GENE THERAPY:

Understanding the Science, Assessing the Evidence, and Paying for Value

A Report from the 2016 ICER Membership Policy Summit

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THE ICER POLICY SUMMIT 2016

Purpose

The 2016 ICER Policy Summit convened an influential group of evidence policy leaders from insurers, pharmacy benefit management firms, and life science companies to discuss gene therapies and to explore the opportunities and challenges of adopting this technology in the US health care system.

Participants

Held from December 7-9, 2016 the Policy Summit brought together 33 health care leaders from 20 payer and life sciences organizations. Senior researchers at the Office of Health Economics in England led the development of a background paper on gene therapy prior to the meeting to provide participants with a common foundation in some of the key scientific, conceptual, and practical issues.

Payer organizations: Aetna, Association of Health Insurance Plans, Anthem, Blue Shield of California, CVS Caremark, Express Scripts, Health Care Services Corporation, Harvard Pilgrim Healthcare, Prime Therapeutics, OmedaRx, Premera, United Healthcare

Life sciences organizations: Genentech, GlaxoSmithKline, Johnson & Johnson, Merck, National Pharmaceutical Council, Sanofi, Spark Therapeutics, Bluebird Bio

Report

This special report presents an analysis of the significant clinical potential of gene therapy and the unique challenges in developing and evaluating evidence on their effectiveness and value. Special attention is given to pricing and payment mechanisms, including new approaches to payment based on long-term amortization of initial costs. Based on the discussions at the Policy Summit this analysis is capped by a set of recommendations for future consideration by payers, manufacturers, and policymakers. It is important to note that no opinion or recommendation included in this report should be viewed as representing the opinion of any participant or their company. In keeping with Chatham House Rules, insights in this paper are not linked to any individual person or company. A manuscript version of this White Paper will be developed at a future date and submitted to a peer-reviewed journal.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment

Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

About OHE

The Office of Health Economics (OHE) has over 50 years' experience of conducting high quality research on the economics of innovation and the life sciences industry, the organisation and financing of health care, and the role for outcomes research and health technology assessment. The OHE's current work programme is supported by research grants and consultancy revenues from a wide range of UK and international sources.

The OHE is a not-for-profit company limited by guarantee. It is a registered UK Charity (registration number 1170829). Its work is overseen by its Editorial and Research & Policy Committees reporting to its Board of Trustees.

EXECUTIVE SUMMARY

Introduction

The first gene therapies are likely to enter use in the US health care system within the next 12-24 months. Many of these products will offer the potential of a short "one-off" treatment regimen promising lifelong benefits. However, evaluating the effectiveness and value of gene therapies at launch will be difficult, and their high cost is likely to present severe affordability challenges for payers and society, raising the question of whether new models of pricing and payment and new or modified HTA assessment methodologies are needed. The Institute for Clinical and Economic Review (ICER) held a Policy Summit on December 7-9, 2016 with 33 health care leaders from the 20 payer and life sciences organizations that comprise the ICER membership group. The purpose of the meeting was to convene senior figures among the pharmaceutical, biotech, and payer communities to share perspectives on the anticipated emergence of gene therapies and to identify possible ways to realize their benefits while addressing the challenges they pose for the US health care system.

Context

Gene therapy is "a novel approach to treat, cure, or ultimately prevent disease by changing the expression of a person's genes" (AMA, 2016). Gene therapies repair, deactivate or replace dysfunctional genes that cause disease, with the aim of (re)establishing normal function. Around 4,000 diseases have been linked to gene disorders, meaning that gene therapy could, in principle, positively affect millions of lives. Although two gene therapies have been approved in the European Union, no gene therapy has been approved by the FDA to date. However, Spark Therapeutics has already begun the process of submitting to the FDA the first-ever Biologics Licensing Application (BLA) for a gene therapy (voretigene neparvovec) to treat patients with vision loss due to confirmed bi-allelic *RPE65* mutation-associated retinal dystrophy, an inherited form of blindness. Approximately 12-14 investigational gene therapies for additional ultra-rare conditions and some for more common conditions, such as haemophilia and sickle cell disease, are progressing through the developmental pathway and are expected to reach regulatory approval within the next 2-3 years. Although there may be important policy distinctions to be made in evidence generation and assessment between ultra-orphan, orphan, and more common conditions, the broad outlines of the key opportunities and challenges are the same.

Key Opportunities and Challenges

1) **The development of gene therapies represents a new frontier in science with the potential to help many patients with serious or fatal conditions.**
   Gene therapy offers the potential to address significant unmet clinical need. Many genetic diseases produce serious or life-threatening clinical consequences. There are often no effective treatments beyond supportive care, and those treatments that do exist may not improve outcomes significantly, may have serious risks and side effects, and may be very expensive. However, as an emerging area of therapeutics, the development of gene therapies is scientifically challenging, and has been marked

by several cases in which there were important set-backs, including unforeseen serious side effects of treatment. The scientific and business risks of developing gene therapies are therefore high, especially for small biotechnology companies. If these therapies are to reach patients, manufacturers are likely to require that these risks be balanced by sufficient financial returns such that investment in the science underlying these technologies can be sustained.

2) **Very small patient populations and the novel aspects of gene therapy make it difficult to generate robust clinical evidence needed by decision-makers.** The combination of small population sizes and serious and progressive symptoms that characterize many (but not all) genetic disorders can raise ethical and practical barriers to using randomized controlled trials (RCTs) in the early evaluation of new treatments. Single-arm trials, or RCTs with early cross-over are therefore likely to be common standards for regulatory approval, and agreement is needed on how to make these trials as robust as possible to guide decision-making by payers and others. Other factors that complicate the generation of robust evidence include the lack of standard patient-centered outcome measures or surrogate measures for some genetic conditions; a lack of standardization of "usual supportive care;" and novel mechanisms of action and viral vector techniques that raise questions about the long-term safety and durability of any early clinical benefits seen with gene therapies.

3) **Uncertainty regarding clinical outcomes further complicates the challenges of assessing the value of potential "cures."** The clinical gains offered by potential "cures" will be difficult to value when, in the absence of long term data, there is no guarantee of long-term safety or of the durability of clinical benefit. Similarly, the potential long-term cost offsets may also be difficult to estimate based on the limited data that will be available at launch. These uncertainties only complicate perennial questions about how "society" values a cure relative to typical incremental gains observed with other therapies. What magnitude of premium pricing is fair for a "cure" that may or may not last? Should it matter whether current treatment for a condition is very expensive (e.g. haemophilia) or not? If a curative effect for a life-threatening condition is demonstrated or assumed, traditional methods of assessing value by cost-per-quality adjusted life year (QALY) thresholds may justify extremely high initial treatment regimen costs, raising questions about whether these costs are affordable. Manufacturers may seek high prices irrespective of the health gain because of the small number of patients over which to recover R&D cost, also raising the question of how much society values treating rare diseases.

4) **Gene therapies will heighten concerns about the affordability of emerging treatments under existing paradigms of pricing and payment.** More than any other challenge, that of affordability looms the largest over this area. The health budgets of public insurers (Medicaid and Medicare), and payers in the private insurance system (employers, health plans) are already constrained, and pressure to control costs are expected to increase in future years. Estimates suggest that 10% of Americans have a rare condition related to a genetic defect. Based on the initial pricing experience with gene therapy in Europe, should a growing number of gene

therapies come into use at costs of $1-2 million, the cumulative budget impact would be substantial, and perhaps unsustainable. Even if gene therapies are developed to treat only one in ten patients with a genetic condition – approximately 1% of the total population -- the cumulative budget impact at that price could rise to $3 trillion, as much as is currently spent in a year on all healthcare in the US. Of course, a genetic therapy will not be found for every rare condition (although some may not be for rare conditions), and the emergence of gene therapies will not snowball quickly enough over the next few years to approach this budget impact. In addition, some gene therapies may produce significant cost offsets by replacing expensive existing treatments. But the general expectation that the health system will be confronted with the challenge of absorbing treatment prices over $1 million per patient for even a relatively small number of patients has raised significant concerns among payers and policymakers. Manufacturers also recognize that existing payment mechanisms and other strategies to manage affordability may not be adequate to support the introduction of a growing number of gene therapies, highlighting the need for collaboration on further policy development to create a stable pricing, financing, and health insurance structure for these technologies.

Mechanisms to Address Affordability

The prospect of one-time curative gene therapy regimens for populations has driven expectations of extremely high up-front prices. Like organ transplantation, gene therapy replaces a defective function, which may offer a curative or long-lasting benefit, but some payers and policymakers, feel that this scenario does not create an *a priori* justification for per patient prices of $1 million or more. To them it is important to question the justification for high prices by considering formal value assessments to determine the price range reasonably aligned with how much clinical benefit is gained by patients, and by asking for transparency regarding development costs and contributions from federal funding and other sources.

Several strategies have been used in the past to manage expenditures for other types of high-cost treatments. These strategies include negotiating lower prices through discounts or rebates, requiring patients to pay more out-of-pocket as an incentive to use preferred options, restricting eligible populations or requiring that patients try other treatments first before receiving coverage for the preferred option, and implementing outcomes-based agreements in which payment is tied in some way to how well the treatment performs in real-world use. However, none of these approaches are without limitations, and it has been claimed that, when bluntly applied, some can overly restrict access to needed treatment, stifle innovation, and fail to reward value adequately. Alternative payment and financing strategies for gene therapies may be needed to manage short-term affordability while fairly rewarding value and providing the needed incentives to maintain investment in future innovative therapies.

The most promising alternative strategies include outcomes-based agreements, reinsurance, and various modes of payment amortization. Outcomes-based agreements can serve a critical function in addressing the inherent uncertainty in longer-term outcomes of gene therapy by linking payment levels to the real-world outcomes achieved by patients. Small patient populations and regulatory requirements for post-approval monitoring will also help make outcome-based agreements a cornerstone of gene therapy payment mechanisms, but important challenges remain with establishing long-

term tracking systems linked to financial arrangements in the pluralistic US health care system. In addition, in the current policy landscape there are regulatory and legal hurdles that need to be addressed for certain types of outcomes-based payment arrangements to come to fruition. These barriers, such as the Medicaid Best Price provision and the Federal Anti-Kickback Statute, have hampered the ability of payers and the biopharmaceutical industry to enter into outcomes-based payment structures beyond moderate discount and rebate arrangements.[1]

Reinsurance could theoretically offer a short-term option for the first few gene therapies, but concerns were raised at the policy forum that commercial reinsurers may look to exclude such high cost therapies. In addition, stakeholders believe that the reinsurance model will not work well over the long term given how quickly future risk will be priced into the premium. Amortization of payments therefore figures prominently in many discussions of payment strategies for gene therapies. Amortization refers to some mechanism for paying for a large upfront cost by making a number of smaller payments over a period of time. Home mortgages are the most commonly known example, but stakeholders at the ICER Policy Summit objected to this comparison as being overly simplistic given the many differences between the choices involved in home ownership and those related to payment for a novel gene therapy. [2]

Although it is not currently clear whether some form of amortization will emerge as a viable option for managing the affordability of gene therapies, there does appear to be certain characteristics that would make some gene therapies better candidates for consideration of such a strategy. These characteristics include:

- A one-time or very short-term treatment regimen with a "curative" clinical impact, meaning that benefits accrue over a long period of time. In such circumstances, spreading costs over a longer duration means that these can be paid alongside the realisation of benefits;

- A durability of clinical benefit that is well-established or that can be monitored through a linked outcomes-based mechanism. This means that data can be collected to facilitate an ongoing payment schedule. This is particularly important where amortization is used in combination with a outcomes based payment approach;

- A population size that is big enough to create concerns that upfront payment would not prove easily manageable. If this is not the case amortization may not be necessary;

- A method by which the overall regimen price is fairly set to reflect the added value for patients and underlying development costs.

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[1] A full analysis of these constraints is included as part of a previous ICER Policy Summit paper on indication-specific pricing, available at http://icer-review.org/wp-content/uploads/2015/03/Final-Report-2015-ICER-Policy-Summit-on-Indication-specific-Pricing-March-2016_revised-icons-002.pdf.

[2] Differences noted included the lack of choice for patients, no equity or ability to re-sell, and the fragmentation of insurance markets vs. a single residential housing market.

This set of circumstances is shown in Figure 1 below.

Figure 1. Characteristics of gene therapies that merit consideration for amortized payment strategies.
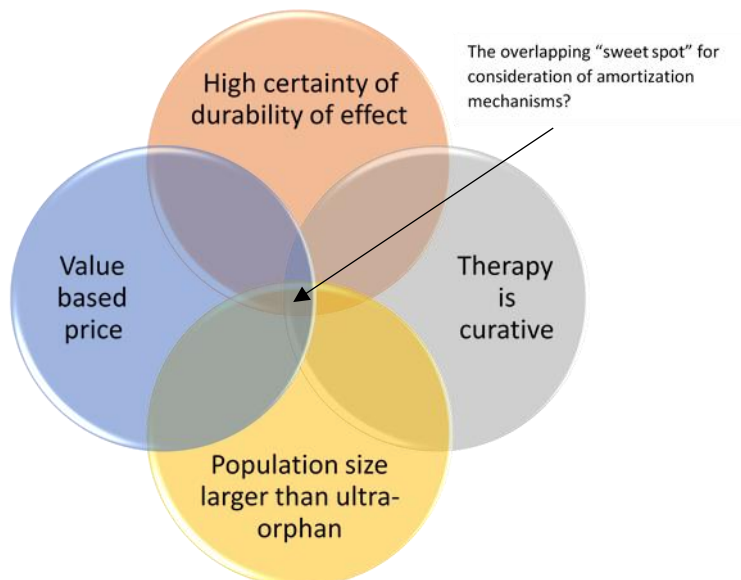
Options for the Amortization of Gene Therapy Payment

The options for amortization can be divided into categories dependent on who bears the financial risk and who provides the financing. The major categories are: 1) consumer loans to pay large up-front prices to manufacturers; 2) third-party financial institution financing for payers to obtain financing for large up-front prices to manufacturers; 3) government financing for payers to pay large up-front prices to manufacturers; and 4) manufacturer managed financing, in which long-term payment plans are negotiated with payers as part of outcomes-based agreements. The pros and cons of these different mechanisms are described in detail in the body of the paper.

The Policy Summit discussion did not favour consumer loans, viewing them as being inadequate to provide fair and affordable patient access to these treatments. The focus thus fell upon financing by third-parties, such as Wall Street financial institutions, the government, or manufacturers. The risk and high costs of gene therapies may prove very difficult to manage within the fragmented private insurance system, and some stakeholders believe that the federal government will need to intervene and take over coverage, much as it did with renal dialysis. Among the forms of amortization it is felt unlikely that Wall Street institutions will of their own volition come forward with a financing option for payers, and payers expressed limited interest in this option. It became clear through the discussion of the Policy Summit that if private insurers were going to consider some kind of payment through amortization, the proposal and the vehicle for doing so would have to come from the manufacturer. Some manufacturers might have the size and financial resources to provide the financing themselves, and offer the payer some form of instalment payment plan; others would most likely need to work with third-parties to come up with some kind of financial instrument that they could then offer to payers.

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Even though amortization of some kind seems inevitable to many stakeholders, over all the options hangs a sense of great difficulty and uncertainty. A great deal of further discussion and planning will be required in order for these potential arrangements to find a place among the options for managing affordability in the US health care system. Unfortunately, time is short, with the first gene therapies expected to receive regulatory approval within the next year. To sustain future innovation in gene therapies while managing the very real concerns regarding affordability, all stakeholders will need to take vigorous and collaborative action to establish clear outlines for a comprehensive approach to evidence generation, assessment, pricing, and payment.

Policy Recommendations

Incorporating the discussion of this topic at the Policy Summit, the following specific policy recommendations reflect a combination of analysis and opinion of multiple stakeholders. Greater explanation of each recommendation is provided in the body of the report.

These recommendations should be viewed in the larger context of the need for a broad and ongoing collaboration among manufacturers, payers, patients, and policymakers. Only with collaborative efforts can the opportunities presented by gene therapies be realized while addressing the significant challenges related to evidence generation, value assessment, and payment. Central to this broad dialogue will be continued discussion of how best to assess the clinical value of new treatments that offer a potential cure, and how to create new pricing and payment structures that can support innovation in a way that is stable and affordable for patients, payers, and society. The risk of new treatments meeting an affordability "wall" is real; a sustained and determined focus on this policy area will be needed.

Recommendations for Manufacturers

1. Seek dialogue with payers and regulators as early as possible in the development of new gene therapies in line with recent FDA guidance facilitating dialogue between sponsors and payers on investigational product information. Topics of discussion should include:

    a. ways to include or create meaningful patient-centered outcomes or validated surrogate outcomes in developmental trials;

    b. options for making the registration studies as robust as possible, especially if RCTs will not be performed;

    c. options for partnership on post-approval studies to reduce residual uncertainty about the safety and effectiveness of new therapies (particularly important in the context of possible adaptive licensing);

    d. methods of determining patient eligibility that can be feasibly translated into coverage criteria;

    e. criteria for designation of potential centers of excellence for the delivery of the therapy;

    f. size of potential patient population;

g. the role envisioned of a therapy within the care pathway;

h. the elements of value that patients, clinicians, manufacturers, and payers can agree should be considered in assessing value and judging what price fairly reflects the added value of the therapy.

2. Whenever possible, seek ways to perform at least one RCT comparing the new therapy to any existing treatment. Consider the use of adaptive trial designs, weighted randomization, and cross-over to meet ethical requirements. In cases where RCTs are not possible, work with payers and regulators to establish the most appropriate feasible method of clinical evidence generation.

3. Work with clinicians, patient groups, regulators, and payers to establish robust Patient Registries to facilitate collection of real world evidence before and after regulatory approval.

4. Be prepared to address concerns about high prices by presenting clear information and evidence on how the price is related to the costs of development and/or stakeholders' perceptions of a therapy's value.

5. Where appropriate, collaborate with payers and health technology assessment groups on value assessment reports. Providing input on the scoping parameters of assessments is helpful, and special consideration should be given to sharing patient-level clinical and economic data when possible.

6. For gene therapies whose characteristics make them good candidates for possible amortized payment options, be prepared to come to payers with a specific manufacturer-financed mechanism for instalment payments combined with an outcomes-based agreement.

Recommendations for Payers

1. Develop internal sophistication in knowledge about gene therapies, including understanding of the basic scientific techniques and of the usual approach taken by the FDA in assessing the safety and effectiveness of these agents.

2. Engage in early dialog with manufacturers of promising new gene therapies. The topics of mutual interest will include those listed above for manufacturers:

    a. ways to include or create meaningful patient-centered outcomes or validated surrogate outcomes in developmental trials;

    b. options for making the registration studies as robust as possible, especially if RCTs will not be performed;

    c. options for partnership on post-approval studies to reduce residual uncertainty about the safety and effectiveness of new therapies (particularly important in the context of possible adaptive licensing);

    d. methods of determining patient eligibility that can be feasibly translated into coverage criteria;

    e. criteria for designation of potential centers of excellence for the delivery of the therapy;

    f. size of potential patient population;

g. the role envisioned in therapy within the care pathway;

h. the elements of value that patients, clinicians, manufacturers, and payers can agree should be considered in assessing value and judging what price fairly reflects the added value of the therapy.

3. Work with clinicians, patient groups, regulators, and manufacturers to establish robust Patient Registries to facilitate collection of real world evidence following regulatory approval. Individual insurer in-house registries could be pooled with those of other insurers and/or with manufacturers.

4. Develop categorizations of different types of gene therapies based on their method of delivery, mechanism of action, and other key characteristics so that coverage policies can be clearly tailored to meet distinctive types of therapies.

5. Work with plan sponsors to familiarise them with the challenges in this area and to explore options for coverage that will meet their needs for value and affordability while creating a mechanism to help patients gain access to effective new therapies.

6. Collaborate with manufacturers to explore outcomes-based agreements. Outcomes-based agreements can be combined with different potential methods of amortized payments when health benefits are expected over a long time horizon.

INTRODUCTION

1.1. The Challenge of Gene Therapy

Gene therapy is coming to the US health care system. The product development pipeline includes many gene therapies, including Spark Therapeutics' voretigene neparvovec, being studied for the treatment of patients with vision loss due to confirmed bi-allelic *RPE65* mutation-associated retinal dystrophy, which is the subject of a BLA to be submitted to the FDA in 2017. These therapies offer the promise of a short "one-off" treatment regimen leading to potentially lifelong benefits, but are likely to pose major affordability challenges if paid for using traditional methods. This raises concerns about the sustainability of this model of innovation for health systems. What challenges do these therapies give rise to, and how should payers and manufacturers address them? These issues were the subject of discussion at the 2016 ICER Policy Summit meeting; this Briefing Paper develops the challenges that are likely to be faced by the introduction of gene therapies and explores policy recommendations arising from the ICER Policy Summit.

This White Paper is informed by a literature review, six interviews with policy experts and discussions at the Policy Summit:

- The literature review was designed to be pragmatic rather than systematic, and was undertaken to identify challenges around gene therapies, rather than to identify all relevant papers;

- The six experts were selected and invited to interview by ICER. They included payers, industry representatives and academics, all of whom were experienced in thinking through the implications of gene therapy research.

This White Paper sets out:

- A definition of gene therapy and related treatments and an overview of the pipeline;

- Aspects of gene therapy that complicate its evaluation and payment within existing paradigms for drugs (such as the potentially "curative" nature of the therapies[3]);

- Evidence requirements (and challenges) for both regulators and payers;

- Challenges in assessing long term value for money;

- Challenges in assessing the total potential budget impact;

- Options for innovative payment mechanisms.

None of the challenges we discuss are unique to gene therapy. However, these therapies are likely to face a higher concentration of these hurdles than conventional therapies.

1.2. What is gene therapy?

The American Medical Association describes gene therapy as "a novel approach to treat, cure, or ultimately prevent disease by changing the expression of a person's genes" (AMA, 2016). Genes are composed of DNA that contains necessary information for making proteins that are vital for the human body to function optimally. Some gene mutations result in these proteins not being made correctly (or not being made at all) and can lead to genetic disorders. Gene therapy works by repairing, dis-activating ("turning-off") or replacing dysfunctional genes that cause disease with the aim of (re)establishing normal function (AMA 2016; Genetics Home Reference, 2016; MedlinePlus, 2016).

Typically a carrier (a "vector"), which often takes the form of a virus (one that has been modified so that it does not cause disease), is engineered to deliver the gene. Once delivered to the human tissue, either by injection, intravenously or outside of the human body in a lab, the virus then integrates its genetic material into the human cells. As a consequence, gene therapies are typically invasive in nature (the majority via intravenous, subcutaneous, intraperitoneal or intramuscular injection). Assuming treatment is successful, the new gene will make a functioning protein (Genetics Home Reference, 2016).

The American Medical Association reports that around 4,000 diseases have been linked to gene disorders, including cancer, AIDS, cystic fibrosis, Parkinson's and Alzheimer's diseases, amyotrophic lateral sclerosis (Lou Gehrig's disease), cardiovascular disease and arthritis (AMA, 2016). Therefore the promise of successful treatment with gene therapy could positively affect millions of lives. However there are many challenges to be overcome: the science is complex, particularly when we move away from single gene disorders. Treatment is technically difficult and often very costly, and regulation is necessarily different to that for drugs (or "conventional" therapies).

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[3] We use the definition of "curative" proposed by Tapestry Networks (Tapestry Networks, 2016), i.e. (i) an innovative one-off treatment; (ii) an irreversible process and (iii) a long term durable effect. We note that many commentators do not accept that the term "curative" is appropriate in the absence of evidence about long term effectiveness.

1.2.1.Cellular, Tissue and Gene Therapies

Note that gene therapies are often grouped with cell therapies and with tissue engineering techniques, sometimes under the umbrella of 'regenerative medicines' or 'advanced therapies'. These other techniques have advanced further than gene therapies in reaching the market: Currently, 13 products (none of which are gene therapies) have been licensed by the FDA's Office of Tissue and Advanced Therapies (OTAT), (formerly known as the Office of Cellular, Tissue and Gene Therapies)[4]. In the European Union, seven regenerative medicine products have been granted marketing authorization. However, only one of these (ChondroCelect, a tissue-engineered therapy) has achieved national reimbursement, and this has only been achieved in three countries (Spain, Belgium and the Netherlands) (Abou-El-Enein et al., 2016a).

FDA classifies gene therapy products as therapeutic biological products. They are subject to the licensing provisions of the Public Health Service (PHS) Act & drug provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA). For approval, a biologic license application (BLA) is required.

1.3. The Gene Therapy Pipeline

Gene therapy is an attractive area for drug development because with the right target and approach, it can address the root cause of a severe disease. For certain disorders where known genetic mutations lead to deficient or non-functional protein production, gene therapy can "fix" the underlying defect and/or provide a path to producing the functional protein. Genetic mutations in the cystic fibrosis conductance regulator (CFTR) gene, for example, lead to changes in mucous secretions resulting in respiratory impairment, chronic respiratory tract infections, high morbidity and early mortality. Cystic fibrosis has long been a target for gene therapy development because of the potentially devastating nature of the condition and the known biology underlying the disease. A cure could mean improved quality of life, quantity of life, and avoidance of healthcare costs (medications, physical therapy, lung transplantation, etc.). As understanding of the human genome advances, the number of potential molecular targets for gene therapy grows as does the anticipation of rectifying genetic pathways of diseases that have seen only incremental advances or no advanced at all. At the ICER Policy Summit, there was general agreement that all stakeholders need to work to bring these potentially transformative treatments to the patients that desperately need them.

At present, gene therapy is still considered to be "experimental" (AMA, 2016; Genetics Home Reference, 2016; MedlinePlus, 2016). The first gene therapy, Glybera from UniQure for the treatment of lipoprotein lipase deficiency, was approved for use in the European Union in 2012, but has not been approved by the FDA (for further details see section 2.3.1). Furthermore, in Europe it has to date only been paid for use in one patient, most likely due to its $1.4 million price tag (Ylä-Herttuala, 2015). Another therapy, Strimvelis for severe combined immune deficiency in children, is also approved in Europe (as of 2016), but not yet in the US.

The FDA has yet to approve a gene therapy, however, a recent report from Pharmaprojects (Boliter, 2016) suggests that the number of gene therapies in development has increased rapidly in the last 2-3 years. Figure 1 shows the number of

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[4] For example PROVENGE (Dendreon Corp.), Clevecord, HPC Cord Blood (various) and IMLYGIC (BioVex Inc). For more information see www.fda.gov

gene therapies in development (at all stages) per disease group (see Appendix 1 for further pipeline details).

Figure 1: Number of gene therapies per disease group
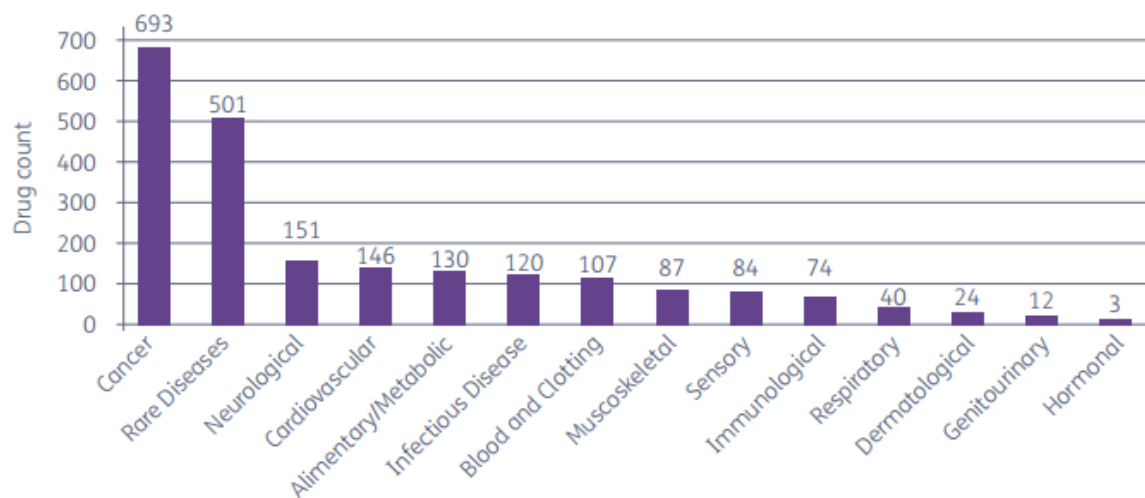
Source: Pharmaprojects, 2016

Note: The treatments in the rare disease category are double counted in the graph as they also appear in the numbers for the relevant therapy area. We can see that rare diseases (501) account for 30% of the total of 1671 therapies. Others may also be for orphan indications, albeit within larger disease categories.

Of these, 23 gene therapies are currently in active phase III development. If one can assume the same success rates as for conventional therapies at phase III, then up to 12-14 of the gene therapies that are currently in active phase III development (around 5-6 non-cancer therapies and 7-8 cancer therapies) may submit a new license application in the next couple of years.

The current front-runner, is Spark Therapeutics' voretigene neparvovec for the treatment of inherited retinal disease caused by RPE65 mutation. Results from a pivotal phase 3 study indicate that this therapy has the potential to provide clinically meaningful and long-lasting improvements in retinal sensitivity, which allows for patients to have improved functional vision, leading, for example, to improvements in mobility. Spark Therapeutics has begun the process of submitting Biologics Licensing Application with the FDA and aims to complete the application sometime in early 2017.[5]

1.4. The Challenges for gene therapies in the US health care system

From the literature and our interviews we identified a list of potential challenges that could be faced by gene therapies on their path through development, regulation, evaluation (in terms of establishing both clinical effectiveness and value for money), and payment within the US healthcare system. In the next sections we look at three key areas: evidence generation; assessing value; and affordability. We also discuss possible solutions.

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[5] With this kind of "rolling BLA", the FDA may start reviewing portions of the application before the manufacturer finishes completing the full application. This is a process that is usually followed for breakthrough drugs to expedite the review.

There are two other key challenges also mentioned in the literature and in our interviews, which we touch on briefly now:

- **Manufacturing and distribution.** The personalised nature of gene therapies, along with limited shelf life and stability (Bailey et al., 2015), means that products cannot necessarily be manufactured in bulk, unlike small and large molecule drugs. Therefore, even if the manufacturer does manage to secure market authorization and reimbursement, there may still be practical delivery challenges to address. Concerns have also been raised that a lack of clarity around manufacturing and quality standards may result in inefficient product development and act as a barrier for development. Indeed Bailey et al. (2015) comment that there are few, if any industry standards for the manufacturing of cell and gene therapy products. This is likely to be particularly problematic in rare diseases where no precedents exist (van Schothorst et al., 2014). There may be a trade-off between allowing flexibility in the manufacturing process to account for the patient-specific nature of the products whilst establishing good manufacturing practice (Abou-El-Enein et al., 2016b) and reducing costs through experience and standardization. The unique nature of manufacturing gene therapies may also complicate the development of gene "biosimilars" in the future.

- **Ethical dilemmas.** The ethical dilemmas associated with gene therapy are similar to those for cancer treatments for small populations and include: (i) the challenge of denying coverage on grounds of cost for an apparently effective therapy for patients with substantial morbidity; (ii) the difficulty of running a randomised clinical trial with a poor current standard of care, when the new therapy appears to be performing well. In such cases where no alternative treatments exist, and when the intervention is for a life-threatening condition, it may be deemed unethical to withhold experimental treatment from participants within a trial, due to the lack of clinical equipoise.

Note that not all of the challenges listed will be applicable to all gene therapies. For example, not all gene therapies will be for small populations. We discuss several potential challenges around evidence generation, especially in relation to RCT design, but conventional RCT designs will be (and have been) possible in some cases. The potential issues should not be thought of as insurmountable barriers, and will not apply uniformly across all gene therapies. In addition, some of the challenges are likely to be much more common than others.

2. EVIDENCE GENERATION

2.1. Evidence of Clinical efficacy

Conducting RCTs can be problematic for gene therapy due to the characteristics of these therapies (Bubela et al., 2015, Hettle et al. 2016). Those targeting small populations make recruitment to an adequately sized RCT expensive and time consuming, and pose statistical challenges, typically resulting in substantial uncertainty around estimates of clinical effectiveness. Because of the small numbers of patients, the regulator may deem it appropriate to give all of the patients the active comparator, in order to ensure that the maximum possible is learned about the new gene therapy.

When a placebo or comparator arm is possible, invasive methods of administration[6] may require sham operations in order to conduct blinded RCTs. Such sham operations can be unethical and may prevent fully blinded placebo-controlled trial designs (van Schothorst et al., 2014).

It can also be difficult to identify the appropriate comparator for the gene therapy to be assessed against, particularly where the therapy leads to marked changes in clinical practice or where there is no existing treatment. A report published by the European Commission (van Schothorst et al., 2014) explains that where no standard treatment is available, there may not be any clear clinical pathway (i.e. there is no conventional "usual care") or established measure of clinical outcomes.

Trials are short, typically limited to a few years at most, and thus do not provide long term data. Many include a longer follow up period through which patients are monitored, but, as one interviewee pointed out, in order for manufacturers to provide data that these cures last a lifetime, or at least that the length of clinical benefit outweighs the short-term risks, they would need to observe patients for an extended time.

Due to small patient numbers and perceived ethical and statistical benefits of crossover trials, it may be difficult to power studies adequately to evaluate the health outcomes ultimately being sought. As a result, key trials may necessarily depend on surrogate outcomes requiring extrapolation to estimate the key clinical and health endpoints. This can be a substantial source of uncertainty in estimates of effect. Hettle et al. (2016) conducted a literature review (of publications and statistical reports on evidence for the use of surrogate endpoints in medicine) and found that trials using surrogate outcomes tend to report larger estimates of treatment effect (28%-48%) than those reporting clinical endpoints. Additionally, appropriate surrogate outcomes may not exist for gene therapies, requiring development and validation of outcome measures currently unfamiliar to patients, clinicians and payers.

When comparative data are obtained from elsewhere rather than an RCT, the lack of head to head comparison can give rise to further uncertainty around estimates of relative effectiveness. The literature review by Hettle et al. (2016) found that, unless historical control data are available, single arm trials are likely to produce optimistic estimates of benefit. As mentioned earlier, if adaptive licensing with surrogate markers is used, there will be substantial uncertainty requiring confirmatory studies post regulatory approval.

Complicating evaluation of clinical effectiveness further, the risks and benefits of a product may in some cases vary depending on the delivery protocol and, if relevant, the skill of the surgical team (Abou-El-Enein et al., 2016a). This could generate high variation in response across individuals and centres, leading to implications for the generalizability of efficacy and safety estimates. Where skill of the surgical team is a relevant concern, there could also a 'learning effect' over time which serves to improve the effectiveness of the treatment. These issues can arise in any surgical RCT, but nonetheless can give rise to further uncertainty around clinical effectiveness.

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[6] For example, Glybera requires up to 60 intramuscular injections in the thigh while under sedation or anaesthetic.

2.2. Safety evidence

Gene therapies come with their own set of safety concerns; when delivered through viral mechanisms they can be tumorigenic and can give rise to proliferation in tissues which have not been intentionally targeted (van Schothorst et al., 2014). They can also stimulate immune reactions, requiring immunotherapy, adding to overall risks (Abou-El-Enein et al., 2016a).

As gene therapies are new to medicine, there is no long-term experience with which to gauge the potential for serious safety consequences that might emerge years after the initial treatment phase. This problem of unknown long term safety consequences was stressed by several of the interviewees: it was noted that the FDA has been pushing for long trials in order to gather as much information as possible, but the reality is that we may not know the true effects of some of these therapies for 5-10 years after administration. Ultimately there is an uncertainty around the potential for harm given that we have incomplete knowledge about the consequences of manipulating the gene. Further concerns were raised at the ICER Policy Summit meeting that use of these therapies today may affect future generations in ways we do not yet understand. Manufacturers clarified that this is not expected to be the case because many of the pipeline gene therapies augment or supplement existing genes rather than editing germ line DNA sequences.

2.3. Regulatory agency processes to date

2.3.1. The US

No gene therapy has been approved by the FDA to date. We noted that Spark Therapeutics has begun the process of submitting the first-ever Biologics Licensing Application submission of a gene therapy to FDA. Of the two approved in the European Union, UniQure abandoned plans to gain FDA approval for Glybera in 2015 when additional trials were requested to enable a decision to be reached; GSK have stated their intention to seek FDA approval for Strimvelis, but have noted that the clinical trial requirements for FDA approval are different to that of the EMA, and as such this may not be straightforward (Adams, 2016). The FDA's process for gene therapies is summarised in Box 1.

Our interviewees commented that the US system is close to approving other gene therapies (possibly 2-3 years away from potential approvals). They added that several therapies have ongoing late stage clinical trials, and efficacy looks good – it is the long term safety concerns that are not yet fully understood. Safety concerns will most likely need to be tackled before regulatory approval is achieved in the US. There are concerns over immune response in the short term, in addition to the possibility for significant severe side effects in the longer term. The FDA has had strong concerns around this in the past, and is requiring developers of gene therapies to provide long-term post-trial follow-up observations of patients who have been exposed to these treatments.

2.3.2. Europe

As mentioned previously, Glybera and Strimvelis, have been granted marketing authorization in the European Union by the European Medicines Agency (EMA):

- Glybera was approved by the EMA in 2012, but has since become the world's most expensive short-term treatment (Adams, 2016), and as such has not been

widely successful - it has only been used by one patient, with the prescribing clinician overcoming steep bureaucratic hurdles to obtain insurer funding (Abou-El-Enein et al., 2016a).

- Strimvelis received marketing authorization in 2016. Patients can currently only be treated in Milan, due to the treatment's extremely short shelf life which dictates that cells must be infused back into the patient in less than six hours.

Both treatments are for orphan conditions and are subject to ongoing monitoring. The EMA's process for regulating gene therapies is summarised in Box 2. From UniQure's experience with Glybera, evidence requirements between the two bodies (FDA and EMA) are not the same. Manufacturers have taken different strategic approaches to addressing regulatory requirements, with UniQure and GSK approaching EMA for regulatory approval of Glybera and Strimvelis respectively before FDA, whilst Spark Therapeutics has begun its application with FDA first.

Box 1: The FDA and gene therapies

Classification

The FDA refers to gene therapies as human gene therapy products. They are often considered alongside cell therapies, collectively referred to as "Cellular & Gene Therapy Products". The majority are biologics, although some may be medical devices or combination products.

Pathway

The Office of Tissue and Advanced Therapies (OTAT), formerly the Office of Cellular, Tissue and Gene Therapies (OCTGT), and part of the Center for Biologics Evaluation and Research (CBER), regulates gene therapies alongside cell therapy products and related devices. CBER provides management and support to the Cellular, Tissue and Gene Therapies Advisory Committee, who review and evaluate data relating to the safety, effectiveness, and appropriate use of these products.

The regulatory approach for gene therapies is similar to other medical products, but does include flexibility related to the biological and technical complexity of the products. For example, phase I studies for gene therapies are typically conducted in a population who has the disease being studied (rather than in healthy volunteers). This is mainly due to unknown risks, but also allows sponsors to look for preliminary evidence of bioactivity on the characteristics of the disease.

Gene therapies may also be able to achieve orphan status (which qualifies manufacturers for benefits such as tax credits) and/or be eligible for one of the four available mechanisms for expediting FDA assessment: breakthrough designation, fast-track designation, accelerated approval or priority review.

Guidance

There are several guidance documents available on the FDA website to support manufacturers in developing, reporting on, and conducting studies of cell and gene therapy products. Key documents include:

- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry (http://www.fda.gov/downloads/Biologi.../UCM359073.pdf);

- Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory Information/Guidances/CellularandGeneTherapy/ucm078719.pdf);

- Recommendations for Microbial Vectors Used for Gene Therapy; Guidance for Industry (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory Information/Guidances/CellularandGeneTherapy/UCM466625.pdf).

CBER is also able to provide early scientific and regulatory advice.

Gene therapies to date

No gene therapy has received FDA marketing authorization to date, although one may be close (see section 2.3.1).

There have been gene therapies that have achieved orphan drug designations (for example Agilis' AGIL-FA for the treatment of Friedreich's ataxia and Spark Therapeutics for the treatment of inherited retinal dystrophy due to biallelic *RPE65* mutations) and been eligible for expedited development and review (for example Spark Therapeutics voretigene neparvovec and Spark/Pfizer's SPK-9001, which is for the treatment of haemophilia B, have both achieved breakthrough designation).

Source: www.fda.gov; Bailey et al. (2015)

Box 2: The EMA and gene therapies

Classification

The EU classifies gene therapies, cell therapies and tissue engineering products as advanced therapy medicinal products (ATMPs) under Regulation (EC) No.1394/2007 and Directive 2001/83/EC.

Pathway

ATMPs are required to be assessed through the centralised authorization procedure, via a single marketing-authorization application to EMA for all EU citizens at the same time.

ATMPs are the responsibility of the Committee for Advanced Therapies (CAT). The CAT is a multidisciplinary committee tasked with delivering recommendations on whether or not a medicine can be classified as an ATMP, as well as assessing the quality, safety and efficiency of ATMPs to produce recommendations on marketing authorization. For gene therapies, there is also a Gene Therapy Working Party (GTWP), made up of people with expertise specific to gene therapies. The GTWP provides recommendations to the CAT on gene therapy matters.

As with the FDA, the pathway for gene therapies is similar to that for other medicinal products, but allows a tailored approach for individual ATMPs. There is an acknowledgement that large confirmatory studies may not be feasible due to small population sizes, and evaluation may need to be based on a limited amount of data. In addition, as with the FDA approach, all clinical studies are conducted in a relevant patient group, rather than amongst healthy volunteers.

Companies developing ATMPs are eligible for reductions in the EMA fees (both for submissions and for scientific advice). Further incentives are available for products with an Orphan designation, such as possibility of obtaining 10 years' market exclusivity.

Guidance

Guidance documents that relate specifically to marketing-authorization applications of gene therapies are available on the EMA's website. One of the key documents is the EMA's draft Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014). The document aims to provide guidance on the development and evaluation of gene therapies, focusing on quality (i.e. the specific requirement for development and manufacture), and the design of clinical and non-clinical study programmes.

Gene therapies to date

Since 2009 the CAT has recommended that 170 products be classified as ATMPs: 31 of these are gene therapies; the rest are cell therapies or tissue engineering products. Of these only two have received market authorization: Strimvelis, Glybera.

Source: www.ema.europa.eu; Salmikangas et al. (2015)

2.4. Possible solutions to the evidence challenges

2.4.1.Use of Early Dialogue

The FDA provides opportunities for scientific dialogue and the provision of advice to companies. Early dialogue between payers and companies in the US has been more difficult, however, in part because of FDA regulations that restrict the sharing of pre-approval information on a product, and also, in the event of multi-stakeholder dialogue, because of concerns about anti-trust law. The FDA does not engage in the three-way early scientific dialogue including payers/HTA bodies such as is now routinely available in Europe, but the FDA will consider joint regulatory dialogue with the Sponsor and the EMA. The benefits of early scientific dialogue that included payers could be:

- Ensuring that manufacturers take care to make the best use of the small available population, using appropriate trial designs (possibly including adaptive trial designs and cross-over studies[7]) and methods of statistical analysis that are likely to maximise the usefulness of the evidence to payers and providers;

- Discussion about whether surrogate end points are adequate for decision-making, and how surrogate endpoints can best be validated and evaluated in terms of meaningful benefits to patients;

- Choice of comparator and understanding of current standards of care for patients with these diseases;

- Consideration of follow-up periods for tracking patients and collecting and analysing post-launch evidence on effectiveness and safety.

Attendees at the ICER Policy Summit meeting considered that early dialogue is typically an extremely useful exercise, but also noted that it is resource intensive and should only be carried out when there is value to be gained.

2.4.2.Collection of post-launch Real World Evidence

Collection of real world evidence via post launch registries tracking treated patients will usually be a safety requirement of obtaining regulatory approval. However, it can also be used to mitigate the 'leap of faith' that short term evidence of improvements in surrogate indicators is proof of long term health benefits.

Observational level evidence is generally less well received by payers as it has greater risk of bias unless potential confounding can be addressed. Potential partnership between payers and manufacturers, with agreement on the outcomes to be collected, might mitigate some of these concerns. Hettle et al. (2016) comment that use of retrospective studies and historical control studies carry a risk of biased estimates of effect. The design of post-launch evidence collection is likely be crucial for establishing medium to long term evidence of effectiveness and comparative effectiveness.

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[7] Cross-over trials can be helpful when population sizes are small (Wellek and Blettner, 2012), as patients receive both treatments, but the order that they receive them in is randomised. In a de-layed cross-over approach, patients are monitored for a period of time before crossing over to re-ceive the other treatment. In discussion with the FDA, Spark Therapeutics designed an RCT that allowed for a delayed crossover to the investigational treatment.

2.4.3.Use of Centers of Excellence for Diagnosis and Treatment

The potential problems with accurate diagnosis of patients may require centralization of diagnostic processes at Centers of Excellence. Uncertainty about whether the delivery of the treatment itself will reap the benefits seen in the trial data may lead payers to consider limiting coverage of these "cures" to Centers of Excellence as well. Centers of Excellence could also be formed in a way to manage provider payments in a way that eliminates any concern about large provider margins being added to therapy delivery costs. This option was viewed favourably by many attendees at the ICER Policy Summit meeting. For example, Spark Therapeutics is proposing to limit administration of voretigene neparvovec to Centers of Excellence that meet strict capabilities and training requirements to support appropriate patient care.

3. VALUE ASSESSMENT, PRICING AND BUDGET IMPACT

The challenges noted above around evidence generation and uncertainty lead to challenges in assessing value – for example, short term trials mean that we have significant uncertainty around estimates of clinical effect, which makes it difficult to produce robust estimates of health and economic impact.

Four additional types of issue come up in assessing the value of, and agreeing a price for a gene therapy:

- What extra value, if any, should be attached to the potential that these therapies may cure severe and life threatening diseases – compared to the value attached for more incremental benefits;

- whether there are elements of value to patients, the health care system, or society, that are not captured in the usual payer value assessment;

- the impact on price of high R&D and manufacturing costs, together with small patient numbers;

- methods to estimate and incorporate budget impact as part of value assessment. This could be through a direct adjustment of the value assessment; through separate consideration of how to finance gene therapy; or both.

We discuss these briefly in turn.

3.1. The value of a potential cure

Gene therapies are expected to offer greater clinical gains than conventional therapies: Bubela et al. (2016) comment that "the promise … is to break out of the marginal value mould of traditional pharmaceuticals with curative therapies for indications with limited treatment options". On the other hand, one of the interviewees commented that we are often assuming that these therapies provide cures, but in reality we do not have long term data, and there is no guarantee that the effects will not wane. Assuming that the effects are at least long term, if not curative, has two key implications:

- Long lasting curative effects are likely to reduce ongoing costs of patient support and of managing chronic comorbidities, thereby offsetting high upfront costs and helping to justify the high costs of these therapies (Abou-El-Enein et al., 2016b). However this 'offsetting' of future costs is less likely to be seen as beneficial in private insurance-based systems such as the US where patients can move from

one insurer to another, as it reduces the incentive for an insurer to make big payments upfront for health benefits (and long term cost savings) that will be realised throughout the lifetime of the patient (Basu, 2015). However, an insurer could also be on the receiving end of a new member whose disease has already been cured, having been paid for by another insurer. This challenge is discussed further in section 4.1 of this report;

- Curative therapies may be valued more highly by society than treatments that offer the same "total" health gains through marginal gains over many years and/or patients, as curative therapies have the potential to put an end to the need for long term chronic treatments and provide longer term increases in quality of life. Early cures or substantial benefits at a young age could help produce significant gains in work productivity for patients compared to treatments that bring marginal gains over many years. Little evidence is available to suggest whether or not this preference exists, and as such typical HTA value assessments do not give additional weight to curative treatments.

3.2. Identifying Relevant Elements of Value

Payers typically focus primarily on health gain for the patient and net direct costs to the health system when looking at their willingness to pay for a therapy in particular circumstances. However, other elements of value may be considered relevant in general or in specific circumstances (Towse and Barnsley, 2013; ICER, 2016; Oortwijn, 2016). Tapestry (2016) notes it has been argued that existing quality adjusted life year (QALY) based frameworks may not be appropriate for assessing the value of cures, suggesting that there could be scope for a revised value framework.

Elements of value, beyond the health gain for the patient and costs to the health system, that may be relevant for payers, patients and society include:

- Taking account of disease severity, age of onset, and lifetime burden of illness. There is evidence that society expects some priority to be given to addressing the health needs of people with severe unmet need. There is also evidence that society expects priority to be given to children, over and above that already factored into an estimate of life long health gain from treatment. It is likely that several early gene therapies will be aimed at young patients with severe conditions. The implication is that payers might need to make some adjustment for their willingness to pay for treatment based on disease severity and *who* is getting the health gain;

- Non-health individual benefits such as the potential to return to work or study, increases in productivity, and reductions in burden of care for family members ('informal' care)[8]. These elements are likely to be important for gene therapies due to the offer of a cure which means that the individual is able to contribute to society in ways that may not have been possible before. The extent of these

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[8] These individual level effects are one just of three "wealth effects" identified by Garau et al. (2015). The authors shows health interventions not only reduce morbidity and mortality, but can also have a variety of positive economic effects through: Individual non-health effects (see above); Impacting economic growth at a macro level; Impacting the non-health public sector (for example, education, social care, and criminal justice). It is not obvious that these factors will apply in the case of gene therapy.

benefits will depend on the nature of the condition and the age of the population in question;

- Additional potential elements of value have been identified by Garrison et al. (2016). Of possible relevance to gene therapy are (i) indications of patients' willingness to become "risk loving" when facing end-of-life conditions (i.e. to prefer treatments which may have a lower average life expectancy but with a larger tail of patients living for much longer than on current therapy), and (ii) evidence of an "option value" to patients of being kept alive with less than ideal therapies (perhaps with substantial side effects) whilst research continues into therapies that may be curative.

Payer representatives at the ICER Policy Summit meeting commented that they believe that existing value frameworks broadly include the correct elements of value for assessment of gene therapies, although their application may need modifying (for example to consider the effect of different financing mechanisms). From a payer's perspective, information on wider elements of value (i.e. those beyond the health gain for the patient) is helpful to have but is unlikely to have a material influence on reimbursement decisions.

3.3. High production and R&D costs

The two gene therapies that have been marketed to date have been associated with high per patient prices. Glybera is priced at €1.1million for a course of treatment (Ylä-Herttuala, 2015). The price for Srimvelis agreed with the Italian Medicines Agency is €594,000 (Abou-El-Enein et al., 2016a), significantly less than Glybera, but still a high cost treatment. Given these experiences, and similar ones with conventional ultra-orphan therapies, we expect that high per patient prices will be the case for many gene therapies. Manufacturers argue that they face high per-patient development costs, driven by:

- The personalised nature of the medicines, meaning that manufacturing costs are likely to be higher; products cannot necessarily be prepared, tested, and manufactured in bulk as they would be with small or large molecule drugs;

- Higher costs for clinical delivery where changes in infrastructure are required;

- Small patient numbers, meaning that manufacturers have fewer potential patients from whom they are able to recover R&D costs.

The challenge for payers is that at these price levels it may be difficult to establish value for money at normal cost-per-QALY thresholds (or other similar decision rules). But it is not clear whether or not payers should therefore include consideration of R&D and manufacturing costs in their assessments of value and/or decisions on reimbursement in an implicit "cost plus" approach. A similar debate has arisen in the context of orphan drugs more generally. Some argue that the same value assessment or willingness to pay criteria should be used, with no special considerations given for small patient numbers or the attributes of the technology. Others have noted that without higher prices, and/or longer-term market exclusivity as is provided in Europe, these therapies will not be developed; incentives to promote innovation should be recognised as part of the problem requiring long-term solutions.

3.4. The NICE CAR T-cell review exercise

The National Institute for Health and Care Excellence (NICE) in the UK conducts "technology appraisals" (including an assessment of value) of new drugs and devices in order to inform national reimbursement decisions in England. NICE has recently undertaken a review to determine whether or not its existing evidence and value assessment frameworks are suitable for assessing the value of regenerative medicines, including gene therapies. See Box 3 for details.

Box 3: The NICE CAR T-cell review exercise

NICE was asked by the UK Government to undertake a review of its methods to explore whether or not existing appraisal processes are appropriate for assessing the value of regenerative medicines including gene therapies. To do this NICE conducted a 'mock appraisal' of a hypothetical regenerative medicine product CAR (chimeric antigen receptor) T-cell therapy for treating B-cell acute lymphoblastic leukaemia (NICE, 2016; Hettle et al., 2016).

A mock dataset was developed and used to calculate clinical and cost-effectiveness estimates of CAR T-cell therapy compared to current practice in the UK. The results were discussed by an expert panel made up of clinicians and others who had previously served on expert panels for previous (real) NICE appraisals.

In addition to the usual information presented to panels (evidence of clinical and cost-effectiveness), the review team also presented quantitative estimates of population health benefits and the consequences of decision uncertainty. They also explored various different payment mechanisms (such as a lifetime leasing method) and the effect that these would have on the quantitative estimates of the consequences of decision uncertainty and the incremental cost-effectiveness ratio (ICER). Note that the mock dataset and proposed price were constructed such that the estimates of cost-effectiveness were within the range of acceptability to NICE using its current assessment criteria, including end-of-life cost-effectiveness threshold of (approximately) £50,000 per QALY. This was done so that the panel focussed on the elements of evidence, uncertainty, and payment that would make the technology acceptable or not acceptable for reimbursement.

Points raises by the panel on evidence uncertainty included:

- The level of uncertainty in the evidence base caused significant concern, with single-arm trials and extrapolation from short term data to long term benefits. Exploration of this uncertainty was key to decision making;

- Guidance should be in place for manufacturers on how to account for uncertainty around trial results, given short term data and potential long term effects;

- Sources of potential bias and uncertainty will be important considerations within future appraisals; manufacturers should explain clearly how these have been addressed within their submission;

- The level of decision uncertainty seen in this mock appraisal may be greater than that which is accounted for in NICE's current methods guide;

- Quantitative estimates of population health benefits and the consequences of decision uncertainty provided important information for decision making;

- There may be issues around irrecoverable costs incurred by the health service, and that a clear 'exit strategy' would be important where uncertainty was high.

On the choice of pricing models, the study reported that:

- The various pricing scenarios had important effects on the decision ICER including outcomes-based agreements and a lifetime leasing model.

> - Innovative payment mechanisms could therefore be an important consideration within future appraisals. The panel noted that the lifetime leasing model would require further exploration by NICE and manufacturers in terms of logistics, costs and feasibility.
>
> The review team concluded that some modifications to the methods guide could be useful (Hettle et al., 2016). For example, they suggest that presenting the scale of decision uncertainty using population level health effects may be a helpful addition; issues of irrecoverable costs may need to be formally considered where upfront costs are expected to be high; the existence and possible impact of learning curves may also be an important issue for clinical and cost-effectiveness assessments. They also noted the importance of considering various different payment mechanisms.
>
> Source: Hettle et al. (2016); NICE (2016)

3.5. Pricing

Once the value of the treatment has been established, this could be considered to reflect the <u>maximum</u> price society might be prepared to pay for it. Value does not dictate the price we should *expect* to pay or *should* pay. There is a trade-off between rewarding the innovator with a price close to or equal to value (creating the maximum incentive for future innovation) and ensuring access to the treatments by pricing much lower, but covering manufacturer costs, including research and development costs. In most markets, competition means that the price is in practice below that associated with "value", but for many gene therapies there may be little or no competition. In the context of gene therapies, where large sums are involved, this becomes a societal issue, and this is why payers - on behalf of society - are questioning costs, commercial models, margins and returns. Solutions to these challenges must ensure fair returns from innovations to innovators, investors and society more widely.

3.6. Possible Solutions to the Value Assessment challenge

3.6.1. A Shared Value Framework

There are a number of value frameworks that have been proposed in the US, several combining descriptions of the elements of value with an algorithm for how the evidence for each of the elements of value should be evaluated. These value frameworks have been subject to review and critical comment (Neumann and Cohen, 2009; Westrich 2016). None of the frameworks has been developed to address the specific challenges we have set out above that may arise in valuing a gene therapy. There is a case for stakeholders to:

- Debate and seek consensus on the elements of value relevant to gene therapy;

- Identify relevant evidence to assess each element of value;

- Consider how the evidenced elements of value could be weighted in a decision making process to determine reimbursement policy and price.

Where budget impact is included in value frameworks or coverage decisions, it will be important to carefully consider the appropriate time horizon for these estimates. Typically payers consider short time horizons (often only 1-2 years) in line with their annual budgets, but this will not capture the true budget impact of these therapies as substantial savings are expected to be realised over the patient's lifetime. In order to

accurately assess the budget impact, payers will need to consider these longer term benefits.

3.6.2. Understanding how budget impact will be addressed

Once the potential net budget impact has been assessed there are three main options that can be explored:

(i) A direct adjustment to the calculation of value. This has been proposed in the ICER value framework, and also by health economists who have argued that, in the short run when budgets are fixed, the scale of budget impact has an increasing effect on technologies displaced, meriting a downward adjustment of willingness to pay;

(ii) It can be taken as a ceiling value, with a negotiation taking place on price, leading to discounts and/or some form of revenue caps. The outcome will reflect relative bargaining power which will in part depend on whether there are competing therapies. In theory, however, what is at stake is achieving an appropriate balance between a low price that increases coverage of the therapy to optimal levels (which economists call static efficiency) and having a price that reflects full value in order to incentivise future R&D (which economists call dynamic efficiency);

(iii) As a challenge for financing, looking at alternative payment and funding arrangements. Some of these – such as phased payment options – can help to address uncertainty about value, by linking payment to the continuing performance of the therapy. These mechanisms are discussed further in Chapter 4.

These are not mutually incompatible and payers may in practice combine elements of all three in different proportions. In the next section we discuss the challenge of affordability and in the following section we explore alternative financing options that have been put forwards.

4. AFFORDABILITY

Many of the evidence challenges for curative gene therapies are not too dissimilar to those faced by disease modifying therapies for chronic diseases: short term trials relying on surrogate markers; outcomes that may not be sustained over time; and the prospect of safety problems emerging. The real difference is budget impact (Towse, 2014). This has clearly been the case for curative therapies now in use in the US health care system for Hepatitis C virus (HCV). These drugs come at a high cost, yet due to the significant level of benefits offered, they have typically been considered to be cost-effective over the long term at traditional threshold levels. In practice, affordability concerns have led payers to aggressively seek discounts, helped by manufacturer competition in the therapy area, and to payer restrictions on patient eligibility.

Our interviewees commented that curative therapies present a new type of challenge. One conceptualised the problem as the contrast between paying a lump sum up front to buy long term health (much like buying a house), as opposed to renting health on a monthly basis through payments for a new dose of a chronic disease treatment (much

like renting an apartment)[9]. One way to think of meeting this challenge is to find routes to raise sufficient capital from third parties to fund these therapies upfront. But, to continue our analogy, who provides the mortgage and who meets the repayments?

Several interviewees were concerned that curative gene therapy generating additional costs from high priced treatments had the potential to push the US healthcare system to the breaking point. Indeed attendees at the ICER Policy Summit meeting raised concerns that there are existing affordability problems due to treatments that are already being funded, even before we consider adding additional high cost therapies.

Furthermore, whilst high cost treatments for very rare populations may be able to be absorbed in the short run, even here, the cumulative effect of having several of these come to market every year will be substantial. Attendees at the ICER Policy Summit meeting noted that multiple products are expected to reach the market, and even if each one is for a rare condition, this could still in aggregate amount to (say) 10% of the US population. Even if gene therapies are developed to treat only one in ten patients with a genetic condition – approximately 1% of the total population -- the cumulative budget impact at that price could rise to $3 trillion, as much as is currently spent on all healthcare in the US in a year (CMS, 2016). Of course, a genetic therapy will not be found for every rare condition, and the emergence of gene therapies will not snowball quickly enough over the next few years to approach this budget impact. And, in addition, some gene therapies may produce significant cost offsets by replacing expensive existing treatments. Nonetheless, Should gene therapies become available for more common diseases, the financing challenge may be insurmountable without either large increases in premiums or government funding of some sort.

Importantly, attendees at the ICER Policy Summit meeting also suggested that the challenges around affordability also affect our comfort with the available evidence. This is hardly surprising – it is human nature to require greater certainty in a decision of greater impact, and there are indications that payers around the world already behave in this way. It emphasises yet further the importance of satisfactory approaches to tackling the evidence challenges discussed earlier in this paper.

We consider solutions that have been proposed below.

4.1. Potential solutions to the affordability challenge

We have already noted that the affordability challenge is not unique to gene therapies and has arisen in other areas, with the most recent examples being the high cost cures for HCV. The advent of HCV cures and the potential for gene therapy to offer cures has stimulated a literature on to "how to pay for cures?" We look at methods that have been used and at those that have been proposed, noting the strengths and weaknesses of each approach where appropriate.

4.1.1. Discounts and revenue caps

These have been used to control spending on high cost treatments (as has been seen with treatments for HCV in the US and around the world). They are designed to reduce the initial price or to set a total budget restriction (at the patient level, at the product

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[9] Objections to this analogy were raised at the ICER Policy Summit meeting on the grounds that you can pick the type (and price) of house you buy, but you don't have same choice when it comes to healthcare, and also that you can resell your house but you can't resell your (improved) health state. In addition, gene therapies are not the only health care needs that patients will have.

level, or at the therapy class level), within the payers ability to pay. However, this type of mechanism will send signals to industry about the importance (or lack of importance) of gene therapies. If efforts to develop cures are not rewarded sufficiently, researchers may switch effort to incremental rather than breakthrough therapy. The choice of cap is also important. To date this has been rather ad hoc. Using the same caps across different therapy areas or types of treatment would send the signal that payers are indifferent between these, which may not be the case.

4.1.2. Targeting the highest value patient groups

One route long favoured by payers is to prioritise and target expensive therapies at those patient groups who are most at risk and/or who get the most health gain. Wider use can take place when follow-on therapy class competition reduces prices or when products come off-patent. But it is important to note that, because the trials supporting registration for gene therapies may be smaller than typical development programs, it may be more difficult to perform meaningful subgroup analyses to assist in identifying these potential high-value groups with high certainty. Even if high-value subgroups can be identified, however, problems remain: manufacturers may conclude that innovation is not valued, and patients are likely to object to being denied access to treatments of value to them. In the case of many gene therapies, the health burden on the patient is likely to be immediate, making the option of delaying therapy until later, more serious, stages of the disease are reached, a less viable one.

4.1.3. Risk-sharing agreements and Outcomes-based payments

Agreements can be formed which offer money back guarantees if the expected outcomes are not achieved. However, this will require payers to fund the up-front costs of the therapy. In the case of the HCV drugs, agreements were established in Spain and France (amongst other countries) such that health care payers would only pay for the HCV drugs for cured patients. Another approach would be to pay the manufacturer per unit of health delivered, for example, per year that a patient remains free of disease. Such agreements mean that the risk of non-performance is shared between the health care payer and the manufacturer, thereby mitigating payer concerns over uncertainty and spreading budget impact over the duration of the cure.

The challenges of reaching and managing these agreements have been well documented (Garrison et al., 2013, Garrison et al. 2015). The biggest obstacle is the difficulty and cost of collecting evidence on outcomes. However, the regulatory requirement to track patients receiving gene therapy is likely to make this much easier to organise. The second biggest obstacle is agreeing on contractual terms – what constitutes "success" and "failure" and what will be paid for or not paid for. The inherent nature of a cure may make this easier to agree, but careful delineation of how to measure success will still be needed. Risk-sharing agreements and outcomes-based payments were generally perceived favourably by attendees at the ICER Policy Summit meeting.

4.1.4. Reinsurance

Reinsurance is where insurers seek insurance of their own to cover catastrophic pay-outs. Tapestry (2016) explains that payments could be annuitized and linked to outcomes, but note the caveat that the requirements for reinsurance can be very specific, and that this only spreads the risk, it does not solve the long term sustainability issues. In addition, attendees at the ICER Policy Summit meeting suggested that some reinsurers are already looking to exclude gene therapies from reinsurance policies.

4.1.5. Amortization

A recent OHE / CMPT literature review (Britton et al., forthcoming) found that the most commonly proposed solution to the affordability challenge of curative therapy is to spread high upfront costs over a longer period of time, i.e. the manufacturer is paid in installments. Gottlieb and Carino (2014) argue that mechanisms such as these help to align the cost of the cure with its long-term economic benefits, thereby allowing payers to fund the treatments whilst balancing their budgets within a single year. They note that such agreements are already common with medical equipment, with which payers often spread the cost over the time horizon that the equipment will be used.

Amortization can be considered to be similar to mortgages or loans (credit market solutions), whereby the government (or another third party) issues loans to payers to fund the upfront bill, and then the health care payer pays instalments over time, in line with realization of the benefits (Philipson and von Eschenbach, 2014). An example of this type of mechanism can be seen in Spain, where the national government announced low-interest loans for regional payers to fund high cost HCV therapies (APMHealthEurope, 2015). We discuss various different approaches to amortization in the following sections.

4.1.5.1. Third-party amortization

In some instances, amortization could be combined with a third party absorbing the risk. For example, Montazerhodjat et al., (2016) propose that Hedge Funds are well placed to provide loans for high cost therapies. On the assumption that they bear the risk, i.e. the payer stops repayments if the patient dies or the therapy stops working, they can make the necessary actuarial risk calculation and build in a risk related premium into the interest rate included in the repayment schedule. The higher the risk, i.e. the higher chance that the patient dies or stops receiving benefit, the higher the interest rate that would be required. Such transactions are common in many industries outside of healthcare. This scenario would require the outstanding balance to move with the patient, i.e. it would need to become part of a patients pre-existing condition, which would require a small change to existing legislation (the pre-existing conditions clause in the Affordable Care Act) to extend to pre-existing financial "conditions".

Amortization models were discussed in depth at the ICER Policy Summit meeting. Attendees noted the advantages described above, but also raised several concerns including: (i) that such models could have the unwanted effect of increasing prices; (ii) these models do not 'solve' the problem, but push it into the future (and possibly exacerbate it if (i) above pertains); (iii) they add another party who will take a cut (thereby increasing the total cost even further); and (iv) the condition in question is only *one* part of a person's overall health – the patient may still have other conditions to contend with, raising the per-patient cost even further. These drawbacks must be considered alongside the benefits of amortization models.

4.1.5.2. Manufacturer managed financing

This is an approach to amortization in which payers (either private insurance firms or government) pay the manufacturer for the therapy over a number of years. This would continue until the debt is repaid, the payer defaults, or the benefit from the drug ends, whichever occurs first (there is thus an outcomes-based payment element). By amortising the payment over a number of years, the payment for a potential cure becomes like payment for an ongoing treatment.

However, payers need to make sure they won't be disadvantaged if the patient leaves the plan (therefore they pay the bill but don't get the benefits). One way to deal with this would be for the outstanding balance to leave the plan with the patient and be taken over by the new health plan.

It is important to understand the key issue here which is how the manufacturer absorbs the risk of the therapy not working. The manufacturer can (i) loan the payer the money to pay upfront for the drug and receive cash upfront, with a pay back on the loan, as long as the drug works and the patient lives; (ii) assume risk but not get an upfront payment in full (matched by a loan) in a risk sharing outcomes based agreement as we discuss above; or (iii) see a third party taking on the risk by providing the payer with a loan, but almost certainly the premium interest rate demanded by the third party will be passed back to the manufacturer by the payer who will insist on a lower price for the therapy.

4.1.5.3. Consumer mortgage

In this scenario patients are able to take out loans themselves to finance the cost of the therapy. Costs would be amortised over time, repayable with interest. Tapestry (2016) points out the caveat that this means the patient is "double paying" as they have a loan plus their healthcare premium. Montazerhodjat et al. (2016) suggest that whilst patients taking on substantial debts in return for healthcare is not equitable, it is preferable to them not having access at all.

However, not all patients would be able to afford these treatments and so get access, even if loans were to be available. Whilst an $84,000 treatment might require repayments of $800 per month, a sum potentially affordable to some households, a $1million treatment could easily require payments of more than $10,000 per month. Multiple attendees at the Summit viewed consumer mortgages as a poor option for amortizing payment.

4.1.5.4. Government Loans funded by Bond Issues

It is worth noting that these various payment mechanisms will not just be needed by private insurance companies but also government schemes. Interviewees commented that many patients who will receive gene therapies will be covered by Medicare/Medicaid (i.e. this is the "high-risk" pool) so there will also need to be a government response to gene therapies. This could be particularly relevant for diseases that have larger populations (and therefore greater total budget impact) and that are particularly amenable to gene therapies such as sickle cell. One interviewee also commented that high cost issues of life and death are political issues; they are unlikely to be handled sufficiently well by the private sector and are thus likely to become the responsibility of governments.

Thus there are two reasons for government to get involved – its own patients and as a back stop insurer to the population as a whole. By issuing bonds for private payers to buy, it could set repayment terms that took account of – for example – continued achievement of outcomes, the age of the patient (i.e. payments stopped if the patient became eligible for Medicare), or the numbers of patients being handled by a particular insurer, to reduce risk exposure.

We summarise the thinking of the various mechanisms in Table 1 on the following page.

Table 1 Summary of Mechanisms to Handle Affordability

	Outcomes-based Agreements	Reinsurance	Consumer Loan	Third-Party Financing	Manufacturer Managed Financing	Government Financing
Features	Payment for results	Payer purchases reinsurance to reduce financial risk of having to pay extremely high costs for individual patients	Patient obtains a personal loan to enable upfront payment for the treatment outside of regular health insurance and repays the loan in periodic instalments. Payments stop if the patient dies or the treatment fails	Payer receives a loan from a financial institution to enable upfront payment to the manufacturer, with loan repayment in periodic instalments. Payments stop if the patient dies or the treatment fails	Manufacturer offers an instalment payment option allowing the payer to pay the cost of treatment in periodic instalments. Payments stop if the patient dies or the treatment fails	Payer receives a loan from the government to enable upfront payment and repays the loan in annual instalments. Payments stop if the patient dies or the treatment fails
Strengths	Addresses uncertainty about clinical benefits Can be combined with amortization methods	Relieves short term budget pressure	Addresses uncertainty about clinical benefits Moves upfront payment to annual fee for performance	Addresses payer uncertainty about clinical benefits Moves upfront payment to annual fee for performance	Addresses payer uncertainty about clinical benefits Moves upfront payment to annual fee for performance	Addresses payer uncertainty about clinical benefits Moves upfront payment to annual fee for performance
Weaknesses	Difficulty of measuring outcomes Difficulty of agreeing criteria for "success"	May be substantial premiums to pay Spreads the risk, but does not address long term sustainability	Untested mechanism Many people unable to afford payments Patient is taking on financing costs unless manufacturer offers a lower price	Untested mechanism Need to address patient switch of health insurer Payer is taking on financing costs	Untested mechanism Needs to address patient switch of health insurer Negotiation of responsibility for financing costs	Untested mechanism Need to address patient switch of health insurer Payer is taking on financing costs

Additional considerations

All of these approaches come with disadvantages. Touchot and Flume (2015) argue that annualization and risk sharing are not acceptable to payers, stating that they are "theoretically attractive but impossible to implement in most current healthcare systems". Their claims are based on interviews with 29 payers in the US and Europe, which reveal that whilst payers like the idea of annuities, they favour lump sum payments "in the real world". This is because transferring financial contracts between plans is not considered to be possible and risk sharing is difficult to implement (definition of sustained response may vary; patients may be lost to follow up; adjunctive therapies may prolong efficacy).

Further concerns were raised at the ICER Policy Summit that these schemes don't address the fundamental issue of long-term affordability of these treatments and the sustainability of the system. Rather, they push costs into the future. Furthermore, they could lead to price inflation.

5. POLICY RECOMMENDATIONS

Following discussion of this topic at the Policy Summit, the following policy recommendations reflect a combination of analysis and opinion of multiple stakeholders. Greater explanation of these recommendations is provided in the body of the report.

5.1. Recommendations for Manufacturers

1. *Seek dialogue with payers and regulators as early as possible in the development of new gene therapies in line with recent FDA guidance facilitating dialogue between sponsors and payers on investigational product information. Topics of discussion should include:*

    a. *ways to include or create meaningful patient-centered outcomes or validated surrogate outcomes in developmental trials;*

    b. *options for making the registration studies as robust as possible, especially if RCTs will not be performed;*

    c. *options for partnership on post-approval studies to reduce residual uncertainty about the safety and effectiveness of new therapies (particularly important in the context of possible adaptive licensing);*

    d. *methods of determining patient eligibility that can be feasibly translated into coverage criteria;*

    e. *criteria for designation of potential centers of excellence for the delivery of the therapy;*

    f. *size of potential patient population;*

    g. *the role envisioned in therapy within the care pathway;*

    h. *the elements of value that patients, clinicians, manufacturers, and payers can agree should be considered in assessing value and judging what price fairly reflects the added value of the therapy.*

There appeared to be general agreement at the ICER Policy Summit meeting that payers, manufacturers and other key stakeholders all need to consider changes to

current approaches if significant numbers of these therapies are to reach patients. For example, legislators need to understand the practical limits around evidence generation and create the right structure to promote innovation; manufactures need to understand financial constraints faced by payers, and payers need to be willing to explore new approaches. The first pathways that are explored are unlikely to be perfect, but it is important that all parties are willing to try something new. In order for new approaches to be found, stakeholders will need to engage in conversation.

The advent of Spark Therapeutics' investigational voretigene neparvovec should necessitate a broader stakeholder discussion of systemic solutions. It is thus important that all stakeholders engage quickly and constructively, and that all parties consider the broad long term consequences of possible approaches.

2. *Whenever possible, seek ways to perform at least one RCT comparing the new therapy to best any existing treatment. Consider the use of adaptive trial designs, weighted randomization, and cross-over to meet ethical requirements. In cases where RCTs are not possible, work with payers and regulators to establish the most appropriate feasible method of clinical evidence generation.*

Section 2 of this report explains why the typical means of and standards for generating clinical evidence may be problematic for many gene therapies. Yet, evidence is still essential for licencing and reimbursement decisions. RCTs remain the gold standard for evidence collection and should be conducted when possible. However, in some cases, the FDA and manufacturers may need to consider alternative means, outside of traditional trial designs, that allow the best use to be made of the available populations. Payers may be needed as contributors to registries for continued monitoring of safety and long-term outcomes data.

In the case of Spark Therapeutics' voretigene neparvovec, the manufacturer worked with the FDA to develop a new clinical outcome measure to assess the effectiveness of the treatment. They also used a 2:1 stratification scheme with the control group crossing over to active treatment after 1 year as a way to maintain clinical equipoise. This approach allowed full use to be made of the available population. However, because ethical considerations required switching to active treatment of the control group after one year, long term comparison of the two groups is not possible.

The pros and cons of new study designs and novel outcome measures to ensure robust evidence generation should be carefully considered by all stakeholders.

3. *Work with clinicians, patient groups, regulators, and payers to establish robust Patient Registries to facilitate collection of real world evidence before and after regulatory approval.*

Collection of real world evidence will be useful in determining the long term effectiveness of gene therapies. This could be key to establishing the durability of effect and identifying any unintended consequences over time. Registries devoted to evidence collection and monitoring could be an efficient way to approach this. Such registries may need to collect data to address payer's concerns as well as those of the FDA.

Such post-launch data collection may also be useful for (or a requirement of) novel approaches to financing, or more specifically for outcomes based payments.

4. *Be prepared to address concerns about high prices by presenting clear information and evidence on how the price is related to the costs of development and/or stakeholders' perceptions of a therapy's value.*

Payer representatives at the Policy Summit meeting raised questions about how much it costs to develop gene therapies, and suggested that more transparency and visibility would help both sides to find mutual ground. There are two parts to this. The first is about what is driving the high costs, and the true cost of research and development and production. The second part is about the value the technology brings and how this is translated into a price. For example, is there an assumption about whether QALYs have any role in judging the value (and therefore the value-based price_ for gene therapy? If QALYs have a role, should any QALY threshold vary systematically with the size of the population or the severity of the disease? More transparency will facilitate the discussions recommended in suggestion 1 above.

5. *Where appropriate, collaborate with payers and health technology assessment groups on value assessment reports. Providing input on the scoping parameters of assessments is helpful, and special consideration should be given to sharing patient-level clinical and economic data when possible.*

Little is known about the elements of value that are specifically relevant to gene therapies. For example, does a "curative" effect, or an outcome that halts the progression of a serious disease, lead to higher value for these therapies? Should the burden on caregivers or on the disability system be formally considered? And should we be willing to pay higher prices to reward innovation, over and above the patient benefits delivered?

Research and discussion is needed to identify the key elements of benefit associated with genetic therapies and the value society attaches to these, and ways in which they can be assessed and combined to determine how much payers should really be willing to pay to provide fair access to gene therapies for patients in their covered population. Manufacturers should work with payers to investigate these questions and develop appropriate value frameworks.

6. *For gene therapies whose characteristics make them good candidates for possible amortized payment options, be prepared to come to payers with specific manufacturer-financed mechanism for instalment payments combined with an outcomes- based agreements.*

There appeared to be broad agreement amongst payers that the responsibility should rest with manufacturers to instigate amortization arrangements. The manufacturer is the party wishing to sell the product, and may also be in the best position to fully understand the risks associated with the product and whether it is appropriate for them to bear the risk themselves, or whether to pass this to a third party, recognising that if they take the latter approach the third party will require payment.

However, concerns were raised that amortization would result in increased overall prices for already expensive treatments. More work is required to establish the feasibility and usefulness of various arrangements – this should be in the form of multi-stakeholder dialogue and pilot programmes.

If amortization is to be carried forward, this will also require a change in legislation, to allow debt to move with the patient when they move plans. This would involve amending ERISA, which would require an act of Congress.

It was suggested that there may be a set of circumstances (a 'sweet spot') in which the use of amortization could be most useful. This would be when the price of the treatment has been based on an agreed approach to assessing value, there is a population group of a size that merits incurring the transaction costs of such an arrangement, the therapy is curative, and there is a high certainty of durability of effect (see Figure 2). This is based on the idea that such treatments have long enduring high value to justify their high price, thus making them suitable candidates for long term payments.

Figure 2: Characteristics of gene therapies that merit consideration for amortized payment strategies.
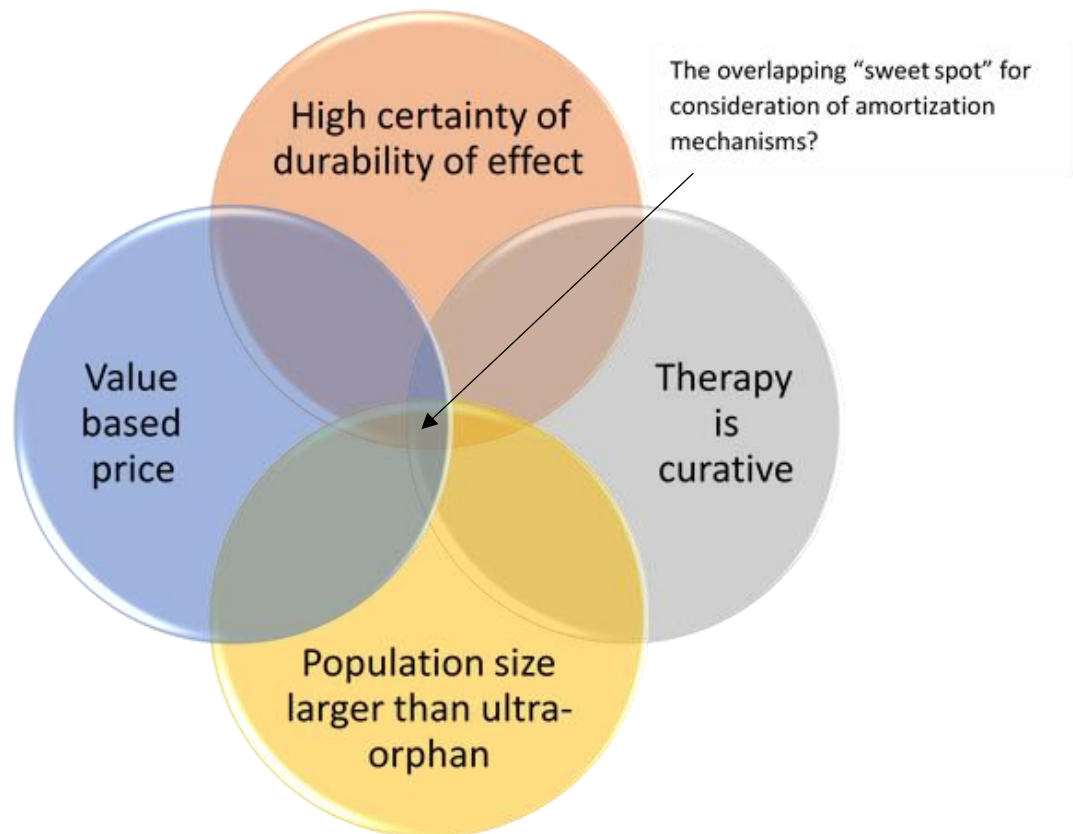
5.2. Recommendations for Payers

1. *Develop internal sophistication in knowledge about gene therapies, including understanding of the basic scientific techniques and of the usual approach taken by the FDA in assessing the safety and effectiveness of these agents*.

Such internal knowledge generation will support productive discussions and collaborations with manufacturers. It will also enable payers to understand the challenges associated with the development of these therapies and contribute to the development of practical solutions.

2. *Engage in early dialog with manufacturers of promising new gene therapies. The topics of mutual interest will include those listed above for manufacturers:*

   a. *ways to include or create meaningful patient-centered outcomes or validated surrogate outcomes in developmental trials;*

    b. *options for making the registration studies as robust as possible, especially if RCTs will not be performed;*

    c. *methods of determining patient eligibility that can be feasibly translated into coverage criteria;*

    d. *criteria for designation of potential centers of excellence for the delivery of the therapy;*

    e. *size of potential patient population;*

    f. *the role envisioned in therapy within the care pathway;*

    g. *the elements of value that patients, clinicians, manufacturers, and payers can agree should be considered in assessing value and judging what price fairly reflects the added value of the therapy*.

In order for agreements to be made about appropriate means and standards for evidence generation or new outcomes to be developed, early dialogue could be a useful tool. We set out above the effect of Spark Therapeutics' engagement in early dialogue with FDA.

Early dialogue involving payers as well as regulators allows manufacturers to ensure that they are developing the treatments in line with reimbursement (as well as regulatory) decision requirements. It also gives payers a chance to better understand the new therapies, and it was noted that manufacturers cannot easily offer information or engage in dialogue with payers outside of this type of arrangement, as they are at risk of being perceived to be promoting their drug[10]. The new draft guidances from FDA, which came after 21st Century Cures was passed late last year, look to make pre-approval dossiers and exchange an acceptable practice. Finally, early dialogue also provides FDA and payers with an opportunity to input into the way a treatment is developed.

The use of centres of excellence would mean that devoted experts would be responsible for the delivery of these highly technical procedures within dedicated facilities. For example, Spark Therapeutics is proposing to limit administration of voretigene neparvovec to centers of excellence that meet strict capabilities and training requirements to support appropriate patient care. Such an arrangement would promote quality assurance and improvement in the delivery of treatment and the follow-up of patients, and promote better and cheaper collection of data for registries. Centres of excellence would also allow registries to be established more economically and reliably as they would mean that a smaller number of centres see more patients each. Finally, delivery gene therapies through centers of excellence would make sure that only highly-trained specialists determine which patients should receive the treatments. Only appropriate patients would get the treatment. And, through payment structures designed for these centers, steep provider fees on top of treatment costs may be avoided, helping to manage overall costs.

    3. *Work with clinicians, patient groups, regulators, and manufacturers to establish robust Patient Registries to facilitate collection of real world evidence following*

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[10] It was noted that AMCP (Academy of Managed Care Pharmacy) executive committee is working on regulations to help guide early discussions between payers and manufacturers

regulatory approval. Individual insurer in-house registries could be pooled with those of other insurers and/or with manufacturers.

Payers will have an interest in collecting real world evidence to help determine the long term effectiveness of gene therapies. Registries devoted to evidence collection and monitoring could be an efficient way to approach this. Such post-launch data collection may also be useful for (or a requirement of) novel approaches to financing, or more specifically for outcomes based payments.

4. *Develop categorizations of different types of gene therapies based on their method of delivery, mechanism of action, and other key characteristics so that coverage policies can be clearly tailored to meet distinctive therapies.*

A key theme that arose from the meeting was this idea of categorising (or 'bucketing') gene therapies. Attendees noted that not all gene therapies are the same: some types use gene augmentation which boosts production or adds in a functional copy of a gene, whilst others alter the patient's genetic makeup by editing out a genetic mutation; some gene therapies will emerge in areas where there are already existing treatments, whereas others will emerge where there are none; some gene therapies will be curative, but not all of them will be; some gene therapies will address rare diseases, others more common conditions. It was suggested that treating all of these the same may be inappropriate, whilst concluding that all are different and must have their own specific pathway is unlikely to be appropriate or efficient. Some system of categorization that enables a balance between allowing for the differences between gene therapies, whilst grouping them to a level that enables practical steps to be taken for each group, would be useful.

Stakeholders should also be aware that the nature of gene therapies may change over time – the gene therapies we see in the next five years are likely to be different from those we see in 10 years. We need to consider that some categories may emerge before others and we may need to think about different solutions over different timelines.

5. *Work with plan sponsors to familiarise them with the challenges in this area and to explore options for coverage that will meet their needs for value and affordability while creating a mechanism to help patients gain access to effective new therapies.*

6. *Collaborate with manufacturers to explore outcomes-based agreements. Outcomes-based agreements can be combined with different potential methods of amortized payments when health benefits are expected over a long time horizon.*

There was broad agreement at the meeting that outcomes based payments and risk sharing mechanisms that reward effective treatment represent a sensible way forward. However, these types or arrangements are dependent on the feasibility of collecting data on the long term effect of the treatment. Outcomes based payments help to increase the overall value of the treatment to payers by reducing costs for those cases where the treatment is not effective. The manufacturer also benefits since they are able to use the outcomes data generated to demonstrate greater effectiveness amongst those who do benefit from the therapy in the long term.

Overall, these recommendations have been designed to be specific and actionable. They should be used to build upon ongoing dialogue between manufacturers and payers about the challenges of gene therapies and the possible solutions. Once stakeholders are communicating effectively, the recommendations above can be used to develop pilot

programmes and overcome some of the inevitable inertia in the system. Useful topics to cover as part of these broader conversations include categorization of gene therapies into different groups; elements of value that are specifically relevant for gene therapies and how these can be combined within a value framework; approaches to amortization; types of evidence generation.

In terms of future research, little is known about society's willingness to pay for gene therapies. High prices might imply that society places a high value on these treatments, but we do not know how society values all the various benefits that the treatments might offer. And even if high prices are justified by the benefits offered to patients, to what extent is society willing to pay for certain members of the population to receive such large payments for their treatment (given that these high cost therapies are likely to increase the cost of health plans for everyone)?

6. CONCLUSION

Gene therapies represent an exciting opportunity, but also pose great challenges, with concerns being raised that these therapies could bankrupt the health system. The 2016 ICER Policy Summit set out to explore the issues posed by, and faced by, the emergence of gene therapies within the US healthcare system. Attendees at the meeting discussed what constitutes a gene therapy, aspects of gene therapy that complicate its evaluation and payment within existing paradigms, challenges specific to evidence generation, assessing value and budget impact and affordability, and finally options for taking these issues forwards.

6.1. Evidence generation

Conducting RCTs can be problematic for developers of gene therapies due to small populations and a lack of a clear care pathway (or existing treatment) in many of the relevant conditions. Invasive methods of administration may also require sham operations, often deemed unethical, in order to conduct blinded RCTs. In addition, trials are short, typically limited to a few years at most, and thus do not provide long term data. Attendees at the ICER Policy Summit discussed these issues and agreed that post launch collection of data, use of early dialogue, and a flexible approach to evidence generation (i.e. through quasi-experimental or adaptive trial designs) could be beneficial in overcoming these challenges.

6.2. Value assessment and budget impact

The challenges around evidence generation lead to challenges in assessing value. In addition, there may be wider elements (beyond health gains to the patient) of value that are of particular relevance for gene therapies that are not picked up in typical value assessments. High costs can mean it is difficult to establish value at conventional thresholds, whilst the curative element of these therapies may mean that they are truly valued more highly by society than treatments that over similar total health gains over many years. Attendees at the ICER Policy Summit deliberated these challenges and recommended that research is conducted into society's true willingness to pay for curative therapies, and into the elements of value that should be captured within the assessment. Attendees felt that delivery of gene therapies through centres of excellence could increase their value, by increasing the effectiveness of the treatment and reducing costs.

6.3. Affordability

Finally, arguably the biggest challenge is that of affordability. Indeed concerns were raised that curative gene therapies have the potential to push the US healthcare system to breaking point. Whilst costs for very rare populations may be absorbed in the short run, the cumulative effect of having several of these come to market could be substantial. Many attendees at the ICER Policy Summit meeting felt that more transparency around pricing is required; stakeholders should explore financing strategies through pilot programmes; and outcomes based payments should be utilised if ongoing data collection is feasible. It was felt that more work is required to establish the most appropriate mechanism for amortization schedules.

Overall, it seems that whilst none of these issues may be unique to gene therapy, the unique problem is that these treatments are likely to face a higher concentration of these problems. In order to overcome the challenges stakeholders need to communicate, and there needs to be movement on all sides of the debate if patients are to receive access to these therapies. The first pathways that are explored are unlikely to be perfect, but will still represent progress. Gene therapies will arrive imminently, and it is time to prepare a clear roadmap for evidence generation, assessment, pricing, and payment, that will allow current and future patients to benefit from these innovations within an affordable, sustainable framework.

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8. APPENDIX 1: THE PIPELINE FOR GENETIC THERAPIES

A recent report from Pharmaprojects (Boliter, 2016) provides a comprehensive summary of the pipeline for genetic therapies, and thus sheds some light on how many gene therapies are likely to enter the US health care market in the coming years. Figure 3 shows how the number of gene therapies in active development has increased significantly in the past couple of years to be higher than ever. Boliter suggests that recent successes are linked to advances in understanding the vector to use to carry the therapy, a suggestion that was echoed by one of our expert interviewees.

**Figure 3: Number of gene therapies in active development**
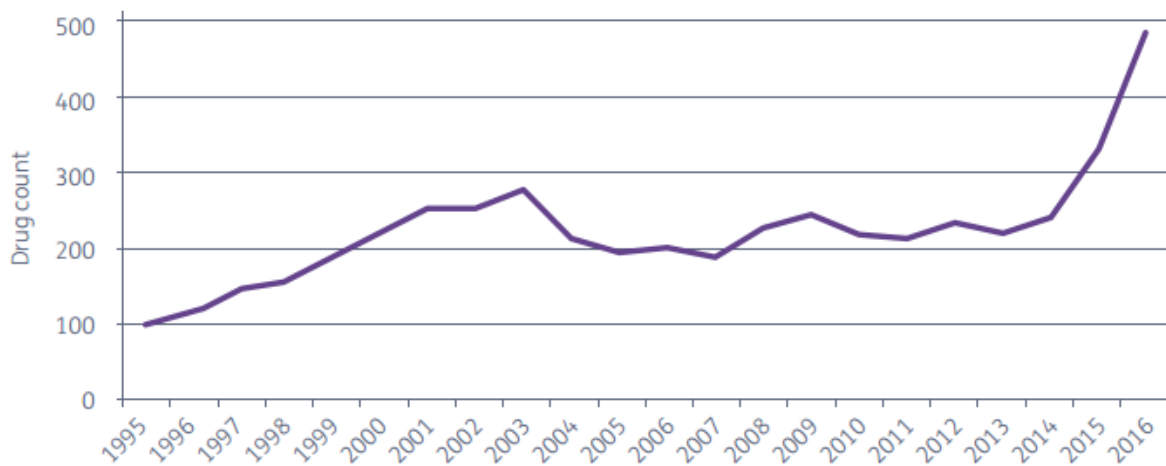
Source: Pharmaprojects, 2016

This growth is supported by FDA evidence showing the number of applications for investigational new drugs (IND) and investigational device exceptions (IDE) relating to cellular and gene therapies has steadily increased since 2010 (Figure 4).

Figure 4: Annual IND and IDE submissions

Yearly New IND and IDE Submissions to OCTGT

www.fda.gov
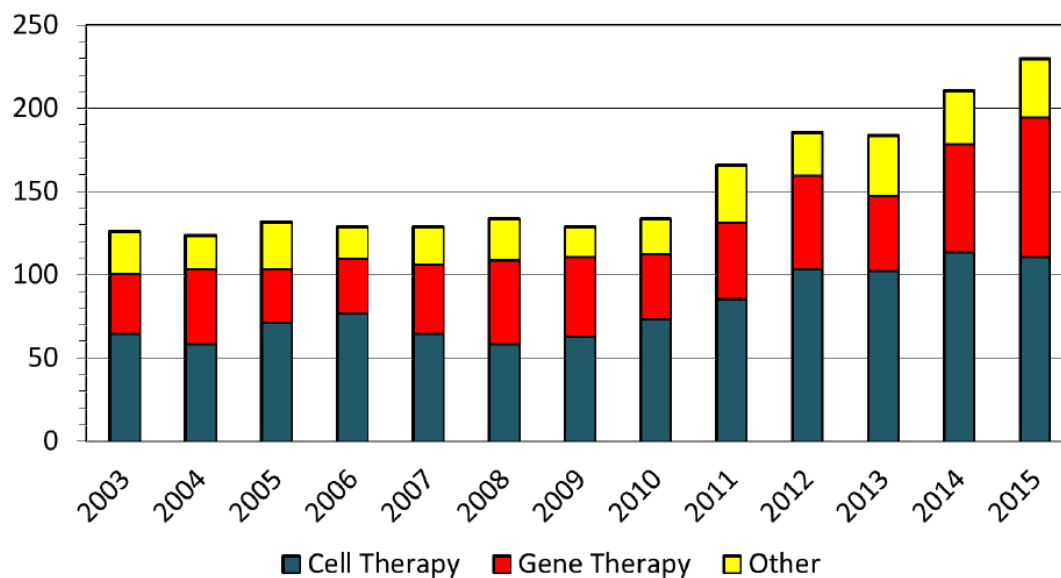
Source: Witten, 2016.

501 gene therapy compounds are currently classed as being currently in "active development": 6 of these have already been launched[11]; 2 are around the registration phase; 23 are in phase III development; 88 in phase II and 66 in phase I. The remaining 316 are in preclinical stages, and the majority of these will not progress further. An additional 977 are in "inactive" development, which means they have been suspended, discontinued, or no developments have been reported.

The report focuses on non-cancer gene therapy developments, highlighting nine different therapies which have progressed to phase III development: CardioNovo for Angina (Taxus Cardium Pharmaceuticals); Collategene for Peripheral vascular disease, Buerger's syndrome, Ischaemia and Atherosclerosis (AnGes MG); LentiGlobin for Thalassaemia (Bluebird Bio); Lenti-D for Adrenoleukodystrophy (Bluebird Bio); VM-202 for Neuropathy (Reyon Pharmaceutical); Invossa for Arthritis (TissueGene); GS-010 for Leber's hereditary optic neuropathy (Genethon); voretigene neparvovec, being studied for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy (Spark Therapeutics); ADA-lentiviral gene therapy for Adenosine deaminase deficiency (Orchard Therapeutics). There are also up to 14 cancer products in phase III development to make up the total of 23 products in active phase III development.

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[11] The report records one of these launches (Imlygic, Amgen) being in the US in 2015. Having consulted with our expert interviewees we do not consider this to be a 'typical' gene therapy; whilst it does include a genetic element, it is more appropriately characterised as a cancer immunotherapy. We have therefore not included it in our discussions of regulated gene therapies.

Hay et al. (2014) calculate 'phase success rates'[12] across 835 drug developers using data on phase transitions for the period 2003 – 2011 (note that these are success rates for drug development and are not specific to gene therapies - as discussed in section 2 gene therapies are likely to be subject to additional challenges). They indicate a success rate of 60.1% across all therapy areas at phase III, and a success rate of 54.7% for oncology drugs, which is the therapy area with the lowest success rates across all categories that they calculate. Assuming that these estimates can be used as an upper bound for the success rate for gene therapies at phase III, we can expect up to 12-14 of the gene therapies that are current in active phase III development (around 5-6 non-cancer therapies and 7-8 cancer therapies) to progress to submitting a new license application in the next couple of years.

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[12] The success probability is calculated as the number of drugs that are successful in moving to the next phase (i.e. from phase III to submitting a new drug application) divided by the total number of drugs in phase III.