



PRECISION the cell &  
**ADVANCE** gene therapy  
collective™

Perspectives on Gene Therapy:  
Defining and Demonstrating  
Value to Payers

 **PRECISION**  
value & health

# INTRODUCTION

Since August 2017, we have seen the approvals of the first chimeric antigen receptor (CAR) T-cell therapies—Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel)—and the first directly administered gene therapy, Luxturna™ (voretigene neparvovec-rzyl).

Though these novel treatments are offering new hope to patients with unmet medical needs, they come at a significant cost, raising important questions about how novel therapies should be evaluated and paid for.

In this white paper, we explore the current landscape of gene therapy to highlight the challenges payers, health systems, and manufacturers face in bringing these innovative medicines to the patients who need them most.

# Experience With Gene Therapies in Europe

The European Medicines Agency (EMA) defines gene therapy medicinal products (GTMPs) as biological medicinal products that<sup>1</sup>:

- Contain an active substance that 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
- Have a therapeutic, prophylactic, or diagnostic effect that relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence

Since 2009, the EMA has classified 57 products as GTMPs. To date, 3 gene therapies have been approved in the EU:



**Glybera** (alipogene tiparvovec) was approved in August 2012 for adult patients diagnosed with familial lipoprotein lipase deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions.<sup>2</sup>



**Imlygic** (talimogene laherparepvec) was approved in December 2015 for adults with unresectable melanoma that is regionally or distally metastatic (Stage IIIB, IIIC, and IVM1a) with no bone, brain, lung, or other visceral disease.<sup>3</sup> Imlygic was also approved by the US Food and Drug Administration (FDA) in October 2015.<sup>4</sup>



**Strimvelis**, the first ex-vivo stem cell gene therapy, was approved in May 2016 for patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.<sup>5</sup>

In contrast to the United States, where a product is available for commercialization immediately after approval, products that receive regulatory approval in the EU still need to undergo additional evaluation for reimbursement by the pricing and reimbursement agencies in each market.

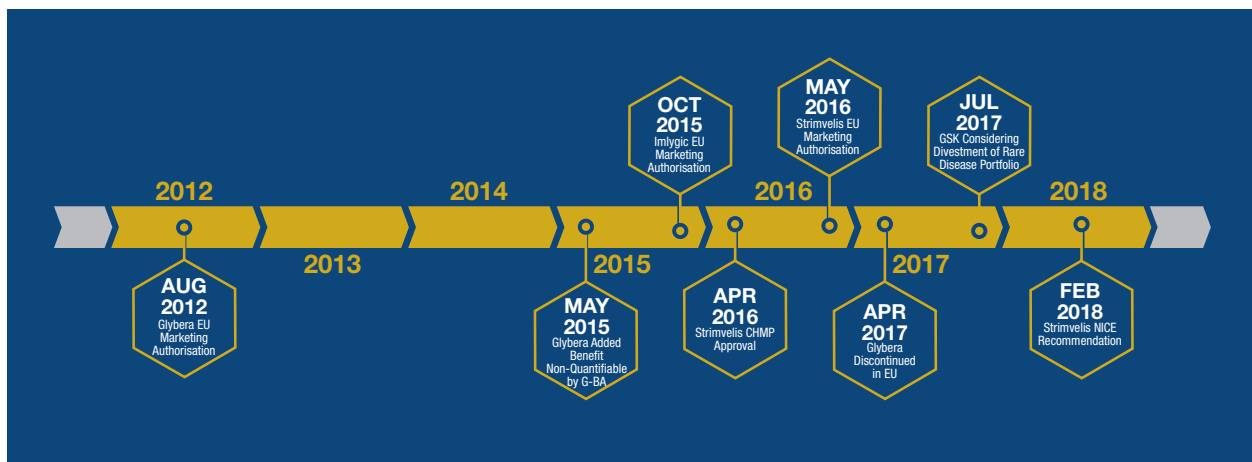
## Value demonstration and evidence

All EU countries use different methods for assessing value, but all follow the same basic principles of measuring incremental benefit against unmet need. Incremental benefit is a function of added clinical, economic, and humanistic benefits compared with standard of care. Unmet need is a function of disease severity and the availability of alternative treatment options. In its guidance on Strimvelis, National Institute for Health and Care Excellence (NICE) noted uncertainties in clinical effectiveness and cost-effectiveness,

but concluded that gene therapy was associated with higher survival rates and lower incidence of graft versus host disease compared with hematopoietic stem cell transplant. NICE also took into consideration wider societal benefits such as reduced parental anxiety and the opportunity for patients to go to school and become functioning adult members of society. Ultimately, NICE concluded that the ratio of costs and quality-adjusted life years for Strimvelis fell within the acceptable range for highly specialized technologies.

Due to the uncertainty surrounding long-term outcomes, there may be a significant disparity between a payer's expectations for long-term outcomes and the manufacturer's expectations. The example of Glybera—and its discontinuation in the EU market—highlights the critical importance of a robust demonstration of benefit. Health technology assessments (HTAs) for Glybera were performed by the pricing and reimbursement agencies in France and Germany, and both agencies found insufficient or unquantifiable benefit to justify reimbursement.

Figure 1. Gene therapy landscape in the EU



## Unique attributes of gene therapies require new pricing models

Gene therapies have a number of important attributes that distinguish them from conventional pharmaceutical products:

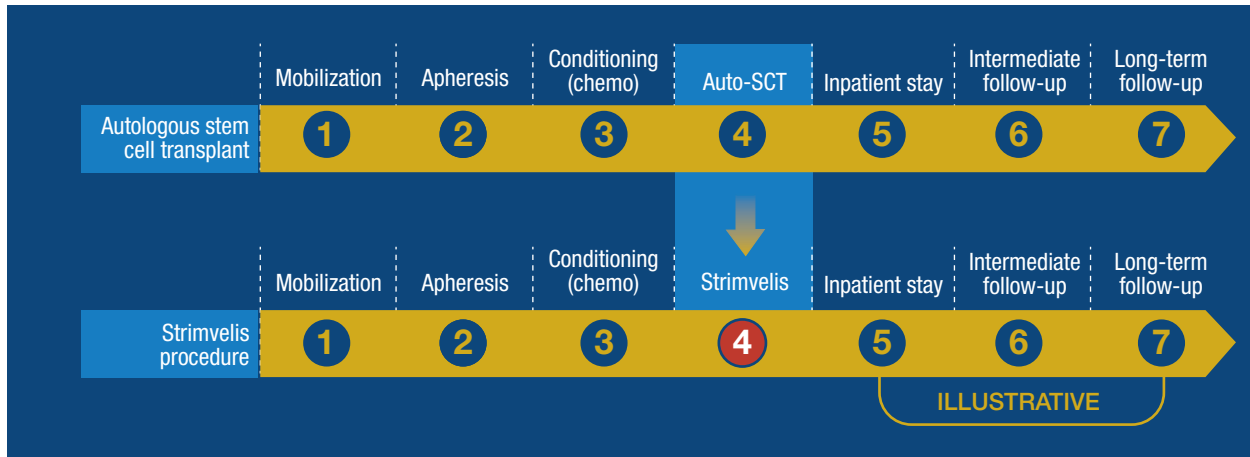
**Clinical attributes.** Gene therapies are potentially curative, but are supported by limited or no evidence to substantiate their long-term efficacy and safety at the time of launch.

**Economic attributes.** Gene therapies are expensive to manufacture and come with a high price tag, creating funding challenges and affordability concerns.

**Administration.** Often, the administration of gene therapies involves individualized, multi-step procedures

that must be performed in highly specialized centers.

Market access and funding pathways. The example of Strimvelis can be used to highlight the complexities of incorporating gene therapies into existing funding mechanisms. Like the autologous stem cell transplant procedure that it replaces, the process of treating a patient with Strimvelis requires multiple steps.



This raises questions such as:

- Which elements of the treatment process will be included in the product cost?
- Which components will be funded via existing reimbursement mechanisms?
- Are there top-up mechanisms in place to account for the additional cost associated with gene therapy?
- Given that these are highly specialized treatments administered in a very small number of centers, what cross-regional or cross-market funding mechanisms are in place to reimburse the hospital?

In February 2018, NICE published guidance on Strimvelis in which it recommended gene therapy for patients when no suitable matched related stem cell transplant is available. According to this guidance, all costs associated with Strimvelis—including screening, travel to the specialized treatment center in Italy, and the initial hospitalization—would be covered by NHS England under Highly Specialised Commissioning.<sup>6</sup>

**Pricing and contracting schemes.** As mentioned previously, at launch, the evidence base for gene therapies will not support the potential long-term benefits at product launch. From a payer perspective, this represents a risk, particularly if the indication has a high incidence and prevalence.

While the downstream benefits of gene therapies may last for many years, the high costs associated with

these therapies will be concentrated at the time of treatment. As such, it is important to consider which entity in the healthcare system pays the up-front costs, as this may create disincentives if another entity yields the benefits. One innovative option for offering a true risk-share to payers is an annuity model, where treatments costs are spread over a number of years and payments are made only if the patient continues to benefit from the intervention.

The example of Strimvelis demonstrates that, in practice, payers may require a risk-sharing pricing agreement based on near-term criteria. In Italy, GlaxoSmithKline initially approached Agenzia Italiana del Farmaco (AIFA) with a price of approximately €900,000. However, because the development of Strimvelis was funded by charitable donations, AIFA was able to reduce the price to €594,000, in addition to including performance-based criteria as part of the pricing agreement.

Taken together, the characteristics above raise a number of important questions around how payers will evaluate these novel treatments in terms of market access and funding pathways, value demonstration and evidence, and pricing and contracting schemes.

## Translating the European Experience to the United States

Manufacturers of gene therapies face similar obstacles in the United States as in the EU, with the added complexity of a fragmented healthcare delivery system in which patients often move from insurer to insurer every few years. Regardless of geography, the challenges associated with commercializing gene therapies include:

- Significant up-front costs
- Difficulty in calculating long-term effectiveness
- Uncertainty surrounding long-term durability and the potential need for retreatment
- Complex logistics associated with obtaining therapy and providing access to the patients who need it

In the United States, aspects of the healthcare system that may impede the commercial success of gene therapy include:

**Focus on short-term results.** On average, patients only stay with the same health plan for 2 to 3 years. Payers may also be under pressure to provide quarterly earnings reports.

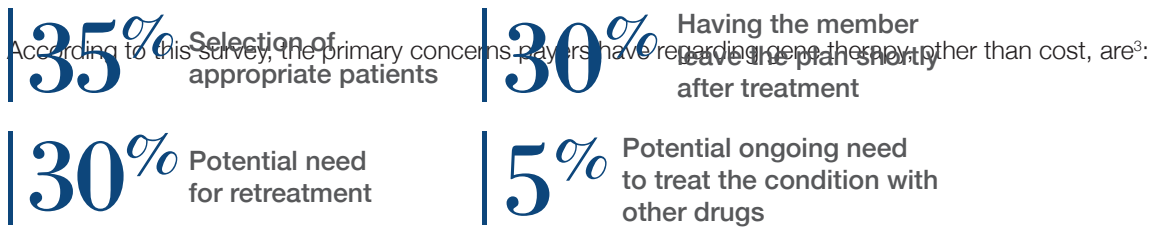
**Lack of incentive for long-term savings.** Long-term savings are difficult to quantify. In addition, payers may be reluctant to pay for high-cost therapies when patients are likely to leave the health plan before the

long-term benefits are realized.

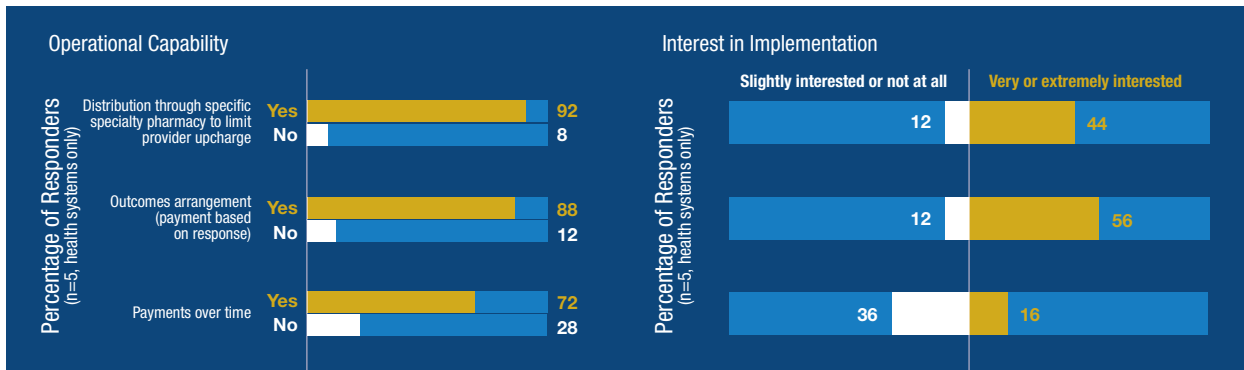
# Exploring Payer and Health System Perspectives in the United States

To gain insight into payer perspectives in the United States, PRECISIONValue conducted a survey of payers and integrated delivery networks (IDNs) and evaluated input from 25 respondents representing approximately 108 million covered lives.<sup>7</sup>

## Payer perspectives



The survey revealed that the most common technique US payers have been using to manage gene therapy is prior authorization before administration. When asked about potential cost mitigation options proposed by manufacturers, payers expressed the most interest in outcomes-based arrangements for gene therapy, but were also interested in the option of distribution through specific specialty pharmacies to limit provider upcharges (see Figure 3).<sup>3</sup>



## Health system perspectives

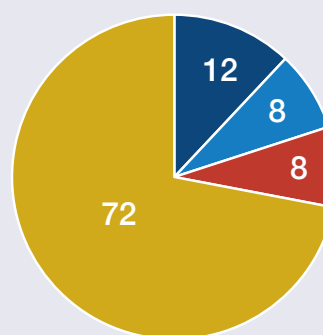
When asked what they anticipate to be the primary challenge of gene therapy, health system respondents expressed concerns about paying the up-front cost, obtaining coverage, and identifying appropriate patients. When asked what they would do if the patient was eligible for gene therapy but payer approval was pending, the majority of health system respondents indicated they would require the patient to wait until payer approval was secured prior to administration, without exception.<sup>3</sup>

## New pricing models for gene therapy

To date, the costs of gene therapies have had a minimal impact on spend. However, as the number of approved gene therapies increases—including those for indications with larger populations of eligible patients—this impact is expected to become more significant. Both payers and health systems face challenges in adapting to the management of gene therapies, and survey results indicate that respondents have the most need for information on the durability of response with gene therapies.<sup>3</sup>

There is consensus that new models are needed, and according to the survey, most payers and health systems feel that payment models need to evolve toward outcomes-based arrangements. However, outcomes-based arrangements with gene therapy manufacturers are still uncommon among both payers and health systems (see Figure 4).<sup>3</sup>

Figure 4. Existing outcomes-based arrangements for gene therapy<sup>3</sup>



Percentage of responders (n=25)

- Luxturna™ (voretigene neparvovec-rzyl)
- Kymriah® (tisagenlecleucel)
- Yescarta® (axicabtagene ciloleucel)
- None of the above

## Strategies for demonstrating value to payers

Beyond the challenges associated with clinical development, manufacturers of gene therapies are tasked with creating a compelling value story around their products and working with payers on pricing agreements that enable access. To facilitate these conversations, manufacturers may want to consider the following strategies:

- Build a real-world evidence strategy with a focus on durability of response
- Offer flexible payment options
- Establish a billing code as quickly as possible
- Educate payers on their pipeline and its potential impact
- Provide resources detailing ideal patient characteristics
- Develop an economic model that demonstrates the long-term value of the therapy



## Conclusion

Gene therapies represent the next major pillar in medicine, with the potential to cure diseases ranging from cystic fibrosis to cancer. As more gene therapies enter the market, manufacturers are under pressure to establish the true value of their treatments and work with payers on pricing agreements. For manufacturers of gene therapies, it is never too early and never a wasted effort to plan for how to engage the payer stakeholder.

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Find out more about Precision's scalable, end-to-end support for gene therapy innovators—accelerating drug development with expert biomarker, clinical, regulatory, quality system, and market access solutions.

### *Contributing Authors*

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#### **Jeremy Schafer, PharmD, MBA**

PRECISIONvalue – Senior Vice President, Director of Payer Access Solutions

Jeremy Schafer provides leadership across the PRECISIONvalue payer strategy team. His valuable insights enhance our work in health economics outcomes research, provider marketing, and access and analytics. Jeremy has great experience with specialty pharmacy programs and networks, P&T Committee processes, Medicare Part D, health outcomes research, and payer data analysis.



#### **Alex Grosvenor**

PRECISIONxtract – Vice President, Global Pricing & Product Strategy

Alexander Grosvenor is an expert in global pricing and market access, with specific knowledge of European markets and the disciplines of launch sequencing, cross-indication pricing, international price referencing, and global launch pricing. Specialized focus in orphan indications and cell and gene therapies, backed by extensive knowledge of oncology, cardiovascular disease, central nervous system diseases, human immunodeficiency virus, and multiple sclerosis.

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## PRECISIONvalue

### About PRECISIONvalue

PRECISIONvalue supports commercial excellence for global pharmaceutical and life sciences clients through the demonstration and communication of product value and outcomes. The PRECISIONvalue teams provide clients with services grounded in decades of industry knowledge, demonstrated analytics proficiency, and marketing and communications prowess—making PRECISIONvalue the preferred strategic partner in the industry. PRECISIONvalue is part of Precision Value & Health, the leading partner to pharmaceutical and life sciences companies in improving health outcomes by establishing the value of medical innovations and expanding global market access for patients. For more information, please visit: [precisionvalue.com](http://precisionvalue.com).

## PRECISIONxtract

### About PRECISIONxtract

PRECISIONxtract, the health economics, market access, and payer analytics consulting arm of Precision Value & Health, is comprised of top-tier talent including scientists, former payer and pharma executives, and world-respected academicians ready to partner with clients throughout the United States, Europe, and beyond. With over 140 employees in 7 offices worldwide, PRECISIONxtract's breadth and depth of expertise complements an integrated, interdisciplinary approach to informing and guiding pharma, biotech, and device clients to commercial success.

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Precision ADVANCE, a collection of interconnected services and complementary teams, uniquely focuses on the complexities of clinical, regulatory, manufacturing, and commercial needs to successfully bring cell or gene therapies to market.

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**Connect with one of our experts.** Contact us at [precisionadvance@precisionmedicinegrp.com](mailto:precisionadvance@precisionmedicinegrp.com).  
To learn more about Precision ADVANCE, visit [precisionmedicinegrp.com/advance](https://precisionmedicinegrp.com/advance).

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2 Bethesda Metro Center, Suite 850  
Bethesda, MD 20814  
[precisionvh.com](https://precisionvh.com)