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Managing the Challenges of Paying for Gene Therapy: Strategies for Market Action and Policy Reform

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Introduction

Gene therapies delivered through a single administration have revolutionized treatment possibilities for many patients living with serious or fatal conditions such as spinal muscular atrophy, hemophilia, and sickle cell disease. In less than seven years, the number of US Food and Drug Administration (FDA) approved single-dose gene therapies has grown from zero to 17.^{1,2} Shadowing the excitement about the transformational potential of many gene therapies has been widespread concern about the combination of uncertainty in the durability of their benefits over the long term and the short-term financial shock of high prices. Prices for gene therapies are now cresting above \$3 million dollars.^{3,4} Although the aggregate costs of gene therapies at these prices have not proven yet to be unmanageable to large payers given the small number of patients currently treated, growth in the approval of gene therapies for larger populations is on the horizon. All told, 85 new gene therapies across more than 12 therapeutic areas are expected to receive regulatory approval by 2032.⁵ The list price spend in the United States for these treatments over the next decade has been estimated at \$35 to \$40 billion, raising concerns that gene therapies will create budget pressures and consequent constraints on access even for larger payers, while smaller employers, state Medicaid plans, and regional health plans may find providing access financially impossible without some modification in pricing or payment methods.⁶⁻¹⁰ Therefore, achieving the right balance of providing incentives for innovation while ensuring equitable and affordable access for health systems and for patients, represents a collective responsibility for all participants in the health system that will require overcoming substantial challenges.

The routine methods for managing the balance of costs and access include utilization management and formulary design to ensure that only those patients for whom a given treatment is clinically appropriate receive insurance coverage. However, the transformative clinical benefits of many gene therapies, combined with limitations in the clinical trial evidence, make it difficult for insurers to design coverage policies narrower than often broadly framed FDA approval language. Increasingly, many payers (a term we use to include not only insurers and pharmacy benefit managers (PBMs) but also employers and other health benefit plan sponsors) report that they are exploring innovative insurance models and payment mechanisms meant to address the intertwined challenges presented by small insurance pools, the financial shock of single-time payment, and the substantial uncertainty regarding the longer-term benefits, safety, and durability of gene therapies.

Individual patient cost sharing requirements have an important impact on access to gene therapies, but the purpose of this white paper is to explore the range of emerging market approaches and possible policy reforms that have the potential to help the broader US health system achieve equitable and affordable access to gene therapies. We analyze the relative advantages and potential unintended consequences for each option, along with an exploration of unique opportunities for combination or layered approaches. None of the tools or policy reforms we will

discuss are “silver bullets” that can singlehandedly solve all the barriers and tensions inherent in the current healthcare insurance and payment landscape. Still, we seek to present policymakers and industry leaders with insights and lessons learned from experts and market experience to date that will help all stakeholders take action to be part of an innovative future of gene therapy pricing, coverage, and payment.

Structure of This Paper

To understand the payment challenges presented by gene therapies first requires an understanding of the current payment landscape and how the costs of gene therapies impact different payer types. We also present an analysis of the limitations of stop loss insurance and reinsurance to protect payers against potentially catastrophic costs.

We then examine three core payer challenges in more detail, tools to address these challenges, implementation issues and best practices, and policy and collaboration opportunities. This is followed by sections considering new ways to combine solutions and on how multistakeholder collaboration may provide more holistic solutions than are currently available.

Methods

This paper relies on information, data, and perspectives gathered from a targeted literature review, and draws upon the body of work on gene therapy issues by the Institute for Clinical and Economic Review (ICER) and NEWDIGS FoCUS (Financing and Reimbursement of Cures in the US) Project.¹¹ We also performed interviews with stakeholders engaged in the execution of market solutions for gene therapies and with a sample of organizations participating in the ICER Policy Leadership Forum and NEWDIGS FoCUS Project at the September 2023 NEWDIGS Design Lab.

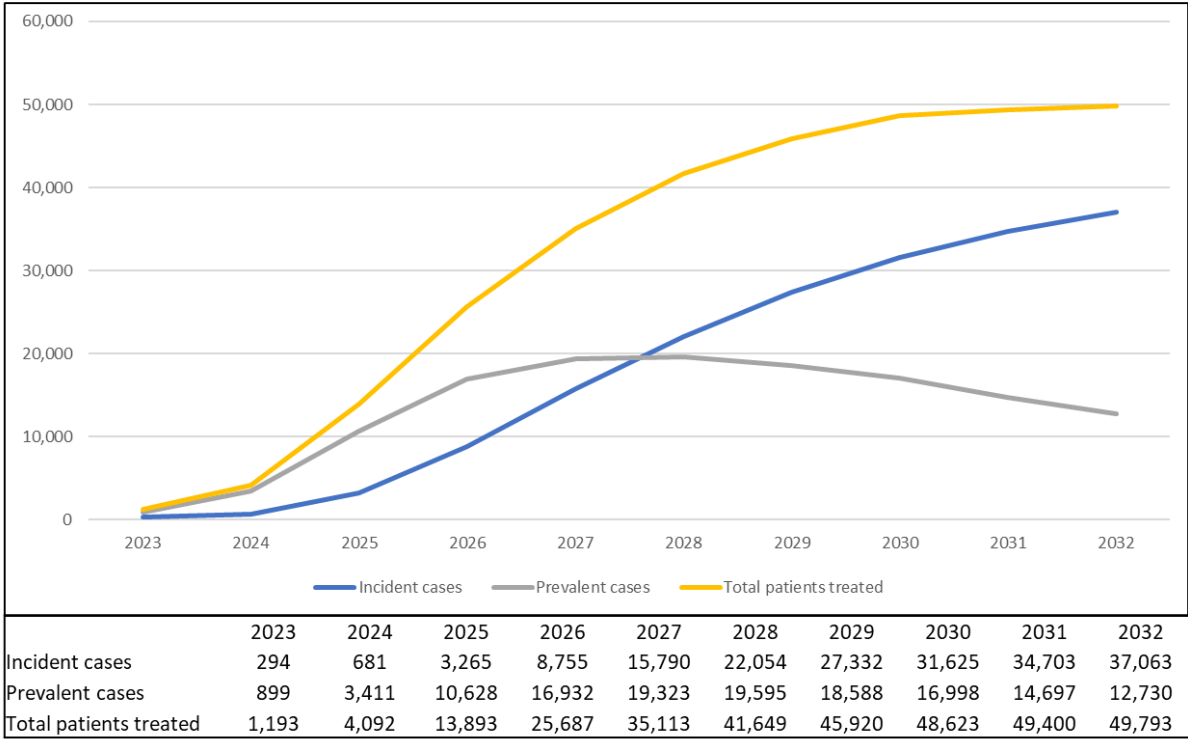
Our targeted literature review included keyword and hand searches for peer-review and gray literature to understand the impact that payment challenges have on payer affordability and the downstream impact on patient access. For interviews, we used a structured discussion guide to collect input from twenty-two experts from payer organizations, large and small biopharmaceutical manufacturers, patient advocacy groups, providers, and ancillary vendors offering or providing necessary execution support for potential solutions.

Representatives from patient advocacy groups, purchasers, and employers joined senior policy leaders from 28 payer and life science companies at a two-day meeting in December 2023 to deliberate on the potential market strategies and policy solutions and provide suggestions for revisions to a draft version of this paper. The participants in this meeting are shown in Appendix A. None of these participants or their organizations should be considered as approving of any element of this paper. The perspectives and recommendations presented here are those of the editorial team at ICER and NEWDIGS alone.

Background

Gene therapies modify the DNA or RNA of cells. Nearly all gene therapies are intended to provide a durable effect lasting from a single administration.¹² As noted earlier, there are currently 17 single-administration gene therapies approved in the US market, but the number of new therapies is expected to increase rapidly over the coming decade. Figure 1 below estimates the number of patients that will be treated over that period, with the treatable patient population anticipated to exceed 48,000 per year by the year 2030.⁵

Figure 1: Estimated gene therapy treatable patient population by 2032



As the healthcare payment ecosystem prepares for this anticipated growth, three key interconnected challenges must be addressed: determining a fair price, managing clinical uncertainty, and managing short term budget impacts.

Determining a Fair Price

Gene therapies entering the market in the US have been priced at very high levels. It is true that these one-time prices, if they are associated with durable major health improvements, may, in many cases, represent a good long-term value and, in some cases, may even represent net savings

over an extended timeframe when compared to the cost of existing treatments. Nonetheless, prices between \$1 million to \$3 million or more, if paid in full at the time of treatment, are very difficult to manage for smaller employers and Medicaid, and pose a long-term risk to the affordability of overall costs and resulting insurance premiums for state budgets and all commercial plan sponsors.

If the pricing for gene therapies were regulated as utilities are in the US, determining a fair price would emerge from a process of calculating a “reasonable” profit margin on top of the risk-adjusted cost of research and development, manufacturing, and distribution costs. But given the magnitude of risk inherent in drug discovery and the need to incentivize the development of drugs that produce substantial health gains, health economists and governments outside the US have favored a paradigm that would align launch pricing with the magnitude of the added health benefits to patients, a form of drug pricing generally called “value-based” pricing. Value-based pricing can be done through a relatively qualitative approach linked to implicit or explicit categories of added overall benefit, or it can be done through formal cost-effectiveness analysis in which fair prices must meet some pre-established cost-effectiveness threshold or range. Whichever approach is used, there are several important questions about evaluating the evidence and determining fair value-based pricing for any single-administration therapy that offers the possibility of a substantial and durable effect.

Question 1: How should value-based prices for gene therapies reflect substantial uncertainty regarding their clinical effectiveness owing to limitations in study design, outcome measures, and the size and duration of clinical trials?

Most gene therapies to date have been targeted at serious progressive or life-threatening conditions. These conditions are also often notable for affecting a small population, thereby qualifying as orphan conditions.¹³ The combination of severity and small population size can raise ethical and practical barriers to using randomized controlled trials (RCTs) in the early evaluation of new treatments. Single-arm trials, or randomized controlled trials with early crossover, have become common standards for regulatory approval, and the possibility of selection bias or other biases inherent in these study designs makes it more difficult to trust in the magnitude of benefits seen among patients in the trials. Other factors that can complicate the generation of robust evidence include the lack of standard patient-centered outcome measures or validated surrogate measures; a lack of standardization of “usual supportive care”; and novel mechanisms of action and therapy delivery techniques that raise questions about long-term safety and the durability of early clinical benefits.^{14,15} Methodological research has refined various methods to display uncertainty in cost-effectiveness findings, but it remains unclear what the best options are for transparently judging the uncertainty inherent in the evidence on cell and gene therapies and reflecting it in the calculation of a value-based price.

Question 2: How should value-based prices for potential cures reflect special ethical priorities related to treatments for very severe conditions, rapidly fatal conditions, rare conditions, illnesses that affect children, and conditions that have a high lifetime burden of illness?

Whether qualitative approaches or cost-effectiveness analyses are used to help evaluate fair pricing levels for new interventions, policymakers must have some mechanism to integrate considerations of special ethical priorities into evaluations of evidence to guide a broader judgment of value. The most common ethical priorities considered by Health Technology Assessment (HTA) groups and insurers relate to treatments that address conditions that are particularly severe, that extend life near the end of life, and/or that involve children. Most or all of these considerations will be factors in conditions treated by gene therapies, highlighting the challenging interplay of evidence and values in setting priorities and pricing levels for these treatments.

Question 3. For gene therapies that have evidence suggesting substantial and durable benefits, how should the determination of value-based prices factor in a fair sharing of the economic surplus over the lifetime of the treatment and the cost “savings” from preventing the future costs of chronic care over many years?

Many gene therapies are likely to offer the promise of health gains far greater than most new drugs, and one-time therapies for chronic conditions may also produce substantial cost offsets in the health system over the lifetime of patients, as the cumulative costs of many years of previously required care are avoided. Traditional cost-effectiveness methods translate these large potential health gains and cost offsets into one-time pricing recommendations that represent a much greater capture of the economic surplus provided by the treatment than would be the case were the same treatment provided and reimbursed in a chronic fashion.¹⁶ For example, it has been noted that value-based prices suggested by traditional cost-effectiveness analysis could be in the range of \$20-\$25 million in the US context for cures of an expensive chronic condition such as hemophilia.^{17,18} Gene therapies may never face competition from generic or biosimilar versions even after exclusivity ends, and therefore their upfront price may result in the innovator capturing all the economic surplus from the treatment in perpetuity. These prices, and the increase in capture of economic value by manufacturers, may be viewed as representing unacceptable opportunity costs within the health budget or between health and other desirable social spending.¹⁸

Managing Clinical Uncertainty

All drugs have some level of uncertainty at the time of launch regarding their long-term safety and effectiveness, but as noted above, for multiple reasons gene therapies enter practice with more limited data and unique levels of uncertainty regarding the durability of their beneficial effects. Paying millions of dollars all at once at the time of administration magnifies the concerns that payers have about whether they will receive a reasonable clinical value for their investment.

Payers we spoke with expressed more concern about the uncertainty in clinical durability than safety. In part this was because side effects or longer-term risks of gene therapy have been relatively minor among the treatments approved so far. The other reason that the uncertain durability of effect has troubled payers is because they feel that the high prices being set by manufacturers are being justified implicitly, if not explicitly, by assuming that the durability of effect will be complete and everlasting. Since some prominent gene therapies have not turned out to be the “one and done” treatments that many had hoped for, some payers expressed to us that more conservative assumptions about the durability of benefit are warranted moving forward when justifying high prices.

It is certainly true that substantial uncertainty regarding longer-term clinical effectiveness is not unique to gene therapies. Payers and policy analysts have noted similar challenges with the rising number of drugs approved through the accelerated approval pathway.¹⁹ Nonetheless, the very small number of patients enrolled in pivotal trials for gene therapies, combined with limited options to avoid paying very high one-time pricing, has made managing clinical uncertainty one of the primary goals of innovative payment mechanisms which will be discussed later in this paper.

Managing Short Term Budget Impact

We heard the term “lightning strike” frequently when payers described the difficulty in predicting and managing gene therapy costs. Some gene therapies are intended to treat chronic conditions such as beta-thalassemia, hemophilia, and sickle cell disease. For these conditions, it is possible to know how many individuals are likely to be eligible before regulatory approval of a gene therapy, thus reducing uncertainty in the costs to be expected once the treatment is available. However, this ability to predict which individuals would be eligible for very high-priced treatments creates a problem for addressing short term budget impact through stop-loss and reinsurance programs. Employers or other plan sponsors with known individuals likely to be eligible for gene therapies may seek out stop-loss or reinsurance coverage, thereby creating significant adverse risk for these insurance providers. Some in the market have reacted to exclude certain individuals or conditions from eligibility for stop-loss/reinsurance coverage.

When gene therapies are intended to treat newly incident cases of genetic disorders such as spinal muscular atrophy or cerebral leukodystrophy, the primary insurance problem is often called an actuarial risk: the risk that smaller self-insured employers and plan sponsors without adequate stop loss or reinsurance protection could be financially destabilized by an unexpected cluster, or even a single case requiring a multi-million-dollar treatment. A disproportionately large short-term budget impact could also significantly threaten smaller health plans and state Medicaid programs.²⁰

Potential Market Strategies and Policy Solutions

Determining a Fair Price

The main thrust of this white paper is to explore innovative insurance and payment mechanisms to help address these tensions. But pricing is an inextricable element in any model to improve access and affordability. Whether the price for a cell or gene therapy is paid as a single fee at the time of administration or is paid through some form of installment payment agreement, determining a “fair” price remains a foundational step in managing uncertainty while providing incentives aligning the cost of new treatments with their benefits to patients.

Strategy 1: Reduce pricing to reflect uncertainty

The basic goal of all methods used to adjust initial one-time pricing to reflect uncertainty in longer-term outcomes is to increase financial risk sharing between the plan sponsor and the manufacturer. We have heard many plan sponsors describe their desire for an “uncertainty discount” on the launch price. In contrast, manufacturers would usually prefer to share risk by building in downstream outcomes-based arrangements that will reimburse the payer for failure to meet the clinical goals of treatment.

There are several technical methods that could be applied to cost-effectiveness modeling to produce lower pricing recommendations in the context of enhanced uncertainty.²¹ The simplest approach would be to set a lower cost-effectiveness threshold. For example, if established parameters for value-based pricing range from \$100,000 to \$150,000 per quality-adjusted life year (QALY) or equal value of life year gained (evLYG), the lower threshold alone could be used when determining a fair value-based price for gene therapies that lack data on outcomes beyond a certain time point (for example 5 years).

A second approach would use the same range or threshold for all treatments but would calculate a scenario for gene therapies using conservative assumptions about the duration of benefit beyond that shown in clinical trials. In modeling, the usual “base case” assumption on duration of effect beyond that directly demonstrated in clinical data would be driven by clinical expert opinion or extrapolated results from similar treatments. Often this base case assumption about the durability of benefit extends for many years past that shown directly in clinical trials, extending even to the patient's full lifetime. In contrast, a formal conservative scenario could assume that the benefit of treatment ends or begins to decline rapidly at the time horizon of existing data, thereby producing a lower value-based price range. Cost-effectiveness analysis could also be done to calculate the value-based prices needed to meet established cost-effectiveness thresholds with an assumed duration of benefit ending at different time points (e.g., 5 years, 10 years, 20 years, and lifetime). However, for consistency, when longer-term data are lacking, policymakers might want to consider setting a

formal conservative time horizon for assumed benefit in all cost-effectiveness analyses at no more than approximately 5 years.

Any method for modulating initial pricing to address uncertainty would serve to share financial risk between plan sponsors and manufacturers. Conceptually, lower prices at launch should be paired with price increase (or decrease) mechanisms later in the life cycle of the treatment should evidence demonstrate longer (or shorter) durability of benefits than initially assumed. It must also be considered whether establishing a framework using lower cost-effectiveness thresholds for gene therapies would shift incentives for investment away from one-time treatments towards chronic treatments. Patients and the health care system are likely to benefit more from effective one-time treatments, so unintended consequences of structural approaches to discounting the calculated value of value-based pricing for these treatments should be carefully deliberated.

Strategy 2: Integrate considerations of special ethical priorities into value-based pricing

Whether qualitative approaches or cost-effectiveness analyses are used to help evaluate fair pricing levels for new interventions, policymakers must have some mechanism to integrate considerations of special ethical priorities into evaluations of evidence to guide a broader judgment of value. The most common ethical priorities considered by HTA groups and insurers relate to treatments for conditions that are particularly severe, that extend life near the end of life, and/or that involve children. Most of these considerations will be factors in conditions treated by gene therapies, highlighting the challenging interplay of evidence and values in setting priorities and pricing levels for these treatments.

Quantitative methods for varying value-based pricing according to the relative severity of the condition are being used by a few HTA agencies, notably those in the United Kingdom, Norway, Sweden, and the Netherlands. Still, no established best practice exists, and each agency uses a different method. There have also been attempts to create a broader quantitative weighting system for multiple value dimensions, including special ethical priorities. This approach, multi-criteria decision analysis (MCDA), continues to be the focus of vigorous academic investigation. However, the complexity of identifying mutually exclusive categories of value considerations, and of assigning empiric weights to each category and then weaving this quantitative element into real-time decision-making, has prevented MCDA from becoming an established practice within HTA programs.

Without a clear set of quantitative methods to guide the integration of special ethical priorities into value-based price determination, HTA programs have emphasized the vital role that public deliberation can play in achieving this goal. Although the public deliberation methods of HTA programs vary widely, there is a common attempt to have some structured discussion related to ethical priorities that might influence thinking on fair pricing. ICER's methods for public deliberation have served as one model in which assessment reports have structured sections related to the

“benefits beyond health” and “special ethical priorities” relevant for treatments. The special ethical priorities considered include health equity and unmet need (i.e., severity). Guided deliberation on these elements during ICER public meetings culminates in voting on specific issues by independent appraisal committees. This approach seeks to make integrating special ethical priorities into pricing as tangible and routine as possible without reducing the process to an algorithmic quantitative approach that would raise substantial concerns among many stakeholders. However, the major risk of relying on a deliberative process remains. Deliberation will prove less consistent and lack the concrete power to affect value-based pricing considerations in the way that quantitative methods could.

Strategy 3: Calculate value-based prices with “shared savings”

ICER has introduced the concept of a “shared savings” approach for calculating value-based price benchmarks for one-time gene therapies. In this shared savings approach, health gains are valued in a traditional manner, but the value of cost offsets assumed from successful treatment are not assigned entirely to the manufacturer (in the price of the treatment). Instead, the value of cost offsets is split between the manufacturer and the health system.^{13,21} This approach is controversial because it decreases the calculated value-based price of a one-time gene therapy, but its philosophical justification arises from the idea that society should be able to share in the long-term cost savings from one-time treatments, especially when those cost savings are substantial and often based on eliminating future treatments that have not been priced at cost-effective levels.

There is no empirical way to determine the most appropriate division of potential cost savings when calculating a value-based price under a shared savings scenario. Through a formal methods development program with extensive input from industry, plan sponsors, and other stakeholders, ICER developed two methods for performing a shared savings scenario: 1) a method in which 50% of the lifetime health system cost offsets from a new treatment are “assigned” to the health system instead of being assigned entirely to the new treatment; and 2) a cost-offset cap method in which the health system cost offsets generated by a new treatment are capped at \$150,000 per year but are otherwise assigned entirely to the new treatment. These two methods for shared savings scenarios are needed given the variety of the time course and magnitude of potential cost savings, but both have the same conceptual goal: to reflect a conceptual belief that fair value-based pricing should require some sharing in the potential cost savings when those cost savings are based on unfairly elevated baseline costs of care. Some would also view it as promoting equity in that value-based prices for gene therapies would reflect the social value that the price of a cure for one person should not be worth more than that for another just because one person’s condition is currently expensive to treat.

The potential downside of adopting a shared savings approach to value-based pricing centers on the risk that it may be viewed as seriously undervaluing cures that help reduce healthcare costs, thereby reducing incentives for innovators to tackle the most expensive conditions. In addition,

selecting a 50% share in cost savings is arbitrary. Criteria could be developed to guide whether innovators get a larger or smaller proportion of cost-offset savings, but ultimately the selection of a “fair” sharing of this component of the value of a one-time therapy would be subjective.

A summary of the advantages and disadvantages of each potential strategy is shown in Table 1 on the following page.

Table 1: Tools to determine a fair price

Tool	Distinctive Advantages	Distinctive Barriers/Disadvantages
Reduce pricing to reflect uncertainty	<p>Plan sponsor simplicity</p> <p>Would share financial risk between plan sponsors and manufacturers</p> <p>Mechanism for price increases when more evidence is generated on durability would incentive post-launch studies</p> <p>Would not require additional data collection/reporting infrastructure</p>	<p>No governmental program in US for regulating launch price and different arbiters of value producing disagreement on calculations of fair pricing</p> <p>May shift manufacturer incentives for investments away from gene therapies and toward chronic therapies</p> <p>Reduced pricing + mandated discounts for Medicaid and 340B might jeopardize small manufacturer financial stability</p>
Integrate special ethical priorities into value-based pricing	<p>Can build upon current international experience</p> <p>Accounts for difficult to quantify benefits of treatments for specific patient populations who have disproportionate unmet need and health inequity</p>	<p>No government HTA body in US reduces consensus on methods for integrating these elements into value-based pricing</p>
Calculate value-based pricing with “shared savings”	<p>May promote equity in savings calculations for those conditions that are severe but do not have established treatments available/are low cost without gene therapy but have a significant impact on quality or of life</p>	<p>No empiric way to determine the appropriate allocation of potential cost savings to value-based price</p> <p>Unintended consequences for patients and society if incentives shifted away from treatments to tackle the most expensive conditions</p>

Managing Clinical Uncertainty

The core goal of payment mechanisms to manage clinical uncertainty is to share the financial risk that may occur when the treatment benefit seen in clinical trial populations over a relatively short time frame fails to occur in real-world treated patients over a longer period. This financial risk can be a combination of factors. First, failure of real-world benefit commensurate with earlier clinical trial performance means that a core part of the justification for the initial price is no longer valid, suggesting that payers have “overpaid” for the health benefits ultimately delivered. Second, this reduced level or duration of benefit likely produces unexpected costs of care for patients beyond that assumed if the gene therapy were a “cure” or as effective over the long term as early data suggested. The lack of these cost offsets also undermines an important part of the justification for high one-time prices.

In our discussions with payers, we often heard that sustained benefit over five-years was the minimum duration that could justify the one-time prices being seen in the market. Since gene therapies are unlikely to enter practice with robust evidence on outcomes at five years, the potential payment solutions all represent some form of value-based contract that links the generation and assessment of real-world outcomes to some modulation of the total price paid for the treatment.

Value-based contracts fall broadly into three categories: milestone-based rebates, warranties, and performance-based installment payments (sometimes referred to as an annuity). Note that we use ‘value-based’ as the overarching term for contracts in which some aspect of payment is linked to clinical outcomes. Market experience with these tools is still in the early stages, with mixed implementation success to date. All versions of these contracts face several common barriers.

First, patients treated with gene therapies may change insurers during the term of any payment contract, greatly complicating efforts to track outcomes and link it to additional rebates, a warranty, or performance-based installment payments. In our discussions with payers and manufacturers, member turnover was also cited as undermining the basic tenet that the value of one-time treatments would accrue to the payer paying the upfront high cost. We heard that members tend to only stay in the same insurance plan for two to three years, which is consistent with the national average of 21.5% external turnover annually.²² Additionally, members may move between private and public payers over time, increasing the difficulty in structuring longer-term value-based agreements.

A second common barrier to value-based contracts is a lack of agreement between payers and manufacturers on meaningful and practical outcomes to use as the dispositive elements of any contract. Without a third party involved in determining the outcomes for a value-based contract, the terms are subject to the relative negotiating power of payers and the manufacturer. We heard from some payers that the outcomes and thresholds that they preferred were not acceptable to

manufacturers, thus reducing in their view the degree of clinical uncertainty that manufacturers would bear. Conversely, we heard from manufacturers that a barrier to value-based contracts was the desire of each individual payer to negotiate a unique set of terms. Trying to create multiple variations has proven administratively complex and has led many companies to favor a “one-size fits all” contract that they are not willing to reconsider.

Similarly, a third barrier common to all forms of value-based contracts is varying degrees of difficulty in agreeing to the amount of money at risk. Some payers with whom we spoke argued that manufacturers were unwilling to put meaningful amounts of money on the table, while others felt that risk sharing is greater today than it was in the past. Some payers felt frustrated because they felt that they had little leverage in either the amount of money at risk or the outcomes that would be used to determine treatment performance. This experience sometimes led them to bypass any value-based contract option in favor of some additional discount off the one-time price.

A fourth barrier, Medicaid Best Price (MBP) provisions, applies to all value-based contracts except warranties.^{23,24} Under regulations for the Medicaid Drug Rebate Program (MDRP), Medicaid is to be provided with net prices comparable to or lower than the lowest price received by any other payer in the commercial market, i.e. Medicaid is guaranteed to receive the “best” price. Deep rebates triggered by milestone-based rebate contracts would, therefore, in principle, be included in calculating the MBP and be available to the Medicaid programs in all 50 states.

MBP has historically included the net price effects of rebates for a single treated patient, leading manufacturers to assume that any rebates they include in milestone-based rebate contracts for a single patient could be generalized to millions of Medicaid recipients. Manufacturers have also avoided value-based contracts lasting more than 3 years because of specific reporting requirements for MBP, and manufacturers have also feared that an initial payment as part of a stepwise annuity payment structure would be interpreted in MBP rules as the only payment for the therapy, thereby creating inappropriately high immediate rebates. Each remaining payment would result in a reduced rebate but would require a claw back from each state Medicaid program – a process not well supported in the MDRP systems.

Attempting to address the conflicts between the MBP regulations and the goals of value-based contracts, the Centers for Medicare and Medicaid Services (CMS) finalized a new rule for drug value-based purchasing arrangements in December 2020, which took effect on July 1, 2022.²⁵ These include options for a multiple best prices approach or a bundled sales approach. Under multiple best prices, developers report the best price available for each unique, contract-defined performance tier offered in a “value-based performance arrangement” within a quarter, eliminating MBP volatility that can occur from a single patient. Further, such arrangements are excluded from the average manufacturer price (AMP) calculation. In combination, this eliminates the MBP rebate volatility that can occur from a single patient.

Under the revised bundled sales approach, all therapeutic sales and associated standard and value-based rebates for a quarter within a single payer's value-based arrangement are averaged together and the developer reports the lowest of the average discounts across their value-based arrangements.^{26,27} This approach may work well for larger treated populations, but does not avoid the single patient problem and has not been used by manufacturers of gene therapies for rare conditions to date. The impact of these reforms is still uncertain as CMS continues to clarify their application in additional rules such as the May 26, 2023 proposed rule, "Misclassification of Drugs, Program Administration and Program Integrity Updates under the MDRP."²⁸

A fifth common barrier to value-based contracts is a lack of data infrastructure and personnel with skills adequate for the clinical analytics needed to track outcomes.²⁹ Determining the extent to which performance thresholds have been met requires patient outcomes tracking that is timely (often quarterly), accurate, low cost, and auditable among other characteristics. To date, the use of practical, low-cost claims data has been preferred in most cases despite the desire of most payers for more detailed clinical (medical record) or patient quality of life (patient-reported outcome) data. Additionally, determining who does the tracking of data is a point of intense negotiation among payers, manufacturers, and even providers. All stakeholders we talked to noted that negotiating this element of value-based contracting presents a significant hurdle.

Lastly, developing and implementing any value-based contract requires time and effort, not only at the outset of the contract but over multiple years. Payers have been largely willing to explore these types of contracts, but all payers acknowledge that the internal effort and expertise required has proven very challenging. The appetite for more value-based contracts varies across payers, and the rising number of new gene therapies expected over coming years is expected to burden payer resources and dampen interest even further.

Nonetheless, each of the three versions of value-based contracts described in greater detail below has gained a foothold in the market, and each has the potential to help manage the combination of high prices and clinical uncertainty that is central to the tensions surrounding gene therapy.

EARLY USE OF A GENE THERAPY VALUE-BASED CONTRACT: A CASE STUDY*

LUXTURNA® (voretigene neparvovec-rzyl), the first FDA-approved gene therapy in the US to treat a rare, inherited form of vision loss that can result in blindness, serves as an early example for the reimbursement of gene therapies through performance-based contracts. Within weeks of approval the developer of LUXTURNA, Spark Therapeutics and Harvard Pilgrim Health Care announced they had agreed on an outcomes-based rebate model that tied the level of payment to both short and longer patient outcomes measured at a 30-to-90-day interval and again at 30 months. Additionally, the agreement allowed Harvard Pilgrim to buy LUXTURNA directly from Spark, avoiding mark-up of the drug from other distribution channels. Since that time Harvard Pilgrim (now Point32 Health), has expanded the number of performance-based agreements to include ZOLGENSMA® (onasemnogene abeparvovec-xioi) and ZYNTEGLO® (betibeglogene autotemcel).

*For case study references and more information see ³⁰⁻³⁴

Strategy 1: Upfront payment with milestone-based rebates

A milestone-based rebate contract involves upfront payment with some percentage or absolute rebate amount, up to a full 100% rebate, returned if the gene therapy does not meet performance expectations. For example, Lyfgenia™ (lovotibeglogene autotemcel), bluebird bio's gene therapy for sickle cell disease, launched in December 2023 with an option for payers to select a milestone-based rebate contract that offers a rebate for patients who are hospitalized for a vaso-occlusive event within the first three years after administration.³⁵ These contracts can cover a single patient, or a group of patients, and any rebate received may be fully retained by the first line payer (such as a PBM) or shared with downstream risk carriers such as self-insured employers and their stop loss carriers.

Milestone-based rebate contracts for gene therapies need to specify the following elements:

- The contract term and specific time points for outcomes measurement
- The covered population for the performance agreement
- Outcome performance metric(s)
- Minimum performance thresholds at each time point
- The amount of the rebate associated with failure to meet the performance standard
- The rebate basis and methodology (by patient, by population, by time period)
- The mechanics and individual stakeholder responsibilities for gathering performance data, measuring, and adjudicating the outcome metric, and triggering and processing any rebate
- How disputes will be adjudicated

State Medicaid programs considering milestone-based rebate contracts should also carefully consider interactions of value-based contracts with the inability to include 340B purchased drugs in those contracts, and draft agreements accordingly.³⁶

Payers usually leverage their internal resources to administer milestone-based rebate contracts, although smaller payers may outsource some of these functions to the administrative services organization arm of a larger insurer or engage the services of one of the existing market solution providers.³⁷ Market solution providers consider pharmaceutical companies, self-insured employers, health plans, Medicare, and Medicaid as potential customers. They can be paid either by the payer or the pharmaceutical company on behalf of the payer and offer services such as negotiation of performance-based contracts, contract administration, and data capture (clinical and patient-reported outcomes). These market solutions providers are slowly growing in importance as the number of gene therapies increases.

Milestone-based rebate contracts are most appropriate for therapies for which clinical uncertainty can be addressed with outcomes seen over a relatively brief period. These contracts are also best suited for payers with the infrastructure (or willing to contract with a third party) to track patients and assess outcomes. Longer-term milestone-based rebate contracts are possible,³⁸ but we consistently heard from payers that most are only willing to extend a performance-based contract length to two years due to member turnover and the administrative burden of outcomes tracking.

Strategy 2: Upfront payment with warranty

A warranty provides reimbursement for future payer expenses incurred (either demonstrated or estimated) in the event the covered therapy does not meet a manufacturer's promise of a specific magnitude or duration of benefit. For example, Roctavian™, launched with an outcomes-based warranty offered to all U.S. insurers which will reimburse payers on a pro-rated basis over the first four years from the time of dosing if the patient loses response – up to 100% of wholesale acquisition.³⁹

Warranties may be self-administered by the manufacturer as a performance-based rebate agreement or may be administered by a third party as an insurance-based instrument with premiums paid by the manufacturer.⁴⁰ Like consumer product warranties such as automobile extended warranties, warranty payments in gene therapy contracts represent covered damages as opposed to a payment associated with the price of the therapy.

The primary advantage of third-party administered warranties over milestone-based rebate contracts is that only the manufacturer premiums to the warranty program are considered rebates under MBP regulations, not the warranty payments themselves that are triggered if treatment fails and some or all of the upfront payment is returned. However, public information on the use and impact of warranty contracts is limited. There are some new insurance efforts and other

partnerships that have launched to aid manufacturers in providing warranties to payers, including Medicare and Medicaid.⁴¹⁻⁴³

Strategy 3: Performance-based Installment Payments

A performance-based installment payment arrangement helps payers manage clinical uncertainty associated with a therapy by spreading payments over time and linking these payments to positive performance targets. This strategy helps address short-term budget impact concerns as well as manage the clinical uncertainty about the duration of benefit. This approach might include an up-front payment of some portion of the product price and a commitment to further payments every year for a defined number of years, with “out-year” payments triggered as desired outcomes are achieved.

The use of performance-based installment payments with future payments contingent on the therapy meeting performance thresholds is still limited due to the practical difficulties plan sponsors encounter.⁴⁴ One disadvantage of these arrangements is that they raise accounting complexities. Some payers operating under accrual accounting may need to recognize future payments upfront or have reserves to cover them. Medicaid plans operating under cash accounting would recognize only the current year’s payment, though single-year budgeting rules may hamper them. The FoCUS Project has identified potential finance solutions for these challenges, but each organization would need to engage with its technical experts to identify the best solution for its circumstances.⁴⁵

Some payers may have other challenges with paying for a gene therapy in installments over multiple years. For example, many states prohibit multi-year Medicaid contracts. Additionally, a one-year stop loss contract may not be compatible with performance-based installment payments. Payers should also be sensitive to the risk that breaking a single payment into multiple installments will trigger multiple co-insurance cost sharing requirements for patients, increasing their financial burden.

PERFORMANCE-BASED CONTRACTS AT THE FEDERAL LEVEL: CMMI GENE THERAPY

In February 2023, the Department of Health and Human Services (HHS), instructed CMMI to advance a gene therapy access model. The model would allow states to assign CMS the ability to negotiate multi-state performance-based contracts for selected gene therapies starting in 2025. This model aims to pool state bargaining power for gene therapies, condition the cost on outcomes, and shift the burden of administering performance-based contracts from state Medicaid agencies to CMS. This model could start with gene therapies used to treat a single condition such as sickle cell disease and later be expanded to other therapies and conditions. Details on the program are still forthcoming.

A summary of the distinctive advantages and disadvantages of each tool is shown in Table 2. Note that the challenges common to all value-based contracts are not included for brevity but should be considered by payers considering value-based contract options.

Table 2: Strategies to manage clinical uncertainty

Tool	Distinctive Advantages	Distinctive Barriers/Disadvantages
Upfront payment with milestone-based rebate	Simpler to design and administer than value-based installments	<p>Payer remains responsible for the upfront full cost of the gene therapy</p> <p>Difficult to agree on meaningful and practical outcome measures</p> <p>May be difficult to agree on meaningful amount of money at risk</p> <p>Single patient’s net price after rebate may impact Medicaid Best Price for all Medicaid programs</p>
Upfront payment with warranty	<p>Allowable by Medicare and Medicaid</p> <p>Does not impact Medicaid Best Price in most circumstances</p> <p>Reduced administrative burden on plan sponsors</p>	<p>Plan sponsor responsible for the upfront full cost of the gene therapy</p> <p>Warranty amount for incurred health care expenses due to treatment failure may not account for much of the initial price</p>
Performance-based installment payments	Spreads payments over time with future payments contingent on the therapy meeting performance thresholds	<p>Payments over time problematic from a payer accounting perspective and for secondary insurance</p> <p>Member turnover - Original payer responsible for full cost even if the patient leaves plan and benefit can no longer be tracked</p> <p>State Medicaid programs may be prohibited from multi-year contracts</p> <p>May not be compatible with self-insured employer stop loss contracts</p>

Managing Clinical Uncertainty: Needed Policy Reforms and Market Actions

Several potential policy reforms and broader actions within the private market to support value-based contracts were noted in many of our conversations with payers, manufacturers, and patient advocacy groups.

State Medicaid programs should enhance their capabilities to enter value-based purchasing arrangements. More than half of states have not sought approval from CMS to enter directly into value-based payment (VBP) arrangements.⁴⁶ State Medicaid programs should also build organizational capacity in personnel skilled in designing outcomes-based contracts, design procedures for working with manufacturers, and invest in needed computer and medical record systems to track outcomes. States should also actively consider joining the emerging Centers for Medicare and Medicaid Innovation (CMMI) model for gene therapy coverage and payment to benefit from centralized expertise and resources.

CMS should clarify the Medicaid Prescription Drug Rebate Program regulations to allow innovative payment methods to be tested and improved upon. CMS Proposed Rule CMS-2482-P takes an important step in addressing calculation barriers to the broader adoption of milestone-based rebate contracts. However, further clarification is needed regarding the specific mechanics and interpretations. For example, one manufacturer we spoke to noted that they needed guidance on how to enter their warranty model into the MDRP data system, and CMS was very responsive. CMS has emphasized flexibility to accommodate the many emerging payment innovation variations. Unfortunately, the lack of established practices (regulatory “case law”) also leads to uncertainty regarding the degree to which customization of the terms for a commercial customer triggers a distinctly reportable value-based purchasing agreement, the extent of accommodation that will be given to a state Medicaid program to enable implementation of a performance-based contract, and the specific mechanics for reflecting terms and reporting in the MDRP computer systems. Additional explicit examples and a more public corpus of acceptable practices from CMS are needed to reduce uncertainties and spur payment innovation.

CMS should update the Average Sales Price calculation in Medicare Part B to match the MBP multiple-best prices approach. The AMP calculation and the Medicare Part B Average Sales Price (ASP) calculation were identical until the Multiple Best Prices refinement was introduced which excluded value-based performance arrangement transactions from AMP calculations. By continuing to include these transactions in the calculation of the ASP, CMS has introduced volatility that can disincentivize provider prescribing due to reimbursement often being tied to ASP. Re-aligning ASP calculations to AMP would eliminate these disincentives.

State, federal, and private market leaders should collaborate to develop a robust data infrastructure to support the tracking of outcomes needed to support value-based contracts.

Potential action areas include:

- ***Develop disease or therapeutic area outcomes databases for tracking performance.***
Rather than attempting some approach to unifying all data systems, targeted demonstrations building on existing disease areas or geographic capabilities would seem more practical. The Center for International Blood and Marrow Transplant Research outcomes database of every allogeneic transplantation and many autologous transplantations may be a model for tracking other disease categories.⁴⁷
- ***Grant CMS renewed authority to share Medicare, and perhaps Medicaid, claims data.***
CMS collects all Medicare claims but is prevented by Part D law from sharing it as it did in the 1990s. States such as Massachusetts have all-payer claims databases that include Medicaid claims. Providing CMS authority to provide timely (monthly or quarterly data with minimal time lags) with patient identification to payment partners (as allowed by HIPAA) could provide a foundational outcome tracking resource.
- ***Leverage manufacturer registries for cost-effective outcomes-tracking data.*** Manufacturers are required by FDA to track patients treated by their gene therapies for safety and in some circumstances to generate further efficacy evidence. This is often accomplished via registries created or supported by manufacturers. These registries could be used, perhaps with some enhancement, to provide outcomes tracking data to adjudicate value-based outcomes contracts, particularly if they can be designed to minimize positive outcomes bias from voluntary patient participation and with overall credibility enhanced by instituting transparent audits that can be shared with all stakeholders.

CMS and the HHS Office for Civil Rights should clarify HIPAA regulations to ensure appropriate data access for all entities engaged in value-based agreements. Clarification is needed so developers, prior payers, data intermediaries, and others can access required outcomes and other data needed for payment adjudication. Additional rulemaking would also be helpful to clarify the criteria for being a Business Associate who has rights to see patient data without needing a separate legal agreement. These clarifications would help address the uncertainties that magnify the member turnover barrier of value-based rebate contracts.

Payers and manufacturers should engage in routine early dialogue to foster consensus on meaningful and practical outcomes and sets of outcomes by therapeutic area to be used in value-based contracts.

As noted in the 2017 ICER Policy Leadership Forum white paper focused on assessing the value of gene therapies, early dialogue with manufacturers and plan sponsors will not only allow manufacturers to share information and increase the body of knowledge on these complex

therapies, but also allow for discussions around meaningful patient-centered outcomes, provide additional options for partnerships, help plan sponsors to determine coverage criteria and estimate the actual size of the potential patient population.¹⁵ Smaller biopharmaceutical manufacturers may have difficulty marshalling the resources needed to meet with a broad range of payers but should engage with as many as possible, including smaller regional payers who may have different data capabilities. Whenever possible, patient groups should be integrally involved in this effort as well. These groups can themselves serve as leading conveners, as shown in the positive experience of the role of patient groups in the development of a core data set for hemophilia, coreHEM, that includes outcomes metrics that can be used in value-based contracts.⁴⁸

Managing Short Term Budget Impact

Managing the short term budget impact of gene therapy is a problem for many small payers, especially self-insured employers or other plan sponsors with <10,000 employees. For these payers an unpredictable \$1-3M treatment may be such a large percentage of their annual health costs that an upfront payment would be financially destabilizing. The actuarial nightmare of such a “lightning strike” cost has led some plan sponsors to exclude coverage for all gene therapies,⁴⁹ while others have begun considering various “financial protection plans” offered by insurers. Even larger payers, however, may experience cost and income statement volatility from statistical variation in patient numbers in rare conditions and cost surges from new gene therapy approvals in larger indications. Performance-based installment payments and any other mechanism to pay through installments can help manage the short-term budget impact of gene therapies. Still, challenges in launching those contracts mean that additional strategies are needed that can work for both small and larger payers. Most current strategies employ pooling across larger and larger populations to spread the costs and smooth the impact of high one-time gene therapy payments. Current and potential strategies are discussed below.

Strategy 1: Stop Loss and Reinsurance

Stop loss insurance protects self-insured plan sponsors or payers administering full-risk benefits against unexpected catastrophic healthcare costs.^{50,51} Reinsurance functions similarly to stop loss but is offered to smaller payers who administer full-risk benefit designs. Because of the similarity in how these two programs function, we will use the term stop loss to represent both unless there is a distinct practical or policy difference. For more information on the distinctions between stop loss and reinsurance, readers are encouraged to watch the webinar on stop loss and reinsurance found on the Paying for Cures website <https://newdigs.tuftsmedicalcenter.org/stop-loss-innovation/>.

Stop loss insurance comes in many forms but generally takes on the role originally played by fully insured insurance plans to protect against unexpected, catastrophic, unpredictable health care

claims.⁴⁹ Approximately 72% of covered workers enrolled in a self-funded plan with at least fifty workers are covered by some form of stop loss insurance.⁵⁰

Under what is called a “specific” stop loss policy, the stop loss carrier (an insurance company other than the primary insurer) becomes liable for healthcare costs that exceed certain limits for a specific member. Stop loss insurance generally works well for unexpected incident cases in which gene therapy may be prescribed. For example, the birth of an infant with a genetic condition such as spinal muscular atrophy or cerebral leukodystrophy constitutes an unexpected event and is generally well covered by existing stop loss policies.

When considering stop loss insurance policies, self-insured employers must understand in detail how gene therapies will be treated, including:

- the base contract coverage period and any renewal periods
- whether members eligible for gene therapy are covered or excluded as previously known risks (lasered out)
- if a No New Laser (NNL) contract is appropriate for their needs. Under a NNL contract, the carrier agrees not to impose any further exclusions or lasers to the policy beyond those imposed at the inception of the policy. An NNL provision is typically accompanied by a rate cap on first-year renewal premiums.
- whether gene therapy is included in the general stop loss policy or if a separate gene therapy product is required
- where the attachment point (deductible) is set and any co-insurance responsibility

Stop loss insurance therefore can play a vital role in helping to manage the short term budget impact of treatment with certain gene therapies. Further information on stop loss policies is available at the NEWDIGS Paying for Cures website at <https://newdigs.tuftsmedicalcenter.org/paying-for-cures/>.

As helpful as stop loss policies can be, they are severely limited in addressing the insurance dilemma of patients with easily predictable future costs of gene therapy. Stop loss carriers often exclude any payment for conditions known to be eligible for gene therapy. Thus, costs for conditions such as sickle cell disease or hemophilia are usually not covered by stop loss policies, shifting the costs for gene therapy for these individuals back to the plan sponsor. In some cases, the stop loss carrier may not fully exclude payment but will use other mechanisms such as raising the deductible for known high-risk members or entire conditions, or increasing the stop loss premium, or both.⁵² Our discussions with stakeholders suggested that the most common scenario is the exclusion of known future high-cost conditions, a practice known as “lasering.”

Stop loss contract terms also routinely include elements that do not fit well with some value-based contracts. Stop loss is typically administered annually, requiring claims to be incurred and paid within the contract year or at least paid within a specified “run out” period. This structure does not accommodate value-based agreements that use installment payments over time.

When anticipating the larger number of gene therapies coming into practice over the next decade, many stakeholders expressed concerns to us that stop loss insurance, while viable and very helpful today, will see increased premiums to cover the rising tide of gene therapies, adding to the continued increase in costs of healthcare and putting pressure on smaller self-insured employers and payers.

Strategy 2: Gene Therapy Subscription Models

Gene therapy subscription models seek to aggregate vast pools of covered lives and “carve out” coverage for gene therapies so that smaller plan sponsors and payers can join and pay a relatively small per-member per month (PMPM) fee to gain coverage for any needed gene therapy treatments. These programs, also known as gene therapy “financial protection programs” are now offered by many large payers with a vertically integrated pharmacy benefit manager, including Aetna/CVS (Gene Therapy Stop Loss), Cigna/Evernorth (Embarc[®] Benefit Protection), and United Healthcare/Optum (Optum Gene Therapy Risk Protection).³⁷

Since these gene therapy subscription models provide “unlimited” access to gene therapies for a single fee, they have also sometimes been called “Netflix models.”⁵³ These programs have reportedly only gained limited market traction to date but as the number of gene therapies rises, we may see increased use by employers as a way to manage short term budget impact. Like stop loss policies, gene therapy subscriptions require ongoing monthly payments without any guarantee that premiums will increase and/or coverage for certain gene therapies will be reduced or excluded. At the time of this writing, CVSHealth offers the choice of covering all FDA-approved and pipeline gene therapies for \$1.70 PMPM or less, or the option of only covering seven FDA-approved gene therapies (Luxturna, Zolgensma, Zynteglo, Skysona, Hemgenix, Elevidys, and Roctavian) for \$0.85 PMPM.⁵⁴ Evernorth’s Embarc program is priced at \$0.99 PMPM and their website shows coverage for six of the seven gene therapies included in the CVS program (excluding Elevidys), but this program has several limitations, such as limiting Zolgensma coverage to treatment of children born after the employer/payer initially joins the program.⁵⁵ Similar to how stop loss policies are managed, excluding coverage for known cases is viewed as the only way to avoid creating an incentive for employers and payers to wait to sign up for the subscription program until they have a known need.

Subscription or similar models are currently only offered to risk-bearing (primary) payers by intermediaries such as PBMs and not directly by manufacturers. Subscription models can have significant variations in quarterly prices per dose when volumes fluctuate while revenue (cost)

remains fixed. This price per dose (also called the “unit price”) fluctuation in commercial contracts would flow through to Medicaid rebate fluctuations and Average Sales Price fluctuations, which can affect provider reimbursement as well as possibly trigger excess price increase (inflation) rebates. With no mechanism under current Federal programs to smooth these effects, manufacturers perceive significant financial risks in offering commercial subscription models. Depending on their detailed structure, subscription models may also fall outside the safe harbors for payment discounts and rebates under Physician Self-Referral rules (the Stark Law) and Anti-kickback statutes.

As the number of gene therapies in practice grows, it may be that these gene therapy subscription models will become more attractive to employers and smaller payers, but the current PMPM premiums for these models may appear too high for many potential buyers, limiting the current uptake.

Strategy 3: Federal Gene Therapy Coverage Benefit

A strategy not in place today but one that garnered considerable support in our stakeholder discussions is a federal “carve-out” benefit for gene therapy. It is possible that, despite the private insurance market’s attempts to manage the tension between cost and access for gene therapies, that the actuarial problem of both predictable and unpredictable prices at this level will not lead to private insurance models that can provide adequate, affordable access. Thus, much like Medicare was extended to cover all patients needing renal dialysis, a federal benefit for gene therapy could be created to cover the costs for all patients deemed eligible for this type of treatment. With a federal program, lasering and other barriers to access would be eliminated. To avoid too broad a scope of coverage, the benefit might be limited to potentially curative gene therapies, only the one-time costs of the gene therapy might be covered, and a new separate federal benefit might be limited initially to state Medicaid programs. In 2021, the Medicaid and CHIP Payment and Access Commission (MACPAC) considered a proposal to implement a federal carve out for gene therapies to pool coverage and consolidate purchasing power for these products across state Medicaid programs.⁵⁶ However, to achieve the broader advantages of a federal coverage benefit it would ideally be designed to allow coverage eligibility for patients with any form of primary health insurance.

A federal gene therapy carve-out could be financed by general tax revenues or by per capita payer fees. The mechanics could range from full federal operation, including product and provider contracting, to federal funding with reimbursement schedules (as is done with coverage for renal dialysis), to private sector implementation with competing entities, as is done in Medicare Advantage and Medicare Part D benefits.

There are several important implementation issues that would arise with any federal gene therapy benefit program. Federal coverage would likely raise the need for some centralized process for review of clinical effectiveness and perhaps cost-effectiveness as well to constrain program costs.

In addition, historical experience suggests that steps might need to be taken to avoid adverse selection by insurers hoping to shift rather than share costs. Prior to the Affordable Care Act, some states established high-risk pools to aid patients with high-cost preexisting conditions who were either priced out of insurance markets, refused coverage, denied employment due to insurance cost concerns, or some combination of these and other factors. The states' experience of these risk pools was generally poor due to inadequate funding for the costs of the patients included.

A summary of the advantages and disadvantages of each strategy to manage the short term budget impact of gene therapies is shown in Table 3 on the following page.

Table 3: Tools to address the short term budget impact of gene therapies

Tool	Distinctive Advantages	Distinctive Barriers/Disadvantages
Stop Loss and Reinsurance	<p>Protects against very high claims and unpredictable costs</p> <p>Established and well understood by plan sponsors</p>	<p>Policies subject to gene therapy exclusion “lasering” for known gene therapy candidates, high-cost members, conditions, and/or products</p> <p>Annual premiums may be volatile based on prior year claims experience</p>
Gene Therapy Subscription Model	<p>Fixed per member per month fee which is similar to other PBM/insurance programs</p> <p>May include some additional patient services</p>	<p>May limit gene therapies included and exclude certain patients depending on enrollment date</p> <p>Limited market traction to date with reports of high premiums and too few gene therapies included</p>
Federal Gene Therapy Coverage Benefit	<p>Single pool provides scale and broader cost sharing</p> <p>Creates universal access that prevents private market risk of lasering or of some employers opting out of coverage entirely</p> <p>May support price negotiation/setting that achieves lower prices in return for guaranteed broad access</p> <p>May provide alternative funding tools such as mandatory fees or tax funds</p>	<p>If federally operated may lead to inefficiency, inadequate patient appeal, or misuse of single buyer power that could raise administrative costs, reduce patient access, or provide inadequate innovation incentives, and, like Medicare Part D, may inhibit integrated medical and therapeutic management</p>

Managing Short Term Budget Impact: Needed Policy Reforms and Market Actions

Congress should revise ERISA law governing self-insured plan sponsors to require them to cover gene therapies when medically necessary just as fully insured commercial plans must do under both federal and state laws. The resulting increased risks, and perhaps costs, to smaller self-insured plans would likely encourage them to rejoin the larger pools operated by traditional insurers. This would eliminate ‘lightning strike’ risks, improve coverage for patients, and reduce volatility for traditional insurers through greater scale. Premiums for the small plans may exceed their prior total health spending if the traditional insurer economies of scale do not offset (or are not passed through) to employers.

CMS should reduce private payer risk by including patients undergoing treatment with gene therapies in risk-adjustment programs such as those used in Medicare Advantage, some state Medicaid plans, and Affordable Care Act exchanges. Subsidies received by plans are adjusted based on patient characteristics that significantly influence spending. Risk adjustment distributes payments according to the risk of enrollees.

Congress should modify the Medicaid Drug Rebate Program (MDRP), the Physician Self-Referral law, and anti-kickback statute to enable developer-offered subscription models.

The MDRP requires manufacturers to report a unit price on each contract from which a ‘best price’ may then be calculated and used to set the Medicaid drug rebate amount for the product. With gene therapies, volatile product volumes under a fixed subscription price will naturally lead to unpredictable unit price volatility, and this uncertainty disincentivizes developers from offering or agreeing to subscription models. Reforming MDRP to eliminate unit price reporting or exempt subscription models from the unit pricing rule would foster greater acceptance of subscription models. Similarly, expanding the safe harbor provisions in the Physician Self-Referral law (commonly known as the Stark law) and anti-trust regulations to include subscription models is needed.

Combining Strategies to Address Gene Therapy Payment Challenges

A single strategy cannot currently address the full complement of gene therapy payment challenges for all payers.⁵⁷ Different market segments face the challenges outlined in this paper in different degrees. Thus, some strategies are better suited to some markets than others. Whether within a single market, or across markets, differences among diseases, products, and payer types require a set of strategies that can be customized and possibly combined to meet the challenges of each specific situation. During stakeholder interviews one consistent theme that emerged was that there was no perfect model based on a single strategy, so efforts to experiment with new strategies or to link others together are needed.

Stacking Strategies

One option payers can consider is to “stack” two or more separate strategies. For example, a plan sponsor can purchase reinsurance to mitigate the high-cost budget impact of any gene therapy, and then for specific therapies negotiate a standard rebate to gain a fair price while seeking a value-based or warranty agreement from a manufacturer to mitigate the clinical performance risk. In this example, each strategy entails its own contract but in combination the plan sponsor has addressed the three core challenges of paying for gene therapies.

State Medicaid programs could combine existing mandatory rebates with value-based milestone rebates and reinsurance. This might allow states disproportionately impacted by certain diseases such as sickle cell disease to balance their budgets and provide patients access.

Many such stacking combinations can be envisioned, with payers and manufacturers having the flexibility to customize each strategy or ignore certain strategies as needed. For example, large national insurers have sufficient patient pool sizes that they do not need reinsurance.

Integrating Strategies into a New Offering

Integrating two or more tools into a new solution, sometimes called “layering,” may allow for efficiencies for all parties.

- **Traditional and milestone rebates** are already offered together today by manufacturers who combine a milestone-based rebate with a reduced upfront discount in a single contract.
- **Value-based gene therapy subscription models** that integrate a warranty or other value-based contract with a subscription model could be offered by national insurers/pharmacy

benefit managers (PBMs) to smaller health plans and self-insured plan sponsors. Current subscription models may implicitly do this if the payer negotiates multiple value-based contracts with manufacturers and uses the estimated payouts to reduce the gene therapy subscription PMPM premium for all participating employers. There may be advantages to a more explicit pass through of performance rebates for plan sponsors who incur increased costs for members for whom a particular gene therapy does not perform well.

- **Value-based contracts integrated with processes to determine fair pricing** could be considered an offering by private gene therapy subscription offerings or could be developed for piloting by CMMI in its gene therapy coverage model. The premise is that accelerated and broad access through a private or governmental model would be offered to gene therapy manufacturers based on their agreeing to have the initial upfront payment fit within transparent fair pricing guidelines and for rebates or warranties also be included in a broader value-based contract. This combination and integration of three different strategies would face significant challenges, potentially including changes to ERISA regulations to require self-insured plan sponsors to cover gene therapies, naming acceptable sources of independent pricing benchmarks, and procedures for negotiating the outcomes, time horizons, and amount of money at risk in the value-based contract.

Value-based milestone contracts with a volume cap or modifier could be developed between manufacturers and PBMs to manage clinical uncertainty while using a volume target to manage short-term budget impact concerns by sharing some or all financial risk of greater utilization with the manufacturer. Volume targets can be used to cap total costs for a payer or to create a ladder approach to rebates that increase with utilization beyond certain targets.

Multi-year stop loss policies with pass-through warranties could integrate stop loss insurance with a pass-through warranty that reimburses smaller health plans and plan sponsors when clinical effectiveness or durability measures are unmet. This type of integrated product would not only protect against lighting strikes to plan sponsor budgets. It would also reimburse plan sponsors for at least part of their portion paid by the claim fund, and possibly help offset potential premium increases for stop loss policies as gene therapy claims increase. It would also enable stop loss carriers to better manage gene therapy costs through multi-year engagement with clients and enable them to directly contract with manufacturers and even clinical providers.

Combining Strategies:

Needed Policy Reforms and Market Actions

Policy reforms and market actions to enable the stacking and layering of solutions would encompass those necessary for the enablement of the individual components. At times more than one policy reform would be needed to allow the various components to be implemented by payers.

The most critical policy reforms to allow combining strategies are briefly listed below. Details for each reform/market action can be found in the prior sections.

CMS should clarify the Medicaid Prescription Drug Rebate Program regulations to allow innovative payment methods to be tested and improved upon.

CMS should update Average Sales Price calculation in Medicare Part B to match the MBP multiple-best prices approach.

State, federal, and private market leaders should collaborate to develop a robust data infrastructure to support the tracking of outcomes needed to support value-based contracts.

CMS and the HHS Office for Civil Rights should clarify HIPAA regulations to ensure data access for all entities engaged in value-based agreements.

Congress should modify the Medicaid Drug Rebate Program (MDRP), the Physician Self-Referral law, and anti-kickback statute to enable developer-offered subscription models.

Conclusion

Gene therapies have the potential to transform thousands of lives, but only if all stakeholders find feasible and economically sustainable ways to price these therapies and pay for them. The need to find new market and policy solutions will only grow, as increasing numbers of gene therapies are approved, including those for larger populations, such as sickle cell disease. NEWDIGS FoCUS has estimated that gene therapies will generate average annual list price revenues of \$10-15 billion annually through 2032. Even if the short-term budget impact were to be twice this number, it represents a relatively small additional cost in a setting in which costs for other treatments, such as new obesity drugs, will represent a far larger economic challenge to the entire health system. Nonetheless, Medicaid systems, and smaller employers and health plans will struggle to manage the actuarial burdens of therapies priced at over \$3 million therapies for individuals, leading to risks that benefit designs and insurance products will exclude coverage for these therapies or take other steps that will not produce the equitable access to transformative therapies that should be our nation's goal. Market and policy innovations for gene therapy therefore justify concerted action in order to ensure patients can access and benefit from gene therapies while maintaining overall health system affordability.

This paper is intended to call for thoughtful consideration of both market actions and policy reforms as detailed in the sections above. Our analysis has sought to emphasize that, although each specific action or reform has the potential to address one of the major challenges presented by gene therapies, there is no one single solution, no “magic bullet” that will establish a fair price, manage uncertainty, eliminate the actuarial shock of all gene therapies, and ensure patient access. Each option has the potential to address one or more of these challenges to some extent, but each option also carries its own set of limitations and potential downsides.

What, therefore, is the best way forward? We have emphasized that combining or “layering” of different innovative approaches is likely to be the best way to address their limitations and balance their risks and benefits. In addition, key policy reforms that we highlight will be needed to buttress and facilitate any market-based effort. We encourage market leaders to advocate for these policy reforms, and to take early action to pilot test models of combination approaches. The unmet patient need and the tremendous scientific advances underpinning the new era of gene therapy will not wait. Gene therapies were still just on the horizon seven years ago. Today, they represent among the most transformative advances in our health care system. Starting today, we need innovative pricing and payment options to assure that those advances reach all individuals who can benefit while strengthening the overall sustainability of our health care system. The time for action is now.

Appendix A: 2023 ICER Policy Summit Attendees

Representatives from the following companies and organizations attended ICER's 2023 Policy Summit, which was held from December 12 – 14, 2023 in Phoenix, Arizona:

- Abbott
- AHIP
- Alnylam Pharmaceuticals
- AstraZeneca
- AT&T
- ATI Advisory
- Bayer Healthcare LLC
- Boehringer Ingelheim Pharmaceuticals
- CalPERS
- Carelon
- Centene Pharmacy Services
- CRISPR Therapeutics
- CVS Health
- Express Scripts
- GlaxoSmithKline
- Health Care Service Corporation
- Humana
- JPMorgan Chase & Co
- Kaiser Permanente
- Mallinckrodt Pharmaceuticals
- Merck & Co.
- National Organization for Rare Disorders
- National Pharmaceutical Council
- Novartis
- Novo Nordisk
- Otsuka Pharmaceutical
- Point32Health
- Premera Blue Cross
- Prime Therapeutics
- Regeneron Pharmaceuticals
- Sanofi
- Sun Life
- UnitedHealthcare

Appendix B: Definitions

Commercial Health Insurance - Commercial health insurance, also referred to as private insurance, is the most common form of health insurance in the United States, covering nearly two-thirds of Americans, most of whom receive coverage through their employer. These plans cover a wide range of healthcare services and cover most of the costs of these services. They are generally governed by state and federal requirements.⁵⁸ Commercial health plans differ in size from large such as UnitedHealth Group, Elevance Health Group, Centene Corporation, Kaiser Foundation Group, Humana Group, CVS Group, and HCSC group which together have more than half of the cumulative market share, to smaller commercial health plans such as Elderplan, Driscoll Childrens Health Plan, and BCBS of North Dakota, which typically have fewer than 2 million members.⁵⁹

Gene Therapy - Gene therapies are intended for one-time treatment and are anticipated to have lasting clinical effects. These products employ genetic manipulation to cells (either *in vivo* or *ex vivo*) and typically provide at least 18 months of effect from a single administration.¹² They are often referred to as durable gene therapies although long-term durability for these new treatment modalities is often unknown.

ERISA – The Employee Retirement Income Security Act of 1974 (ERISA) is a federal law that sets minimum standards for most voluntarily established retirement and health plans in private industry to provide protection for individuals in these plans.⁶⁰

Milestone-based contracts - A type of value-based contract in which a pharmaceutical company guarantees to refund the cost of therapy (partially or fully) if an agreed outcome is not achieved.³⁷

Value-based installment - A type of value-based contract in which payments for a cell or gene therapy are spread over multiple years and future payments are linked to therapy performance. If a therapy fails to deliver an agreed outcome, no further payments are made.³⁷

Plan Sponsor – A plan sponsor is the entity that ultimately pays for coverage, benefit, or insurance product. A sponsor can be an employer, union, government agency, association, or insurance agency.⁶¹

Rebates – Rebates are payment from drug manufacturers to pharmacy benefit managers (PBMs) or health plans in relation to prescription drugs dispensed to plan members.⁶²

Reinsurance - Reinsurance, often referred to as “insurance for insurance companies,” is a contract between a reinsurer and an insurer. In this contract, the insurance company—the cedent—transfers risk to the reinsurance company, and the latter assumes all or part of one or more insurance

policies issued by the cedent. Reinsurance contracts may be negotiated with a reinsurer or arranged through a third party, i.e., a reinsurance broker or intermediary.⁶³

Risk pools - Health insurance risk pools are large groups of individual entities (either individuals or employers) whose medical costs are combined to calculate premiums. The pooling of risk is fundamental to insurance as large pools of similar risks exhibit stable and measurable characteristics that enable actuaries to estimate future costs with an acceptable degree of accuracy. Pooling risks together allows the costs of those at higher risk of high medical costs to be subsidized by those at lower risk.⁶⁴

Self-insured employer (also known as self-insured health plan or self-funded health plan) - Coverage offered by an employer or association in which the employer or association takes on the risk involved with providing coverage, instead of purchasing coverage from an insurance company. Self-insured plans are not subject to state insurance regulations. Instead, they are regulated at the federal level under ERISA.⁶⁵

Stop loss insurance - Stop loss insurance provides protection against catastrophic or unpredictable losses. It can be purchased by self-funded employers who do not want to assume 100% of the liability for losses arising from the plans. Under a stop loss policy, the insurance company becomes liable for losses that exceed certain limits called deductibles. Stop loss insurance may be specific (member level) or aggregate (population level).⁶⁶

Subscription model - A pharmaceutical company provides treatment for a set fee regardless of the number of patients treated or a set price per patient.³⁷

Warranty – a pharmaceutical company purchases a patient-specific warranty policy that reimburses treatment-related costs for suboptimal performance to plan sponsors over an agreed time period. The value is related to covered healthcare costs and is not a refund for the cost of the treatment.³⁷

Appendix C: Acronyms and Abbreviations

Acronym	Abbreviation for
AMP	Average manufacturer price
CMMI	Centers for Medicare and Medicaid Innovation
CMS	Centers for Medicare and Medicaid Services
evLYG	Equal value of life years gained
FDA	US Food and Drug Administration
FoCUS	Financing and Reimbursement of Cures in the US
HHS	United States Department of Health & Human Services
HIPAA	Health Insurance Portability and Accountability Act
HTA	Health technology assessment
ICER	Institute for Clinical and Economic Review
MACPAC	Medicaid and CHIP Payment and Access Commission
MBP	Medicaid Best Price
MCDA	Multi-Criteria Decision Analysis
MDRP	Medicaid Drug Rebate Program
PBM	Pharmacy benefit manager
QALY	Quality adjusted life year
RCT	Randomized control trial

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