CADTH

CADTH ISSUES IN EMERGING HEALTH TECHNOLOGIES

Informing Decisions About New Health Technologies

Issue 171 Mar 2018

Gene Therapy: An Overview of Approved and Pipeline Technologies

CADTH

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Cite as: Gene therapy: an overview of approved and pipeline technologies. Ottawa: CADTH; 2018 Mar. (CADTH issues in emerging health technologies; issue 171).

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ISSN: 1488-6324 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Summary

- Gene therapy is an area of therapeutics aimed at curing, or significantly improving the management of, diseases with few or no treatment alternatives.
- A large proportion of the candidates for gene therapy include advanced-stage cancer or hematological conditions. In addition, rare or inherited disorders are also frequent targets of gene therapy.
- While gene therapy developments are still largely in the research stage, companies are increasingly investing in these technologies. Recently, a number of products have been approved outside of Canada or are in the advanced stage of clinical research.
- The upfront current cost of gene therapy is generally very high. Multi-stakeholder dialogues around management of cost and reimbursement of these products are necessary.
- Specialized manufacturing facilities, care centres, and clinicians trained to conduct customized procedures for such therapies are vital to ensure accessibility and quality of care.

Scope

This bulletin summarizes information on gene therapies that have been marketed in at least one country or are currently at an advanced or priority stage of development and are therefore most likely to appear on the market in the next two to three years. General aspects of adoption and implementation are considered, but clinical and cost-effectiveness of individual therapies are not reviewed. Details on mechanisms, processes related to manufacturing and administration, and regulatory aspects are not within the scope of this bulletin.

A comprehensive list of ongoing clinical trials on gene therapy around the world or in Canada is also not within the scope of this bulletin. This information may be found at ClinicalTrials.gov, maintained by the US National Library of Medicine,[1] and Health Canada's Clinical Trials Database.[2]

Methods

These bulletins are not systematic reviews of the literature and do not involve a detailed critical appraisal of identified studies. They are not intended to provide recommendations for or against a particular technology.

Literature Search

A limited literature search was conducted on key resources, including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination databases, and Canadian and major international health technology agencies. As well, a focused Internet search was conducted. Methodological filters were applied to limit retrieval to randomized controlled trials, controlled clinical trials, and clinical studies. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between

January 1, 2016, and December 8, 2017. Regular alerts updated the search until project completion; only citations retrieved before January 30, 2018, were incorporated into the report.

Study Selection

The search results were divided between two authors by topic area. No duplicate screening was completed. In addition to the studies identified by the literature search, publications of interest cited by identified sources were also included in the report. As the report was intended to focus on the therapies most likely to appear on the market in the next two to three years, journal articles, database entries, or Web pages were considered for inclusion if they provided information on a gene therapy that has been approved for marketing anywhere in the world or was in active development, either in phase III or in earlier phases with a special regulatory designation. All indications were eligible.

Stakeholder Review

A draft version of this bulletin was posted publicly for stakeholder review.

Background

What is Gene Therapy?

According to the FDA, gene therapy is "the administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use."[3] In Canada, gene therapies are included in the definition of "drug" under the *Food and Drugs Act* and are regulated under the *Food and Drug Regulations*.[4-6] Both the US and Canada regulate gene therapies as biologic drug therapies.[3-5,7] Other jurisdictions, such as Europe, have a separate regulatory pathway for gene therapies.[7,8]

Gene therapy involves the administration of specific genetic material (i.e., DNA or RNA) via a carrier, known as a "vector," that enables the foreign genetic material to enter the target cells.[9] Most gene therapies use modified versions of natural viruses as vectors, as they are an efficient way of introducing DNA or RNA into a cell.[8-10] The gene therapy agent can be injected into the body (in vivo gene therapy) or used to modify cells taken from the body, which are then re-infused (ex vivo gene therapy; Figure 1). Replacement gene therapy aims to provide a working copy of the damaged gene(s), boost the availability

Figure 1: Schematic of Approaches to Gene Therapy Applicable to Both Gene Editing and Gene Transfer

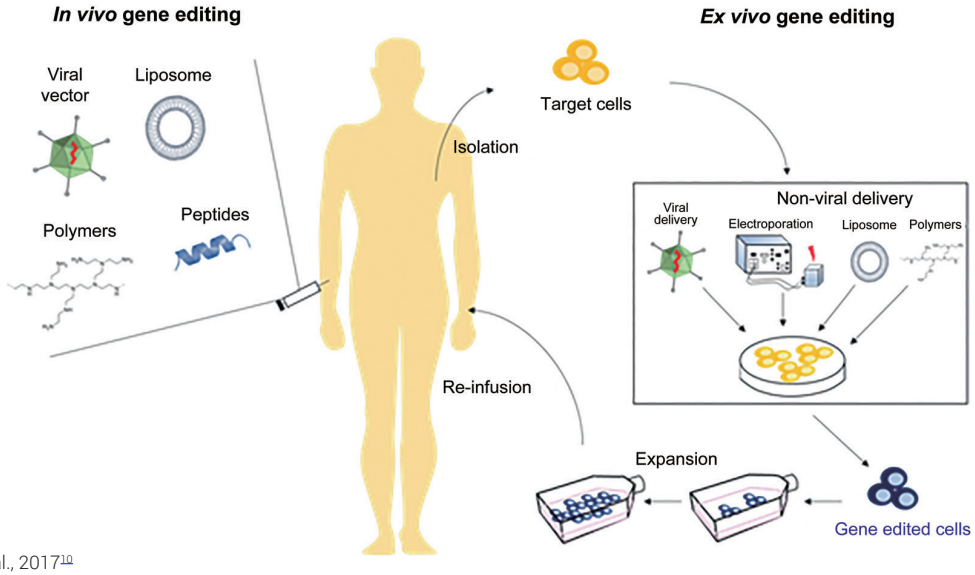

Figure from Shim et al., 2017[10]

of a disease-modifying gene, or suppress the production of a damaged gene.[8-10] Gene therapy for the treatment of cancer primarily aims to selectively kill, or suppress the growth of, malignant cells.[11,12] Emerging "gene editing" technologies aim to modify chromosomal DNA and repair genetic errors directly.[10]

Gene therapy has been an active area of research for at least the past two decades.[13] As of January 28, 2018, ten gene therapy products have been approved for marketing in at least one country in the world. Recent predictions for the near future range from 12 to 14 new gene therapies submitted for approval in the next couple of years,[14] to around 40 new therapies approved by the end of 2022.[15]

This horizon scan focuses on the gene therapies that have been approved for marketing in one or more jurisdictions in the world or are in phase III of clinical development or phase I or II of clinical development with one or more special regulatory designations from the FDA or the European Medicines Agency (EMA). These designations are intended to accelerate development of drugs for underserved populations or unmet medical needs and are as follows:

- Orphan Product (FDA)[16]
- Fast Track (FDA)[17]
- Breakthrough Therapy (FDA)[18]
- Priority Review (FDA)[19]
- Rare Pediatric Disease Priority Review (FDA)[20]
- Orphan designation (EMA)[21]
- PRIME (EMA)[22]
- Priority Review (Health Canada)[23]
- Notice of Compliance with Conditions (Health Canada).[24]

Further information concerning the regulatory context of gene therapy is reported in the concurrent CADTH Environmental Scan,[25] while this horizon scan summarizes briefly the technologies, indications, status, and implementation issues surrounding gene therapies. CADTH has also produced a more comprehensive Horizon Scanning bulletin on voretigene neparvovec, a recently introduced gene therapy for an inherited retinal dystrophy.[26]

Who Might Benefit?

A 2017 brief by the Massachusetts Institute of Technology's New Drug Development Paradigms Initiative (NEWDIGS) projected that around 40 gene therapies technologies would be approved by the end of 2022. The prediction is that 45% of these would be cancer treatments, 34% would be for the treatment of orphan diseases, 17% for common diseases, and 4% (one therapy) for extremely rare diseases (i.e., fewer than 100 patients within the US).[15]

The gene therapies that have made the most progress toward market availability treat disorders that are caused by single-gene mutations.[9,10] Many of these are rare or ultra-rare diseases with few treatment options apart from supportive and symptomatic care. Development of gene therapies is also influenced by ease of administration in target tissues, e.g., diseases of the eye[27] and of the hematopoietic system (immunity and blood).[28,29]

Until recently, progress in well-characterized single-gene conditions such as cystic fibrosis and the muscular dystrophies was slowed by the limitations of replacement gene strategies;[30,31] gene editing approaches are now being investigated[31] to address such shortcomings. Research groups and companies are also interested in replacement gene therapy for more prevalent acquired disorders, in which the production of certain proteins may have become insufficient,[32,33] including cardiovascular and peripheral vascular disease; degenerative diseases of the nervous system (e.g., Parkinson disease, Huntington disease, and Alzheimer disease);[34] and disorders of aging (such as osteoarthritis).

Cancers that have been targeted for gene therapy are primarily those that do not respond well to conventional treatment, such as metastatic melanoma, glioblastoma, cancer of the pancreas, and hepatocellular carcinoma.[12] The first gene therapies to be approved in any country were approved in China for squamous cell carcinoma of the head and neck but have subsequently been used in other cancers.[35] Hematopoietic cancers (lymphoma and leukemia) have also been the subject of investigation because of gene therapy's ability to manipulate immune cells outside the body. Current gene therapy trials involve patients with relapsed or refractory disease whose treatment options are limited.[11,12]

Given the uncertainties around the use of novel therapies, gene therapies may initially be approved for patients who are lacking other treatment options. These include conditions that, in the absence of treatment, can cause disability or early death. Other patient groups that might benefit include those with conditions that require intensive and onerous maintenance therapy in the form of enzyme or protein replacement. Gene therapy could potentially offer all of these patients long-term stabilization or improvement of their health, with the ultimate objective being a cure. A review of the efficacy of these products is outside the scope of this review, but promising results have been obtained in several difficult-to-treat conditions.[36-38]

The Technologies

Vectors for Gene Transfer

Vectors used for gene therapy include modified versions of natural viruses and plasmids. Viruses have been modified to remove disease-causing genes and replace them with the gene(s) being transferred and the sequences that control its expression, while keeping the viral envelope or coat, which aids transfer.[9,39] Plasmids are small circular segments of DNA that do not have a natural coat or envelope, but that can be encapsulated in an artificial lipid membrane or polymer to improve transfer.

Commonly used DNA viruses are adeno-associated virus (AAV) (a nonpathogenic but abundant small virus), adenoviruses (responsible for upper respiratory infections), and herpesviruses. RNA viruses include retroviral vectors derived from lentiviruses (such as human HIV-1) and gamma-retroviruses, all of which can integrate a DNA copy of their genetic material into the host genome.[39]

Choice of vector depends on the size of the gene or genes that it can carry, the target cells (dividing or nondividing, and cell type), whether the virus will insert into the target cells' genome or remain separate, and the antibody status of potential patients. Insertion into the genome gives the most durable expression because the gene is retained after cell division. However, control over the location of insertion is essential, since insertion in the wrong place may lead to lack of expression of the inserted gene (if the gene inserts into a silenced part of the genome), or tumours arising from the disruption or activation of neighbouring genes involved in the development of cancer.[40] Antigenic potential is important because many of the vectors are derived from native viruses; antibodies from a previous exposure to the native virus or to a therapeutic form can attack and destroy the administered vector or cells carrying it.[41,9] Table 1 summarizes important properties of some common vectors.[9,39]

In Vivo Gene Therapy

In vivo gene therapy involves direct injection of the gene therapy agent into the body. Depending upon the vector and the target, in vivo gene therapy can be administered intravenously, injected into the muscles, infused or injected into an organ or bodily structure, or injected directly into a tumour.[39]

Table 1: Virus-Derived Vectors Commonly Used for Gene Therapy

	Adeno-Associated Virus	Adenovirus	Retrovirus/Lentivirus	Herpesvirus
Genome	ssDNA	dsDNA	ssRNA	dsDNA
Allowable size of foreign DNA	~5 kb	7.5 kb	8 kb	> 25 kb
Type of cells targeted	Nondividing cells	Nondividing cells	Dividing and nondividing cells	Dividing and nondividing cells
Integration into genome	No	No	Yes	No
Duration of expression	Potentially long duration	Transient	Long duration	Potentially long duration
Immunogenicity	Presence of antibodies varies by serotype	Antibodies prevalent	Used ex vivo	Antibodies prevalent

Ex Vivo Gene Therapy

In an ex vivo delivery system, cells are harvested from the patients' own body (autologous) or other healthy individuals (allogeneic or donor).[10] They are then modified using genetic engineering tools outside the body and purified, enriched, and/or activated before being transplanted back into the patient.[10] These modified cells then further replicate and spread in the body. The ex vivo strategy allows the transfer of a gene or genes to a specific cell subpopulation without affecting other cells or organs; however, the vectors used must be able to integrate the genetic material in the genome for successful long-term clinical effect.[10] Most ex vivo therapies are based on cells from autologous sources, with a few exceptions.[10] Autologous cells are less likely to be the targets of immune reactions than allogeneic cells. However, the latter have fewer supply and manufacturing issues, thus making them ideal candidates for off-the-shelf products, although their propensity for immune rejection or reaction against the recipient's tissues still poses technical challenges.[10]

Gene Editing

In this approach, gene editing machinery is directly transferred into host cells (using either ex vivo or in vivo approaches) to modify the genome within the recipient rather than using vectors to transfer the modified genes. Unlike viral vectors, which may have a transient effect and supplement missing or defective genes, gene editing technologies can be used to add, inactivate, or correct a gene with a permanent effect.[10]

Gene editing is carried out using nucleases, enzymes that bind to DNA with varying degrees of specificity and produce breaks on both strands. The breaks are then fused together (foreign gene from another source) using the genetic template supplied, resulting in the insertion, deletion, or correction of a gene. The three major types of nucleases used for gene editing are:[10]

- zinc finger nuclease (ZFN)
- transcription activator-like effector nuclease (TALEN)
- clustered regularly interspaced short palindromic repeats–associated nuclease Cas9 (CRISPR/Cas9).

Genome editing technologies vary in their complexity of design, manufacturing process, activity, and specificity. For example, ZFN- and TALEN-based technologies are difficult to engineer, time-consuming, and expensive, limiting their clinical application.[10] CRISPR/Cas9-based technologies have design features that make them better suited to gene editing in ex vivo settings and have recently seen a surge in clinical applications. However, no individual gene editing therapy was sufficiently advanced in development to be addressed in this report.[10]

Chimeric Antigen Receptor T-Cell Therapy

Chimeric antigen receptor (CAR) T-cells are a relatively recent development in the area of gene therapy, which have shown significant potential in recent years and therefore warrant a separate discussion. These are T-cells genetically engineered to express receptors to recognize antigens that are commonly expressed on tumour cells. Upon recognizing tumour-specific antigens, CAR T-cells are activated, leading to an increase in their numbers and to the secretion of immune activators, which work towards the targeting and destruction of tumours.[9] To date, various tumour antigens (e.g., CD19, B cell maturation antigen [BCMA]) and vector or editing systems (e.g., lentiviral vectors, transposons, mRNA, CRISPR/Cas9) have been investigated in the CAR T-cell approach. CAR T-cells combine the ability of monoclonal antibodies (mAbs) to identify specific targets and the ability of T-cells to activate the immune system and kill target cells.[9]

The general approach for CAR T-cell therapy is similar to ex vivo methods for cell-based therapies (Figure 1). First, cells from patients are collected by leukapheresis in the primary care centre, and then specific T-cells are isolated, enriched, and activated in the manufacturing facility. Next, viral vectors are used to transfer CAR genes into T-cells, and the cells are grown before being transferred back to the hospital to be infused into the patient. Patients are conditioned with lymphodepleting chemotherapy before CAR T-cell infusion in order to minimize host immune reaction and to enhance T-cell growth and antitumour activity. CAR T-cells, therefore, have significant overlap with cell-based therapies in their manufacturing and administration process, while having the distinct property of acquiring new function through the introduction of new genetic material, albeit exogenously, without altering host DNA.[9]

Current research is aimed at expanding the CAR T-cell approach to myeloid malignancies and solid tumours. However, due to the lack of confirmed tumour-specific cell surface antigens and delivery method into solid tumours or immune-privileged sites, CAR T-cell treatment has yet to be successfully used in solid tumours. Research is also under way to develop allogeneic CAR T-cell therapies that can be used "off the shelf" without invoking rejection or graft-versus-host disease. Success in treatment of certain cancers has led to T-cell–based therapies for other diseases, such as autoimmune disorders and AIDS[9] (Table 2).

Table 2: Summary of the Development and Regulatory Status of Gene Therapies Described in this Bulletin

Therapies are organized by virus and method of administration (in vivo or ex vivo).

Name	Manufacturer	Indication	Administration	Phase	Orphan Drug FDA	Fast Track FDA	Breakthrough FDA	Priority FDA	Orphan Drug EMA	PRIME EMA	Priority EMA	Accelerated Assessment
AAV												
Voretigene neparvovec-rzyl	Spark	Vision loss due to *RPE65* mutations	In vivo	M	Y			Y			Y	
Valoctocogene roxaparvovec	BioMarin	Hemophilia A	In vivo	III	Y		Y			Y	Y	
GS010	Gensight	LHON	In vivo	III	Y				Y			
AVXS-101	AveXis	SMA Type 1	In vivo	III[a]	Y	Y	Y		Y			
AMT-061	uniQure	Hemophilia B	In vivo	III[a]			Y			Y		
NSR-REP1	Nightstar Therapeutics	Chloroideremia	In vivo	II[a]	Y							
Mydicar	Theragene	Heart failure	In vivo	II[a]			Y					
SPK-9001	Spark/Pfizer	Hemophilia B	In vivo	II	Y		Y			Y		
ABO-102	Abeona	MPS IIIA	In vivo	II	Y	Y			Y			
AAV1-Follistatin	Milo	Becker MD	In vivo	II	Y							
Adenovirus												
Gencidine	Shenzen Sibiono GeneTech	Head and neck cancer	In vivo	M								
Oncorine	Shanghai Sunway	Head, neck, esophagus	In vivo	M								
Alferminogene tadenovec	Gene Biotherapeutics	Angina	In vivo	III[a]		Y						
RT-100	Renova	Heart failure	In vivo	III[a]		Y						
DNX-2401	DNAtrix	Glioblastoma / gliosarcoma	In vivo	II	Y							
ONCOS-102	Targovax	Mesothelioma	In vivo	I/II					Y			
Ofranergene obadenovec (VB-111)	VBL Therapeutics	Glioblastoma	In vivo	III	Y	Y			Y			

Name	Manufacturer	Indication	Administration	Phase	Orphan Drug FDA	Fast Track FDA	Breakthrough FDA	Priority FDA	Orphan Drug EMA	PRIME EMA	Priority EMA	Accelerated Assessment
Herpervirus												
Talimogene/ laherparepvec	BioVec/Amgen	Melanoma	In vivo	M								
Sepravir	Virtuu	Mesothelioma	In vivo	I/II								
Vaccinia												
Pexastimogene devacirepvec (Pexa-Vec)	SillaJen	Hepatocellular carcinoma	In vivo	III								
Plasmid												
Neovasculgen	Human Stem Cells Institute	Critical limb ischemia	In vivo	M								
Beperminogene perplasmid (Collategene, AMG0001, HGF plasmid)	Mitsubishi Tanabe Pharma	Critical limb ischemia	In vivo	III[a]								
VM202	ViroMed	Diabetic foot ulcers, neuropathy	In vivo	III								
CAR T-cell												
Tisagenlecleucel (Kymriah)	Novartis	Relapsed or refractory B cell ALL Relapsed or refractory DLBCL	Ex vivo	M				Y				Y
Axicabtagene ciloleucel (Yescarta)	Gilead Sciences	Relapsed or refractory BCL	Ex vivo	M	Y		Y	Y		Y		
Lisocabtagene maraleucel (JCAR017)	Juno Therapeutics, Celgene	Relapsed or refractory DLBCL	Ex vivo	I			Y			Y		
bb2121	Bluebird Bio, Celgene	Relapsed or refractory MM	Ex vivo	I, II			Y			Y		
Lentivirus												
LentiGlobin (LentiGlobin BB305)	Bluebird Bio	Beta-thalassemia, SCD	Ex vivo	I, II, III			Y		Y	Y		Y
Elivaldogene tavalentivec (Lenti-D)	Bluebird Bio	CALD	Ex vivo	II/III								

Name	Manufacturer	Indication	Administration	Phase	Orphan Drug FDA	Fast Track FDA	Breakthrough FDA	Priority FDA	Orphan Drug EMA	PRIME EMA	Priority EMA	Accelerated Assessment
GSK2696274	GSK	MLD	Ex vivo	III								
OTL-101[b]	Orchard Therapeutics	ADA-SCID	Ex vivo	I/II	Y		Y					Y
G1XCGD	Genethon	X-CGD, WAS	Ex vivo	I/II					Y			
Retrovirus												
Strimvelis	GSK	ADA-SCID	Ex vivo	M[c]	Y				Y			
Nalotimagene carmaleucel (Zalmoxis)	MolMed SpA	Blood cancers	Ex vivo	M[c], III					Y			
Tonogenchoncel-L (Invossa/ TG-C)	TissueGene Inc.	OA	Ex vivo	M, III[a]								
Vocimagene amiretrorepvec (Toca 511)	Tocagen	Glioma	Ex vivo	III			Y			Y		
NY-ESO-1(c259) T-cells	Adaptimmune, GSK	SS, MM	Ex vivo	I/II			Y			Y		

ALL = acute lymphocytic/lymphoblastic leukemia; AAV = adeno-associated virus; ADA-SCID = adenosine deaminase severe combined immunodeficiency; BCL = B cell lymphoma; CAR T = chimeric antigen receptor T-cells; CALD = cerebral adrenoleukodystrophy; DLBCL = diffuse large B cell lymphoma; HSV = herpes simplex virus; LHON = Leber hereditary optical neuropathy; MD = muscular dystrophy; MLD = metachromatic leukodystrophy; MM = multiple myeloma; MPS IIIA = Sanfilippo syndrome type A; OA = osteoarthritis; Plas = plasmid; SCD = sickle cell disease; SMA = spinal muscular atrophy; SS = synovial sarcoma; WAS = Wiskott-Aldrich syndrome; X-CGD = X-linked chronic granulomatous disease; Y = yes.
Note: Trials in phase are ongoing unless otherwise indicated.
[a] Initiating trials.
[b] OTL-101 has received a Rare Pediatric Disease Designation.
[c] Conditional Market Authorization in EU.

Regulatory and Development Status

Approved Gene Therapies

North America

Canada

No gene therapies have been approved in Canada as of January 30, 2018.

US

Two ex vivo and two in vivo gene therapies have received marketing approval in the US. All four use gene transfer technologies rather than gene editing; no gene editing technologies have been approved in the US.

The approved therapies are listed below in order of date of approval. Special regulatory designations are presented in Table 2.

- **Talimogene laherparepvec** (Imlygic, BioVec, a subsidiary of Amgen) was granted conditional approval by the FDA in October 2015 for the treatment of patients with subcutaneous or lymph node melanoma that cannot be surgically removed.[42] It consists of recombinant herpesvirus that contains specific deletions that allow the virus to replicate and lyse tumour cells, as well as a gene carrying granulocyte-macrophage colony-stimulating factor (GM-CSF), intended to stimulate a systemic immune response against the remaining tumour and metastases. It is administered by intratumoural injection. [43]

- **Tisagenlecleucel** (Kymriah, Novartis Pharmaceuticals Corporation) is a cancer treatment approved in the US for patients up to 25 years old who have acute lymphoblastic leukemia (ALL) that is either relapsed (returned post-remission) or refractory (did not go into remission following other leukemia treatments). It is the first CAR T-cell therapy approved by the FDA (August 2017).[44] It consists of autologous T-cells genetically modified using a lentiviral vector to encode an anti-CD19 CAR. Tisagenlecleucel has been submitted for approval to the EMA for relapsed or refractory B cell ALL in children or young adults[45] and submitted to the FDA and EMA for a second indication, relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults,[45,46] for patients who are ineligible for auto-hematopoietic stem cell transplantation (HSCT).[45]

- **Axicabtagene ciloleucel** (Yescarta, Kite, a subsidiary of Gilead Sciences, Inc.[47]) was approved by the FDA in October 2017 for the treatment of adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including patients with DLBCL not otherwise specified, primary mediastinal large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma.[48] It is a CD19-directed autologous T-cell immunotherapy genetically modified using a retroviral vector. An application for European marketing authorization has been submitted to the EMA.[49]

- **Voretigene neparvovec-rzyl** (Luxturna, Spark Therapeutics) was granted approval by the FDA in December 2017[50] for the treatment of patients with progressive vision loss due to a confirmed biallelic (affecting both copies) mutation in the RPE65 gene.[51] Voretigene neparvovec-rzyl consists of a recombinant adeno-associated virus serotype 2 (AAV2) vector carrying a functional RPE65 gene, with the aim of supplying a functional RPE65 protein. It is given by bilateral subretinal injection.[52] An application for European marketing authorization has been submitted.[53] In addition, CADTH has published a Horizon Scanning bulletin on voretigene neparvovec, including an overview of the evidence of its efficacy and safety.[26]

Other Countries

An additional seven gene therapies have received marketing authorization elsewhere in the world. All approved gene therapies use gene transfer technologies. Therapies with approval in the European Union (EU) and other jurisdictions are as follows, in the order of their approval date.

- **Gencidine** (Shenzhen Sibiono GeneTech) was approved by the Chinese State Food and Drug Agency in 2003 for the treatment of squamous cell carcinoma of the head and neck.[35] Gencidine is a recombinant adenovirus engineered to express wildtype p53, a tumour suppressor protein, intended to induce programmed cell death in tumour cells. It is administered by intratumoural injection.

- **Oncorine** (H101, Shanghai Sunway Biotech) was approved by the Chinese State Food and Drug Agency in 2005 for the treatment of squamous cell carcinoma of the head, neck, and esophagus.[35] Oncorine is a recombinant adenovirus

engineered to selectively replicate in and destroy tumour cells and is administered by direct intratumoural injection.

- **Neovasculgen** (PI-VEGF-165, Human Stem Cells Institute) was approved by the Russian Ministry of Healthcare in 2011 for the treatment of peripheral vascular disease with critical limb ischemia. Neovasculgen is a plasmid-carrying vascular endothelial growth factor that induces the growth of new vessels.
- **Talimogene laherparepvec** (Imlygic, BioVec, a subsidiary of Amgen) was approved in the EU in December 2015 for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC, and IVM1a) with no bone, brain, lung, or other visceral disease.[43]
- **Strimvelis** (GlaxoSmithKline) was approved in the EU in May 2016 but saw the first clinical application on a single patient in March 2017. This therapy is targeted for the treatment of a rare genetic disorder, adenosine deaminase deficiency–severe combined immunodeficiency (ADA-SCID) in patients for whom no suitable, matched stem cell donor is available.[54] It uses autologous CD34+ enriched cells transduced with retroviruses to encode the human adenosine deaminase (ADA) gene. The genetically modified autologous CD34+ cells act by repopulating the hematopoietic system with cells that express active levels of the ADA enzyme, reversing the enzyme deficiency.[55,56] This therapy was given orphan medication designation by the EMA.[55,56]
- **Nalotimagene carmaleucel** (Zalmoxis, MolMed SpA) was granted a conditional marketing authorization (CMA) by EMA on August 2016 and was designated an orphan medicinal product. The CMA authorization indicates that an unmet need is filled by the treatment.[57] A phase III trial is underway around the world for this treatment.[58] Nalotimagene carmaleucel consists of allogeneic T-cells genetically modified with a retroviral vector encoding for the human low-affinity nerve growth factor receptor and the herpes simplex I virus thymidine kinase. It is recommended as an adjunct treatment for adult patients who have undergone HSCT.[57,59]
- **Tonogenchoncel-L** (TG-C, Invossa, TissueGene) received marketing approval from the Korea Ministry of Food and Drug Safety in July 2017. In the US, a phase III trial is ongoing.[60] This is an allogeneic cell therapy in which a mix of unmodified and genetically modified chondrocytes made to express transforming growth factor beta-1 (TGF-beta-1), and anti-inflammatory mediator are injected.[61]

In addition, alipogene tiparvovec (Glybera, uniQure) was awarded a five-year marketing authorization in the EU in October 2012 for the treatment of monogenic lipoprotein lipase deficiency, an ultra-rare inherited disease.[62] One patient received treatment, post-marketing. The company decided not to re-apply for marketing authorization for October 2017.[63]

Gene Therapies in Advanced Development

Fourteen gene therapies are in advanced development, either with (1) current phase III trials or with (2) completed phase II or phase I/II trials with one or more special regulatory designations and plans to initiate phase III trials in 2018. Eleven involve in vivo administration of viruses or plasmids, and three involve ex vivo manipulation and infusion of autologous cells. Special regulatory designations are presented in Table 2.

- **GS010** (Gensight Biologics) for the treatment of patients with vision loss from Leber hereditary optical neuropathy involving the ND4 gene — a subunit of an important enzyme of the mitochondrial energy pathway.[64] GS010 consists of an AAV9 vector carrying a functional copy of ND4, administered by intravitreal injection.[65,66]
- **NSR-REP1** (Nightstar Therapeutics) for the treatment of patients with vision loss due to choroideremia.[27,67] NSR-REP1 consists of an AAV2 vector carrying human REP1 administered by intraretinal injection.
- **Valoctocogene roxaparvovec** (BioMarin Pharmaceuticals) for the treatment of patients with hemophilia A.[68] Valoctocogene roxaparvovec consists of an AAV vector carrying a functional coagulation factor VIII gene, administered by intravenous infusion.[69,70]
- **AMT-061** (uniQure) for the treatment of patients with hereditary hemophilia B.[68] AMT-061 consists of an AAV5 vector carrying a functional gene for coagulation factor XI administered by intravenous infusion.[71]
- **AVXS-101** (AveXis) for the treatment of children with spinal muscular atrophy (SMA) Type I.[72] AVXS-101 consists of a recombinant AAV9 virus carrying a functional copy of the SMN1 gene, administered by intravenous injection.[56]
- **Alferminogene tadenovec** (Generx, Gene Biotherapeutics [formerly Taxus Cardium Pharmaceuticals Corporation][73]) is entering phase III development for the treatment of patients with angina pectoris due to cardiac insufficiency

in association with advanced coronary disease.[74] Alferminogene tadenovec consists of an adenoviral (Ad5) vector carrying fibroblast growth factor 5, administered by intracoronary injection. It is intended to improve collateral circulation in the heart by promoting angiogenesis in patients whose symptoms could not be relieved by conventional treatment of coronary artery disease.

- **RT-100** (Renova Therapeutics[75]) is entering phase III development for the treatment of patients with reduced left ventricular ejection fraction heart failure.[76] RT-100 consists of an Ad5 vector carrying human adenylyl cyclase 6 administered by intracoronary injection. It is intended to improve the contractility of the heart muscle in patients with heart failure that has not responded to best current care.
- **Ofranergene obadenovec** (VB-111, VBL Therapeutics[77]) is in phase III development for recurrent glioblastoma multiforme[78] and recurrent platinum-resistant ovarian cancer.[79] Ofranergene obadenovec is an Ad5 vector carrying a proprietary anti-angiogenic function and a viral immuno-oncology mechanism. It is administered by intravenous injection in conjunction with chemotherapy.
- **Pexastimogene devacirepvec** (Pexa-Vec, SillaJen, Inc.[80]) is currently in phase III development [81] for the treatment of hepatocellular carcinoma in conjunction with immunotherapy. Pexastimogene devacirepvec is a recombinant oncolytic vaccinia virus administered by injection directly into the tumour or tumours.
- **Beperminogene perplasmid** (Collategene, AMG0001, hepatocyte growth factor (HGF) plasmid; AnGes MG / Mitsubishi Tanabe Pharma) for the treatment of peripheral vascular disease with critical limb ischemia. It consists of a plasmid containing human HGF gene. A phase III study has been completed in Japan. A separate phase III multi-national study was terminated in 2016,[82] with plans to revise the scope and re-initiate.
- **VM202** (VM Biopharma) is being developed for the treatment of diabetic foot ulcers [83] and painful diabetic peripheral neuropathy.[84] It is a plasmid containing human HGF gene. Phase II studies have been completed for critical limb ischemia.[85]
- **LentiGlobin** (BB305, Bluebird Bio) consists of autologous CD34+ hematopoietic stem cells (HSCs) transduced ex vivo with a recombinant lentiviral vector that restores the function of the beta-globin gene that is defective in patients with beta-thalassemia.[86] This is considered an orphan medication in the EU.[86] Currently, this therapy is in a phase III trial for beta-thalassemia[87] and a phase I trial for sickle cell disease.[88,89]
- **Elivaldogene tavalentivec** (Lenti-D, Bluebird Bio) is another autologous CD34+ HSC product being tested on patients with cerebral adrenoleukodystrophy in a phase II/III study.[90,91]
- **GSK2696274** (GlaxoSmithKline) consists of cryopreserved autologous CD34+ cell clusters transduced with lentiviral vector to express arylsulfatase A and used for the treatment of metachromatic leukodystrophy, a lysosomal storage disorder characterized by severe and progressive demyelination affecting the central and peripheral nervous system. This therapy is currently being tested in a phase III trial.[92]

Gene Transfer Therapies in Earlier Development

A number of other gene therapies are in phase II or earlier development. Thirteen technologies that have received one or more forms of special regulatory designation intended to accelerate development are described in brief. Special regulatory designations are presented in Table 2.

- **SPK-9001** (Spark Therapeutics) is in phase I/II development for the treatment of patients with hereditary hemophilia B.[68] SPK-9001 consists of an AAV vector carrying the gene for coagulation factor XI, administered by intravenous infusion.[93]
- **ABO-102** (Abeona Therapeutics, Inc.) is in development for the treatment of children with Sanfilippo syndrome type A (MPS IIIA, a lysosomal storage disorder).[94,95] ABO-102 consists of a recombinant AAV9 vector carrying the N-Sulfoglucosamine Sulfohydrolase gene, administered by intravenous infusion.
- **AAV1-Follistatin** (Milo Biotechnology) is in development for the treatment of Becker muscular dystrophy.[96] AAV1-Follistatin consists of a recombinant AAV1 vector carrying the follistatin gene. Treatment is by intravenous infusion.[97]
- **Mydicar** (Theragene Pharmaceuticals) is for the treatment of heart failure. Mydicar consists of an AAV1 vector carrying sarcoplasmic reticulum calcium ATPase (SERCA2a, down-regulated in heart failure), administered by intracoronary

injection. The phase IIb clinical trial for Mydicar did not reach its primary end point,[32,98] but the drug was acquired by Theragene Pharmaceuticals and is continuing in active development.

- **Lisocabtagene maraleucel** (JCAR017, Juno Therapeutics, in collaboration with Calgene Corporation) is one of a range of CAR T-cell products developed by these companies. JCAR017 is an immunotherapy that targets CD19 receptors on malignant B cells. The therapy is currently being tested in patients with relapsed or refractory chronic lymphocytic lymphoma or small cell lymphocytic lymphoma (phase I/II)[99] and relapsed or refractory B cell non-Hodgkin lymphoma.[100]
- **bb2121** (Bluebird Bio[101] / Celgene) is in phase I/II development in patients with previous treatment for multiple myeloma.[102,103] bb2121 consists of autologous T lymphocytes transduced with an anti-BCMA02 CAR lentiviral vector carrying an anti-BCMA CAR).
- **DNX-2401** (DNAtrix[104]) is in phase II development for glioblastoma or gliosarcoma with disease progression.[105] DNX-2401 is a recombinant adenovirus and is administered by direct intratumoural injection.
- **ONCOS-102** (Targovax[106]) is in phase I/II development for malignant pleural mesothelioma.[107] ONCOS-102 is a recombinant adenovirus expressing GM-CSF, intended to lyse tumour cells and stimulate an immune response to the remaining tumour and remote metastases. It is administered by injection into the pleural space in conjunction with intravenous chemotherapy.
- **Sepravir** (Virtuu Biologics[108]) has completed phase I/II trials for treatment of malignant pleural mesothelioma.[109] Sepravir is a recombinant oncolytic herpes simplex I virus administered intrapleurally in conjunction with intravenous chemotherapy.
- **Vocimagene amiretrorepvec** (Toca 511, Tocagen[110]) is a cancer-selective immunotherapy consisting of a retroviral vector encoding a modified cytosine deaminase gene (Toca 511) that expresses cytosine deaminase, an enzyme that converts the orally administered antifungal prodrug 5-flurocytosine to the anticancer drug 5-fluorouracil in transfected cells.[111,112] The treatment is tested in phase II/III clinical trial on patients with recurrent high-grade glioma.[113]
- **NY-ESO-1** (Adaptimmune, in collaboration with GlaxoSmithKline) is an autologous T-cell therapy transduced with a retroviral vector encoding a T-cell receptor specific for the cancer-testis antigens NY-ESO-1 and L antigen family member 1 (LAGE-1). The product is in phase I/II trial worldwide for synovial sarcoma[114] and multiple myeloma.[115]
- **OTL-101** (Orchard Therapeutics Limited) has received FDA Rare Pediatric Disease, Orphan Drug, and Breakthrough Therapy designations. It is an autologous CD34+ HSC treatment encoding for the ADA gene for use in ADA-SCID patients. Its safety and efficacy are being tested in a phase I/II trial.[116,117]
- **G1XCGD** (Genethon) involves autologous CD34+ cells transduced with lentiviral vectors to restore function of the Nicotinamide adenine dinucleotide phosphate oxidase enzyme for the treatment of X-linked chronic granulomatous disease, a rare genetic disorder affecting boys that weakens the immune system and makes the carrier prone to infection. Genethon is testing another lentivirus-mediated therapy for Wiskott-Aldrich syndrome (WAS),[118] an inherited immune deficiency primarily affecting males that causes hemorrhaging and eczema as a result of a defective WAS gene and subsequent impaired blood clotting. Both of these therapies are currently in phase I/II trials.[119 120]

Gene Editing Therapies in Earlier Development

As of 2017, there were 18 gene editing–based technologies being tested in clinical trials in at least one country in the world, most in phase I trials.

No clinical trials (ongoing or completed) using gene editing–based technologies have progressed beyond phase II. The few studies in phase I/II are as follows.

- Sangamo Biosciences has completed a phase I/II trial of a ZFN-based product, SB-728-T, which is an autologous CD4+ T-cell therapy for silencing the CCR5 gene to combat HIV infection.[121]
- CRISPR/Cas9-based technology is currently ongoing and in early stages of clinical trials in China. In one ongoing phase II trial, PD-1 (Programmed cell death protein 1) knockout T-cells created using CRISPR/Cas9 technology ex vivo are used to treat advanced esophageal cancer.[122] CRISPR/Cas9-mediated PD-1 knockout Epstein-Barr virus (EBV)–specific cytotoxic T-cells are tested in phase I/II for treatment of a number of EBV-positive advanced stage malignancies — gastric carcinoma, nasopharyngeal carcinoma, lymphoma,

Hodgkin lymphoma, and diffuse large B-cell lymphoma.[123] Finally, allogeneic CAR T-cells, UCART019, engineered to target relapsed or refractory CD19+ leukemia and lymphoma, are being tested in a phase I/II trial.[124]

Costs

No gene therapies have been approved in Canada; therefore, Canadian list prices are unavailable.

US list prices are available for the following five gene therapies marketed in the US. A review of the cost-effectiveness and health system value of these technologies is out of scope for this report, but the Institute for Clinical and Economic Review has reviewed the cost-effectiveness of two CAR T-cell therapies.[125]

- **Voretigene neparvovec-rzyl** (Luxturna) has a list price of US$425,000 (per eye treatment).[126] Administration requires a bilateral subretinal injection in two separate procedures no less than six days apart.[127] Subretinal injection requires vitrectomy to access the retina and is specialized eye surgery that will likely be available only in a limited number of centres. Travel costs, therefore, may be incurred.
- **Talimogene laherparepvec** (Imlygic) has an estimated average cost of US$65,000 according to the manufacturer,[128] but this may vary by patient. It is administered as a series of injections over at least six months, in conjunction with standard chemotherapy, until there are no remaining injectable lesions or other treatment is needed.[42] Injections are subcutaneous or intranodal, so no surgical procedure costs are anticipated.
- **Tisagenlecleucel** (Kymriah) has a list price of US$475,000, but estimates are up to US$750,000.[129] It is administered by intravenous infusion, following lymphodepleting chemotherapy. There is no information on cost per dose. Additional costs are incurred pre-treatment and for the management of treatment side effects. Therefore, the total cost may surpass the estimated cost.[130-132]
- **Axicabtagene ciloleucel** (Yescarta) has a list price of US$373,000.[125,133-135] It is administered by intravenous infusion, preceded by lymphodepleting chemotherapy (fludarabine and cyclophosphamide). Additional costs are incurred pre-treatment and for the management of treatment side effects.
- **Strimvelis** has a list price of €594,000.[54] It is administered as a single dose through intravenous infusion.[55,56] It is recommended that Strimvelis infusion be preceded by intravenously administered busulfan to eliminate abnormal bone marrow cells andantihistamine to reduce the risk of allergic reactions.[55,56] Strimvelis should be administered in a specialized transplant centre, by a physician experienced with ex vivo cell therapy products and management of patients with ADA-SCID.

Concurrent Developments

Gene therapy is a very active area of research and development, in which existing technologies are being further developed for additional indications. For example, the same or a closely related vector is used to deliver different genes (e.g., for inherited retinal disease),[27] and different gene therapies are being developed for the same conditions (e.g., multiple companies are developing treatments for hemophilia A or B).

Additional Indications for Existing Technologies

The following gene therapies are being investigated for additional indications. The primary indication is shown in brackets after the gene therapy name.

- **Voretigene neparvovec-rzyl** (vision loss due to RPE65 gene mutations) is being developed for the treatment of patients with retinitis pigmentosa and has received breakthrough designation for this indication. It is also in pre-clinical development for wet age-related macular degeneration, a much more common condition.[136]
- **Neovasculgen** is being investigated for Raynaud syndrome secondary to scleroderma, as well as diabetic foot ulcers, and peripheral nerve injury.[137]
- **AVXS-101** (SMA Type 1) is in phase II/III development for patients with SMA Type 2, who are able to sit unassisted but not walk. These patients have a nonfunctioning SMN1 gene but have extra copies of a similar gene, SMN2, that partially corrects the deficit.[138]
- **AAV-Follistatin** is in phase I development for Duchenne muscular dystrophy[139] and inclusion body myositis.[139]
- **Oncorine** (head and neck cancer) is also used to treat lymph node metastases of these cancers, hepatocellular cancer, and pancreatic cancer.[35,140]

- **Pexastimogene devacirepvece** is in phase II and earlier development for other cancers.[80]
- **Ofranergene obadenovec** is in phase II development for thyroid cancer and lung cancer.[77]
- **DNX-2401** is also in phase I development for pediatric pontine glioma.[141]
- **ONCOS-102** is also in phase I development for melanoma and advanced peritoneal cancers.[106]
- **Beperminogene perplasmid** is also being developed, in alliance with Mitsubishi Tanabe Pharma, for arteriosclerosis obliterans and Buerger's disease.[142]
- **VM202** has completed phase I/II trials for amyotrophic lateral sclerosis and received a Fast Track designation for this indication, and is in development for coronary artery disease.[143]

Implementation Issues

Some of the main implementation issues for gene therapy involve the adequacy of evidence for decision-making, the cost of treatment, and health care system requirements that need to be in place (e.g. relevant procedures and aftercare).[9,10]

Adequacy of Evidence for Decision-Making

Because some gene therapy technologies are supported by regulators through accelerated review mechanisms, there is a risk that they will reach the market on the basis of early evidence (e.g., a small number of patients, use of surrogate end points, short duration of treatment or follow-up, lack of safety information), posing challenges for health technology assessment agencies and payers.[144] In these cases, decision-makers may be required to determine eligibility for reimbursement on the basis of a small body of evidence, which may result in contradictory decisions neighbouring jurisdictions, or resistance to the withdrawal of a therapy even if later evidence does not support its effectiveness, particularly if there are no alternatives. Availability of ongoing research that provides effectiveness and safety data may help to overcome these limitations. Regulatory agencies may have mechanisms for ongoing review or reassessment that could be applied in these scenarios.

Areas of particular uncertainty concern the predictability and durability of the response to treatment and the long-term safety of gene therapies for patients, those in contact with them, and the environment. Most trials have observed a variable response among patients. The clinical response to gene therapy technologies does not always follow a pattern similar to conventional pharmaceutical or biologic drugs, and instead may demonstrate rapid turn-on or turn-off effects.[10] To date, most studies of gene therapies involve relatively short follow-up for treatment intended to be long-term or permanent. The ability of these technologies to produce long-term or even permanent genome changes may also pose unique challenges related to safety.[10] Gene therapy has been associated with unexpected adverse effects, such as leukemia in children successfully treated for severe inherited immunodeficiency.[40] Safety concerns associated with gene therapies also vary by technology. Tisagenlecleucel and axicabtagene ciloleucel, for example, have been associated with a potentially life-threatening side effect called cytokine release syndrome as well as serious neurologic changes and weakening of the immune system.[132,134] There is at least a theoretical risk of transfer of viral vectors capable of gene editing to sexual partners, others, or the environment.[5,10] Not all of these risks have been fully elucidated, and long-term data (covering the expected duration of effect) are not yet available. Ongoing research and development may support advancements in the effectiveness and safety of gene therapy, as it has over the past 20-plus years of gene therapy research.[13,145]

Cost of Therapy and Need for Reimbursement Across Jurisdictions

Gene therapies approved to date have been expensive, with costs ranging from US$65,000 to greater than US$1 million (alipogene tiparvovec). This reflects the initial investment in a new technology and the very small patient pool for the initial therapies. Costs for individual treatments are expected to decrease as additional therapies enter the market and more common diseases are targeted,[146] although the potential budget impact of a gene therapy cure for highly prevalent diseases could be substantial. The budget impact of advanced therapy medicinal products for heart failure has been estimated at €348 billion[147] and for Alzheimer disease, £72 billion.[144,148] Most complex, multifactorial disorders are not, however, immediate targets for gene therapy.

It is critical to engage the organizations responsible for insurance and reimbursement, government regulatory bodies, and relevant stakeholders to develop models for reimbursement that account for one-time treatment with high upfront costs and potential long-term benefits that would offset a lifetime

of medical costs.[144] The likely need for gene therapies to be developed and administered at specialist centres further increases the challenges. Approval for treatment and reimbursement across boundaries (national, regional, district, between insurers/formularies) is complex, even for costs that are a fraction of the expected cost for gene therapy, and such cross-boundary treatment must involve negotiated agreements between the treating centre and multiple jurisdictions.[29] Costs and challenges in reimbursement were cited as reasons that the manufacturer decided not to apply for renewal of the five-year European marketing authorization originally granted to alipogene tiparvovec.[63]

Procedural Requirements and Aftercare

Gene therapies often require specialized manufacturing facilities, care centres, and clinicians trained to conduct customized procedures for such therapies. Manufacturers are required to strictly follow FDA and EMA regulations to control consistency, purity, and sterility of the vectors for administration to cells or people, and the viability and number of gene-modified cells.[10] Administration may require specialized surgical intervention; for instance, the administration of voretigene neparvovec requires removal of the posterior cortical vitreous humour of the eye before the subretinal injection,[52] and the administration of Parkinson disease therapy is intracerebral.[34] Administration of cellular therapies involving HSCT and CAR-Ts require pre-treatment conditioning, such as myeloablation to diminish immune reaction; specialized procedures such as leukapheresis to harvest and isolate cells; and shipment of cells to and from the primary care centre and the manufacturing facility. In addition, gene therapy recipients often require supportive care in case of adverse events.

Ultimately, given the technical and skill requirements, it may prove more feasible to offer gene therapy at a limited number of centres, as is currently done for transplants. In this case, however, travel and prolonged stays for patients and their caregivers may be required. Experiences in developing the processes and infrastructure for HSC transplants should help to inform the development of those for gene therapies. With refinements, standardization, and technical innovation, eventually data or isolated cells might be transmitted to a manufacturing centre and virus or transfected cells returned, but there will still be a need for specialized care before, during, and after treatment.[10,29]

In addition, for many diseases, early diagnosis and treatment minimizes irreversible damage and disability. Once therapies become available, screening programs (e.g., neonatal screening for metabolic disorders) may have to be expanded to include treatable conditions. Such screening would ensure the best possible individual and societal benefit but would further impact on system capacity and costs.[29]

Legal and Ethical Concerns

The cost of gene therapies may place them outside the reach of health care systems in developing nations, with implications for international aid. In developed nations, rare genetic diseases are unevenly distributed across subpopulations, some of whom may be socially or economically disadvantaged, e.g., sickle cell anemia appears predominantly in people of African descent, and ADA-SCID occurs more frequently in First Nations and Mennonite groups.[29] It will be essential to consider the specific needs of various population groups when making overall decisions.

For cell therapy–based technologies, transparency on the downstream commercialization of the cells, subsequent control rights, data protection, and privacy are needed. Risks and benefits associated with each technology should be considered from different stakeholders' perspectives, and this information should be communicated appropriately to the intended patients.[144]

Another important ethical issue concerns the potential misuse of gene-modifying technologies for genetic enhancements. National laws vary considerably in what they prohibit, and many jurisdictions have not yet addressed this concern.[149] On the other hand, the communal nature of DNA, the availability of gene-modifying technology (albeit not at the stage of established drugs or medical devices), and continuing scientific advances offer an argument in favour of gene therapy.[150]

Canadian Gene Therapy Initiatives

Canadian researchers are or have been involved in numerous gene therapy trials, including two of the three trials for alipogene tiparvovec for monogenic lipoprotein lipase deficiency,[151-153] which has a high prevalence in Quebec due to a founder effect. Current gene therapy trials are listed in Health Canada's Clinical Trials Database.[2] A few of the initiatives

supporting translational research and implementation of gene therapy or active production of gene therapy products are the following:

The Conconi Family Immunotherapy Lab, in BC Cancer's Deeley Research Centre in Victoria, British Columbia, which has been established to provide custom immunotherapy production for cancer patients in British Columbia, in the form of CAR T-cells and oncogene-targeted T cells[154]

BioCanRx,[155] a network of stakeholders formed to develop cancer immunotherapies through their support of educational initiatives, early clinical trials, and initiatives to address socioeconomic considerations for their adoption, including the Getting better Outcomes with Chimeric Antigen Receptor T cell therapy (GO–CART) program[156]

Centre de commercialisation en immunotherapie du cancer, at the Hôpital Maisonneuve-Rosemont, which is part of the Centres intégrés universitaires de santé et de services sociaux (CIUSS) de l'Est-de-l'Ile-de-Montréal.[157]

In Canada, gene therapy is expected to develop within a strong existing environment supporting stem cell therapeutics and regenerative medicine, transfusion and blood donation, and the treatment of cancer and rare diseases. Groups with a possible supportive role include the Stem Cell Network (national), Centre for Commercialization of Regenerative Medicine (national), Regenerative Medicine and Cell Therapy Network (CellCAN, national), Cell and Tissue Therapy Network (ThéCell, Quebec), Ontario Institute for Regenerative Medicine, the Canadian National Transplant Program and Transplant Registry, and the Canadian Association of Provincial Cancer Agencies.[158]

Final Remarks

- Gene therapy technologies offer an alternative, and often the only alternative treatment option for patients with advanced ailments or rare genetic conditions.
- Recently approved products and fast-track regulatory review for many technologies are offering hope of benefit for those affected by these conditions. Continued product development and refinement, monitoring of long-term clinical efficacy and safety, and development of frameworks for the assessment of these technologies are important for continued momentum.
- The unique characteristics of gene therapy offer new treatment opportunities but will also pose new challenges to the health care system. An open dialogue among all relevant stakeholders is crucial to overcoming these hurdles.

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