November 2023

The Paradigm Shift: Navigating the emergence of value-based contracts for future gene therapies

Summary

Value-based contracting (VBC) has been difficult to execute in the pharmaceutical arena, especially in the gene therapy space. This has been driven by several factors, including the lack of long-term data, the imbalance of upside and downside risk between manufacturers and payers, and difficulties with implementation.

However, gene therapy manufacturers should prepare for VBC given the evolving policy and market access landscape in the US, driven largely by the Medicaid Cell and Gene Therapy (CGT) Access Model. Manufacturers should be strategic in designing and utilizing long-term outcomes studies, as the data will be central to contract terms that impact reimbursement amounts and timelines under the CGT Access Model.

Current gene therapy landscape

In recent years, genetic engineering technology has made impressive strides in providing life-changing benefits. As of August 2023, 15 gene therapy products (including CAR-Ts)\(^1\) received FDA approval (shown in Table 1), and the FDA is expected to render seven more decisions in 2023 alone.\(^2\)

By 2030, it is estimated that up to 74 cell and gene therapies could be approved in the US, reaching 93,000 patients and generating $24.4 billion in revenue.\(^3\) Utilizing CRA’s proprietary tool, Pipeline Scout\(^4\), and secondary research, we have identified close to 200 gene therapy products/programs currently in clinical development across 15 therapeutic areas and over 100 indications. Gene therapy’s most popular therapeutic targets include oncology, ophthalmology, neurology, and hematology.

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\(^1\) Cell-based gene therapy that involves altering genes inside T-cells to attack cancer.


\(^4\) CRA’s machine-learning asset search tool.
Table 1: Current FDA-approved gene therapies

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>FDA approval</th>
<th>WAC (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCTAVIAN</td>
<td>BioMarin</td>
<td>Hemophilia A</td>
<td>June 2023</td>
<td>$2.9 Million</td>
</tr>
<tr>
<td>ELEVIDYS</td>
<td>Sarepta</td>
<td>Duchenne Muscular Dystrophy</td>
<td>June 2023</td>
<td>$3.2 Million</td>
</tr>
<tr>
<td>VYJUVEK</td>
<td>Krystal Biotech</td>
<td>Epidermolysis Bullosa</td>
<td>May 2023</td>
<td>$24,250/vial</td>
</tr>
<tr>
<td>BREYANZI</td>
<td>Bristol Myers Squibb</td>
<td>Large B-Cell Lymphoma</td>
<td>June 2022</td>
<td>$410,300</td>
</tr>
<tr>
<td>CARVYKTI</td>
<td>Janssen</td>
<td>Multiple Myeloma</td>
<td>Feb 2022</td>
<td>$465,000</td>
</tr>
<tr>
<td>ADSTILADRIN</td>
<td>Ferring Pharmaceuticals</td>
<td>High-Risk, Non-Muscle-Invasive Bladder Cancer</td>
<td>Dec 2022</td>
<td>N/A</td>
</tr>
<tr>
<td>HEMGENIX</td>
<td>CSL Behring</td>
<td>Hemophilia B</td>
<td>Nov 2022</td>
<td>$3.5 Million</td>
</tr>
<tr>
<td>SKYSONA</td>
<td>bluebird bio</td>
<td>Cerebral Adrenoleukodystrophy (CALD)</td>
<td>Sep 2022</td>
<td>$3 Million</td>
</tr>
<tr>
<td>ZYNTEGLO</td>
<td>bluebird bio</td>
<td>Beta-thalassemia</td>
<td>Aug 2022</td>
<td>$2.8 Million</td>
</tr>
<tr>
<td>ABECMA</td>
<td>Bristol Myers Squibb</td>
<td>Multiple Myeloma</td>
<td>March 2021</td>
<td>$419,500</td>
</tr>
<tr>
<td>TECARTUS</td>
<td>Kite Pharma</td>
<td>Mantle Cell Lymphoma</td>
<td>July 2020</td>
<td>$373,000</td>
</tr>
<tr>
<td>ZOLGENSMA</td>
<td>Novartis</td>
<td>Spinal Muscular Atrophy (Type I)</td>
<td>May 2019</td>
<td>$2.1 Million</td>
</tr>
<tr>
<td>KYMRIAH</td>
<td>Novartis</td>
<td>Acute Lymphoblastic Leukemia (ALL); Diffuse Large B-cell Lymphoma; Follicular Lymphoma</td>
<td>May 2018</td>
<td>$475,000</td>
</tr>
<tr>
<td>LUXTRUTTNA</td>
<td>Spark Therapeutics</td>
<td>Confirmed Biallelic RPE65 Mutation-Associated Retinal Dystrophy</td>
<td>Dec 2017</td>
<td>$850,000</td>
</tr>
<tr>
<td>YESCARTA</td>
<td>Kite Pharma</td>
<td>Large B-Cell Lymphoma</td>
<td>Oct 2017</td>
<td>$373,000</td>
</tr>
</tbody>
</table>

Due to a perceived lack of evidence in support of high prices relative to potential alternatives, commercial payers have attempted to control gene therapy use through prior authorizations to trial inclusion/exclusion criteria. Some state Medicaid programs have also heavily restricted utilization by limiting coverage to criteria beyond the FDA label, and approving case-by-case exceptions instead of implementing formal coverage policies. As newer therapies enter the market, manufacturers’ contracting strategies will need to account for insurers’ resistance to high prices in the context of a potentially limited evidence base.

**Historical challenges to value-based contracting for pharmaceuticals**

In general, VBCs for pharmaceuticals have been slow to gain traction due to an imbalance of upside and downside risk between manufacturers and payers, compounded by high implementation costs. There are substantial complexities and costs for determining and measuring appropriate outcomes for contracting that are feasible in the real world. Further, payers have become accustomed to receiving simple rebates that provide predictable revenue with minimal administrative complexity. These factors lead to payer reluctance to engage in VBCs. Likewise,
manufacturers have been hesitant to fully embrace downside risk, fearing financial repercussions if the outcomes are not as promising as anticipated.

However, gene therapies have unique characteristics that, combined with policy and market landscape changes, make VBCs more attractive moving forward. The high unmet need for solutions addressing uncertainty around drug value creates a strong case for VBCs. Payers and manufacturers alike are negatively impacted by this uncertainty—payers feel obligated to offer coverage despite high costs and uncertain long-term benefits, while manufacturers face challenges in demonstrating the enduring effectiveness of therapies that often receive accelerated approvals. This uncertainty is further exacerbated by the high prices of gene therapies, making it imperative to align reimbursement with actual clinical outcomes.

Another reason why gene therapies are particularly suited for VBCs is the feasibility for tracking long-term outcomes. Since gene therapies are administered in a limited number of specialized medical facilities, and often to relatively small patient populations, it is potentially easier to collect comprehensive long-term data. This enables more accurate outcomes tracking, thus mitigating some of the risks associated with VBCs and offering a viable pathway for the widespread adoption of these innovative payment models.

**A market access shift towards VBC**

In February 2023, in line with President Biden’s Executive Order 14087 on reducing drug costs, the Health and Human Services Secretary recommended the Cell & Gene Therapy Access Model for implementation by the Center for Medicare and Medicaid Innovation (CMMI).\(^5\)\(^6\) The CGT Access Model lets state Medicaid programs grant CMS the power to negotiate multi-state, outcome-based deals for select CGTs. Medicaid serves a significant proportion (21%) of the US population, including 36% of children.\(^7\)\(^8\) The CGT Access Model indicates that the US market is shifting towards VBCs for gene therapies, tying payments to outcomes and distributing costs for faster and broader patient access.

The CGT Access Model enhances CMS’ ability to negotiate cost-effective VBCs for participating states by spreading administrative costs over a larger patient base. As the primary drug access decision maker for multiple states, it strengthens Medicaid’s bargaining power for coverage and pricing. CMS can link reimbursements to long-term CGT value, reflecting a broader base of outcomes data and extending payment timelines. Per Medicaid’s best price policy, the CGT Access Model price must be reported to CMS and offered to all state Medicaid plans, increasing risk for gene therapy manufacturers and emphasizing their need to be ready for VBCs.

While the model poses risks to manufacturers, it can be an attractive pathway to access a large, multi-state patient population more quickly. The CGT Access Model allows manufacturers to engage with CMS directly, align on VBC structures, build out real-world data collection capabilities, and access patients in state Medicaid programs that may not otherwise expand coverage to gene therapies quickly.

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In practice, voluntary manufacturer involvement in the CGT Access Model is uncertain. The risk of slower or restrictive coverage from individual state Medicaid formularies might drive manufacturers towards the model. This likelihood increases if the model becomes the norm for Medicaid coverage of new therapies over individual state assessments. Then, the CGT Access Model might prompt large commercial plans to engage in VBCs by emulating CMS’ contracting terms.

Given these new pricing and market access dynamics, manufacturers of cell and gene therapies should be prepared to negotiate VBC terms that are administratively feasible and not prohibitively risky from a business perspective.

Existing innovative contracting with gene therapies

VBC models that are most utilized for gene therapies in the US include outcomes-based contracting and long-term “annuity-style” payment plans. Subscription models (i.e., payers pay a flat fee for access to unlimited treatments) and warranty programs are increasingly discussed but have not yet been implemented for gene therapies.

Among currently FDA-approved gene therapies, Kymriah, Luxturna, Zolgensma, and Zynteglo have engaged in innovative contracting with payers. As more expensive gene therapies win approval (most recently Roctavian and Elevidys in June 2023), VBC negotiations are likely to continue evolving due to the benefits of spreading risk across payers and manufacturers, lowering budget impact, and mitigating evidence uncertainties.

Existing innovative contracting with Kymriah, Luxturna, Zolgensma, and Zynteglo are noted in Table 2 below.

Table 2: Innovative contracting with currently approved gene therapies

<table>
<thead>
<tr>
<th>Value-based contracting with currently approved gene therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KYMRIAH</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Outcomes program</td>
</tr>
<tr>
<td>• Offers reimbursement linked to outcomes at 30 days for only one of its indications (B-cell precursor acute lymphoblastic leukemia) with certified treatment centers or providers.</td>
</tr>
<tr>
<td><strong>LUXTURNA</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Outcomes program</td>
</tr>
<tr>
<td>• Offers payers rebates if patient outcomes fail to meet a specified short-term efficacy (30-90 days) and longer-term durability (30 months) threshold based on full-field light sensitivity threshold (FST) testing scores, measured against a patient-specific baseline.</td>
</tr>
<tr>
<td>Long-term payment plan</td>
</tr>
<tr>
<td>• In discussions with CMS on a proposal to offer payers the option to spread payment over multiple years.</td>
</tr>
</tbody>
</table>

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Long-term payment plan

• Offers payers the option to pay over five years.

Outcomes program

• Offers payers rebates, depending on product efficacy.

Outcomes program

• Offers to reimburse payers up to 80% of the therapy cost if a patient fails to achieve and maintain red blood cell transfusion independence over the two years following infusion.

Key challenges to future value-based contracting

Improving access to gene therapies requires collaboration and compromise across key stakeholders, including governments, pharmaceutical companies, and payers. VBC has the potential to unlock market access where financial feasibility and clinical uncertainty pose barriers to coverage. However, manufacturers must take proactive measures (e.g., technological investments and multi-stakeholder collaboration) to overcome key challenges for innovative payment models.

Payers have not historically focused on long-term outcomes when negotiating contracts. From a payer perspective, there has been limited value in long-term outcomes-based agreements since patients switch commercial health insurance providers on average every 2-2.5 years. As commercial insurers are increasingly engaging in VBCs, however, the new Medicaid CGT Access Model has the potential to accelerate payer willingness to engage in VBCs. Accordingly, manufacturers will need to navigate the piecemeal adoption of VBCs across different insurer types in their evidence plans and contracting terms.

Payers have limited capability to assess the long-term durability, efficacy, and safety of new gene therapies. For payers, tracking long-term outcomes is burdensome and ambiguous, and tracing patient data across insurer changes is not feasible. The uncertainty of clinical value is even greater for gene therapies that target rare diseases because smaller trial sizes and expedited FDA reviews further limit available data at product launch. Therefore, the onus of measuring long-term outcomes is likely to fall on the manufacturers, who will need to invest in processes to track them.

Payers may not perceive the high administrative costs of long-term VBCs as justifying uncertain rebates. Payers may prefer guaranteed rebates in the short term rather than engage in outcomes monitoring. This has been the case for Hemgenix, which, despite its $3.5 million list price, is expected to have too small a budget impact for any one payer given the small eligible population to justify the administrative costs. Minimizing the administrative costs of long-term

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VBCs for payers may make them more likely to engage in such contracts, allowing manufacturers to avoid short-term rebates in favor of shared risks linked to outcomes.

**Government price reporting requirements expose manufacturers to unintended risks for engaging in outcomes-based agreements and therefore may limit manufacturers’ willingness to engage.** For example, the Medicaid Drug Rebate Program gives manufacturers two reporting options. Manufacturers that offer a VBC to all states will report the best prices within the VBC in addition to a non-VBC best price. If manufacturers do not offer a VBC to all states, they must report a single best price that includes all discounts, rebates, and adjustments, which could be substantially lower than a typical non-VBC best price. Reporting requirements for average sales price (ASP) and average manufacturer price (AMP) raise similar concerns.

In response, gene therapy manufacturers are considering warranty programs, offering refunds to payers if patients do not see positive outcomes within a set time. While similar programs exist for other products like Xalkori and Panzyga, a distinct feature is that a third party can offer the warranty, ensuring the best price reported to CMS remains unaffected.

**Some therapies do not have a clear choice of outcomes that should be used as the basis of VBCs.** While some therapies have clear binary outcomes, others may incorporate relative improvements that are difficult to reliably capture. bluebird bio cited the complexity of cerebral adrenoleukodystrophy (CALD) as an implementation barrier to an outcomes-based payment model for Skysona. Even when outcomes have been measured in clinical trials, certain tests may be infeasible for payers to rely on or require in the real world purely for contracting reasons (e.g., biopsies, complex scans, genomic re-sequencing). Manufacturers will need to be strategic in their early clinical evidence-generation plans to account for potential outcomes that could be used in VBCs, particularly if they become an avenue for broader coverage.

**Leveraging real-world evidence to define outcome measures**

On March 20, 2023, Novartis Gene Therapies presented long-term Zolgensma data, showing sustained benefits up to 7.5 years after dosing. All dosed children reached the motor milestones specified in the study. With such substantial long-term data, Zolgensma highlights the modality’s potential for sustained benefits.

Zolgensma’s data provides a blueprint for outcome-based agreements. Novartis showcased how gene therapy manufacturers can spearhead real-world evidence (RWE) monitoring across diverse treatment sites. Future gene therapy manufacturers can consider taking an expanded approach to the Phase IV trial to enable better potential for VBC.

**Defining the optimal outcome measures for VBCs.** Selecting real-world outcomes during Phase IV study planning helps determine the measures and timeframes for VBCs. Identifying

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these outcomes early allows for more time to gain agreement from clinical experts as opposed to waiting until contract negotiation stages.

**Addressing payers’ limited capability for outcome evaluation and concerns regarding high administrative costs for small patient cohorts.** Manufacturers can mitigate the burden of VBC by transitioning their Phase IV study approach into a patient registry tied to payments. This unified registry removes the burden from individual payers to create separate monitoring systems and can synchronize with clinical outcome assessments.

In an environment where CMS is consolidating market power to negotiate contracts with gene therapy manufacturers, linking reimbursement to evidence of long-term outcomes is a promising path forward for manufacturers to achieve broad patient access. However, manufacturers will be continually challenged to generate appropriate evidence with investments in tools to track long-term outcomes and consideration of payer contracting implications.

**Implications for gene therapy manufacturers**

In the evolving landscape of gene therapy reimbursement, manufacturers must be prepared to generate and utilize RWE to meet payer expectations. VBC is likely to grow as a focal point for creating access to high-cost gene therapies, and manufacturers will need to navigate this trend and effectively collaborate with payers to ease their concerns about long-term clinical benefits and financial risk. By adopting tailored strategies for market access and reimbursement, manufacturers can realize several key benefits, as shown in Figure 1.

**Figure 1: The role of VBCs in gene therapy reimbursement**

Manufacturers will have to understand evolving payer value drivers and challenges for executing VBC. By making strategic decisions about clinical evidence generation plans while accounting for payer feedback and preparing for VBC negotiations, manufacturers can leverage the trend toward VBCs to expand access to novel gene therapies. Manufacturers who strategically embrace VBC and effectively utilize RWE will not only secure market access but also drive meaningful improvements in patient outcomes.
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Contacts

Ayushman Ghosh  Ashutosh Mishra  Jared Levine
Vice President  Consulting Associate  Associate
+1-212-520-7145  +1-212-520-7130  +1-212-294-8870
aghosh@crai.com  amishra@crai.com  jlevine@crai.com

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