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Exploring the Financial Sustainability of Gene Therapies

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CONSULTING | REPORT
MAY 2021



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Please cite this report as:

Firth I, Schirmmacher H, Zhang K, Hampson G, Towse A, 2021. Exploring the financial sustainability of gene therapies. OHE Consulting Report, London: Office of Health Economics. Available at: [Exploring the Financial Sustainability of Gene Therapies | OHE](#)

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Funding and Acknowledgements

This consulting report was commissioned and funded by Novartis Gene Therapies.

We would like to acknowledge the contribution made to this paper by the expert interviewees and by Mary Harney, Annie Hubert and Simone Boselli whose involvement in a webinar linked to this project helped develop our thinking. A report of the webinar can be found [here](#) or via our [website](#). We would also like to thank Jane Hollywood and Frances Denny from law firm CMS for their advice on the intellectual property issues discussed in this paper.

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Executive Summary

Introduction

Gene therapies represent a paradigm shift in medicine, with the potential to address the root causes of chronic diseases. They offer one-time treatment regimens and, in some cases, potentially a cure. As a result, they offer transformative value for patients, physicians, health systems and society. However, with the prospect of more gene therapy approvals, there is concern in Europe that these technologies could threaten the financial sustainability of health systems. This paper explores whether gene therapies can be sustainable for health systems, drawing from a literature review and a series of expert interviews.

What do gene therapies offer patients and health systems?

Economic evaluations of new healthcare technologies typically focus on the health gain for the patient and the costs for the health system of delivering a new therapy relative to standard care. The health gains for existing gene therapies are substantial, with higher average increases in quality-adjusted life-years (QALYs) compared to both small molecules and biologics. Gene therapies may also be particularly beneficial in areas of high unmet medical need, thereby offering a major step-change for patients who would otherwise have no effective treatment options.

From the perspective of the health system, not all gene therapies offer the same kind of value. For illustrative purposes, we outline three categories of gene therapy that deliver different profiles of value to the health system depending on whether they generate health gain primarily by increasing length and/or quality of life. These categories demonstrate that different gene therapies will have different financial implications for health systems and for wider society.

Category 1 therapies deliver substantial health gains through extension of **length** of life. These are typically therapies for diseases with high early mortality and no effective treatment alternatives. Despite the substantial QALY gain, these therapies are not accompanied by savings to the health system.

Therapies that deliver health gain through increases in **quality** of life fall into categories 2 and 3.

Category 2 represents therapies that will provide cost offsets for the health system through reductions in the cost of chronic care, i.e. therapies for diseases with existing treatments that are inefficient (high cost and/or poor outcomes).

Category 3 represents therapies that are not likely to generate savings in direct health costs, but will deliver cost offsets outside of the health system. This will include therapies for serious conditions that are not treatable within the health system (e.g. blindness) but require patients to have supportive care outside the health system for at least some part of their lives.

The three categories are intended to be illustrative, and we note that some therapies may sit between categories and/or exhibit the characteristics of multiple categories. The categories are used to demonstrate that different gene therapies will have different financial implications for health systems.

Do gene therapies offer value for money? Are they affordable?

Payers are concerned about the affordability and uncertain duration of long-term effectiveness (and hence cost-effectiveness) of gene therapies. The model that health systems use to deliver and pay for therapies was designed for chronic treatments. As a result of high upfront costs, one-time treatments like many gene therapies represent an affordability challenge for health systems. In addition, the promise of potentially life-long effectiveness of gene therapy means the short-term clinical trials used for chronic treatments inevitably fail to demonstrate the full duration of effectiveness for gene therapies. Therefore, there are unresolved uncertainties about the duration of effect, and therefore cost-effectiveness, of gene therapies. Managed entry agreements (MEAs), particularly performance-linked agreements, can reduce these concerns by both spreading the costs over multiple budget cycles and by linking payments to observed efficacy in patients.

Are gene therapies financially sustainable?

Linked to the challenge of affordability, there is concern that gene therapies threaten the financial sustainability of health systems. We consider three factors that will influence whether the adoption of gene therapies is sustainable in the long term.

1. Pipeline factors: The speed and number of products gaining marketing approval and the size of the eligible patient populations will influence total spend on gene therapies. The cell and gene therapies pipeline is growing with 362 products in phase I-III clinical trials in 2019 – up by 25% from 2018 (Hargreaves 2020).

2. Pricing factors: There are two main pricing factors that impact the financial sustainability of gene therapy for health systems:

- **Prices should reflect value.** Value-based pricing promotes efficiency in the long term by incentivising the development of high-value medicines. However, there is some evidence in the literature of decreasing marginal willingness to pay for high QALY gains (i.e. the amount people are willing to pay for each additional QALY decreases). This trend was echoed in the expert interviews.
- **Cost-offsets.** A particular concern to payers regarding the concept of value-based pricing is whether or not cost offsets to the health system (e.g. from reductions in the cost of chronic care as illustrated by category 2 gene therapies) are taken into account in the price. This arises in part because the comparator is often not cost-effective by normal value-for-money standards. To increase the chance that a gene therapy in this context is financially sustainable, pragmatic adjustments to Health Technology Assessments (HTA) need to be made. For example, cost offsets could not be (fully) incorporated into the price (Pearson 2019; Towse and Fenwick 2019; ICER 2019b; Kerpel-Fronius et al. 2020), or the price of the comparator could be adjusted to a cost-effective level to calculate the price of the gene therapy (Garrison, Jiao, and Dabbous 2021). Alternatively, the price calculations could capture benefits to patients and the health system over a set time period (e.g. reflecting an artificial construct which may or may not reflect a typical patent period), after which value (or 'economic surplus') is transferred from the manufacturer to the health system (Garrison, Jiao, and Dabbous 2021; Chapman et al. 2019).

3. Competition factors: Where there are therapeutic competitors during the patent period, payers can choose the best value for money from multiple, comparable, on-patent products. This can result in lower list prices and greater power to negotiate discounts. Following the expiry of patent protection, payers can transition to using generics or biosimilars if they become available. Given the relatively recent entry of gene therapies to health systems, it is difficult to predict the level of competition for them in the future. However, lessons can be learned from the experience with biosimilars and generic competition for rare diseases. For gene therapies, factors such as the declining prevalent population following entry of the originator, high manufacturing costs, and the fact many gene therapies target rare diseases may serve as barriers to competition.

Conclusions

Gene therapies have the potential to deliver substantial benefits. However, the fear of ‘opening a Pandora’s box’ of spiralling costs, combined with the challenges of uncertainty and affordability, is making some decision-makers cautious about adopting gene therapies.

The various factors explored in this paper could be leveraged by stakeholders to realise the value of effective gene therapies whilst balancing their impact on financial sustainability. In the short-to-medium term, policy makers can work with manufacturers to overcome the barriers and operationalise MEAs, thereby transforming the risk associated with the adoption of gene therapies and managing short-term budget impact. Simultaneously, manufacturers can work with payers and HTA bodies to deliver responsible pricing strategies which allow the health system to share the economic value.

In the longer term, the extent of emerging on-patent and off-patent competition will impact financial sustainability. Manufacturing costs, which may represent a barrier to generic competition, are expected to decrease over time. Policy makers could work with patients and physicians to encourage the uptake of generic entrants if available. Pricing strategies can also be designed to take account of the barrier that the one-time nature of gene therapies poses to competition (i.e. the lack of ability to switch to a generic product post-treatment for any one patient).

Finally, financial sustainability is a critical issue that must not be considered in isolation, but in the context of transformative health improvements, value-based care, and appropriate incentives for innovation.

1 Introduction

A number of gene therapies have been approved, and many more are in late-stage clinical development (Ramezankhani et al. 2020). As more gene therapies receive marketing authorisations, there is concern in Europe that these technologies, which often have high upfront prices, may not offer good value for money, and their widespread adoption could threaten the financial sustainability of health systems. Gene therapies bring important challenges, particularly in relation to affordability and uncertainty around their long-term effects at time of launch. However, the potential for transformative benefits over an extended duration and, for some diseases, the potential for a cure is motivating stakeholders to explore how to overcome these challenges.

Gene therapies represent a step-change in medicine. They address the underlying genetic causes of disease rather than managing symptoms over a patient's lifetime. There is great hope that this technology will bring significant value and, for diseases with a genetic cause, a new era of personalised medicine. It also has the potential to alleviate the burden of chronic diseases on health systems. However, gene therapies are disruptive technologies that also pose challenges to health systems. As a result, they may require a change in the way that healthcare is delivered and paid for. Decision-makers need to understand i) what value these therapies can bring to patients and health systems and ii) how health systems can make the adoption of gene therapies financially sustainable. We aim to address these issues in this paper.

1.1 What are gene therapies?

Gene therapies modify gene expression to change the biological properties of cells (FDA 2018). By altering gene expression, they are able to address the genetic root cause of disease and can halt or modify disease progression if patients are treated early. As a result of targeting the cause of disease rather than managing symptoms as chronic therapies generally do, they offer one-time or short-duration treatment regimens.

In Europe, gene therapies are categorised as Advanced Therapy Medicinal Products (ATMPs), a term that also encompasses somatic-cell therapies and tissue-engineered therapies (EMA 2018a). Gene therapies encompass products that employ a range of technological approaches which continue to evolve (Wang and Gao 2014b; 2014a). These technological approaches can be broadly categorised as shown in Box 1.

Box 1: Technical overview of gene therapy

Gene therapy approaches

Different gene therapy approaches can be used as summarised in Table 1 below. These can broadly be grouped as follows: gene replacement, gene addition, gene inhibition and gene editing (Wang and Gao, 2014b). The most appropriate approach depends on the cause of the disease.

| Method | Application | Therapeutic potential | Example products |
|-------------------------|--|--|--|
| Gene replacement | Replaces the function of a dysfunctional or missing gene with a healthy gene. | Monogenic diseases | Zolgensma (onasemnogene abeparvovec) (for SMA) Luxturna (voretigene neparvovec) (for inherited retinal disease) |
| Gene addition | Addition of therapeutic genes that target a specific disease mechanism, often used to supplement a targeted therapy. | Monogenic, complex and infectious diseases | Kymriah (tisagenlecleucel) (for B-cell precursor acute lymphoblastic leukaemia) Yescarta (axicabtagene ciloleucel) (for relapsed or refractory large B-cell lymphoma) |
| Gene inhibition | Silences expression of a mutant gene that codes for a toxic protein or causes protein to be over-expressed. | Disorders linked to toxic or over-expressed protein. | No approved products to date |
| Gene editing | The patient's genome is edited to correct a mutant gene that promotes disease. | Monogenic diseases and cancers | No approved products to date |

TABLE 1 SUMMARY OF GENE THERAPY APPROACHES

In vivo vs ex vivo gene therapies

Gene therapy can either take place inside the body (in vivo) or outside of the body (ex vivo) (Wang and Gao, 2014a). In vivo therapies are administered directly to the patient. For ex vivo gene/cell therapies the targeted cells are removed from the patient, gene therapy is administered to the cells in vitro, and the treated cells are returned to the patient's body. Ex vivo approaches can only be used for cell types that can be safely removed from the body for a period of time (e.g. cells within the blood such as hematopoietic stem cells or immune cells).

1.2 Overview of this paper

This paper was developed to analyse the value that gene therapies can bring and whether gene therapies can be sustainable for health systems. The paper focuses on the value of gene therapies to patients and to health systems as these are the main factors considered by payers and health technology assessment (HTA) agencies in Europe. The paper has been informed by a literature review and expert interviews.

1.2.1 Literature review

We conducted a literature review to identify relevant publications on gene therapies to build on our existing knowledge in this area. It was not intended to be systematic as the aim was to identify key topics rather than to review all the literature in this area. We used a pearl-growing search strategy that uses the references from a small group of primary papers to identify relevant secondary papers. The process is continued until no additional relevant papers are identified. We supplemented this with a search in Google and PubMed to collect any unpublished or grey literature.

1.2.2 Expert interviews

OHE conducted semi-structured interviews with ten experts between December 2020 and January 2021. The experts interviewed included current or former policy makers, HTA experts, academics, and politicians. One interviewee was included from each of France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the UK. The one-hour interviews aimed to cover the full range of experiences and opinions on gene therapies and were not intended to reach consensus between interview participants. The range of experiences, perspectives, and country-contexts that each of the experts were recruited from were designed to enable us to understand a range of perceptions across Europe. Findings from the interviews informed the conclusions of this paper, and quotes are used throughout to highlight specific points.

1.2.3 Paper structure

Chapter 2 provides a discussion of the value that gene therapies can bring to patients and presents three illustrative categories to demonstrate the different potential value that gene therapies may offer health systems. In Chapter 3 we discuss the need for gene therapies to be affordable and offer value for money. We then discuss the question in Chapter 4 of whether gene therapies are financially sustainable for health systems. Finally, we will conclude in Chapter 5 by summarising the required conditions for financial sustainability, suggesting possible solutions for the timely adoption of gene therapies and proposing areas for future research.

2 What do gene therapies offer?

Many health systems in Europe use health technology assessment (HTA) to ensure that new technologies meet the aims of the health system. HTA involves an assessment of incremental health gain (the health gain of the new technology compared to the existing standard of care) via, for example, an assessment of clinical added value or measurement in units such as quality-adjusted life years (QALYs). Health gains can be due to an increase in length of life, quality of life, or both, relative to the existing standard of care. HTA may also include an assessment of the economic impact of a new technology. One way to do this is via cost-effectiveness analysis, which takes the incremental health gain and costs of a technology and compares them to the health gain and costs of existing standard of care. Costs are commonly assessed from the perspective of the health system.

In this chapter we will discuss the value of gene therapies by discussing the two factors traditionally considered in HTA in turn: the health benefit to patients, and the cost impact on the health system. We note that some HTA agencies take a broader perspective by considering other factors, such as productivity gains that may result from improvements in health. There is also ongoing debate around the inclusion of wider elements of value in HTA and decision-making (Lakdawalla et al. 2018). Many of these wider elements of value have been discussed in the context of gene therapies elsewhere (Coyle et al. 2020; Jönsson et al., 2019).

2.1 Value of gene therapies for patients

Gene therapies address the genetic root cause of disease, and as a result, they can achieve substantial health gains – and potentially a cure – for otherwise debilitating or fatal conditions with high unmet medical need. These health gains have the potential to be truly transformative for patients. Gene therapies offer health benefits to patients of a magnitude much greater than most traditional treatments (see Table 2).

| Product | Indication | QALY gain |
|---|---|--|
| Luxturna (voretigene neparvovec) | Inherited retinal disease due to mutations in both copies of the RPE65 gene, a condition that may lead to blindness | Between 12.1-17.7 QALYs compared to best supportive care accounting for uncertainty (NICE 2019). |
| Zolgensma (onasemnogene abeparvovec) | Spinal Muscular Atrophy. | For SMA type 1, 18.6 QALYs compared to best supportive care (NICE 2021). |
| Strimvelis (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence) | Rare metabolic disorder adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID) which causes severe immunodeficiency and recurring infections in patients. | 13.6 QALYs compared to hematopoietic stem cell transplant from a matched-unrelated donor (NICE 2018). |

TABLE 2: EXAMPLE GENE THERAPIES AND MAGNITUDE OF QALY GAIN

One review of products from 1992-2017 found that cell and gene therapies had a mean QALY gain of 5.78 QALYs compared to 0.49 and 0.43 QALYs gained for small molecules and biologics respectively (see Figure 1) (Cohen et al. 2019; Chambers et al. 2019). A study of the impact of gene therapies currently in end-stage development estimated that over the 15 year period 2020 to 2034, gene therapies currently in development are expected to account for a QALY increase of 5.59 million QALYs in the US, an average of 5.12 QALYs per person treated (Wong et al. 2020). These figures suggest that gene therapies offer the potential to offer substantial health gains compared to chronic therapies.

Average QALY gain across different modalities

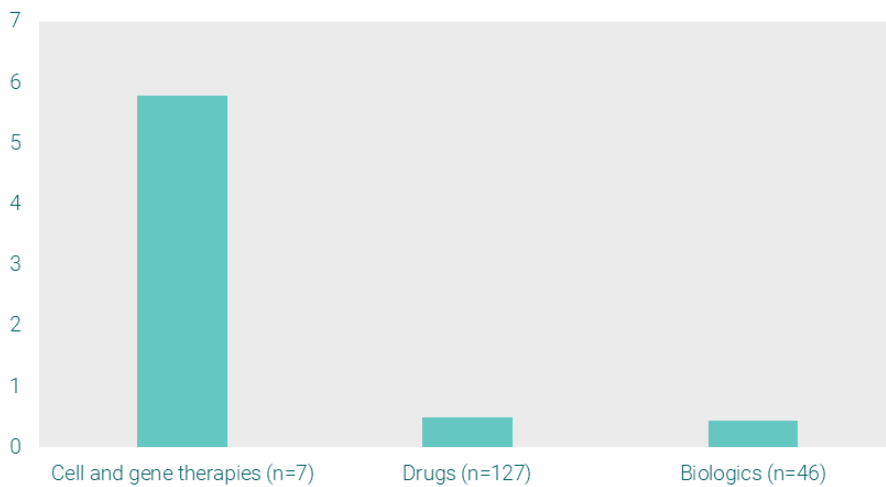


FIGURE 1 THE AVERAGE QALY GAINS OF A SAMPLE OF CELL AND GENE THERAPIES, OTHER BIOLOGICS AND SMALL MOLECULES (COHEN ET AL. 2019)

Gene therapies could be particularly beneficial in areas of high unmet medical need, thereby offering a major step-change for patients who may otherwise have poor treatment options. In 2016, in recognition of the importance of targeting conditions with unmet need, the EMA established its PRiority MEDicines (PRIME) scheme. The scheme enhances support for the development of medicines that target an unmet medical need to accelerate assessment and patient access. Since the introduction of PRIME, three of the five cell and gene therapies that have been approved for use by the EMA within this window (Kymriah, Yescarta and Zynteglo) have received PRIME designation (EMA 2018c), thereby highlighting that gene therapies have value in addressing unmet medical need.

2.2 Value of gene therapies for health systems

The economic impact of a specific therapy on the health system will differ depending on whether the QALY gains (compared to the current standard of care) are primarily driven by an increase in length of life or an improvement in quality of life. This is independent of the health gain that a therapy provides to patients. In this section we present three illustrative categories of gene therapies, distinct in their expected financial impact on the health system and wider society. The categories aim to demonstrate that not all gene therapies will have the same financial impact on the health system. The three categories are intended to be illustrative, and we note that some therapies may sit between categories and/or exhibit the characteristics of multiple categories.

The categorisation of a specific gene therapy will be influenced by its relative effectiveness (and therefore also the standard of care that is used for comparison) and by the characteristics of the disease it targets. While the long-term efficacy of many gene therapies is not yet known (which we discuss in subsequent chapters) for these categories we have assumed that efficacy is durable. It is worth noting that the efficacy of gene therapy also depends on how early a patient is treated, as gene therapies are not currently able to reverse the effects of disease progression. The earlier a patient is treated, ideally in the pre-symptomatic phase, the greater the value the gene therapy will bring, regardless of the category within which it sits.

The three illustrative categories described below and in Table 3 are:

- Category 1: therapies with a large increase in length of life and limited expected cost offsets
- Category 2: therapies with large increases in quality of life and substantial cost offsets within the health system
- Category 3: therapies with large increases in quality of life and substantial cost offsets outside of the health system.

| | Primary driver of QALY gain | | Where do the cost offsets accrue? | |
|------------|-----------------------------|-----------------|-----------------------------------|------------------------------|
| | Length of life | Quality of life | Inside the health system | Outside of the health system |
| Category 1 | ✓ | | | |
| Category 2 | | ✓ | ✓ | |
| Category 3 | | ✓ | | ✓ |

TABLE 3 SUMMARY TABLE OF THREE CATEGORIES OF GENE THERAPIES

Category 1: Gene therapies with a large increase in length of life and limited expected cost offsets

This category is exemplified by a therapy for which the majority of the health gain results from a substantial increase in length of life. This may be seen for an effective gene therapy for a condition with high early mortality and no alternative effective treatment options. Gene therapies for these diseases, whilst potentially offering transformative patient value, are the least likely to demonstrate cost offsets to the health care system. This is because the early death of the patient means that any healthcare costs are only incurred for a very short period of time. Even in the case of a hypothetical therapy that restored the patient to full health and life expectancy, that patient would still consume at least the same healthcare as a healthy individual across their lifetime. Thus, the therapy would not generate cost offsets.

An example of a gene therapy that falls into category 1 by providing a large increase in length of life is Zolgensma for SMA type 1 when compared to best supportive care¹. Zolgensma has been modelled to have a higher rate of survival (18.6 life years) compared to best supportive care (2.4 life years) (ICER 2019a) for SMA type 1. Without care, life expectancy is around 2 years (NICE 2021).

Category 2: Gene therapies with large increases in quality of life and substantial costs offsets within the health system

Gene therapies for conditions which do not have high early mortality or target diseases that are currently treated with relatively inefficient care (high cost and/or poor outcomes), are set to deliver health gains primarily via improvements in quality of life, with little impact on the length of life. In such cases, the result of improving quality of life may be a reduction in costs associated with managing their condition (Cohen et al. 2019). These cost offsets may translate into cost savings to the health system if the reduction in treatment cost outweighs the cost of providing the gene therapy².

Examples are gene therapies in development for haemophilia A, a disease that causes excessive bleeding due to a genetic deficiency in a protein needed to cause the blood to clot (Sharma et al. 2020). Patients with untreated haemophilia suffer chronic disability and pain as a result of excessive bleeding resulting in a substantially lower quality of life (O'Hara et al. 2017). Haemophilia treatment can cost up to 1 million EUR per year, with one study from 2014 estimating that the average annual cost per patient in Europe was EUR 200,000 (O'Hara et al. 2017). A study in the US estimated a similar annual treatment cost (USD 250,000 per patient) and found the average lifetime cost of treatment per patient was USD 16.7 million and could be as high as USD 73.9 million (Cook et al. 2020). A gene therapy that eliminated the need for this expensive chronic therapy while delivering improvements in quality of life would have the potential to deliver substantial cost offsets within the health system.

Category 3: Gene therapies with large increases in quality of life and substantial cost offsets outside of the health system

Gene therapies for diseases that limit quality of life but do not require additional healthcare do not have cost offsets within the health system. However, these diseases may have a substantial burden on services outside of the health system. These costs may fall on families, the social care system, the education system or the welfare system (Aballéa et al. 2020; Alliance for Regenerative Medicine 2020). Gene therapies for these diseases generate cost offsets that accrue predominantly outside of the health system through a reduction in the need for supportive services that patients may need to compensate for their disease in day-to-day life.

An example of a therapy that falls into this category is Luxturna. Luxturna is a gene therapy to treat vision loss due to the dysfunctional RPE65 gene which is needed for the healthy function of cells in the retina. One study in Germany estimated that the total cost of blindness and visual impairment from a societal perspective was EUR 49.6 billion (Chubarayan, Finger, and Köberlein-Neu 2019). Around 71% of those costs were non-medical, for example, due to informal care given by relatives, formal care given in the home, and loss of productivity for the patient due to absenteeism and occupational disability. Therefore, Luxturna is likely to have substantial cost offsets outside of the health system associated with patients who would go blind without treatment.

¹ Note that for the purpose of this example we are focusing on Zolgensma for SMA type 1 as SMA type 1 has particularly high infant mortality. The EMA approved indication is wider than this. Note also that this example compares Zolgensma to best supportive care – in countries where Spinraza (nusinersen), an alternative therapy for SMA, is routinely available, the relevant comparator would be Spinraza rather than best supportive care. In such cases, the relative life extension from Zolgensma would be smaller, although still substantial.

² This depends in part on the pricing strategy of the manufacturer. Savings will not be realised if the cost offsets are fully captured in the price. This is discussed further in Chapter 4.

Summary

There is great excitement that gene therapies offer the potential for substantial health gains. However, different types of gene therapies will have different financial implications for health systems – and more broadly – depending on the nature of those health gains (i.e. whether they are mainly due to length of life or quality of life). The three categories are designed to illustrate this variation and highlight that effective gene therapies will offer different value profiles from the perspective of the health system and wider society.

Where a specific gene therapy sits within this categorisation is influenced by the therapy itself (i.e. its relative effectiveness), but also the wider context (including the relevant comparator, care burden within and outside the health system, characteristics of the disease targeted, and how early in disease progression the patient is treated). In some cases, gene therapies may sit between categories, giving rise to some gains in length of life, in addition to increases in quality of life that generate some cost offsets within and outside the health system.

All three categories potentially offer huge value for society, driven either by health gains or through costs offsets and could transform care in certain disease areas. However, they are likely to be judged very differently in cost-effectiveness analyses depending on the perspective taken. It is also crucial that the financial impact on the health system is not considered in isolation. Category 1 therapies that are not expected to offer cost offsets to health systems are those which save lives and may offer the greatest health gains for patients.

3 Do gene therapies offer value for money? Are they affordable?

As outlined in the previous chapter, gene therapies could offer transformative value for patients, health systems and societies both in terms of health gain and cost offsets. However, there are currently two key concerns surrounding gene therapies which may delay their adoption in the short term: how certain can we be that they will offer value for money in the long term? and are they affordable?

There are characteristics of gene therapies that may challenge value for money and affordability (Marsden and Towse 2017; Jönsson et al. 2019; Coyle et al. 2020; Carvalho, Sepodes, and Martins 2021). Interviews undertaken as part of the research for this paper indicated that there are two such features of particular relevance to payers, they are:

- 1) uncertainty about the durability of effects in the long-term at the time of approval
- 2) 'high' upfront prices

These features generate the challenges of uncertainty in long-term value and affordability, respectively. In this chapter we will first discuss the challenges themselves then outline mechanisms that can be used to mitigate these challenges.

3.1 Uncertainty about the durability of effects leading to uncertainty in the value for money of gene therapies

Assessing the value of new technologies is an important process within European health systems. Value assessments often include modelling the costs and benefits of treatments over time as part of a wider HTA. Such assessments rely on data, mostly from relatively short clinical trials, to inform the economic modelling.

The cause of the concern around whether gene therapies offer value for money is the uncertainty of whether treatment effects seen in clinical trials are durable in the long term. Gene therapies in clinical trials have shown substantial short-term treatment effects. However, higher upfront costs of gene therapies are only justified if the treatment effects that have been demonstrated over relatively short timeframes are durable in the long term, preferably for the lifetime of the patient. One study quantifying the differences in ATMP submissions and other biologics shows that ATMPs are often approved with less clinical and non-clinical evidence compared to other biologics (Elsallab, Bravery, et al. 2020). The data is often from small non-randomised trials with variation in treatment response, with short-term follow up and use of surrogate outcomes (Hanna et al. 2016). Interviews conducted for this paper also highlighted concerns around the uncertainty in the duration of treatment effects (selected quotes presented in Box 2 below).

Box 2: selected quotes demonstrating concerns about uncertainty from expert interviews

"Right now, the claim is that it's curative for a long time, and that when you have an intervention once, that will save a lot of health costs in the future. But it's not proven." - **Netherlands**

"[We] don't know what happens in the long-term. Pre-clinical data are completely convincing, [it's] very shaky ground to argue the value because it has not been proven, especially not a mid- or long-term perspective." - **Germany**

Given the potential for life-long durability of effects with gene therapies, it is not practical for the full duration of treatment effects to be demonstrated in clinical trials before regulatory approval and value assessment are carried out. These evidence limitations present problems for payers relying on usual value assessment methods to assess the value of gene therapy products. Applying value assessment methods to gene therapies requires a trade-off between choosing a time horizon that allows the full value of the product to be modelled while managing uncertainty in the analysis (Aballéa et al. 2020).

However, while more prevalent for gene therapies, the challenges of carrying out HTA for gene therapies are not unique to these products (Hettle et al. 2017; Marsden and Towse 2017). For example, the challenges of short-term trials, use of surrogate markers, uncertainty around whether outcomes are sustained over time, and uncertainty about future safety issues also apply in other areas (Marsden and Towse 2017). In addition, approaches exist to mitigate the risks posed by the uncertainty in clinical evidence at the time of approval (Elsallab, Levine, et al. 2020), as explored in section 3.3 below.

3.2 The affordability challenge

As a result of their higher upfront costs, gene therapies are perceived to be unaffordable and could put pressure on health budgets (Danzon 2018). Even when judged to provide good value for money, gene therapies may present a short-term budget impact challenge, despite the potentially transformative health gain, and the potential cost offsets they could offer in the long term (Hampson et al. 2017; Danzon 2018). The concern around affordability of healthcare technology in general is reflected in the introduction of measures to assess affordability as part of the value assessment process, such as the budget impact test in the UK (NICE 2017)³.

The processes for assessing and reimbursing pharmaceuticals are designed for chronic therapies. Chronic therapies are paid for and delivered to patients over the long term, spread over multiple budget cycles, which has a lower short-term financial risk for payers. In short, the instalments are relatively small, and if the treatment proves to not offer the value for money that was estimated during HTA, payers can stop paying for it. Regulators have shown they are able to account for uncertainty in the durability of effectiveness and safety through conditional approval or approval with

³ *If the annual cost of a drug in the NHS exceeds £20 million in any of the first 3 years, NHS England can engage in commercial discussions with the company to seek a discount to limit the impact of that drug on the NHS. If there is not an agreement, NHS England can request a change to the statutory funding requirement from the NICE recommendation.*

a requirement to follow treated patients in a registry. However, even when regulators deem products to be safe and effective, concerns from HTA bodies and payers around affordability and long-term uncertainty could lead to delays in adoption (Jørgensen and Kefalas 2017).

3.3 Solutions to the problems of affordability and uncertainty

For chronic therapies, payers have used discounts and discontinuation of treatment to manage uncertainty and affordability issues (Jørgensen, Mungapen, and Kefalas 2019). However, these mechanisms are not always appropriate for one-time gene therapies where discontinuation of treatment for individual patients is not possible and substantial discounts do not represent a sustainable commercial option.

Managed Entry Agreements (MEAs) offer potential solutions to the problems of affordability and uncertainty by reducing the risk of decisions made by payers and HTA bodies. There are various forms of MEA which enable decision-makers to manage different challenges. The types of MEA can be grouped into financial, coverage with evidence development, and performance-linked reimbursement (Garrison et al. 2013). The three main groups are summarised in Table 4 below. We explore in the rest of this chapter how MEAs can be used to reduce the risk for payers (Grimm et al. 2017).

| Type | Explanation | Problem addressed | Examples |
|---|---|-------------------------------|--|
| Financial | Reduces costs or spreads costs over multiple budget cycles. Commitment to pay is made once and upfront. | Affordability | Cap on annual expenditure, phased payments e.g. annuity payments (similar to a mortgage) |
| Coverage with Evidence Development (at patient or population level) | Data is collected over a specified period in clinical use. The product is then re-evaluated. | Uncertainty | Cancer Drugs Fund in the UK, collection of Real World Evidence following initial assessment in Germany (Kipentzoglou 2021) |
| Performance-linked reimbursement | Upfront cost is paid in instalments linked to a patient meeting a pre-defined clinical outcome. | Affordability and uncertainty | Annual payments linked to assessment of efficacy, e.g. Italy agreement for Zolgensma (Eversana 2021) |

TABLE 4 SUMMARY OF MANAGED ENTRY AGREEMENT MECHANISMS

Addressing affordability - annuity payments

Annuity payments allow the upfront cost of a product to be paid in instalments over a prespecified period (Jørgensen and Kefalas 2017). Commitment to pay the annuity to the manufacturer is made upfront. Payers could also take out a loan to reimburse the manufacturer upfront and repay the loan in instalments (Jørgensen and Kefalas 2017)⁴. The payment instalments are structured to overcome the affordability issue in each budget cycle. Such annuity payments were leveraged in Spain for regional payers to procure hepatitis C treatments (Jönsson et al. 2019), and similar leasing mechanisms are used for medical devices (such as expensive PET or MRI scanners).

Addressing uncertainty - coverage with evidence development

Registry data or post-approval studies allow data to be collected over a longer period to monitor the durability of the treatment effect and the long-term safety (Abou-El-Enein, Grainger, and Kili 2018). There is evidence that this mechanism is already being leveraged by regulators as ATMPs that received marketing authorisation from the EMA had higher post-approval data collection arrangements than other biologics (Elsallab, Bravery, et al. 2020). As well as ongoing monitoring to meet regulatory requirements, this data could also be used to reassess the value of the therapy. When used by HTA bodies and payers, post-approval data collection has the potential to be useful for reducing uncertainty in future clinical and cost-effectiveness analyses and reimbursement decisions, particularly regarding long-term effectiveness.

Addressing affordability and uncertainty – performance linked reimbursement

Where annuity payments are conditional on a patient meeting a defined clinical outcome, they become performance-linked reimbursement agreements. These agreements track outcomes in treated patients, and the level and duration of reimbursement are based on whether a certain pre-defined clinical outcome is reached (Garrison et al. 2013). This mechanism changes the risk relationship between payers and manufacturers (Grimm et al. 2017). Performance-linked reimbursement controls cost-effectiveness by ensuring reimbursement is triggered by performance (Garrison et al. 2013). As a result, the total cost that the health system pays for a treatment is aligned with the value delivered to patients.

Whilst it may not be practical to agree to a performance-linked reimbursement scheme for the full duration of expected benefit (i.e. the patient's lifetime), it may be possible to design a series of agreements. For example, multiple consecutive performance-linked reimbursement agreements could be negotiated after set time points (e.g. every 3-5 years). Each subsequent agreement could potentially include consideration of the increased data available at that time.

3.3 Challenges to implementing novel managed entry agreements

The adoption of ATMPs has generated some progress with the use of performance-based agreements in Europe (Jørgensen, Hanna, and Kefalas 2020; Ronco et al. 2021). However, there are still barriers to their widespread and timely adoption. A study in 2017 found that the pace of adoption of these mechanisms varies across countries (Carlson, Chen, and Garrison 2017). In addition, most MEAs in use are financial (adjusting payments to manage budgets in a way that is not linked to clinical outcomes, e.g. through price-volume caps or discounts). The use of performance-based MEAs has been less common (Wenzl and Chapman 2019). There are a number of explanations in the literature as to why MEAs are inconsistently implemented across Europe (Michelsen et al. 2020) which we discuss below.

⁴ There are various ways this can be organised (see Hampson et al. 2017), but it is commonly expected that either the manufacturer or a third party (via a loan) would assume the debt for the duration of the agreement.

Lack of willingness to engage with novel Managed Entry Agreements

Manufacturers may be more willing to enter into outcomes-based contracts than payers, who are concerned about their complexity and their ability to change the reimbursement decision in practice if the evidence changes (Bouvy, Sapede, and Garner 2018). MEAs are rarely evaluated, which may reduce the willingness of different stakeholders to enter into these kinds of arrangements. For example, a small number of MEAs that have been evaluated have failed to resolve the uncertainties around cost-effectiveness that they were intended to address, mainly due to the poor quality of data collected (Wenzl and Chapman 2019). Other issues with performance-based MEAs were: the administrative burden on the payer, the high level of confidentiality, difficulties in reducing prices or delisting treatments for the payer, and the financial uncertainty for companies of the impact of new evidence on future prices and revenues (Vreman et al. 2020; Wenzl and Chapman 2019).

Legislative hurdles to financial Managed Entry Agreements

In some jurisdictions, there may be legislation that limits long-term payment agreements (Michelsen et al. 2020). European accounting standards (ESA 2010) also require that the full cost of a product be budgeted within the year of treatment administration (Maes et al. 2019). This impacts payments over multiple years that are not linked to a clinical outcome. Such payments are classed as a loan to the supplier and therefore count towards government debt. Accounting standards also constrain the flexibility of the manufacturer to accommodate payments spread over multiple years. Experts interviewed for this project also suggested that national legislation on accounting and procurement of medicines may be a further barrier to implementing annuity payments in certain health systems. However, simple legislative changes may be able to overcome this barrier.

Practical and administrative challenges of performance-based agreements

There is concern that managing performance-based contracts will present an administrative and cost burden on the health system (Bouvy, Sapede, and Garner 2018). Studies suggest that flexibility is needed to adapt MEAs to different systems and for different products (Vreman et al. 2020). However, flexibility is costly for decision-makers and manufacturers and makes evaluation of MEAs more complex in practice, which is important for payers.

Performance-based agreements require infrastructure within the health system to monitor outcomes in treated patients. The readiness of infrastructure to support the implementation of performance-based agreements varies across different systems. A review in the UK showed that data systems within electronic health records are not sufficient to support outcomes-based payments, particularly for conditions treated outside of specialist settings (Jørgensen, Mungapen, and Kefalas 2019; Bouvy, Sapede, and Garner 2018). Some countries in Europe are better equipped to support performance-based agreements, with Italy's universal data collection infrastructure an example of an information system that is used for this purpose. The heterogeneity in expertise and readiness for these agreements was highlighted in the expert interviews. Some selected quotes are presented in Box 3 below.

Registries are one mechanism that has been used for post-registration data collection. There is substantial variation in the existence and quality of registries across diseases and countries. There is also concern that having indication-specific registries reduces the interoperability and integration of health data with electronic health records across the health system. Such interoperability is needed for performance-based agreements to be implemented, particularly for diseases that are managed across different health settings (e.g. primary care, hospital care, specialist care) (Jørgensen, Mungapen, and Kefalas 2019).

The design of the schemes themselves may also be complex, as they must consider how the myriad of possible patient outcomes relate to payments. For example, what happens to the payment schedule if a patient dies of a cause independent of the treatment. There may also be clinically complex cases where it is difficult to assess whether or not a payment-related outcome has been reached. Some payers are concerned about possible legal challenges from the manufacturer if there are disputes over whether the outcomes have been met. These themes were reflected in the expert interviews carried out for this project (see Box 3 below). Given the complexity of performance-based agreements and concerns around legal challenges, the contracts that underpin them are administratively burdensome to negotiate for both payers and manufacturers. It is particularly burdensome for payers if the structures of contracts have to remain confidential and cannot be shared or reused.

Box 3: selected quotes from expert interviews demonstrating heterogeneity in the ability of health systems to utilise MEAs

“Outcome-based mechanisms [...] if they're complex, it makes it really difficult for the NHS. And if those criteria against which the payments are made can be disputable, that potentially could make things [...] administratively very complex indeed, and that's the sort of thing that NHS England is very much trying to avoid.” – England

“The idea that the Minister of Health decides more or less everything...it's pretty much ingrained in the in the culture of the health system in Portugal. So this idea that you have a contract that then [you] need to respect the contract and if you don't respect the contract, [you] may be taken to court to fulfil the contract is actually still alien to many people in the in the health system.” – Portugal

“In our system it's easier to have spread paybacks from the company then spread payments.” – Netherlands

“We have 21 regions that basically handle our healthcare and there's also a big difference between these 21 regions when it comes to financial strain, when it comes to skills, when it comes to competence, and when it comes to [...] awareness – Sweden

4 Are gene therapies financially sustainable?

Healthcare expenditure is rising globally due to demographic and epidemiological changes, increased societal expectations, and technological advances in healthcare (Liaropoulos and Goranitis 2015; Thompson et al. 2009). As a result, there is a growing focus on the financial sustainability of healthcare. The concept of financial sustainability in healthcare is not well defined but is linked to the need for payers to balance rising costs against limited resources in the long term (Thompson et al. 2009). The financial sustainability of gene therapies also depends on factors relating to the R&D pipeline, pricing, and post-launch competition. These factors are explored in this chapter.

4.1 Pipeline factors

The rate of new gene therapies coming to market, total numbers of products launched, and the numbers of patients targeted by those products all factor into the financial sustainability of gene therapies. Most analyses of the gene therapy pipeline group gene therapies and cell therapies together given the overlap in the therapeutic processes. These analyses show the cell and gene therapies pipeline is growing with 362 products in phase I-III clinical trials in 2019, up by 25% from 2018 (Quinn et al. 2019)(Hargreaves 2020) and increasing numbers of products approved. A significant minority (49%) of the estimated cell and gene therapy products expected to be launched by 2030 are for haematological cancer indications, followed by ophthalmology (13%) and haematology indications (Quinn et al. 2019). These are summarised in Figure 2 and Figure 3 below.

Cumulative estimated cell and gene therapy launches 2018-2030

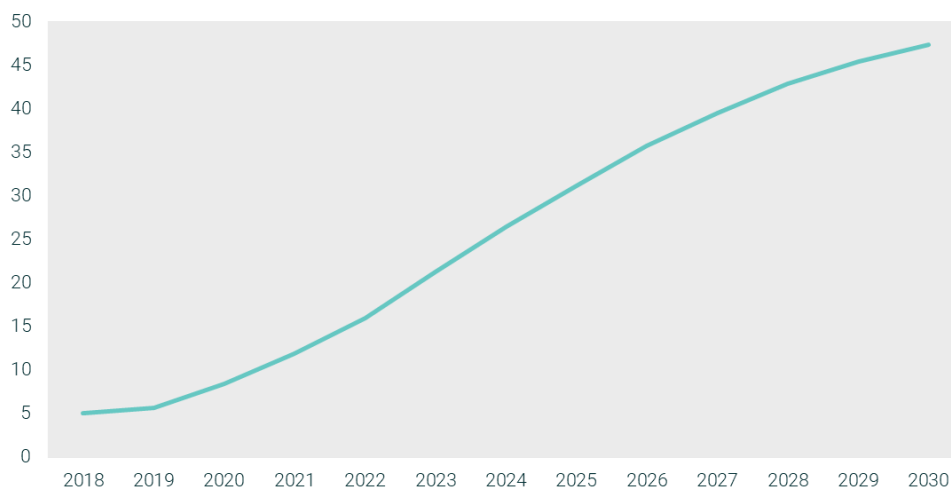


FIGURE 2 CUMULATIVE ESTIMATED CELL AND GENE THERAPIES APPROVED BETWEEN 2018 AND 2030. SOURCE QUINN ET AL. (2019).

Cumulative estimated cell and gene therapy products launched between 2018-2030 by disease

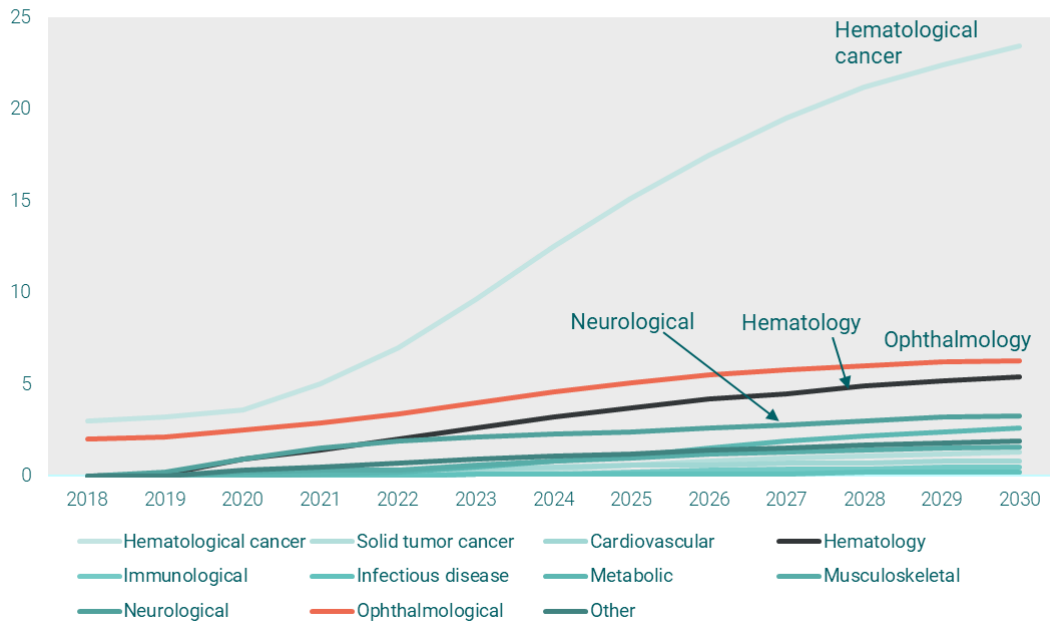


FIGURE 3 CUMULATIVE ESTIMATED CELL AND GENE THERAPY PRODUCTS BY DISEASE LAUNCHED BETWEEN 2018-2013 (QUINN ET AL. 2019)

To assess the financial impact of this growing pipeline on a health system, Wong et al. (2000) modelled the total costs of the current gene therapy pipeline in the US over 15 years from January 2020 to December 2034 (Wong et al. 2020). The authors used a projection of the number and type of gene therapies that are likely to come onto the market over this time based on the therapies already in late-stage clinical trials (phase 2/3 and beyond), adjusted for probability of success and time to market. To estimate prices of therapies currently in development, they use roughly \$41K per QALY for non-rare diseases and \$102K per QALY for rare diseases, reflective of the list prices of existing gene therapies. The paper also estimated the size of the eligible patient population and the market size for each of the therapies in the US.

Wong et al. estimate the following for the US:

- 1.09 million patients in the US will be treated by the end of 2034 with gene therapies that are currently either available or in late-stage development (phase 2/3 and beyond).
- The annual number of US patients treated is projected to grow from 16,244 in 2020 to peak at 94,696 in 2025, and then decline to 65,612 in 2034.
- Annual expenditure on gene therapies in the US is estimated to be \$5.15 billion (approximately €3.77 billion) in 2020, increasing to peak at \$25.3 billion (€18.5 billion) in 2026 and declining to \$21 billion (€13.6 billion) in 2034. The projected expenditure is represented in the graph below in Figure 4. To put this in context, it has been estimated elsewhere that total annual pharmaceutical spending in the US will grow to \$600 billion by 2023 (IQVIA 2019).
- The cumulative spending during this period (to 2034) is estimated to be \$306 billion (€224 billion).

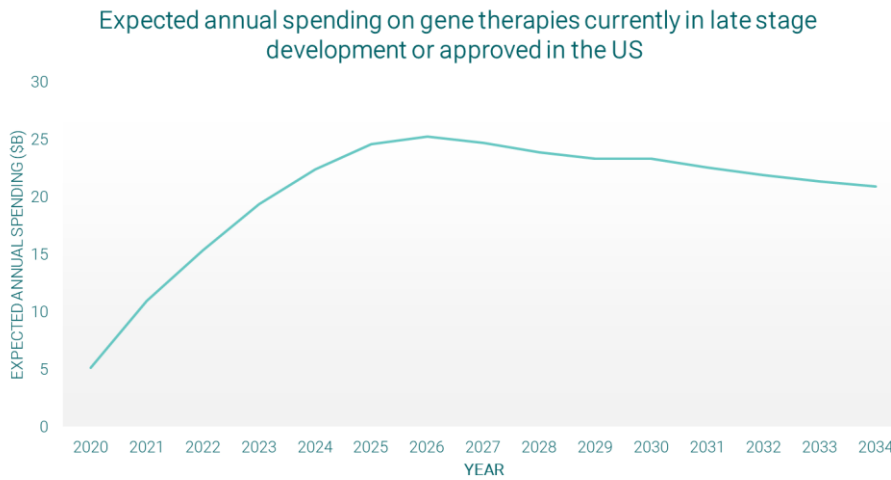


FIGURE 4 PROJECT EXPENDITURE ON GENE THERAPIES IN THE UNITED STATES (WONG ET AL. 2000)

The authors note that their estimates are likely to be conservative as the analysis did not include new gene therapies likely to be added to the pipeline between 2020 and 2034. Another analysis estimates that a further 20-30 cell and gene therapy products are likely to come to the market by the end of 2034 (Quinn et al. 2019).

While these numbers give us an idea of the cost of the gene therapies currently in late-stage development, they are not representative of all gene therapies likely to be approved during this period, only those already in late-stage development. Therefore, it does not give the whole financial picture. Estimates of expenditure are also sensitive to assumptions of the eligible patient population and the proportion of that eligible population treated with gene therapies. Wong et al. has much higher estimates of the proportion of patients treated compared to another analysis by Quinn et al. which looks at cell and gene therapies combined.

The paper also only considers the price of the gene therapies, and not any further cost implications for health systems, such as the costs of administering gene therapies or any potential cost offsets. The estimates therefore do not reflect the total cost of gene therapies to the health system. The analysis also does not allow for the different financial implications of different types of gene therapies, as set out in Chapter 2 of this report. Based on the limitations of the Wong et al. analysis, we expect annual spending on gene therapies will not decrease from 2026, unlike suggested in Figure 4 above.

4.2 Pricing factors

Two main pricing factors affect the financial sustainability of gene therapy: whether the price reflects value, and whether the price incorporates any cost offsets within the health system.

Price should reflect value

The price of gene therapies should reflect the value of the health gain that a product delivers. 'Value' is defined by what the payer is willing to pay for, but typically includes benefits to the patient and the health system. Value-based pricing reflects the payers' need to maximise an output (e.g. health gain), subject to a given budget constraint and ensures efficiency in the long-term (dynamic efficiency) but can have short-term affordability challenges (Danzon 2018). Value-based pricing promotes efficiency in the long term by incentivising the development of high-value medicines. By contrast, cost-based reimbursement creates a perverse incentive where low-value, high-cost drugs get higher prices than low-cost, high-value drugs.

However, there is concern among decision-makers that in cases where gene therapies are compared to – and potentially replace – inefficient care (e.g., category 2 therapies discussed in Chapter 2), a value-based price would not allow health systems to realise the benefits of replacing that inefficient care. This would mean that the full cost-saving potential of gene therapies will not be realised.

There may also come a point where the value is so high that the value-based price is considered too great, regardless of the value offered. The literature supports this, with a decreasing marginal willingness-to-pay found for high QALY gains (i.e. the amount people are willing to pay for each additional QALY decreases). This finding suggests a diminishing marginal societal value (Rowen et al. 2016; Hampson et al. 2019). The experts interviewed as part of this project also suggested that ‘pure’ value-based pricing was a concern with gene therapies. A number of quotes are presented in Box 4 below.

Box 4: selected quotes on value-based pricing and cost of gene therapies from expert interviews

“Value-based pricing in its essence as it is used in the pharmaceutical industry is no longer sustainable. So what you see in value-based pricing ...[is you] collect all the arguments you can think of to get the price as high as you can.” – The Netherlands

“The pharmaceutical industry has been successful in having the price equal value. The relative statement has been changed into the absolute statement in favour for themselves, to push the price up and up” – Portugal

“As a society we cannot invest in everything, we have to accept that there are limits...it's not only because it's gene therapy... and not only because it's an ATMP [should] it cost 10 times the current costs. Why? There is no reason for that” – Germany

Cost-offsets

A particular concern to payers regarding the concept of value-based pricing is whether or not cost offsets to the health system (e.g. from reductions in the cost of chronic care) are taken into account in the price. If cost-offsets from replacing cost-ineffective treatments with gene therapies are fully reflected in the price, then there will be no cost savings for the health system in adopting a gene therapy relative to standard care. This is of particular concern for gene therapies that fall in category 2 presented in Chapter 2 of this report.

The concerns of payers arise in part because the comparator is not cost-effective by normal value-for-money standards. An example we have illustrated above is haemophilia. Patients are currently receiving high-cost treatment to keep them alive and with a reasonable quality of life, but treatments are not cost-effective because prices do not reflect societal value by normal standards, i.e. those applied in other disease areas (Garrison, Jiao, and Dabbous 2021).

For gene therapies in category 2 outlined in Chapter 2, a substantial portion of the value that they bring to the health system is in the form of cost-offsets by replacing high-cost care. There are various methods by which health systems can realise the efficiency generated by gene therapies that generate cost offsets. For example, cost-offsets could not be fully incorporated into the price (Pearson 2019; Towse and Fenwick 2019; ICER 2019b; Kerpel-Fronius et al. 2020), or the price of the comparator could be adjusted to a cost-effective level to calculate the price of gene therapy (Garrison, Jiao, and Dabbous 2021). Alternatively, the price calculations could capture the benefits to patients and the health system over a set time period (e.g. reflecting an artificial construct which may or may not reflect a typical patent period), after which value (or ‘economic surplus’) is transferred from the manufacturer to the health system (Garrison, Jiao, and Dabbous 2021; Chapman et al. 2019).

Each of these approaches has different practical limitations, and there may be other approaches that have not been considered here. However, financial sustainability will be supported if the prices for gene therapies that generate cost offsets enable the sharing of those cost offsets between the manufacturer and the health system.

Evidence of cost offsets

A paper by the Alliance for Regenerative Medicines (2020) models the economic value of cell and gene therapies for patients with Multiple Myeloma, Sickle Cell Disease and Haemophilia A in the US from 2020-2029 (Alliance for Regenerative Medicine 2020). They focus on single-administration therapies with a durable effect that lead to a significant reduction in the patient's interactions with the health system. These are therapies that are likely to have significant cost offsets within the health system, i.e., they represent category 2 gene therapies in Chapter 2 of this report. This analysis is thus not generalisable to gene therapies that are not expected to generate cost-offsets for the health system (i.e., those in categories 1 or 3).

The study compares total costs associated with each disease against the predicted costs if a proportion of the eligible patient population had access to a gene therapy with durable clinical outcomes over the whole 10-year period. They assume an average base case price of \$373,000 for Multiple Myeloma and \$1.5 million for Sickle Cell Disease and Haemophilia A. They model the treatment replacing standard care would be a cell therapy treatment for Multiple Myeloma and a Gene Replacement Therapy for Sickle Cell and Haemophilia A. They also assume that 20% of the eligible patient population would be treated with gene therapies each year. Treatment costs were assumed to be the same as for CAR-T therapies⁵.

The study suggests that savings in medical costs for the three diseases will reach \$31 billion (€25.5 billion) in 2029. The study estimates that an initial increase in spending due to the cost of gene therapies will be followed by savings from cost offsets (see Figure 5⁶). The analysis shows that changes in patient eligibility and access have the greatest impact on savings, with a 10% expansion in eligibility and access associated with increased savings of greater than \$3 billion (€2.5billion). The price also had an impact on overall savings, as for every 10% decrease in price, savings increased by \$500 million, and the hypothetical minimum price (\$271,000 for multiple myeloma and \$1.1 million for sickle cell and haemophilia A) brought forward the initiation of cost-savings by two years (from 2025 to 2023).

⁵ Some gene therapies that are delivered in vivo are likely to have lower treatment costs than CAR-T given there is no need to personalise these therapies.

⁶ This graph includes savings due to gains in productivity which we do not discuss here. Over the 10-year period, productivity gains were modelled to account for around \$3 billion in savings and therefore the conclusions are not affected by removing these savings from the discussion.

Net savings from Cell and Gene Therapies

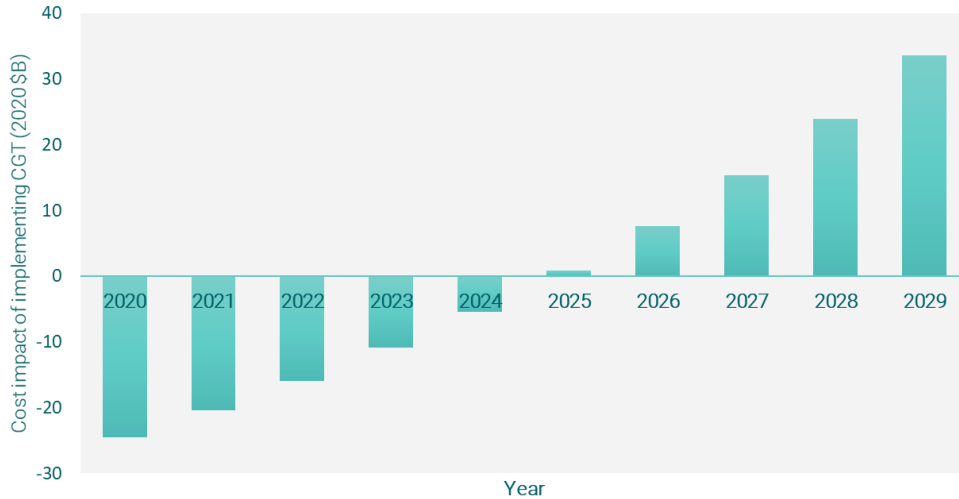


FIGURE 5 PROJECTED COST SAVINGS DUE TO CELL AND GENE THERAPIES (ALLIANCE FOR REGENERATIVE MEDICINE 2020)⁶.

This study suggests that specifically those therapies that sit in category 2 (i.e. those that are likely to generate cost offsets for the health system) could lead to substantial cost savings in the long term in the US. The finding is robust for assumptions on price of between £1-2 million per patient for gene therapies and \$271k-\$475k for cell therapy (for Multiple Myeloma). Therefore, even at high prices per patient and relatively low uptake, cost savings are projected to be captured by the health system in the long-term with this category of gene therapy. However, this analysis is not reflective of the gene therapy pipeline as a whole, as many gene therapies will not generate cost offsets within the health system.

4.3 Post-launch competition factors

Competition helps payers to maintain financial sustainability both during and after the patent life of a product. During the patent period, if there are therapeutic competitors, payers can choose the best value for money from multiple, comparable on-patent products. This can result in lower list prices and greater power to negotiate discounts. For example, branded competition generated intense competition for direct-acting antivirals for Hepatitis C in Europe (Berdud et al. 2018).

After patent expiry, generic competitors can enter the market. If competitors enter the market at this time, payers can transition to using lower-priced generics or biosimilars. Generic competition can have a dramatic impact on prices. For example, it has been estimated that for small molecules, the price can reduce by up to 93% depending on the number of generics on the market (Vondeling et al. 2018). One study in the US found that for each additional generic entrant, the relative price decreases by 13% (Kelton et al. 2014). The use of generics has been estimated to have saved the US Medicaid and Medicare programmes \$137 billion in 2018 (AAM 2019).

Complexities of on-patent and off-patent competition for gene therapies

Given the relatively recent entry of gene therapies to health systems, it is difficult to predict the level of competition for them in the future. However, a number of aspects of the technology suggest that there may be high barriers to competition (Hollywood and Denney 2019; Seoane-Vazquez, Shukla, and Rodriguez-Monguio 2019):

- For gene therapies that are potentially curative and treat genetic diseases, once the prevalent patient population is treated, the market size reduces to the size of incident patients only. Therefore, the incentives for a second product may be substantially lower than for the originator, particularly if the incidence of a disease is low.
- Unlike chronic therapies, the one-time nature of gene therapies means that ‘generic switch’ is not possible for individual patients. Even if payments are made in instalments, the commitment to pay is made upfront.
- Portfolios of patents are used to protect the vectors that are needed to deliver genetic materials into cells. These vectors are platforms, i.e. they are used for many different on-patent products at the same time. Their value is reflected in high license fees and the number of patent challenges they face in Europe. If a vector’s patents are upheld, competitors will have to develop new vectors or pay high license fees to use patented vectors. Payment of license fees as royalties on sales may reduce the size of this barrier to entry for new competitors, but this remains an additional cost for the manufacturer.
- Current gene therapies have extremely high manufacturing costs. In addition, for gene therapies that are delivered ex vivo, there are high costs associated with adapting the product using the patient’s own cells, those of their relatives, or another donor (see Box 1 for more discussion of ex vivo techniques). However, it is likely that manufacturing costs will decrease over time.
- There may be a lack of willingness to accept generic gene therapy products from patients or physicians due to the invasiveness of the procedure. A number of studies have found that biosimilars, generic forms of biologics, are less trusted than originators among patients and physicians. Among other factors, this has been shown to be a barrier to the uptake of biosimilars (Riner et al. 2017; Petit et al. 2021; Moorkens et al. 2016). However, as with biosimilars, it is likely that when and if generic gene therapies are developed, acceptance will increase over time.

The case of biosimilars

Biosimilars may provide some insight into the potential effects of competition for gene therapies. Biosimilars are replicas of on-patent biologic drugs. A recent report found that biosimilars now account for 9% of the total biologics market by value in Europe, and this proportion is projected to grow (Troein, Newton, and Kirstie 2020). A number of studies have shown that the introduction of biosimilar monoclonal antibodies has resulted in price competition in Europe (Moorkens et al. 2020). For example, the loss of exclusivity of Humira (adalimumab), a blockbuster monoclonal antibody, had a variable impact on list-price reduction of the originator across different European countries. The presence of biosimilars on the market appeared to offer price competition that led to lower list prices of the originator (Moorkens et al. 2020), and net prices are likely to be substantially lower still.

However, the scale of the impact of biosimilars is mixed, with some suggesting that the slow rate of entry of biosimilars has failed to reduce costs to the extent that was expected. For example, there is a less marked drop in the price of the originator for biologics after patent expiry than with generic small molecule drugs (Calo-Fernández and Martínez-Hurtado 2012). The launch of a number of biosimilar monoclonal antibodies lagged a number of years after the patent expiry of the originators. This suggests that there are additional barriers to market entry for biosimilar monoclonal antibodies, including regulatory complexity to show bioequivalence (Moorkens et al. 2016). Barriers may also take the form of more complex manufacturing and development processes, and therefore higher costs, for biologics compared to small-molecules, and greater clinician resistance to their adoption relative to the comparator (Atteberry et al. 2019; Mestre-Ferrandiz, Towse, and Berdud 2016; Blackstone and Joseph 2013).

Generic competition for rare diseases

Market size is a major determinant of the level of competition expected for drugs. A number of estimates suggest that therapies for orphan⁷ or rare diseases account for up to a third of the cell and gene therapy pipeline (Wong et al. 2020). Studies have shown that generic competition for drugs treating orphan diseases is low. Only 42% of generic-eligible rare disease drugs had a generic in use within the Medicaid programme between 1973 and 2017 (Beall et al. 2020), compared to up to 88% for generic eligible non-rare disease drugs (Gupta et al. 2016). Generic usage is likely to be even lower for gene therapies that are single-administration – and potentially curative – because the market size could decrease over the patent life of the originator as prevalent patients have received the one-time treatment and incidence may be low (Wong et al. 2020; Quinn et al. 2019).

Existing competition for gene therapies

The potential for competition for products within their patent life can be seen for some gene therapies. For example:

- Gene therapies can face continued competition from non-gene therapies. For example, within SMA, Zolgensma faces competition from Spinraza (nusinersen) and the recently approved Evrysdi (risdiplam).
- Two CAR-T therapies (Yescarta and Kymriah) have received marketing authorisation from the EMA, while many more are in development (Moreno-Cortes et al. 2021). Yescarta and Kymriah have overlapping indications for diffuse large B cell lymphoma, which could generate price competition (the list prices were the same for the overlapping indications at launch). Elsewhere, it is possible that the increasingly widespread development of this technology may drive some level of price competition even in distinct indications, although this remains to be seen.
- The numerous treatments in the pipeline for Haemophilia A and Haemophilia B may generate price competition within this clinical area (Perrin, Herzog, and Markusic 2019).

Overall, because of the complexity of the technology, and the small patient populations, it is possible that the emergence of competition may be slow for gene therapies. That said, it is possible to identify nascent competition, and the barrier of small population sizes may not be relevant for all gene therapies going forwards. In addition, competition may take time to emerge – as was seen with monoclonal antibodies – as barriers to entry fall over time.

Competition at any level would be an important contributor to maintaining the financial sustainability of gene therapies for health systems. There may be an opportunity for policy and legislative change to lower the barriers to competition for gene therapies, both during the patent period and post-patent. Initiatives have been used to support generic and biosimilar competition and their adoption in the US and Europe (FDA 2020; European Commission 2020; The Council of Economic Advisers 2018).

⁷ In Europe, a product can obtain orphan designation if the condition it is targeting has a prevalence of less than 5 in 10,000 (EMA 2018b)

5 Conclusion

In this paper, we have discussed the value of gene therapies, the challenges that this disruptive technology brings, and conditions for the financially sustainable adoption of gene therapies into health systems. We have indicated the potential importance of gene therapies by exploring how they can offer transformative health gain for patients by addressing the genetic root cause of disease and for health systems by displacing inefficient care. We have also presented a novel illustrative categorisation of gene therapies which demonstrates that the financial impact on the health system (and wider afield) will be different across three categories of gene therapies. The category that a specific gene therapy will fall into will depend on the type of health gain it delivers (i.e., whether it is primarily through increased length of life or quality of life) in the context of the characteristics of the target condition and whether an alternative treatment exists.

Concerns around affordability and uncertainty about durability of effect are barriers to the adoption of gene therapies. These challenges are the result of high upfront prices compared to chronic therapies, and of relatively short-term clinical trials compared to the expected duration of the clinical effect. These challenges fuel uncertainty on the long-term value that gene therapies offer. To overcome these challenges, Managed Entry Agreements (MEAs) could be leveraged to manage affordability and uncertainty around value for money. While progress is being made in the use of MEAs, the practical challenges to their successful implementation (such as data requirements, poor infrastructure, and lack of acceptance) remain complex. Further research is recommended to explore the extent of the legislative and practical barriers at both the national and European level, and how these barriers could be overcome. Also needed is a deeper exploration of how cross-border or consistent data collection could be set up, managed, and utilised. These challenges will require multi-stakeholder collaboration for progress to be made.

We have explored three key factors that will influence whether gene therapies will be financially sustainable for health systems:

1. **Pipeline factors:** Financial sustainability will be influenced by the speed and number of products gaining marketing approval, the size of the eligible patient populations, and the category (see Chapter 2) of the therapies that emerge. Some gene therapies (category 2) will decrease costs by removing inefficient care.
2. **Pricing factors:** Prices should reflect the value offered, whilst allowing the health system to realise some of the cost offsets.
3. **Competition factors:** The existence and extent of on-patent and off-patent competition are yet to be determined. Competition for gene therapies may well be muted due to the one-time nature of many gene therapies, various barriers to entry that we have identified, and small populations sizes for a notable proportion of gene therapies.

The various factors explored in this paper could be leveraged by stakeholders to realise the value of effective gene therapies, thereby delivering transformative health benefits to patients while balancing their impact on financial sustainability.



In the short-to-medium term, policymakers can work with manufacturers to overcome the barriers and operationalise MEAs, thereby transforming the risk profile of the adoption of gene therapies and managing the short-term budget impact. As mentioned, further research and multi-stakeholder collaboration will be required to achieve this. At the same time, manufacturers can work with payers and HTA bodies to deliver responsible pricing strategies which generate value-based prices that allow the health system to realise efficiency gains. In the longer term, the extent of competition will impact financial sustainability. Policymakers should work with patients and physicians to encourage the uptake of biosimilar gene therapy entrants in the post-patent period, and there may be a role for policy in reducing the barriers to competition both during the patent period and in the post-patent period. Further research into the potential design of appropriate incentives in this area is recommended.

It is crucial when working to ensure financial sustainability that the financial impact of gene therapies is not considered in isolation. The promise of gene therapies is the potential to transform patient lives and deliver health gains on a much greater scale than ever seen previously. If policymakers support this type of step-change in medicine – which addresses the underlying cause of disease rather than chronically managing symptoms, thereby alleviating the burden of chronic disease on health systems and society – then innovation must be adequately rewarded. Financial sustainability is a critical issue that must be considered alongside the delivery of transformative health improvements, value-based care, and appropriate incentives for innovation.

References

- AAM. 2019. 'The Case for Competition: 2019 Generic Drug & Biosimilars Access & Savings in the US'. Association for Accessible Medicines.
- Aballéa, Samuel, Katia Thokagevistik, Rimma Velikanova, Steven Simoens, Lieven Annemans, Fernando Antonanzas, Pascal Auquier, et al. 2020. 'Health Economic Evaluation of Gene Replacement Therapies: Methodological Issues and Recommendations'. *Journal of Market Access & Health Policy* 8 (1): 1822666. <https://doi.org/10.1080/20016689.2020.1822666>.
- Abou-El-Enein, Mohamed, David W. Grainger, and Sven Kili. 2018. 'Registry Contributions to Strengthen Cell and Gene Therapeutic Evidence'. *Molecular Therapy* 26 (5): 1172–76. <https://doi.org/10.1016/j.ymthe.2018.04.007>.
- Alliance for Regenerative Medicine. 2020. 'A Transformative Therapy Value Model for Rare Blood Diseases'. Alliance for Regenerative Medicine.
- Atteberry, Preston, Peter B. Bach, Jennifer A Ohn, and Mark R Trusheim. 2019. 'Biologics Are Natural Monopolies (Part 1): Why Biosimilars Do Not Create Effective Competition.' *Health Affairs*, April. <https://www.healthaffairs.org/doi/10.1377/hblog20190405.396631/full/>.
- Beall, Reed F., Amity E. Quinn, Aaron S. Kesselheim, Frazer A. Tessema, and Ameet Sarpatwari. 2020. 'Generic Competition for Drugs Treating Rare Diseases'. *Journal of Law, Medicine & Ethics* 48 (4): 789–95. <https://doi.org/10.1177/1073110520979391>.
- Berdud, Mikel, Martina Garau, Margherita Neri, Phill O'Neill, Chris Sampson, and Adrian Towse. 2018. 'R&D, Competition and Diffusion of Innovation in the EU: The Case of Hepatitis C'. OHE Consulting Report. Office of Health Economics. <https://www.ohe.org/publications/rd-competition-and-diffusion-innovation-eu-case-hepatitis-c>.
- Blackstone, Erwin A., and P. Fuhr Joseph. 2013. 'The Economics of Biosimilars'. *American Health & Drug Benefits* 6 (8): 469–78.
- Bouvy, Jacqueline C., Claudine Sapede, and Sarah Garner. 2018. 'Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe'. *Frontiers in Pharmacology* 9 (March). <https://doi.org/10.3389/fphar.2018.00280>.
- Calo-Fernández, Bruno, and Juan Leonardo Martínez-Hurtado. 2012. 'Biosimilars: Company Strategies to Capture Value from the Biologics Market'. *Pharmaceuticals (Basel, Switzerland)* 5 (12): 1393–1408. <https://doi.org/10.3390/ph5121393>.
- Carlson, Josh J., Shuxian Chen, and Louis P. Garrison. 2017. 'Performance-Based Risk-Sharing Arrangements: An Updated International Review'. *PharmacoEconomics* 35 (10): 1063–72. <https://doi.org/10.1007/s40273-017-0535-z>.
- Carvalho, Marta, Bruno Sepodes, and Ana Paula Martins. 2021. 'Patient Access to Gene Therapy Medicinal Products: A Comprehensive Review'. *BMJ Innovations* 7 (1). <https://doi.org/10.1136/bmjinnov-2020-000425>.
- Chambers, J., M. C. Silver, P. J. Lin, J. T. Cohen, C. Paramore, S. Baumann, and P. J. Neumann. 2019. 'PMU77 CELL AND GENE THERAPIES ARE ASSOCIATED WITH SUBSTANTIALLY LARGER QUALITY-ADJUSTED LIFE YEAR GAINS THAN CONVENTIONAL DRUGS AND BIOLOGICS'. *Value in Health* 22 (May): S263. <https://doi.org/10.1016/j.jval.2019.04.1238>.
- Chapman, Rick, Varun Kumar, Sumeyye Samur, Celia Segel, and Steven D. Pearson. 2019. 'Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief'. Technical Brief. ICER. <https://icer.org/wp-content/uploads/2020/10/Valuing-a-Cure-Technical-Brief.pdf>.
- Chubarayan, Y, RP Finger, and J Köberlein-Neu. 2019. 'Economic Burden of Blindness and Visual Impairment in Germany from a Societal Perspective: A Cost-of-Illness Study.' *The European Journal of Health Economics : HEPAC : Health Economics in Prevention and Care* 21 (1): 115–27. <https://doi.org/10.1007/s10198-019-01115-5>.
- Cohen, Joshua T., James D. Chambers, Madison C. Silver, Pei-Jung Lin, and Peter J. Neumann. 2019. 'Putting The Costs And Benefits Of New Gene Therapies Into Perspective'. *Health Affairs*. 4 September 2019. <https://www.healthaffairs.org/doi/10.1377/hblog20190827.553404/full/>.

- Cook, Keziah, Shaun P. Forbes, Kelly Adamski, Janice J. Ma, Anita Chawla, and Louis P. Garrison Jr. 2020. 'Assessing the Potential Cost-Effectiveness of a Gene Therapy for the Treatment of Hemophilia A'. *Journal of Medical Economics* 23 (5): 501–12. <https://doi.org/10.1080/13696998.2020.1721508>.
- Coyle, D, I Durand-Zaleski, Farrington J, Garrison L, Graf von der Schulenburg Jm, Greiner W, Longworth L, et al. 2020. 'HTA Methodology and Value Frameworks for Evaluation and Policy Making for Cell and Gene Therapies.' *The European Journal of Health Economics : HEPAC : Health Economics in Prevention and Care* 21 (9): 1421–37. <https://doi.org/10.1007/s10198-020-01212-w>.
- Danzon, Patricia M. 2018. 'Affordability Challenges to Value-Based Pricing: Mass Diseases, Orphan Diseases, and Cures'. *Value in Health* 21 (3): 252–57. <https://doi.org/10.1016/j.jval.2017.12.018>.
- Elsallab, Magdi, Christopher A. Bravery, Andreas Kurtz, and Mohamed Abou-El-Enein. 2020. 'Mitigating Deficiencies in Evidence during Regulatory Assessments of Advanced Therapies: A Comparative Study with Other Biologicals'. *Molecular Therapy. Methods & Clinical Development* 18 (September): 269–79. <https://doi.org/10.1016/j.omtm.2020.05.035>.
- Elsallab, Magdi, Bruce L Levine, Alan S Wayne, and Mohamed Abou-El-Enein. 2020. 'CAR T-Cell Product Performance in Haematological Malignancies before and after Marketing Authorisation'. *The Lancet. Oncology* 21 (2): e104–16. [https://doi.org/10.1016/S1470-2045\(19\)30729-6](https://doi.org/10.1016/S1470-2045(19)30729-6).
- EMA. 2018a. 'Advanced Therapy Medicinal Products: Overview'. Text. European Medicines Agency. 17 September 2018. <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview>.
- . 2018b. 'Orphan Designation: Overview'. Text. European Medicines Agency. 17 September 2018. <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview>.
- . 2018c. 'PRIME: Priority Medicines'. Text. European Medicines Agency. 17 September 2018. <https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines>.
- European Commission. 2020. 'Pharmaceutical Strategy for Europe'. European Commission. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN>.
- Eversana. 2021. 'Italy Reimburses Zolgensma Through "Payment at Result" Model, Priced at EUR 2.155 M'. 18 March 2021. <https://www.eversana.com/2021/03/18/italy-reimburses-zolgensma-through-payment-at-result-model-priced-at-eur-2-155-m/>.
- FDA. 2018. 'What Is Gene Therapy?' *What Is Gene Therapy?* (blog). 25 July 2018. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy>.
- . 2020. 'FDA Drug Competition Action Plan'. FDA. 21 December 2020. <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan>.
- Garrison, Louis P., Boshen Jiao, and Omar Dabbous. 2021. 'Gene Therapy May Not Be as Expensive as People Think: Challenges in Assessing the Value of Single and Short-Term Therapies'. *Journal of Managed Care & Specialty Pharmacy* 27 (5): 674–81. <https://doi.org/10.18553/jmcp.2021.27.5.674>.
- Garrison, Louis P., Adrian Towse, Andrew Briggs, Gerard de Pouvourville, Jens Grueger, Penny E. Mohr, J. L. Hans Severens, Paolo Siviero, and Miguel Sleeper. 2013. 'Performance-Based Risk-Sharing Arrangements-Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force'. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 16 (5): 703–19. <https://doi.org/10.1016/j.jval.2013.04.011>.
- Grimm, Sabine Elisabeth, Mark Strong, Alan Brennan, and Allan J. Willoo. 2017. 'The HTA Risk Analysis Chart: Visualising the Need for and Potential Value of Managed Entry Agreements in Health Technology Assessment'. *PharmacoEconomics* 35 (12): 1287–96. <https://doi.org/10.1007/s40273-017-0562-9>.
- Gupta, Ravi, Aaron S. Kesselheim, Nicholas Downing, Jeremy Greene, and Joseph S. Ross. 2016. 'Generic Drug Approvals Since the 1984 Hatch-Waxman Act'. *JAMA Internal Medicine* 176 (6): 1391–93. <https://doi.org/10.1001/jamainternmed.2016.3411>.
- Hampson, G, D Mott, N Devlin, and K Shah. 2019. 'Public Preferences for Health Gains and Cures: A Discrete Choice Experiment'. OHE Consulting Report. Office of Health Economics. <https://www.ohe.org/publications/public-preferences-health-gains-and-cures-discrete-choice-experiment>.

Hampson, Grace, Adrian Towse, Steven D Pearson, William B Dreitlein, and Chris Henshall. 2017. 'Gene Therapy: Evidence, Value and Affordability in the US Health Care System'. *Journal of Comparative Effectiveness Research* 7 (1): 15–28. <https://doi.org/10.2217/ceer-2017-0068>.

Hanna, Eve, Cécile Rémuzat, Pascal Auquier, and Mondher Toumi. 2016. 'Advanced Therapy Medicinal Products: Current and Future Perspectives'. *Journal of Market Access & Health Policy* 4. <https://doi.org/10.3402/jmahp.v4.31036>.

Hargreaves, Ben. 2020. 'Pipeline of Cell and Gene Therapies Expands by 25%'. Biopharma-Reporter.Com. 16 March 2020. <https://www.biopharma-reporter.com/Article/2020/03/16/Growing-pipeline-of-cell-and-gene-therapies>.

Hettle, Robert, Mark Corbett, Sebastian Hinde, Robert Hodgson, Julie Jones-Diette, Nerys Woolacott, and Stephen Palmer. 2017. 'The Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: An Exploration of Methods for Review, Economic Evaluation and Appraisal'. *Health Technology Assessment (Winchester, England)* 21 (7): 1–204. <https://doi.org/10.3310/hta21070>.

Hollywood, Jane, and Frances Denney. 2019. 'The Rise of Patent Wars in Europe's Gene Therapy Space'. *The Rise of Patent Wars in Europe's Gene Therapy Space* (blog). 17 December 2019. https://www.cms-lawnow.com/ealerts/2019/12/the-rise-of-patent-wars-in-europes-gene-therapy-space?cc_lang=en.

ICER. 2019a. 'Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report'. https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_110220.pdf.

———. 2019b. 'Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs)'. Institute for Clinical and Economic Review. https://icer.org/wp-content/uploads/2020/10/ICER_SST_ProposedAdaptations_080619-2.pdf.

IQVIA. 2019. 'The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch'. IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf?_=1620295534178.

Jönsson, Bengt, Grace Hampson, Jonathan Michaels, Adrian Towse, J.-Matthias Graf von der Schulenburg, and Olivier Wong. 2019. 'Advanced Therapy Medicinal Products and Health Technology Assessment Principles and Practices for Value-Based and Sustainable Healthcare'. *The European Journal of Health Economics* 20 (3): 427–38. <https://doi.org/10.1007/s10198-018-1007-x>.

Jørgensen, Jesper, Eve Hanna, and Panos Kefalas. 2020. 'Outcomes-Based Reimbursement for Gene Therapies in Practice: The Experience of Recently Launched CAR-T Cell Therapies in Major European Countries'. *Journal of Market Access & Health Policy* 8 (1): 1715536. <https://doi.org/10.1080/20016689.2020.1715536>.

Jørgensen, Jesper, and Panos Kefalas. 2017. 'Annuity Payments Can Increase Patient Access to Innovative Cell and Gene Therapies under England's Net Budget Impact Test'. *Journal of Market Access & Health Policy* 5 (1): 1355203. <https://doi.org/10.1080/20016689.2017.1355203>.

Jørgensen, Jesper, Laura Mungapen, and Panos Kefalas. 2019. 'Data Collection Infrastructure for Patient Outcomes in the UK - Opportunities and Challenges for Cell and Gene Therapies Launching'. *Journal of Market Access & Health Policy* 7 (1): 1573164. <https://doi.org/10.1080/20016689.2019.1573164>.

Kelton, Christina M. L., Lenisa V. Chang, Jeff J. Guo, Yan Yu, Edmund A. Berry, Boyang Bian, and Pamela C. Heaton. 2014. 'Firm- and Drug-Specific Patterns of Generic Drug Payments by US Medicaid Programs: 1991-2008'. *Applied Health Economics and Health Policy* 12 (2): 165–77. <https://doi.org/10.1007/s40258-014-0083-z>.

Kerpel-Fronius, Sandor, Varvara Baroutsou, Sander Becker, Roberto Carlesi, Luis Colliá, Brigitte Franke-Bray, Peter Kleist, et al. 2020. 'Development and Use of Gene Therapy Orphan Drugs-Ethical Needs for a Broader Cooperation Between the Pharmaceutical Industry and Society'. *Frontiers in Medicine* 7: 608249. <https://doi.org/10.3389/fmed.2020.608249>.

Kipentzoglou, Nasos. 2021. 'The G-BA Implements Post Launch Real World Evidence Generation for Zolgensma®'. *Lightning API* (blog). 18 February 2021. <https://www.lightning-api.com/news/the-g-ba-implements-post-launch-real-world-evidence-generation-for-zolgensma/>.

Lakdawalla, Darius N., Jalpa A. Doshi, Louis P. Garrison, Charles E. Phelps, Anirban Basu, and Patricia M. Danzon. 2018. 'Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]'. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 21 (2): 131–39. <https://doi.org/10.1016/j.jval.2017.12.007>.

- Liaropoulos, Lycourgos, and Ilias Goranitis. 2015. 'Health Care Financing and the Sustainability of Health Systems'. *International Journal for Equity in Health* 14 (September). <https://doi.org/10.1186/s12939-015-0208-5>.
- Maes, Ingrid, Hafida Boufraioua, Walker Van Dyck, and Lies Schoonaert. 2019. 'Innovative Funding Solutions for Paradigm Changing Advanced Therapy Medicinal Products (ATMP) in Belgium'. Round table report. Inovigate. https://www.inovigate.com/media/filer_public/e8/9c/e89ca2b0-1dcf-48fb-9afc-9e911ddcef84/innovative_funding_solutions_-_short_version_without_appendix_vs09.pdf.
- Marsden, Grace, and Adrian Towse. 2017. 'Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: Is the NICE Approach Fit for Purpose?' Office of Health Economics. <https://www.ohe.org/publications/exploring-assessment-and-appraisal-regenerative-medicines-and-cell-therapy-products>.
- Mestre-Ferrandiz, Jorge, Adrian Towse, and Mikel Berdud. 2016. 'Biosimilars: How Can Payers Get Long-Term Savings?' *PharmacoEconomics* 34 (6): 609–16. <https://doi.org/10.1007/s40273-015-0380-x>.
- Michelsen, Sissel, Salma Nachi, Walter Van Dyck, Steven Simoens, and Isabelle Huys. 2020. 'Barriers and Opportunities for Implementation of Outcome-Based Spread Payments for High-Cost, One-Shot Curative Therapies'. *Frontiers in Pharmacology* 11: 594446. <https://doi.org/10.3389/fphar.2020.594446>.
- Moorkens, Evelien, Brian Godman, Isabelle Huys, Iris Hoxha, Admir Malaj, Simon Keuerleber, Silvia Stockinger, et al. 2020. 'The Expiry of Humira® Market Exclusivity and the Entry of Adalimumab Biosimilars in Europe: An Overview of Pricing and National Policy Measures'. *Frontiers in Pharmacology* 11: 591134. <https://doi.org/10.3389/fphar.2020.591134>.
- Moorkens, Evelien, Clara Jonker-Exler, Isabelle Huys, Paul Declerck, Steven Simoens, and Arnold G. Vulto. 2016. 'Overcoming Barriers to the Market Access of Biosimilars in the European Union: The Case of Biosimilar Monoclonal Antibodies'. *Frontiers in Pharmacology* 7 (June). <https://doi.org/10.3389/fphar.2016.00193>.
- Moreno-Cortes, E., J. V. Forero-Forero, P. A. Lengerke-Diaz, and J. E. Castro. 2021. 'Chimeric Antigen Receptor T Cell Therapy in Oncology - Pipeline at a Glance: Analysis of the ClinicalTrials.Gov Database'. *Critical Reviews in Oncology/Hematology* 159 (March): 103239. <https://doi.org/10.1016/j.critrevonc.2021.103239>.
- NICE. 2017. 'Budget Impact Test | NICE Technology Appraisal Guidance | NICE Guidance | Our Programmes | What We Do | About'. CorporatePage. NICE. 2017. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/budget-impact-test>.
- . 2018. 'Strimvelis for Treating Adenosine Deaminase Deficiency–Severe Combined Immunodeficiency'. NICE. <https://www.nice.org.uk/guidance/hst7/resources/strimvelis-for-treating-adenosine-deaminase-deficiencysevere-combined-immunodeficiency-pdf-1394905926085>.
- . 2019. 'Voretigene Neparvovec for Treating Inherited Retinal Dystrophies Caused by RPE65 Gene Mutations'. NICE. <https://www.nice.org.uk/guidance/hst11>.
- . 2021. 'Onasemnogene Apeparvovec for Treating Spinal Muscular Atrophy. Evaluation Consultation Document.' National Institute for Health and Care Excellence. <https://www.nice.org.uk/guidance/gid-hst10026/documents/evaluation-consultation-document-2>.
- O'Hara, Jamie, David Hughes, Charlotte Camp, Tom Burke, Liz Carroll, and Daniel-Anibal Garcia Diego. 2017. 'The Cost of Severe Haemophilia in Europe: The CHES Study'. *Orphanet Journal of Rare Diseases* 12 (1): 106. <https://doi.org/10.1186/s13023-017-0660-y>.
- Pearson, Steven. 2019. 'Early Experience with Health Technology Assessment of Gene Therapies in the United States: Pricing and Paying for Cures'. In . Office of Health Economics. <https://www.ohe.org/publications/early-experience-health-technology-assessment-gene-therapies-united-states-pricing-and>.
- Perrin, George Q., Roland W. Herzog, and David M. Markusic. 2019. 'Update on Clinical Gene Therapy for Hemophilia'. *Blood* 133 (5): 407–14. <https://doi.org/10.1182/blood-2018-07-820720>.
- Petit, Juliette, Marie Antignac, Rose-Marie Poilverd, Régine Baratto, Sylvie Darthout, Sandra Desouches, Karine Louati, Nathalie Deparis, Francis Berenbaum, and Catherine Beauvais. 2021. 'Original Research: Multidisciplinary Team Intervention to Reduce the Nocebo Effect When Switching from the Originator Infliximab to a Biosimilar'. *RMD Open* 7 (1). <https://doi.org/10.1136/rmdopen-2020-001396>.

- Quinn, Casey, Colin Young, Jonathan Thomas, and Mark Trusheim. 2019. 'Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System'. *Value in Health* 22 (6): 621–26. <https://doi.org/10.1016/j.jval.2019.03.014>.
- Ramezankhani, Roya, Shukoofeh Torabi, Neda Minaei, Hoda Madani, Siamak Rezaeiani, Seyedeh Nafiseh Hassani, Adrian P. Gee, et al. 2020. 'Two Decades of Global Progress in Authorized Advanced Therapy Medicinal Products: An Emerging Revolution in Therapeutic Strategies'. *Frontiers in Cell and Developmental Biology* 8 (December). <https://doi.org/10.3389/fcell.2020.547653>.
- Riner, Béatrice, Adèle Bussy, Jeannie Hélène-Pelage, Nycrees Moueza, Sébastien Lamy, and Philippe Carrère. 2017. "No Generics, Doctor!" The Perspective of General Practitioners in Two French Regions'. *BMC Health Services Research* 17 (1): 707. <https://doi.org/10.1186/s12913-017-2682-5>.
- Ronco, Virginia, Myriam Dilecce, Elena Lanati, Pier Luigi Canonico, and Claudio Jommi. 2021. 'Price and Reimbursement of Advanced Therapeutic Medicinal Products in Europe: Are Assessment and Appraisal Diverging from Expert Recommendations?' *Journal of Pharmaceutical Policy and Practice* 14 (March). <https://doi.org/10.1186/s40545-021-00311-0>.
- Rowen, Donna, John Brazier, Clara Mukuria, Anju Keetharuth, Arne Risa Hole, Aki Tsuchiya, Sophie Whytle, and Phil Shackley. 2016. 'Eliciting Societal Preferences for Weighting QALYs for Burden of Illness and End of Life'. *Medical Decision Making* 36 (2): 210–22. <https://doi.org/doi.org/10.1177/0272989X15619389>.
- Seoane-Vazquez, Enrique, Vaishali Shukla, and Rosa Rodriguez-Monguio. 2019. 'Innovation and Competition in Advanced Therapy Medicinal Products'. *EMBO Molecular Medicine* 11 (3). <https://doi.org/10.15252/emmm.201809992>.
- Sharma, Akshay, Manu Easow Mathew, Vasumathi Sriganesh, and Ulrike M. Reiss. 2020. 'Gene Therapy for Haemophilia'. *Cochrane Database of Systematic Reviews*, no. 4. <https://doi.org/10.1002/14651858.CD010822.pub4>.
- The Council of Economic Advisers. 2018. 'Reforming Biopharmaceutical Pricing at Home and Abroad'. <https://trumpwhitehouse.archives.gov/wp-content/uploads/2017/11/CEA-Rx-White-Paper-Final2.pdf>.
- Thompson, Sarah, Tom Foubister, Josep Figueras, Joseph Kutzin, Govin Permanand, and Lucie Bryndová. 2009. 'Addressing Financial Sustainability in Health Systems'. Policy Summary. World Health Organisation. https://www.euro.who.int/__data/assets/pdf_file/0005/64949/E93058.pdf.
- Towse, Adrian, and Elisabeth Fenwick. 2019. 'Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment?' *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 22 (6): 677–83. <https://doi.org/10.1016/j.jval.2019.03.013>.
- Troein, Per, Max Newton, and Scott Kirstie. 2020. 'The Impact of Biosimilar Competition in Europe'. White Paper. IQVIA.
- Vondeling, Gerard T., Qi Cao, Maarten J. Postma, and Mark H. Rozenbaum. 2018. 'The Impact of Patent Expiry on Drug Prices: A Systematic Literature Review'. *Applied Health Economics and Health Policy* 16 (5): 653–60. <https://doi.org/10.1007/s40258-018-0406-6>.
- Vreman, Rick A., Thomas F. Broekhoff, Hubert Gm Leufkens, Aukje K. Mantel-Teeuwisse, and Wim G. Goettsch. 2020. 'Application of Managed Entry Agreements for Innovative Therapies in Different Settings and Combinations: A Feasibility Analysis'. *International Journal of Environmental Research and Public Health* 17 (22). <https://doi.org/10.3390/ijerph17228309>.
- Wang, Dan, and Guangping Gao. 2014a. 'STATE-OF-THE-ART HUMAN GENE THERAPY: PART I. GENE DELIVERY TECHNOLOGIES'. *Discovery Medicine* 18 (97): 67–77.
- . 2014b. 'State-of-the-Art Human Gene Therapy: Part II. Gene Therapy Strategies and Clinical Applications'. *Discovery Medicine* 18 (98): 151–61.
- Wenzl, Martin, and Suzannah Chapman. 2019. 'Performance-Based Managed Entry Agreements for New Medicines in OECD Countries and EU Member States: How They Work and Possible Improvement Going Forward'. 115. OECD Health Working Papers. OECD. https://www.oecd-ilibrary.org/social-issues-migration-health/performance-based-managed-entry-agreements-for-new-medicines-in-oecd-countries-and-eu-member-states_6e5e4c0f-en.
- Wong, Chi Heem, Dexin Li, Nina Wang, Jonathan Gruber, Rena Conti, and Andrew W. Lo. 2020. 'Estimating the Financial Impact of Gene Therapy*'. *MedRxiv*, October, 2020.10.27.20220871. <https://doi.org/10.1101/2020.10.27.20220871>.



About us

Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

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Areas of expertise

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

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