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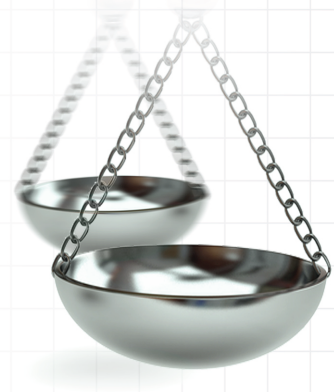

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Improving access to gene therapies: a holistic view of current challenges and future policy solutions in the United States

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Gene therapies hold the promise of delivering groundbreaking improvements in health outcomes for previously intractable diseases. These therapies possess unique characteristics that differ from traditional small molecule or biologic treatments, posing new challenges for healthcare stakeholders. While previous analyses have predominantly focused on the payment challenges associated with emerging gene therapies, a more holistic examination reveals numerous obstacles that currently hinder optimal patient access. In the United States (US), these include production and distribution issues, logistical and treatment administration challenges and coverage and reimbursement limitations imposed by US healthcare payers. Several opportunities exist to address these challenges and improve patient access, including the use of appropriate value assessment methods, the development of innovative payment solutions, the removal of inappropriate access barriers imposed by payers and improving education and awareness regarding treatment availability, benefits and risks. Moving forward, we must collectively strive for comprehensive policy and market solutions that are sensitive to the uniqueness of gene therapies to ensure their full potential is realized and these treatments are made available to those in need.

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Innovative gene therapy treatments have the potential to deliver groundbreaking improvements in patient health outcomes across a wide range of diseases including hemophilia, sickle cell disease (SCD) and several types of cancer. However, realizing this potential is contingent upon the United States (US) health system recognizing the value of these treatments and dismantling the structural and financial barriers that curtail meaningful patient access [1].

The transformative and potentially curative nature of gene therapies represents a paradigm shift in healthcare delivery. Gene therapies differ from traditional medicines in that they are often single-administration treatments that involve a complex, sometimes personalized manufacturing process and many target rare diseases with small patient populations with few or no available disease-modifying treatment options. As single-administration treatments, gene therapies hold the promise to unlock substantial value for patients and society through accrued long-term benefits, but this promise must also be financially rewarded to ensure sustainable innovation. The unique characteristics of gene therapy treatments, in conjunction with uncertainties about long-term durability and future market competition, necessitate the development of innovative models to assess the value of these treatments, promote appropriate payment and advance meaningful patient access while maintaining incentives for future research and development.

Previous analyses of the gene therapy landscape have narrowly focused on the price of emerging gene therapies and identified challenges facing US payers related to short-term budget impact, plan coverage and reimbursement [2–4]. Although such analyses contribute to the literature, identifying appropriate and sustainable payment models is one of many challenges in the gene therapy landscape. A more holistic multistakeholder examination of the unique policy challenges associated with innovative gene therapies is needed to inform the advancement of appropriate, evidence-based policy and market solutions that reward value and improve access.

The goal of this article is to complement earlier assessments of the gene therapy landscape by identifying these broader challenges currently impacting access to gene therapies, exploring policy and market reforms to improve patient access and highlighting potential consequences and implications of proposed market solutions.

Current challenges & barriers impacting access to gene therapies

To date, 14 gene therapies have been approved for use in the US [5]. However, numerous challenges currently prevent optimal patient access to these treatments, including those related to the production and distribution of gene therapy treatments, logistical and treatment administration obstacles and coverage and reimbursement limitations imposed by healthcare payers. A greater understanding of these challenges can promote more comprehensive and informed policy solutions to improve access to current and future gene therapy treatments.

Challenges related to the production & distribution of gene therapies

Gene therapies are challenging to produce compared with traditional small molecule drugs or biologic treatments [6]. For example, 72% of approved gene therapies use *in vivo* gene transfer strategies, which often use viral vectors to deliver modified genes to the patient [7]. Additionally, a growing number of gene therapy treatments are *ex vivo* gene therapies, which require extracting cells from an individual patient, isolating and genetically modifying the cells and re-administering the cells back into the same patient. These treatments are exceptionally complex and time-intensive to produce [8]. Complex manufacturing processes, and the fact that gene therapies are often indicated for conditions with small patient populations, may limit economies of scale in production [9], which may ultimately impact the widespread availability of current and future treatments. Consideration of these challenges is essential when weighing policy proposals and market solutions related to innovative gene therapies to ensure that future breakthroughs in gene therapy development are incentivized.

Logistical & treatment administration challenges

Gene therapies require special diagnostic testing and treatment administration, which can carry a substantial logistical burden for patients and caregivers, including traveling significant distances and spending time away from home to receive treatment [10]. Depending on the therapy, each step along the treatment process can take place over weeks or even months [11]. Gene therapies can only be administered by a subset of healthcare providers and locations that are qualified and equipped to handle these complex treatments. The specific providers and facilities may vary for each therapy, depending on the expertise and resources required. These specialized centers must have properly trained staff, appropriate product storage facilities and reliable product sourcing, all of which can amount to a significant administrative and financial burden for health systems. As healthcare decision-makers examine opportunities to optimize patient access to gene therapies, further research is needed on the logistical, administrative and care delivery hurdles patients and caregivers face throughout their care journey.

Coverage & reimbursement challenges

There is significant variation in health plan coverage for gene therapies, which holds important implications for equitable patient access to life-changing treatments. Some healthcare payers are imposing strict utilization management requirements on approved gene therapies. A recent analysis of healthcare coverage policies in the US found that for 11 cell and gene therapies, Medicaid plans had coverage policies more restrictive than the FDA label 68.3% of the time, while commercial health plans had more restrictive policies 53.5% of the time [12]. Additionally, an analysis of Medicaid coverage determinations for 16 states and three managed care organizations found substantial variation in coverage for three cell and gene therapies [13]. For certain products, researchers found that Medicaid coverage policies frequently included additional exclusionary criteria or clinical information beyond the labeled indication, which could result in treatment denials or delays in care delivery. As payers often cite uncertainty about long-term durability and patient churn to justify coverage exclusions and strict utilization management, policy and market solutions aimed at improving patient access should consider opportunities to address these concerns.

Opportunities to address current challenges & improve patient access

Improving access to current and future gene therapies will require health policy proposals and market-based solutions that consider the full spectrum of challenges that affect a broad constituency of healthcare stakeholders, including patients, manufacturers, providers, payers, policymakers and regulators. Several opportunities exist to

address these challenges and improve access to gene therapy treatments, including relying on appropriate value assessment methods, advancing innovative payment solutions, removing inappropriate access barriers imposed by healthcare payers and improving education and awareness of treatment availability, benefits and risks.

Rely on appropriate value assessment methods

As healthcare decision-makers consider policy and market solutions related to gene therapies, any discussion of price and payment must be supported by a discussion of value and appropriate incentives for innovation. Policies that focus exclusively on cost containment rather than evaluating and delivering value to patients and society likely have unintended consequences. Solutions designed to address the challenges related to gene therapies must include comprehensive value assessment methodologies.

Recognizing the unique attributes associated with single and short-term therapies, the Institute for Clinical and Economic Review (ICER) developed a 'shared savings' approach for calculating their 'value-based' price of gene therapies in which the value of the cost offsets is 'shared' between the manufacturer and the health system [14]. ICER's 'shared savings' method does not appear to be supported by scientific research or empirical evidence [15].

By applying the 'shared savings' method, ICER is converting saved dollars into cents when it comes to incentivizing gene therapies for the very conditions that have the most unmet need – conditions that are costly to treat with usual care. Some argue that innovative gene therapies that generate substantial cost savings should not be penalized or disincentivized simply because they offset other healthcare costs [16]. While ICER aims to provide comprehensive assessments, their 'shared savings' methods applied to their 'Health Benefit Price Benchmarks' move their conventional framework away from a holistic value-based price by emphasizing a particular definition of health benefits and potentially discounting cost savings. Given the limitations associated with ICER's 'shared savings' method, its inclusion in ICER's value assessment reports or broader healthcare decision-making raises a cautionary flag, as its application in payment and reimbursement decisions could lead to further underestimation of treatment value and may undermine incentives for future innovation.

Contrary to ICER's methodological approach, leading healthcare experts suggest that value assessments of gene therapies should be based on the treatments' associated costs and health benefits over patients' lifetimes, as well as their broader societal benefits [17]. The lifetime costs of gene therapy may be far less than the cumulative costs of chronic treatments they aim to replace, depending on their long-term effectiveness. A durable single-administration gene therapy could create substantial savings for the healthcare system, including reducing the need to treat patients with existing chronic treatments [18]. In addition, severe rare diseases affecting children not only impact the patients but also have significant spillover effects on their families and caregivers, which are generally underappreciated when assessing the value of health improvements that can last three to five decades [19]. Effective, curative treatments available early in the lives of children with hereditary diseases have large saving potential, both in terms of indirect and direct costs [20].

Emerging methods, such as those that build dynamic and more comprehensive inputs into cost–effectiveness analysis (CEA), may provide a more realistic sense of the cost–effectiveness of curative treatments over time. Ultimately, cost–effectiveness is one of many inputs into value, and value assessment methods must acknowledge the unique attributes of gene therapy treatments and reflect a comprehensive spectrum of the benefits provided to patients, caregivers, the health system and society more broadly.

Implement innovative, fit-for-purpose payment solutions

Innovative payment strategies such as outcome-based payments, warranties, risk pooling and other approaches can improve patient access to treatments while addressing payer concerns about long-term durability and patient churn. A recent white paper from ICER and NEWDIGS at Tufts Medical Center identified opportunities to implement and stack these strategies, noting that there is no silver bullet that can singlehandedly solve all the challenges in the payment landscape [2]. The paper also recommended modifications to federal laws and regulations that may prevent the implementation of innovative payment arrangements.

Further exploration of the gene therapy landscape reveals additional considerations for developing fit-for-purpose payment solutions. First, policy proposals and market solutions should leverage lessons learned from several years of gene therapy availability in the US market and draw on established practices for access and reimbursement [13,21–23]. Moreover, there are instances in the market where payers and manufacturers have entered into arrangements aimed at managing the affordability of gene therapies and ensuring patient access [24–27]. While these collaborations have shown promise in improving access, the extent to which they have successfully removed all potential barriers

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or undue restrictions remains unknown. Further exploration of these approaches may inform new strategies to overcome access barriers.

Second, the gene therapy landscape is dynamic, and concerns about treatment pricing should be carefully assessed to ensure that policy solutions aimed at promoting affordability and health system sustainability reflect real-world market conditions. Despite widespread handwringing over the affordability of gene therapies, actual market uptake of approved gene therapies has been lower than initially anticipated and multiple expert predictions of therapy price, market adoption and aggregate costs to the health system have not been realized [24,28,29].

Third, as healthcare decision-makers pursue value-based payment arrangements, implementation of these arrangements must be fit-for-purpose rather than a blunt policy instrument that is applied indiscriminately to all treatments. Just as patients are unique and heterogeneous, so are gene therapies. For example, it is important to recognize that outcomes-based arrangements (OBA) may not be good solutions for every gene therapy. Currently, OBAs are being established for SCD between manufacturers, states and Medicaid through the voluntary Cell and Gene Therapy Access Model by the Centers for Medicare and Medicaid Innovation (CMMI). SCD could serve as a reasonable test case for OBAs, as it is a disease with outcomes that can potentially be tracked efficiently and objectively. However, selecting appropriate outcomes for SCD poses several challenges, such as the lack of clinically validated patient-reported outcomes, the potential disconnect between clinical trial blood markers and meaningful patient outcomes and the limitations of claims data in reflecting treatment failure [30]. Alternatively, gene therapies with outcomes that are challenging to measure, subjective end points, or inconsistent data reporting may not be ideal candidates for OBAs [31]. OBAs are particularly valuable when there is greater uncertainty in treatment durability; however, for treatments with well-established durability, implementing OBAs may add unnecessary costs and complexity without substantially reducing payer risk. As the current voluntary model evolves, policymakers should be mindful of the limitations of OBAs and refrain from making participation mandatory for all treatments.

Remove access barriers to high-value treatments

Despite the potential for gene therapies to treat and even cure medical conditions with few or no alternative treatments, poorly designed health benefit plans can create barriers that prevent meaningful patient access to necessary care. A recent study found that payers are imposing coverage restrictions on gene therapies at a much higher rate than for traditional specialty or orphan drugs [12]. However, many gene therapies are high-value treatments capable of generating substantial cost offsets compared with the standard of care, which may result in net savings to the US health system. For example, Roctavian (Valoctocogene roxaparvovec), a gene therapy for the treatment of hemophilia A, approved by the FDA in June 2023, has been projected to save $6.8 million per patient over the course of the disease in comparison to standard prophylactic coagulation factor VIII treatment, which requires frequent infusions and life-long medication [13].

There is growing consensus among healthcare stakeholders that payers should remove undue access barriers for high-value treatments, as evidenced by the advancement of numerous policy efforts that eliminate cost-sharing or utilization management requirements for high-value medications [32–34]. Looking ahead, further implementation of strategies that hold payers accountable for providing access in line with the value of the therapy may help mitigate access barriers for high-value gene therapies [35].

Improve education & awareness of treatment availability, benefits & risks

Improving patient engagement and access to gene therapies requires a collaborative effort from all stakeholders involved, including manufacturers, healthcare providers, payers, patient advocacy groups and policymakers. The gene therapy patient journey is a complex, multi-step process that involves navigating myriad challenges, from the initial diagnosis and treatment decision to the coordination of care, logistical and financial arrangements and long-term follow-up, all of which require significant support and collaboration from these stakeholders. Generating greater awareness of treatment solutions, designing programs that address the evolving and complex needs of patients and helping to remove barriers to treatment are essential steps in this process.

One of the most significant challenges patients face is the lengthy diagnostic odyssey, with many rare disease patients waiting 7–8 years or more for a correct diagnosis [36]. Healthcare providers can improve diagnostic pathways by staying informed about gene therapy advancements and incorporating screening tools into their practice [37]. Patient advocacy groups play a crucial role in raising rare disease awareness, advocating for early diagnosis and intervention policies and providing educational resources. Manufacturers should invest in patient education initiatives that help patients make informed decisions by providing clear, accessible information about

gene therapy options along with their potential benefits and risks. Collaboration between patient advocacy groups, providers and manufacturers is essential to ensure that these resources reach the patients who need them most.

Ensuring patient access to gene therapies requires a coordinated effort to address the multifaceted barriers patients face throughout the treatment journey, including financial, logistical, psychosocial and emotional hurdles. Comprehensive patient support services can play a crucial role in mitigating these challenges. Such services may include financial assistance programs to help with high out-of-pocket costs and insurance coverage limitations, care coordination and travel assistance to ease the burden of receiving treatment at specialized centers far from home [38], and patient education, counseling and support services to address emotional and psychosocial needs of the patient, family, and/or caregiver. Certain support services may not be required if payer barriers, such as out-of-pocket costs, were eliminated for gene therapies. By providing holistic support and working together to remove these barriers, stakeholders can help ensure that all eligible patients have access to potentially life-changing gene therapies.

Conclusion

Gene therapies hold the promise to transform healthcare and deliver groundbreaking improvements in patient health outcomes for previously intractable diseases. However, numerous challenges currently limit optimal patient access to gene therapy treatments. Moving forward, it is imperative that we collectively strive for policy and market solutions that are comprehensive and sensitive to the uniqueness of gene therapies and are geared toward improving patient health and society. To ensure that their potential is realized, we must incentivize the development of gene therapies for those most in need. Several opportunities exist to improve patient access to gene therapy treatments, including relying on appropriate value assessment methods; advancing innovative payment solutions; removing inappropriate access barriers imposed by health; and improving education and awareness of treatment availability, benefits and risks.

Summary points

- Gene therapies hold the promise to unlock substantial value for patients and society through accrued long-term benefits, but this value must be recognized and rewarded to ensure sustainable innovation.
- Previous analyses of the gene therapy landscape have focused on the price of emerging gene therapies and predominantly identified challenges facing US payers related to short-term budget impact, plan coverage and reimbursement.
- To advance comprehensive, evidence-based policy and market solutions that reward value and improve access, a more holistic, multistakeholder examination of the unique policy challenges associated with innovative gene therapies is needed.
- Examination of the broader policy landscape reveals that numerous challenges currently prevent optimal patient access to gene therapy treatments, including challenges related to the production and distribution of gene therapy treatments, logistical and treatment administration obstacles and coverage and reimbursement limitations imposed by healthcare payers.
- Several opportunities exist to address these challenges and improve access to gene therapy treatments, including relying on appropriate value assessment methods, advancing innovative payment solutions, removing inappropriate access barriers imposed by healthcare payers and improving education and awareness of treatment availability, benefits and risks.
- Moving forward, it is imperative that we collectively strive for policy and market solutions that are comprehensive, sensitive to the uniqueness of gene therapies and geared toward improving patient health and society.

Author contributions

All authors (TD Wagner, L Buelt, K Westrich, JD Campbell) were responsible for the white paper conception, drafting and revision of the manuscript.

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TD Wagner, L Buelt, K Westrich, JD Campbell are employed by the National Pharmaceutical Council. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

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