

THE CHALLENGES ASSOCIATED WITH EVALUATING THE COST BENEFIT OF GENE THERAPIES AND ENABLING PATIENT ACCESS

Overview

Despite the growing availability of approved gene therapies, decision-makers face significant challenges when evaluating pricing and reimbursement of these novel therapeutics. From determining cost-benefit ratios, setting out patient access criteria and designing reimbursement plans, this white paper explores some of the complex aspects of value assessment for gene therapies, and discusses results from a survey of key decision-makers across Germany, Sweden and the UK responsible for making pricing and reimbursement decisions.

The Rise of Gene Therapies

While gene therapies may appear to be the new kids on the block in terms of current approaches to treating disease, research into editing human genes to produce a therapeutic benefit has been active for nearly 50 years. In 1971, in a laboratory in Maryland, U.S., scientists first used a virus to deliver exogenous DNA into human cells of patients with galactosemia, thereby increasing the activity levels of the missing enzyme responsible for the disease that affects how the body converts galactose.¹ Shortly afterwards, the potential of using gene therapy to treat human disease was discussed openly and an appeal was made by two other scientists, Friedmann and Roblin, to establish ethical and scientific standards before the technology was used in human medicines.² The first clinical trial of a gene therapy was conducted in 1990, which enrolled a single child with severe combined immunodeficiency disorder as a result of a mutation to adenosine deaminase (ADA-SCID).³ In 2012, 41 years after scientists first established the principles of gene therapy in a petri dish, Glybera (Novartis) became the first commercially available gene therapy after receiving marketing authorization by the European Medicines Agency (EMA) for the treatment of lipoprotein lipase deficiency (LPLD).⁴

Fast forward another few years to today and now gene therapies are reinventing how we approach the treatment of disease. Rather than managing symptoms and necessitating chronic long-term disease management, gene therapies offer the promise of a one-off treatment to potentially cure patients of previously incurable diseases, including various cancer types, rare diseases, immunological disorders, metabolic disorders, and infectious diseases.⁵ As of September 2019, six gene therapies have marketing authorization by the EMA and five have been approved by the U.S. Food and Drug Administration (FDA)⁶ (Figure 1). In addition, according to the U.S. National Library of Medicine's website, clinicaltrials.gov, globally there are around 300 recruiting or active clinical trials of gene therapies.⁷ With so many products in clinical trials, there is likely to be a rapid rise in approved gene therapies over the next decade. The challenge for manufacturers and healthcare providers will be to ensure that those patients who need these treatments can get access to them.

Figure 1. Gene therapies with current EMA or FDA marketing authorization and gene therapies anticipated to receive marketing authorization before 2024.

		Now									
Therapy (U.S./E.U. license holder)		2015	2016	2017	2018	2019	2020	2021	2022	2023	
Approved	Imlygic (Amgen) Melanoma		EMA approval in Dec 2015								
	Strimvelis (GSK/Orchard) ADA-SCID		EMA approval in May 2016								
	Kymriah (Novartis) ALL, DLBCL				EMA approval in Aug 2018						
	Yescarta (Kite/Gilead) DLBCL, PMBCL				EMA approval in Aug 2018						
	Luxturna (Spark Therapeutics/Novartis) IRD*				EMA approval in Nov 2018						
	Zynteglo (Bluebird bio) TDT					EMA approval in Mar 2019					
	Zolgensma (AveXis/Novartis) SMA					FDA approval in May 2019					
In late clinical development	Lenti-D (Bluebird bio) CALD						2020				
	GS010 (GenSight Biologics) LHON						2020				
	JCAR017 (Juno/Celgene) DLBCL						End of 2020				
	Bb2121 (Bluebird bio/Celgene) r/r MM						2020/early 2021				
	BMN270 (Biomarin) Hemophilia A								2022		
	OTL-200 (Orchard therapeutics) MLD									2022	

*As a result of biallelic RPE65 gene mutations

ADA-SCID=adenosine deaminase deficiency - severe combined immunodeficiency; ALD=adrenoleukodystrophy; ALL=acute lymphoblastic leukemia; DLBCL=diffuse large B cell lymphoma; EMA=European Medicines Agency; EU=European Union; FDA=U.S. Food and Drug Administration; IRD=inherited retinal disease; GSK=GlaxoSmithKline; LHON=Leber's hereditary optic neuropathy; MLD=Metachromatic Leukodystrophy; PMBCL=Primary mediastinal large B-cell lymphoma; r/r MM=relapsed/refractory multiple myeloma; SMA=Spinal muscular atrophy; TDT=transfusion-dependent β-thalassemia; U.S.=United States

How Expensive Are Gene Therapies?

With so many ongoing clinical studies of gene therapies, and more in preclinical development, there is likely to be a rapid rise in the availability of curative gene therapies over the next decade.⁷ Although these treatments may represent an evolution in the way we treat and view diseases, they are likely to bring considerable challenges for decision-makers who are already managing stretched healthcare budgets.

Of those gene therapies currently marketed in Europe, the average list price is \$634,000 (€559,647) per course of treatment [range \$358,000–\$1,212,000 (€316,606–€1,069,966)] (Table 1).⁶ Manufacturers state that the time and high development costs associated with gene therapies, along with the often small patient population for which they're targeted, justify the expense.⁸ Furthermore, compared with traditional small molecule therapies, gene therapies often require bespoke manufacturing processes and complex administration methods.⁹

While it could be argued that the cost of these therapies is, therefore, at least partially justified, there seems to have been little work undertaken to prepare payers and decision-makers (i.e., those stakeholders critical for ensuring patient access) for how to assess the value of these products and overcome the challenge of affordability.

While curative gene therapies may have high one-off costs, their health effects, which could last a lifetime, may make them less expensive in the long term than current standard of care. For example, a cost-effectiveness analysis comparing gene therapy and prophylaxis treatment of hemophilia A, found gene therapy to be the more favorable option. Over a 10-year time period, the gene therapy was clinically more effective and less costly.¹⁰ Furthermore, the Institute for Clinical and Economic Review (ICER) in the U.S. evaluated the cost effectiveness of two treatments for spinal muscular atrophy (SMA), Zolgensma (AveXis/Novartis) (a gene therapy) and Spinraza (Biogen) (the only available management treatment of SMA). Although at the time of evaluation Zolgensma was not approved by the FDA and its price was not yet known, ICER estimated a price of \$2 million for a one-off treatment could meet cost-effective thresholds of \$100,000 to \$150,000 per quality-adjusted life year (QALY) gained, whereas Spinraza was deemed to have low long-term value at its current price.¹¹

In addition, where gene therapies are intended for children who have longer to benefit from a cure, cost-effectiveness over chronic management may be even more likely. For example, in 2018, National Institute for Health and Care Excellence (NICE) recommended Kymriah (Novartis) for inclusion in the cancer drug's fund to treat acute lymphoblastic leukemia (ALL) in people <25 years old,¹² however, this gene therapy was initially rejected for the treatment diffuse large B-cell lymphoma (DLBCL) in adults.¹³ In both cases, the therapy was not deemed cost-effective for routine commissioning due to a lack of clinical evidence but for the treatment people <25 years old with ALL, Kymriah was found to have plausible potential to be cost-effective.¹³ Although Kymriah was ultimately approved for both indications, this illustrates how differences between the cost-effectiveness of curative therapies between adults and children could affect patient access to treatments.

Even if at a price of \$2M per treatment a therapy is deemed cost effective, this doesn't negate the fact that payers simply may not be able to afford to pay this upfront. Compared to no treatment, Glybera (uniQure) was found to be cost-effective¹⁴ but this did not prevent it from becoming a commercial failure.¹⁵ With a price tag of >\$1,000,000 (>€1,000,000) per patient, Glybera was the most expensive drug ever at launch in 2012. However, after five years on the market, Glybera had been used to treat just one patient and countries were unwilling to reimburse the drug.¹⁶ In 2017, uniQure made the decision withdraw Glybera from the market.¹⁵ Upon withdrawal, the CEO of uniQure noted "Glybera's usage has been extremely limited, and we do not envision patient demand increasing materially in the years ahead," highlighting the problems with developing expensive therapies for ultra-orphan indications.¹⁵

Table 1. The prices of gene therapies marketed in Europe.*

Brand Name	List Price of Full Treatment (Country)
Glybera**	€900,000 (Germany) ¹⁷
Imlygic†	Max. price £73,480 (UK) ¹⁸
Strimvelis	€594,000 (Italy) ¹⁷
Kymriah†	£282,000 (UK) ¹⁹
Yescarta†	£300,000 (UK) ²⁰
Luxturna†	£613,410 (UK) ⁶

*Prices are the list prices of gene therapies in the first country in Europe that gene therapy was marketed in.

**Removed from the market in 2017.

†Confidential commercial arrangement between NHS England and the manufacturer is in place.

Decision-Maker Perceptions

While authorization of gene therapies is the responsibility of the European Medicines Agency (EMA) and their guidelines apply to all countries within the EU, countries make their own decisions regarding payment and reimbursement.²¹ Countries use different methods for assessing value, but for many, cost-effectiveness and the clinical benefit a treatment offers compared to the standard of care are essential elements. Some countries also place a high worth on societal and humanistic benefits.

Gene therapies are transforming healthcare, and with many products in the pipeline to add to those already approved, there is likely to be a rapid increase in the number of curative gene therapies decision-makers are expected to evaluate and payers are expected to reimburse.²² Gene therapies are tailored to individuals, and unlike many other treatments, cannot be batch made.⁹ For that reason, it seems unlikely that their high prices will reduce anytime soon.

To better understand decision-maker perceptions on the appropriateness of current methods of evaluating value of gene therapies for pricing and reimbursement, as well as the challenges payers are concerned about and how these can be overcome, Covance Market Access conducted an online survey. Stakeholders from Germany, Sweden and the UK, who are responsible for making pricing and reimbursement decisions on a national, regional and local level, were asked for their opinions on various aspects relating to the pricing and reimbursement of gene therapies. Stakeholders had diverse backgrounds and included pharmacists, senior prescribers, members of government agencies and those responsible for commissioning drugs at local levels. These countries were chosen, in broad terms, due to their varied perspectives of reimbursement decision-making criteria. In Germany, assessment of medicinal products focuses on clinical benefit; in Sweden the focus is on cost-effectiveness from a societal perspective; and in the UK, assessment focuses on cost-effectiveness for national payers.

Assessing the Value of Gene Therapies

Understanding the Challenges

The challenges associated with assessing the value of gene therapies for pricing and reimbursement are considerable. Market authorization decisions are based on clinical trial data from which it is impossible to verify the claim of a cure. Many gene therapies currently in development also target rare diseases with small patient populations, increasing the difficulty of generating sufficient clinical evidence to support significant health improvement claims. Without knowing the long-term effectiveness of potentially curative therapies, and the certainty that a cure is actually a cure, it seems that decision-makers do not have the information they need to adequately evaluate gene therapies using current pricing and reimbursement methods, thus risking under- or over-valuation of these therapies. The uncertainty surrounding these issues translates into uncertainty of the long-term cost-effectiveness and complicates the question, “how do we value a cure?”

In addition to uncertainty around clinical effectiveness and safety, curative gene therapies may bring unique elements of value which are challenging to capture. If someone is cured of a disease, how do you value the rest of their life? Furthermore, how do you assess the value of avoided health impact of genetic conditions that may otherwise have been transferred to offspring? Additional elements of value from a societal perspective may include productivity, adherence-improving factors and reduction in caregiver burden, and these are likely to be dependent on the severity of disease.²³ There are also likely to be psychological well-being benefits to the “cured” patient not seen with chronic long-term treatment. Again, these benefits are difficult to measure and assign value to. Although incorporating societal value into pricing and reimbursement assessments isn't a challenge unique to gene therapies, for some gene therapies, societal value may be the only benefit.

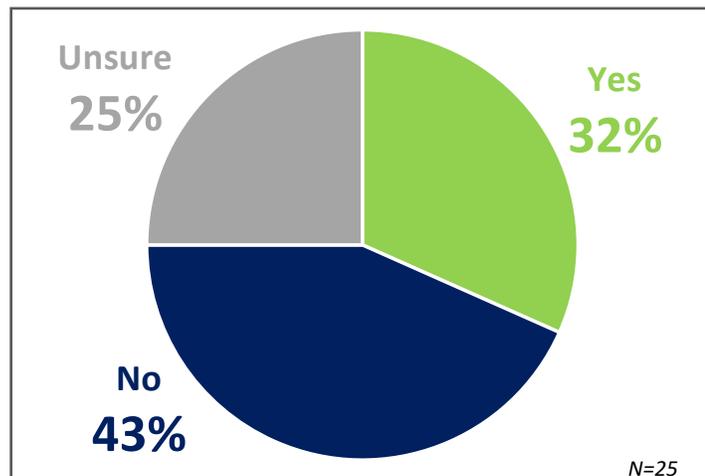
In some situations, social values are difficult to quantify because these are unique to individuals. For example, Luxturna (Spark Therapeutics) is a gene therapy developed to treat an inherited form of blindness and was recently approved by the FDA and EMA.^{24,25} The loss of sight will be seen as detrimental to some people, while others will continue to have a high quality of life and productivity equal to that of a sighted person.²⁶ This makes it difficult to measure the value objectively. Recently, NICE issued draft guidance recommending Luxturna for reimbursement by NHS England.²⁷ Health-related quality of life was not measured during clinical trials of Luxturna, and this was considered to be a crucial limitation of the evidence. Within the evaluation, the effect of blindness on the quality of life of patients and caregivers was discussed, including its impact on achievement in schools, long-term independent living and the ability to work. With these aspects and clinical effectiveness noted, Luxturna was considered to offer significant QALY gains and value for money despite uncertainties around duration of effect and only a small patient population in the clinical trial.²⁷

Another challenge associated with gene therapy is the complexity of administration methods. Strimvelis (GSK), a gene therapy for ADA-SCID, was recently recommended by NICE in the UK. Although only administered once, the process requires several steps and patients must travel to Italy because the only approved manufacturing center is in Milan, Italy.²⁸ This increases costs and complicates the reimbursement processes. Although NICE incorporated these costs into assessments, some countries may view this as the manufacturer's responsibility. At present, the lack of treatment centers and medical professionals with the required expertise in European countries may decrease the value of gene therapies.

What Do Decision-Makers Think?

Given that assessing the value of gene therapies poses unique challenges, we asked 25 decision-makers whether they thought the current pricing and reimbursement methods for evaluating medicines were appropriate for gene therapies. Only a third of those surveyed responded "yes," with the remaining 68% responding "no" or "unsure" (Figure 2).

Figure 2. Do you think current pricing and reimbursement mechanisms are fit for purpose to evaluate potentially curative gene therapies?



From the survey, 40% of German stakeholders thought the reliance on evidence generated by randomized controlled trials (RCTs) to assign value to medicinal products is a problem when evaluating gene therapies. RCTs, while typically considered the “gold standard” evidence upon which the value of a new therapy is assessed, have a relatively short duration, providing evidence of efficacy for a limited period, and cannot reflect the lifetime health benefits pledged by gene therapies. Some of the treatment benefits of gene therapies are likely to be highly valued by society but unlikely to be captured during RCTs, and until real-world evidence is available these may not come to light. The problem with relying on RCTs to generate evidence is amplified when considering gene therapies for rare diseases with small patient populations.

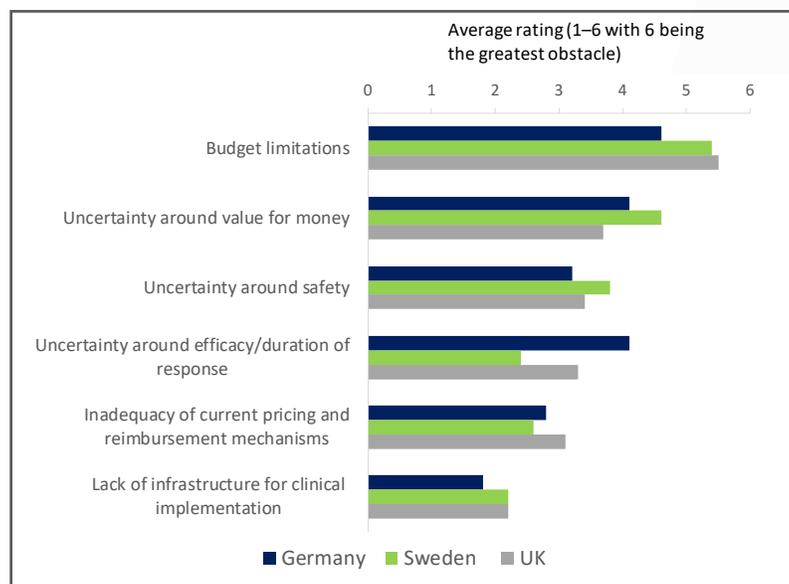
When stakeholders were asked what activities manufacturers could undertake to ensure uptake of gene therapies, the use of real-world evidence to support efficacy claims was suggested. Real-world evidence could build on RCT data to help establish long-term effectiveness and safety of gene therapies, societal benefits, effects on patient subpopulations, and even the burden placed on the healthcare system.²⁹ Furthermore, it could be more extensively utilized with innovative payment methods to mitigate risk to payers and healthcare budgets.

Paying for Gene Therapies

There are a number of obstacles for healthcare systems to overcome to ensure patient access to gene therapies.²² We categorized what we see as the main obstacles to patient access and asked our survey participants to rank them in order of which they believe have the most influence on the reimbursement and purchasing of gene therapies.

For all markets surveyed, budget limitations were considered to be the biggest obstacle by decision-makers (Figure 3). It is interesting that despite the high uncertainty around the long-term efficacy and safety, and therefore cost-effectiveness, of these treatments, the biggest challenge for stakeholders is still how they will afford the high prices. Even in Germany, where there is a predominant focus on clinical benefit, affordability was still the main concern for decision-makers.

Figure 3. Please order the following obstacles according to your perceptions of their influence on the reimbursement/purchasing of gene therapies.



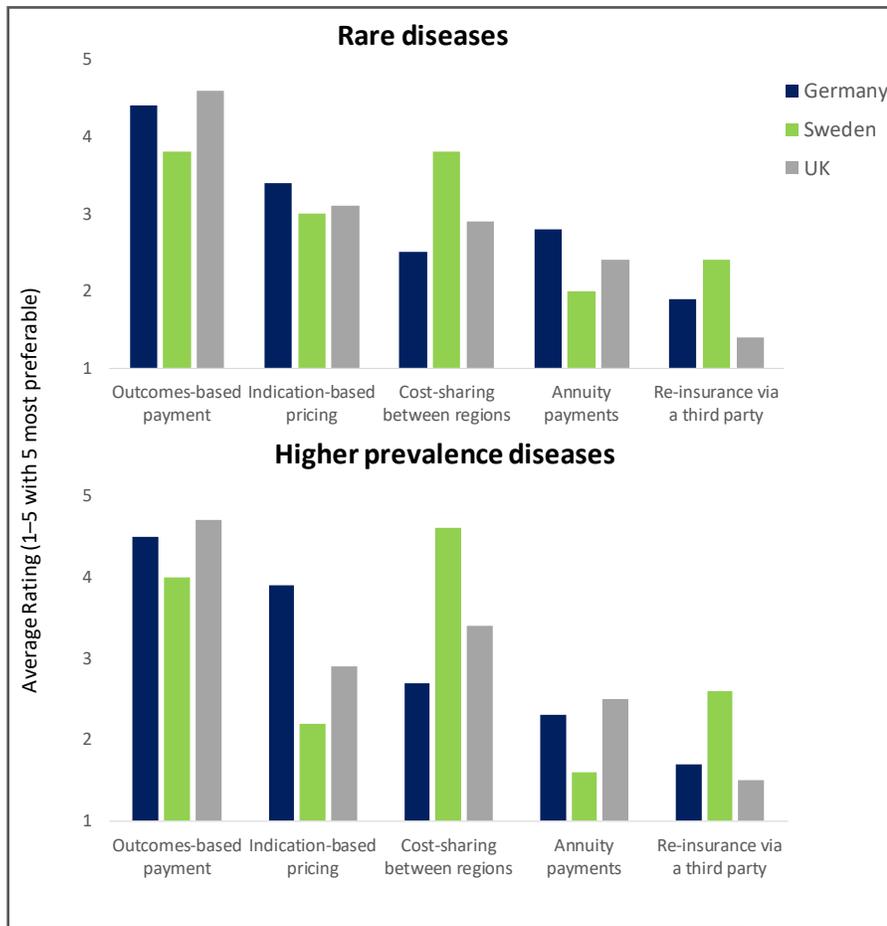
In many countries, health budgets are strained and decision-makers may find it difficult to accommodate the high costs of gene therapy into their budgets without compromising the healthcare of other patients.³⁰ For rare or orphan diseases with small patient populations, the high costs may be manageable while only a few gene therapies are on the market. However, estimations suggest 6-8% of the EU population have a rare disease³¹ and many of the gene therapies in clinical trials are targeting rare diseases.⁷ Consequently, the cumulative budget impact of routinely treating rare diseases with gene therapy could be considerable. The capacity of the UK system for reimbursing gene therapies in light of the huge number expected in the next few years was a concern expressed by one stakeholder in our survey. In addition, gene therapies are also being developed to target diseases of higher prevalence, meaning budget impact challenges will only increase. For example, hemophilia A affects 1 in 5,000 male births; both BioMarin and Spark Therapeutics have gene therapy products currently in Phase III clinical trials for the treatment of hemophilia A.³²⁻³⁴

If the cost burden of gene therapy is the biggest obstacle, what can manufacturers and decision-makers do to address this while maximizing the commercial potential of the product? One option that has been proposed is to use new and innovative payment models. Ideally, these will reduce the upfront costs to payers and minimize budget impact. We asked decision-makers to identify which payment models could be introduced to address the uncertainty in their respective countries to lessen the cost burden of gene therapies for rare diseases and those of higher prevalence (Figure 4).

When considering markets together, payment based on outcomes or efficacy was broadly the most favored method of those proposed in the survey. However, in both rare diseases and those of higher prevalence, Swedish decision-makers favored cost-sharing between regions, also a popular option with UK decision-makers. Indication-based pricing was a favorable idea to German decision-makers, but less so among Swedish and UK decision-makers.

While payment based on outcomes/efficacy would allow payers to share the risk of uncertainty with manufacturers, there are numerous logistical and legal hurdles to overcome in order to implement such agreements in many markets. For example, the clinical outcomes of a cure need to be defined, agreed and measured objectively, and the length of time needed to pass before the patient is considered “cured” be defined. Defining a “cure” was a concern expressed by survey participants when asked for opinions on innovative payment models. Once defined and agreed, patients need to be monitored to ensure clinical outcomes are met. This monitoring could use a considerable amount of resources and place an administrative burden on healthcare staff. Moreover, in Germany, for example, payers have access only to ICD-10 codes and data protection laws mean indications cannot be written on prescriptions; this could make data monitoring difficult.³⁵ Beyond the law changes that may be required, there is the question of who should be responsible for maintaining data registries and who should finance them. Despite these obstacles, Novartis and GWQ ServicePlus AG, a German social insurance company, recently announced an outcomes-based contract for Kymriah until a final price conclusion has been made by GKV-Spitzenverband (National Association of Statutory Health Insurance Funds).³⁶ This suggests the data protection laws of Germany could be overcome to implement innovative payment methods,³⁶ however it remains to be seen whether this method will work well in Germany, and whether it could set an example and open up new options for payers.

Figure 4. Do you think current pricing and reimbursement mechanisms are fit for purpose to evaluate potentially curative gene therapies?



Conclusions

Achieving acceptable pricing and reimbursement outcomes for gene therapies that satisfy all stakeholders is likely to continue to be a difficult task. Development of gene therapies is expensive, risky and time consuming, and manufacturers want a fair price to reflect this.^{9,23} But decision-makers and payers need to feel they are getting value for money. Both are under pressure from patients wanting access to the most effective and innovative treatments.

From our survey of those responsible for the purchasing and reimbursement of gene therapies in Germany, Sweden and the UK, and from broader discussions, it is clear there are a lot of unanswered questions:

- ▶ How do we define a cure? By society’s definition of a cure, the disease should be eliminated and the patient should be free from that disease for a lifetime. Clearly this makes cures highly valuable, but the truth is, no one knows if these therapies are curative.
- ▶ Are gene therapies safe long-term?
- ▶ Who should be financing the risk of uncertainty associated with gene therapies?
- ▶ Should we pay more for a cure for certain patient populations (e.g., children)? Is this ethical?
- ▶ What are the patients’ views of these medicines?

The difficulty with some of these questions is that there is no scientific answer. When asked what activities could be undertaken by manufacturers to ensure patient access to gene therapies, decision-makers were eager to have open discussions. Suggestions included the sharing of trial designs to ensure payer expectations were covered, to share price setting between manufacturers, government and payers, and for manufacturers to have trusted partnerships with local authorities. One comment from a national UK decision-maker suggested that the education of health professionals and setting up medical centers to administer gene therapies would be welcomed. Importantly, all these discussions should also involve patients. Patient involvement in treatment decision-making is being actively encouraged in many countries, and ultimately, it is for this stakeholder group that these high cost therapies are developed.

Financing of gene therapies is the biggest concern for payers. Although lifetime costs of these treatments may be reasonable, and fall within established cost-effectiveness thresholds, payers are still faced with the challenge of accommodating the high prices into their budgets. Payers cannot be sure that gene therapies are worth the cost without certainty that a cure is actually a cure. To ensure patients have access to gene therapies, new payment models may need to be used together with real-world evidence.

To address the challenges associated with evaluating gene therapies, influential organizations are taking a proactive approach. In January 2019, NICE, ICER and CADTH (Canadian Agency for Drugs and Technologies in Health), along with other agencies, announced a collaboration to develop alternative methods of evaluating curative therapies and how to translate positive cost-effectiveness results into value-based payments which reflect the uncertainty associated with these treatments.³⁷ This move is encouraging, and an important discussion that needs to continue. The science is evolving quickly, and the volume of these exciting treatments is set to expand in the next decade. All stakeholders – manufacturers, payers, patients and healthcare professionals – need to be a part of this ongoing discussion to ensure patient access to the most innovative treatments.

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