An Overview of Developments in Gene Therapy

Summary

- Gene therapy is a new, emerging area of therapeutics aimed at curing or significantly improving 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, and recently a number of products have been approved or are in the advanced stage of clinical research.
- The upfront current cost of gene therapy is generally very high. Multi-stakeholder dialogues are necessary to manage and reimburse the cost of these products. In addition, specialized care centre and training to manufacture, deliver or administer these treatments are vital to ensure accessibility and quality of care.

Methods

These bulletins are not systematic reviews and do not involve a detailed critical appraisal. 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 (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. 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 30th, 2018 were incorporated into the report.

Study Selection

The search results were divided between two authors by topic area. No duplicate screening was completed. 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 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 “a set of strategies that modify the expression of an individual’s genes or repair abnormal genes.” Health Canada does not have a specific
definition of gene therapy. In both countries, gene therapies are regulated as biologic drug therapies.2

Gene therapy involves 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, and protects it from being broken down by the cell’s defenses or recycling systems once inside. 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.3-5 The gene therapy agent can be injected into the body (in vivo gene therapy) or used to modify cells taken from the body, which will then be re-infused (ex vivo gene therapy; see Figure 1, which applies to both gene editing and gene transfer). Replacement gene therapy aims to provide a working copy of the damaged gene(s), boost the availability of a disease-modifying gene, or suppress the production of a damaged gene.3-5 Gene therapy for the treatment of cancer primarily aims to selectively kill or suppress the growth of malignant cells.6,7 Emerging “gene editing” technologies aim to modify chromosomal DNA and repair genetic errors directly.3

Gene therapy is a very active area of development. As of January 28, 2018, nine gene therapy products have been approved worldwide. Predictions for the near future include (from 2016) 12-14 new gene therapies submitted for approval in the next couple of years,8 and (from 2017) around 40 new therapies approved by the end of 2022.9

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

- Orphan Product (FDA),10
- Fast Track (FDA),11
- Breakthrough Therapy (FDA),12
- Priority review (FDA),13
- Rare Pediatric Disease Priority Review (FDA),14
- Orphan designation (EMA),15 and
- PRIME (EMA).16

Further information concerning the regulatory context of gene therapy development will appear in the concurrent CADTH Environmental Scan,12 while this horizon scan summarizes briefly the technologies, indications, status and implementation issues surrounding gene therapies. CADTH is also producing a more fulsome prospective assessment of voretigene neparvovec, a recently introduced gene therapy for an inherited retinal dystrophy, in a distinct report.18

Indications

The gene therapies that have made the most progress towards market availability treat disorders that are underlain by single gene mutations.3 Many of these are rare or ultra-rare diseases with few treatment options besides supportive and symptomatic care. Development of gene therapies is also influenced by ease of administration in target tissues, e.g., diseases of the eye19 and of the hematopoietic system (immunity and blood).20-21 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;22-23 gene editing approaches are now being investigated24 to address such shortcomings.
Research groups and companies are also interested in replacement gene therapy for more prevalent acquired disorders, including cardiovascular and peripheral vascular disease, in which the production of certain proteins has become insufficient, degenerative diseases of the nervous system (e.g., Parkinson’s Disease, Huntington’s Disease, and Alzheimer’s Disease), and disorders of aging (such as osteoarthritis).

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

Who Might Benefit?

A 2017 MIT NEWDIGS (Massachusetts Institute of Technology New Drug Development Paradigms Initiative) brief, projected that around 40 gene therapies technologies would be approved by the end of 2022. Forty-five percent of these would be cancer treatments, 34% would be for the treatment of orphan diseases, 17% for common diseases, and 4% (one therapy) for the treatment of extremely rare diseases (i.e. fewer than 100 patients within the US). Given the uncertainties around the use of novel therapies, gene therapies will be approved for patients who are lacking other treatment options, either because their disease has no effective treatments, or because it has proven unresponsive to other treatments.

The Technologies

Vectors for gene transfer

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

Commonly used DNA viruses are adeno-associated virus (a non-pathogenic but abundant small virus), adenovirus (responsible for upper respiratory infections), and herpes virus. RNA viruses include retroviral vectors derived from lentiviruses (such as human HIV-1) and gammaretroviruses, all of which have the ability to integrate a DNA copy of their genetic material in the host genome.

Choice of vector depends on the size of the gene or genes that it can carry, the target cells (dividing or non-dividing, and cell type), whether or not 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 neighboring genes involved in the development of cancer. Antigenic potential is important because many of the vectors are derived from native viruses; antibodies from a previous exposure to native virus or to a
therapeutic form can attack and destroy the administered vector or cells carrying it. Table 1 summarizes important properties of some common vectors.

**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.

**Ex vivo gene therapy**

In ex vivo delivery system, cells or are harvested from the patients’ own body (autologous) or other healthy individuals (allogeneic). They are then modified using genetic engineering tools outside the body and purified/enriched and/or activated before being transplanted back into the patient. 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. Most ex vivo therapies are based on cells from autologous sources, with a few exceptions. Autologous cells are less likely to be the targets of immune reactions, unlike 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 pose technical challenges.

**Genome editing**

In this approach, gene editing machinery is directly transferred into host cells (using either ex vivo or in vivo approaches) such that the modification of genome occurs within the recipient as opposed to using vectors to transfer the modified genes themselves. Unlike viral vectors, whose effect may be transient and can only supplement missing or defective genes, genome editing technologies can be used to add, inactivate, or correct a gene with a permanent effect.

Gene editing is carried out using nucleases, enzymes which bind to DNA with varying degree 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:

- zinc finger nuclease (ZFN),
- transcription activator-like effector nuclease (TALEN), and
- 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, are time-consuming, and expensive, limiting their clinical application. 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 genome editing therapy was sufficiently advanced in development to be included in this report.

**CAR-T cell therapy**

Chimeric antigen receptor (CAR)-T cells are T cells genetically modified to express receptors to recognize antigens that are commonly expressed on tumour cells. CAR T-cells combine the
ability of monoclonal antibodies (mAbs) to identify specific targets with the ability of T-cells to activate the immune system and kill target cells. Upon recognizing tumour-specific antigens, CAR-T cells activate leading to an increase in their numbers, and the secretion of immune activators, which work towards targeting and destruction of tumours. To date, different tumour antigens (e.g. CD19, B-cell maturation antigen [BCMA]) and vector/delivery systems (e.g. lentiviral vectors, transposons, mRNA, CRISPR/Cas9) have been investigated in the CAR-T approach.4

The general approach for CAR-T therapy is similar to ex vivo methods for cell-based therapies listed in Table 2. First, cells from patients are collected by leukapheresis in the primary care centre followed by isolation, enrichment, and activation of specific T cells 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 lymphodepletion-chemotherapy prior to CAR-T cell infusion in order to minimize host immune reaction and to enhance T-cell growth and anti-tumour activity.

Current research is aimed at expanding the CAR-T 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 treatment has yet to be successfully used in solid tumours. Research is also underway to develop allogeneic (donor) CAR-T cell therapies that can be used “off the shelf” without invoking rejection or graft-versus-host disease (GVHD). Success in treatment of certain cancers has led to T cell-based therapies into other diseases such as autoimmune disorders and AIDS4, also described in Table 2.

Regulatory and Development Status

Approved Gene Therapies

North America

Canada

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

United States

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. They are listed in order of date of approval.

- **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.31 It consists of recombinant herpes virus 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.32

- **Tisagenlecleucel** (Kymriah, Novartis Pharmaceuticals Corporation) is the first CAR-T cell therapy approved by the FDA (August 2017) for the treatment of pediatric and young adult patients (up to 25 years of age) with B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse, who are ineligible for a hematopoietic stem cell
transplant HSCT. It consists of autologous T cells genetically modified using a lentiviral vector to encode an anti-CD19 CAR. The FDA granted tisagenlecleucel Priority Review and Breakthrough Therapy designations. Tisagenlecleucel has been submitted for approval to the EMA for two indications, relapsed or refractory B-cell acute lymphoblastic leukemia in children or young adults, and relapsed or refractory diffuse large B-cell lymphoma in adults, both ineligible for HSCT.

- **Axicabtagene ciloleucel** (Yescarta, Gilead Sciences, Inc) was approved by the FDA in October 2017 for the treatment of adult patients with unresponsive or relapsing diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is a CD19-directed autologous T cell immunotherapy genetically modified using a retroviral vector. It has received Orphan designation for several rare lymphomas and Breakthrough Therapy Designation for refractory, aggressive non-Hodgkin lymphoma. An application for European marketing authorization has been submitted to the EMA.

- **Voretigene neparvovec-rzyl** (Luxturna, Spark Therapeutics, US) was granted approval status by the FDA in December 2017 for the treatment of patients with progressive vision loss due to confirmed biallelic (affecting both copies) mutation in the RPE65 gene. 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. CADTH is currently preparing a horizon scanning bulletin on voretigene neparvovec, including an overview of the evidence of efficacy and safety. An application for European Marketing authorization has been submitted.

**Other Countries**

A total of nine gene therapies have received marketing worldwide. All approved gene therapies use gene transfer technologies. Therapies with approval in the European Union (EU) and other jurisdictions are listed below, 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. Gencidine is a recombinant adenovirus engineered to express wildtype-53, a tumour suppressor gene, 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. Oncorine is a recombinant adenovirus engineered to selectively replicate in and destroy tumour cells, 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, which 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 was
regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. 

- **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) for whom no suitable, matched stem cell donor is available. It is an autologous CD34+ enriched cell therapy transduced with RV 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, thereby reversing the enzyme deficiency. This therapy was given orphan medication designation by the EMA. 

- **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 an unmet need filled by the treatment. An ongoing phase III trial is underway across the world for this treatment. Zalmoxis constitutes of allogeneic T cells genetically modified with a retroviral vector encoding for the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2). It is recommended as an adjunct treatment for adult patients who received a HSCT.

- **TG-C/ Invossa** (Tonogenchoncel-L, 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. This is an allogeneic cell therapy where a mix of unmodified and genetically modified chondrocytes made to express Transforming Growth Factor β1 (TGF-β1), and anti-inflammatory mediator, are injected.

**Gene therapies in advanced development**

Thirteen gene therapies are in advanced development, either with current Phase III trials or completed Phase II or Phase I/II trials with one or more special regulatory designations, and plans to initiate Phase III trials in 2018. Nine involve in vivo administration of virus or plasmids, and three involve ex vivo manipulation and infusion of autologous cells.

- **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. GS010 consists of an AAV9 vector carrying a functional copy of ND4, administered by intravitreal injection.

- **NSR-REP1** (Nightstar Therapeutics) for the treatment of patients with vision loss due to choroideremia. NSR-REP1 consists of an AAV2 vector carrying human REP1 administered by intraretinal injection.

- **Valoctocogene roxaparvovec** (BioMarin Pharmaceuticals, US) for the treatment of patients with hemophilia A. Valoctocogene roxaparvovec consists of an AAV vector carrying a functional coagulation factor VIII gene, administered by intravenous infusion.

- **AMT-061** (uniQure) for the treatment of patients with hereditary hemophilia B. AMT-061 consists of an AAV5 vector carrying a functional gene for coagulation factor XI administered by intravenous infusion.
• AVXS-101 (AveXis) for the treatment of children with spinal muscular atrophy Type I. AVXS-101 consists of a recombinant AAV9 virus carrying a functional copy of the SMN1 (“survival motor neuron 1”) gene, administered by intravenous injection.

• Alferminogene tadenovec (Generx, Gene Biotherapeutics [formerly Taxus Cardium Pharmaceuticals Corp]) is entering Phase III development for the treatment of patients with angina pectrosis due to cardiac insufficiency in association with advanced coronary disease. 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 could not be relieved by conventional treatment of coronary artery disease.

• RT-100 (Renova Therapeutics) is entering Phase III development for the treatment of patients with reduced left ventricular ejection fraction heart failure. RT-100 consists of an Ad5 vector carrying human adenyl cyclase 6 administered by intracoronary injection. It is intended to improve the contractility of the heart muscle. It is intended for use in patients with refractory heart failure unrelated by best current care.

• Pexastimogene devacirepvec (Pexa-Vec, SillaJen, Inc) is currently in Phase III development 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 perplamid (Collategene, AMG0001, 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 Hepatocyte Growth Factor (HGF) gene. A Phase III study has been completed in Japan. A Phase III international study was terminated in 2016 with plans to revise the scope and re-initiate.

• VM202 (VM Biopharma) is being developed for the treatment of diabetic foot ulcers and painful diabetic peripheral neuropathy. It is a plasmid containing human HGF gene. Phase II studies have been completed for critical limb ischemia.

• LentiGlobin BB305, developed by Bluebird Bio, consists of autologous CD34+ HSCs transduced ex vivo with a recombinant lentiviral vector that restores the function of the β-globin gene which is defective in patients with β-thalassemia. This gene therapy has been given Breakthrough Therapy and PRIME designation from FDA and EU, respectively. Additionally, this is considered an orphan medication in the EU. Currently, this therapy is in phase III trial for β-thalassemia and phase I for sickle cell disease.

• Elivaldogene tavalentivec (Lenti-D, Bluebird Bio) is another autologous CD34+ HSC product being tested on patients with cerebral adrenoleukodystrophy (CALD) in a phase II/III study.

• GSK2696274 (GlaxoSmithKline) consists of cryopreserved autologous CD34+ cell clusters transduced with lentiviral vector to express arylsulfatase A 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 tested in a phase III trial.

Gene Transfer Therapies in Earlier Development
A number of other gene therapies are in Phase II or earlier development. Twelve technologies that have received one or more forms of special regulatory designation intended to accelerate development are described in brief.

- **SPK-9001** (Spark Therapeutics) is in Phase I/II development for the treatment of patients with hereditary hemophilia B. SPK-9001 consists of an AAV vector carrying the gene for coagulation factor XI, administered by intravenous infusion.

- **ABO-102** (Abeona Therapeutics, Inc) is in development for the treatment of children with Sanfilippo Syndrome Type A (MPS IIIA, a lysosomal storage disorder). ABO-102 consists of a recombinant AAV9 vector carrying the SGSH gene, administered by intravenous infusion.

- **AAV1-Follistatin** (Milo Biotechnology) is in development for the treatment of Becker Muscular Dystrophy. AAV1-Follistatin consists of a recombinant AAV1 vector carrying the follistatin gene. Treatment is by intravenous infusion.

- **Mydicar** (Theragene Pharmaceuticals) 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 intra-coronary injection. The Phase IIb clinical trial for Mydicar did not reach its primary endpoint, but the drug was acquired by Theragene Pharmaceuticals and is continuing in active development.

- **JCAR017 (Lisocabtagene maraleucel)** Juno Therapeutics in collaboration with Calgene Corporation (Summit, New Jersey) have developed a range of CAR-T cell products, including JCAR017. JCAR017 is an immunotherapy that targets CD19 receptors on malignant B cells. The therapy is currently being tested in patients with refractory or relapsed chronic lymphocytic lymphoma or small cell lymphocytic lymphoma (Phase I/II) and refractory or relapsed B-cell non-Hodgkin Lymphoma.

- **DNX-2401** (DNATrix) is in Phase II development for glioblastoma or gliosarcoma with disease progression. DNX-2401 is a recombinant adenovirus administered by direct intratumoural injection.

- **ONCOS-102** (Targovax) is in Phase I/II development for malignant pleural mesothelioma. 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) has completed Phase I/II trials for malignant pleural mesothelioma. SEPRAVIR is a recombinant oncolytic herpes simplex I virus administered intrapleurally in conjunction with intravenous chemotherapy.

- **Toca 511 and Toca FC (Vocimagene amiretrorepvec)** Toca 511, developed by Tocagene, is a cancer-selective immunotherapy comprising of retroviral vector encoding a prodrug activator enzyme, cytosine deaminase (CD) gene, that converts the orally administered antifungal prodrug 5-fluorocytosine (5FC) to the anticancer drug 5-fluorouracil (5-FU) in transfected cells. The treatment is tested in phase II/III clinical trial on patients with recurrent high-grade glioma (HGG).
• **NY-ESO-1** (Adaptimmune, in collaboration with GSK) have developed NY-ESO SPEAR T-cell, an autologous T cell therapy transduced with a retroviral vector encoding a T-cell receptor (TCR) specific for the cancer-testis antigens (CTAs) NY-ESO-1 and L antigen family member 1 (LAGE-1; Cancer/Testis Antigen 2; CTA2; CT2). The product is in phase I/II trial worldwide for synovial sarcoma and multiple myeloma.

• **OTL-101** Orchard Therapeutics Limited received a Rare Paediatric Disease Designation by the FDA, in addition to Orphan Drug and Breakthrough Therapy Designations, for OTL-101, an autologous CD34+ HSC treatment encoding for the ADA gene for use in ADA-SCID patients. Its safety and efficacy is being tested in a phase I/II trial.

• **G1XCGD** (Genethon) is currently testing an autologous CD34+ cell transduced with lentiviral vectors to restore function of the NADPH oxidase enzyme for the treatment of X-linked chronic granulomatous disease (CGD), 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), an inherited immune deficiency primarily affecting males that manifests in hemorrhaging and eczema as a result of a defective WAS gene and subsequent impaired blood clotting ability. Both of these therapies are currently in phase I/II stage.

**Gene Editing Therapies in Early Development**

As of 2017, there are 18 gene editing-based technologies being tested in clinical trials worldwide, mostly in phase I (see Figure 2).

There are no clinical trials (ongoing or completed) using gene editing-based technologies that have progressed beyond phase II stage. The few studies in phase I/II stages are described below.

• **Sangamo Biosciences** has completed a phase I/II trial with a ZFN-based product, SB-728-T, which is an autologous CD4+ T cell therapy for silencing the CCR5 gene to combat HIV infection.

• **CRISPR/Cas9-based technology** is currently ongoing and in early stages of clinical trials only 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. CRISPR/Cas9-mediated PD-1 knockout EBV-specific cytotoxic T-cells are tested in Phase I/II for treatment of a number of Epstein-Barr virus-positive advanced stage malignancies — gastric carcinoma, nasopharyngeal carcinoma, lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma. Finally, allogeneic CAR-T cells, UCART019, engineered to target refractory or relapsed CD19+ leukemia and lymphoma are tested in a phase I/II trial.

**Costs**

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

US list prices are available for the five gene therapies marketed in the US.
• **Voretigene neparvovec-rzyl (Luxturna)** has a list price of US$425,000 per eye.\textsuperscript{107} Administration requires a bilateral subretinal injection in two separate procedures separated by no less than six days.\textsuperscript{108} Subretinal injection requires vitrectomy to access the retina and is a specialist eye surgery that will likely only be available 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,\textsuperscript{109} but this will vary by patient. It is administered as a series of injections over at least six months until there are no remaining injectable lesions or other treatment is needed,\textsuperscript{31} given in conjunction with standard chemotherapy. Injections are subcutaneous or intranodal, so no surgical procedure costs are anticipated.

• **Tisagenlecleucel (Kymriah)** has a list price of USD $475,000 but estimates go up to USD $750,000.\textsuperscript{110} There is no information on cost per dose. It is administered intravenously and is available as a suspension in a patient-specific infusion bag. Lymphodepleting chemotherapy (Fludarabine and cyclophosphamide) course is recommended prior to Kymriah infusion, and tocilizumab should be made available during and post-infusion for emergency treatment of cytokine release syndrome. Due to the nature of the treatment, multiple hospital visits and other health care interventions are necessary. Additional pre and post-treatment medications are also likely to be suggested. Therefore, the total cost may surpass the estimated cost.\textsuperscript{34-36}

• **Axicabtagene ciloleucel (Yescarta)** has a list price of USD $373,000.\textsuperscript{39-42} It is administered by IV infusion, preceded by fludarabine and cyclophosphamide.

• **Strimvelis** has a list price of €594,000, or US$648\textsuperscript{USD $648,000}.\textsuperscript{48} It should be administered through IV infusion, and once only.\textsuperscript{49,50} It is recommended that Strimvelis infusion should be preceded by IV busulfan and antihistamine to eliminate abnormal bone marrow cells and to reduce the risk of allergic reactions, respectively.\textsuperscript{49,50} Administration of Strimvelis should be done in a specialist transplant centre, and a physician experienced with *ex vivo* cell therapy products and management of patients ADA-SCID.

**Concurrent Developments**

Gene therapy is a very active area of research and development in which existing technologies are being developed for additional indications, where the same or a closely related vector is used to deliver different genes (e.g., for inherited retinal disease),\textsuperscript{19} or 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.\textsuperscript{111}

- **Neovasculgen** is being investigated for Raynaud’s syndrome secondary to scleroderma, diabetic foot ulcers, and peripheral nerve injury.\textsuperscript{112}
• **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 non-functioning SMN1 gene but have extra copies of a second similar gene, SMN2 that modulates the severity.  

• **AAV-Follistatin** is in Phase I development for Duchenne muscular dystrophy, and inclusion body myositis.  

• **Oncorine** (head and neck cancer) is also used to treat lymph node metastases of these cancers, hepatocellular cancer, and pancreatic cancer.  

• **Pexastimogene devacirepvec** is in Phase II and earlier development for other cancers.  

• **DNX-2401** is also in Phase I development for pediatric pontine glioma.  

• **ONCOS-102** is also in Phase I development for melanoma and advanced peritoneal cancers.  

• **Beperminogene perplasmid** is also being developed for arteriosclerosis obliterans and Buerger's Disease in alliance with Mitsubishi Tanabe Pharma.  

• **VM202** has completed Phase I/II for amyotrophic lateral sclerosis and received a Fast Track designation, and is in development for coronary artery disease.  

### Implementation Issues

Some of the main implementation issues revolve around the adequacy of evidence for decision-making, the cost of treatment, and its requirements of the health care system in terms of procedures and aftercare.  

**Adequacy of evidence for decision-making**

Because some gene therapy technologies are supported by regulators through accelerated review schemes, 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 endpoints, short duration of treatment or follow-up, lack of safety information), posing challenges for health technology assessment agencies and payers.  

Decision-makers may be required to determine eligibility for reimbursement on the basis of a small body of evidence, potentially resulting in contradictory decisions for neighbouring jurisdictions, or resistance to the withdrawal of a therapy if later evidence does not support its effectiveness, particularly where there are no effective alternatives.  

Areas of particular uncertainty concern the predictability and durability of the response and the safety of gene therapies for patients, those in contact with them, and the environment. Most trials have observed a variable response across patients. Gene therapy technologies do not always follow a pattern similar to conventional pharmaceutical or biologic drugs, and instead may demonstrate rapid turn-on or turn-off effects.  

To date, most studies of gene therapies involve relatively short follow-up for treatment intended to be permanent or long-term. Safety concerns associated with gene therapies vary by technology and are different than drugs or devices, owing to their capacity to produce long-term or even permanent genome changes.  

Gene therapy has, in the past, been associated with unexpected adverse effects, e.g., leukemia in children successfully treated for severe inherited immunodeficiency.  

There is at least a theoretical risk of transfer to sexual partners, others, or the environment. Not all these risks have been fully elucidated.
Cost of therapy and need for reimbursement across jurisdictions

Gene therapies approved to date have been expensive, with costs ranging from USD $65,000 to greater than a million (for the recently discontinued Glybera). The potential budget impact of a gene therapy cure for common diseases is immense; one estimate puts the budget impact of a cure for heart failure at €348 billion, and Alzheimer disease, £72 billion.\textsuperscript{119} 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 be offsetting a lifetime of medical costs.\textsuperscript{119} The likely need for gene therapies to be developed and administered at specialist centres further increases the difficulties. Approval for treatment and reimbursement across boundaries (national, regional, district, between insurers/formularies) is non-trivial, even on costs that are a fraction of the expected cost for gene therapy, and will involve negotiated agreements between the treating centre and multiple jurisdictions.\textsuperscript{21}

Procedural Requirements and Aftercare

Gene therapies often require specialized manufacturing facilities, care centres, and clinicians trained with customized procedures for such therapies. Manufacturers are required to strictly follow regulations by the FDA and EMA guidelines to control consistency, purity and sterility of the vectors for administration to cells or peoples, and viability and number of gene-modified cells.\textsuperscript{3} Administration may require specialist surgical intervention; for instance, the administration of voretigene neparvovec requires removal of the posterior cortical vitreous humour of the eye before the subretinal injection,\textsuperscript{46} or the intracerebral administration of Parkinson’s disease therapy.\textsuperscript{26} Administration of cellular therapies involving HSCT and CAR-Ts require pre-treatment conditioning such as myeloablation to diminish immune reaction, specialized procedure such as leukapheresis to harvest and isolate cells, and shipping cells to and from the primary care centre and the manufacturing facility. In addition, gene therapy recipients often require supportive care for adverse events.

Ultimately, given the technical and skill requirements, it may prove more feasible to offer gene therapy at a limited number of centres, which will require travel and prolonged stays for patients and their caregivers. 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 specialist care before, during and after treatment.\textsuperscript{3,21}

In addition, for many diseases, early diagnosis and treatment minimizes irreversible damage and disability. Once therapies become available, screening programs may have to be expanded, so as to obtain the best possible individual and societal benefit, but with further impact on system capacity and costs.\textsuperscript{21}

Legal and ethical concerns

The cost of these therapies may place them outside the reach of health care systems in developing nations, with implications for international aid. Within 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 predominately in people of African descent, and ADA-SCID occurs more frequently in First Nations and Mennonite groups.\textsuperscript{21} It will be essential to consider the needs of sub-populations 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’ perspective, and this information need to be communicated appropriately to the intended patients.\textsuperscript{119}

Another important ethical issue concerns the potential misuse of gene-modifying technologies leading to “designer” individuals or inappropriate enhancements. National laws vary considerably in what they prohibit, and many jurisdictions have not yet addressed the question.\textsuperscript{120} On the other hand, the communal nature of DNA, availability of gene-modifying technology (albeit not at the stage compared to established drugs or medical devices), and continued advances of science offer an argument in favor of gene therapy.\textsuperscript{121}

**Final Remarks**

- Gene therapy technologies offer an alternative and often only 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 to those affected by these conditions. It is, therefore, necessary for the clinical efficacy, safety and market access of these technologies to build on the recent advances.
- The unique characteristics of gene therapy will pose new challenges to the health care system. An open dialogue between all relevant stakeholders will be crucial to overcome these hurdles.
References


33. FDA. FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome. 2017; [Link](https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm).

34. Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice. August 30 2017; [Link](https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019), 2018.


Tables & Figures

Figure 1  Strategies for gene therapy

![Strategies for gene therapy](https://example.com/strategy_image.png)

Figure from Shim, 2017


[https://creativecommons.org/licenses/by-nc-nd/3.0/](https://creativecommons.org/licenses/by-nc-nd/3.0/)

Table 1  Virus-Derived Vectors Commonly used in Gene Therapy

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| Immunogenicity            | Presence of antibodies varies by serotype | Antibodies prevalent | Used ex-vivo | Antibodies prevalent.
Figure 2  Summary of Gene Editing Therapy Trials, as of Early 2017

Figure 5. Current status of therapeutic gene editing clinical trials. Clinical

Table 1  Summary of Development and Regulatory Status of Gene Therapies Described in this Bulletin

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<tr>
<td>NY-ESO-1(c259) T Cells</td>
<td>Adaptimmune, GSK</td>
<td>SS, MM</td>
<td>Ex vivo</td>
<td>I/II</td>
<td>Y</td>
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Note: Trials in Phase are ongoing unless otherwise indicated.

* Initiating trials.

b OTL-101 has received a Rare Paediatric Disease Designation

c Conditional Market Authorisation in EU