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Regulatory and Economic Challenges for Gene Therapy Utilization

Posted 17 April 2018 | By Vidya Narayanaswami, PhD Dr. Stephen F. Amato

This article addresses pricing and reimbursement challenges associated with clinical utilization of approved gene therapies. The authors recommend potential approaches to resolve these challenges, the implementation of which may help solve issues related to the high cost of these therapies and encourage continued innovation and further development of advanced gene therapies.

Introduction

Gene therapy is an experimental technique using genes to treat or prevent diseases either by replacing a mutated disease-causing gene with a healthy copy of the gene (knocking out a mutated gene entirely) or introducing a new gene into the body to reduce the physiological impact of disease causing phenotypes.[1] Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a gene editing technology generating excitement in the biotech world. The excitement comes from CRISPR's potential for breaking two DNA strands and enabling either the elimination of mutated genes or the insertion of healthy ones.[2] Because this approach to editing genes can result in errors and off-target effects, researchers are exploring potential alternatives aimed at eliminating associated risks. To this end, Yale scientists reported a recently developed alternative gene editing technique, "eukaryotic multiplex genome engineering" (eMAGE), which is believed to allow new genes to be inserted into DNA without multiple double-strand breaks.[3] Broad Institute scientists also have developed a system, "RNA Editing for Programmable A to I Replacement" (REPAIR), which targets RNA instead of DNA and holds the potential of fixing gene mutations without permanently changing the genome.[4]

FDA's Gene Therapy Approvals

Gene therapy holds the promise to transform medicine and create options for patients who are living with difficult and incurable diseases, including inherited disorders, various types of cancer and certain viral infections. As scientists discover more genes, determine how they function in diseases and also refine gene editing techniques, the therapeutic potential of gene therapy may become limitless. The US

Food and Drug Administration (FDA) is committed to helping speed up drug development by prompt review of ground-breaking treatments that have the potential to save lives and has approved three novel gene therapy products since August 2017. Kymriah (tisagenlecleucel; Novartis Pharmaceuticals Corp.), the first gene therapy approved for the treatment of pediatric and young adult acute lymphoblastic leukemia in August 2017, was a landmark in oncology.[5] While the science underlying Chimeric Antigen Receptor T (CAR-T) cells signifies a new era of treatment, the drug price of $475,000 delivered as a one-time infusion shattered oncology drug pricing norms.[6,7] Shortly after the approval of the first gene therapy, FDA approved Yescarta (axicabtagene ciloleucel; Kite Pharma Inc.), another CAR-T cell therapy to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.[8] Yescarta also comes at a hefty, one-time price of $373,000. Luxturna (voretigene neparvovec-rzyl; Spark Therapeutics Inc.) is a new gene therapy that was approved towards the end of 2017 to treat children and adult patients with an inherited form of vision loss that may result in blindness.[9] The proposed price for this ground-breaking one-time gene therapy for a rare form of blindness that affects only 1000 to 2000 people in the US is $850,000 or $425,000 per eye.[10] In addition to these recent FDA approvals, as of February 2018, several gene therapy clinical trials are underway worldwide, sponsored by manufacturers hoping to commercialize these therapies in the US market. At least 200 of these clinical trials are in Phase 2 and approximately 24 are in Phase 3 of clinical development.[11]

As gene therapies rapidly advance toward commercialization, it is imperative to recognize the financial impact of this therapeutic approach on the US healthcare system. In 2016, US healthcare expenditure grew by 4.3% to $3.3 trillion. National health spending is projected to grow at an average rate of 5.6% per year between 2016 and 2025.[12] Given the pricing experience with gene therapy in the European market and a rich pipeline of gene therapy candidates already in clinical trials, there may be a surge in the number of gene therapies approved over the next few years in the US market. Consequently, cumulative budget impact due to gene therapy is likely to rise to $3 trillion, which is as much as is currently spent in one year on all healthcare in the US.[13]

Over the past two decades, the biotech industry has invested more than $10 billion in gene therapy and related technologies without generating return on investment.[14] Clinical advances in gene therapy are rapidly unfolding amid a complicated debate about drug pricing and reimbursement policies. There is a great need to reform pricing and reimbursement strategies for approved gene therapies in the US that is mutually agreed upon by multiple stakeholders involved. The authors underscore the urgency for initiating dialogue between policy makers, manufacturers, regulators, payers and healthcare providers early in the clinical development process and to design an efficient pricing and reimbursement strategy.

Gene Therapy Commercialization: Economic Concerns

uniQure, a Dutch Pharma Company, launched Glybera (EU) in 2012, the world's first approved Adeno-Associated Virus (AAV)-based gene therapy to treat a rare inherited disorder (lipoprotein lipase deficiency) at a one-time cost of $1.4 million per patient.[15] Despite being a clinical success, Glybera has been rendered a commercial failure as only one patient has been treated with the commercial form since its approval.[16] Given its limited usage, Glybera was withdrawn from the European market. A major lesson learned from market withdrawal of the first-ever approved gene therapy is despite successful clinical development of such novel therapeutic approaches, the potential high cost of such therapies may hinder access to patients. The main challenge is that in the current US healthcare system for drug development

and reimbursement, there have been no provisions established for gene therapy.[17] It also is unclear how insurance coverage for such therapies might work or whether these therapies would qualify as "essential benefits," as specified by the *Patient Protection and Affordable Care Act* in the US.[18]

Commercialization of gene therapies will add substantial up-front cost burdens to the US healthcare system. Drug makers argue that the high cost of gene therapy is justified as they reflect the value of curative treatment and long-term transformative benefits that replace chronic therapy. From a patient's perspective, savings associated with one-time gene therapy versus chronic treatment appear straightforward. For example, the price of $475,000 for a single treatment with Kymriah may be cost-effective compared to traditional, chronic cancer treatments that typically cost $10,000-$20,000 per month and may involve hospitalizations and/or long-term infusion treatments.[19] Another argument justifying the high cost of gene therapy is it is targeted for a limited population with rare disease and therefore, the overall effect on healthcare costs will be manageable. However, the potential expansion of CAR-T cell therapy for treatment of common solid tumors, such as lung, prostate, pancreas, breast and colon cancers, may be more difficult to justify. If CAR-T therapies are successful at improving the outcomes for patients with these disease conditions, the health benefits could be great, but the cost to patients and the healthcare system could be detrimental.

The Institute for Clinical and Economic Review (ICER), an independent non-profit research institute, promotes multiple stakeholder engagement and transparency in producing reports analyzing evidence regarding the effectiveness and value of drugs and medical services.[20] 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 healthcare system. In December 2016, ICER convened a Policy Summit with a group of leading experts and representatives from 20 payer organizations and life sciences companies. The aim was to create policy recommendations promoting innovation and sustainable access to gene therapies within the US healthcare system. The major economic challenges presented by gene therapies are briefly discussed in **Figure 1** and include insights from multiple stakeholders in the ICER Policy Summit meeting.[21]

Figure 1: Regulatory and Economic Challenges of Gene Therapy Utilization

Regulatory and Economic Challenges of Gene Therapy Utilization

Regulatory concern:
- Lack of evidence that establish long-term safety and effectiveness during regulatory approval

Hindrance in value assessment:
- Challenges with evidence generation creates uncertainty about estimate of health impact which is imperative for pricing and reimbursement decisions

Affordability:
- High upfront treatment prices over $1 million per patient raises significant concerns about patient access, reimbursement strategies and overall economic impact

High cost of development and lack of return on investment:
- Should payers and policy makers consider R&D and manufacturing costs in their assessments of value and/or decisions on reimbursement of gene therapy?

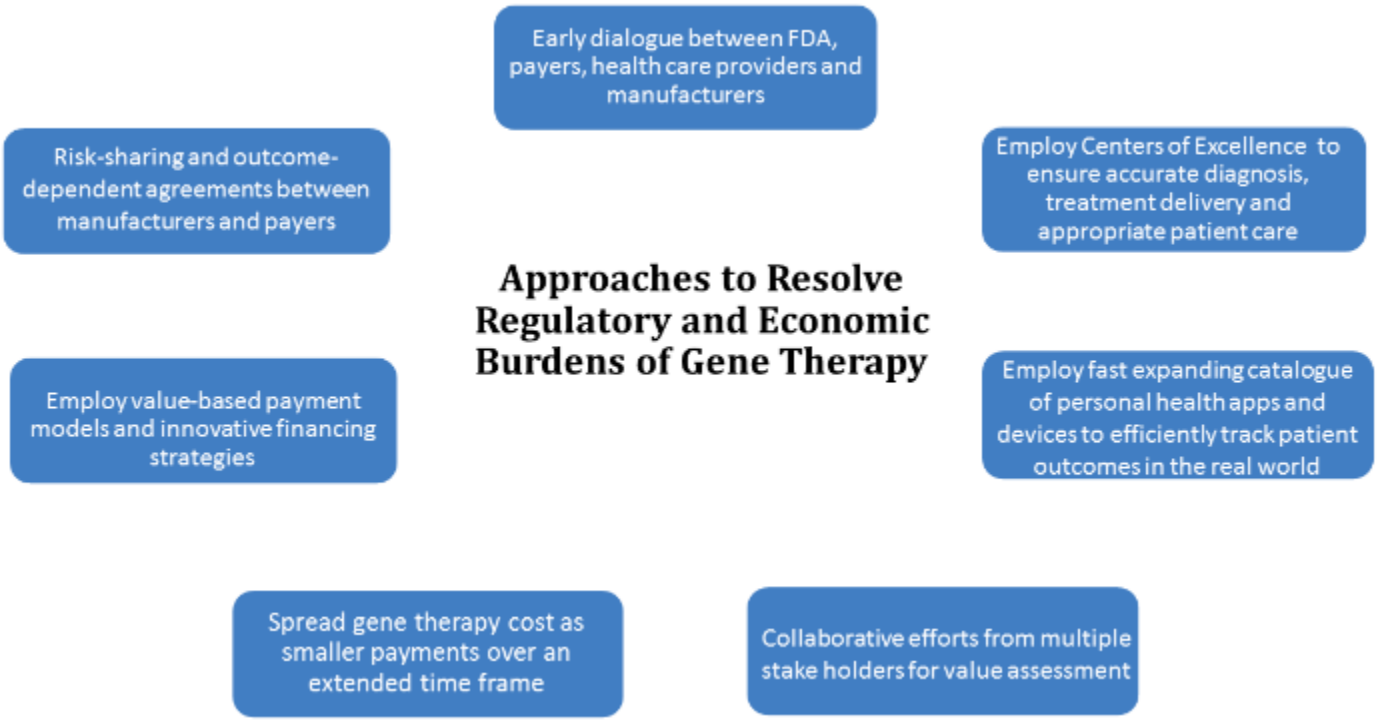
- **Lack of evidence demonstrating long-term safety and effectiveness -** while Randomized Controlled Trials (RCTs) remains the gold standard, conducting RCTs for gene therapies can be problematic due to small population sizes, invasive methods of administration, a lack of clearly defined patient centric outcomes and existing management approaches for comparison. The long-term effectiveness and safety implications of these emerging therapies are yet unknown. Although gene therapies hold the potential to improve patient outcomes over a lifetime, evidence of long-term safety and benefits could not be provided at the time of FDA approval. These unknowns create uncertainty about any up-front, one-time payment.[22]
- **Value assessment -** generation of clinical evidence is problematic for many gene therapies. Yet, evidence is still essential for licensing, pricing and reimbursement decisions. Challenges with evidence generation hinder the estimate of health and economic impact, data imperative for value assessment. While there are questions arising when assessing the value of and agreeing on a price for gene therapy, it also remains unclear whether extra value should be attached to potentially curative therapies as compared with long-term incremental benefits. Curative therapies may be valued more highly by society than treatments that offer only marginal gains over many years.
- **Affordability -** affordability and patient access are major concerns. Some curative gene therapies may present a cost-effective healthcare option as it would subsequently replace long-term treatments and/or reduce frequent hospitalizations. These potential long-term savings should be included in affordability considerations. Nevertheless, the challenge of absorbing upfront treatment prices of 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.
- **Will innovators recover the high cost of development and get a return on investment?** Manufacturers of gene therapies targeting very rare conditions face high per-patient development costs. For a one-time therapy that is an outcome of a time-consuming and expensive preclinical and clinical R&D effort, questions remaining unanswered include: What is the appropriate price to charge the patient? How should that price be determined? Who will pay? It is not clear whether

payers should include consideration of R&D and manufacturing costs in their assessments of value and/or decisions on reimbursement of gene therapy. Should special considerations be given for gene therapies targeting very rare diseases? It is important to note that without high per-patient prices and/or longer-term market exclusivity, these therapies may not be developed. Gene therapy can replace long-term costs of traditional treatment approaches but, at the same time, they provide a less attractive return for investors, making future investment in gene therapy a problem.

The rapid advancement of gene therapy in the US market demands improvised pricing and reimbursement approaches to provide a recognition of value for developers, broad access to patients and an acceptable budget impact on health systems.[23] Both manufacturers and payers recognize that existing payment mechanism and strategies to manage affordability are inadequate to support the growing number of gene therapies. Collaborative efforts are needed to create stable pricing and financing strategies and, at the same time, stabilize the health insurance structure for these innovative therapeutic approaches.

Potential Approaches to Resolve Challenges and Economic Burdens of Gene Therapy (Figure 2)

Figure 2: Potential Approaches to Resolve Regulatory and Economic Burdens of Gene Therapy



- To address gaps in knowledge about long-term safety and efficacy, an early dialogue between FDA, payers, healthcare providers and manufacturers is encouraged. This will help manufacturers optimize the use of small patient populations, develop mutually agreed trial designs and data analysis methods, identify surrogate end points that can be validated and evaluated, discuss the design of real-world evidence collection strategies through patient registries.[24] Early dialogue involving payers and regulators allows manufacturers to ensure treatments are developed in line with reimbursement and regulatory requirements.
- Centers of Excellence could be used to solve potential accuracy problems with respect to patient

diagnoses as well as delivery of the treatment. Spark Therapeutics has proposed limiting administration of Luxturna to Centers of Excellence specializing in treating inherited retinal disorders meeting strict capabilities and training requirements to support appropriate patient care.[25]

- It will be beneficial to seek consensus from multiple stake holders on the elements of value for determining the price and fairly reflect the value of gene therapy.
- One approach to reduce the financial burden associated with gene therapy is to devise pay-for-performance and risk-sharing agreements between pharmaceutical companies and healthcare payers, whereby payment for gene therapy is tied to how well the therapy performs in the "real world," evidenced by appropriate patient outcomes.[26] However, hurdles in implementation of performance-based deals include costs and complexities in tracking patient outcomes. It also may be challenging to agree upon contractual terms for therapy success and failure as well as payment, such as how much insurance companies will pay for gene therapies and how much financial risk should be assumed by patients.
- Implementation of capped annuity with risk-sharing and outcome-dependent agreements between manufacturers and payers may allow health systems to spread the cost over several years and to limit risk if efficacy is not maintained.[27,28] This could be comparable to reimbursement for organ transplant therapies where diseased organs are replaced surgically with healthy organs donated by volunteers. Hurdles with outcome-based annuity schedules arise when patients change insurers.[29] Transferring annuity contracts from one plan to another without an associated provision of services may result in complications, presenting an issue needing to be addressed.
- Amortization schedules may allow the cost of the treatment to be spread as smaller payments over an extended of time. Options for amortization of gene therapy payment include third-party financial institution, manufacturer-managed financing and consumer and government loans.[30]

Value-based payment models and innovative financing strategies are proposed to alleviate the short-term budgetary pressures created by one-time payments for curative therapies.[31] Value-based payment models link payment to a treatment's value—expected or realized—with the goal of encouraging higher-value treatment choices, better outcomes and lower overall healthcare costs. In case of upfront payment with outcomes-based rebates, payers would provide upfront payment to manufacturers for the full expected value of a therapy, with manufacturers providing rebates if patients fail to meet pre-specified performance or clinical outcome measures collected at pre-specified time intervals. This approach does not address the budget impact of high upfront costs or the availability of efficient and reliable ways to track patient outcomes over the long term. If the patient moves to a new health plan, information to determine the rebate would still need to flow back to original payer and manufacturer. Outcome-based payments over time allow payers to deliver payments to manufacturers over time instead of up-front (quarterly or annual basis for multiple years), based on pre-specified outcome and performance measures. This would substantially alleviate initial budget pressures.

Conclusion

In the current US healthcare system, drug development, pricing and reimbursement are not well structured for the commercialization of advanced therapeutic products such as gene therapies. New models for market access must be developed for these treatments to establish significant market penetration. Benefits of potentially curative treatments, such as saving a patient's eyesight or treating

drug-resistant forms of cancer, ideally should outweigh any price or cost considerations. However, recovering the costs associated with gene therapy discovery and clinical development is important for facilitating future therapy development. Early dialogue among stakeholders is strongly advised for surmounting the challenges of gene therapy commercialization. New approaches must be created. Spark Therapeutics' recent launch of Luxturna provides an example whereby the company chose to conduct market research with payers, formed alliances, agreed on performance-based contract and spread payment over years. These approaches were developed prior to launching Luxturna and helped lead to active endorsement. Gene therapies require innovative pricing and reimbursement approaches that provide fair recognition of value for drug developers and broad access for patients and do so without adversely impacting the healthcare system.

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Cite as: Narayanaswami V and Amato S F. "Regulatory and Economic Challenges of Gene Therapy Utilization." *Regulatory Focus*. April 2018. Regulatory Affairs Professionals Society.

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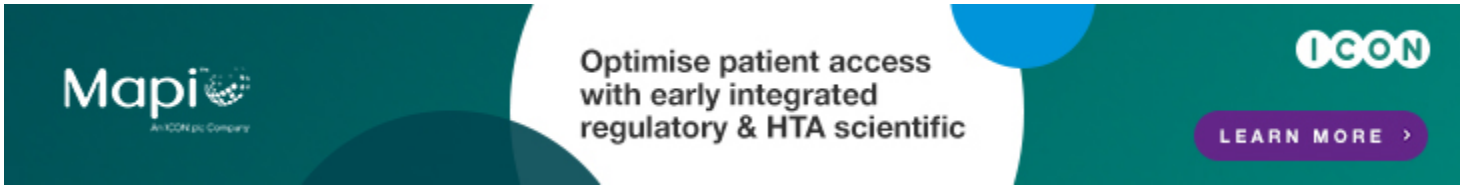

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