SPECIAL REPORT

BlueCross BlueShield Association

# One-Time Gene Therapies for Monogenic Disorders

# EXECUTIVE SUMMARY

## BACKGROUND

This Special Report reviews the science and regulatory background for one-time gene therapies for monogenic disorders, which are defects caused by a single gene. It describes issues of importance to payers such as evaluation of clinical evidence, health equity issues and alternative payment models. It also includes recommendations for multiple stakeholders to enhance equitable access to one-time gene therapies.

While individually monogenic disorders are rare, collectively there are nearly 10,000 disorders.[1] As of August 2024, the US Food and Drug Administration (FDA) has approved twelve one-time gene therapies with curative intent. Projected approvals for the next decade will continue to concentrate on rare diseases. By 2032, 85 new gene therapies are expected to receive approval.[2] The treatable patient population is anticipated to exceed 48,000 per year by 2030 and the list price spend in the United States will be in the range of $10 to $15 billion annually through the year 2032.[2]

## EVIDENTIARY EVALUATION

This Report provides readers an overview of the methodology used by the scientific staff at the Blue Cross Blue Shield Association (BCBSA) to make determinations about clinical evidence. BCBSA uses Technology Evaluation Criteria (TEC) to determine whether a technology improves health outcomes such as length of life, quality of life and functional ability. The Report contains multiple examples to describe the difficulties in generating and evaluating evidence to support therapies for these rare, monogenic diseases. Conducting trials for these rare diseases is challenging due to the small number of affected individuals, which limits the population available for clinical trials. Standard outcome measures for common diseases may not effectively capture the unique aspects of rare conditions, making it difficult to select reliable and validated outcome measures. Most evidence for these therapies comes from single-arm trials, which can introduce biases and affect confidence in

estimating benefits and harms. Additionally, the long-term durability and safety of these innovative gene therapies remains uncertain.

## HEALTH EQUITY

The treatment process for gene therapy can take weeks to months and requires a significant time commitment to complete. Patients and caregivers without financial support may face hardships, hindering access to gene therapy. Regional disparities also arise, as these treatments are typically available in advanced healthcare facilities in urban areas, limiting access for those in rural settings who face additional expenses like travel and accommodation. Sickle cell disease disproportionately affects the Black population who has historically received inadequate care due to racial biases in pain management.[3,4] Historical medical racism has led to distrust of the medical establishment and limited participation of minorities in trials.[3,4] Candidates should be informed about the benefits, risks, and burdens of gene therapy, including the administration process, potential infertility, unknown long-term health consequences, and the need for ongoing follow-up assessments and registry participation.

## COST AND PAYMENT MODELS

While gene therapies will hopefully represent an excellent long-term value over an individual's lifetime, the high upfront costs are challenging for payers. Smaller employer funded plans, which have less protection from risk pooling, and plans in regions with higher prevalence of specific diseases targeted by gene therapy, may be more prone to unpredictable risk exposure.

The uncertainty regarding efficacy, safety and long-term durability of gene therapies coupled with the extremely high upfront price create challenges in using conventional reimbursement models.[5] Several innovative payment models are being explored to address these challenges including outcome or value-based models and stop-loss or reinsurance models. Outcomes- or value-based models are contracts that link payment to future clinical outcomes through rebates, warranties or annuities. The potential advantage of these models is that they share financial risk between manufacturers and payers. The challenges in implementation include frequent member turnover and difficulty in data collection for outcomes.[5] Reinsurance and stop-loss insurance offer protection for payers against unexpected catastrophic claims as they transfer the actuarial risk to excess loss insurers.

An example of an innovative reimbursement model is Synergie Medication Collective® LLC. Synergie is a health plan medication supply chain purchasing collective owned by Blue Cross Blue Shield companies and BCBSA launched in January 2023. Synergie has developed an industry-leading integrated solutions portfolio for cell & gene therapies that includes Gene+ Outcomes (outcome-based contracts), Gene+ Risk Protection (stop loss solutions) and Cell & Gene+ Patient Navigation (assists patients in identifying and accessing top-quality treatment centers).

## RECOMMENDATIONS

Gene therapy represents a transformative advancement in healthcare, offering patients access to potentially curative treatments for previously untreatable genetic conditions. All health care stakeholders including payers have a duty to promote access to such treatments when benefits outweigh the risks. We propose several systemwide recommendations to ensure patients can access these therapies while balancing potential risks and benefits:

- **Centralized registry:** The federal government should establish mechanisms for creation of a centralized registry to track health outcomes and adverse effects for all gene therapy recipients in the US irrespective of the type of the payer (Medicare, Medicaid, Commercial).

- **Benefit coverage**: A few employers have opted to exclude coverage for gene therapies due to high costs. Exclusion of gene therapies from coverage benefit presents a moral dilemma, creates health inequity, compliance risks, and public relations challenges. All stakeholders in the health care system must work together to support innovative payment models, and work to educate employers and benefit consultants about the transformative effects of gene therapies, potential for long-term societal impact and future cost savings.

- **Partner with Manufacturers and FDA:** There is a need for early dialog between payers, the FDA and manufacturers. Fostering early dialogue between payers, the FDA, and manufacturers will facilitate generation of public health and payer-relevant evidence and streamline the gap between FDA approval and payer coverage.

# BACKGROUND

The scope of this report is limited to one-time gene therapies that are intended to cure monogenic disorders, which are defects caused by a single gene. Monogenic disorders have been early targets for gene therapy because replacing the one mutated or deleted gene with a normally functioning version of the gene holds curative potential.

## GENE AND CELL THERAPY

Gene therapy involves using genetic material to modify an individual's genome to treat or prevent disease. While related, cell therapy is distinct from gene therapy. Cell therapy entails transplanting cells into the body to prevent or treat disease. The definitions of cell therapy and gene therapy can vary and sometimes overlap.[6-8] For instance, cell therapies can be gene modified. In chimeric antigen receptor-T cell therapy, a gene is inserted into immune cells outside of the body to create proteins that enable the immune cells to target specific cancer cells once re-implanted.[9] This process alters the immune cell's biological properties but does not affect the genome of the host stem cells.[9] This report does not review cell therapies such as chimeric antigen receptor-T therapies and synthetic genetic materials such as antisense oligonucleotides and small interfering RNAs. Gene therapies that require chronic treatment such as Vyjuvek, a herpes-simplex virus type 1 vector-based gene therapy for dystrophic epidermolysis bullosa are also outside the scope of this report.

## DESCRIPTION OF GENE THERAPY APPROACHES

Gene therapy uses genetic material (DNA, RNA) to modify an individual's somatic genome and has the potential for cure with a one-time dose. Gene therapies are defined by the Food and Drug Administration (FDA) as products that "modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use". Approaches to gene therapy include inserting new genes (gene addition) or correcting underlying gene defects (genomic editing).

### WHAT ARE VECTORS?

Gene addition involves adding a working gene to augment the production of a functional protein. A vector, such as an adeno-associated viral (AAV) vector, is often used to deliver the working gene to the cell's nucleus. After delivery, this gene lives in the nucleus which gives a greater chance of creating a permanent change and is only given one time. For example, Zolgensma® is a recombinant AAV9-based gene therapy for Spinal Muscular Atrophy (SMA) that delivers a copy of the gene encoding the human survival motor neuron (SMN) protein.

### WHAT IS CRISPR?

Genomic editing includes use of CRISPR or clustered regularly interspaced short palindromic repeats.[10] CRISPR editing is accomplished using two core components.[10] The first component is a small piece of RNA, called a guide RNA, which finds the sequence of a patient's DNA code that needs to be edited. The second component is a protein, called a Cas enzyme or nuclease, which can cut and make the edit to the patient's DNA at the DNA location defined by the guide RNA. After this process is completed, the cell's natural DNA repair process occurs which makes the desired change permanent. Casgevy®, for the treatment of sickle cell disease and beta-thalassemia, is the first gene therapy to utilize CRISPR technology approved in the United States.

Multiple clinical trials evaluating CRISPR based products are in progress across a wide range of diseases, from blood disorders to cancer. Unlike rare diseases, these are common medical conditions and will mean larger patient populations may qualify for gene therapies in the future.

### IN SITU AND SYSTEMIC GENE THERAPIES

Gene therapy may be given locally (*in situ*) or systemically. For example, Luxturna® provides a functional *RPE65* gene to individuals with Leber congenital amaurosis or retinitis pigmentosa and is directly injected into the retina.[11] All other gene therapies are given as intravenous infusions.

### IN VIVO AND EX VIVO GENE THERAPIES

Gene therapy can be delivered *in vivo* or *ex vivo*. *In vivo* therapy involves injecting vector containing the target gene directly into the body. In *ex vivo* gene therapy, cells are removed from the body, replicated, expanded, and then treated with vectors to add the target gene. The genetically modified cells are then returned to the body. After that, the treated cells begin to divide and generate new cells. Luxturna®, Zolgensma®, Hemgenix®, Elevidys®, Roctavian™, Beqvez™ are all examples of *in vivo* gene therapies while Zynteglo®, Skysona®, Lyfgenia™, Casgevy® and Lenmeldy™ are all examples of *ex vivo* gene therapies.

## TREATMENT PROCESS AND PATIENT BURDEN

Some *in vivo* gene therapies, such as Luxturna®, do not even require an overnight stay at the hospital.[12] In contrast, e*x vivo* gene therapies are complicated and time-intensive. They involve a multi-step process of stem cell collection, bone marrow ablation, and transplantation of the modified stem cells which takes place over multiple hospital visits and can take eight to twelve months from initiation to completion.[13] These factors potentially create a significant physical and psychological burden for the individual undergoing treatment.

## SICKLE CELL DISEASE- A COMPLEX TREATMENT JOURNEY

Treatment of sickle cell disease with gene therapy uses an *ex vivo* complex multi-step process that can take up to a year to complete.[13] Individuals first undergo blood transfusions to reduce sickle cells. This is usually done on an outpatient basis, but it can take multiple transfusions over a period of two months or more. They then spend a week in the hospital to have their stem cells collected. If the first collection is not sufficient, doctors may try once or twice more. After collection, these cells are sent to a lab for modification using CRISPR or a viral vector. It takes a few days to add the new gene to stem cells. Then the product must be tested for purity, potency, and safety which takes several weeks to months to complete.[14] Once the modified cells are ready, the individual is admitted to the hospital to ablate the existing bone marrow with intensive chemotherapy to make way for the new modified stem cells. The individual remains in the hospital until the new cells begin to reproduce, and the immune system starts to show signs that it is rebounding in a robust way. Once the bone marrow is functioning, the individual is discharged but continues additional follow-up visits.[13]

## MANUFACTURING AND TREATMENT SITES ARE RATE LIMITING FACTORS

Operational challenges exist for manufacturers and providers as well. For example, the Bluebird Bio (manufactures Lyfgenia™) single facility is in New Jersey and with existing infrastructure, Bluebird Bio can only treat cells of 85 to 105 individuals annually, including those with sickle cell and beta thalassemia.[14] Vertex (manufactures Casgevy®) operates a single gene editing facility each in the US (Tennessee) and Europe (Scotland).[15]

The intensity of resources required to administer treatment limits the number of individuals that authorized medical centers can handle annually. For example, Children's National in Washington DC, a qualified treatment center to administer Lyfgenia™ and Casgevy®, can only accept about 10 individuals needing gene therapy a year.[14] In addition, a limited number of medical centers are authorized by the manufacturers to provide gene therapies. For example, Vertex has approved 18 centers for Casgevy®, with plans to expand to 50,[16] while Bluebird Bio has 29 centers for Lyfgenia™ and intends to increase this number to 37.[17]

## CURRENT US MARKET

Twelve one-time gene therapies with curative intent have been approved by the FDA. The first approved gene therapy was Luxturna® approved in 2017 for treatment of a form of retinal dystrophy. Therapies have also been approved for SMA, β-thalassemia and sickle cell disease, cerebral adrenoleukodystrophy (CALD), hemophilia A and B, Duchenne muscular dystrophy (DMD) and metachromatic leukodystrophy (MLD). There were three approvals in 2022, four approvals in 2023 and so far, five approvals in 2024. Table 1 lists the FDA-approved gene therapies for monogenic diseases with curative intent.

The FDA-approved gene therapies have primarily been approved through the traditional FDA approval pathway for drugs and biologics. However, three therapies, Skysona®, Kebildi®, and Elevidys® were approved via the accelerated approval pathway

### TABLE 1. List of FDA Approved Gene Therapies Intended as Once in a Lifetime Use Only

| | Gene Therapy Product | Year approved | Manufacturer | Indication | Disease Prevalence in US | Estimated Target Population in US | Approval Pathway |
|---|---|---|---|---|---|---|---|
| 1 | Luxturna® (voretigene neparvovec-rzyl) | Dec 2017 | Spark Therapeutics, Inc. | Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy | 1:330,000 to 130,000[18] | 1000 to 2500 | Traditional |
| 2 | Zolgensma® (onasemnogene abeparvovec-xioi) | May 2019 | Novartis Gene Therapies, Inc. | Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene. | 9.1 and 10 per 100,000[19] | 500 pediatric patients annually | Traditional |
| 3 | Zynteglo® (betibeglogene autotemcel) | Aug 2022 | bluebird bio, Inc. | Treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell transfusions. | Unknown | 1000-1300 pediatric and adult patients | Traditional |
| 4 | Skysona® (elivaldogene autotemcel) | Sep 2022 | bluebird bio, Inc. | To slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy. | 800 males[20,21] | 700 pediatric patients | Accelerated |
| 5 | Hemgenix® (etranacogene dezaparvovec-drlb) | Nov 2022 | CSL Behring LLC | Treatment of adults with Hemophilia B (congenital Factor IX deficiency) who meet one of the following criteria:<br>• Currently use Factor IX prophylaxis therapy.<br>• Have current or historical life-threatening hemorrhage.<br>• Have repeated, serious spontaneous bleeding episodes | 3.7 per 100,000 males[22] | 2600 adult patients | Traditional |
| 6 | Elevidys® (delandistrogene moxeparvovec-rokl) | Jun 2023 | Sarepta Therapeutics, Inc. | Treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy with a confirmed mutation in the DMD gene. | 1 in 3500 live male birth[23] | 1360 boys | Accelerated |

| | Gene Therapy Product | Year approved | Manufacturer | Indication | Disease Prevalence in US | Estimated Target Population in US | Approval Pathway |
|---|---|---|---|---|---|---|---|
| 7 | Roctavian™ (valoctocogene roxaparvovec-Rvox) | Jun 2023 | BioMarin Pharmaceutical Inc | Treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. | 12 per 100,000 males[22] | 8000 adult patients | Traditional |
| 8 | Lyfgenia™ (lovotibeglogene autotemcel) | Dec 2023 | bluebird bio, Inc. | Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. | 100,000[24] | 9000 patients 12 years of age or older | Traditional |
| 9 | Casgevy® (exagamglogene autotemcel) | Dec 2023 | Vertex Pharmaceuticals Inc. | Treatment of sickle cell disease with recurrent vaso-occlusive crises in patients 12 years and older. | 100,000[24] | 9000 patients 12 years of age or older | Traditional |
| | | Jan 2024 | Vertex Pharmaceuticals Inc. | Treatment of transfusion-dependent β-thalassemia in patients 12 years and older. | Unknown | 1300 | Traditional |
| 10 | Lenmeldy™ (atidarsagene autotemcel) | Mar 2024 | Orchard Therapeutics (Europe) Limited | Treatment of children with pre-symptomatic late infantile, pre-symptomatic early juvenile or early symptomatic early juvenile metachromatic leukodystrophy. | 1 in 40,000 to 1 in 100,000[25] | 400–1,700 pediatric patients worldwide | Traditional |
| 11 | Beqvez™ (fidanacogene elaparvovec-dzkt) | Apr 2024 | Pfizer, Inc. | Treatment of adults with moderate to severe hemophilia B who are receiving routine prophylaxis, have a current life-threatening bleed or a history of life-threatening bleeds, or have repeated serious spontaneous bleeds | 3.7 per 100,000 males[22] | 2600 adult patients | Traditional |
| 12 | Kebilidi (eladocagene exuparvovec-tneq) | Nov 2024 | PTC Therapeutics, Inc. | Treatment of adult and pediatric patients with aromatic 13 L-amino acid decarboxylase deficiency. | Unknown | 50 pediatric patients | Accelerated |

## ROBUST PIPELINE

The cell and gene therapy sector will continue to grow, with a promising pipeline and an increasing number of approvals expected in the near future. A strong commitment to cell and gene therapy development by the FDA will continue to enhance the potential for gene therapies approvals. The FDA has released multiple guidance documents to support clinical development for cell and gene therapy, including use of the accelerated approval pathway. Advancements with groundbreaking approvals such as the first CRISPR-based therapeutic approval in December 2023, also serves to further use of this innovative technology. In a global survey of over 1430 researchers of rare genetic diseases conducted in 2021, the majority (>50%) anticipate gene therapies becoming the standard of care for rare genetic diseases by 2036. CRISPR-Cas9 was considered the most likely approach to fixing or replacing defective genes in the next 15 years.[26]

The role of the FDA's Orphan Drug designation has become crucial as well as strategic in the setting of gene therapies. The Orphan Drug designation is granted to drugs and biologics that treat, diagnose, or prevent rare diseases affecting fewer than 200,000 people in the US.[27] This designation is aimed to act as a catalyst for innovation and targeted patient care by offering tax credits for clinical trial costs, exemption from FDA application fees, and seven years of market exclusivity upon approval. Orphan gene therapies are 2 to 3.5 times as likely to be approved when entering Phase 1 as the average drug in clinical trials, outperforming in every clinical development phase. The likelihood of approval was 28% for orphan gene therapies versus 8 to 13% for average drugs in clinical trials, respectively.[28] It is expected that projected approvals in the next decade will concentrate on rare diseases in a few therapeutic areas such as hematology, metabolic, neurology, and ophthalmology. Rare diseases are estimated to affect 3.5 to 5.9% of the world's population.[29] Currently, six to seven thousand rare diseases are reported in the medical literature, many with unknown causes. While some of these diseases are infections, cancers, and autoimmune, the majority are genetic in origin. Presently, the therapeutic options for these diseases are limited, with approved treatments available for only about 5% of them.[30]

NEWDIGS-FoCUS, an MIT led project that aims to collaboratively address the need for new, innovative financing and reimbursement models for durable therapies in the US, projects that by the year 2032, 85 new gene therapies across more than 12 therapeutic areas are expected to receive regulatory approval.[2]

The treatable patient population is anticipated to exceed 48,000 per year by 2030 and the list price spend in the United States will be in the range of $10 to $15 billion annually through the year 2032.[2] Therefore, the healthcare ecosystem should focus on creating innovative options for financing these life-saving therapeutic treatments.

Table 2 summarizes one-time gene therapies that are expected to be approved by 2026. These therapies are currently in phases 1 to 3 of development. Additional gene therapies for hemophilia A are expected to be reviewed by the FDA as early as 2025. The first available therapies are in the pipeline for conditions such as leukocyte adhesion deficiency, aromatic L-amino acid decarboxylase deficiency, Fanconi anemia, Sanfilippo Syndrome or mucopolysaccharidosis type III, Von Gierke or glycogen storage disease Type I, ornithine transcarbamylase deficiency, Leber hereditary optic neuropathy, Fabry disease, and Gaucher disease.

## TABLE 2. Pipeline for Upcoming Gene Therapies

| Expected Approval Year | Gene Therapy | Target Indication | Developer | Phase of Development | Delivery Mechanism | Estimated Potential US Candidates[a] | Market Entry Position |
|---|---|---|---|---|---|---|---|
| 2025 | Giroctocogene fitelparvovec (SB-525) | Hemophilia A | Pfizer / Sangamo | Phase 3 | In vivo (AAV6) | 3,000 (adults) | 3rd entrant |
| | Marnetegragene autotemcel (Kresladi) | Leukocyte Adhesion Deficiency | Rocket | Phase 3 (delayed due to CRL) | Ex vivo (LVV) | 150 (pediatrics | 1st entrant |
| | Mozafancogene autotemcel (RP-L102) | Fanconi Anemia | Rocket | Phase 2, EMA accepted MAA on April 30, 2024 | Ex vivo (LVV) | 1,000 (pediatric) | 1st entrant |
| | UX111 | Sanfilippo Syndrome or Mucopolysaccharidosis type III | Abeona / Ultragenyx | Phase 3 | In vivo (AAV9) | 1,500-4,000 (pediatric) | 1st entrant |
| | RGX121 | Hunter Syndrome or Mucopolysaccharidosis type II | Regenxbio | Phase 3 | In vivo (AAV9) | 25 (pediatric) | 1st entrant |
| | Pariglasgene brecaparvovec (DTX401) | Von Gierke or Glycogen Storage Disease Type I | Ultragenyx | Phase 3 | In vivo (AAV-8) | 3,000 | 1st entrant |
| | Sonpiretigene isteparvocec (MCO-010) | Retinitis Pigmentosa | Nanoscope | Phase 2 | In vivo (AAV-2) | 2,800-6,400 | NA |
| | Laruparetigene zosaparvovec (AGTC-501) | X-Linked Retinitis Pigmentosa | Beacon/AGT | Phase 2 | In vivo (AAV-2) | 2,800-6,400 | NA |
| | Botaretigene sparoparvovec (AAV-RPGR) | X-Linked Retinitis Pigmentosa | Janssen / MeiraGTX | Phase 3 | In vivo (AAV-5) | 2,800-6,400 | NA |
| | Avalotcagene ontaparvovec | Ornithine Transcarbamylase Deficiency | Ultragenyx | Phase 3 | In vivo (AAV-8) | 3,600-5,700 | 1st entrant |
| 2026 | Lenadogene nolparvovec | Leber Hereditary Optic Neuropathy | GenSight | Phase 3 | In vivo (AAV-2) | NA | 1st entrant |
| | Avalotcagene ontaparvovec | Ornithine Transcarbamylase Deficiency | Ultragenyx | Phase 3 | In vivo (AAV-8) | 3,600-5,700 | 1st entrant |
| | Dirloctogene samoparvovec (SPK-8011; RG6357) | Hemophilia A | Roche / Spark | Phase 3 | In vivo (AAV3) | 3,000 (adults) | 3rd entrant |
| | Laruparetigene zosaparvovec (AGTC-501) | X-Linked Retinitis Pigmentosa | Beacon/AGT | Phase 2 | In vivo (AAV-2) | 2,800-6,400 | NA |
| | Isaralgagene civaparvovec | Fabry Disease | Sangamo | Phase 1/2 | In vivo (AAV-2/6) | NA | 1st entrant |
| | AVR-RD-02 | Gaucher Disease | Avro Bio | Phase 1/2 | Ex vivo (LVV) | NA | 1st entrant |

AAV: adeno-associated viral vector; CRL: complete response letter; EMA: European Medicines Agency; LVV: Lentiviral Vector; NA: not available
[a] Estimated potential US candidates defined as individuals who may qualify for product. Actual uptake is expected to be less than this number.
Source: CVS Health Gene Therapy Report[31]

# EVIDENTIARY ASSESSMENT

All 12 FDA approved one-time gene therapies are intended for treatment of rare diseases. Designing trials for rare diseases presents a distinct set of challenges. Rare diseases affect a limited number of individuals, resulting in small populations available for clinical trials. Ethical and practical limitations, especially in pediatric populations, further restrict trial sizes. As a result, trial recruitment is difficult. There is often a lack of comprehensive knowledge about the natural progression of rare diseases. Without a clear understanding of how the disease evolves over time, designing clinical trials becomes complex. Generic outcome measures used for common diseases may not adequately capture the unique aspects of rare conditions. As a result, developing reliable and validated outcome measures specific to rare diseases can also be demanding. While having multiple, blinded randomized controlled trials (RCTs) might be the ideal for traditional therapeutics, in practice, it may not be reasonable or even possible to conduct blinded RCTs for rare diseases. Therefore, balancing rigorous evidence requirements with the practical realities of rare disease trials is essential.

## BCBSA PROCESS FOR EVIDENTIARY EVALUATION

The Blue Cross Blue Shield Association (BCBSA) is a national federation of independent, community-based and locally operated Blue Cross and Blue Shield (BCBS) Plans that collectively provide health care coverage for nearly 118 million people or 1 in 3 Americans. BCBS Plans are in nearly every zip code in the U.S., the District of Columbia and Puerto Rico.

BCBSA provides an evidence assessment of medical technologies to member BCBS Plans to assist their independent determination of the eligibility for coverage of new and emerging technologies. The

BCBSA scientific staff use an evidence-based assessment process to address critical questions about the efficacy, safety, and appropriate use of medical technologies.

BCBSA uses Technology Evaluation Criteria (TEC) to determine whether a technology improves health outcomes such as length of life, quality of life and functional ability. These are summarized in Table 3. Briefly, the available evidence must be sufficient to permit conclusions concerning the effect of the technology on health outcomes and the technology must improve the net health outcome compared to established alternatives. To evaluate TEC criteria #2, BCBSA staff apply a set of rubrics to best available evidence and extract information on the relevance, quality, risk of bias and consistency in studies of diagnostics, devices, and therapeutics. To reach conclusions that evidence is sufficient to determine that the technology results in an improvement in the net health outcome, benefit must outweigh harms.

The TEC criteria have been applied across multiple technologies such as devices, diagnostics and therapeutics for over 2 decades and more recently have been used to evaluate FDA approved gene therapies as well. While the BCBSA TEC criteria do not promote specific study designs, the ideal clinical study design for testing new medical technologies is the randomized, controlled trial (RCT) with blinding of study treatment groups. Random allocation minimizes potential confounding variables that could impact outcomes while blinding helps reduce biases related to how participants are managed during the study and how outcomes are assessed. To address consistency, multiple and independent clinical studies are ideal. Given that the BCBSA TEC criteria do not require specific study designs, flexibility can be applied in evaluation of studies for rare diseases.

## TABLE 3. The BCBSA Technology Evaluation Criteria

| Five criteria are used to assess whether a technology improves health outcomes such as length of life, quality of life and functional ability: | |
|---|---|
| 1 | The technology must have final approval from the appropriate governmental regulatory bodies.<br>a. This criterion applies to drugs, biological products, devices, and any other product or procedure that must have final approval to market from the Food and Drug Administration or any other federal governmental body with authority to regulate the technology.<br>b. Any approval that is granted as an interim step in the U.S. Food and Drug Administration's or any other federal governmental body's regulatory process is not sufficient.<br>c. The indications for which the technology is approved need not be the same as those which Blue Cross and Blue Shield's Association is evaluating. |
| 2 | The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.<br>a. The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.<br>b. The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects the health outcomes.<br>c. Opinions and evaluations by national medical associations, consensus panels, or other technology evaluation bodies are evaluated according to the scientific quality of the supporting evidence and rationale. |
| 3 | The technology must improve the net health outcome.<br>a. The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes. |
| 4 | The technology must be as beneficial as any established alternatives.<br>a. The technology should improve the net health outcome as much as, or more than, established alternatives. |
| 5 | The improvement must be attainable outside the investigational settings.<br>a. When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy criteria #3 and #4. |

## FDA APPROVAL PROCESS

The FDA has its own review process for marketing approval and authorization for drugs and devices including gene therapies that is distinct from the review for coverage decisions by the insurance industry. The FDA assesses gene therapies as "biological products." According to the Federal Food, Drug, and Cosmetic Act, manufacturers of drugs or biological products must demonstrate effectiveness based on the "substantial evidence" standard. [32,33] This typically is interpreted as requiring at least two well-controlled clinical investigations. The FDA has several guidance documents which are relevant to FDA review of evidence for gene therapy. These are summarized in Table 4.

### TABLE 4. Summary of FDA Guidance Relevant to Gene Therapy Evidentiary Evaluation

| Topic | Brief Summary of Relevant Points |
|---|---|
| *General Guidance* | |
| **Accelerated Approval**[34] | • Serious conditions<br>• Unmet medical need<br>• Allows demonstration of effect on surrogate or intermediate endpoint, defined by FDA as:<br>  ○ Surrogate: marker thought to predict clinical benefit, not itself a measure of clinical benefit<br>  ○ Intermediate: measure considered *reasonably likely* to predict clinical benefit |
| **Approval based on one study**[35] | • One adequate, well controlled clinical investigation and confirmatory evidence can be sufficient.<br>• Confirmatory evidence:<br>  ○ Related indication<br>  ○ Mechanistic or pharmacodynamic<br>  ○ Animal model<br>  ○ Members of same pharmacological class<br>  ○ Natural history<br>  ○ Real-world data/evidence<br>  ○ Expanded Access Use |
| **External controls**[36,37] | • Case-by-case assessment of appropriateness<br>• Informed by heterogeneity of disease, preliminary evidence regarding product, approach to outcome ascertainment, superiority vs non-inferiority.<br>  ○ Distinguish treatment effect from natural history, prognostic differences, lack of blinding.<br>• Historical information may potentially serve as a control:<br>  ○ Natural history is well-defined, highly predictable.<br>  ○ Disease does not improve in absence of intervention or with available therapies.<br>  ○ Effect of treatment is dramatic.<br>  ○ Endpoints are objective.<br>  ○ Impact of baseline and treatment variables on endpoints is well characterized |
| **Rare disease: natural history studies**[38] | • Information about subtype (e.g., phenotypic, genotypic) signs, symptoms, rates, and patterns of progression are useful for developing inclusion criteria, duration of a trial, frequency of data collection, specific outcome measures.<br>• External controls may be acceptable in certain situations: disease course is predictable; treatment effect is dramatic.<br>• External control is most interpretable when treatment effect-<br>  ○ is large in comparison to potential biases and variability.<br>  ○ is not affected by patient or investigator motivation or choice of individuals for treatment.<br>  ○ is objectively measured.<br>  ○ is measured in a way that manages and minimizes bias.<br>  ○ has a strong temporal association with treatment administration.<br>  ○ is consistent with expected pharmacological activity and animal models.<br>• Retrospective natural history studies are limited by several factors that affect their utility.<br>• Prospective studies can address limitations of retrospective studies but generally require more time.<br>• Natural history studies should have an a priori, well-defined, carefully documented protocol and statistical analysis plan.<br>• Patient advocacy or support groups are important partners for keeping the patient community engaged, providing perspectives on minimizing burdens and on the acceptability of proposed studies.<br>• FDA will likely need patient-level data from natural history studies. |

| *Gene Therapy Specific Guidance* | |
|---|---|
| **Rare disease**[39] | • If genetic disease, perform genetic testing.<br>• Exclude participants with pre-existing antibodies to the gene therapy product.<br>  ○ Companion diagnostic(s) may be needed for genetic testing and/or antibody testing.<br>• Randomized, concurrent, placebo-controlled, blinded trials are ideal.<br>• Single-arm studies with historical controls may be considered.<br>  ○ Natural history data may be a historical control if the control and treatment populations are adequately matched in terms of demographics, concurrent treatment, disease state, etc<br>• Identify relevant biomarkers.<br>• Include assays to measure product-directed immune responses |
| **Genome Editing**[40] | • First-in-human trials:<br>  ○ Generally, should enroll those for whom no other treatment options are available or justified.<br>  ○ Should use staggering interval enrollment with interval of sufficient duration to detect acute and subacute adverse events.<br>• Monitor for off-target editing and unintended consequences of on-target editing.<br>• Monitor for adverse events related to aberrant cellular and chromosomal changes, immunogenicity, and tumorigenicity.<br>• Monitor for long term effects for up to 15 years after product administration |
| **Long Term Follow-Up**[41] | • Capture delayed adverse events and persistence of gene therapy product.<br>• Duration of LTFU considerations:<br>  ○ Observed duration of in vivo product persistence<br>  ○ Observed duration of transgene expression<br>  ○ Product characteristics in vivo<br>  ○ Route of administration<br>  ○ Expected survival rates, known background rates of events of interest.<br>  ○ Durability of the clinical effect<br>• Current recommendations for duration of follow-up based on product type:<br>  ○ 15 years for integrating vectors (e.g., gammaretroviral, lentiviral, transposon elements).<br>  ○ Up to 15 years for herpes virus vectors (or oncolytics) capable of establishing latency.<br>  ○ Up to 15 years for microbial vectors known to establish persistent infection.<br>  ○ Up to 15 years for genome editing products.<br>  ○ Up to 5 years for adeno-associated virus vectors.<br>• Follow-up protocol should detail visit schedules, sampling plan, methods of monitoring. |
| **Hemophilia**[42] | • Efficacy endpoint for accelerated approval could be factor activity levels.<br>  ○ Provide evidence, specific to gene therapy product, that correlates factor levels with clinical outcomes<br>• Recommend annualized bleeding rate as primary endpoint for traditional approval.<br>• Observe participants for a lead-in period to collect annualized bleeding rate data.<br>• Recommend within-subject, non-inferiority design compared to current prophylaxis therapies |
| **Retinal Disorders**[43] | • Recommend a careful natural history study.<br>• Randomized, concurrently controlled, masked study is recommended, when possible.<br>• Use of contralateral eye as control is possible but generally not recommended:<br>  ○ Eyes may be at different stages of disease.<br>  ○ May lead to unmasking.<br>• Late-phase studies should include primary endpoints measuring function or symptoms such as visual acuity or photoreceptor loss. |

FDA: Food and Drug Administration; LTFU: lost to follow-up

Table 5 provides a summary of the pivotal clinical evidence that supported the FDA approval of available gene therapies. The subsequent sections will use this evidence to illustrate the challenges in generating and evaluating data to support therapies for rare, monogenic diseases. These sections will highlight key considerations in assessing evidence related to gene therapy. Each section will offer guiding questions for evaluation and examples from existing gene therapy studies, as previously summarized in Table 5. The sections are organized according to the PICO (Populations, Interventions, Comparator, Outcomes) framework.

## POPULATIONS

Table 1 provides an overview of disease prevalence in the United States for FDA-approved gene therapies. Disease prevalence for approved gene therapies ranges from one per million for leukocyte adhesion deficiency to one per 5000 males for DMD (Table 1). The recent approval of two gene therapies for sickle cell disease has expanded the population eligible for treatment with gene therapy as approximately 100,000 Americans live with sickle cell disease (Table 1).

Given the rarity of these conditions, it is crucial to meticulously identify and select the appropriate population for inclusion in the pivotal studies. This approach enhances the likelihood of demonstrating therapeutic benefits while minimizing potential risks. Table 6 outlines important questions to consider regarding relevant populations when evaluating evidence for a gene therapy.

### TABLE 5. Summary of Evidence for FDA Approved Gene Therapies Intended as Once in a Lifetime Use Only

| | Gene Therapy Product | Indication | Pivotal Studies | Primary Outcome(s) | Summary of Efficacy | Summary of Harms | Citation(s) |
|---|---|---|---|---|---|---|---|
| 1 | Luxturna® (voretigene neparvovec-rzyl) | Retinal dystrophy | 1 open-label, RCT (NCT00999609) | • 1-year change in functional vision at specified light levels measured by multi-luminance mobility testing score | • At 1-year, median bilateral change in score was 2 in intervention group (n=21) versus 0 (n=10) in the control group (difference of 2, p=0.001).<br>• 65% (13 out of 29) of all participants had a score change of ≥2 at 1 year | • Serious adverse reactions were not observed in the trials.<br>• Warnings and precautions include risk of endophthalmitis, permanent decline in visual acuity, retinal abnormalities, increased intraocular pressure and cataract. | 44 |
| 2 | Zolgensma® (onasemnogene abeparvovec-xioi) | Spinal muscular atrophy | 2 open-label single-arm trials for symptomatic SMA (NCT02122952 & NCT03306277) | • Event-free survival[a] at 14-months<br>• Functional, independent sitting for ≥30 seconds | • 91% (20/22) were alive and free of permanent ventilation at 14-months.<br>• 59% (13/22) achieved sitting without support for ≥30 seconds.<br>• In natural history, untreated patients do not survive or achieve such motor milestones. | • Black box warning for serious liver injury and acute liver failure<br>• In the trials, 27% (12/44) reported elevated aminotransferases >ULN and 7% (3/44) reported vomiting.<br>• Warnings and precautions include systemic immune response, thrombocytopenia, thrombotic microangiopathy, elevated troponin I, AAV vector integration and risk of tumorigenicity. | 45-47 |
| | | | 1 open-label single-arm trial for presymptomatic SMA (NCT03505099) | • Functional, independent sitting for ≥30 seconds up to 18 months of age (2 copies of SMN2)<br>• Ability to stand without support for ≥3 seconds up to 24 months of age (3 copies of SMN2) | • 100% (14/14) of those with 2 copies of SMN2 and 100% (15/15) achieved the primary endpoint. | | 48 |

| | Gene Therapy Product | Indication | Pivotal Studies | Primary Outcome(s) | Summary of Efficacy | Summary of Harms | Citation(s) |
|---|---|---|---|---|---|---|---|
| 3 | Zynteglo® (betibeglogene autotemcel) | β-thalassemia | 2 open-label single-arm trials (NCT02906202 & NCT03207009) | • Transfusion independence[b] lasting 12 months or greater | • 91% (20/22) and 86% (12/14) achieved the primary endpoint in the two studies respectively. | • Adverse events profile consistent with myeloablative conditioning.<br>• Warnings and precautions include delayed platelet engraftment, risk of neutrophil engraftment, risk of insertional oncogenesis and hypersensitivity reactions | 49 |
| 4 | Skysona® (elivaldogene autotemcel) | Cerebral adreno leukodystrophy | Post-hoc analysis from 2 open-label single-arm trials (NCT02204904 & NCT01896102) and 2 non-concurrent historical control studies | • Post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms to first MFD[c] or death to historical control | • Estimated MFD-free survival at month 24 from time of symptom onset was 72% (95% CI: 35%, 90%) for the intervention group (n=11) and 43% (95% CI: 10%, 73%) for the natural history cohort untreated patients (n=7) | • Black box warning for hematologic malignancy<br>• Adverse events profile consistent with myeloablative conditioning.<br>• Warnings and precautions include serious infections, prolonged cytopenia's, delayed platelet engraftment and risk of neutrophil engraftment failure. | 50,51 |
| 5 | Hemgenix® (etranacogene dezaparvovec-drlb) | Hemophilia B | 1 open-label single-arm trial (NCT03569891) | • ABR during months 7-18 after treatment compared with 6-month lead-in period | • Estimated mean ABR was 1.9 bleeds/year (95% CI 1.0, 3.4) in the intervention arm versus 4.1 (95% CI: 3.2, 5.4) during the lead-in period (n=54).<br>• The ABR ratio was 0.46 (95% CI: 0.26, 0.81] demonstrating NI of ABR during months 7 to 18 compared to the lead-in period. | • No serious adverse reactions were reported.<br>• Warnings and precautions include infusion reactions, hepatotoxicity, hepatocellular carcinogenicity, and monitoring laboratory tests. | 52,53 |
| 6 | Elevidys® (delandistrogene moxeparvovec-rokl) | Duchenne muscular dystrophy | 1 double-blind RCT (NCT03769116) and external prospective cohort (NCT04626674) | • Change in expression of micro-dystrophin protein from baseline to week 12.<br>• Change in NSAA total score from baseline to week 48. | • Mean change in NSAA total score was 1.7 (±0.6) in the intervention arm versus 0.9 (±0.6) in the placebo arm (p=0.37). | • Common adverse reactions (incidence ≥5%) were vomiting and nausea, liver function test increased, pyrexia, and thrombocytopenia.<br>• Warnings and precautions include acute serious liver injury, immune-mediated myositis, myocarditis, and pre-existing immunity against AAVrh74. | 54,55 |

| | Gene Therapy Product | Indication | Pivotal Studies | Primary Outcome(s) | Summary of Efficacy | Summary of Harms | Citation(s) |
|---|---|---|---|---|---|---|---|
| 7 | Roctavian™ (valoctocogene roxaparvovec-Rvox) | Hemophilia A | 1 open-label single-arm trial (NCT03370913) | • ABR during 3 years after treatment compared with 6-month lead-in period | • Estimated mean ABR was 2.6 bleeds/year in the intervention arm versus 5.4 during the lead-in period (n=112).<br>• The difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. The NI analysis met the pre-specified NI margin of 3.5 bleed per year. | • 6 serious adverse reactions including ALT elevation, presyncope, maculopapular rash, anaphylaxis, and hypersensitivity reaction.<br>• Warnings and precautions include infusion-related reactions, hepatotoxicity, thromboembolic events, monitoring laboratory tests and malignancy. | 56,57 |
| 8 | Lyfgenia™ (lovotibeglogene autotemcel) | Sickle cell disease | 1 open-label single-arm trial (NCT02140554) | • Complete resolution of VOE[d] and sVOE[e] | • sVOEs eliminated for 94% (30/32) and all VOEs eliminated for 88% (28/32) participants between 6- and 18-months post-infusion | • Black box warning for hematologic malignancy | 58,59 |
| 9 | Casgevy® (exagamglogene autotemcel]) | Sickle cell disease | 1 open-label single-arm trial (NCT03745287) | • Complete resolution of sVOC[f] | • sVOC eliminated for 93.5% (29/31) participants within 24 months of infusion | • Adverse events associated with busulfan myeloablative conditioning.<br>• Warnings and precautions include neutrophil engraftment failure, delayed platelet engraftment, hypersensitivity reactions and off-target genome editing risk | 60 |
| | | β-thalassemia | 1 open-label single-arm trial (NCT03655678) | • Transfusion independence[g] lasting 12 months or greater | • 91% (32/35) achieved the primary endpoint. | | |
| 10 | Lenmeldy™ (atidarsagene autotemcel) | Metachromatic leukodystrophy | 2 open-label single-arm trials (NCT01560182 & NCT03392987) and 1 expanded access program | • Severe motor impairment-free survival[h] | • At the age of 5 years, 100% of pre-symptomatic late infantile children remained event-free in the intervention arm compared with 0% in untreated children in historical control. | • Adverse events associated with busulfan myeloablative conditioning.<br>• Warnings and precautions include thrombosis and thromboembolic events, encephalitis, serious infection, veno-occlusive disease, delayed platelet engraftment, risk of neutrophil engraftment failure, risk of insertional oncogenesis and risk of hypersensitivity reactions | 61,62 |
| 11 | Beqvez™ (fidanacogene elaparvovec-dzkt) | Hemophilia B | 1 open-label single-arm trial NCT03861273 | • ABR during week 12 after treatment to | • Estimated mean ABR was 2.5 bleeds/year (95% | • No serious adverse reactions were reported. | None |

| | Gene Therapy Product | Indication | Pivotal Studies | Primary Outcome(s) | Summary of Efficacy | Summary of Harms | Citation(s) |
|---|---|---|---|---|---|---|---|
| | | | | month 15 compared with 6-month lead-in period | CI 1.0, 3.9) in the intervention arm versus 4.5 (95% CI: 1.9, 7.2) during the lead-in period (n=45).<br>• The difference was -2.1 bleeds/year (95% CI: -4.8, 0.7]. The upper bound of the 95% CI was less than 3.0 meeting the NI success criterion. | • Warnings and precautions include infusion reactions, hepatotoxicity, hepatocellular carcinogenicity, and monitoring laboratory tests. | |

AAV: adeno-associated vector; ABR: annualized bleeding rate; ALT: alanine transaminase; CI: confidence interval; MFD: major functional disabilities; NSAA: North Star Ambulatory Assessment; NI: non-inferiority; SMA: spinal muscular atrophy; SMN2: survival motor neuron; sVOC: severe vaso-occlusive crises; sVOE: severe vaso-occlusive events; RCT: randomized controlled trial; ULN: upper limit of normal

[a] Survival was defined as time from birth to either death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation.

[b] Transfusion independence defined as a weighted average Hb ≥ 9 g/dL without any packed red blood cells transfusions for a continuous period of ≥ 12 months at any time during the study, after infusion of gene therapy.

[c] Major functional disabilities are defined as loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.

[d] VOEs were defined as any of the following events requiring evaluation at a medical facility: 1) an episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more
than 2 hours 2) acute chest syndrome 3) acute hepatic sequestration 4) acute splenic sequestration.

[e] Severe VOE were defined as either of the following events: 1) VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit 2) priapism requiring any level of medical attention.

[f] Severe VOC is defined as an occurrence of at least one of the following events: 1) Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or RBC transfusions 2) Acute chest syndrome 3) Priapism lasting > 2 hours and requiring a visit to a medical facility 4) Splenic sequestration.

[g] Transfusion independence defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time within the first 24 months after gene therapy infusion, evaluated starting 60 days after the last RBC transfusion for post-transplant support or transfusion disease management.

[h] Severe motor impairment-free survival, defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support

## TABLE 6. Evidence Assessment Questions Related to Populations

| | |
|---|---|
| **PREVALENCE** | |
| **1** | What is the prevalence of the disease in the United States? |
| **2** | How does prevalence vary by demographic characteristics and geography? |
| **DIAGNOSIS** | |
| **3** | How is the confirmatory diagnosis made in practice? |
| **4** | How was the confirmatory diagnosis made for enrollees in clinical studies? |
| **5** | Is there an existing molecular test for diagnosis? |
| **6** | Has there been an evolution in the way the disease is diagnosed? |
| **7** | If a new molecular test for diagnosis was developed, what is the validity of the test? |
| **8** | What is the average length of time from clinical suspicion to a confirmed diagnosis? What factors may delay and/or prevent a confirmed diagnosis? |
| **9** | What difficulties are typically encountered in diagnosis from a patient, provider, and health system perspective? |
| **SUBTYPES** | |
| **10** | Are there different genotypic subtypes that may affect prognosis or efficacy / safety of therapy? |
| **11** | Are there different phenotypic subtypes that may affect prognosis or efficacy / safety of therapy? |
| **12** | Are there different stages of disease that may affect efficacy or safety? |

## DIAGNOSIS

For gene therapy to be effective, the causal gene must be identified, and diagnosis should be standardized and reliable. When molecular testing is needed to confirm the diagnosis, legacy assays may be adequate, or more sensitive assays may be needed.

Testing for monogenic disorders involves sequencing the gene and/or non-sequencing based tests such as deletion/duplication studies. Sequencing identifies gene mutations such as substitutions. For example, a single nucleotide substitution can lead to the most common form of sickle cell disease. The normal GAG sequence is changed to GTG, and this results in the amino acid glutamic acid being changed to valine in the beta chain of hemoglobin.[63]

Sequencing can be performed on a single gene using Sanger sequencing, or more commonly, as part of a multigene panel using next generation sequencing, whole exome sequencing, or whole genome sequencing. In addition to sequencing, deletion/duplication or other non-sequencing studies may be necessary. Depending on the laboratory and the specific disorder, these studies may be conducted simultaneously with sequencing, after sequencing if no abnormalities are found, or as the initial diagnostic test before sequencing. Not all laboratories that offer gene sequencing also perform or other non-sequencing studies. It is therefore important to know which tests were completed, particularly for a negative “gene test”.

## PHENOTYPIC HETEROGENEITY COMPLICATES BENEFIT-RISK ASSESSMENT

SMA is primarily caused by mutations in the *SMN1* gene, which encodes the SMN protein. However, there is wide phenotypic heterogeneity in SMA due to the presence of a second gene called *SMN2, which is* nearly identical to *SMN1*. Despite its similarity, *SMN2* produces much less functional SMN protein due to a single nucleotide difference in exon 7.[64] The number of copies of the *SMN2* gene varies widely across individuals (range, 0-6), resulting in a less severe form of SMA among those with more copies of the *SMN2* gene and vice-versa.[65] Individuals with 1 or 2 *SMN2* copy numbers have the highest likelihood of developing the most severe phenotype of SMA (type 1 SMA) while those with 3 copies of *SMN2* have the highest likelihood of developing a less severe phenotype (type 2 SMA). Individuals with type 1 SMA have symptom onset between 0 to 6 months of age and are not expected to survive beyond 2 years without respiratory support. Those with type 2 SMA generally have symptom onset between 6 to 18 months of age and are not expected to stand or walk independently in their lifetime. Conversely, individuals with more than 3 copies of *SMN2* are more likely to develop type 4 adult-onset SMA, which does not impact life expectancy but presents with a varying degree of muscle weakness.[66] Zolgensma® was approved by the FDA in 2019 with a black box warning due to the risk of serious liver injury and acute liver failure. The risk of thrombotic microangiopathy was identified as a safety signal based on post-marketing safety surveillance and subsequently added later to the black box warning.[67] While the potential benefit of Zolgensma® may be smaller for individuals who are unlikely to develop the most severe phenotype, the risks associated with therapy remain unchanged. Despite this difference in benefits versus risks across phenotypes, the FDA-approved indication is agnostic of *SMN2* gene copy number and is approved for all individuals with SMA less than 2 years of age.[67]

Another example is the recently approved Lenmeldy™ for treatment of MLD. It is a rare genetic lysosomal storage disorder that arises due to mutation in the *ARSA* gene that encodes for the enzyme **arylsulfatase A.** This enzyme plays a crucial role in metabolizing sulfatides, a major component of myelin membranes in the nervous system. When this enzyme is deficient, sulfatides accumulate within the nervous system causing progressive demyelination, neurodegeneration, and ultimately resulting in the loss of motor and cognitive functions.[68] Over 100 mutations have been identified as causes of MLD. In more than 50% of cases, "**A"** and "**I" alleles are identified as** pathogenic variants. "I" alleles are associated with completely abolished enzyme activity while "A" alleles are associated with reduced but not absent enzyme activity. Individuals who inherit two copies of the "I" allele generally develop the severest phenotype of late infantile onset MLD. In this phenotype, symptom onset typically occurs before the age of two and results in rapid loss of motor function with cognitive decline, and survival beyond childhood is unlikely. Individuals who inherit two copies of the "A" allele or inherit an "I" allele from one parent and an "A" allele from the other parent generally develop a milder form of the disease such as juvenile or adult-onset MLD. In these phenotypes, symptom onset typically occurs between 3 and 16 years for juvenile MLD and after age 16 for adult-onset MLD. In juvenile MLD, survival is generally less than 20 years after symptoms begin while in adult onset MLD, individuals may survive for 20 to 30 years after onset. The current FDA approval of Lenmeldy™ is limited to infantile and early juvenile onset MLD because Lenmeldy™ has not been evaluated in adult-onset patients and treatment benefits might not outweigh the risk.

## VECTOR IMMUNOGENICITY

Vectors are typically derived from viruses given their innate ability to infiltrate cells effectively. To ensure viral vectors are safe for use, the majority of viral genes are removed (except non-coding inverted terminal repeats), and the vector is modified to deliver only therapeutic genes. The virus's outer layer, also known as the capsid, is retained to facilitate the delivery of these therapeutic genes to the intended host cell.[8]

## ADENO-ASSOCIATED VIRAL VECTORS

All adeno-associated viral vectors (AAVs) share a similar structure having a single-strand of DNA and all are thought to be biologically stable. They are considered safe, effective and efficient for *in vivo* gene therapy because they are non-integrating, meaning the DNA they carry doesn't insert itself into the host cell's genome.[8] They also have a low immunogenicity profile. Vectors used in gene therapies have not been known to be associated with human disease. AAV vectors can also be targeted to preferred host tissues through selection of an AAV serotype. For example, Zolgensma® is an AAV9-SMN vector and can cross the blood-brain barrier and transduce motor neurons.[69]

There are multiple serotypes of adenoviruses. AAVs are widely found in humans, with some serotypes (AAV1, AAV2, AAV3, AAV5, AAV6, AAV7, AAV8, AAV9) thought to be endemic.[70] Generally AAVs have a low immunogenicity profile but individuals can develop neutralizing antibodies to the viruses. Studies suggest that approximately 80% of humans will have neutralizing antibodies in their lifetime from natural exposure.[71] Presence of neutralizing antibodies increases with age and varies across ethnic groups and geography.[70] Preexisting neutralizing anti-AAV antibodies can hinder transgene expression and diminish treatment effectiveness of gene therapy delivered via AAVs.

Examples of gene therapies delivered via AAVs include Zolgensma®, Elevidys®, Hemgenix®, Roctavian™ and Beqvez™. The prescribing labels of these therapies either preclude use or recommend against use in individuals for whom antibody titers exceed a pre-specified threshold. However, there are only two therapies for which FDA has approved a companion diagnostic test for detecting neutralizing antibodies to an AAV vector: Roctavian™ (AAV5 DetectCDx, Arup Laboratories) and Beqvez™ (NAbCyte Anti-AAVRh74var HB-FE Assay, LabCorp). The FDA maintains a list of cleared or approved companion diagnostic devices.[72] For gene therapies approved without a companion diagnostic test, laboratory developed tests are likely to be used as a replacement.

## LENTIVIRAL VECTORS

*Ex vivo* gene therapies that involve stem cells generally use lentiviruses. Stem cells are difficult to modify and are refractory to insertion of genetic material.[73] Genes transferred into stem cells by lentiviruses integrate into the host genome and thereby hold the potential for durability of effect. Persistent gene alteration within stem cells would lead to ongoing gene alteration in future cell lines. The potential risks of such genomic integration include random insertions into unwanted areas and consequent potential for oncogenesis.[73] Examples of gene therapies using lentiviruses include Skysona®, Lyfgenia™, Zynteglo® and Lenmeldy™. Table 7 summarizes the vector delivery mechanisms and labeled warnings for FDA-approved one-time gene therapies.

## TABLE 7. Summary of Vector Delivery for FDA Approved One-Time Gene Therapies

| Approved Therapies | Delivery mechanism | Vector Issue | Black Box | Warning and Precautions |
|---|---|---|---|---|
| Luxturna® (voretigene neparvovec-rzyl) | AAV2 | None noted | No | • None noted.<br>• No language on vector integration |
| Zolgensma® (onasemnogene abeparvovec-xioi) | AAV9 | • Perform baseline testing for the presence of anti-AAV9 antibodies.<br>• Patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50 measured using ELISA assay in trials.<br>• Safety and efficacy in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.<br>• Following infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. Titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients.<br>• Re-administration in the presence of high anti-AAV9 antibody titer has not been evaluated. | Yes (serious liver injury and acute liver failure) | • Serious liver injury and acute liver failure<br>• Thrombotic Microangiopathy<br>• Theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome |
| Zynteglo® (betibeglogene autotemcel) | BB305 LVV | Not an issue here because it is an ex vivo gene therapy | No | Risk of insertional oncogenesis |
| Skysona® (elivaldogene autotemcel) | LVV | Not an issue here because it is an ex vivo gene therapy | Yes (hematologic malignancies) | |
| Hemgenix® (etranacogene dezaparvovec-drlb) | AAV5 | • In AAV-vector based gene therapies, preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired therapeutic levels. Following treatment with Hemgenix® all subjects developed neutralizing anti-AAV antibodies. Currently, there is no validated neutralizing anti-AAV5 antibody assay.<br>• In the clinical studies, an unvalidated clinical trial assay was utilized to assess preexisting neutralizing anti-AAV5 antibodies. The subject sub-group with detectable preexisting neutralizing anti-AAV5 antibodies up to titers of 1:678 showed mean Factor IX activity that was numerically lower compared to that subject sub-group without detectable preexisting neutralizing anti-AAV5 antibodies.<br>• Patients who intend to receive treatment with Hemgenix®are encouraged to enroll in a study to measure pre-existing anti-AAV5 neutralizing antibodies by calling CSL Behring at 1-800-504-5434. The study evaluates the effect of pre-existing anti-AAV5 neutralizing antibodies on the risk of bleeding. | No | • Hepatotoxicity<br>• Hepatocellular carcinogenicity |

| | | | | |
|---|---|---|---|---|
| Elevidys® (delandistrogene moxeparvovec-rokl) | AAVrh74 | • In AAV-vector based gene therapies, preexisting anti-AAV antibodies may impede transgene expression at desired therapeutic levels. Following treatment with Elevidys® all subjects developed anti-AAVrh74 antibodies. Perform baseline testing for the presence of anti-AAVrh74 total binding antibodies prior to Elevidys® administration.<br>• Elevidys® administration is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers (≥1:400).<br>• The observed incidence of anti-AAVrh74 antibodies is highly dependent on the sensitivity and specificity of the assay.<br>• In clinical studies, patients were required to have baseline anti-AAVrh74 total binding antibodies of ≤1:400, measured using ELISA, and only patients with baseline anti-AAVrh74 total binding antibodies <1:400 were enrolled in those studies.<br>• Across clinical studies evaluating a total of 84 patients, elevated anti-AAVrh74 total binding antibodies titers were observed in all patients following a one-time Elevidys® infusion. Anti-AAVrh74 total binding antibody titers reached at least 1:409,600 in every subject, and the maximum titers exceeded 1:26,214,400 in certain subjects. | No | • Acute Serious Liver Injury<br>• Immune-mediated Myositis<br>• Myocarditis |
| Roctavian™ (valoctocogene roxaparvovec-Rvox) | AAV5 | Only indicated for individuals without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test | No | • Hepatotoxicity<br>• Monitor for hepatocellular malignancy |
| Lyfgenia™ (lovotibeglogene autotemcel) | BB305 LVV | Not an issue here because it is an ex vivo gene therapy | Yes (hematologic malignancies) | Risk of insertional oncogenesis |
| Casgevy® (exagamglogene autotemcel) | CRISPR | Not an issue here because it is not a vector delivered gene therapy | No | Off-Target Genome Editing Risk |
| Lenmeldy™ (atidarsagene autotemcel) | LVV | Not an issue here because it is an ex vivo gene therapy | No | Risk of insertional oncogenesis |
| Beqvez™ (fidanacogene elaparvovec-dzkt) | AAVRh74var | Only indicated for individuals without pre-existing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid detected by an FDA-approved test | No | • Hepatotoxicity<br>• Monitor for hepatocellular malignancy |

AAV: adeno-associated viral vector; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; FDA: Food and Drug Administration; LVV: Lentiviral Vector

## INTERVENTION

It is important to understand both the pathophysiology of the disease and the mechanism of action of the gene therapy to evaluate the evidence for the intervention.

For many neurodegenerative diseases such as SMA, CALD, and MLD, timing of treatment is critical. Early intervention is necessary to either prevent or mitigate permanent damage.

It is also crucial to understand how the gene therapy will fit into the existing management pathway. Will the gene therapy be an adjunct to or replace existing therapies? For example, in the case of hemophilia, the original supposition was that gene therapy would replace the need for exogenous factor replacement. However long-term follow-up data showed that the treatment effect waned several years after administration.[74] Manufacturers must therefore be clear regarding whether the upcoming gene therapies are adjunct or replacement therapies. Table 8 describes questions for consideration related to study interventions when reviewing evidence for a gene therapy.

### TABLE 8. Evidence Assessment Questions Related to Interventions

| | |
|---|---|
| **1.** | What is the ultimate goal(s) of therapy (e.g., lengthening life, reducing functional disability, etc.)? |
| **2.** | Is there an optimal time for treatment based on age, phenotype, or symptom onset? |
| **3.** | Is the gene therapy the first in its class? |
| **4.** | If existing therapies exist, is the gene therapy meant to be used as an adjunct or replacement to existing therapies? |
| **5.** | Does the gene therapy require stem cell transplant? If yes, are there any notable differences in the total episode of care compared to the standard stem cell transplant? |

## COMPARATOR

As mentioned previously, clinical studies should ideally have a concurrent control group as the comparator. The concurrent control group could be a placebo or sham, or it could be another active therapy. A concurrent control group helps to distinguish treatment effects from other effects that might differ *over time* such as natural disease progression, diagnostic methods, participant demographic or clinical characteristics, investigator or setting characteristics, standard of care, and outcome ascertainment methods.

Because of the rarity of the genetic diseases and because many of the diseases have no other available treatments, most pivotal studies of gene therapies have not had concurrent controls but instead have been single arm, i.e., all participants receive the experimental therapy and have been compared to an external or historical control (Table 5). A study design with historical controls can reliably distinguish treatment effects when the disease has a well-characterized, predictable, homogenous natural history.[36,37] In some studies of gene therapies, the historical control was a pre-treatment period of observation on the same enrolled participants, sometimes referred to as a pre-post design (Table 5). While pre-post designs can control for the potential confounding due to characteristics of individuals that are not changing over time, it still has the potential for confounding due to factors that are related to time.

Table 9 describes questions for consideration related to study comparators when reviewing evidence for a gene therapy.

## Table 9. Evidence Assessment Questions Related to Comparators

| | |
|---|---|
| **Standard of care** | |
| **1.** | What is the standard of care or guidelines-based care in the United States? Is it well-described? Does it differ by genotype/phenotype/stage? |
| **2.** | How does usual care differ across geography and urban/rural locations? |
| **Available therapy** | |
| **3.** | If an available therapy exists, what are known limitations of the existing therapy (e.g., invasiveness, discomfort, complexity, cost, availability, performance) |
| **4.** | If an available therapy exists, would the gene therapy be used in addition to, or instead of the existing therapy? |
| **Concurrent Controls** | |
| **5.** | If the studies had a placebo or sham concurrent control group, did the placebo/sham effectively mask treatment assignment? |
| **6.** | If the studies had an active (not placebo) concurrent control group, was the therapy in the control arm delivered according to standard of care? |
| **Nonconcurrent controls**<br>Note: single-arm studies are inherently compared to historical controls. | |
| **7.** | Is the natural history of the disease highly predictable? If not, what are the sources of heterogeneity? |
| **8.** | What is the length of time between the observation of the historical controls and the current clinical studies? |
| **9.** | Have standard of care practices changed between those used for historical controls and current clinical studies? |
| **10.** | Have methods for diagnosis or staging changed between those used for historical controls and current clinical studies? |
| **11.** | Were participants in the historical control population recruited from similar populations as the current clinical studies with respect to clinical and geographic settings? |
| **12.** | Were the enrollment criteria similar in the historical control studies compared to current clinical studies? |
| **13.** | Were participants in the historical control populations similar to those in the current studies with respect to baseline demographics, clinical characteristics and confounders? |
| **14.** | Have methods for measuring the outcomes changed between those used for historical controls and current clinical studies? |
| **15.** | Was the historical control group selected before statistical analysis? |

## CHARACTERIZATION OF NATURAL HISTORY CONTROL GROUP

Relatively recent examples utilizing retrospective natural history data are the FDA's approval of Zolgensma® for SMA and Lenmeldy™ for MLD. Both are rare diseases with high unmet need. Infantile-onset SMA is a serious, life-threatening disease where untreated individuals will either die or require permanent ventilation by 24 months of age. Given the rare nature of the disease, data from 23 patients were successfully used as an external control. In this case, the natural history of SMA was predictable, the efficacy of Zolgensma® was objectively measured, there was a large treatment effect (90% alive without ventilation versus 25% based on natural history), and there was evidence of a temporal association with the intervention.

Similarly, in the case of MLD, treatment with Lenmeldy™ demonstrated improvement in severe motor impairment-free survival compared to natural history cohort. All children with the pre-symptomatic late infantile form of disease treated with Lenmeldy™ were alive at 6 years of age, compared to only 58% of children in the natural history group. At 5 years of age, 71% of treated children were able to walk without assistance.

In contrast with SMA and MLD, the disease progression is heterogeneous in DMD. Reflecting this heterogeneity and the limitations of historical controls in this context, the pivotal trial of Elevidys® that was provided as part of the submission to the FDA used an RCT design with a concurrent placebo control arm.

## EVOLUTION OF DIAGNOSIS

Researchers need to carefully address the impact of diagnostic evolution when using non-concurrent controls. Skysona® was approved by the FDA in September 2022 in boys 4 to 17 years of age with early, active CALD. This indication was approved under accelerated approval based on 24-month major functional disability-free survival. The approval was based on a post-hoc enrichment analysis of 11 individuals treated with Skysona® who were compared with 11 untreated individuals from an external, non-concurrent, natural history control. Data for the natural history population was retrospectively collected from existing medical records. The original submission by the manufacturer included efficacy data from 46 participants. The FDA review team considered the potential for traditional approval but found multiple limitations in the analyses. The data collected in the natural history control were from a time (1988-2010) when disease understanding was evolving. Newborn screening for CALD was added to the Recommended Uniform Screening Panel in 2016.[75] From this point on, identification of cases due to newborn screening increased and led to genetic testing of family members of affected individuals. Routine magnetic resonance image screening allowed for diagnosis at earlier stages of cerebral disease, often prior to onset of neurologic dysfunction or neurocognitive changes. The natural history cohort lacked data on a population that was followed from such an early stage of disease to inform understanding of the clinical course of asymptomatic early, active cerebral disease. Study participants in the natural history control were, therefore, generally older and had more advanced disease at baseline compared to the Skysona®-treated study population who were younger. As a result, it is difficult to determine if the observed effects reported in the post-hoc analysis were due to a treatment effect of Skysona® or due to observation of an earlier stage of disease with insufficient duration of follow-up to detect progression to major functional disabilities or death.

## OUTCOMES

BCBSA TEC criteria assess whether a technology improves health outcomes such as length of life, quality of life and functional ability. However, for many rare diseases there will have been little development and validation of appropriate health outcome measures for function and quality of life specific or relevant to that disease. Table 10 describes questions for consideration related to outcome measures when reviewing evidence for a gene therapy.

### TABLE 10. Evidence Assessment Questions Related to Outcome Measures

| | |
|---|---|
| **Existing health outcome measures** | |
| **1.** | What is the ultimate goal(s) of therapy (e.g., lengthening life, reducing functional disability, etc.)? |
| **2.** | What outcomes are important to patients and their families or caregivers? |
| **3.** | Are there existing, validated tools for measuring important health outcomes? Are the relevant for the specific target population of the study? |
| **4.** | Is there information available on changes in health outcomes that are clinically meaningful? |
| **5.** | Can existing health outcomes be measured in a practice setting? |
| **Novel outcome measures** | |
| **1.** | What was the process for development and validation of the novel outcome measure? |
| **2.** | Does the novel outcome measure capture factors important to patients and their families or caregivers? |
| **3.** | Is there information available on changes in the novel outcome that are clinically meaningful? |
| **Intermediate outcomes** | |
| **1.** | What evidence supports the use of the intermediate outcome as a potential surrogate for important health outcomes? |
| **Timing of outcome measures** | |
| **1.** | How was the natural history of the disease considered in selecting the timing of outcome assessment? |
| **2.** | Is the timing of outcome assessment sufficient to assess the intended beneficial effects of the therapy being tested? |
| **3.** | Is the timing of outcome assessment sufficient to assess potential harmful effects of the therapy being tested? |

### NOVEL OUTCOME MEASURES

Developing novel outcome measures is a technically and logistically arduous process likely to span many years.[76-78] During the testing of Luxturna® for retinal dystrophy, a novel outcome measure was developed by the manufacturer due to a lack of existing measures capturing the specific functional disability of the disease. Because the hallmark of the disease is night blindness, the manufacturer developed an outcome measure to measure functional vision by evaluating the effects of illumination on speed and accuracy of navigation.[79]

### INTERMEDIATE OUTCOMES

Skysona® and Elevidys® gene therapies were approved through the FDA's accelerated approval pathway which allows demonstration of treatment effect on an intermediate outcome considered *reasonably likely* to predict clinical benefit. In the case of Elevidys®, the intermediate outcomes were physiologic measures, i.e., expression of microdystrophin in skeletal muscle in individuals treated with Elevidys®. A common limitation of using physiologic parameters as outcome measures is that most are not validated surrogates for important health outcomes. Surrogates are intermediate outcomes that 'yield a valid test of the null hypothesis of no association between treatment and the true response'[80] which essentially requires the surrogate to 'capture' any relationship between the treatment and the true outcome. Intermediate outcomes may fail to be surrogates because a correlated physiologic measure may not represent the causal pathway of the disease, the disease may have multiple causal pathways, or the intervention may have other mechanisms of action, such as toxicity.[81]

## INTERPRETING RESULTS

The BCBSA TEC criteria require that benefits of a new technology should outweigh risks. To make the determination of risk versus benefit, sufficient estimates of both risk and benefit are needed. Many uncertainties remain at the time of evidence evaluation for gene therapies, complicating interpretation of results. There is uncertainty in short-term efficacy and safety due to bias in estimation and small sample sizes as well as uncertainty in long-term efficacy (durability of effect) and safety due to limited follow-up.

As previously described, most of the pivotal clinical studies performed thus far in the gene therapy space have used historical controls and this design can lead to many different biases that increase uncertainty in observed results. Large treatment effects are unlikely due to bias alone and are more likely to be convincing. For example, in studies of Zolgensma® for SMA[45-48] and Lenmeldy™ for MLD[61,62] most to all participants in the treated group remained alive and event-free during the observation period. This outcome is highly atypical compared to the historical control group.

In trials of gene therapy, sample sizes have typically been fewer than 35 participants. As a result, the estimated effect sizes often come with wide confidence intervals. While the observed treatment effect may appear substantial, it is important to recognize that in many cases, a much smaller effect size cannot be ruled out. For example, in the pivotal study of Skysona® for treatment of CALD, the estimated major functional disability-free survival at month 24 from time of first neurologic function score ≥ 1 was 72% for the symptomatic Skysona®-treated individuals and 43% for the natural history control. The 95% confidence interval around the estimate in the Skysona® group was from 35% to 90% while it ranged from 10% to 73% in the natural history group. On the other hand, 100% of

Lenmeldy™ treated children remained event-free compared with 0% of untreated children in the natural history control group but confidence interval around these estimates were not reported.[82] Given that there were only 20 and 28 children in the Lenmeldy™ and natural history groups, respectively, confidence intervals would be wide. In the pivotal trial of Zolgensma®, there were 21 study participants in the treated group and 23 in the natural history control. Point estimates for the survival analysis were not reported in the prescribing label of Zolgensma®.[83]

Viral delivery therapies carry the potential for adverse effects. Due to the small sample sizes of the pivotal studies, estimates of adverse events are often imprecise. Studies are more likely to detect common adverse events, leaving uncertainty about rare adverse events.

Potential short term adverse events are related to aberrant cellular and chromosomal changes, immunogenicity, off-target editing and unintended consequences of on-target editing. Long-term adverse events are related to oncogenesis. In April 2024, the prescribing label for Skysona® was revised to include updated safety information related to hematologic malignancy. The revisions included information on patient monitoring and counseling, and clarifications to improve readability of warnings and precautions and adverse reactions. Given the importance of early diagnosis in hematologic malignancies, the prescribing label recommends lifelong monitoring of patients treated with Skysona®. Specifically, for the first fifteen years post-treatment, the label recommends monitoring for hematologic malignancies via complete blood count at least every 3 months and through integration site analysis or other testing for evidence of clonal expansion and predominance at least twice in the first year and then annually. As of April 2024, hematologic malignancies have been diagnosed in 6 out of 67 (9%) clinical study patients.[82]

Given that the gene therapies replace or edit the defective or missing gene, the hope is that these gene therapies will be curative and will last a lifetime. However, the studies of these therapies have only included periods of follow-up spanning months to years. With the approval of the first gene therapy in 2017, long-term experience in real-world use is limited. While their long-term durability is generally assumed based on mechanism of action, it has to be proven. When early results of Roctavian™ clinical trials were released, it was assumed that the treatment effect would be durable. However, as the long-term data accrued, almost a quarter of patients lost response to treatment over a median time of 3.6 years.[84]

## DIFFERENCES BETWEEN FDA, BCBSA, AND BCBS PLANS DECISION MAKING

The FDA's approval process is a separate and independent procedure from BCBSA's method for evidence evaluation and the payers' processes for making coverage decisions. The BCBSA evidentiary evaluation methods have been described previously. BCBS Plans make independent decisions on coverage based on a myriad of factors, such as evidence, applicable state and federal laws and local market dynamics.

BCBSA's conclusions on evidence often align with those of the FDA. However, there are occasional differences, particularly when it comes to drugs approved through the accelerated pathway. The BCBSA framework requires demonstrating an improvement in the net health outcomes, whereas through the accelerated pathway, the FDA can grant approval based on an intermediate outcome that is reasonably likely to predict a clinical benefit. Within the FDA's accelerated approval framework, a physiological measure may be deemed an acceptable intermediate outcome. Continued approval via this pathway may be contingent upon verification and description of clinical benefit in a confirmatory

trial. Drug manufacturers must continue to study these therapies to confirm a clinical benefit to patients, while health insurers are asked to pay for claims as evidence is being developed. Unfortunately, confirmatory trials often are not completed by the FDA deadlines. For drugs granted accelerated approval from January 2012 through July 2021, only 46% of confirmatory trials were completed on time.[85] A study by the Health and Human Services Office of the Inspector General found Medicare and Medicaid spent more than $18 billion from 2018 to 2021 for accelerated approval drugs with incomplete confirmatory trials past their original planned completion dates.[86] It is critical Congress and the FDA require manufacturers to complete confirmatory trials in a timely manner to answer specific questions related to safety and efficacy of these therapies.

Timely access to effective and safe treatments is the shared goal for all stakeholders in the health care space, particularly for rare diseases where there is a lack of effective treatments. Nonetheless, there is a balance to be struck between expediting access to treatments and collecting sufficient data on safety and efficacy. Early approval of treatments based on limited data about intermediate outcomes allows patients earlier access, but it also risks introducing treatments that may be ineffective or unsafe to the market. Early access can also complicate the conduct of trials in rare disease, as the pool of treatment-naïve patients quickly diminishes, and patients lack the incentive to participate in trials with the possibility of receiving a placebo. Conversely, delaying the approval of potentially effective treatments could lead to avoidable morbidity and mortality. Authors analyzed FDA approvals for 19 gene and RNA therapies between 2016 and 2023. They noted multiple limitations of the pivotal studies, including having no clinical endpoint, lack of demonstrated benefit or inconsistent results and for multiple pediatric drugs, the labeled indications included a broader age group compared with the trial populations.[87]

Elevidys® was discussed previously. Its initial approval came in June 2023, based on a physiological measure, specifically the expression of microdystrophin in skeletal muscle. The evidence submitted to the FDA by the manufacturer only demonstrated the presence of the transgene product in the target muscle cells but did not provide any information about its pharmacological effects on the known disease pathways. The continuation of its regulatory approval depended on showing clinical benefit in functional outcomes in the confirmatory, phase 3 RCT (Embark). However, the confirmatory trial did not achieve the pre-specified primary endpoint. Despite this, the FDA did not withdraw the gene therapy from the market. Instead, the FDA granted traditional approval and even broadened the therapy's indication to include all age groups regardless of ambulatory status. The approval was based on the post-hoc exploratory analysis of secondary outcome measures.[88] Since both placebo-controlled RCTs failed to show a statistically significant difference in the pre-specified functional primary endpoint, BCBSA concluded that the evidence was insufficient to determine that Elevidys® improved the net health outcome.

While the accelerated approval pathway may be appropriate in some situations, the FDA's decision to grant traditional approval to Elevidys® has lowered the evidentiary threshold significantly. The full consequences of this regulatory action, including risks to patients, and the precedent it establishes are still unclear. Payers are now faced with the challenging decision of whether to cover this therapy, with the possibility of negative media attention and public backlash if they do not. Should Payers choose to deny coverage, they may also encounter legal challenges on coverage for FDA-approved treatments.

All stakeholders in the healthcare space should make efforts to bridge the gap between FDA approval and payers' coverage decisions. For example, the use of microdystrophin expression as an intermediate outcome for the accelerated approval of Elevidys® would not meet the BCBSA definition of a health outcome. This gap may be bridged by having early discussions between payers and

manufacturers during the clinical development process so that the manufacturers can incorporate the needs of payers in evidence generation in their clinical development program. FDA has a precedent for this kind of program in the device space. The FDA's Center for Devices and Radiological Health established the Payor Communication Task Force to facilitate communication between device manufacturers and insurers. The goal of this effort is to potentially shorten the time between FDA marketing authorization and coverage decisions, which may expedite patient access. BCBSA has participated in the Payor Communication Task Force since its inception.

## PATIENT REGISTRIES

Patient registries are designed to collect real-world data over time on individuals with predefined conditions. Registries could serve multiple purposes in the context of gene therapies. They are valuable for identifying individuals who might be eligible for clinical trials or treatment with gene therapy. Additionally, they can help fill post-approval evidence gaps regarding long-term safety and durability. Finally, although registries have not been traditionally designed or used for this purpose, they could potentially provide outcomes data needed for outcomes-based contracts.

Outcomes based contracts link payment to future clinical outcomes such as success (which triggers payment) or failure (which triggers rebate) of therapy. Outcomes based contracts are discussed in more detail in a subsequent section of this report. Tracking outcomes from a pre-existing registry would avoid duplicating efforts for outcome-based contracts that may be executed by multiple stakeholders in the healthcare system.

Registries for individuals with genetic diseases may be sponsored by multiple entities. As part of post-marketing requirements for gene therapies, FDA may require manufacturers to perform long-term follow-up of individuals who have received or are receiving the therapy. Manufacturers may establish registries to fulfill this requirement. Table 11 shows long-term follow-up studies of FDA-approved gene therapies registered by the manufacturer on clinicaltrials.gov. The more recently approved therapies may not yet have long-term studies registered. In some cases, the manufacturers have long-term follow-up only of individuals from the clinical studies used for regulatory approval (for example, NCT02698579 for Skysona®) while in other cases, manufacturers also have studies including individuals receiving the treatment in the commercial market after approval (for example, NCT06224413 for Skysona®). Most of the long-term studies are primarily designed for safety but also include collection of secondary outcomes related to durability of efficacy outcomes.

## TABLE 11. Long-Term Follow-Up Studies of FDA-Approved Gene Therapies Registered on Clinicaltrials.gov1

| Gene Therapy Product | Manufacturer | Registration | Study Start Date | Study Completion Date | Population | Summary of Primary Outcome(s) | Summary of Secondary Outcomes (examples)[2] |
|---|---|---|---|---|---|---|---|
| Luxturna® (voretigene neparvovec-rzyl) | Spark Therapeutics, Inc. | NCT03602820 | Jun 2015 | Jun 2030 | Individuals who received gene therapy in the prior Phase 1 or Phase 3 clinical trials | Mobility testing for up to 15 years | Light sensitivity and visual acuity for up to 15 years |
| | | NCT03597399 | Jan 2019 | Jun 2025 | Individuals who received gene therapy in at least one eye in US | Adverse events for up to 5 years | Pregnancy outcomes for up to 5 years |
| Zolgensma® (onasemnogene abeparvovec-xioi) | Novartis Gene Therapies, Inc. | NCT03421977 | Sep 2017 | Dec 2030 | Individuals who received gene therapy in the clinical trial for SMA Type 1 | Long-term safety up to 15 years | NA |
| | | NCT04042025 | Feb 2020 | Dec 2035 | Individuals who received gene therapy in a clinical study | Developmental milestones, functional scales, and others at up to 5 years; ventilatory support, Serious Adverse Events, and others up to 15 years | All outcomes listed as primary |
| | | NCT05335876 | Dec 2022 | Oct 2039 | Individuals who received gene therapy in a prior clinical trial | Serious adverse events for up to 15 years | Developmental milestones and functional scales for up to 5 years |
| Zynteglo® (betibeglogene autotemcel) | bluebird bio, Inc. | NCT06271512 | Jan 2024 | Dec 2043 | Individuals treated with gene therapy in the post-marketing setting at a center in the US | Adverse events for up to 15 years | Event-free survival and transfusion independence for up to 15 years |
| Skysona® (elivaldogene autotemcel) | bluebird bio, Inc. | NCT02698579 | Jan 2016 | Aug 2038 | Individuals who received gene therapy in a prior clinical study | Functional disability, malignancies, graft vs host disease, adverse events and others for up to 15 years | Stem cell transplant, neurological function for up to 15 years |
| | | NCT06224413 | Mar 2024 | Dec 2047 | Individuals treated with gene therapy in the post-marketing setting in the US | Adverse events, malignancies and functional disability for up to 15 years | Survival for up to 15 years |

| Gene Therapy Product | Manufacturer | Registration | Study Start Date | Study Completion Date | Population | Summary of Primary Outcome(s) | Summary of Secondary Outcomes (examples)[2] |
|---|---|---|---|---|---|---|---|
| Hemgenix® (etranacogene dezaparvovec-drlb) | CSL Behring LLC | NCT06008938 | Jun 2023 | Aug 2043 | Individuals treated with gene therapy in a post-authorization setting or individuals treated with FIX prophylaxis | Bleeding for up to 15 years | FIX therapy for up to 15 years |
| | | NCT05962398 | Aug 2023 | Mar 2035 | Individuals treated gene therapy in 2 prior clinical studies | Adverse events for up to 15 years | Bleeding episodes, FIX replacement therapy, health utility and quality of life for up to 15 years |
| Elevidys® (delandistrogene moxeparvovec-rokl) | Sarepta Therapeutics, Inc. | NCT05967351 | Sep 2023 | Nov 2030 | Individuals who received gene therapy in a prior clinical study | Adverse events up to 5 years | Ambulation and function up to 5 years |
| | | NCT06270719 | Feb 2024 | Dec 2038 | Individuals who are 4 or 5 years old who are ambulatory; includes those receiving gene therapy and those not receiving gene therapy | Walking/running at 1 year | Ambulation and function up to 10 years |
| Roctavian™ (valoctocogene roxaparvovec-Rvox) | BioMarin Pharmaceutical Inc | NCT05768386 | Jan 2023 | Jan 2040 | Individuals who received gene therapy in a prior clinical study | Long-term safety up to 10 years | Annualized bleeding rate, concomitant hemostatic medications, quality of life for up to 10 years |
| Lyfgenia™ (lovotibeglogene autotemcel) | bluebird bio, Inc. | NA | | | | | |
| Casgevy® (exagamglogene autotemce) | Vertex Pharmaceuticals Incorporated | NCT04208529 | Jan 2021 | Sep 2039 | Individuals who received gene therapy in a prior clinical study | Malignancies, hematologic disorders, mortality, adverse events up to 15 years | Quality of life and functional outcomes for up to 15 years |
| Lenmeldy™ (atidarsagene autotemcel) | Orchard Therapeutics (Europe) Limited | NA | | | | | |

FIX: factor IX; NA: not applicable; SMA: spinal muscular atrophy
[1] Date of search, 24Apr2024
[2] Examples of secondary outcomes related to long-term durability; not an exhaustive list of all secondary outcomes.

Registries may also be funded by professional societies or advocacy groups. The exemplar model for this type of registry is from the World Federation of Hemophilia (WFH), who collaborated with scientific and patient organizations to establish the WFH gene therapy registry. It is an international registry with the goal of collecting long-term data on all individuals with hemophilia who receive gene therapy.[89,90] Table 12 briefly describes features of this registry. The WFH has established a minimum dataset for monitoring both efficacy and safety in the registry, security and data privacy protocols, and transparent data usage policies. The registry was developed with engagement of US and European regulatory agencies to ensure that the data collected would be acceptable for regulatory purposes. The registry is governed by a multistakeholder structure with representation from patient groups, professional societies, treatment centers and industry groups. The registry is supported by funding from manufacturers with the aim of avoiding the need for each manufacturer to separately develop their own registry. This approach allows for independent, centralized and standardized data collection on a global scale which will maximize the ability to assess efficacy and safety outcomes and minimize duplication of efforts. However, it is not currently providing the identifying data that would be needed for attribution in outcomes-based contracts.

**Table 12. Features of the World Federation of Hemophilia Gene Therapy Registry[89]**

| | |
|---|---|
| **Scope** | International; all individuals with hemophilia treated with any gene therapy product |
| **Stakeholders involved in development** | Patients, professional societies, scientists, industry, regulators |
| **Data collection** | Standardized set of outcomes related to efficacy, safety and quality of life |
| **Data privacy** | Security protocols regarding data breach, storage, authorized access; complies with HIPAA |
| **Ethical approvals** | Ethics approval required from all participating centers; consent required from all participants; consent forms are available in all requested languages |
| **Governance** | Steering Committee includes patients, professional societies, scientists; advises on development and implementation.<br>Scientific Advisory Committee does not include industry representatives; makes decisions regarding analyses, use, reporting and publication |

# HEALTH EQUITY

Health equity is a principle that focuses on providing everyone with a fair and just opportunity to attain their highest level of health.[91] Several health equity issues are specific or particularly relevant to gene therapies. These include affordability, treatment burden, regional and racial disparities in access to care and clinical uncertainty.

## AFFORDABILITY

Gene therapies are often expensive. It is estimated that annual spending by insured clients on gene therapy may reach over US$12 billion.[92] Insurance coverage for gene therapies varies. Most individuals with sickle cell disease who have health coverage receive coverage through Medicaid, the Children's Health Insurance Program, and/or Medicare.[93] In order to manage these potential costs, employers, especially small employer funded plans, might exclude gene therapies from benefit coverage. The coverage policies may also restrict patient access based on trial criteria. This may make them inaccessible to individuals from lower socio-economic backgrounds especially when they are uninsured or underinsured and exacerbate social inequalities and further marginalize vulnerable populations.[92]

## TREATMENT BURDEN

When gene therapies require bone marrow transplantation, the challenge of access is more than financial. Each step in the treatment process involves burdens to individuals and their caregivers and can take place over weeks or even months, depending on a number of factors such as the disease being treated, the individual's current health status, travel, and time spent at the treatment center. For instance, gene therapies for sickle cell disease entail collecting a patient's blood stem-cells, modifying them, and administering high-dose chemotherapy to destroy the damaged cells in the bone marrow. The modified cells are then infused into the patient through a hematopoietic stem cell transplant. A period of observation is required to determine if the new cells have replaced the bone marrow (engraftment). These treatments may take up to a year to complete and require several hospital visits posing significant burden on the patient as well as on caregiver and family. Both the recipient and caregivers will need prolonged time off in order to complete the treatment as the hospital stay alone may last for months.[14] If caregivers lack sufficient mechanisms to cover their expenses while they take time off work to care for their family member, such families could potentially face financial hardship and may not opt to get gene therapy treatments.

## REGIONAL DISPARITIES

In the United States, there are regional disparities in healthcare accessibility.[94] These disparities could become more pronounced for gene therapies, especially those targeting ultra-rare diseases or those necessitating stem cell transplants. Such treatments are typically administered at advanced healthcare facilities that possess the necessary expertise in the disease area and are found primarily in urban areas. This may limit access to therapy for individuals outside of these areas. These individuals are more likely to face additional expenses such as cost of travel, food and stay while they are caring for the affected family member.

## RACIAL DISPARITIES

Racial disparities in health and healthcare are prevalent in the health care system as a whole. Because treatment disparities have existed in diseases such as sickle cell disease for which new gene therapies are available, additional attention should be paid to assure disparities are not exacerbated. Sickle cell disease is known to cause excruciating pain, and disproportionately affects the Black population.[3,4] In general, studies have shown Black patients have historically been denied pain medications, and receive lower doses of pain medications when compared to White patients.[95] Racial bias has also limited access to adequate pain control for patients with sickle cell disease, who are more likely to be labeled as drug-seeking.[96,97]

## CLINICAL UNCERTAINTY & DECISION MAKING

Gene and cell therapies are a relatively new form of treatment, and there is considerable uncertainty around their efficacy and long-term durability. Rare diseases, in particular, face the hurdle of small patient populations in clinical trials, making effectiveness determination challenging. While these factors are true for all patients, racial and ethnic minority groups are further disadvantaged by limited participation in clinical trials due to systemic bias in the health care system, access and affordability concerns, and in some cases, mistrust of research in general.

Unique genetic variants common among certain racial groups may not be represented in trials. As a result, gene therapy may not work as expected, side effects may not be well documented or therapeutic effects may not last as long as anticipated for these groups of patients.

## WHAT PAYERS MUST DO?

Addressing these health equity issues is crucial to ensure that advancements in gene therapy benefit all individuals, regardless of their race, socio-economic status or geographical location. Addressing these disparities requires integrating genetic knowledge, improving healthcare delivery systems, promoting inclusivity in healthcare trials, and enhancing diversity in genomic sequencing efforts, building partnerships with systemically disadvantaged populations through transparency, trust, and cultural humility that advances care for all.[98] Payers have a critical role to play in mitigating some of these factors that exacerbate health inequity. To directly address these healthcare inequities, alignment on several issues must be addressed by the payers.

- In order to assure equity in access to gene therapy treatments, all stakeholders, including payers, should ensure that patients have access to comprehensive culturally appropriate, coordinated multidisciplinary care. This includes services such as mental health, and services which address health related social needs.
- Prior authorization is a tool to ensure patients receive safe, effective treatments supported by current, credible clinical evidence. Use of these tools helps reduce inappropriate care and provide safeguards for coverage of gene therapies. Payers should maintain a transparent process that clearly explains gene therapies coverage, the populations it covers, and the time it takes to review and approve prior authorizations. Efforts should be made to minimize unnecessary information requirements for prior authorization, as this can delay approval and potentially lead to irreversible negative clinical outcomes.
- In the conversation with all stakeholders, payers should stress that ongoing and future clinical trials should enroll racially and ethnically diverse populations. They should also advocate that post-approval studies should be done appropriately with timely and transparent and regular frequent publication of results.

# COST & PAYMENT MODELS

Clinical evidence supporting new therapies always has limitations and unknowns. This is amplified in the case of gene therapies due to the evidentiary issues and clinical study limitations outlined in the previous section. Gene therapies that have entered the market so far have been priced at very high levels. While gene therapies will hopefully represent an excellent long-term value over an individual's lifetime, the high upfront costs are challenging for payers, particularly for smaller employer funded Plans which get less protection from risk pooling and plans in geographic regions with higher prevalence of diseases targeted by gene therapy such as sickle cell disease.

The uncertainty regarding efficacy, safety and long-term durability of gene therapies coupled with the extremely high upfront price create challenges in using conventional reimbursement models.[5] Several innovative payment models are being explored to address these challenges including outcome or value-based models and stop-loss or reinsurance models. These various models are not necessarily mutually exclusive although they can be challenging to use together. For more information, the NEWDIGS collaboration from Tufts Medicine offers a 'Paying for Cures' toolkit that has a detailed description of financing models for gene therapy.[99] Table 13 shows the list prices of gene therapies at market entry.

## OUTCOMES- OR VALUE-BASED MODELS

Outcomes- or value-based models are contracts that link payment to future clinical outcomes. This might be accomplished through rebates, warranties or annuities.[2]

In a rebate model, the payer makes an upfront total payment for acquisition of the gene therapy product. If the gene therapy does not meet performance expectations, the payer receives a percentage or absolute rebate amount from the manufacturer. For example, Lyfgenia™, a gene therapy for sickle cell disease, was launched with an option for a rebate if the patient experienced hospitalization for a vaso-occlusive event within the first three years after administration.[100]

In a warranty model, the payer makes upfront total payment, but the warranty provides reimbursement for future payer expenses incurred if the therapy does not meet the manufacturer's promise of a specific magnitude or duration of benefit. For example, if an individual treated with Roctavian™ for hemophilia A loses response at any time in the first four years after dosing, BioMarin will reimburse payers on a prorated basis for the cost of exogenous factor prophylaxis treatment.[101]

In an annuity model, there is not a total upfront payment. Instead, payments are made on a performance-based installment arrangement so that payments are spread over time and linked to achieving performance targets. For example, when Zynteglo® was approved in the European Union, Bluebird Bio had proposed spreading payments over five years and linking each installment to patient benefit.[102] Annuity models are not common in the US.

The potential advantage of outcomes-based models is that they share financial risk between manufacturers and payers. However, there are several challenges in implementation. Individuals change insurance providers on average every few years which limits the long-term value of the upfront cost to the insurer making the original payment. Collecting the data on clinical outcomes is complicated by issues relating to agreement on which outcomes to track, who is responsible for tracking and adjudicating outcomes, time frames for evaluating outcomes, and privacy and confidentiality protections for health information. In addition, Medicaid Best Price Rule requires manufacturers to offer Medicaid the lowest price available to any other buyer. While intended to ensure affordability, it can discourage manufacturers from entering into outcome-based contracts, as these contracts might result in lower prices being offered to other payers.[2]

Payers are usually responsible for tracking outcomes. They can track outcomes via claims data or a third-party vendor that may collect data directly from the provider and/or patient. While some outcomes such as those coded in claims are easier to track, outcomes not coded in the claims data can be difficult to collect and may require additional expense and time using a third-party vendor. For example, outcomes of interest in sickle cell disease such as vaso-occlusive events are coded distinctly in claims data via ICD-10 and procedure codes. Conversely, therapies for disorders that are progressive in nature such as DMD may impact the disease trajectory. Outcomes that capture stopping or delaying disease progression are difficult to capture from claims data.

The Center for Medicare and Medicaid Innovation has developed a Cell and Gene Therapy Access Model in which Center for Medicare and Medicaid (CMS) negotiates key terms for outcomes-based agreements with manufacturers. The agreements will be structured as a supplemental rebate agreement and CMS will negotiate the clinical outcomes that form the basis of the agreement. Subsequently, manufacturers make those agreements available to participating state Medicaid programs.[7] CMS has also committed to reconciling the data, monitoring results, and evaluating outcomes. CMS intends to leverage claims data and patient registries for data collection. The first pilot of the model will focus on sickle cell gene therapies going live in January of 2025.[7]

## REINSURANCE AND STOP-LOSS MODELS

Reinsurance and stop-loss insurance are similar products provided by excess loss insurers that offer protection for payers against unexpected catastrophic claims. Policies can be for claims related to a specific covered individual or in aggregate for overall claims that are higher than expected. The advantage of these models is that they transfer the actuarial risk to excess loss insurers. However, some excess loss insurers specifically exclude genetic conditions ('lasering') that are eligible for gene therapy or raise deductibles for those individuals or conditions.[2]

## SYNERGIE

Synergie is a health plan medication supply chain purchasing collective launched in January 2023.It is jointly owned by BCBS Plans and founding investors include BCBSA, Elevance Health, Evio Pharmacy Solutions and Prime Therapeutics. Their mission is to improve affordability and access to costly medical benefit drugs.

Synergie has developed an industry-leading integrated solutions portfolio for cell & gene therapies that includes Gene+ Outcomes, Gene+ Risk Protection and Cell & Gene+ Patient Navigation.

Gene + Outcomes tools is intended to provide value-based contracts in partnership with Evio Health Solutions, who executes longitudinal tracking of outcomes. The tracking of outcomes extends beyond the treatment period to ensure follow-up regardless of changes in the patient's employer, carrier, or provider. The intention is to leverage the scale of participating BCBS Plans for outcomes-based contracts with manufacturers and improve medication affordability. For example, Synergie has secured risk-sharing agreements with Bluebird Bio and Vertex to cover Lyfgenia™ and Casgevy®, aiming to improve access and affordability of these high-cost treatments.[103]

Gene+ Risk Protection is intended to alleviate the volatility and financial burden for plans associated with multimillion dollar upfront payments for gene therapies, at the most competitive rates and best protection. When plans participate in Gene+ Risk Protection with coverage over their stop loss segment, the solution offering includes a risk-based solution and a stop loss solution for gene therapies in partnership with BCS Financial. Members from both self-funded and fully insured employers may be covered. To participate, employers must have stop loss in place with their respective BCBS Plan and the BCBS Plan must participate in Gene+ Risk Protection. Participating BCBS Plans leverage their expansive membership base to create the largest, most diversified risk pool in the US. For employers who do not purchase stop loss with their respective BCBS Plan, BCS has developed a standalone stop loss solution with similar pooled pricing with no lasers/exclusions.

Cell & Gene+ Patient Navigation assists patients in identifying and accessing top-quality treatment centers across the United States to ensure access to these therapies. The solution offering includes a navigation tool in partnership with Emerging Therapy Solutions who have a background in the organ transplant space. The tool navigates patients to the sites of care based on the merits of quality and cost. Other features include end-to-end support for members for care delivery and programs to secure financial assistance for patients.

## TABLE 13. Gene Therapy List Prices at Market Entry

| Gene Therapy Product | Indication | ICER[a] Report | Assumptions | Results and Conclusions | Health-Benefit Price Benchmark | WAC at market entry |
|---|---|---|---|---|---|---|
| Luxturna® (voretigene neparvovec-rzyl) | Retinal dystrophy | February 2018 here | • CEA assumed both health care system perspective (included only direct medical costs), and societal perspective (indirect benefits related to education, greater productivity, reduced caregiver time, and other factors).<br>• Rx fully effective for 10 years and then steadily declines over following 10 years. | ICER (Health Care System Perspective): $643,813/QALY<br>ICER (Modified Societal Perspective): $480,130/QALY<br>Does not meet commonly accepted CE thresholds of $50,000-$150,000 per QALY | Price to achieve $100,000 to $150,000 per QALY gained: $153,000 to $217,000. | $850K |
| Zolgensma® (onasemnogene abeparvovec-xioi) | Spinal muscular atrophy | May, 2019 here | • CEA assumed placeholder price of $2,000,000 for Zolgensma® | ICER (Health Care System Perspective): $243,000/QALY (Type I SMA)<br>Results for the presymptomatic and Type II/III SMA were not published as data on Zolgensma® effectiveness in this population did not exist at the time of publication of ICER's report. | Price to achieve $100,000 to $150,000 per QALY gained: $310-$890,000 | $2.125 M |
| Zynteglo® (betibeglogene autotemcel) | β-thalassemia | July, 2022 here | • Patients with transfusion dependent thalassemia and a mean age of 22.2 years<br>• Anticipated acquisition cost of beti-cel ($2.1 million) | ICER (Health Care System Perspective): $95,000/QALY<br>ICER (Modified Societal Perspective): $34,000/QALY<br>Meet commonly accepted CE thresholds of $50,000-$150,000 per QALY | $1.3 to $1.8 million | $2.8M |
| Skysona® (elivaldogene autotemcel) | Cerebral adrenoleukodystrophy | None | - | - | - | $3.0M |
| Hemgenix® (etranacogene dezaparvovec-drlb) | Hemophilia B | Dec 2022 here | • CEA used list price of $3,500,000 for Hemgenix® | Hemgenix® was projected to be a dominant treatment (i.e. lower total costs and higher QALY) | $2.93 to 2.96 million | $3.5M |
| Elevidys® (delandistrogene moxeparvovec-rokl) | Duchenne muscular dystrophy | None | - | - | - | $3.2M |
| Roctavian™ (valoctocogene roxaparvovec-Rvox) | Hemophilia A | Dec 2022 here | • CEA assumed placeholder price of $2,500,000 for Roctavian™ | Roctavian™ was projected to be a dominant treatment (i.e. lower total costs and higher QALY) | $1.96 million | $2.9M |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lyfgenia™ (lovotibeglogene autotemcel) | Sickle cell disease | Aug 2023 here | • CEA assumed placeholder price of $2,000,000 for Lyfgenia<br>• After year seven, patients revert to costs and outcomes of standard care at a rate used in ICER's beta thalassemia report | ICER (Health Care System Perspective): $193,000/QALY<br>ICER (Modified Societal Perspective): $162,000/QALY | $1.35M to $2.05M | $2.2M |
| Casgevy® (exagamglogene autotemcel) | Sickle cell disease, β-thalassemia | Aug 2023 here | • CEA assumed placeholder price of $2,000,000 for Casgevy®<br>• After year seven, patients revert to costs and outcomes of standard care at a rate used in ICER's beta thalassemia report | ICER (Health Care System Perspective): $193,000/QALY<br>ICER (Modified Societal Perspective): $162,000/QALY | $1.35M to $2.05M | $3.1M |
| Lenmeldy™ (atidarsagene autotemcel) | Metachromatic leukodystrophy | Oct 2023 here | • CEA assumed placeholder price of $2,800,240 for Lenmeldy™ | ICER (Health Care System Perspective): $127,000/QALY<br>ICER (Modified Societal Perspective): $115,000/QALY | $2.3M to $3.9M | $4.25M |
| Beqvez™ (fidanacogene elaparvovec-dzkt) | Hemophilia B | None | - | - | - | $3.5M |

CE: cost effectiveness; CEA: cost effectiveness analysis; QALY: quality adjusted life years; SMA: spinal muscular atrophy; WAC: wholesale acquisition cost

[a]ICER: Institute for Cost Effectiveness Research

[b]ICER: incremental cost-effectiveness ratio

# RECOMMENDATIONS

Gene therapy represents a transformative advancement in healthcare, offering patients access to innovative treatments. Payers should promote access to such treatments when benefits outweigh the risks. It is important that we find workable solutions that balance access to cutting-edge gene therapies for patients with affordable financing and coverage polices. To ensure patients can access these therapies while balancing potential risks and benefits, we propose several systemwide recommendations.

## NEED FOR CENTRALIZED REGISTRY

The federal government should establish mechanisms for creation of a centralized registry that tracks health outcomes and adverse effects for all gene therapy recipients in the US irrespective of the payer (Medicare, Medicaid, Commercial). Creation of centralized registries will reduce redundancy as multiple stakeholders are collecting long-term data following administration of gene therapies. For example, manufacturers are following-up trial participants for 15 years as part of FDA requirements for post-marketing surveillance. In addition, some manufacturers are also following patients who receive gene therapy post FDA approval. Other stakeholders such as professional societies have also established independent registries to track long-term outcomes. As part of outcomes- or value-based contracts, payers are also tracking outcomes available in claims data as well contracting with vendors to track data not captured in the claims process. Tracking all patients via a centralized and unified mechanism increases the sample size and the statistical power to detect rare events such as side effects and improves the precision for all estimates. In creating a centralized registry, it will be crucial to establish guardrails to protect patient privacy and data security while allowing for equitable access to data for all stakeholders including payers.

## PROVIDE BENEFIT COVERAGE

The current expense for gene therapies represents only a small fraction of the total annual budget for major national plans. However, for small employer funded Plan with 100 to 500 employees, just one or two claims for multi-million-dollar gene therapies could consume half of their annual budget.[104] Consequently, many small employer funded Plans are considering excluding gene therapies from coverage.

This decision, driven by financial considerations, presents a moral dilemma, compliance risks, and public relations challenges for employers and insurers. Excluding these benefits could lead to claims of disability-based discrimination, even if the exclusion targets an employee's dependent. Additionally, such exclusions pose significant public relations risks, as these treatments are often seen as essential, particularly for children. Not covering FDA-approved gene therapies for children with life-threatening conditions and limited treatment options could result in negative publicity. Conversely, it is premature to mandate coverage of cell and gene therapies given the significant uncertainty regarding long-term outcomes and durability of treatments – as well as the vast differences in covered services, benefits and options chosen by employers, individuals, and public programs.

While upfront financial risks are a key consideration for employers in determining their benefit offerings, payers should actively educate employers and benefit consultants about the transformative effects of gene therapies. Highlighting their potential for long-term cost savings and advocating for alternative payment models to fund access to these therapies can help address these challenges.

## NEED FOR EARLY DIALOG BETWEEN PAYERS, FDA AND MANUFACTURERS

Fostering early dialogue between payers, the FDA, and manufacturers will facilitate generation of payer-relevant evidence and streamline the gap between FDA approval and payer coverage. The FDA has a precedent for this kind of program in the Center for Devices and Radiological Health to facilitate communication between device manufacturers and insurers. By sharing information early, payers can make informed decisions about coverage and reimbursement by better planning and budgeting for the introduction of new therapies, reducing the likelihood of unexpected costs and coverage issues. Overall, early dialogue fosters a collaborative environment where all stakeholders can work together toward the shared goal of improving patient outcomes and ensuring the sustainability of healthcare systems.

# REFERENCES


1. Ferreira CR. The burden of rare diseases. *Am J Med Genet A.* Jun 2019;179(6):885-892. PMID 30883013
2. Phares S, Trusheim M, Emond SK, Pearson SD. Managing the Challenges of Paying for Gene Therapy: Strategies for Market Action and Policy Reform. Institute for Clinical and Economic Review created in collaboration with NEWDIGS at Tufts Medical Center. Published 2024. Avilable at https://icer.org/wp-content/uploads/2024/04/Managing-the-Challenges-of-Paying-for-Gene-Therapy-_-ICER-NEWDIGS-White-Paper-2024_final.pdf.
3. Pokhrel A, Olayemi A, Ogbonda S, et al. Racial and ethnic differences in sickle cell disease within the United States: From demographics to outcomes. *Eur J Haematol.* May 2023;110(5):554-563. PMID 36710488
4. McCune JM, Kiem HP. Extending Gene Medicines to All in Need. *N Engl J Med.* May 9 2024;390(18):1721-1722. PMID 38657269
5. Breakthrough Cures, Blockbuster Costs: Future Directions. Summary of a cross-sector dialogue sponsored by Blue Cross Blue Shield Association and Health Medicine & Society Program of the Aspen Institute. Available at. https://www.aspeninstitute.org/wp-content/uploads/2022/02/Breakthrough-Cures-Blockbuster-Costs-white-paper-FINAL.pdf. Accessed May 8, 2024.
6. Food and Drug Administration. What is Gene Therapy? Available at https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy. Accessed May 23, 2024.
7. Center for Medicare and Medicaid Innovation. Cell and Gene Therapy (CGT) Access Model. Available at. https://www.cms.gov/priorities/innovation/innovation-models/cgt. Accessed May 8, 2024.
8. American Society Cell and Gene Therapy. Gene and Cell Therapy FAQ's. Available at. https://www.asgct.org/education/more-resources/gene-and-cell-therapy-faqs. Accessed May 23, 2024.
9. Feins S, Kong W, Williams EF, et al. An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. *Am J Hematol.* May 2019;94(S1):S3-S9. PMID 30680780
10. Xu Y, Li Z. CRISPR-Cas systems: Overview, innovations and applications in human disease research and gene therapy. *Comput Struct Biotechnol J.* 2020;18:2401-2415. PMID 33005303
11. Henderson ML, Zieba JK, Li X, et al. Gene Therapy for Genetic Syndromes: Understanding the Current State to Guide Future Care. *BioTech (Basel).* Jan 3 2024;13(1). PMID 38247731
12. Boston Children Hospital. Luxturna- What is involved in Luxturna gene therapy? Available at https://www.childrenshospital.org/treatments/luxturna. Accessed June 2, 2024.
13. Casgevy and Lyfgenia: Two Gene Therapies Approved for Sickle Cell Disease by Carrie Macmillian. Published December 19, 2023. Available at https://www.yalemedicine.org/news/gene-therapies-sickle-cell-disease#:~:text=However%2C%20the%20gene%20therapies%20are,replaced%20with%20modified%20stem%20cells. Accessed June 2, 2024.
14. New York Times. First Patient Begins Newly Approved Sickle Cell Gene Therapy. Published May 6, 2024. Available at. https://www.nytimes.com/2024/05/06/health/sickle-cell-cure-first.html. Accessed June 2, 2024.
15. Kolata G. F.D.A approves sickle cell treatments, including one that uses CRISPR. *The New York Times.* Dec 8, 2023, 2023.
16. Find a CASGEVY™ Treatment Center. Available at https://www.casgevy.com/sickle-cell-disease/find-an-ATC. Accessed June 2, 2024.
17. Start your search for a Qualified Treatment Center. Available at https://www.lyfgenia.com/find-a-qualified-treatment-center?status=8e4cd0d054c24874a394a949fd3e65a6&coordinate=41.947205%2C-87.656521&place_type=postcode&searchkeyword=Chicago%2C%20Illinois%2060613%2C%20United%20States. Accessed June 2, 2024.
18. Morimura H, Fishman GA, Grover SA, et al. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or leber congenital amaurosis. *Proc Natl Acad Sci U S A.* Mar 17 1998;95(6):3088-3093. PMID 9501220

19. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet.* Jan 2012;20(1):27-32. PMID 21811307

20. Moser HW, Loes DJ, Melhem ER, et al. X-Linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. *Neuropediatrics.* Oct 2000;31(5):227-239. PMID 11204280

21. Mosser J, Douar AM, Sarde CO, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. *Nature.* Feb 25 1993;361(6414):726-730. PMID 8441467

22. Soucie JM, Miller CH, Dupervil B, et al. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. *Haemophilia.* May 2020;26(3):487-493. PMID 32329553

23. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol.* Feb 2010;9(2):177-189. PMID 19945914

24. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med.* Apr 2010;38(4 Suppl):S512-521. PMID 20331952

25. Lugowska A, Poninska J, Krajewski P, et al. Population carrier rates of pathogenic ARSA gene mutations: is metachromatic leukodystrophy underdiagnosed? *PLoS One.* 2011;6(6):e20218. PMID 21695197

26. Braga LAM, Conte Filho CG, Mota FB. Future of genetic therapies for rare genetic diseases: what to expect for the next 15 years? *Ther Adv Rare Dis.* Jan-Dec 2022;3:26330040221100840. PMID 37180410

27. Food and Drug Administration. Designating an Orphan Product: Drugs and Biological Products. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products. Accessed June 12, 2024.

28. Are Cell and Gene Therapy programs a better bet? By NEWDIGS at Tufts Medical Center FoCUS Project. Published 9 October 2023. Available at. https://newdigs.tuftsmedicalcenter.org/wp-content/uploads/2023/10/NEWDIGS-Success-Rate-Comparison-2023F210v056.pdf, June 19, 2024.

29. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet.* Feb 2020;28(2):165-173. PMID 31527858

30. Roessler HI, Knoers N, van Haelst MM, et al. Drug Repurposing for Rare Diseases. *Trends Pharmacol Sci.* Apr 2021;42(4):255-267. PMID 33563480

31. CVS Health Clinical Affairs. Gene Therapy Report Q1 2024-Q4 2026. Projected Treatments and Launch Timelines. Available at. https://insightslp.cvshealth.com/rs/161-LXO-491/images/REPORT-Q1-2024-Gene-Therapy-Pipeline-CVS-Health-February-2024.pdf?version=0&trk=public_post_comment-text. Accessed June 5, 2024.

32. Food and Drug Administration. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Published 1998. Available at https://www.fda.gov/media/71655/download. Accessed March 26, 2024.

33. Code of Federal Regulations. 21CFR314.126. Published 2023. Available at. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126. Accessed March 26, 2024.

34. Food and Drug Administration. Accelerated Approval. Published 2023. Available at. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval. Accessed March 26, 2024.

35. Food and Drug Administration. Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Guidance for Industry. Published 2023. Available at. https://www.fda.gov/media/172166/download. Accessed March 26, 2024.

36. Food and Drug Administration. Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials. Published 2001. Available at. ; https://www.fda.gov/media/71349/download Accessed March 26, 2024, .

37. Food and Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry. Published 2023. Available at https://www.fda.gov/media/164960/download. Accessed March 26, 2024.

38. Food and Drug Administration. Rare Diseases: Natural History Studies for Drug Development Guidance for Industry. Published 2019. Available at. https://www.fda.gov/media/122425/download. Accessed May 13, 2024.

39. Food and Drug Administration. Human Gene Therapy for Rare Diseases: Guidance for Industry. . https://www.fda.gov/media/113807/download. Accessed March 26, 2024.

40. Food and Drug Administration. Human Gene Therapy Products Incorporating Human Genome Editing: Guidance for Industry. . https://www.fda.gov/media/71349/download. Accessed March 26, 2024.

41. Food and Drug Administration. Long Term Follow-Up After Administration of Human Gene Therapy Products: Guidance for Industry. Published 2020. Available at https://www.fda.gov/media/113768/download. Accessed March 26, 2024.

42. Food and Drug Administration. Human Gene Therapy for Hemophilia: Guidance for Industry. Published 2020. Available at. https://www.fda.gov/media/113799/download. Accessed March 26, 2024.

43. Food and Drug Administration. Human Gene Therapy for Retinal Disorders: Guidance for Industry. Published 2020. Available at https://www.fda.gov/media/124641/download. Accessed March 26, 2024.

44. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet.* Aug 26 2017;390(10097):849-860. PMID 28712537

45. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med.* Nov 2 2017;377(18):1713-1722. PMID 29091557

46. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. *JAMA Neurol.* Jul 1 2021;78(7):834-841. PMID 33999158

47. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol.* Apr 2021;20(4):284-293. PMID 33743238

48. Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med.* Jul 2022;28(7):1390-1397. PMID 35715567

49. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non-beta(0)/beta(0) Genotype beta-Thalassemia. *N Engl J Med.* Feb 3 2022;386(5):415-427. PMID 34891223

50. Chiesa R, Boelens JJ, Duncan CN, et al. Variables affecting outcomes after allogeneic hematopoietic stem cell transplant for cerebral adrenoleukodystrophy. *Blood Adv.* Mar 8 2022;6(5):1512-1524. PMID 34781360

51. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. *N Engl J Med.* Oct 26 2017;377(17):1630-1638. PMID 28976817

52. Pipe SW, Leebeek FWG, Recht M, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. *N Engl J Med.* Feb 23 2023;388(8):706-718. PMID 36812434

53. Coppens M, Pipe SW, Miesbach W, et al. Etranacogene dezaparvovec gene therapy for haemophilia B (HOPE-B): 24-month post-hoc efficacy and safety data from a single-arm, multicentre, phase 3 trial. *Lancet Haematol.* Apr 2024;11(4):e265-e275. PMID 38437857

54. Mendell JR, Shieh PB, McDonald CM, et al. Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy. *Front Cell Dev Biol.* 2023;11:1167762. PMID 37497476

55. Zaidman CM, Proud CM, McDonald CM, et al. Delandistrogene Moxeparvovec Gene Therapy in Ambulatory Patients (Aged >/=4 to <8 Years) with Duchenne Muscular Dystrophy: 1-Year Interim Results from Study SRP-9001-103 (ENDEAVOR). *Ann Neurol.* Nov 2023;94(5):955-968. PMID 37539981

56. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. *N Engl J Med.* Mar 17 2022;386(11):1013-1025. PMID 35294811

57. Mahlangu J, Kaczmarek R, von Drygalski A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. *N Engl J Med.* Feb 23 2023;388(8):694-705. PMID 36812433

58. Kanter J, Walters MC, Krishnamurti L, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. *N Engl J Med.* Feb 17 2022;386(7):617-628. PMID 34898139

59. Kanter J, Thompson AA, Pierciey FJ, Jr., et al. Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study. *Am J Hematol.* Jan 2023;98(1):11-22. PMID 36161320

60. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and beta-Thalassemia. *N Engl J Med.* Jan 21 2021;384(3):252-260. PMID 33283989

61. Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet.* Jan 22 2022;399(10322):372-383. PMID 35065785

62. Sessa M, Lorioli L, Fumagalli F, et al. Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. *Lancet.* Jul 30 2016;388(10043):476-487. PMID 27289174

63. Inusa BPD, Hsu LL, Kohli N, et al. Sickle Cell Disease-Genetics, Pathophysiology, Clinical Presentation and Treatment. *Int J Neonatal Screen.* Jun 2019;5(2):20. PMID 33072979

64. Lorson CL, Hahnen E, Androphy EJ, et al. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc Natl Acad Sci U S A.* May 25 1999;96(11):6307-6311. PMID 10339583

65. Feldkotter M, Schwarzer V, Wirth R, et al. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genet.* Feb 2002;70(2):358-368. PMID 11791208

66. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* Aug 26 2014;83(9):810-817. PMID 25080519

67. Chand DH, Zaidman C, Arya K, et al. Thrombotic Microangiopathy Following Onasemnogene Abeparvovec for Spinal Muscular Atrophy: A Case Series. *J Pediatr.* Apr 2021;231:265-268. PMID 33259859

68. Gomez-Ospina N. Arylsulfatase A Deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews((R))*. Seattle (WA)1993.

69. Haggerty DL, Grecco GG, Reeves KC, et al. Adeno-Associated Viral Vectors in Neuroscience Research. *Mol Ther Methods Clin Dev.* Jun 12 2020;17:69-82. PMID 31890742

70. Issa SS, Shaimardanova AA, Solovyeva VV, et al. Various AAV Serotypes and Their Applications in Gene Therapy: An Overview. *Cells.* Mar 1 2023;12(5). PMID 36899921

71. Elangkovan N, Dickson G. Gene Therapy for Duchenne Muscular Dystrophy. *J Neuromuscul Dis.* 2021;8(s2):S303-S316. PMID 34511510

72. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices. Available at. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. Accessed May 10, 2024.

73. Roig-Merino A, Urban M, Bozza M, et al. An episomal DNA vector platform for the persistent genetic modification of pluripotent stem cells and their differentiated progeny. *Stem Cell Reports.* Jan 11 2022;17(1):143-158. PMID 34942088

74. Report at a glance: hemophilia a and b. 2022; https://icer.org/wp-content/uploads/2022/12/Hemophilia-RAAG_December-2022.pdf. Accessed Dec 6, 2024.

75. Executive Summary: X-linked adrenoleukodystrophy (X-ALD) to the Recommended Uniform Screening Panel. Available at. https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/x-ald-exsum.pdf. Accessed Sep 11, 2023.

76. Lohr KN. Assessing health status and quality-of-life instruments: Attributes and review criteria. *Quality of Life Research.* 2002/05/01 2002;11(3):193-205. PMID

77. Weinfurt KP. Constructing arguments for the interpretation and use of patient-reported outcome measures in research: an application of modern validity theory. *Qual Life Res.* Jun 2021;30(6):1715-1722. PMID 33630235

78. Boateng GO, Neilands TB, Frongillo EA, et al. Best Practices for Developing and Validating Scales for Health, Social, and Behavioral Research: A Primer. *Front Public Health.* 2018;6:149. PMID 29942800

79. Chung DC, McCague S, Yu ZF, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. *Clin Exp Ophthalmol.* Apr 2018;46(3):247-259. PMID 28697537

80. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med.* Apr 1989;8(4):431-440. PMID 2727467

81. Fleming TR. Surrogate endpoints and FDA's accelerated approval process. *Health Aff (Millwood).* Jan-Feb 2005;24(1):67-78. PMID 15647217

82. Prescribing label: SKYSONA® (elivaldogene autotemcel) suspension for intravenous infusion. Initial U.S. Approval: 2022. Available at https://www.bluebirdbio.com/-/media/bluebirdbio/Corporate%20COM/Files/SKYSONA/SKYSONA_prescribing_information.pdf. Accessed August 6, 2024.

83. Prescribing Label: ZOLGENSMA® (onasemnogene abeparvovec-xioi) suspension, for intravenous infusion. Initial U.S. Approval: 2019. Available at. https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf. Accessed August 8, 2024.

84. Prescribing Label: ROCTAVIAN (valoctocogene roxaparvovec-rvox) suspension for intravenous infusion. Initial U.S. Approval: 2023. https://d34r3hkxgxjdtw.cloudfront.net/6f836309-d95f-42af-b717-2efa058ad82d/78bf2bcb-7068-4774-b962-a35c53704fc1/78bf2bcb-7068-4774-b962-a35c53704fc1_source__v.pdf. Accessed August 6, 2024.

85. Deshmukh AD, Kesselheim AS, Rome BN. Timing of Confirmatory Trials for Drugs Granted Accelerated Approval Based on Surrogate Measures From 2012 to 2021. *JAMA Health Forum.* Mar 3 2023;4(3):e230217. PMID 37000434

86. US Department of Health and Human Services. Office of Inspector General Report number: OEI-01-21-00401. Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns. Published Sep 9, 2022. Available at https://oig.hhs.gov/reports-and-publications/all-reports-and-publications/delays-in-confirmatory-trials-for-drug-applications-granted-fdas-accelerated-approval-raise-concerns/, August 15, 2024.

87. Odouard IC, Ballreich J, Lee B, et al. Clinical Evidence Supporting FDA Approval of Gene and RNA Therapies for Rare Inherited Conditions. *Paediatr Drugs.* Aug 5 2024. PMID 39102172

88. Prescribing Label: ELEVIDYS (delandistrogene moxeparvovec-rokl) suspension, for intravenous infusion. Initial U.S. Approval: 2023. https://www.elevidyshcp.com/pi. Accessed August 6, 2024.

89. Konkle BA, Peyvandi F, Coffin D, et al. Landmark endorsement of a global registry: The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), publicly endorses World Federation of Hemophilia Gene Therapy Registry as global standard. *Haemophilia.* Jan 2024;30(1):232-235. PMID 38111095

90. Miesbach W, Konkle B, Chowdary P, et al. Recommendations for a minimum data set for monitoring gene therapy in hemophilia: communication from the ISTH SSC Working Group on Gene Therapy. *J Thromb Haemost.* Jan 18 2024. PMID 38242208

91. CDC. What is Health Equity? Published June 11, 2024. Available at. https://www.cdc.gov/health-equity/what-is/index.html#:~:text=Health%20equity%20is%20the%20state,their%20highest%20level%20of%20health. Accessed July 25, 2024.

92. Wong CH, Li D, Wang N, et al. The estimated annual financial impact of gene therapy in the United States. *Gene Ther.* Nov 2023;30(10-11):761-773. PMID 37935855

93. CMS Launches Action Plan for Sickle Cell Disease Month. By: CMS Administrator Chiquita Brooks-LaSure and Acting Director CMS Office of Minority Health, Dr. Aditi Mallick. Published Sep 28, 2023. Available at. https://www.cms.gov/blog/cms-launches-action-plan-sickle-cell-disease-month. Accessed November 13, 2024.

94. U.S Government Accountability Office. Why Health Care Is Harder to Access in Rural America? Published May 16, 2023. Available at https://www.gao.gov/blog/why-health-care-harder-access-rural-america. Accessed July 25, 2024, .

95. Hoffman KM, Trawalter S, Axt JR, et al. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci U S A.* Apr 19 2016;113(16):4296-4301. PMID 27044069

96. Lee L, Smith-Whitley K, Banks S, et al. Reducing Health Care Disparities in Sickle Cell Disease: A Review. *Public Health Rep.* Nov/Dec 2019;134(6):599-607. PMID 31600481

97. Labbe E, Herbert D, Haynes J. Physicians' attitude and practices in sickle cell disease pain management. *J Palliat Care.* Winter 2005;21(4):246-251. PMID 16483093

98. Steele E. How Genetic Factors Contribute to Racial Health Disparities? Psychology Today. Published July 21, 2024. Accessed July 25, 2024.

99. NEWDIGS. Paying for Cures. Available at https://newdigs.tuftsmedicalcenter.org/payingforcures/. Accessed May 8, 2024.

100. bluebird bio Announces First Outcomes-Based Agreement with Medicaid for Sickle Cell Disease Gene Therapy. Available at. https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-first-outcomes-based-agreement-medicaid. Accessed August 7, 2024.

101. REIMBURSEMENT GUIDE ROCTAVIAN™ (valoctocogene roxaparvovec-rvox). Avialable at https://hcp.biomarin.com/en-us/roctavian/wp-content/uploads/sites/3/2023/08/ROCTAVIAN-Reimbursement-Guide.pdf?v=0.85. Accessed August 7, 2024.

102. Press Release: bluebird bio Announces Launch in Germany of ZYNTEGLO™ (autologous CD34+ cells encoding βA-T87Q-globin gene) Gene Therapy for Patients 12 Years and Older with Transfusion-Dependent β-Thalassemia Who Do Not Have $\beta^0/\beta 0$ Genotype. Jan. 13, 2020. Available at https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-launch-germany-zynteglotm-autologous-cd34. Accessed August 7, 2024.

103. Tepper N. Blue Cross first to open sickle cell gene therapy floodgates. Published in Modern Healthcare on January 19, 2024. Available at https://www.modernhealthcare.com/insurance/sickle-cell-gene-therapy-blue-cross-insurers-medicare-medicaid. Accessed August 14, 2024.

104. New Medicare, Manufacturer Coverage Are Among Solutions for Cell and Gene Therapies. Published 2024. Available at. https://www.mmitnetwork.com/aishealth/spotlight-on-market-access/new-medicare-manufacturer-coverage-are-among-solutions-for-cell-and-gene-therapies/. Accessed September 13, 2024.

## List of Abbreviations

AAV: adeno-associated viral vector
ABR: annualized bleeding rate
ALT: alanine transaminase
CALD: cerebral adrenoleukodystrophy
CE: cost effectiveness
CEA: cost effectiveness analysis
CI: confidence interval
CMS: Center for Medicare and Medicaid
CRISPR: clustered regularly interspaced short palindromic repeats
DMD: Duchenne muscular dystrophy
EMA: European Medicines Agency
EU: European Union
FDA: Food and Drug Administration
LTFU: lost to follow-up
LVV: lentiviral vector
MFD: major functional disabilities
MLD: metachromatic leukodystrophy
NA: not available
NI: non-inferiority
NSAA: north star ambulatory assessment
QALY: quality adjusted life years
RCT: randomized controlled trial
RCTs: randomized controlled trials
SMA: spinal muscular atrophy
SMN: survival motor neuron
sVOC: severe vaso-occlusive crises
sVOE: severe vaso-occlusive events
TEC: Technology Evaluation Criteria
ULN: upper limit of normal
WAC: wholesale acquisition cost