The affordability hurdle for gene therapies

The viewpoint of US payers

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Introduction

Advanced therapy medicinal products – cell and gene therapies – offer tremendous hope for patients either by actually curing serious diseases or by alleviating suffering. However, gene therapies in particular come at a staggering cost to the healthcare system. Until now, US payers have absorbed and managed the cost of ultra-expensive therapies, but how long can they continue to do so?

The structure of the US payer system (distinct from single-payer systems elsewhere in the world) creates unique pressures on payers and will demand new solutions to support access. With a bolus of new gene therapies expected to hit the market in the next few years, the time is ripe to understand the payer perspective and plan for ways to work with payers to find solutions.

ICON conducted in-depth interviews with a cross-section of US payers to understand how payers perceive the value of advanced therapies, to assess their approach to determining coverage, and to identify solutions for the challenges they face specific to cell and gene therapies. This whitepaper summarizes the findings of this primary research and highlights our recommendations for the biopharmaceutical industry.

The basics

Cell and gene therapies are related forms of advanced treatment that have the potential to prevent or cure diseases by alleviating the underlying cause, although they use different approaches.

Cell therapy restores or alters certain sets of cells or uses cells to carry therapy systemically. (Friedman T, "A brief history of gene therapy," Nat Genet. 1992; e: 93-98) Cells are cultivated or modified outside of the body and are then re-injected into the body. The source can either be the patient (autologous cells) or a donor (allogeneic cells).

Gene therapy replaces, activates, or introduces genes into cells. (American Society of Gene & Cell Therapy. https://www.asgct.org/education/different-approaches)

The EU refers to these therapies as Advanced Therapy Medicinal Products (ATMP); for our purposes, we will refer to them simply as cell and gene therapies.

The cell and gene therapy marketplace: Poised for explosive growth

Advanced treatments such as cell and gene therapies have ushered in a new era of treatment for many devastating diseases, often offering the hope of a cure. At the time of this paper there are at least nine approved gene therapies in the US. **Figure 1** is a list of FDA approved gene therapies.

The field is expanding rapidly, as evidenced by the number of clinical trials in progress. Currently, there are at least 372 advanced therapy products in clinical development, with over half in Phase 2.[i]

The impact on the healthcare budget – even in the foreseeable future – will be immense. Just 11 of these products nearing marketing approval will cost the US healthcare system a staggering $15bn to $45bn by the end of 2024.[ii]

An important aspect of the coming tsunami of advanced therapies is that many of the products are being developed for more prevalent conditions than has been the case to date. Healthcare budgets have been able to absorb the cost of these therapies targeting rare diseases, but their ability to do so will be strained when products are available for more prevalent diseases such as hemophilia, for instance. In the case of hemophilia, multiple gene therapy products are in development, and it is likely that competitive forces will help drive prices down. Where only one product is marketed, though, there are very few mechanisms to constrain prices. Five of the nine FDA approved gene therapy products are CAR-T therapies (Kymriah, Yescarta, Tecartus, Abecma and Breyanzi) across a range of indications. With more CAR-T therapies in development, it will be interesting to see how the pricing also develops for this category.

What is CAR T-cell therapy?

Chimeric antigen receptor (CAR) T-cell therapy is a way to get immune cells called T cells (a type of white blood cell) to fight cancer by changing them in the lab so they can find and destroy cancer cells. CAR T-cell therapy is a type of cell-based gene therapy because it involves altering the genes inside T cells to help them attack the cancer. This type of treatment can be very helpful in treating some types of cancer, even when other treatments are no longer working.

Figure 1: Example gene therapy products marketed in US

Product	Approval	Product Type	Indication	Current treatment
Kymriah	US: May 2018 EU: Aug 2018	Ex vivo gene therapy Cell based CAR-T	Relapsed / refractory DLBCL and ALL	Salvage chemotherapy
Luxturna	US: Dec 2017 EU: Nov 2018	Gene therapy	Inherited retinal dystrophy (IRP) Vision loss due to RPE65 genetic mutations	Best supportive care
Zynteglo	US: N/A* EU: May 2019	Gene therapy	Transfusion dependent beta thalassemia	Lifetime transfusions with iron chelation therapy
Zolgensma	US: May 2019 EU: May 2020	Gene therapy	SMA type 1 or up to 3 copies of SMN2	- Best supportive care - Spinraza (anti-sense nucleotide)

* BLA in process

Payers are bracing for impact

It is advisable for sponsors of cell and gene therapies to understand the difficulties that an influx of new products will pose for US payers; ultimately, what keeps payers up at night will cause business challenges for life sciences companies. Many of the issues facing payers are inextricably linked to the unique characteristics of the US marketplace. (See Sidebar: The Idiosyncratic US Market) Their pain, if not exactly shared, must be acknowledged and addressed to the extent possible, since payers will find ways to alleviate it by controlling access, and some of those ways may be counter to manufacturers' goals.

Affordability is a key issue.

The currently marketed gene therapy treatments range in cost from $373k to $2.15m for a one-time treatment, and payers will not be able to sustain coverage for products indicated for more prevalent diseases if their cost is on the higher end of the spectrum. The economics will require new payment mechanisms.

The benefits may not accrue to the payer.

Insureds move between commercial insurers, meaning there is a risk to the payer that they fund a gene therapy without seeing the long-term benefit if or when the patient moves. This makes outcomes harder to track and limits the ability to use outcomes-based contracting or phased payments. It could also mean that a new insurer would be reluctant to take on a treated patient whose treatment will be paid in several future installments.

The cost offset is not a given.

In some therapeutic areas (such as hemophilia), a one-time gene therapy replaces costly life-long "factor" therapy, and payers can rationalize the savings. In other areas (such as vision loss due to Inherited Retinal Disease (IRD), which Luxturna® treats), a patient's untreated condition/unmet medical need may not pose a great expense to payers, and the savings can't be rationalized in the same way.

Access depends on the acceptance (or assumption) of long-term benefit based on short-term results.

Although many gene therapies are thought to be curative and may offer a lifetime benefit, long-term data is not available at the time of launch. Often, advanced therapies make it to the market via one of the expedited approval mechanisms, sometimes without Phase 3 data. For these products the US Food and Drug Administration (FDA) typically requires a 15-year follow up period to assess long-term safety issues. There is, however, no formal reassessment of efficacy in the long term, and US payers do not require such data. (In contrast, EU payers are requesting long-term efficacy and safety data to re-evaluate the clinical benefit.)

The idiosyncratic US market

The structure of the US healthcare system, being supported by multiple payers rather than a single, government-sponsored payer, presents unique challenges for payers with respect to cell and gene therapies.

Approximately 63 percent of Americans under the age of 65 are covered by commercial insurance,[iii] with a significant percentage of insureds moving carriers each year.

Payers typically will cover treatments that FDA approves for marketing, and so must find ways to manage the clinical and financial risk of that coverage. In many other countries, Health Technology Assessment (HTA) bodies are tasked with assessing the clinical and economic value of healthcare products, and their assessments determine access and play an integral role in price negotiations. In the US, however, no such government-sponsored body exists, and new products are evaluated independently by insurance companies and the Centre for Medicare and Medicaid Services (CMS). The current presidential administration has floated the idea of creating a national HTA, but the reality is that it would be very difficult to implement centralized, mandated assessments prior to reimbursement in the current political environment.[iv]

Although a non-profit search organization, ICER, performs analyses in the US similar to that of an HTA, it has no authority over reimbursement decisions. It does, however, wield influence – and that influence is steadily growing. Please see our paper, ICER's Impact on Payer Decision Making: Results of a Third Annual Survey for details on the role and reach of ICER in payer decision making.

Currently, CMS, the largest payer in the US, is not permitted by law to make coverage decisions based on price, with the result being that the agency is at risk of a substantial financial impact from advanced therapies. While many states rely on managed Medicaid programs to care for beneficiaries, some are beginning to create "carve-out" coverage decisions for ultra-high cost gene therapies. In these cases, they are contracting directly with the manufacturer on a fixed-fee basis. When managed Medicaid plans are at risk, they often seek extra premium from their local state Medicaid program partners as a means to cover the costs of these new therapies.

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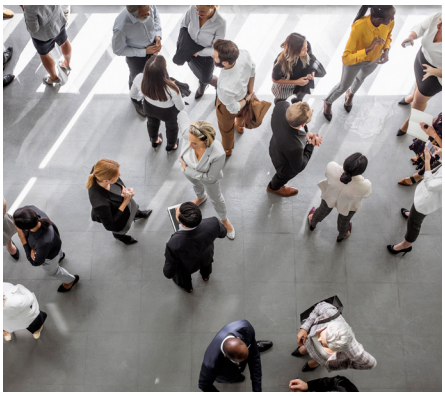

What payers are thinking

ICON's Market Access team conducted in-depth interviews in late 2020 with a select group of US payers to understand their views and practices around cell and gene therapies. Interviewees represented integrated delivery networks (IDNs) national and regional managed care organizations (MCOs), hospital pharmacy and therapeutics (P&T) committees, hospital pharmacy directors, and former employees of CMS.

Evaluation and coverage

Importantly, payers do appreciate the clinical value of advanced therapies, although the long-term benefit remains a common question mark in their minds. As one respondent from a regional MCO put it, "There's great clinical value, but we don't know how long it will last. Long-term data is a big concern."

Payers evaluate cell and gene therapies using their standard processes; they apply no special criteria, and much like other therapies they consider the unmet need, current treatments, target population, clinical data, price, and cost offsets. A representative from an IDN said, "Cell and gene therapies are evaluated the same as other drugs. The evidence is reviewed as to how it demonstrates a meaningful improvement for the condition."

Payers said that upon the availability of new data, they might reevaluate cell and gene therapies. (This is a notable difference from payers' views in the EU where they have very pointedly indicated to ICON that they'll review data at a certain point in the future and approved therapies are formally being reevaluated.) Payers initially base their prior authorization (PA) criteria on the inclusion criteria from clinical trials to ensure appropriate use of advanced therapies with uncertain long-term benefits and to mitigate their own exposure. If new clinical data were to become available, they would look to bring their PA criteria in line with it. They suggested that the process would be more likely to loosen their PA criteria than to lead to further restrictions.

Contracting solutions

Given that payers often must make reimbursement decisions without the benefit of Phase 3 and longer-term data, most payers would like to use outcomes-based contracts and payments over time to handle advanced therapies. This solution would address both the uncertainty of long-term benefits and the challenge of high, up-front cost. However, there's a cost to implementing this approach, and there are logistical challenges. "Value-based contracts are something we use and would like to use more for these types of therapy," explained a representative of a national MCO. "Pragmatically, it becomes a question of how many resources we would need to implement and track value-based contracts vs. the potential savings."

"Many of the issues facing payers are inextricably linked to the unique characteristics of the US marketplace."

Members moving plans

People moving between insurance plans is common in the US. This occurs, for example, when people move between jobs or spouses move to one another's plans upon a life event, like a birth or job loss. This represents a particular challenge for payers when considering how to cover therapies that are a onetime treatment with high up-front cost and long-term benefits.

In the case of outcomes-based contracts (OBC) and/or annuity payments, it remains unresolved how these would be handled if the member changes plans.

- Would the payer who agreed to the terms of the OBC and/or annuity payment continue with those arrangements or would the member's new plan be responsible?
- If the new plan is responsible, would they be also required to adhere to the original contracting terms?

Some payers view outcomes-based contracting and phased payments as a non-starter given how frequently their members change plans. One payer expressed strong preference that the member's first plan would continue with the agreed terms, although acknowledging this has not been established.

Another conundrum that comes with members moving plans, is it can mitigate their perception of the relative value of the cost-offset that many gene therapies offer. Using hemophilia gene therapy as an example, payers understand the long-term cost-offset represented by replacing the need for high-cost routine factor replacement therapy, however, this is less compelling when taking into account that the member could potentially move plans in a few years. This would leave the first payer having covered the up front-cost but left out of the long-term savings if the member moves plans. Despite this concern, if in theory it is assumed that the rate of member turnover is constant between plans, this should balance out over time for the payers.

> "Many payers would like to see all payers contribute to a risk pool of funds to cover the cost of advanced therapies."

Pooling risk

Many payers raised the potential for risk pools as a solution to paying for therapies with a high up-front cost and long-term benefit. This would entail a collaboration between payers to set forth funds that would be reserved to cover an established set of gene therapies. Payment for the therapies would then be covered by this joint fund, irrespective of which plan the member is on. This could in theory eliminate the concerns outlined above around members changing plans.

Gatekeepers

Large academic institutions review and evaluate the clinical merit of advanced therapies as well as the feasibility/ business case for their administration, but require payer coverage to fund treatment. By the same token, payers want to be sure that providers have the necessary experience to administer advanced therapies and in some cases restrict their coverage to procedures performed at specific centres.

Currently, CMS reviews therapy types to determine if they are coverable, but thereafter the agency does not review new treatments individually. (CMS cannot, by law, consider the price/ value or cost offset of a product in these reviews.)

Key takeaways for advanced therapy developers

Based on our in-depth conversations with a range of payers, we have concluded:

– **Payer scrutiny of gene therapies will almost certainly intensify as the number of approved therapies increases.** Manufacturers must, therefore, be prepared for payers to apply new strategies for controlling costs.

– **The population of the pivotal trial, as defined by entry criteria, can have a major impact on payer coverage.** As they develop their inclusion/exclusion criteria, manufacturers should be mindful of this; coverage for their therapy may ultimately be restricted to patients meeting those same criteria.

– **Payers are eager to engage in outcomes-based contracts for cell and gene therapies, but they're hesitant, or in some cases unable, to invest in the infrastructure needed to track outcomes.** (IDNs, on the other hand, are an exception in that they DO have the infrastructure to track outcomes and link to payer-funding systems.) This represents an opportunity for manufacturers to support solutions for advancing outcomes-based contracts. Those who can do this will differentiate themselves, and continuing to invest in long-term outcomes data that is relevant to the payer's own population will be key to optimizing success. It also behooves manufacturers to begin with a deep understanding of payers' views on outcomes-based agreements and to explore the range and scope of agreements that have been successfully employed in the industry.

– **Advocating for the development of risk pools would reduce payers risk and potentially facilitate access.**

– **Cost offsets can be a major value driver for these therapies, but payers can be skeptical of economic data generated by manufacturers.** Relying on objective third parties to generate this evidence can help manufacturers overcome the credibility issue with payers.

– **Payers appear to be willing to reevaluate coverage decisions upon the availability of new data.** Manufacturers should develop a plan for generating this data early in development and ensure that it's in a form that payers will find meaningful.

– **The introduction of an HTA approach in the US is a long shot, as it would require enabling legislation. One payer we interviewed suggested that if an HTA were introduced, it would most likely be implemented for specific products through the innovation centre as a pilot to demonstrate proof of concept.** As this is unlikely to become a reality anytime soon, manufacturers should proceed with a clear-eyed view of the market access challenges a new wave of cell and gene therapies will face. Clinical development decisions should be made in the context of such considerations.

"Payers are eager to engage in outcomes-based contracts for cell and gene therapies, but they're hesitant, or unable, to invest in the infrastructure need to track outcomes."

Conclusion

The prospect of new cell and gene therapies reaching the market is good news for patients, but will challenge payers particularly with respect to those treatments for less-rare diseases. And what challenges payers should concern sponsors. Ideally, biopharmaceutical manufacturers can work with payers to find ways to avoid a budget crisis and ensure that treatments reach patients. Sponsors of cell and gene therapies should be developing long-term evidence plans and be considering ways to support outcomes-based contracting.

"US healthcare budgets have been able to absorb the cost of cell and gene therapies targeting rare diseases, but their ability to do so will be strained when products are available for more prevalent diseases."

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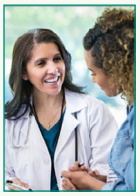
Further reading

ICER's impact on payer decision making

In the absence of a national HTA body in the US, ICER has emerged as a leading voice in evaluating healthcare technologies on their clinical and economic values. Read our third annual payer survey for insights.

ICONplc.com/ICER2020

Will US payers give more consideration to PRO data in coverage decisions?



In the US, payers have historically focused on efficacy and safety endpoints as well as cost, with very little attention given to patient reported outcomes (PROs). With the increase in patient centricity, we surveyed US payers from MCOs, IDNs and PBMs to get their take on the value and use of PRO data.

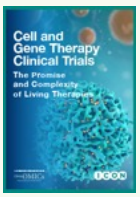
ICONplc.com/USpayersPRO

Using wearables data to support drug reimbursement

Wearables have the potential for assessing outcomes in novel ways, in real time and over extended periods of time. They also have potential for demonstrating the value of drug products by generating more reliable outcomes data. In the context of outcomes based agreements (OBAs) and payer re-evaluation of drug products, both require the generation of real world data to support reimbursement.

ICONplc.com/payerswearables

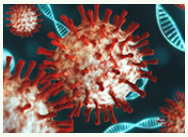
The promise and complexity of living therapies



As development of cell and gene therapies (CGT) accelerates, so will the demand for best practices, and better tools and solutions. For advanced therapies, the product and patient journey is entirely different from traditional trials. As such, biotech and pharma companies will need to overcome challenges and complexities from regulatory pathways and patient recruitment to logistics and manufacturing. Adopting strategic partnerships with deep CGT expertise with a broad spectrum of solutions and services is vital to the success of a development programme.

ICONplc.com/cgt

Stand-alone long-term follow up studies - webinar



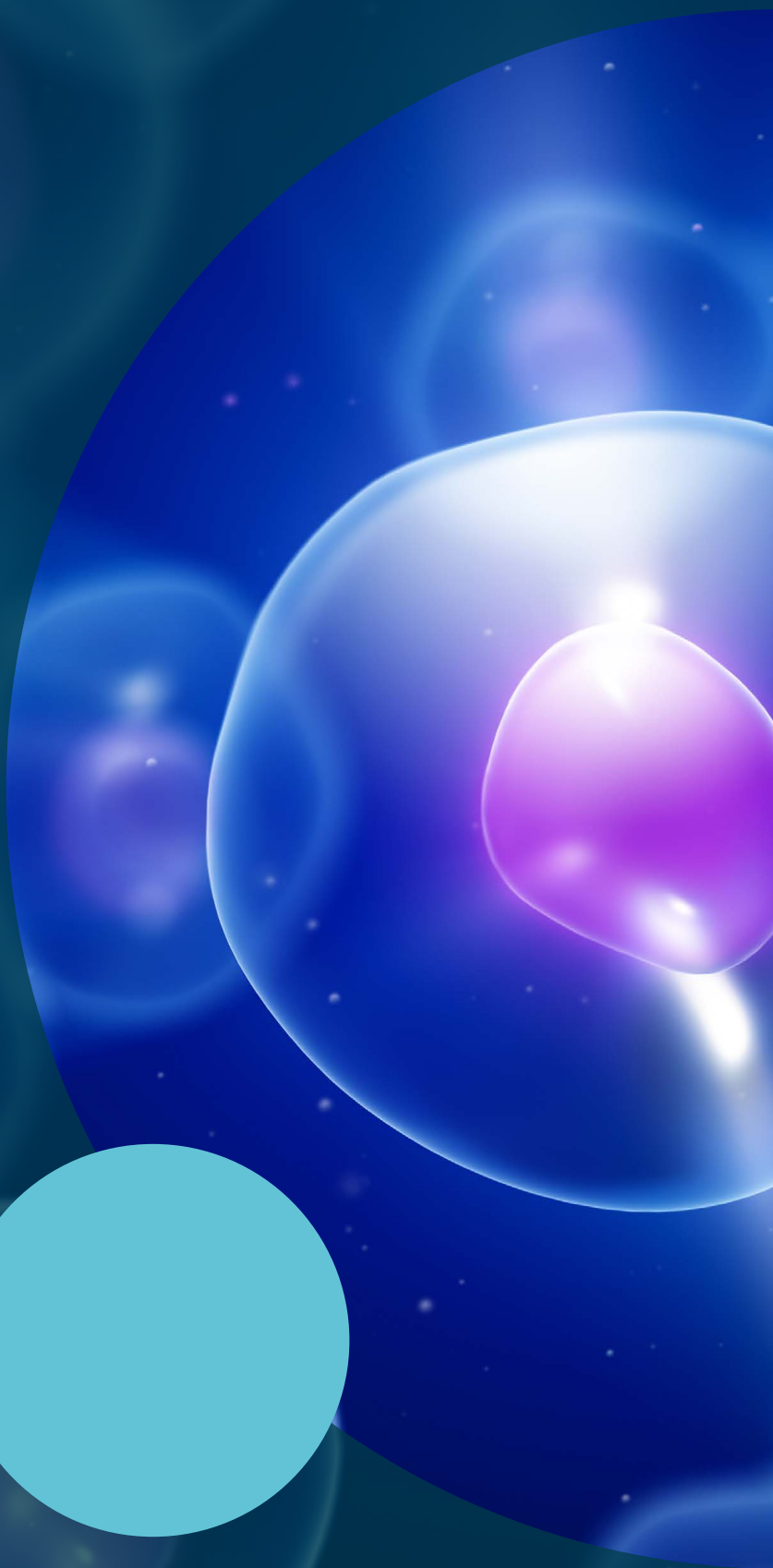
New regulatory requirements have sparked more interest in stand-alone long-term follow up (LTFU) studies for monitoring patient outcomes and safety. The post-study follow up period can range from months to years. The advent of advanced therapy medical products, cellular products and gene therapies have helped evolve stand-alone LTFU studies.

ICONplc.com/LTFUstudies

Experience matters in cell and gene therapy trials

Using experienced-based best practices and documented tools, ICON has conducted over 64 CGT trials across multiple therapeutic areas - from haematology-oncology to rare and orphan diseases. With 400+ team members dedicated to cell and gene therapy, we support preclinical, regulatory and commercial positioning as well as translational and clinical development.

We understand that cell and gene therapy trials must be delivered differently. Because there are no handbooks and few standards, experience matters.



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