# Gene therapies and genetically modified cellular therapies

Balancing access, coverage and affordability for breakthrough therapeutics

CVS Health

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# Gene therapies and genetically modified cellular therapies are now a reality.

These clinical breakthroughs have the potential to provide durable treatment results, or even cure genetic disorders that the medical community once considered incurable. Given their remarkably high prices, however, they also present a real challenge in balancing coverage and cost.

The field is expanding fast. Through 2021, only nine of these therapies were approved by the United States Food and Drug Administration (FDA).* This number is expected to more than double by 2025.* There are more than a thousand gene therapies, genetically modified cellular therapies and other innovative therapies in clinical trials registered with the FDA. As the field matures, the focus is expanding from rare diseases to more common disorders that affect more patients.

These new therapies are very expensive. When Zolgensma (Novartis) launched in 2019 as a treatment for spinal muscular atrophy (SMA), it was by far the most expensive single-dose medication at more than $2 million.* Higher cost therapies have since been introduced. In 2022, the FDA approved Hemgenix (CSL Behring LLC) as a treatment for hemophilia B. It's priced at $3.5 million for a one-time dose.*

**The robust pipeline of gene therapies and genetically modified cellular therapies presents a need for solutions to manage costs and ensure clinically appropriate coverage for these cutting-edge technologies.**

While these therapies may require genetic testing to determine whether patients are appropriate candidates to use them, this white paper does not discuss the broader topic of genetic testing and personalized medicine.

# The basics: How these therapies work

Genes are pieces of DNA that contain information for making RNA, another type of genetic material found in cells. RNA, in turn, makes proteins or influences the regulation of cells. Proteins play a vital role in how our body functions. When genes do not produce the right proteins or produce them incorrectly, it can affect health and cause disease.

**There is a wide variety of genetic-based therapies available to patients. The variety and complexity of these products necessitate a holistic management approach. The broad categories include:**

## Gene therapies

Gene therapies correct a faulty or missing gene that causes disease by inserting a healthy functioning gene into a cell or by modifying an existing gene. This healthy or corrected gene is delivered by viral or non-viral carriers (called vectors) that are modified for this purpose. A newer approach to gene therapy involves the targeted breaking or cutting of DNA to modify the function of the cell. (See gene editing, page 6.)

**Examples include:**

- **Zolgensma** treatment of SMA
- **Roctavian** (BioMarin) treatment of hemophilia A
- **Elevidys** (Sarepta Therapeutics) treatment of Duchenne muscular dystrophy

## Genetically modified cellular therapies

These therapies reprogram the genes of cells (usually blood cells) in the lab. This makes them better at fighting disease, such as attacking certain cancer cells. Chimeric antigen receptor T-cell (CAR-T) products are examples of this class of therapies. In CAR-T, the patient's modified immune cells recognize and attack cancer cells using their enhanced abilities.

**Examples include:**

- **Kymriah** (Novartis) Used to treat specific types of leukemia and lymphoma
- **Yescarta** (Gilead Sciences) Used to treat certain types of lymphoma
- **Abecma** (Bristol Meyers Squibb) Used for patients with multiple myeloma who have not been successful with other treatments.

Gene therapies and genetically modified cellular therapies are biological products regulated by the FDA's Center for Biologics Evaluation and Research.* Most are single-dose therapies administered once per lifetime.

## Other innovative therapies

Other therapies manipulate how genes regulate a cell and the proteins it produces without adding new DNA material into the cell. Many of these products are based on RNA molecules. Examples include antisense oligonucleotides (ASOs) and small interfering RNAs (siRNA), which inhibit the expression of specific genes associated with the disease.* RNA molecules are prone to being degraded by enzymes within cells. This limits how long they are effective, so repeated dosing is required.

These technologies are not classified by the FDA as gene therapies or genetically modified cellular therapies, but they can treat similar genetic conditions. For example, SMA can be treated with the ASO, Spinraza (Biogen), or the gene therapy, Zolgensma. Spinraza requires repeated dosing, while Zolgensma is a one-time infusion.

## How therapies are delivered

For gene therapies to work, the corrected gene must enter the damaged target cells and provide instructions to repair cell function. There are two approaches that accomplish this — *in vivo* and *ex vivo*. Each has implications for the patient journey, care coordination and total cost.

### *In vivo* therapies

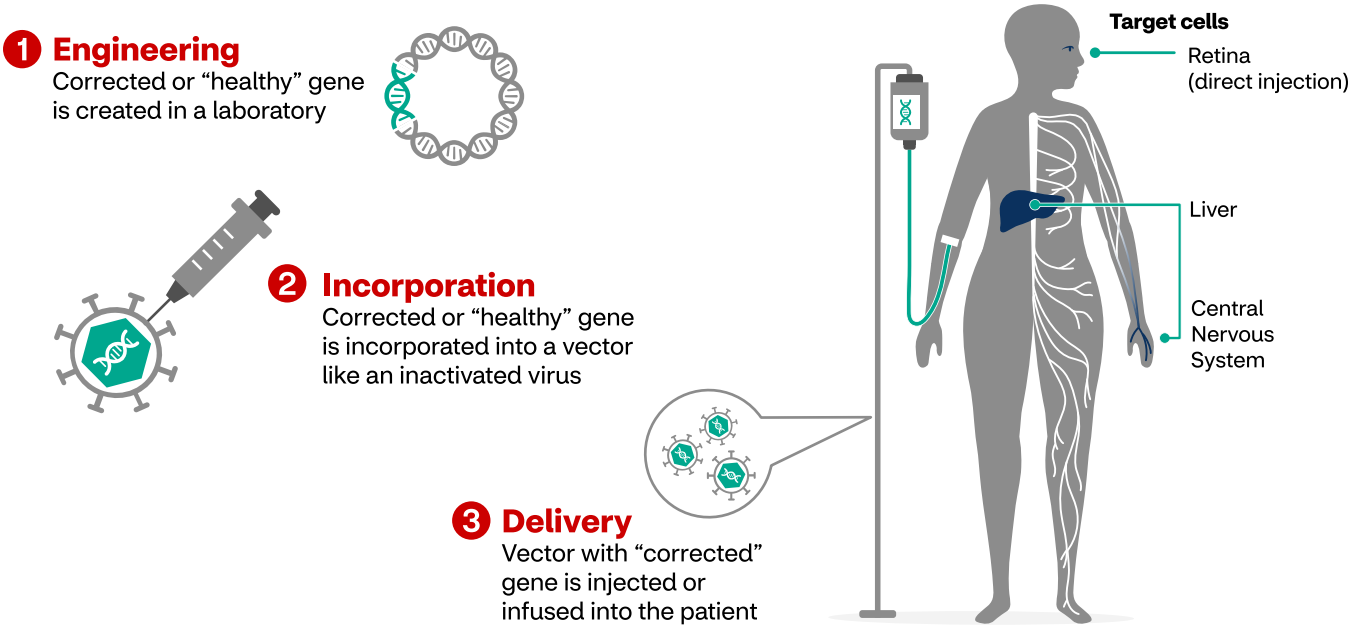
The *in vivo* approach to gene therapy involves packaging a corrected gene into a vector, usually a virus that is modified to not cause disease. The gene-carrying virus is prepared in a lab. Then, a medical professional delivers the "package" directly to the damaged target cells by infusion or injection.

Most *in vivo* gene therapies are once-per-lifetime, one-time infusions and, in many cases, can be administered in an outpatient setting, such as an infusion center. However, Vyjuvek (Krystal Biotech), approved by the FDA in 2023, is an in vivo gene therapy that is a multi-dose, topical gel for the treatment of a rare inherited skin disorder called dystrophic epidermolysis bullosa.

**Examples of *in vivo* therapies include:**

- **Hemgenix**, used to treat the inherited bleeding disorder hemophilia B, is an infused product that acts on the liver
- **Zolgensma**, used to treat SMA, is an infused product that acts on the central nervous system
- **Luxturna** (Spark Therapeutics), used to treat an inherited genetic vision disorder called retinal dystrophy, is injected directly into the retina

## *In vivo* gene therapy



## *Ex vivo* therapies

The *ex vivo* approach to gene therapy involves removing cells from the patient's body. These cells are genetically modified or reprogrammed in a lab, and then infused back into the patient. Before receiving genetically modified cells, the patient may need chemotherapy or other treatments to prepare for the incoming cells.

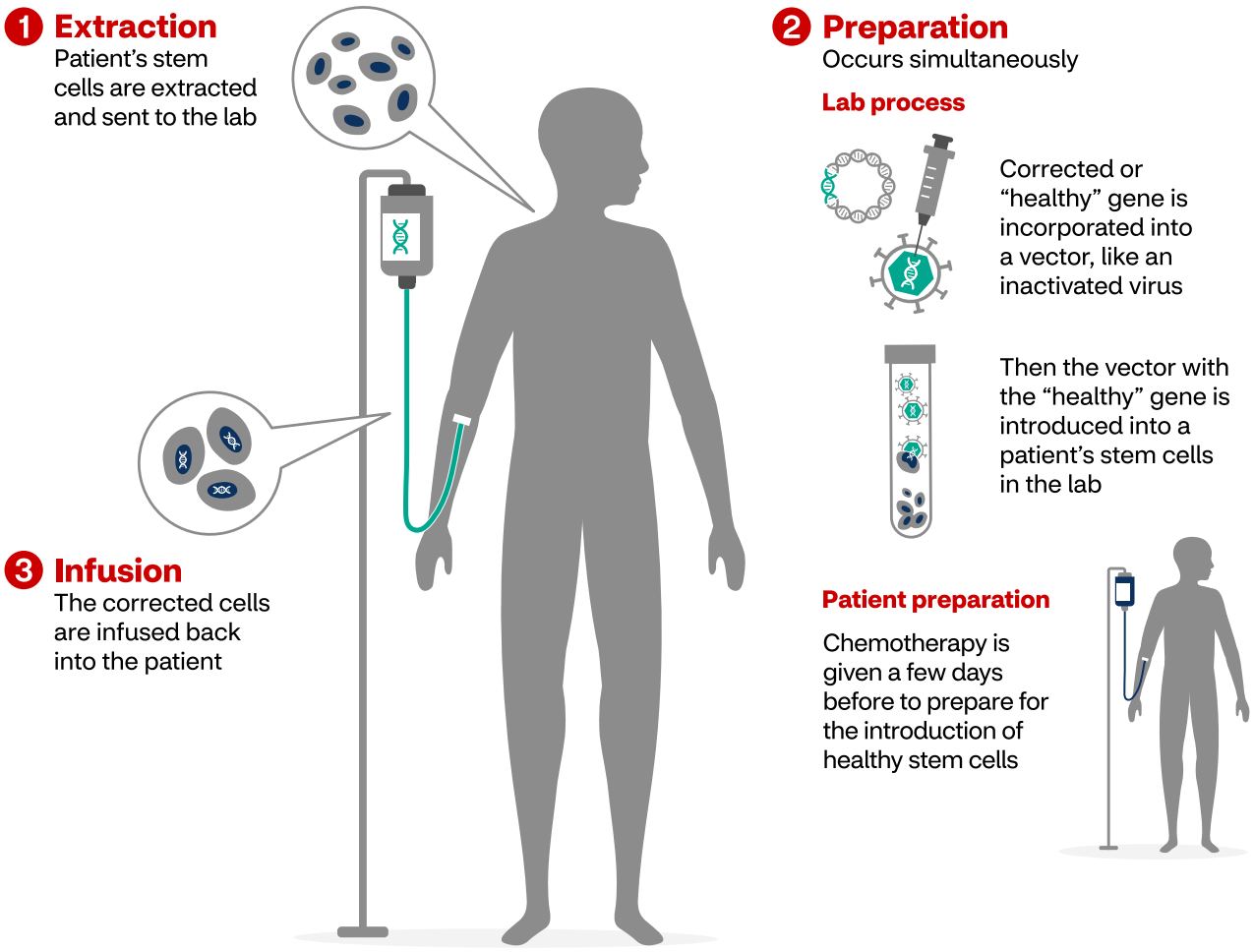
Because ex vivo therapies may require inpatient treatment both before and after the infusion, care is complicated, and the total cost of treatment goes beyond the cost of the therapy itself.

**Examples of *ex vivo* gene therapy include:**

- **Skysona** (bluebird bio), used to slow the progression of neurologic dysfunction in patients with cerebral adrenoleukodystrophy
- **Zynteglo** (bluebird bio), used to treat transfusion-dependent beta-thalassemia
- **Casgevy** (Vertex Pharmaceuticals and CRISPR Therapeutics), used for the treatment of the blood disorders sickle cell disease and transfusion-dependent beta-thalassemia

CAR-T cellular products also are considered *ex vivo* therapies.

## *Ex vivo* gene therapy



## **Gene editing:** A trend to watch

An innovative technique called gene editing is already changing the field of gene therapy. Gene editing enables precise targeted changes to the DNA of faulty genes within cells. It has shown promise in both *in vivo* and *ex vivo* clinical trials, and is being evaluated as a tool for genetically modified cellular therapies such as CAR-T.

CRISPR-Cas9 is the most prominent gene editing technology currently available. It works by creating a genetic guide called gRNA programmed to recognize the abnormal gene target of interest.*

The gRNA guides "molecular scissors" to the gene target and stops the gene from working, cuts out the faulty gene, or swaps out the faulty gene with a corrected gene.

Gene editing has many potential advantages. Because of the precise targeting of gene editing tools like CRISPR-Cas9, it has the potential to correct the root cause of the disease. Given the versatile nature of CRISPR gene editing, therapies based on it are expected to grow.

The first CRISPR-Cas9–based gene therapy for the treatment of sickle cell disease (SCD) and beta thalassemia were FDA approved in December 2023 and January 2024.

More than 70 CRISPR clinical trials are underway across a range of diseases, from blood disorders to cancer.* These conditions represent a move into larger patient populations than those previously targeted by approved gene therapies.

The next generation of gene editing technologies is already in development, including base editing, prime editing and epigenetic editing.

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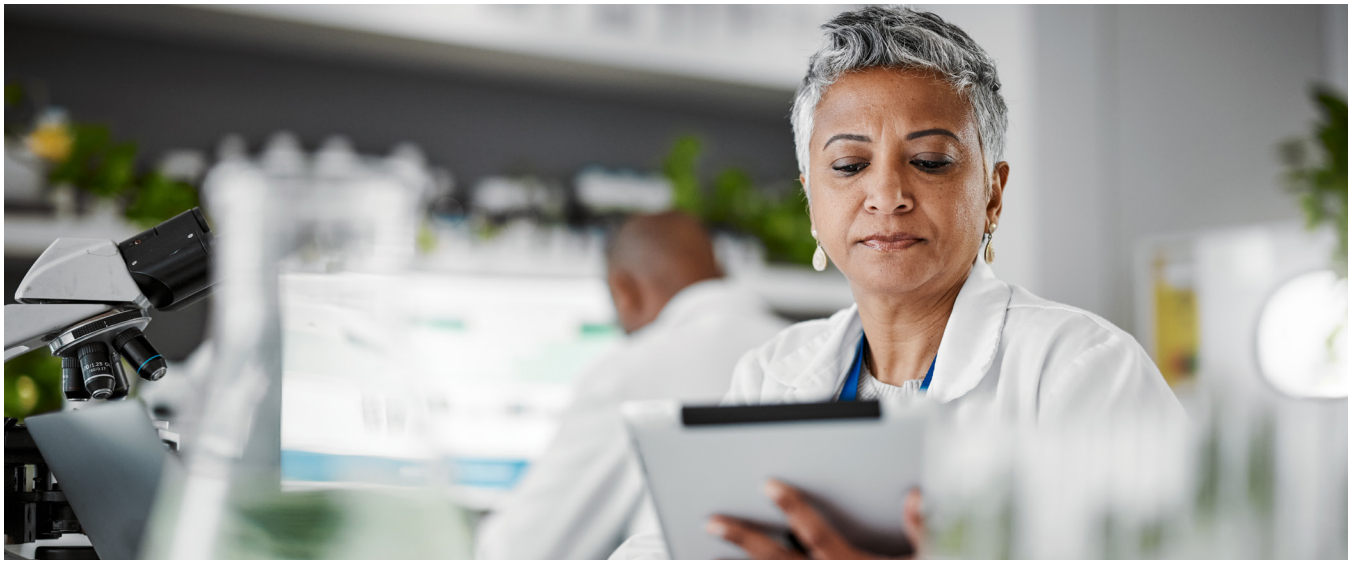
## CRISPR

**1 Identification**
CRISPR-Cas9 identifies target DNA for editing

**2 Cutting and editing**
Gene can be edited through DNA modification



THE FUTURE IS HERE

# Spotlight on gene therapy for the treatment of sickle cell disease

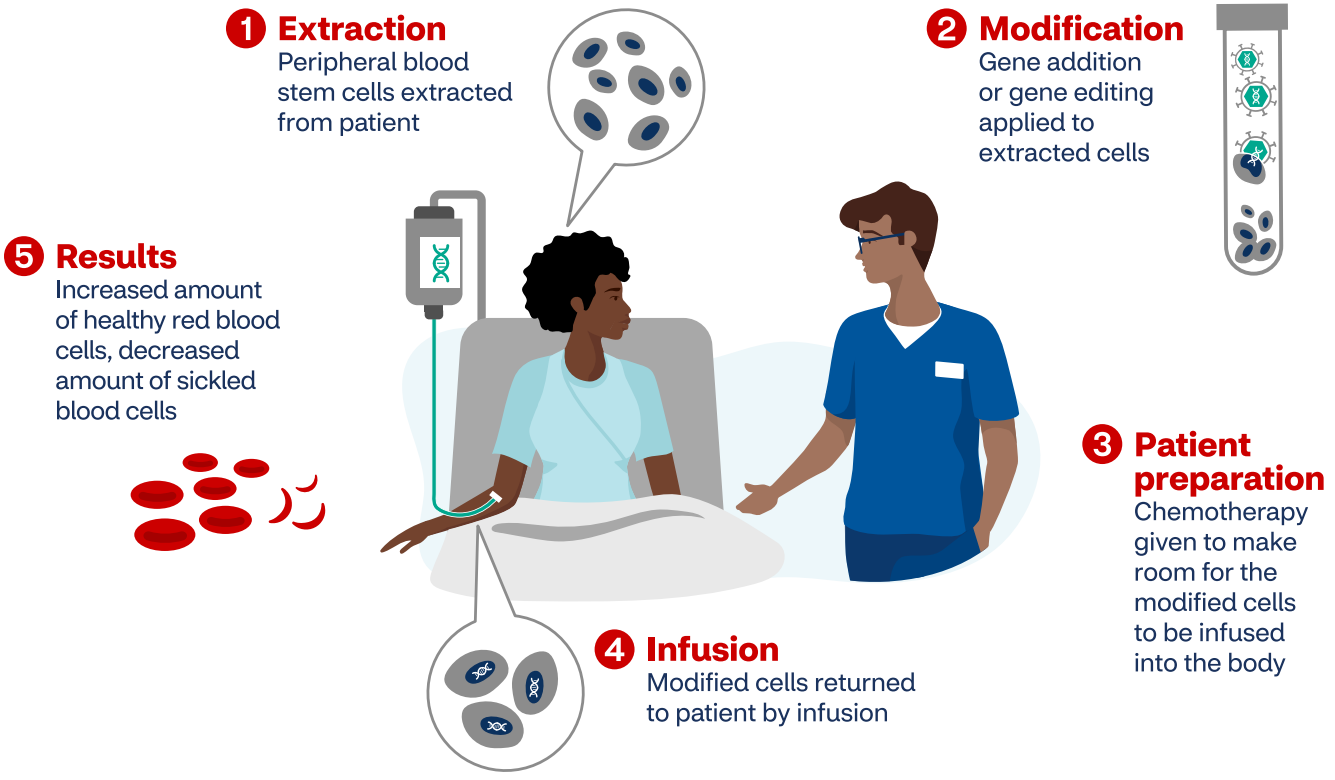
**Sickle cell disease is an inherited condition that gene therapy could potentially cure, improving health and offsetting significant future health care costs.**

The Centers for Disease Control and Prevention estimate about 100,000 adults and children in the United States have SCD. As many as 20,000 people may be candidates for one of two gene therapy products.*

SCD is caused by a faulty gene that produces an abnormal form of hemoglobin protein within red blood cells (RBCs). Hemoglobin carries oxygen to tissues in the body. The resulting malfunctioning hemoglobin (called Hgb S) causes RBCs to change shape or "sickle". Sickle-shaped red blood cells get stuck in blood vessels and prevent the delivery of oxygen to tissues. This causes extreme pain and, over time, organ damage. SCD is more common in people of African, Mediterranean and Middle Eastern descent.

There are two different gene therapies approved for SCD. One, Lyfgenia (bluebird bio), adds a modified working copy of the gene to the patients cells. The other, Casgevy, uses CRISPR-Cas9 technology to edit and "turn on" a gene that makes a fetal form of hemoglobin that is no longer produced after birth. Fetal hemoglobin is non-sickling and enables RBCs to meet the oxygen needs of the individual. Both SCD products are *ex vivo* technologies and require the modification of the patient's stem cells, which are the cells that develop into RBCs and make hemoglobin.

## Sickle cell disease gene therapy approaches



# Payor and employer considerations

Technological advances have ushered in many FDA-approved gene therapies and genetically modified cellular therapies that promise to improve health with a rich pipeline of products in development.

**Several considerations influence coverage, affordability and long-term value of these therapeutics for patients, employers and payors.**

## Long-term efficacy

Clinical trials have demonstrated the effectiveness of gene therapies, and early information has built confidence in the short-term durability of patient response. But long-term data is mostly lacking because many of these therapies are new and long-term durability might be measured over 5 to 10-year periods.

## Safety concerns

Gene and cellular therapies are complex and may carry risks. These can include life-threatening immune responses, higher risk for certain types of cancer, allergic reactions, or damage to organs or tissues. The FDA revised the label of approved CAR-T therapies to warn of their increased risk for secondary blood cancers.*

Gene editing technologies add an additional concern with the possibility of "off-target" effects; the unintentional editing of genes beyond the specific target gene(s). Lab controls are built in to minimize this risk. As with durability of response, there is still limited data on the long-term safety profiles of these products.

## Coverage and affordability

These therapies are costly, making coverage challenging for employers and payors. Models suggest there may be cost savings over time for selected therapies. In one analysis, access to therapies for even a small number of patients each year with multiple myeloma, SCD and hemophilia A, reduced overall 10 year direct medical and disability costs.* Even if validated for a broader number of products, the medical return on investment may not address the challenge of the upfront cost to the employer and payors who may not necessarily benefit from long-term medical and disability savings.

## Fragmentation

The full range of gene-based therapies are covered under medical and pharmacy benefit plans.

Gene therapies and genetically modified cellular therapies are typically covered under medical benefits due to their complex administration needs requiring supervision of medical professionals in healthcare settings, including inpatient hospitalization. Several drugs that work at the genetic level but are

not gene therapies can be covered under pharmacy benefits, typically used for oral and self-administered drugs.

Fragmentation of benefits can occur when therapies requiring complex administration are carved out from the underlying medical benefit plan. This disaggregates the therapeutic product from the underlying medical services such as chemotherapy administration or transplant care. Fragmentation increases the risk of inconsistent decision making, redundant provider work and delayed or poorly coordinated care for the patient. Employers must weigh any savings that may come from fragmented benefit structures against the risk of a disrupted member and provider experience, as well as poor clinical and economic outcomes.

Additionally, coordination of the medical and pharmacy benefit is important for holistic utilization management and care coordination. For example, SMA can be treated with the one-time infused product, Zolgensma, which is most often covered under a medical benefit and/or treated with Evrysdi (Genentech, Inc.), an oral, daily dosed product, most often covered under a pharmacy benefit. Benefit alignment is best accomplished when the medical services and pharmacy benefits plan are all managed under a single entity, such as CVS Caremark® pharmacy benefit management and Aetna benefit plans.

## Manufacturing

The complexity of these products, including the engineering of viruses and synthetic genetic material (for in vivo) and stem cell collection and lab manipulation (for ex vivo), complicate their manufacturing and challenge product scalability to future market sizes. As gene therapies target more common conditions, coordinating manufacturing and distribution will play an increasingly important role in ensuring the availability of high-quality products.

## Scalability

The number of providers who are qualified to administer these innovative products is limited. This is due to complex product handling and administration, as well as the expertise needed to treat rare diseases. Products like CAR-T and other ex vivo therapies require transplant-like procedures in specially equipped facilities and providers with expertise in transplant services. Other products have handling requirements, such as temperature sensitivities, that may limit the number of facilities certified by the manufacturer to administer them. Geographic gaps in available providers may arise. More than other medical services, a national approach to network development with travel and lodging support is needed to ensure quality and equitable access to these products.

## Market timing

Anticipating the timing of FDA approval for pipeline products and planning for their impact is an uncertain process. Some biotech companies have discontinued or delayed development of gene therapy candidates due to regulatory, manufacturing and/or economic factors. On the other hand, the FDA has shown interest in speeding up the approval process for therapies for rare diseases.* We saw this with recent accelerated FDA approval of Elevidys for Duchenne muscular dystrophy.

**Benefit coverage considerations for gene therapies and genetically modified cellular therapies are numerous and multifaceted.**

**Plan sponsors should discuss these considerations with benefit experts, such as those at CVS Health and Aetna.**

## Health equity and stigma

In addition to health care inequities rooted in economics, the historic treatment of underserved populations may impact the uptake of available products. SCD, as one example, disproportionately affects people in under-served communities, impacting health care access, delivery and outcomes.

We must help ensure that all populations can access gene therapies through a robust health equity strategy including:

- Proactive engagement
- Clinical expertise
- Community collaboration

## Medical benefit coverage misconceptions

We are only beginning to see the potential of what gene therapies might offer. As the clinical scope widens, so too does the need to carefully balance coverage and cost. While these products are expensive, a lack of coverage for them under benefit plan designs does not avoid the suffering, disability and cost of the underlying diseases they treat.

For instance, most patients born with SMA Type I become severely disabled and dependent on a ventilator during the first two years of life. Without gene therapy treatment, most die before age three. Others with less severe disease require lifelong, chronic care. In the case of genetically modified cellular therapies, patients with refractory cancer who have failed multiple trials of chemotherapy will continue to require costly and less effective cancer treatment without access to CAR-T therapies.

## Considerations for government payors

Government payors play a vital role in ensuring the availability of gene therapies. These payors account for a sizable percentage of the patients eligible for these therapies and their costs.

Medicaid programs are especially vulnerable, as many of the conditions treated by these therapies occur in childhood. Medicaid and/or the Children's Health Insurance Plan cover nearly half of the children with special health care needs.* The current economic strain will continue as the gene therapy pipeline expands.

For example, Medicaid covers an estimated 50-60 percent of all individuals with SCD who will be eligible for gene therapy products in the pipeline.*

The Centers for Medicare and Medicaid Services (CMS) is attempting payment innovation to support access. CMS's Cell and Gene Therapy (CGT) Access Model proposes multi-state agreements with gene therapy manufacturers to expand risk pools, enhance negotiating power and create a payment model linked to clinical outcomes.* These agreements will initially focus on SCD. CMS will refine the model over the next several years, with an anticipated launch in 2025.

**As the clinical scope of gene therapy widens, offering the promise to potentially cure disease and prevent much suffering, so too does the need to provide plan sponsors with solutions that carefully reduce costs while ensuring coverage.**

# Solutions:
# A multifaceted approach to enabling affordable coverage

There is a critical need for solutions that address the holistic needs of patients and employers to ensure the availability of gene therapies and genetically modified cellular therapies. CVS Health is at the forefront of this effort, collaborating with all stakeholders to enable coverage, ensure evidence-based and coordinated care and support sustainable affordability of these products for plan sponsors.

## 1. Anticipate the pipeline to make informed decisions about benefit management

The pipeline of gene therapies and genetically modified cellular therapies is robust and expected to expand. Plan sponsors can prepare for their impact by learning about the therapeutics in the market, as well as those in the pipeline. For example, these therapies are moving from targeting uncommon disorders to more common conditions like diabetic peripheral neuropathy, retinitis pigmentosa and, much further in the future, familial hypercholesterolemia. Some may reduce the need for other high-cost treatments (such as blood product replacements with SCD), while others may be additions to existing medical care and expenses.

For plan sponsors to make informed benefit decisions, education is critical. CVS Health makes product summaries available to educate plan sponsors about FDA-approved gene therapies and genetically modified cellular therapies and the pipeline of products in development.*

Estimating the precise cost of gene therapies is challenging and requires expertise. CVS Health estimates the financial impact of gene therapies and genetically modified cellular therapies will grow significantly in coming years.

**Overall, CVS Health estimates the five-year projected US gene therapy cost impact through end of 2027 to be about**

**$42 billion***

**The promise of alleviating a significant amount of suffering and replacing a lifetime of expensive maintenance treatments could mean that gene therapies and genetically modified cellular therapies are cost-effective — at the right price point.**

Genetically modified cellular therapies will drive additional cost. Projections are based on a range of inputs including:

- Available public information about therapies in development
- Likelihood of FDA approval
- Estimated prevalence of the targeted conditions in the U.S.
- Estimated price at launch
- Estimated uptake of the products by eligible patient populations

To personalize the potential cost impact to an individual plan sponsor, CVS Health offers a customizable prevalence-based tool. This allows plan sponsors to estimate the potential for incurring gene therapy claims based on the size of the plan membership in any single year.

## 2. Ensure clinically appropriate use through evidence-based guidelines

These therapies are complex and costly, and there is a risk of complications. It is critical to have a comprehensive clinical and utilization framework in place to appropriately manage treatments. Such a framework should include:

- Dedicated clinical teams and tools to help ensure clinically appropriate use with evidence-based standards of care
- Clinical resources and care coordination to support patients and caregivers
- Help for patients navigating benefits and provider networks

The Specialty Guideline Management (SGM) program from CVS Caremark and the Gene-Based, Cellular and Other Innovative Therapy (GCIT®) program from Aetna ensure medically appropriate and cost-effective utilization. SGM has evolved beyond traditional utilization management by using high-touch dedicated medical director review for certain complex conditions and advanced utilization oversight.

The Aetna GCIT program includes a dedicated clinical team with expertise in gene and cellular therapies that supports utilization management, care coordination and management and other services like travel and lodging benefits, when needed. This supports a seamless patient and provider journey.

## 3. Guide patients to high-value sites of care that leverage select provider networks and specialty pharmacy capabilities

The administration of gene therapies and genetically modified cellular therapies can require complex and expensive medical care. Benefit plans designed to encourage the adoption of high-value provider networks are central to driving quality and optimal cost outcomes.

Programs that include high-value networks and specialty pharmacy dispensing capabilities as part of the medical benefit plan support the patient journey and clinical quality, while also helping to control cost of care.

CVS Specialty® capabilities drive value by sourcing gene therapies directly from the manufacturer. Specialty pharmacies with access to these therapies may help reduce the risk of mark-ups through “buy-and-bill.” This is the practice of marking up the cost of a drug above the wholesale price to the payor after buying it from the manufacturer. CVS Specialty access to these therapeutics provides an alternative to

"buy-and-bill" and helps drive more consistent and predictable product costs.

Aetna Institutes® includes a GCIT designated networks program with an aligned plan design that guides members to providers vetted for readiness to administer the products and to cost-optimized sites of care.

The growing GCIT network consists of more than 170 designated providers including hospitals, home and outpatient infusion providers and specialty pharmacy dispensers such as CVS Specialty. These providers have demonstrated expertise in offering these services in line with recommended clinical guidelines. They also have contracts that assure cost protection to control price mark-ups. Aetna offers benefit tiering cost differentials between GCIT providers and non-GCIT providers to encourage use of high value sites of care, with travel and lodging support as needed.

## 4. Smooth actuarial risk with gene therapy stop-loss protection

The ultra-high cost of gene therapies is a concern for all plan sponsors and payors, but especially for self-insured plan sponsors. Stop-loss policies have traditionally helped with large unanticipated medical costs. Plan sponsors looking for ways to manage financial exposure to gene therapies should be aware of the following stop loss considerations to ensure they are protected:

**Coverage for FDA-approved vs. pipeline therapies**
Plan sponsors that select solutions limited to FDA-approved therapies are exposed to the financial risk of new therapies that are approved after the start of the stop-loss plan year. Given the anticipated volume of new FDA approvals expected every year, this risk can be significant.

**Coverage exclusions**
Plan sponsors must carefully review any stop-loss coverage exclusions and eligibility criteria to ensure they minimize their financial risk.

**Other features**
Stop-loss policies can include features that impact the level of protection from large claim risk. One feature called "lasering" applies a higher deductible level to specific individuals (called individual stop-loss) than the rest of the group.

The Aetna traditional stop-loss product is a comprehensive solution that includes both FDA approved and pipeline therapies without lasering for single dose one-time administered gene therapy products. For plan sponsors that choose not to purchase a traditional stop-loss policy, CVS Health offers a flexible insurance product with two options focused on one-time infusion gene therapies.

Customers can choose an option to include only those gene therapies that are FDA approved at the start of the stop-loss policy year or an option to include both currently approved therapies plus pipeline gene therapies. As each new product is approved by the FDA in a stop-loss policy year, it is automatically included in the policy. Neither option has lasering.

**CVS Health offers robust and flexible stop-loss solutions to protect from the financial risk of these expensive therapies.**

**Payors and plan sponsors have different needs and risk tolerances. CVS Health gene therapy stop-loss solutions provide flexibility for each customer's needs.**

**Breakthroughs in gene therapies and genetically modified cellular therapies mean we can now treat and potentially cure genetic disorders that the medical community once considered incurable.**

As the number of these treatments expands, we must collectively find solutions to manage the extraordinary cost of these cutting-edge therapies while ensuring clinically appropriate coverage for those who may benefit from them. CVS Health and Aetna are leading the way with multifaceted solutions. Plan sponsors should consider discussing their options with benefit experts such as those at CVS Health and Aetna.

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# Appendix

## 5-year anticipated gene therapy cost impact: 2023–2027*

| Condition | Launch/ projected launch year | Potential treatment candidates | Estimated market impact (in millions) | |
|---|---|---|---|---|
| | | | Low market impact | High market impact |
| Retinal dystrophy | 2017 | 135 | $34 | $69 |
| Spinal muscular atrophy | 2019 | 2,440 | $1,602 | $3,204 |
| Transfusion-dependent beta-thalassemia | 2022 | 1,735 | $1,457 | $1,943 |
| Cerebral adreno-leukodystrophy | 2022 | 160 | $144 | $192 |
| Hemophilia B | 2022 | 1,549 | $1,626 | $3,253 |
| Dystrophic epidermolysis bullosa | 2023 | 1,023 | $110 | $1,104 |
| Duchenne muscular dystrophy | 2023 | 2,343 | $2,249 | $4,499 |
| Hemophilia A | 2023 | 4,495 | $3,911 | $7,821 |
| Metachromatic leukodystrophy | 2024 | 565 | $307 | $716 |
| Sickle cell disease | 2024 | 20,025 | $10,886 | $25,400 |
| Aromatic L-amino acid decarboxylase deficiency | 2024 | 1,068 | $97 | $339 |
| Fanconi anemia | 2024 | 728 | $66 | $154 |
| Leukocyte adhesion deficiency | 2024 | 20 | $11 | $26 |
| Sanfilippo syndrome type A | 2024 | 21 | $7 | $23 |
| Glycogen storage disease | 2025 | 3,084 | $970 | $3,394 |
| Hunter syndrome | 2025 | 39 | $21 | $73 |
| RPGR-mutated X-linked retinitis pigmentosa | 2025 | 4,732 | $1,488 | $5,207 |
| X-linked myotubular myopathy | 2025 | 93 | $8 | $29 |
| Hepatolenticular degeneration (Wilson's disease) | 2025 | 7,830 | $705 | $2,466 |
| **Gene therapy subtotal** | | | **$25,699** | **$59,912** |

# Appendix

## Genetically modified cellular therapy cost impact: 2023–2027*

| Condition | Launch/ projected launch year | Potential treatment candidates | Estimated market impact (in millions) | |
|---|---|---|---|---|
| | | | Low market impact | High market impact |
| B-cell precursor acute lymphoblastic leukemia (pediatrics) | 2017 | 1,315 | $201 | $267 |
| B-cell precursor acute lymphoblastic leukemia (adults) | 2021 | 5,570 | $709 | $945 |
| Large B-cell lymphoma | 2017 | 14,465 | $1,840 | $2,453 |
| Mantle cell lymphoma | 2020 | 3,165 | $403 | $537 |
| Follicular lymphoma | 2021 | 3,750 | $477 | $636 |
| Multiple myeloma (5th line treatment) | 2021 | 25,850 | $3,253 | $4,338 |
| Multiple myeloma (3rd line treatment) | 2023 | 120,696 | $12,667 | $21,111 |
| Chronic lymphocytic leukemia | 2024 | 206,056 | $3,734 | $6,223 |
| **Genetically modified cellular therapies subtotal** | | | **$23,282** | **$36,510** |
| **Gene therapy and Genetically modified cellular therapy total** | | | **$48,981** | **$96,422** |

*FOR FDA-APPROVED THERAPIES SOURCE: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

*FOR EXPECTED THERAPIES TO DOUBLE SOURCE: https://business.caremark.com/insights/2023/next-in-gene-therapy-w2024-roundup.html.

*FOR ZOLGENSMA COST SOURCE: https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever.

*FOR HEMGENIX COST SOURCE: https://www.managedhealthcareexecutive.com/view/fda-approves-hemgenix-3-5-million-hemophilia-b-gene-therapy.

*FOR GENE THERAPY REGULATIONS SOURCE: U.S. Food and Drug Administration. Cellular and Gene Therapy products. Cellular & Gene Therapy Products | FDA.

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*FOR CRISPR CLINICAL TRIALS SOURCE: Bhokisham N, Laudermilch E, Traeger LL, Bonilla TD, Ruiz-Estevez M, Becker JR. CRISPR-Cas System: The Current and Emerging Translational Landscape. Cells. 2023 Apr 7;12(8):1103. doi: 10.3390/cells12081103. PMID: 37190012; PMCID: PMC10136740 October 12, 2023, 11:31 AM

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*FOR FDA REVISED LABEL SOURCE: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/2024-safety-and-availability-communications.

*FOR MEDICAL AND DISABILITY COSTS SOURCE: http://alliancerm.org/wp-content/uploads/2020/01/ARM-Marwood-White-Paper-FINAL.pdf.

*FOR FDA APPROVAL PROCESS SOURCE: https://www.fdanews.com/articles/212033-cbers-marks-shares-details-on-pilot-for-rare-disease-gene-therapies.

*FOR COVERAGE FOR CHILDREN SOURCE: https://www.kff.org/medicaid/issue-brief/children-with-special-health-care-needs-coverage-affordability-and-hcbs-access.

*FOR MEDICAID COVERAGE FOR SCD SOURCE: https://www.cms.gov/files/document/sickle-cell-disease-action-plan.pdf.

*FOR CELL AND GENE ACCESS MODEL SOURCE: https://www.cms.gov/priorities/innovation/innovation-models/cgt.

*FOR EXPECTED THERAPIES TO DOUBLE SOURCE: https://business.caremark.com/insights/2023/next-in-gene-therapy-2024-roundup.html.

FOR GENE THERAPY REPORTS SOURCE: https://business.caremark.com/insights/2023/q2-2023-gene-therapy-report-promising-new-treatments-horizon.html.

*FOR 5-YEAR GENE THERAPY COST SOURCE: CVS Health, 2023.

*FOR 5-YEAR ANTICIPATED COST IMPACT: Not an all-inclusive list of gene therapies and modified cellular therapies in the pipeline. Estimates cumulative impact for gene therapies and genetically modified cellular therapy products for similar clinical indications.

*FOR GENETICALLY MODIFIED CELLULAR THERAPY COST IMPACT: Not an all-inclusive list of gene therapies and modified cellular therapies in the pipeline. Estimates cumulative impact for gene therapies and genetically modified cellular therapy products for similar clinical indications. Products are listed in order of actual or projected launch date.

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