Unlocking market access for gene therapies in the United States

Gene therapy holds great promise for treating a variety of diseases, but without changes, today’s payment system could limit the number of patients who benefit.

by Toby AuWerter, Jeff Smith, Josh Sternberg, and Lydia The
Gene therapy has the potential to eradicate the increasing number of diseases we know are associated with faulty or missing genes—or at least provide a functional cure for a period of time.1 Take hemophilia A, for example. Patients with this debilitating disease lack a gene that produces an essential blood-clotting protein, factor VIII. Gene therapy replaces that gene. Moreover, in contrast with other forms of therapy for hemophilia, in which weekly or monthly infusions of clotting-factor drugs are often necessary, gene therapy has the potential to be “once and done.” For years after administration, the patient may only require periodic follow-ups with a physician to monitor the continued safety and efficacy of the therapy.

Other gene therapies could have similar benefits, and many of those in development tackle rare diseases for which there are limited—or no—good treatments. Yet for all the promise of gene therapy, the therapy-payment system in the United States will need to change fundamentally to enable widespread access to it. This article explains why and suggests the steps manufacturers, with the cooperation of other stakeholders in the healthcare value chain, can take to help overcome the current challenges and give more patients access to these innovative therapies.

Current headwinds in reimbursement
Reimbursement of pharmaceutical products today occurs on a per-unit basis, which spreads out the costs of drugs and other services for chronic conditions over years. The cost of a gene therapy, however, would be much more concentrated—potentially in a single payment. In addition, given that the treatment is new, its full benefits and risks remain unclear. This combination of concentrated cost and uncertain outcome presents payment risks for two entities: payers and healthcare providers.

High one-time costs would make it hard for payers to underwrite the risk of full payment for the entire range of gene therapies coming to market simultaneously. In addition, a fixed, up-front pricing structure leaves the payer with all the risk of the therapy not working, given that the long-term efficacy of gene therapy as well as the risk of toxicity and other harmful effects to patients are not known with certainty at the time of first regulatory approval, though many risks will be addressed during pivotal studies and US Food and Drug Administration (FDA) review and approval. Payers and pharmacy benefit managers (PBMs) may require real-world data before covering the cost of gene therapy for all potential patients. And even with restricting coverage to a few therapies for which real-world evidence was available—or to a subset of eligible patients—cost spikes in annual budgets would be significant concerns.

Prior experience often shapes payer thinking on coverage for gene therapy. In particular, the concern over budget impact is a direct result of recent payer experience with innovative therapies for conditions like hepatitis C. The high level of unmet need when the first of these products launched in 2013, particularly for populations covered by Medicare and state Medicaid plans, created significant pressure on payer budgets. As more products came to market, increasing competition brought prices down, but the lesson for gene therapy is clear: carefully planning for and managing utilization is critical.

Patient portability also poses a challenge. Patients in the United States frequently switch their health insurers, with the average tenure estimated to be three to six years. The benefits of gene therapy could last years or even a lifetime, however, posing a unique challenge for the treatment when it comes to portability. Who pays for the benefits? A payer could find itself shouldering all the costs but enjoying few of the subsequent benefits when the patient switched to a different insurer. Those benefits would accrue to the new payer, which would now have a healthier patient in its insurance plan.

For healthcare providers, the path to adoption of gene therapy is similarly murky. Reimbursement of many biologic therapies in the United States today occurs under a buy-and-bill model. A treatment facility purchases the therapy for a fixed price,

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1 In this article, “gene therapies” refer to direct, in vivo administration of DNA-based therapies. Their most common delivery method is via a viral vector, such as a lentivirus or adeno-associated virus.
a physician administers it, and the facility then receives reimbursement. The physician receives a separate administration fee. This process can take 30 days or longer, potentially limiting the pool of healthcare providers with enough working capital to assume the reimbursement risk for high-cost gene therapy. In addition, some health plans only cover products in treatment facilities that have negotiated lower reimbursement rates. Given the lower margins, these facilities may be less likely to want to take on reimbursement risks unless they are confident they can attract enough new patients to reduce their costs below reimbursement rates. A smaller provider pool may limit the adoption of gene therapy to nearby patients or those willing to travel but may result in higher-quality, specialized care.

A range of industry stakeholders, including manufacturers, patient-advocacy groups, and payers, have recognized the need to adapt or replace the standard payment system if gene therapy is to become widely available. Several alternative payment mechanisms, including the following, have been proposed:

- **Annuity-based payment.** The payer agrees to pay a fixed price for the therapy but pays in regular installments, like with an annuity, spreading the cost over time.

- **Outcomes-based payment.** The payer pays only a portion of the full price up front. If the therapy achieves prespecified outcomes, the payer pays the remainder in full. This model spreads the risk, therefore, between the payer and manufacturer.

- **Outcomes-based rebate.** The payer pays the full price of the drug up front but receives a rebate if the drug does not achieve prespecified outcomes. This model, again, spreads the risk between the payer and manufacturer.

- **Outcomes-based annuity.** The payer pays a fixed price, with payments spread over many installments, but only if the drug continues to meet certain prespecified outcomes. This model, too, spreads the risk between the payer and manufacturer.

These proposals are promising in theory and are in use for other drug categories. For example, with cell therapies—which have also demonstrated long-term durable responses for certain patients and faced many of the same reimbursement challenges as gene therapies face—manufacturers are experimenting with outcomes-based payment models. While reimbursement remains a challenge for cell therapies, limiting their uptake among eligible patients, the lessons learned in that space will likely be relevant to gene therapies.

We are also seeing manufacturers of the next wave of gene therapies attempt to use alternative payment models. For example, Novartis received FDA approval for Zolgensma, a gene therapy for pediatric patients with spinal muscular atrophy with SMN1 mutations, in May 2019, and it is engaging with payers to create installment- and outcomes-based-payment options. Another example is bluebird bio, which has discussed offering an installment plan for its gene-replacement therapy Zynteglo, a therapy for beta-thalassemia approved in May 2019 in the European Union.

The challenges of alternative payment models, including price-reporting requirements, administration, and patient portability, however, are significant (Exhibit 1). They will need to be addressed to allow any alternative payment scheme to be workable.

**Price-reporting requirements**

Current price-reporting requirements in the United States limit the ability of manufacturers to offer outcomes-based payments and payments over time. Under best-price regulations, they must report all prices paid for therapy, with the lowest price—or the average price minus a specified percentage, likely to be 23 percent for gene therapy—becoming the benchmark paid within US Medicaid programs and the government’s 340B drug-discount program.

With an outcomes-based system, just one patient who failed to respond to gene therapy could set the price paid at a low level for all patients—including those who respond well—unless the rebate or discount was within 23 percent of the average
price. Similarly, payment over time would be limited unless every potential payer was using the same scheme. Otherwise, different payments from different organizations would make the average price reported by manufacturers inconsistent as installment payments came in.

**Administration**
Alternative payment models are more complex to administer than traditional, one-time payments are. Some payers may not have systems in place to carry them out. For example, payers that do not have readily available data on patient outcomes would be reliant on providers or other third parties to share whether patients have experienced durable benefits. Additionally, successful administration of the alternative payment models would require manufacturers and payers to agree on definitions of “positive” outcomes in complex diseases that vary widely in how they present in patients.

**Patient portability and the buy-and-bill model**
Alternative reimbursement models are designed to address payer concerns about high one-time costs and to reduce the risk payers shoulder. However, initial proposals do not address patient portability, as mentioned earlier, and provider challenges with the buy-and-bill model. Conceivably, broadening the contracts could spread the costs over multiple payers if a patient moves. Additionally, similar alternative contracts could reduce up-front payments and risk to providers.

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### Exhibit 1

**The challenges with alternative-payment models are significant.**

**Challenges faced by pricing-model options**

<table>
<thead>
<tr>
<th>Options</th>
<th>Fixed price</th>
<th>Outcomes-based arrangement¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-time payment</td>
<td>Annuity-based payment</td>
</tr>
<tr>
<td>Price reporting</td>
<td>N/A</td>
<td>×</td>
</tr>
<tr>
<td>Patient portability</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Description</td>
<td>Payer pays set price up front, with no subsequent transactions</td>
<td>Payer pays set price for drug, with cost amortized over course of 5–10 years</td>
</tr>
</tbody>
</table>

¹In this type of arrangement, payer and manufacturer share risk.
The way forward in payment options
There are two high-level approaches manufacturers can take to facilitate payment for gene therapy and hence widen availability: work within the system, or change it. The latter would entail changing market structures or changing regulations and legislation. And the options are not mutually exclusive (Exhibit 2).

Option 1: Work within the current system
Working within the current legal and regulatory framework and market structures is the default approach—and the least resource intensive. The aim would be to set a single price for a one-time, up-front payment to a manufacturer based on a robust assessment of the clinical and economic benefits, including cost effectiveness, of a product.

Achieving this would require the engagement of a broad set of stakeholders, including United States–based third-party value-assessment groups, such as the Institute for Clinical and Economic Review and the Patient-Centered Outcomes Research Institute. Manufacturers would also need to seek collective agreement on the merits of different cost-effectiveness methodologies and to share relevant data, such as clinical-trial results. While manufacturers already share data, they may need to collect more data or modify the design of their studies to meet the requirements of cost-effectiveness studies. Additionally, they may need to share more data ahead of launch to enable these assessments to occur in a timely manner.

This solution could provide alignment on the appropriate value of gene therapies across manufacturers and payers but may not address the other payer concerns with one-time costs and the risk they are taking on. Also, it would not address provider challenges with the buy-and-bill model.

Option 2: Change the market structure
Developing different market structures that support different payment models is another way forward that could address payer concerns with risk by distributing it across multiple players.

One such example would be manufacturers experimenting with a new launch strategy that also changes the distribution of payment risk in the market. Rather than a company selling its product

Exhibit 2

Manufacturers have options when considering how to change payment for gene therapy.

Solutions by degree of change

<table>
<thead>
<tr>
<th>Status quo</th>
<th>Rethink paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution</td>
<td></td>
</tr>
<tr>
<td>Work within current system</td>
<td>Change market structure</td>
</tr>
<tr>
<td>Example</td>
<td></td>
</tr>
<tr>
<td>Employ 1-time payment model combined with education, potentially with cost-effectiveness analyses, to garner support for appropriate price points</td>
<td>Pursue innovative partnership models with individual stakeholders to distribute payment risk across greater subset of entities</td>
</tr>
<tr>
<td>Degree of change</td>
<td></td>
</tr>
<tr>
<td>LOWER</td>
<td></td>
</tr>
<tr>
<td>Degree of change</td>
<td></td>
</tr>
<tr>
<td>Degree of change</td>
<td></td>
</tr>
<tr>
<td>HIGHER</td>
<td></td>
</tr>
</tbody>
</table>
directly to payers and other stakeholders, it could enter a partnership with a PBM—and potentially, its associated specialty pharmacy—whereby the PBM would agree to buy a gene therapy and act as its distributor. The intention would be for the PBM to be able to agree on new payment structures with other payers, such as in the annuity or outcomes-based models described earlier or a model that allows payment to “follow the patient” if he or she switches insurers. In other words, the PBM and specialty pharmacy would assume part of the risk rather than the payer.

The arrangement would initially generate fees for the specialty pharmacy for dispensing the product. Over time, however, the PBM would gather patient-outcome data, which would help value the product and set a precedent for similar models for other gene therapies. In addition, this arrangement has the benefit of simplifying contracting for the manufacturer: it receives fixed terms from a single entity. Spark Therapeutics and Express Scripts Holding have pursued such an arrangement for Luxturna, Spark Therapeutics’s adeno-associated virus gene therapy that treats certain inherited retinal diseases associated with loss of sight and, in 2017, became the first FDA-approved gene therapy (Exhibit 3).

The downside of this type of arrangement could be that manufacturers relinquish the ability to control, directly, the payment structures offered by distributors. Under normal contracts with payers, manufacturers can stipulate certain parameters (for example, that therapies are covered consistent with their labels, that benefits are processed rapidly, and that out-of-pocket costs are capped at in-network limits). By no longer selling directly to payers, manufacturers lose some of this contracting control.

Another model that shifts market structures might be one that distributes the payment risk among a greater number of entities, not just between manufacturers and payers (as in the outcomes-based models described). As companies not traditionally in healthcare, such as technology companies and banks, look to gain exposure to the healthcare space, they could be interested in assuming some of the risk.

New forms of insurance aimed at spreading risk might also emerge. For example, in contracts between health-plan sponsors (employers and

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**Exhibit 3**

**Spark Therapeutics has innovative payment programs for its Luxturna retinal-disease gene therapy.**

**3 payment options for Luxturna**

<table>
<thead>
<tr>
<th>Option</th>
<th>Outcomes-based rebate</th>
<th>Direct to pharmacy benefit manager</th>
<th>Centers for Medicare &amp; Medicaid Services demonstration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Spark pays rebates based on outcomes at 30–90 days and 30 months</td>
<td>Spark sells to pharmacy benefit manager that can implement payments over time</td>
<td>Payers amortize cost over time or pursue other rebate-based models through Centers for Medicare &amp; Medicaid Services payment demonstration</td>
</tr>
<tr>
<td>Initial stakeholder engaged</td>
<td>Harvard Pilgrim Health Care</td>
<td>Express Scripts Holding/Accredo Health</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
</tr>
</tbody>
</table>
governments) and PBMs, there could be carve-outs for gene therapy that exclude gene-therapy products from net-cost guarantees. Instead, separate reinsurance funds could be set up to cover these products. Other stakeholders, including manufacturers, that were keen to support the adoption of gene therapy could contribute to the funds along with health-plan sponsors. The US federal government and several states have set up reinsurance programs to protect payers against the risk of covering high-cost Patient Protection and Affordable Care Act enrollees. A reinsurance fund for gene therapy could work similarly—the reinsurance program would pool risk across different payers and be responsible for all or part of the gene-therapy claims that surpass an “attachment point” that triggers reinsurance.

Option 3: Change the legal and regulatory environments
There may be a need for stakeholders to consider jointly some potential changes to the policy framework and the legal and regulatory environments for gene-therapy reimbursement. A number of forums (such as MIT CBI’s New Drug Development Paradigms and Duke University’s Robert J. Margolis, MD, Center for Health Policy2) have brought together multiple stakeholder groups over the past several years to consider changes to the policy framework for gene therapy.

In addition, manufacturers could use Centers for Medicare & Medicaid Services (CMS) demonstration projects to test alternative payment models in an environment that allows for waiving of some requirements (for example, best price) for the purpose of the pilots. Spark Therapeutics has already engaged CMS to examine the economic impact of installment payments and higher rebates tied to clinical outcomes.3 Other demonstration projects could test reinsurance models to generate evidence for a range of different payment models.

Gene therapy holds incredible potential to transform the treatment of debilitating diseases. There are several exciting proposals that could address payer concerns with one-time costs, risk, and patient portability. But manufacturers will have to work creatively with other stakeholders to make these proposals reality. They will also have to develop new solutions to overcome challenges providers face with the buy-and-bill model. Unlocking market access for gene therapy will be critical to its adoption and to meeting patients’ needs.

2 Gregory W. Daniel et al., Overcoming the legal and regulatory hurdles to value-based payment arrangements for medical products, Robert J. Margolis, MD, Center for Health Policy, December 15, 2017, healthpolicy.duke.edu.

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