

ENVIRONMENTAL SCAN

Gene Therapy: International Regulatory and Health Technology Assessment (HTA) Activities and Reimbursement Status

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Summary

- There is widespread variation in the definition of gene therapy used by international regulatory bodies and a lack of definitions specific to reimbursement bodies. In Canada, gene therapies are classified as drugs by Health Canada.
- There is a lack of gene therapy-specific guidelines or frameworks from HTA bodies.
- Several gene therapies have received international regulatory approvals and/or reimbursement recommendations in recent years.
- Regulatory and reimbursement challenges include limited data and uncertainty around efficacy, long-term safety, and cost-effectiveness.

Context

Over the last decade, important scientific advances have been made in the field of gene therapy.

Recently approved gene therapies in the US and Europe are offering one-time treatment for severe or terminal conditions that purportedly result in a lifelong benefit.¹ Transitioning these new advances from bench to bedside is often challenging, given the lack of long-term evidence related to efficacy and safety, and the costs associated with these therapies.² Therefore, the regulatory and reimbursement processes for these novel therapies may require novel pathways and interpretations of value.³

Recent approvals from international regulatory bodies and decision-makers reflect both the rapid development and growing demand for gene therapy. The FDA in the US approved the first gene therapy for acute lymphoblastic leukemia (ALL) in children and young adults in August 2017⁴ and the second gene therapy for aggressive lymphoma in adults in October 2017, granting both chimeric antigen receptor (CAR) T-cell technologies Priority Review and Breakthrough Therapy designations.⁵ In December 2017, the FDA also approved the first non-CAR T-cell, gene therapy for the treatment of a rare inherited form of vision loss.⁶ The National Health Service (NHS) in the UK announced in October 2017 a decision to fund gene therapy for the treatment of adenosine deaminase deficiency in children at a cost of more than £500,000 for the single treatment.⁷

To inform CADTH's approach and process for evaluating gene therapy and to help Canadian jurisdictions understand and prepare for this new health technology, this Environmental Scan has focused on gathering information regarding international regulatory and HTA activities and the reimbursement status of gene therapies.

Objectives

The objective of this Environmental Scan is to identify and summarize information regarding the current context of regulation, reimbursement, and evaluation of gene therapy.

The following specific objectives are addressed:

1. To identify how gene therapy is defined by regulatory and HTA bodies internationally.
2. To identify any guidelines or frameworks for evaluating gene therapy from HTA bodies internationally.
3. To identify any regulatory approvals issued and reimbursement decisions made for gene therapy internationally.

Methods

The findings of this Environmental Scan are based on responses to the *INAHTA Listserv Survey* gathered as of January 12, 2018 (Appendices 1 and 2), and a limited literature search.

An invitation to the survey was distributed through the INAHTA listserv to international HTA organizations on December 4, 2018. Responses to the survey were due by December 22, 2017, and were forwarded to CADTH by the INAHTA secretariat. To increase response rates, a targeted approach was subsequently undertaken, and the survey was shared with key informants on January 5, 2018. The final deadline for survey responses was January 12, 2018.

A limited literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library (2016, Issue 11). Grey literature was identified by searching relevant sections of the Grey Matters checklist (<https://www.cadth.ca/grey-matters>). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012 and December 15, 2017. Regular alerts updated the search until project completion; only citations retrieved before February 12, 2018 were incorporated into the analysis.

The inclusion criteria for the selection of evidence included sources that focused on gene therapy, in any population, with specific outcomes such as regulatory definitions or classifications, regulatory decisions, HTA definitions or classifications, policy, guidelines, or frameworks for HTA, or reimbursement decisions. Grey literature was identified by searching relevant sections of the CADTH *Grey Matters* checklist.⁸ A focus on INAHTA member countries was used in order to limit the volume of sources.

Findings

Objective 1: Definition of Gene Therapy

Literature

The literature search identified evidence from both the peer-reviewed literature and grey literature regarding the international definitions of gene therapy used by regulatory and HTA bodies. There is no consistent definition for gene therapy. Adding to the complexity that arises from multiple definitions, gene therapies are often grouped together with other cell therapies and tissue engineering techniques under the umbrella of “regenerative medicine” or “advanced therapies.”⁹ This Environmental Scan identified several definitions of gene therapy utilized by a number of international regulatory bodies; however, there was a lack of information on gene therapy definitions from HTA organizations.

In the Canadian context, Health Canada does not have specific guidelines or regulations pertaining to gene therapy, and while there is no formal definition, these products are considered biological drugs and fall under the Food and Drug Regulations.^{10,11} A separate definition of gene therapy is not required, as these therapies can be regulated under the existing flexible regulatory frameworks. (Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario: personal communication, 2018 February 21). Specifically, it is the Biologics and Genetic Therapies Directorate of Health Canada that oversees the regulation of these technologies.¹²

The FDA in the US provides an interpretation that “gene therapies, including genetically-modified cells, that lead to a durable modification of cells or tissues”¹³ may fall under the definition of a “regenerative medicine therapy” (RMT)¹³. Furthermore, RMTs used to “treat, modify, reverse, or cure serious conditions”¹³ are eligible for expedited review by the FDA, if the technology meets the criteria for these expedited programs.¹³

For the European Medicines Agency (EMA) (the regulatory body for countries in the European Union [EU]), gene therapy falls under the category of Advanced Therapy Medicinal Products (ATMP). Specifically, gene therapy is defined by the EMA as gene therapy medicinal products (GTMP) typically consisting of “a vector or delivery formulation/system containing a genetic construct engineered to express a specific therapeutic sequence or protein responsible for the regulation, repair, addition, or deletion of a genetic sequence.”¹⁴

Table 1 provides a list of key definitions of gene therapy and related terms used by various international regulatory and HTA bodies identified in the scan. The definitions below demonstrate the diverse terminology and categorization of gene therapies by these agencies.

Table 1: Key Definitions for Gene Therapy and Other Related Terms

Organization	Term	Definitions
Regulatory Bodies		
FDA (US)	a) Biological products	a) “Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources – human, animal, or microorganism – and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.”(p899) ²
	b) Regenerative medicine therapies	b) Regenerative medicine therapies are “Defined in section 506(g)(8) of the FD&C Act, as including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271). As FDA interprets section 506(g), gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. Additionally, a combination product (biologic-device, biologic drug, or biologic-device-drug) can be eligible for RMAT designation when the biological product component provides the greatest contribution to the overall intended therapeutic effects of the combination product (i.e., the primary mode of action in the combination product is conveyed by the biological product component).”(p2) ¹³

Organization	Term	Definitions
EMA (EU)	a) Advanced Therapy Medicinal Product (ATMP)	a) "A medicinal product as defined in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (the Directive), as amended to reflect new innovative therapeutic products. Specifically, an ATMP is a biological medicinal product which is either: <ul style="list-style-type: none"> • a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC; • a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC; or • a tissue engineered product as defined in Article 21(b) of the ATMP Regulation (1394/2007/EC)."(p899)²
	b) Gene therapy medicinal products	b) "Biological medicinal products which <ul style="list-style-type: none"> • contain an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence; • its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. • Note: vaccines against infectious diseases are not included in this definition as an established regulatory pathway for vaccines in the EU."(p341)¹⁵
Therapeutic Goods Administration (TGA) (Australia)	Biological	"Essentially a biological comprises, contains or is derived from human cells or human tissues . . . and is used to: treat or prevent disease, ailment, defect, or injury; or diagnose the condition of a person; or influence, inhibit, or modify a physiological process in persons; or test the susceptibility of persons to a disease or ailment; or replace or modify parts of the anatomy in persons."(p899) ²
HTA Organizations		
CADTH (Canada)	Gene Therapy	Gene therapy is defined as "a set of strategies that modify the expression of an individual's genes or repair abnormal genes," involving the administration of a specific nucleic acid (i.e., DNA or RNA) via a viral or non-viral vector. This includes immunotherapy involving genetically-modified T cells (e.g., CAR T-cell therapy) and regenerative medicine involving genetically-modified cells or tissues, including stem cells, and genome editing. ^a
Other Organizations		
AMA (US)	Gene Therapy	"A novel approach to treat, cure, or ultimately prevent disease by changing the expression of a person's genes."(p15) ¹ "Gene therapy works by repairing, dis-activating ("turning off") or replacing dysfunctional genes that cause disease with the aim of (re)establishing normal function."(p15) ¹

AMA = American Medical Association; ATMP = Advanced Therapy Medicinal Products; EMA = European Medical Agency; EU = European Union; FD&C Act = Federal Food, Drug, and Cosmetic Act; HTA = Health Technology Assessment; RMAT = regenerative medicine advanced therapy; TGA = Therapeutic Goods Administration.

^a This is a working definition from CADTH.

Survey Data

In addition to the information identified from literature sources, six key informants who responded to the survey provided insights into this novel area. Country-specific information on how gene therapy is classified by both the regulatory and HTA bodies, based on survey responses, is provided in Table 2. Respondents were asked to indicate all answers that apply.

In addition to the six responses from Australia, Germany, Sweden, Taiwan, France, and the US, the Instituto de Evaluación Tecnológica en Salud (IETS) in Colombia did not complete a survey, but noted that CAR T-cell technologies have not yet been discussed within the organization (*Aurelio Mejia, IETS, Bogotá, Colombia: personal communication, 2018 Feb 6*).

Table 2: Gene Therapy Categorization – Survey Responses

Category	Australia		Germany		Sweden		Taiwan		France		US	
	Regulator	HTA (AHTA)	Regulator	HTA (G-BA)	Regulator (MPA)	HTA (SBU)	Regulator	HTA (CDE)	Regulator	HTA (HAS)	Regulator (FDA)	HTA (KP)
Drug				X			X	X	X	X		
Biologic	X	X			X							X
Blood or blood product												
Cellular therapy						X	X	X				X
Gene or genetic therapy				X	X	X		X	X		X	X
Vaccine												
Device												
Both drug and device												
Other												
Don't know												

AHTA = Adelaide Health Technology Assessment; CDE = Center for Drug Evaluation; G-BA = Gemeinsamer Bundesausschuss (The Federal Joint Committee); HAS = Haute Autorité de Santé; HTA = Health Technology Assessment; KP = Kaiser Permanente; MPA = Medical Products Agency; SBU = Statens beredning för medicinsk och social utvärdering (Swedish Agency for Health Technology Assessment and Assessment of Social Services).

Note: This table corresponds to Questions 1 and 3 in the survey (Appendix 1).

In summary, the evidence identified through the scan illustrates the varied gene therapy definitions and related key terms across international regulatory and HTA organizations. The classification of gene therapy is challenged by the numerous differences between international regulatory frameworks and the terminology they employ.²

Objective 2: Health Technology Assessment Frameworks for Evaluating Gene Therapy

Literature

The Environmental Scan did not identify any guidelines specific to gene therapy or frameworks produced by HTA bodies internationally. A number of identified sources did speak to the challenges facing HTA bodies, but did not indicate that any gene therapy-specific frameworks or guidelines were in place.¹⁶⁻¹⁹ These challenges often centre around the evidence and pricing requirements of currently utilized frameworks and guidelines, and the fact that gene therapies often do not fulfill these requirements. For instance, and as discussed in detail in Objective 3, there are examples where therapies have achieved regulatory approval or market authorization but then failed to secure reimbursement, often as a result of value-based pricing models, which require evidence of patient benefit against the standard of care.^{18,19} These value-based pricing models quantify and monetize the magnitude of added benefit, which is often a challenge when comparative clinical data are limited such as in the case of gene therapies.¹⁹ As well, the size of the target population, burden of disease, and unmet need are some of the considerations that influence reimbursement

decisions.¹⁸ Another challenge for HTA bodies is the lack of long-term data from clinical trials.¹⁸ Furthermore, restricted health budgets often mean that health care payers are increasingly strict regarding the quality and certainty of the evidence base to demonstrate clinical value for funded therapies.¹⁷

In Europe, while market authorization of a new medicine is centralized by the EMA for countries in the EU, reimbursement bodies are jurisdictional and, therefore, frameworks and processes are often fragmented between countries.¹⁸ In the UK, reimbursement decisions are provided by the National Institute for Health and Care Excellence (NICE), which recently completed a review to determine if its existing frameworks were suitable for assessing the value of regenerative medicines.⁹ The resulting report details a mock appraisal of CAR T-cell therapy for the treatment of B-cell ALL. While it was found that there would be a significant level of uncertainty in determining the long-term costs and benefits to patients, the authors of the report also determined that the existing methods and frameworks available to estimate uncertainty were sufficient.²⁰ Furthermore, the cost-effectiveness estimates using current pricing were within the range of acceptability to NICE using its current assessment criteria.^{9,20} They also suggested that modifications to the methods guide might be useful, and recommended the use of risk-sharing agreements between the NHS and manufacturers of regenerative medicine therapies to manage uncertainty.²⁰ Some of the methodological modifications suggested in this report include: presenting the scale of decision uncertainty using population-level health effects; formally considering irrecoverable costs; and considering the impact of learning curves for clinical and cost-effectiveness assessments.^{9,20} While the reimbursement climate in Canada differs from that of the UK, the authors of a review examining both the regulatory and reimbursement landscapes of the UK and Canada suggest that Canada may learn from the developments in the UK in terms of assessing regenerative medicine therapies and clearing reimbursement hurdles.¹⁶ Specifically, other jurisdictions such as Canada may be able to gain insight from NICE's efforts to develop frameworks and methods to manage uncertainty, including participation in multi-sector discussions, while recognizing the importance of early patient access to therapies that address unmet need.¹⁶ An Institute for Clinical and Economic Review (ICER) report, summarizing a 2016 policy summit, suggests that in the US there is a case for stakeholders to debate and seek consensus on the elements of value that are relevant to gene therapy, identify the relevant evidence to assess each element of value, and consider how these elements of value could be weighted in a decision-making process to determine reimbursement policy.⁹³

Survey Data

Information on HTA guidelines and frameworks was also gathered from the key informant survey. The respondents were asked to describe if their HTA organization has produced or is planning to produce any guidelines or frameworks specifically for the evaluation of CAR T-cell therapy or other gene therapy. Table 3 presents a tabular summary of responses for key informants. The development of a protocol for evaluating gene therapies in Australia is under way and in the planning phase, and both Germany and Sweden will likely use existing HTA frameworks to evaluate these therapies. In Taiwan gene therapies will need to be reviewed by the Taiwan Food and Drug Administration drug evaluation process and until that time the creation of any guidelines or frameworks is out of scope. In France, the evaluation of CAR T-cell therapy is considered to be within scope for existing processes and a link to the evaluation method used for Glybera was provided.²¹ Kaiser Permanente in the US explained that in their context, gene therapy assessment takes place within their existing formulary process.

Table 3: Health Technology Assessment Frameworks and Guidelines for Evaluation of CAR T-Cell Therapy and Other Gene Therapy – Survey Responses

Response	Country					
	Australia (AHTA)	Germany (G-BA)	Sweden (SBU)	Taiwan (CDE)	France (HAS)	US (KP)
No – it is out of scope for us and we will not evaluate it	if so, please explain why it is out of scope:					
				X		
				“CAR T-cell therapy [and other gene therapies] has not been approved by the Taiwan FDA yet. It will need to be reviewed by the new drug evaluation process first.”		
No – it is within scope for us, and we will evaluate it using existing process(es)	if so, please explain which existing process(es) will be used (e.g., for drugs or devices) and if possible, attach or provide links to relevant information:					
		X	X		X ^a	X
		“Early benefit assessment for drugs [will be used] (if the pharmaceutical character is predominant)” assessment for drugs [will be used] (if the pharmaceutical character is predominant).”	It is within our scope ... we would likely follow our standard HTA-procedure”			“At Kaiser Permanente, these therapies are reviewed via our existing physician-driven, evidence-based formulary process.”
Yes	Please explain and if possible, attach or provide links to relevant information:					
	X				X	
	“A protocol for evaluating CAR T-cell therapy, and other gene therapies, is still in the planning stage.”				“Glybera” ²¹	
Don't know						

AHTA = Adelaide Health Technology Assessment; CDE = Center for Drug Evaluation; HAS = Haute Autorité de Santé; KP = Kaiser Permanente; G-BA = Gemeinsamer Bundesausschuss (The Federal Joint Committee); HTA = Health Technology Assessment; SBU = Statens beredning för medicinsk och social utvärdering (Swedish Agency for Health Technology Assessment and Assessment of Social Services).

Note: This table corresponds to Question 4 in the survey (Appendix 1).

^aSpecifically for CAR T-cell therapy.

A misalignment in the criteria needed for regulatory approval versus reimbursement has also been noted as an important issue.¹⁹ In order to bridge this gap between market authorization and reimbursement, a new initiative was started in Europe in July 2017 to offer parallel consultation with the EMA and European Network for Health Technology Assessment (EUnetHTA).²² The main objective of this consultation process is to help generate evidence that meets the needs of both regulators and HTA bodies. A guideline document, detailing the specific pathways and processes involved for this parallel regulatory and HTA dialogue, is published and publicly available.²³ Early collaboration and communication between manufacturers, regulators, and payers will likely become increasingly important to improve harmonization between processes, since, according to one author, “securing market authorization is of little value to all parties if reimbursement cannot be secured.”.(p1726)¹⁸

Objective 3: Regulatory Approvals and Reimbursement Decisions

The following is a summary of information identified regarding regulatory approvals and reimbursement recommendations related to gene therapy products.

Literature

The literature search identified several gene therapies that have undergone a regulatory approval processes and/or an HTA. These therapies are presented below with information on their regulatory and HTA assessment, where available. Table 4 provides a tabular summary of gene therapies with regulatory and/or HTA review. Other gene therapies that have undergone a regulatory approval process and/or an HTA may not have been identified by the literature search.

CADTH is also completing a Horizon Scanning report on gene therapy which identified several products not listed in the summary below (i.e., Zalmoxis [nalotimagene carmaleucl], Tonogenchoncel-L [TG-C/Invossa], Oncorine [H101], Neovasculgen [PI-VEGF-165], Gendicine).²⁴

Glybera (alipogene tiparvovec)

Regulatory Review

Glybera, an orphan drug for the treatment of lipoprotein lipase deficiency, was the first gene therapy to be granted regulatory approval in the EU in July 2012.²⁵ The initial recommendation in 2011 was the refusal to grant market authorization since the efficacy and safety had not been properly or sufficiently demonstrated, but upon re-examination at the request of the applicant, the therapy was granted marketing authorization under exceptional circumstances and for a more restricted indication that targets the patient population with the greatest need (adult patients with a genetically confirmed diagnosis of lipoprotein lipase (LPL) deficiency and suffering from severe or multiple pancreatitis episodes and with detectable levels of LPL protein).²⁶ The manufacturer abandoned plans to gain FDA approval in the US when additional trials were requested.¹ Of note, market authorization for Glybera was not renewed in October 2017, for commercial reasons.²⁷

HTA Review

In terms of HTA assessment, the Haute Autorité de Santé (HAS) in France assessed Glybera and determined that there was insufficient clinical benefit due to moderate and heterogeneous effect on blood triglyceride level and because of uncertainties surrounding its short- and medium-term safety.²⁸ In Germany, Glybera was initially classified as having an

"unquantifiable benefit" through the Pharmaceuticals Market Reorganisation Act (AMNOG) process, but later gained reimbursement status when insurers reclassified it as a tissue engineered product, putting it outside of the AMNOG process.²⁹ Only one German patient has reportedly been treated with this therapy.²⁷

Strimvelis

Regulatory Review

Strimvelis, a gene therapy for the treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase deficiency, is an orphan medicinal product that received EMA approval in the EU in April 2016.³⁰ The therapy is approved for patients for whom no suitable human leukocyte antigen-matched related stem cell donor is available.³¹

HTA Review

Strimvelis has undergone HTA review in Italy with a money-back guarantee for patients failing to sustain the curative benefit.¹⁸ According to conference abstracts, this gene therapy is under assessment in Germany, though a further update on the reimbursement decision was not identified in the literature. Strimvelis was scheduled for a NICE "highly specialized technology appraisal" in the UK.^{29,32} In early 2018, NICE announced that Strimvelis has been approved in final draft guidance; and pending no appeals from consultees, final guidance was published in February 2018.^{7,33}

Kymriah (tisagenlecleucel)

Regulatory Review

Kymriah is the first CAR T-cell therapy to receive FDA approval for the treatment of a hematologic malignancy, and an August 2017 press release reported that it was the first gene therapy available in the US.⁴ Kymriah is approved for the treatment of pediatric and young adult patients with B-cell precursor ALL that is refractory or in second or later relapse.³⁴

It should be noted that due to the risk of cytokine release syndrome and other neurological events, Kymriah was granted approval with a risk evaluation and mitigation strategy (REMS) that requires hospitals that dispense this therapy to be specially certified.⁴ A post-marketing observational study was also required to further evaluate long-term safety.⁴

HTA review

An ICER report identified coverage policies for Kymriah from US insurers including Anthem, Aetna, Humana, UHC, and Health Net, and each had specific requirements.³⁵ In addition, a media release from Novartis states that an outcome-based agreement has been reached with the US Centers for Medicare & Medicaid Services.³⁶

Yescarta (axicabtagene ciloleucel)

Regulatory review

Yescarta is the second CAR T-cell-based gene therapy to be approved by the FDA in October 2017, and it is intended to treat adult patients with "certain types of non-Hodgkin lymphoma who have not responded to or who have relapsed at least two other kinds of treatments."⁵ Due to potential severe side effects, the FDA approved this therapy with a REMS that requires hospitals and clinics to be certified, and a post-marketing observational study is required to further evaluate long-term safety.^{5,37}

It should be noted that due to risk of cytokine release syndrome and neurological toxicities, Yescarta was granted approval with a REMS that requires hospitals that dispense this therapy to be specially certified.⁵ A post-marketing observational study was also required to further evaluate long-term safety.⁵

Luxturna (voretigene neparvovec-rzyl)

Regulatory Review

Luxturna is a gene therapy for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-association retinal dystrophy that has received orphan designation as well as breakthrough therapy designation from the FDA.³⁸ Luxturna was granted regulatory approval in December 2017 and is being called the first gene therapy in the US to target a disease caused by mutations in a specific gene.⁶

Imlygic (talimogene laherparepvec)

Regulatory Review

Imlygic is a tumour-killing virus that is genetically modified to express a human immune signalling gene, stimulating an immune response against tumour cells.³⁹ It has regulatory approval by both the FDA (October 2015) and EMA (December 2015).³⁹

HTA Review

According to conference abstracts, Imlygic obtained an “unquantifiable” outcome under the German AMNOG process since the German reimbursement body (G-BA) considered the choice of comparator to be incorrect.^{29,40} In addition, an identified conference abstract stated that Imlygic was recommended for restricted use by NICE in the UK with a patient access scheme.³²

Table 4: Regulatory Approvals and Reimbursement Decisions for Key Therapies

Therapy	Regulatory Approval	Reimbursement Decision	
	Yes	Yes	No
Glybera	EU – EMA ^a	Germany	France
Strimvelis	EU – EMA	Italy UK	
Kymriah	US – FDA	US	
Yescarta	US – FDA		
Luxturna	US – FDA		
Imlygic	EU – EMA ^b	UK	Germany

EMA = European Medicines Agency; EU = European Union.

^a The market authorization of Glybera was not renewed in October 2017.²⁷

^b The FDA approved Imlygic as a cell therapy.³⁹

Survey Data

The survey key informants were asked to describe if the regulatory body in their country had approved any gene therapies and if any reimbursement decisions had been made regarding these therapies. Results of these questions can be found in Tables 5 and 6, and the responses confirmed the evidence generated by the literature search. No regulatory approvals or reimbursement decisions have been made in Australia, Sweden, or Taiwan, although a current application for CAR T-cell therapy is under way in Australia. Glybera was reimbursed in Germany; however, the manufacturer has not renewed market authorization. In France, a gene therapy has not received regulatory approval, but both regulatory and reimbursement assessments have been made. Regulatory and reimbursement decisions have been made in the US.

Table 5: Regulatory Approval of Gene Therapies – Survey Responses

Response	Australia	Germany	Sweden	Taiwan	France	US
A gene therapy has been approved		X ^b				X ^e
A gene therapy has not been approved	X ^a		X ^c	X	X ^d	

Note: Table 5 corresponds to Question 2 in the survey (Appendix 1).

^a An application for CAR T-cell therapy is under way. This technology is currently available only for clinical trials.

^b Alipogene tiparvovec (Glybera) – manufacturer has not renewed market authorization.⁴¹

^c Regulatory approval is not a national procedure; only approval of clinical trials using CAR T-cells has occurred in Sweden.⁴²

^d Alipogene tiparvovec (Glybera) did not receive a positive decision.

^e Kymriah (tisagenlecleucel), Yescarta (axicabtagene ciloleucel), Luxturna (voretigene neparvovec-rzyl).

Table 6: Reimbursement Decisions for Gene Therapies – Survey Responses

Response	Australia (AHTA)	Germany (G-BA)	Sweden (SBU)	Taiwan (CDE)	France (HAS)	US (KP)
A decision has been made regarding gene therapy		X ^a			X	X
A decision has not been made regarding gene therapy	X		X	X		

AHTA = Adelaide Health Technology Assessment; CDE = Center for Drug Evaluation; G-BA = Gemeinsamer Bundesausschuss (The Federal Joint Committee); HAS = Haute Autorité de Santé;

KP = Kaiser Permanente; SBU = Statens beredning för medicinsk och social utvärdering (Swedish Agency for Health Technology Assessment and Assessment of Social Services).

Note: This table corresponds to Question 5 in the survey (Appendix 1).

^a Drugs in Germany are reimbursed by sickness funds as soon as they enter the market (with the exception of over-the-counter drugs); thus there are no reimbursement decisions for drugs.

While based on the limited evidence identified in this scan, a gap between achieving regulatory approval for a gene therapy and securing funding after HTA evaluation demonstrates that the translation from bench to bedside may be challenging. In the case of the EU where a centralized approach to regulation is utilized, the pathway to reimbursement becomes more complicated as this process differs nationally, and in some cases regionally.⁴³ According to one author, while regulatory bodies are accelerating pathways for innovative therapies, HTA bodies are resistant to recommend these products often due to immature data and high costs of treatment.⁴⁴ In order to optimize patient access to new therapies, innovative pricing contracts may be needed to help share the costs of these therapies.⁴⁵ For instance, the outcomes-based payment agreement in Italy for the use of Strimvelis has a money-back guarantee in cases where patients fail to sustain the curative benefit.¹⁸

Limitations

The findings of this Environmental Scan present an overview of current regulatory, HTA, and reimbursement activities related to gene therapy internationally. A systematic literature search was not conducted. While the literature search drew upon peer-reviewed publications, conference abstracts, and grey literature sources such as the websites of key organizations, the information presented in this scan is reflective of the information that is publicly available. Given that gene therapy is a rapidly evolving area, the latest information may not have been available at the time of this scan. The key informant survey was intended to provide further information on the HTA activities of international organizations; however, the information obtained provides a limited international picture (six complete responses and one incomplete response).

Conclusion

This Environmental Scan was conducted to enhance the current understanding of international regulatory, HTA, and reimbursement activities related to gene therapies to help Canadian jurisdictions prepare for this emerging technology. Gene therapy is a burgeoning area in medicine, and the findings of this scan indicate that it is underscored by complexity and variation. Despite this complexity, the potential benefits of these treatments may fulfill a need for patients with limited treatment options.⁹

The first objective of this scan was to identify how gene therapy is defined by regulatory and HTA bodies. The evidence obtained demonstrates widespread variation for the definition of gene therapy. In contrast to Canada, where no formal definition for gene therapy exists, the FDA and EMA provide specific definitions. In the case of the EMA, gene therapy is grouped together with other cell therapies under the category of Advanced Therapy Medicinal Products,¹⁴ and the FDA provides the interpretation that gene therapy falls under the umbrella of regenerative medicinal therapy.¹³

The second objective of this scan was to identify HTA guidelines and frameworks specific to the evaluation of gene therapies. While the literature search and survey results did not identify any HTA guidelines specific to gene therapy, a mock appraisal conducted by NICE in the UK determined that, with some modification, the existing assessment processes for health technologies would be sufficient.²⁰ Similarly, survey responses from Germany and Sweden indicated that existing HTA processes would be used to evaluate gene therapies. The respondent from Australia indicated that a protocol for evaluating CAR T-cell therapies, and other gene therapies, is in the planning stages.

The third objective, pertaining to regulatory approvals and reimbursement decisions for gene therapies, reinforced the themes of complexity and variation, with inconsistency between regulatory approval and positive reimbursement decisions. Recent regulatory approvals (e.g., Strimvelis, Kymriah, Yescarta, and Imlygic) and positive reimbursement decisions (e.g., Strimvelis, Kymriah, and Imlygic) may indicate that approaches have been developed for managing any uncertainties associated with the clinical trial data.

A number of common recommendations and solutions were suggested in the grey literature to help navigate the future of gene therapies, such as creating early dialogue between manufacturers, regulators, and payers in order to bolster evidence and ensure that criteria are being met.¹⁹ A report summarizing the discussions at a 2016 ICER Policy Summit presented recommendations for both manufacturers and payers.⁹ Recommendations for manufacturers include the collection of real-world evidence, collaborating on value assessments, and considering outcomes-based payments.⁹ The recommendations for payers include developing awareness of emerging therapies and developing categorizations of different gene therapies.¹⁹ A further recommendation includes the use of adaptive pathways, approaches that include early authorization for a limited population and further evidence collection, to promote the development

and adoption of novel products that meet the needs of patients, providers and payers.¹⁶ In general, the harmonization of definitions and processes between manufacturers, regulators and payers may continue to be an important area of discussion in this innovative and rapidly expanding area of medicine.

In the Canadian context, efforts toward this harmonization include the contribution to and adoption of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) consideration documents related to gene therapy issues that were published by the Gene Therapy Discussion Group.⁴⁶ (Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario: personal communication, 2018 February 21). Issues related to the regulatory approval and reimbursement of gene therapy products will become increasingly important in Canada as it is expected that Health Canada will have evaluated and made a decision for one such product, with another evaluation in process, by later this year. (Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario: personal communication, 2018 February 21). Furthermore Canada remains a country of choice for gene therapy development as evidenced by the ongoing clinical trials under way. (Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario: personal communication, 2018 February 21).

Overall, the findings of the scan indicated that there are key challenges surrounding the gene therapy field in the context of regulation, evaluation and reimbursement. For instance, evidence generation was commonly cited as a key challenge since randomized controlled trials are often not appropriate for the intended populations, there is difficulty with identifying appropriate comparators for gene therapy, and there is uncertainty around long-term safety.^{1,47} Stemming from these issues, it is difficult to assess the value of a product and agree on pricing. Evaluating the cost-effectiveness of gene therapies may be difficult within the existing approaches to HTA and, according to one source, potential solutions may include adaptive pathways (reimbursement approval with early data/surrogate end points), collection and analysis of real-world data, and patient and payer involvement during the technology development.⁴⁸ Assessing value is particularly important to payers as budgets are often constrained, and concerns around budget impact and sustainability arise when faced with the high costs of current gene therapies.¹ An additional concern for payers may include a lack of predictability, lack of experience, and lack of robust clinical programs for these novel treatments.⁴⁹

Appendix 1: INAHTA Listserv Survey

Listserv topic title: Gene Therapy: International Regulatory and HTA Activities and Reimbursement Status

Agency: CADTH

Project lead and contact information (who should receive the responses): Teo Quay, TeoQ@cadth.ca

Background: Over the last decade, important scientific advances have been made in the field of gene therapy. Recent approvals from regulatory bodies and decision-makers reflect its promise. The US FDA approved the first gene therapy for acute lymphoblastic leukemia (ALL) in children and young adults in August 2017 and the second gene therapy for aggressive lymphoma in adults in October 2017, granting both CAR T-cell technologies Priority Review and Breakthrough Therapy designations. The NHS in the UK announced in October 2017 a decision to fund gene therapy for the treatment of adenosine deaminase deficiency in children at a price tag of over £500,000. In Canada, New Drug Submissions on gene therapy are anticipated in the near future.

To inform CADTH's approach and process for evaluating gene therapy and to help Canadian jurisdictions prepare for this new health technology, an Environmental Scan is being conducted on international regulatory and HTA activities, and reimbursement status on gene therapy. Your responses to the questions below, in addition to a scan of the published and grey literature, will inform this Environmental Scan to help Canadian as well as international jurisdictions plan for gene therapy.

Definition: Gene therapy is defined as "a set of strategies that modify the expression of an individual's genes or repair abnormal genes," involving the administration of a specific nucleic acid (i.e., DNA or RNA) via a viral or non-viral vector. This includes immunotherapy involving genetically-modified T cells (e.g., CAR T-cell therapy) and regenerative medicine involving genetically modified cells or tissues, including stem cells.

Consent: Please note that your response to the survey will be used to prepare a CADTH Environmental Scan Report, which will be available for public access. Your name (and contact information, if provided) will only be used to contact you about your responses to this survey. Your consent does not give CADTH permission to disclose your name within the report.

Please **type in your first and last name** on the line within the consent provided below, to authorize CADTH to use the information provided by you in the Environmental Scan Report.

This information is provided to assist CADTH in conducting an Environmental Scan entitled "Gene Therapy: International regulatory and HTA Activities and Reimbursement Status." By responding to this survey, I First Name Last Name, give my authorization for CADTH to summarize my responses in the published Environmental Scan report and for my organization to be identified as a source for survey respondents. However, I (and the organization I represent) decline any responsibility for the analyses, conclusions, opinions, and statements expressed in CADTH's Environmental Scan Report.

I agree

I do not agree (your responses will be used internally for information purposes only)

Respondent information:

- **Name (First, Last):**
- **Country:**
- **Region your organization serves (if different from Country):**
- **Email:**

Questions:

The questions below should take you no more than **30 minutes** to complete. Please feel free to add any details or comments to any of the questions. The requested deadline for your responses is **December 22, 2017**.

Regulation

1. In your country, how does the regulator currently categorize CAR T-cell therapy and other gene therapy (please check all answers that apply)?

a. CAR T-cell therapy

- Drug
- Biologic
- Blood or blood product
- Cellular therapy
- Gene or genetic therapy
- Vaccine
- Device
- Both drug and device
- Other
- Don't know

Please explain: _____

b. Other gene therapy

- Drug
- Biologic
- Blood or blood product
- Cellular therapy
- Gene or genetic therapy
- Vaccine
- Device
- Both drug and device
- Other
- Don't know

Please explain: _____

2. In your country, has the regulator approved any CAR T-cell therapy or other gene therapy?

a. CAR T-cell therapy

No

Yes

Please identify which therapies and when they were approved and if possible, attach or provide links to relevant information: _____

Don't know

b. Other gene therapy

No

Yes

Please identify which therapies and when they were approved and if possible, attach or provide links to relevant information: _____

Don't know

HTA (not including reimbursement decisions)

3. In your HTA organization, how are CAR T-cell therapy and other gene therapy currently categorized (please check all answers that apply)?

a. CAR T-cell therapy

Drug

Biologic

Blood or blood product

Cellular therapy

Gene or genetic therapy

Vaccine

Device

Both drug and device

Other

Please explain: _____

Don't know

b. Other gene therapy

Drug

Biologic

Blood or blood product

Cellular therapy

Gene or genetic therapy

Vaccine

Device

Both drug and device

Other

Please explain: _____

Don't know

4. Has your HTA organization produced or is it planning to produce any guidelines or frameworks specifically for evaluating CAR T-cell therapy or other gene therapy?

a. CAR T-cell therapy

No – it is out of scope for us, and we will not evaluate it; if so, please explain why it is out of scope:

No – it is within scope for us, and we will evaluate it using existing process(es); if so, please explain which existing process(es) will be used (e.g., for drugs or devices) and if possible, attach or provide links to relevant information:

Yes – Please explain and if possible, attach or provide links to relevant information:

Don't know

b. Other gene therapy

No – it is out of scope for us, and we will not evaluate it; if so, please explain why it is out of scope:

No – it is within scope for us, and we will evaluate it using existing process(es); if so, please explain which existing process(es) will be used (e.g., for drugs or devices) and if possible, attach or provide links to relevant information:

Yes – Please explain and if possible, attach or provide links to relevant information:

Don't know

Reimbursement

5. In the country/region that your HTA organization serves, have any reimbursement decisions been made regarding CAR T-cell therapy or other gene therapy?

a. CAR T-cell therapy

No

Yes – Please identify which therapies and when the decisions were made and if possible, attach or provide links to relevant information:

Don't know

b. Other gene therapy

- No – no decisions have been made
- Yes – Please identify which therapies and when the decisions were made and if possible, attach or provide links to relevant information:

Don't know

Other Jurisdictions and HTA Bodies

6. In addition to those identified in Questions 1-5, are you aware of any other guidelines or frameworks for evaluating CAR T-cell therapy or other gene therapy or any regulatory, HTA, or reimbursement decisions regarding CAR T-cell therapy or other gene therapy?

a. CAR T-cell therapy

- No
- Yes – Please explain and if possible, attach or provide links to relevant information:

b. Other gene therapy

- No
- Yes – Please explain and if possible, attach or provide links to relevant information:

Requested deadline for responses: **December 22, 2017.**

Appendix 2: Information on Survey Respondents

Country	Organization Represented by Survey Respondents
Australia	Adelaide Health Technology Assessment (AHTA)
France	Haute Autorité de Santé (HAS)
Germany	Gemeinsamer Bundesausschuss (The Federal Joint Committee) (G-BA)
Sweden	Statens beredning för medicinsk och social utvärdering (Swedish Agency for Health Technology Assessment and Assessment of Social Services) (SBU) Medical Products Agency (MPA)
Taiwan	Center for Drug Evaluation (CDE)
US	Kaiser Permanente

Note: A respondent from Colombia (Instituto de Evaluación Tecnológica en Salud) provided an incomplete response.

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