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Exploring the economics of gene therapy innovation and price

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Amanda Whittal
Esther Idicula
Adam Hutchings

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1. Introduction: the value of gene therapies in rare diseases

'Gene Therapy for Human Genetic Disease?' This was the questioning title of an article on gene therapies published in 1972 (Friedmann and Roblin, 1972). The article points to the considerable potential of gene therapies to improve genetic diseases, as well as the very substantial limitations of knowledge on the topic at the time. Although gene therapies have been studied across a range of diseases, it is only relatively recently that the advancements in science have finally translated to a significant upward trend in the numbers of gene therapies gaining marketing approval and transforming the lives of patients with rare genetic diseases.

Gene therapies can work in different ways, by introducing, removing or changing genetic material in a patient's cells. One way this can be achieved is by using 'vectors' as carriers, to deliver the genetic material into the target cells. These vectors, containing their genetic cargo, can be injected directly into the body (in vivo), or delivered to cultured cells outside of the body (ex vivo), after which the modified cells are then reintroduced into the body, as is the case with chimeric antigen receptor T-cells (CAR-Ts – genetically modified cell therapies) (ASGCT, 2021). In Europe, regulators consider gene therapies to be a subset of advanced therapy medicinal products (ATMPs), which also include cell therapies, tissue-engineered materials and combined products (those with one or more medical devices) (EMA, 2018). Including CAR-Ts, in 2021 there were eight gene therapies approved for use by the Food & Drug Administration (FDA) in the U.S. (FDA, 2021), nine approved for use by the European Medicines Agency (EMA) (an additional three were withdrawn) (Ronco *et al.*, 2021; European Commission, no date), and in 2020 there were more than 1300 in development (ranging from pre-clinical to preregistration) (Barrett *et al.*, 2021).

Because gene therapies are designed to address the underlying cause of a disease at a genetic level, they represent the most fundamental of treatments, with the potential to transform the lives of patients suffering from previously intractable diseases. In diseases where diagnosis and treatment can be initiated early enough – before the emergence of disease symptoms and irreversible damage – the therapeutic potential is greatest, and even potentially (FDA, 2019).

Alongside transformative therapeutic potential, a defining characteristic of gene therapies is that they are often single administration or short course treatments. They thus have the potential for lasting long-term benefits without the need for frequently repeated administration.

The idea of a potentially curative, single administration intervention is the holy grail of medicine. While some surgical interventions and medicines, most often those for acute illnesses, can be considered curative, this is not the norm. For the vast majority of chronic diseases, symptom control is the best that can be hoped for, with relapse occurring if treatment is discontinued. Furthermore, many conditions progressively worsen over time, requiring long-term supportive care.

While gene therapies should not be prematurely labelled as 'miracle drugs', expectations about their potential are high. It is therefore not surprising that the level of excitement around gene therapies is so elevated. Hope is particularly high in the rare disease community. Yann Le Cam, CEO of EURORDIS, the European rare disease patient association, captured the mood: *"The fact is that science is breaking through and will increasingly deliver innovative treatments that are potentially transformative or curative for people living with a rare disease. It is now our collective responsibility to turn these indescribable hopes into a reality."* (EURORDIS, 2020)

Currently, gene therapies are being developed for rare diseases because they are the ideal test target for these technologies. Eighty percent of rare diseases are caused by an abnormality affecting a single gene (National Center for Advancing Translational Sciences, 2017). Rare diseases also often affect children and have a disproportionately high unmet need (Narayanan and Privolnev, 2018), with 95% having no approved therapeutic options (European Commission, 2021). All of the gene therapies approved to date in Europe and the US have been in rare diseases (Ronco *et al.*, 2021; FDA, 2021).

While the initial opportunity for gene therapies is in rare diseases, wider applications in diseases with greater prevalence offer the potential for transformative advances in global health. But for that to happen, the science, manufacturing and economics must first be established, proven and refined, all of which are currently evolving in the rare disease space.

Despite their potential life-transforming benefits, the introduction of gene therapies has been associated with controversy, in large part because of their high list prices. Zolgensma, a single administration gene therapy for Spinal Muscular Atrophy (SMA), was labelled in the media at the time as the 'most expensive drug ever', with a public list price of $2.1 million (Stein, 2019). Yet not all gene therapies have prices of that order. Table 1 provides an overview of list prices of approved gene therapies in Europe and the U.S.

Table 1. List prices of approved gene therapies in Europe and the US*

Brand Name	Type of therapy	Prevalence (EU)	FDA Approved	EMA Approved	Reported launch price/patient
Abecma	CAR-T	46/100,000[1]	✓	✓	No data available
Breyanzi	CAR-T	5/100,000[2]	✓	✗	No data available
Imlygic	Gene Therapy	69/100,000[3]	✓	✓	€ 72,288 – € 289,151[14]
Kymriah	CAR-T	12/100,000[4]	✓	✓	€ 275,000[15]
Libmeldy	Gene Therapy	0.1–0.9/100,000[5]	✗	✓	€ 2,875,000[16]
Luxturna	Gene Therapy	30/100,000[6]	✓	✓	€ 821,100[17]
Strimvelis	Gene Therapy	0.4/100,000[7]	✗	✓	No data available
Tecartus	CAR-T	6/100,000[8]	✓	✓	€ 360,000[18]
Yescarta	CAT-T	46/100,000[9]	✓	✓	€ 389,130[19]
Zolgensma	Gene Therapy	4/100,000[10]	✓	✓	€ 2,314,550[20]
Now withdrawn					
Glybera	Gene Therapy	0.1/100,000[11]	✗	✓	€ 53,781[21]
Skysona	Gene Therapy	5/100,000[12]	✗	✓	No data available
Zynteglo	Gene Therapy	7/100,000[13]	✗	✓	€ 1,874,250[22]

***Note.** Information retrieved as of November, 2021. Table 1 references are located at the end of the full document reference list. Prevalence adjusted from original sources to reflect number per 100,000.

Discussions of gene therapy prices generally reference public 'list' prices. In practice, however, the 'net' price paid is typically considerably lower, as a result of confidential national price negotiations, in which discounts, rebates, price caps and other forms of agreements are commonly applied. Still, the headline list prices, often reported in the media, have led to gene therapies becoming a nexus of wider concerns about the cost and value of new medicines, and whether such prices are fair or appropriate. Payers, patients and policymakers have legitimate questions about these technologies.
Does the therapeutic value of gene therapy in rare diseases justify the price? Is it necessary for gene therapy prices in rare diseases to be so high? And can we afford it?

Answering these questions requires understanding the dual role of price as a reflection of a medicine's therapeutic value and as a signal to manufacturers of the types of medicines that society wants to be developed. This paper explores both factors as they relate to the very specific case of gene therapies in rare diseases.

2. Does the therapeutic value of gene therapy in rare diseases justify the price?

In the many countries in which reimbursement of medicines is negotiated between manufacturers and payers, one of the most important determinants of price is the magnitude of additional clinical benefit, relative to current practice.

Studies of some rare diseases, which otherwise have few (if any) treatment options, have shown that their progression appears to have been slowed or halted with gene therapy treatment (Maguire *et al.*, 2019; EMA, 2021). The value of these gene therapies has been stated in published health technology assessment (HTA) reports, for instance for Zolgensma®:

- "The transformative clinical outcomes associated with this treatment have a profound impact on the lives of patients and their caregivers (England, NICE HST, 2019)
- "..we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care" (U.S., ICER, 2019)
- "..on the basis of the evidence that indicates a potential capacity of this gene therapy to modify the natural course of the disease, the added therapeutic value can be considered important" (Italy, AIFA, 2021)

And for Luxturna®:

- "..represents an important innovation that addresses an unmet need and could alleviate the burden of progressive disability" (Scotland, SMC, 2019)

For many genetic diseases progression results in irreversible damage; in such cases, the earlier the detection and treatment the greater the value from gene therapies is likely to be. When comparing gene therapies to conventional medicines using the measurement of quality-adjusted life years (QALYs) to account for gains in both quality and length of life, a recent study showed that gene therapies to date demonstrate impressive health gains, averaging 5.8 QALYs compared to only 0.4 and 0.5 QALYs gained for biologics and conventional therapies, respectively (Cohen *et al.*, 2019).

While the potential therapeutic value of gene therapy is clearly very high, their full benefit is not easily quantified. From a pricing and reimbursement (P&R) perspective, when the duration of the therapeutic effect is anticipated to be sustained far beyond the time of value assessment, even with continued evidence collection there will be uncertainty as to the duration of effect and long-term safety. This is compounded by the difficulty in recruiting adequate sample sizes for gene therapy trials in rare diseases

and following-up on patients long-term. This is a persistent challenge for all rare disease treatments, regardless of whether or not the treatment is a gene therapy. Other challenges faced by all rare disease treatments include limited data on natural history, heterogeneous patient populations, delayed diagnosis, lack of established clinical endpoints and little or no consensus on current treatment (Nestle-Parr *et al.*, 2018; Nicod *et al.*, 2019).

One option to manage the uncertainty regarding the magnitude of the added clinical benefit is through contractual agreements between payers and manufacturers (Ciarametaro *et al.*, 2018). Such agreements can link reimbursement to the achievement of clinical milestones to manage uncertainty of long-term effects, as well as spread payments over time in instalments to manage budget concerns. Gene therapies appear to have stimulated greater willingness of manufacturers and payers to enter into outcomes-based agreements linked to payments, in an attempt to manage the uncertainty; outcomes-based agreements have been used for both Kymriah and Yescarta (Wenzl and Chapman, 2019), as well as Zolgensma and Luxturna (Jørgensen and Kefalas, 2021).

Beyond the clinical value, the possibility for a medicine to create savings elsewhere in the healthcare system is also relevant to P&R. The potentially long-lasting effects of a single administration gene therapy could create healthcare system savings, including reducing the need to treat patients with existing chronic treatments (Cohen *et al.*, 2019). Valoctocogene roxaparvovec, a gene therapy currently in development for the treatment of haemophilia A, has been projected to save $6.8 million per patient over the course of the disease in comparison to standard prophylactic coagulation factor VIII treatment, which requires frequent infusions and life-long medication (Cook *et al.*, 2020).

Additionally, indirect societal costs of illness burden can be high, particularly for rare diseases, which often affect children and are progressive. Many have no approved treatments and there can be substantial costs associated with a lifetime of disability supportive care (Ferreira, 2019; Navarrete-Opazo *et al.*, 2021). These children often miss out on school, and parents miss work to care for their child (Johnson *et al.*, 2019; Querol *et al.*, 2021). The ability to successfully treat such diseases will have financial, social and cultural benefits for the patient, their family and society, corresponding to aspects such as increased productivity for the workplace, and increased tax revenues and economic growth for nations as a whole (Jena and Lakdawalla, 2017; Fan *et al.*, 2018). The CHESS study patient questionnaire estimated the total annual indirect cost of haemophilia in 2014 for France, Germany, Italy, Spain and the UK to be €43 million, averaging € 6,075 per patient (O'Hara *et al.*, 2017).

The uncertainty in long-term clinical effectiveness, however, impacts the estimation of long-term healthcare cost savings. In the absence of sufficient long-term data, as is the case at the time at which the initial P&R negotiations take place, the overall value of the treatment can be disputed. This has caused controversy in recent negotiations. During the German price negotiation for Zynteglo for Beta Thalassemia, the duration of benefits suggested by manufacturers was higher than what payers could comfortably accept (G-BA, 2020). The resulting difference in price potential based on the offset cost of blood transfusions ultimately led to the failure of these negotiations and the manufacturer's decision to withdraw from the European market (Businesswire, 2021).

Overall, a gene therapy that can halt the progression of a rare disease is likely to have high value: such conditions are often serious, can be life-threatening and lack effective treatments. The potential benefits for patients, families, healthcare systems and society can therefore be substantial. However, there will continue to be uncertainty around the exact magnitude of long-term benefit following a one-time therapy. If price negotiations were to reflect the full expected clinical benefit of a gene therapy and the total duration of cost offsets from no longer needing chronic therapy or reductions in other supportive care, then the price potential for these medicines could in some circumstances be quite high, even before considering the rarity of the disease.

In some countries, willingness-to-pay for a given amount of clinical benefit of a treatment is made more explicit through the application of incremental cost-effectiveness thresholds using QALYs. Such thresholds have generally been set for more conventional medicines for prevalent conditions (Nicod *et al.*, 2020). In recent years, the orphan drug legislation has incentivised the development of treatments for rare populations (Neez *et al.*, 2020). Although there is no consensus, there is some recognition of the need for a greater willingness-to-pay for treatments for rare diseases with high severity and unmet need (Garrison *et al.*, 2019). This is exemplified by the higher thresholds applied in the NICE HST programme, which is reserved for medicines that treat very small populations (NICE, 2017), and by ICER in the US, whose value assessment framework highlights that contextual considerations for rare disease treatments may lead to higher funding prices and higher cost-effectiveness ratios (ICER, 2020). In other countries, the relationship between value and willingness-to-pay is less explicit, with payers taking into account a variety of other factors such as high unmet need, price benchmarks of other similar therapies and affordability (Garrison *et al.*, 2019).

The thresholds of what payers are willing to pay for prevalent conditions are often too low to make rare disease treatments economically viable. Yet for gene therapies in rare diseases to be made available to patients, the willingness-to-pay for a price based on value must also align with the price level at which it makes economic sense for manufacturers to invest in gene therapy development.

3. Do gene therapy prices in rare diseases need to be so high?

At what price does it make economic sense for manufacturers to invest in developing gene therapies for rare diseases? To answer this, it is necessary to understand the role that price plays in the process by which manufacturers decide which medicines to invest in, and the costs, risks and time required to bring those medicines to patients (Neez *et al.*, 2020; Neez, Gentilini and Hutchings, 2021). For gene therapies, this process is fundamentally similar to that of all biopharmaceuticals, but with some particular challenges that reflect the special characteristics of these medicines.

The investment in and development of new therapies does not happen in a vacuum. Every aspect of the industry – the research and development (R&D), manufacture and commercialisation of new therapies – is highly regulated. Patents are provided by legislators; R&D, manufacturing and sales practices are governed by legal frameworks of drug regulators; and P&R is managed by payers (Neez *et al.*, 2020). In no other industry are all facets of development, manufacturing, pricing and reimbursement so fully determined by governmentally established rules.

These rules, policies and regulatory frameworks have a direct impact on the amount and direction of investment and development of pharmaceuticals, as they influence the decisions that manufacturers make about the types of medicines and diseases they invest in. For instance, it has been estimated that 74 of the 142 orphan medicinal products (OMPs) developed between 2000–2017 would not have been economically viable without the Regulation the European Regulation (EC) No 141/2000 on Orphan Medicinal Products (OMPs) (Neez *et al.*, 2020). Investment decisions are complex, but ultimately two things are required in order for a potential medicine to be developed: it has to be both clinically and economically viable.

Clinical Viability

This refers to whether a potential new treatment has a high enough probability of demonstrating a significant clinical impact, and the likelihood of it being successfully developed and approved for use. This assessment is done within companies with a range of external inputs, including scientific and medical expertise. Ultimately, there must be a compelling clinical rationale for investment, such as

addressing an important unmet patient need, and whether a drug target is likely to be clinically effective and safe (Neez *et al.*, 2020; Neez, Gentilini and Hutchings, 2021). Clinical viability is impacted by:

- Disease infrastructure: the existence of centres of expertise, accurate diagnostic methods and registries impacts the ability to identify and recruit patients, and conduct clinical trials (Neez, Gentilini and Hutchings, 2021).
- Understanding of the disease: if the underlying cause of the disease is well understood, pharmacological targets exist, patients can be identified and the natural history of the disease is characterised, e.g. through registries, it is much more likely that medicines can be developed. By contrast, in diseases where there is a paucity of basic scientific research, as is the case for many rare diseases, it is much more challenging and risky to develop treatments (Neez, Gentilini and Hutchings, 2021).
- Policy on investment in R&D: a large amount of early basic science is funded by public organisations, such as the National Institute of Health in the US and the European Research Council. This reflects the intertwining roles of the public and private sector in pharmaceutical innovation. Funding by governments and non-profit organisations for research in universities and hospitals tends to lay the foundation of disease knowledge and basic scientific advances, which in turn may stimulate investment and development of new products. The private biopharmaceutical industry, as well as funding some basic research, is responsible for the majority of the investment required to develop and commercialise medicines (Vital Transformation, 2021).

Economic Viability

Besides clinical viability, a new medicine must also be economically viable if it is to be developed. Pharmaceutical R&D is funded by investors who require a return on their investment, and companies need to generate revenue to fund future medicine development.

The economics of drug development are characterised by a large upfront investment (e.g. for clinical trials, manufacturing and regulatory processes), a long period between investment and return (average of 10 years from the first clinical trials to bring a treatment to market (Jayasundara *et al.*, 2019)), and a high risk of failure (> 85% of new therapies fail during clinical development (Wong, Siah and Lo, 2019)).

When deciding whether a medicine represents an economically viable investment, companies assess the following:

1. **Estimate costs:** R&D, manufacturing, commercialisation
2. **Estimate revenue:** the expected number of patients x price potential x duration of the remaining patent

The price potential takes into account the high potential value of gene therapies for rare disease conditions in comparison to conventional therapies, as well as the patient population expected to receive treatment and the duration of patent protection.

3. **Adjust for risk and time:** the probability of achieving marketing authorisation; discount future revenues to reflect the cost of capital.

The third step is perhaps the most frequently misunderstood by stakeholders who argue for pricing based on a markup on the cost of production ('cost-plus pricing'). Adjusting for risk often reduces the likely future revenue by a factor of 10 or more, and discounting that revenue back over 10+ years further worsens the balance of cost and return. Investments that might initially appear very attractive often become uncertain once risk and cost of capital are accounted for.

For rare diseases, the economic viability of drug development is particularly challenging:
Small patient populations greatly limit potential revenue compared with medicines for more common conditions. For example, adenosine deaminase severe combined immunodeficiency (ADA-SCID), an extremely rare immunological condition better known as 'boy in the bubble syndrome', is estimated to affect less than 50 patients per year in Europe and the US (EMA, 2016). By contrast, there are over 50 million patients with Type II diabetes in Europe (Tamayo *et al.*, 2014). Accordingly, for rare disease medicines to be economically viable investments, the price per patient has to be substantially higher than for more common conditions. This has been observed in practice, with higher EU prices for orphan medicines correlating with reduced prevalence (Medic *et al.*, 2017), supporting the idea that payers appear to show greater willingness-to-pay for rare disease treatments. Nevertheless, investments in rare diseases are increasingly economically marginal in Europe (Neez *et al.*, 2020).

For gene therapies the economic viability creates further challenges:
On the revenue side, since gene therapies to date have been one-time therapies instead of regularly administered chronic treatments, manufacturers have the prospect of receiving only a single payment per patient, rather than regular payments that may continue over multiple years. Without a proportionately higher price to reflect the one-time nature of the treatment, revenue would be much lower, and consequently there would be insufficient incentive for companies to develop single-administration treatments in the future. Furthermore, the treatable patient population for a rare genetic disease may be extremely small. Within the potentially eligible patient population there can be many reasons why patients do not receive treatment, e.g. delays in diagnosing the condition, an advanced state of disease progression, contraindications to treatment, etc., potentially decreasing numbers treated even further.

On the cost side, the development and manufacturing of gene therapies are also very different from other medicines. Manufacturing processes are complex and scaling up is much harder than for other medicines. Similarly, the distribution of the product is much more complex and expensive, and there may be a considerable investment required in training sites to administer it.

Some aspects of development economics can be more favourable for gene therapies, such as the relatively small trial sizes and the frequently expedited approval under Conditional Authorisation by the EMA. In the future, the manufacturing and distribution may also become less expensive as experience is gained, however, these efficiencies are unlikely in the short-term and will only arise in the medium term if gene therapies are sufficiently viable to continue to invest in and evolve the technology.

It is the combination of issues associated with rare disease innovation and the characteristics of gene therapies that result in price points that appear very high compared to conventional therapies. However, when costs are spread over the anticipated duration of effect, the annualised price equivalent is comparable to and often lower than existing medicines for similar conditions.

While payers in some European countries have processes to account for specificities of rare disease treatments, few have yet adopted approaches to reflect the challenges of assessing gene therapies. If assessment and P&R systems do not reflect the potential value of gene therapies, or the rarity and equivalent prices of continuously treated similar conditions, manufacturers will respond by switching investment back to more conventional treatments which are more predictable to bring to the market.

4. Can we afford it?

Even if the prices of gene therapies reflect their value and payers judge them to be cost-effective, there are situations in which the ability to pay is constrained. Irrespective of whether gene therapies are considered to be good value for money, it is still important to consider whether they are generally affordable in practice.

Similar questions have been asked of rare disease treatments in general. Despite an increase in rare disease treatment expenditure in Europe, these medicines still comprise a relatively small amount of total health care spending (about 7% of health care expenditure in Western European countries) (Mestre-Ferrandiz *et al.*, 2019; IQVIA, 2020).

In the case of gene therapies, it is relevant to recognise that funding moves across types of therapies and disease areas over time, reflecting trends in science and following existing unmet needs. Disease areas that have a lower burden due to historical investment, and in which treatments are mostly generic, free up resources to invest in high unmet need conditions where therapeutic development has only arrived recently. Thus, expenditure on innovative medicines, including gene therapies may be compensated in part by savings from the use of generic medicines and biosimilars in other diseases (Mestre-Ferrandiz *et al.*, 2019; IGBA, 2021; Vogler *et al.*, 2021). In the U.S., for instance, savings to patients and the healthcare system in 2019 amounted to approximately $313 billion from the use of generics and an additional $2.2 billion from biosimilars.

Nevertheless, with current prices per patient ranging from ~€300K to >€2M, there is concern about the number of gene therapies under development. It has been estimated that over a million patients might benefit from gene therapies between 2020 – 2034 in the U.S. alone (Wong *et al.*, 2020), and Scott Gottlieb, the former FDA commissioner, predicted that by 2025, the U.S. would be approving between 10 and 20 gene therapies each year (FDA, 2019). However, such calculations are unlikely to reflect reality for several reasons related to two key areas:

1. The numbers of therapies coming to market:
   - **Many pipeline gene therapies will not achieve regulatory approval.** Although a large number (1300) (Barrett *et al.*, 2021) are in development, how many will gain approval remains highly uncertain. There are still many outstanding questions regarding the manufacturing, safety and long-term effectiveness of gene therapies. Given the relatively few approved to date, optimising manufacturing and development will take time and regulatory requirements will continue to evolve.

   - **Not all patients with a disease for which a gene therapy is approved will receive it.** The full spectrum of patients with a genetic disease diagnosis may not be eligible or able to benefit from treatment for many reasons such as pre-existing antibodies to the vectors, weight-based dosing which may limit the maximum dose that can be safely administered, or patients having irreversible disease progression.

2. The price and cost of these therapies, which need to be considered within the broader context within which they are placed:
   - **Gene therapies have the potential to offset other healthcare costs.** As described in section 2, in some rare diseases gene therapies will offset the cost of existing, high-priced medicines or treatments.
   - **Difference between list and net prices.** As Espin *et al.* (2018) have shown, the gap between list and net prices in Europe has been growing alongside the shift in prescribing towards specialised, hospital medicines. In practice, public list prices are often significantly higher than the net prices paid because confidential agreements and discounts are used in several countries. Moreover, between 2007 and 2018, list prices increased by 159% while net prices only increased by 60% further widening the difference between the two (Hernandez *et al.*, 2020).

- **Savings elsewhere in pharmaceutical expenditure.** Savings generated by increased generic competition and biosimilar availability facing more conventional medicines for higher-prevalence diseases may also at least partially compensate for the costs of newer innovative medicines, including gene therapies (EFPIA, 2018).

Overall, the development of gene therapies currently encompasses many unknowns and a substantial amount of risk for investment and development. Still, gene therapy development for rare diseases is progressing and expansion of knowledge is likely to lead to more efficient development and greater predictability of success.

Furthermore, gene therapy development will likely eventually expand into less rare indications with larger patient populations, allowing economic viability at lower prices (Melitz and Ottaviano, 2008). When gene therapy development does move into larger populations, more manufacturers may also be drawn into the market, increasing competition and cost containment (Sjöström and Weitzman, 1996). In more common diseases, it is also more likely that conventional treatments will be available, and these would be the benchmarks against which any new therapy would need to prove its added value.

5. Where do we go from here?

For medicines to transform the lives of patients, two things are required: great science and good policy. Gene therapies are undoubtedly great science, but whether that science can deliver on its therapeutic promise will depend in major part on whether the policy environment is supportive.

While the ultimate value of gene therapies may sit in more prevalent conditions, the technology is being piloted in rare diseases. If that experiment fails – either scientifically or economically – the realisation of the gene therapy promise is likely to be substantially delayed, if not lost.

Ultimately, if real-world effectiveness is seen to be good and safety is understood and manageable, the chances are high that these technologies will continue to be adopted and used more widely.

Yet issues of price and economics still have the potential to derail gene therapy progress. Not all gene therapies cost millions of euros per patient, but the ‘sticker shock’ associated with the products launched in the last few years cannot be ignored.

These high prices are not without justification; they are reflective of the value that gene therapies provide to patients, healthcare systems and society, and take into account the rarity of the populations being treated. They are also necessary. If gene therapies are going to ultimately be made available in the thousands of diseases in which they could work, the only feasible model of scale is via biopharmaceutical development and distribution. That will only work when the economics are positive, and currently the economics of drug development in both rare diseases and gene therapy are highly uncertain in Europe. Past and recent gene therapy withdrawals from the European market show that the consequences of failed economics may continue to constrain patient access to innovative gene therapies.

What does ‘getting the policy right’ look like for gene therapies in rare diseases? Most fundamentally, it means balancing the need to make gene therapy in rare diseases economically viable with cost control and efficiency in healthcare systems.

This entails recognising that the economics of gene therapies in rare diseases are particularly challenging, which has implications for pricing. P&R systems need to support viable early investment and development when economics are most challenging.

In practice, this means adapting P&R systems in three important ways:

- **Recognising the full value of gene therapies while managing uncertainty**
  It is impossible for payers to have the long-term data necessary to prove the potential lifetime value of a gene therapy at the time of approval, even for more prevalent conditions. Accordingly, P&R negotiations are based on predictions of expected value. While these come with significant uncertainty, this can be managed through the ongoing collection of real-world evidence and contractual agreements that stage payments over time, linking them to the demonstration of outcomes. Payers should rely on such contractual agreements to manage uncertainty, rather than limiting estimates of effectiveness to an arbitrary period of data collection.

  Even with the acknowledgement of the need for real-world evidence, there are data collection challenges that need to be addressed by policymakers, such as how to '...maintain quality overtime and [ensure] ease of accessibility across stakeholders and geographies' (Khurana and Kumar, 2018). Furthermore, there are greater challenges to following patients long-term after a single administration therapy.

- **Prices of one-time gene therapies, when spread over the duration of potential effect, are comparable to existing medicines for similar conditions**
  Currently, payers have shown reluctance to accept prices for gene therapies that are equivalent to the cost of therapies requiring regular administration over the same duration of potential effect. This approach disincentivises the development of future one-time gene therapies and is conceptually unfair. Payers can manage affordability concerns by introducing innovative financing mechanisms to mimic payment mechanisms used for conventional chronic therapies and spread the cost of gene therapies across several years (Slocomb *et al.*, 2017). This would particularly help during the initial introduction of a new gene therapy for which there is already a group of prevalent patients who have been waiting for treatment. After treatment of this first group, the eligible population would only be newly diagnosed patients.

  Simple estimates of budget impact presume that the full cost of a gene therapy will be incurred in Year 1. However, with a growing move towards innovative agreements, costs can be spread over multiple years through annuity-based (Jørgensen and Kefalas, 2017) or outcomes-based reimbursement (Jørgensen, Hanna and Kefalas, 2020).

- **Pricing should be value-based, encompassing the specificities of rare diseases and gene therapies**
  To be economically viable, gene therapies in very rare indications would need higher prices than those in broader indications. In some countries, P&R systems account for rarity to a certain degree when considering prices, but it is imperfect and often arbitrary. Proposals have been made that would allow payers to more reliably reflect rarity in their decisions (Berdud, Drummond and Towse, 2020), but further work is required. In the absence of such explicit consideration of rarity, research funding is likely to be prioritised to more common disorders, even when the unmet need might be lower.

Evolution in regulatory pathways needs to be matched by P&R assessments. Since the value of gene therapies is not fully demonstrated in traditional short-term trials, there needs to be greater acceptance of uncertainty and flexibility in evidence requirements.

Such changes would improve future access to gene therapies in rare diseases in Europe, but likely worry payers. Yet they do not have to be unsustainable. As gene therapy technologies evolve and mature, and the scope of patients who can benefit widens, population sizes will increase and efficiencies will improve – both will allow for continued investment at lower per patient prices.

Ultimately, the transformative potential of gene therapy, in both rare and non-rare diseases, will only be realised if these pioneering medicines can be shown to be both clinically and economically viable and brought successfully to patients.

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