Considerations and Challenges with Gene Therapies for Neuromuscular Diseases

Gene therapies are giving clinicians more options for treating genetic neuromuscular diseases. Over the past several years, gene therapies have been approved for spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD), and researchers have made significant progress toward developing new treatments that can slow or even halt the damage caused by neuromuscular diseases. However, even as science advances, challenges persist regarding cost, safety, and access.

Approved gene therapies

A breakthrough occurred in 2019, when the US Food and Drug Administration (FDA) approved onasemnogene abeparvovec-xioi (Zolgensma), a gene therapy for children under 2 years old with SMA. This therapy uses an adeno-associated virus (AAV) vector to deliver a functional copy of the missing or faulty SMN1 gene in a single infusion.

Zolgensma is most effective when administered early in life, ideally before symptoms appear. “Many of the individuals treated early have a very different experience of the disease,” says John Brandsema, MD, a pediatric neurologist at Children’s Hospital of Philadelphia. “It is stabilized and not nearly as impactful in terms of symptoms.”

So far, about 3,000 children have received Zolgensma in the United States, according to drugmaker Novartis.

In 2023, delandistrogene moxeparvovec (Elevidys) was approved for children with DMD between 4-5 years old. The following year, the approval was expanded to individuals 4 years and older. Elevidys uses microdystrophin, a shortened yet functional version of the dystrophin gene, which is small enough to fit in an AAV vector.

While these treatments offer new hope, they don't have the same effect on every patient. They may not be effective for patients whose disease progression is more advanced when they begin treatment, and there is always the risk of a strong adverse reaction.

In June 2025, Sarepta Therapeutics announced that a second patient had died of acute liver failure following treatment with Elevidys. In response, Sarepta halted the drug's use in nonambulatory boys with DMD and is reevaluating the drug's safety profile.

This highlights the importance of evaluating the balance between risk and reward when considering gene therapies.

Current gene therapy challenges

Most gene therapies use an AAV vector to carry the gene into the body. However, manufacturing pure and effective viral products at scale is difficult, according to Aravindhan Veerapandiyan, MD, a pediatric neurologist at Arkansas Children's Hospital. Some batches may contain "empty capsids," which are virus shells with no gene inside.

Using a viral vector as a delivery mechanism also limits the size of the gene to be delivered, as large genes like dystrophin won't fit in an AAV. Using shortened versions of genes, such as microdystrophin, may not be as effective as full-length genes.

Additionally, there is a risk associated with adenovirus immunogenicity. "We see many adverse effects with AAV-based gene therapies, particularly immune-related ones," Dr. Veerapandiyan says. "This underscores the need to explore non-viral approaches, which are still in early stages of development."

Another consideration is whether a patient has preexisting immunity to adenoviruses. Adenovirus infections are common in humans, and preexisting immunity can neutralize the viral vector before it reaches target cells, reducing the therapeutic effect. Before receiving an AAV gene therapy, a patient must be tested for antibodies to the virus.

"If people have antibodies, they cannot be dosed," Dr. Brandsema says. Researchers have not yet solved the question of how to dose people who have preexisting immunity or redose patients who have already received an AAV gene therapy.

Considerations for administering gene therapies

Administering a gene therapy requires preparation before and close follow-up after the intravenous (IV) infusion. Before treatment, the care team should ensure that the patient or their parents or guardians understand the potential risks. The patient must be in good health going into the treatment.

John Brandsema, MD
Pediatric Neurologist
Children's Hospital of Philadelphia

After the infusion, the care team will continue to monitor the patient, and they may need to isolate for about two months to avoid infections while their body adjusts to the therapy. If the patient experiences side effects, the team must be ready to respond quickly. Rare but serious reactions have included liver damage, heart inflammation, and even death.

Aravindhan Veerapandiyan, MD
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"It takes an experienced, interdisciplinary team to deliver gene therapy," Dr. Brandsema says. "We need perspectives from people like hepatologists, immunologists, and others besides the standard care team members, like cardiologists and pulmonary specialists."

Barriers to access

The high cost of gene therapies and specialized care required to administer them make it difficult for many families to access them, especially in rural or low-income communities.

"Within the neuromuscular community, certain families are especially proactive and have the ability to travel wherever necessary to pursue these therapies," Dr. Veerapandiyan says. "Then there are others who struggle just to get to the clinic for their regular care."

Zolgensma carries a price tag of $2.1 million for a one-time dose, while Elevidys costs $3.2 million for a dose. Health insurance may cover the treatment through medical benefits, rather than prescription drug coverage. However, first, the hospital and insurer must work out a single case agreement (SCA) to handle payment. An SCA is a one-time contract negotiated between the healthcare provider and insurer to provide coverage for a specialized treatment or out-of-network provider not covered by the insurance plan.

"I don't think the price is going to come down," Dr. Veerapandiyan says. "Centers need to create strategies to implement equity and make sure every single person who is eligible for gene therapy has the opportunity to think about it and discuss it with their clinicians."

What's next for gene therapy?

Researchers are developing numerous new gene therapies, including some that use gene editing tools like CRISPR to modify a patient's DNA. Gene editing methods may lead to fewer side effects and could be effective even for patients who have antibodies to viral vectors.

Dr. Brandsema also hopes that more therapies will become available for rare diseases that currently have no options.

"We care for dozens of disorders, and it's challenging when people with rarer diseases feel left out," he says. "I hope gene therapy will become an option for more patients."

There is also progress in diagnosing and treating genetic diseases earlier. For example, newborn screening for SMA has enabled doctors to treat the disease before symptoms appear, resulting in better outcomes.

"Every step forward opens the door to new possibilities for diseases we couldn't treat before, and for patients who previously had no options," Dr. Veerapandiyan says.

MDA Resources

- MDA's Gene Therapy Support Network provides resources for patients and families, as well as education and professional resources for medical providers (scroll down to "Gene Therapy Clinician Support").
- The Quest Media Gene Therapy content library includes updates on therapy approvals and development, and useful articles about gene therapy concepts and community members' experiences.
- MDA's Newborn Screening for Neuromuscular Diseases page provides information and resources related to newborn screening.