website (www.cca-reports.ca):



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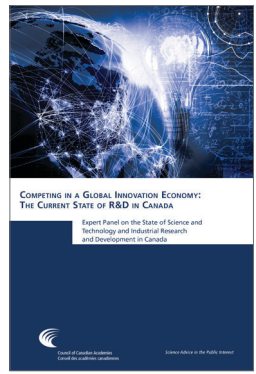

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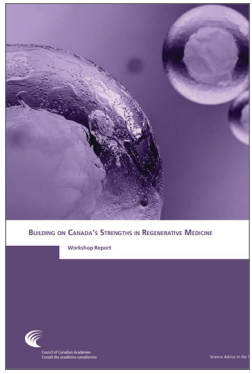

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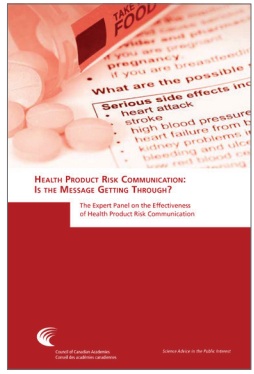
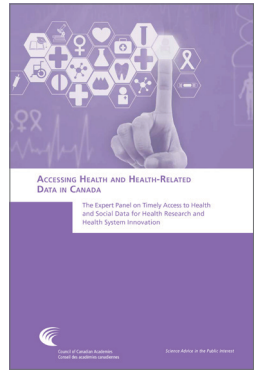


Health Product Risk Communication: Is the Message Getting Through? (2015)



Accessing Health and Health-Related Data in Canada (2015)

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