



News & Highlights

Gene Therapy Sounds and Looks Promising for Inherited Deafness and Blindness



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At a February 2025 meeting, researchers presented their latest findings from a phase 1/2 clinical trial of a gene therapy, DB-OTO, developed by Regeneron Pharmaceuticals (Tarrytown, NY, USA) for a particular type of profound hearing loss in children. Nearly all the 12 participants, with no serious adverse events, experienced clinically meaningful and durable hearing improvements [1]. A toddler born deaf, for example, could hear well enough after treatment to quack when asked, “What sound does a duck make?” [2].

Gene therapies are also demonstrating significant and sustained visual gains in children with congenital blindness. In a February 2025 report published in *The Lancet*, a gene therapy, adeno-associated viral (AAV)-*AIPL1*, from MeiraGTx (New York, NY, USA) improved sight in four children born legally blind with a particular type of early-onset retinal disease [3]. After undergoing the 60 min procedure, the children developed the ability to see small objects, shapes, toys, and their parents’ faces (Fig. 1). The trial has now treated an additional seven children, all of whom gained visual acuity [4]; several treated with the therapy have learned to read and write [5].

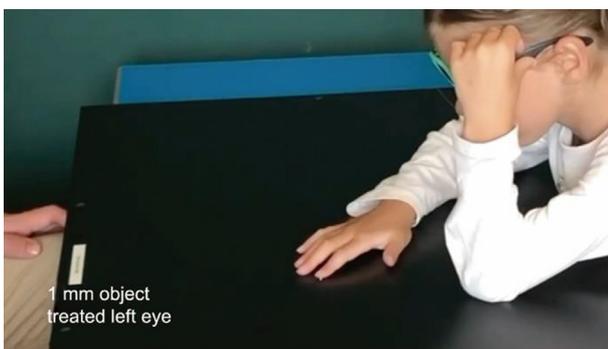


Fig. 1. Born blind with Leber congenital amaurosis, a rare, inherited type of early-onset retinal disease that causes the degeneration of the cone and rod cells in the retina, this child was able to find a 1 mm white object with her treated eye after receiving AAV-*AIPL1*, a gene therapy developed by MeiraGTx. The therapy is available under a special license for physician-led studies outside of commercial clinical development for rare degenerative disorders with no other treatment options. Credit: MeiraGTx, with permission.

“There are some wonderful human stories, and those are pushing research ahead,” said Ian MacDonald, an ophthalmic genetics expert and professor and director of ophthalmology at the University of Montreal in Quebec, Canada. “It changes somebody’s life to be able to see better.”

Technical advances and biological insights have pushed numerous gene therapies into the pharmaceutical development pipeline. The Regeneron and MeiraGTx gene therapies are just two of many. The eye and ear have complex anatomy and development, requiring hundreds of genes to function correctly for these structures to operate as they should. Mutations—mostly inherited but some arising spontaneously—in at least 300 genes are known to cause more than 20 recognized retinal diseases [6], and one in 1300 individuals has such a mutation [7]. “Inherited retinal diseases affect 4 million or more people worldwide, and those are almost all monogenic,” said Ben Shaberman, vice-president of scientific communications at the Foundation Fighting Blindness in Columbia, MD, USA. “That is where gene therapy is potentially a great option.”

Similarly, at least 150 genes are involved in hearing, and dysfunction due to mutations in one of them can cause deafness [8]. “The inner ear has many different cells, each one playing an important role, and as a result, if you have a defect in any of the cells, their function, or their cell survival, you can have hearing loss,” said Zheng-Yi Chen, a professor of otolaryngology at Harvard Medical School in Boston, MA, USA.

About half of the approximately 1.3 of every 1000 cases of congenital deafness in the United States have a genetic cause [8,9]. Children may additionally develop genetic deafness as they age, and there are more than 30 million people with such hearing loss worldwide [9]. “Genetic hearing loss can be very profound. Many are born completely deaf and are unable to speak without interventions,” said Chen. This is why newborn hearing screenings are essential, he said. “We have to actively implement interventions, including cochlear implants, hearing aids, or sign language, within the first three years of life.” These interventions have limitations, including the need for regular surgeries and poor sound quality, especially in noisy environments [10].

Current standard treatments for genetic retinal diseases are similarly limited [11]. There is, however, one gene therapy treatment commercially available for an inherited retinal disease: Luxturna (voretigene neparvovec-rzyl), developed by Spark

Therapeutics (Philadelphia, PA, USA) and approved by the United States Food and Drug Administration in December 2017 [12]. Spark became a subsidiary of Roche, the Swiss pharmaceutical giant when it purchased the smaller company for 4.8 billion USD in 2019. Luxturna treats Leber congenital amaurosis (LCA)-2 [13] and retinitis pigmentosa (RP) [14], both caused by a mutated *RPE65* gene; the gene codes for an enzyme that recycles visual pigments in the retina's photoreceptor cells, which turn light signals into neural signals. Luxturna includes a working *RPE65* gene encoded into a circle of DNA called a plasmid and packaged into an AAV vector that is injected into the retina (Fig. 2). These virus-mimic constructs (Fig. 3) do not cause human disease and can be modified to target many cell types, which makes them a common delivery method for gene therapy. The retina cells take up the AAV and start expressing the introduced DNA, in effect fixing the defective recycling pathway. One year after treatment in the phase 3 trial, 65% of patients who were previously blind could navigate a maze in very dim light [15].

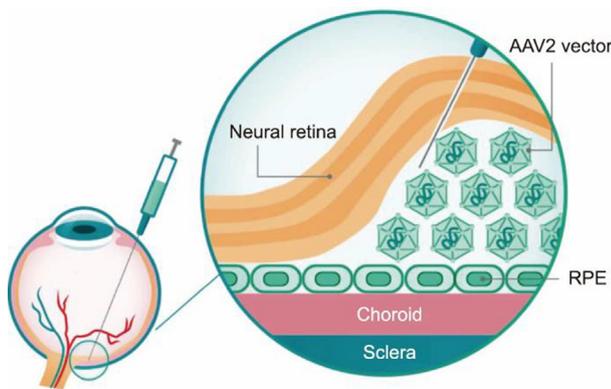


Fig. 2. The gene therapy Luxturna, developed by Spark Therapeutics and approved for commercial use in 2017, delivers a replacement gene for mutated *RPE65* via an AAV2 vector. The *RPE65* gene is defective in some forms of the retinal diseases Leber congenital amaurosis and retinitis pigmentosa. In a delicate, highly specialized surgery, a retinal specialist injects the vector under the eye's retina cells. The cells, that take up the AAV, express the introduced gene and produce the normal protein. RPE: retinal pigment epithelium. Credit: Spark Therapeutics, with permission.

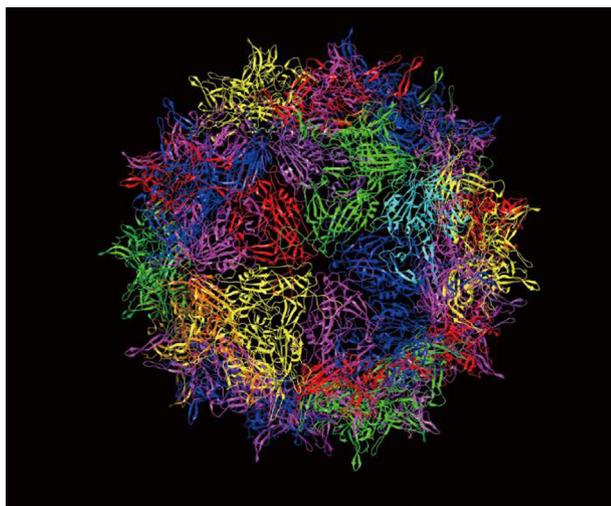


Fig. 3. This ribbon diagram of proteins displays the front half of an AAV2 capsid. Such virus-mimic constructs do not cause human disease and can be modified to target many cell types, making them a common delivery vehicle for gene therapy. Credit: Jazzlw/Wikimedia Commons (CC BY-SA 4.0).

However, the mutated *RPE65* gene that Luxturna targets causes only around 10% of LCA cases [16]; there are at least 20 other genes that, if dysfunctional, can cause some type of LCA [17]. Vision loss typically starts in infancy with LCA and in the teen years for RP, starting with night blindness and peripheral vision loss. “There is a lot of variation in how severe the broad spectrum of inherited retinal disorders can be and how much vision they ultimately take,” Shaberman said. Some patients eventually lose their sight completely [14]. “In many cases, they are considered legally blind by age 40,” Shaberman said. Because of the heterogeneity of genetic retinal diseases, including LCA and RP, no one gene therapy will address all of them—many different gene therapies are needed.

Several other clinical trials of gene therapy for inherited blindness have recently reported promising results. These include one testing Atsena Therapeutic's (Durham, NC, USA) ATSN-101, an AAV5 vector that delivers a normal *GUCY2D* gene to treat patients with LCA1. Phase 1/2 trial results published in September 2024 reported significant vision improvement at the therapy's highest dose [18]. The company is preparing for a phase 3 trial and is collaborating with Nippon Shinyaku (Kyoto, Japan) to eventually commercialize the therapy [19].

Unlike most gene therapies that are precisely targeted to one gene and a specific mutation, OCU400 from Ocugen (Malvern, PA, USA) targets an underlying pathway in many inherited retinal diseases, including *RHO* mutations, the most common cause of RP. Via an AAV5 vector, OCU400 delivers a “master regulator” gene, *NR2E3*, that maintains homeostasis in retinal cells. In phase 1/2 results, released in January 2025, the nine patients who received treatment 2 years earlier showed improvement or preservation of visual function; a phase 3 trial is now underway [20].

Another target of gene therapies in later-stage clinical trials is X-linked RP (XLRP), which primarily affects males. The causative gene, *RPGR*, crucial for cilia function and maintenance, is on the X chromosome [21]. In phase 1/2 trial results, published in November 2024, Johnson & Johnson's (New Brunswick, NJ, USA) botareti-gene sparoparvovec, an AAV5 gene therapy for XLRP, showed significant functional vision improvements in patients, including reduced time to navigate a vision-guided mobility maze [22]. Another AAV treatment for XLRP, AGTC-501 (Iaru-zova) from Beacon Therapeutics (Alachua, FL, USA), has also shown improvements in vision in low light [23]. Both therapies are in late-phase clinical trials.

EDIT-101, a gene-editing therapy developed by Editas Medicine (Cambridge, MA, USA), employs a more complicated but perhaps more lasting CRISPR-based approach. CRISPR—clustered regularly interspaced short palindromic repeats—is a set of molecular mechanisms bacteria used to identify and destroy viral genes [24]. The mechanism, used in several now approved—but very expensive—therapies [25], homes in on a specific spot in a DNA strand and cuts it, changing or deleting sections of the existing gene. EDIT-101 uses targeted CRISPR molecules to edit a mutation in *CEP290*, restoring function and enabling photoreceptor cells to work properly. The phase 1/2 trial results, published in May 2024, showed measurable improvements in most patients [26].

For genetic hearing loss, gene therapy development and trials have mostly focused on *OTOF*, the gene for otoferlin, a protein that relays signals from the ear hair cells to the auditory nerve fibers, enabling sound to be processed by the brain [27]. Mutations in *OTOF* are responsible for between 1.4% and 3.2% of all congenital deafness, affecting around 200 000 people worldwide [28]. Three companies are conducting clinical trials of gene therapy targeting *OTOF*. Chen co-led the first *OTOF* gene therapy clinical trial, which tested RRG-003, developed by Refreshgene Therapeutics (Shanghai, China). Findings published in January 2024 reported restored hearing in five of the six subjects who were born deaf and responded to sound within weeks of receiving the therapy.

In a few months, they danced to music, and, within a year, some were able to speak [29]. Additional results published in June 2024 from trials of patients treated in both ears were also positive [30]. “The children in the trial are born completely without any hearing,” Chen said. “It was the first time in history that hearing has been restored in humans.”

The other *OTOF* targeted gene therapies in clinical trials include the previously mentioned DB-OTO from Regeneron and AK-OTOF, which is being developed by Akouos (Boston, MA, USA), a wholly owned subsidiary of Lilly (Indianapolis, IN, USA). At the Association for Research in Otolaryngology’s MidWinter Meeting in February 2024, researchers reported that the first trial subject receiving AK-OTOF achieved near-normal hearing levels within 30 days of treatment [31].

While the trial results suggest that gene therapy promises to be life-changing for those that can be treated, only a minority of patients with genetic deafness will benefit, as *OTOF* gene mutations only account for a small percentage of patients with genetic hearing loss. Many more mutations must be discovered and treated to meet the substantial needs of affected individuals. As with genetic blindness, there will be, unfortunately, no one gene therapy option that fixes all genetic deafness. Hundreds of different genes may play a role, meaning treatments will likely need to be tailored to every gene and mutation that might be involved.

And, in many cases, mutations may have already damaged the delicate structures of the eye or ear before birth, so gene therapy is no longer an option when the condition is detected. For gene therapy to work, normal ear or eye cells must exist and be in the correct place. “This is a problem for gene therapy in general—for it to work, you have to have a viable target cell,” Chen said. “If the cells do not develop properly or degenerate, you cannot restore function—that is a big hurdle.”

When approved, these gene therapies will carry substantial price tags, likely hundreds of thousands of USD, or more, per treatment. Luxturna, the approved LCA treatment, costs 425 000 USD per eye [32]. “Yes, it is expensive,” Shaberman said. “But this is a one-time therapy that will hopefully last a lifetime.” The price is still less expensive than the gene-editing therapies that have been approved to date, which can cost as much as 4 million USD and involve *ex vivo* procedures and long hospital stays with chemotherapy ablation of the bone marrow [25].

Regarding the cost, it also remains to be determined how long AAV-based therapies will reliably express their target genes. “These are non-integrating viral products—the genes are not becoming a part of the patient’s genome. They are staying there, floating around, probably okay for some years, but then we may have to re-treat for some of these gene therapies,” MacDonald said. Research in non-human primates has shown that such delivered genes can last for decades, but this kind of data could take a long time to collect for humans [33].

Another issue for these therapies is the cost of the research, development, and clinical trial process to get them approved. “It costs a lot of money to develop these products, and the market is very small for each treatment,” MacDonald said. In some cases, this means even successful gene therapies may never make it to market. For instance, in November 2022, Editas Medicine paused enrollment in its EDIT-101 trials to seek a new commercial partner [34]. As of March 2025, there have been no public updates regarding the company’s success in finding a new collaborative sponsor.

“Thankfully, some companies get into the business because their heart is in the right place,” Shaberman said. But “there is a model for advancing gene therapies for regulatory approval as a small company.” For example, he said, with grants from the Foundation Fighting Blindness and the National Eye Institute, Shannon Boye, professor of ophthalmology and chief of cellular and molecular therapy at the University of Florida (Gainesville,

FL, USA), co-founded Atsena [35], a biotech that now has two gene therapies for inherited retinal diseases in early clinical trials.

For dedicated researchers and pharmaceutical companies, there appear to be many opportunities to create gene therapies for genetic deafness and blindness that could substantially improve patients’ lives. “I am super excited—many groups are working on different types of genetic hearing loss,” Chen said. “In the next five years, many trials will be conducted, and maybe a gene therapy will even get approved by the Food and Drug Administration (FDA). At least for hearing loss, we are really in the golden age of gene therapy.”

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