

WHITE PAPER

Gene Therapy

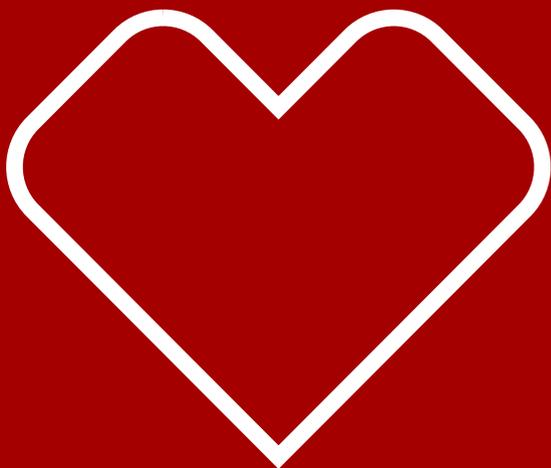
Keeping Costs from Negating
Its Unprecedented Potential

 **CVS**Health.



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Introduction

After many years of scientific promise but few real results, gene therapies are now a reality. These exciting new interventions have the potential to relieve tremendous suffering for patients with genetic disorders. Making sure these treatments are accessible for all those who need them requires innovative partnerships, as well as new ways of providing health insurance and pharmacy benefit design.

Generally speaking, gene therapies use a target gene that expresses protein products at a sufficient level to cure, or at least ameliorate, a disease caused by a genetic defect. So far, the U.S. Food and Drug Administration (FDA) has approved a handful of gene therapies to treat serious diseases that were previously untreatable except through supportive measures. The European Medicines Agency has approved a few more than the FDA — and there are many more in the pipeline.¹

Along with the promise of a potential cure that gene therapies offer, come unprecedented costs. One recent example of this is Zolgensma, a treatment for spinal muscular atrophy (SMA), which debuted at a cost of more than \$2 million — by far the most costly single-dose medication ever.² While Zolgensma is the most prominent example, many similar therapies all likely carrying very high price tags, are under development.

The role of CVS Health — and Aetna as a health insurer — is to reduce the costs of therapy, while ensuring appropriate utilization of cutting-edge therapies.

In this position paper, we review the history and development of gene therapies, the cost of the treatments already on the market, and considerations for policy makers. CVS Health will continue to build a rigorous, evidence-based formulary and apply clinically appropriate utilization management rules to gene therapy. Here, we highlight additional solutions we are developing to help mitigate the financial impact for our clients and their plan members. Without solutions to help payors manage the cost, some may make the choice to exclude coverage, which could jeopardize patient access to these potentially life-saving medications.

Scientific Background: In Vivo and Ex Vivo Therapies

Gene therapies insert DNA containing a functioning gene into a cell, to replace a faulty or missing one, to correct the effects of a disease-causing mutation.³ In order for gene therapy to work, once administered, the new DNA must reach the damaged cell, enter the cell, and either express or disrupt a protein.

Gene therapies fall into two categories: in vivo and ex vivo.

The in vivo approach involves use of a gene inserted into a viral envelope, often an adeno-associated virus (AAV). The gene-carrying virus is prepared in a laboratory and delivered to the target organ either by an injection or a simple infusion, where it is taken up by cells in target organs. It is not integrated into the chromosome, but nonetheless does appear to have a sturdy and long-lasting response, especially in slowly replicating cells like retinal cells, or neurons. Luxturna, which is injected directly into a patient's retina to mitigate vision loss in pediatric and adult patients with a specific type of progressive blindness due to a mutated gene, and Zolgensma, the new therapy for treating SMA, are both examples of in vivo gene therapies.⁴

In Vivo Gene Therapy

1. Engineering

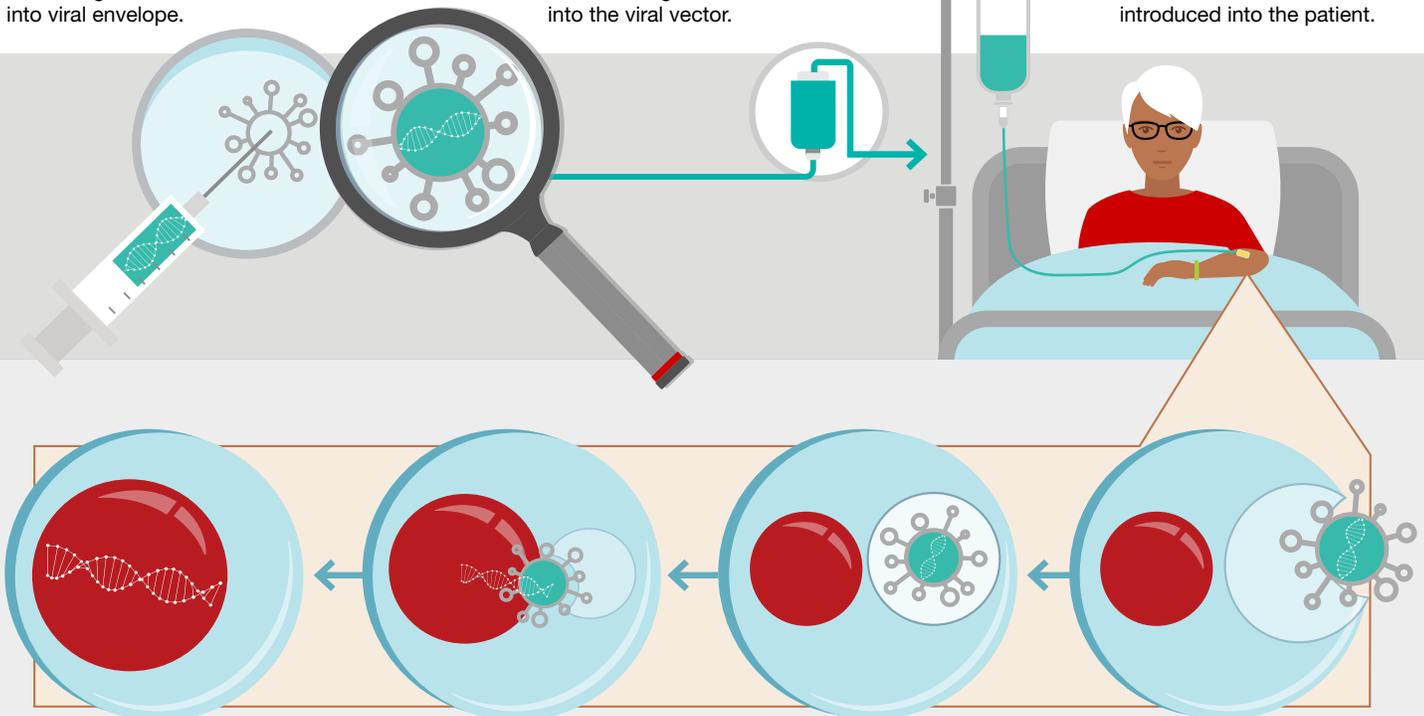
The new gene is inserted into viral envelope.

2. Integration

Gene is integrated into the viral vector.

3. Administration

The modified vector is introduced into the patient.



7. Result

The new gene injected into the nucleus.

6. Break down

Vesicle breaks down releasing the vector.

5. Packaging

Vector is packaged into the vesicle.

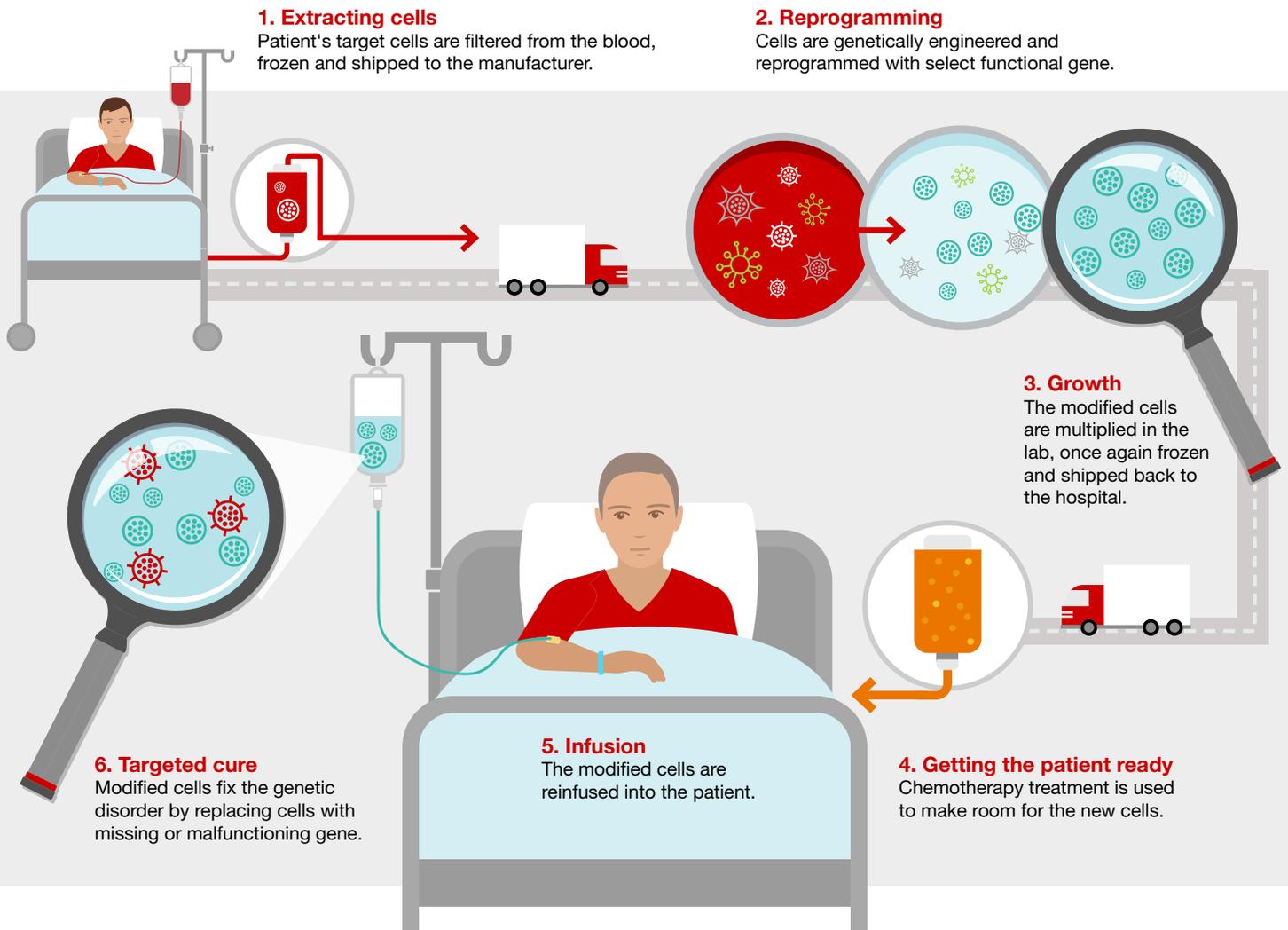
4. Binding

The vector binds to patient's cell.

In ex vivo gene therapy, target cells containing the faulty or missing genes are extracted from the patient in a clinical facility, usually a hospital, and re-engineered in the laboratory to integrate a new — or functional — gene into the chromosome. The reprogrammed cells are then infused into the patient. The new gene is distributed through the patient's system as these cells multiply. Various cell types can be genetically engineered for ex vivo treatment.

Currently, progenitor and mesenchymal stem cells are the ones used most often. The best known examples of an ex vivo approach are **chimeric antigen receptor T-cell (CAR-T) therapies** used to treat certain forms of lymphoma and leukemia. They offer treatment options for patients with advanced, aggressive forms of cancer, which were previously incurable.⁵

Ex Vivo Gene Therapy



Ex vivo gene therapies are highly personalized and complex, and may carry significant clinical risk. In most cases, the treatments need to be administered in a hospital setting under medical supervision. For example, in CAR-T, which is a type of ex vivo therapy, neurological toxicity and cytokine release syndrome (CRS) are serious complications and can lead to life-threatening cardiac and respiratory distress, multi-organ failure requiring intensive care unit admission, or even death.⁶ Generally, patients are advised to stay within two hours of a treatment center for at least four weeks after receiving therapy. Therapies that have been approved so far are only available at select treatment centers across the country which have trained professionals, and have been certified by the manufacturer in the handling and administration of these treatments. Given the complexity of administering these agents — and the relatively limited number of facilities that are fully trained to offer them — patient access remains a challenge.

Two key differences between ex vivo and in vivo gene therapies are how they are developed, and the complexity and cost of administration.

- 1 Ex vivo therapies require a set of procedures akin to a bone marrow transplant. Existing cells may have to be “ablated” — a process that can take weeks — while the patient is hospitalized and under clinical supervision. In vivo therapies, on the other hand, require insertion of the genetically modified virus into the target tissue. Luxturna requires a sub-retinal injection. Zolgensma only requires an infusion.
- 2 There is at least some thought that ex vivo approaches utilizing stem cells may have a greater chance of long-term persistence compared to in vivo transplants. However, because ex vivo therapies require prolonged hospitalization, the total cost of care for administration for these treatments is likely to be considerable. By contrast, in vivo drugs are delivered as infusions or injections and it is likely that they can be administered in outpatient settings.

Gene Therapy: Now and Into the Future

In addition to those already approved, numerous gene therapies are in development, which could help treat, and even cure, other previously untreatable conditions. Some target relatively rare monogenic illnesses, such as cerebral adrenoleukodystrophy, Sanfilippo syndrome, and adenosine deaminase deficiency.^{7,8,9} However, treatments in development, with potential approval and market launch expected by 2021, also include much more common genetic disorders like hemophilia A and B, which together have a prevalence of at least 20,000 individuals in the United States.¹⁰ An estimated 70,000-100,000 Americans have sickle cell disease.¹¹ Muscular dystrophy affects more than 200,000 Americans.¹² Both conditions could potentially have gene therapies available by 2023.

The problem that long bedeviled gene therapies, especially in vivo treatments, was overcoming the immune response

to the viral envelope. The development of the AAV and lentiviral vectors that are now in use, helped overcome the challenge. As a result, there are now many potentially viable products in the pipeline as companies move quickly to design the genes necessary to address the more prevalent monogenetic (single gene defect) disorders.

Prior to the development of gene therapies, many of these disorders were not only untreatable and incurable, but also significantly affected patients' quality of life. For instance, a majority of patients born with SMA progressed to severe disability and dependence on a ventilator during the first two years of their life and most died before age 3. Others, with less severe disease, require lifelong, chronic care. Curative treatments for such genetic disorders were unfathomable a decade ago; unfortunately, so are the costs of the cures currently in development.

A gene therapy treatment, which can effectively cure the disease, could not only prevent much suffering but also lead to cost savings in the long-term from a reduction in the attendant costs of care.

Why it Matters: The Massive Economic Implications

\$2M
potential price of
a single treatment

While the life-changing and life-saving potential of gene therapies is tremendously exciting, finding ways to pay for these treatments is a significant challenge for families and payors. With prices for a single treatment as high as \$2 million, many employers are struggling to find ways to offer coverage without bankrupting their health plans, or even their companies. What's more, these costs will hit plans — and the health care system — in one massive blow rather than being spread out over time.

Extrapolating these costs to a larger population illustrates the problem. Even if we assumed just 5,000 individuals were to be treated by gene therapy each year, if future treatments are priced at par with Zolgensma, it would add \$10 billion per year to the nation's health care bill — an additional \$50 per year of health care costs for every insured American. And that's before accounting for the attendant health care costs of complex administration methods such as the ex vivo processing and reintroduction of genetically altered stem cells, which could require as much as a month-long hospital stay.

Estimating the precise cost impact of gene therapies is very complicated and challenging. It is unclear how many patients with a particular condition may be treated with a given therapy or exactly how much the treatment will cost. To help plan sponsors estimate the impact of these treatments we analyzed the projected cost based on:

- ✓ Publicly available information about therapies in development
- ✓ Likelihood of approval
- ✓ Estimated prevalence of those conditions
- ✓ Lowest estimated cumulative five-year cost impact based on a price of \$1 million and 30 percent market penetration
- ✓ Highest estimated cumulative five-year cost impact based on a price of \$2 million, and market penetration of 40 percent for ex vivo therapies, and 60 percent for in vivo therapies

Near-Term Gene Therapy Pipeline*

Indication	Projected Launch Year	Prevalence + Incidence 2-5 Years	5-Year Total Estimated Cost Impact (2020-2024) (In Millions)	
			Low Market Impact	High Market Impact
Hemophilia A	2020	7,360	\$1,460	\$5,830
Beta-thalassemia major**	2020	1,050	\$210	\$550
Sanfilippo syndrome type A	2021	1,150	\$90 [†]	\$350 [†]
Cerebral adrenoleukodystrophy	2021	6,790	\$670	\$1,790
Adenosine deaminase severe combined immunodeficiency	2021	1,710	\$130	\$340
Leber's hereditary optic neuropathy	2021	5,480	\$1,090	\$4,340
Choroideremia, an inherited retinal dystrophy	2021	4,560	\$900	\$3,610
Hemophilia B	2021	2,620	\$520 [†]	\$2,080 [†]
Wiskott Aldrich syndrome	2022	3,350	\$500	\$1,340
Metachromatic leukodystrophy	2022	3,420	\$510	\$1,370
Sickle cell anemia	2022	117,020	\$8,780	\$23,400

5-Year Total Estimated Cost Impact (2020-2024):



\$14,850M

\$45,000M

*This is a representative sample of monogenetic therapies in development, not an all-inclusive list of gene therapies in the pipeline.



The promise of alleviating a significant amount of suffering could mean that gene therapies are cost effective — at the right price point.

Compounding the challenge of these unprecedented costs is the fact that several things are as yet unknown. For instance, it is too early to tell how long the effects of the treatments — restored vision, disease remission, etc. — will last.

There is not enough patient follow-up data yet to know whether they will truly be "cures" or if the diseases will eventually return. Even if they are not truly cures that are sustained over a patient's lifespan, the promise of alleviating a significant amount of suffering could mean that gene therapies are cost effective — at the right price point. As it stands, the huge, initial costs are clouding that promise.

Because of the potentially prohibitive costs, some employers are considering excluding ultra-high cost gene therapies from their plan benefit coverage. However, doing so might be short-sighted if the treatments are proven to be as effective long-term as they appear to be today. But that can be a tough rationale to accept for plan sponsors facing a large, one-time burst of spending, here and now.

To ensure patients continue to have appropriate access to these therapies, there is a critical need for solutions to reduce the cost impact of these medications to the greatest extent possible. CVS Health is at the forefront of this effort, engaging with manufacturers about how we can partner with them to ensure patients have appropriate access to therapies at a cost that is sustainable to the health care system.

Approaches to Reduce the Cost Impact of Gene Therapies

There are four complementary approaches — encompassing safety, patient access and care, as well as cost management — that health plans and employers can utilize to reduce the cost impact of gene therapies:

- ✓ Extending the National Medical Excellence Program model
- ✓ Evolving the role of specialty pharmacy
- ✓ Value-based contracting
- ✓ Financial protection programs

1 Extending the National Medical Excellence Program Model

The role of CVS Health — with CVS Caremark as a pharmacy benefit manager (PBM), the CVS Specialty pharmacy network and Aetna as a health insurer — is to help reduce the costs of therapy, while ensuring high-level patient care for those receiving such complex treatments. A majority of gene therapies fall into the medical benefit. Aetna's National Medical Excellence (NME) Program is a good role model for providing valuable support to members in special and complex situations, such as gene therapy. The NME program focuses on supporting patients with complex diseases and needs including bone marrow and organ transplants at leading locations that are selected based on their reported clinical experience, quality of outcomes, and economic factors. The selection of participating institutions takes into consideration the previous track record of experience and quality along with mutually acceptable reimbursement in caring for patients with these kinds of conditions and/or providing these procedures. The NME program refers patients to high-volume institutions with a record of acceptable outcomes. Although quality factors, certifications, processes, and publicly reported volumes/outcomes are not yet available for most gene therapies, extending this program to have designated facilities for gene therapy enables patients to have an ongoing relationship with these centers. The program also offers dedicated NME medical directors with expertise in complex case management, transplantation, and genetic disorders to work with these patients and their doctors.

In our past experience, transplant centers welcomed the opportunity to work with experienced and dedicated health plan representatives — NME nurse case managers and medical director — for high-cost, complex transplant activities and care. Similarly, we expect provider teams dealing with gene-based, cellular, and innovative therapies would likely also welcome direct communication and care collaboration with the NME program for their patients.

Extending an NME model to gene therapy enables patients to have an ongoing relationship with these centers. The program also offers dedicated medical directors with expertise in complex case management, transplantation, and genetic disorders to work with these patients and their doctors.

2 Evolving the Role of Specialty Pharmacy

Having specialty pharmacies like CVS Specialty purchase gene therapies directly from the manufacturer is an opportunity to reduce the cost impact. Currently, many hospitals and physician offices mark up the cost of a drug even higher than the stated wholesale acquisition cost, after purchasing, and before administering it. If manufacturers were to not provide access to specialty pharmacies, the risk of mark-ups through buy-and-bill is much greater.

PBMs like CVS Caremark can help mitigate the budget impact for payors by providing an installment pay-over-time plan, which would allow the employer group to pay for the medication over several years, lessening the significant impact of a large, immediate cost.

The important consideration here is that the employer or health plan is responsible for the entire cost of the medication at the time of administration regardless of whether the employee or patient is still covered under their plan. While the cost is spread over an extended period, the payor at the time of administration is responsible for the entire cost. Financing options that let plan sponsors pay over time would enable smaller, self-insured payors, who lack the resources of larger payors, to spread the risk of having to pay for the care of a patient on gene therapy. This would mean they can absorb the cost of such therapies without a significant change in year-over-year total patient care costs.

3 Value-Based Contracting

Given the ultra-high costs of these drugs and the expectation that patients will reap durable clinical benefit from these treatments, gene therapies are perfect candidates for value-based contracting.

Consider that currently, there are no long-term studies proving durability of these treatments. In addition, it is not clear that they will work for all patients. It is expected that there will be cases in which the therapy, unfortunately, does not work as expected. For instance, even though ex vivo therapies for blood or lymphatic cancers often have lower mortality rates than standard practice, they continue to have relatively high mortality rates overall. In vivo programs, on the other hand, which generally treat less acutely ill patients, depend on durable activity of the functioning gene.

Even though manufacturers appear to have confidence in their therapies, value-based contracts, which refund a portion of the cost of the therapy if the patient fails to achieve and sustain an expected clinical response, help tie reimbursement to the expected outcome.

This approach is an especially appealing one for payors because the resulting monitoring would also produce real-world efficacy data, an important consideration for an area where clinical patient trials are likely to be relatively small (given the often low prevalence of the condition) and short.

It does pose some challenges. Patients will have to be followed over a long period of time — typically years — to be able to identify whether the treatment was durable and the patient continues to experience the clinical benefit. This is trackable and can be cost-effective for both the insurer and the payor. However, in order to track outcomes for value-based contracts and support appropriate payment, insurers and manufacturers must be able to stay engaged with patients over time. If the patient moves to a new insurer or employer, it could void the original insurance contract relationship. To account for this, we will need to develop new contractual riders that give insurers the right to continue to engage with the patient, even if he or she no longer has coverage through the original plan and to interact with their former physician even if the patient has changed physicians. This is important because the former employer would still be making installment payments on the patient's behalf.

Given these evolving relationships with the patient at the nexus, patients may also need to agree to participate in long-term outcomes data collection as a condition for ongoing payment. This breaks new ground in insurance coverage but is necessary because without such provisions, value-based contracting for gene therapy would not work. Specialty pharmacies like CVS Specialty use digital technology to help ensure patient engagement and to gather clinically relevant data to support outcomes reporting.

Another potential barrier to this approach may be current federal health care policy governing the Medicaid “best price” rule. Generally speaking, the policy states that Medicaid beneficiaries should have the lowest available discounted price for a therapy. If a manufacturer offered a 100 percent guarantee on a therapy, and the treatment failed to work at all, meaning the entire purchase price had to be refunded, that could be interpreted as the “discounted price” being \$0.

In the unlikely event that happened, policy makers may expect the Medicaid program to have access to the treatment at no cost. The Centers for Medicare & Medicaid Services (CMS) should have access to, and be able to, adopt the most competitive value-based contracts available in the market. However, they should amend the “best price” rule (via waiver or otherwise) to allow for these very highly priced therapies to be covered under value-based arrangements that make them more affordable with less risk over time. Discussions about these issues are ongoing with CMS.

4 Financial Protection Programs

For large employers, even ultra-high cost gene therapies — while they will have an inflationary impact — are likely to be manageable. An added \$66 billion in annual costs in a health care system currently sized at \$3.5 trillion is about 2 percent in new costs.

For smaller employers with self-insured plans, a single patient needing a gene therapy — even one priced at \$1 million dollars, half of the most expensive gene therapy current available — could pose an actuarial risk. For a 2,000-employee client, the impact could represent a substantial increase in total cost.

Stop loss policies have traditionally helped with large unanticipated medical costs and may provide coverage for gene therapies, particularly as the number of available treatments increase over time.

For customers who choose to not purchase a traditional stop loss policy, we are developing a focused insurance product that offers financial protection for gene therapies by spreading the actuarial risk across a pool of enrolled members. Such a product could help mitigate the financial risk posed, minimizing the risk of bankrupting a relatively small employer due to the impact of a single patient who needs an ultra-high cost therapy. If adopted broadly by a large number of clients, it would have a predictable reasonable fixed cost, making it possible for payors to continue offering coverage for gene therapies while ensuring the financial viability of their benefit plan.

Together, these steps can help lower costs for payors while ensuring appropriate access to these life-changing therapies.

Considerations for Government Payors

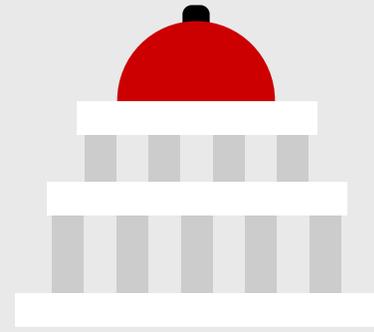
Government payors will have an important role to play in determining the ultimate cost of gene therapies. More than 50 percent of births in the United States today involve mothers and children insured by Medicaid.¹³ In such cases, it will likely fall to the Medicaid program to pay for treatment of genetic disorders, like SMA, that manifest in childhood and need to be treated early in a child's life. The share of children with special health care needs covered by Medicaid or the Children's Health Insurance Plan is about 47 percent.¹⁴ Similarly, someone with sickle cell disease may experience disability and therefore qualify for Medicare, or be dually qualified for Medicare and Medicaid. Many states rely on managed Medicaid programs. However, for treatments such as ultra-high cost gene therapies, some states are beginning to create "carve-out" coverage decisions, and are directly contracting with the manufacturers on a fixed-fee basis. We may continue to see more evolution in how regulatory authorities look to manage the cost of these treatments.

We are actively working with CMS as policy makers contemplate ways to make these treatments more affordable.



The age of the genome, and gene therapies, is upon us and we should all applaud and support the promise it brings to alleviate a tremendous amount of human suffering.

At CVS Health, we are designing programs for our clients that can help mitigate the cost impact and ensure better access to appropriate therapies. Most of what is outlined here are straightforward changes that most stakeholders, including manufacturers, can support. If implemented, they are likely to prove extraordinarily important in helping ensure that the price of gene therapies do not prove unsustainable for our health care system.



~47%

of children with special health care needs are covered by Medicaid or the Children's Health Insurance Plan¹⁴

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1. <https://www.nejm.org/doi/full/10.1056/NEJMra1706910>.
 2. <https://www.cnn.com/2019/05/24/health/novartis-zolgensma-gene-therapy-fda-approval-bn/index.html>.
 3. <https://ghr.nlm.nih.gov/primer/basics/dna>.
 4. <https://www.nbcnews.com/health/health-news/luxturna-gene-therapy-blindness-cost-850-000-n834261>.
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 13. <https://www.kff.org/medicaid/state-indicator/births-financed-by-medicaid/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D>.
 14. <https://www.kff.org/medicaid/issue-brief/how-do-medicaid-chip-children-with-special-health-care-needs-differ-from-those-with-private-insurance/>.

**Supplemental indication for transfusion-resistant beta-thalassemia expected 2021. Cost impact analysis shown is for both indications.

†Estimates cumulative impact for distinct pipeline products for the same clinical indication.

Pipeline products are listed in approximate projected order of approval.

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