Sensorion

Gene Therapy Information For Families

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Gene Therapy for Hearing Loss

How Gene Therapy Works

- Gene therapy aims to address the underlying cause of disease, such as changes in our genes. If genes are like the blueprint to our body, **gene therapy can fill in missing parts or correct errors** in the drawings.

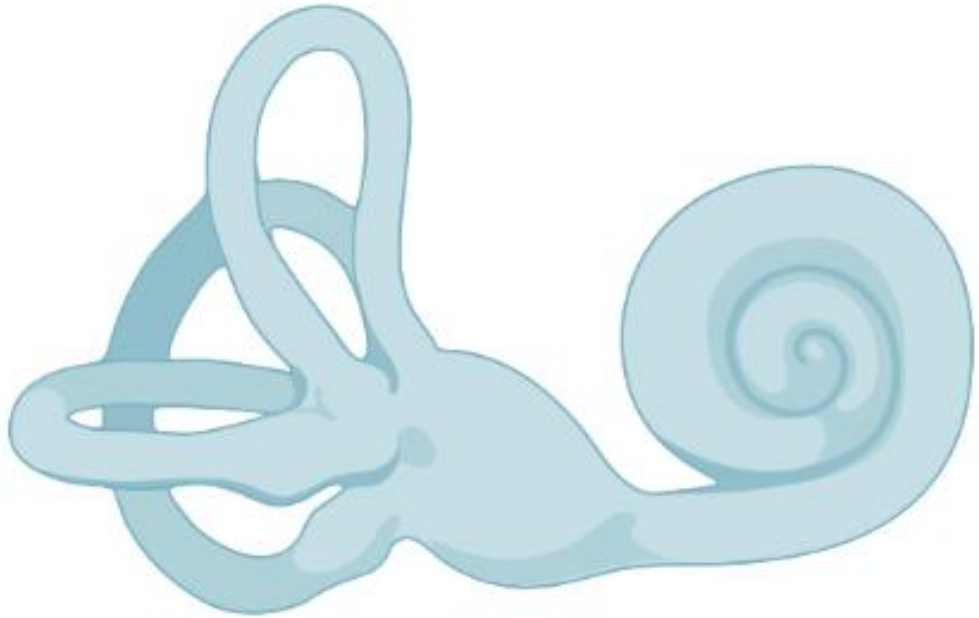
- Gene therapy is the **use of genetic material** to treat or prevent disease. The **genetic material** that is **delivered**, DNA or RNA, **has instructions to change how a protein**—or group of proteins—**is produced by the cell**. For some diseases, this means making changes to account for too much, not enough, or incorrect essential proteins being produced within cells.

- This new genetic material, such as a working gene, is **delivered into the cell using a vector**. A vector is like a package used to deliver a specific message. **Viruses can be used as vectors** because they have evolved to be very good at getting into cells. Scientists have learned how to remove the viral genes and use this same ability to treat or prevent disease. In this case, **their goal is to insert the new genetic material into the cell**.

Source: ASGCT.org: gene Therapy Basics

The Cochlea Is a Suitable Target Organ for Gene Therapy

- **Precision**: **The inner ear is enclosed**, making it easier to deliver the treatment specifically to the desired spot without it spreading to other parts of the body and reduces potential side effects.
- **Small amount/volume is needed**: The inner ear is small, so only a **tiny amount of the treatment** is needed.
- **One-time delivery**: The cells in the inner ear being targeted don't divide or renew, so **a single treatment** can provide lifelong benefits.
- **Anatomy fully developed at birth:** Treatment can be applied early in life as **there are no significant structural changes that are going to occur and will affect the therapy's effectiveness**.



Process

GENETIC TESTING

- To complete genetic testing, a swab of the child's saliva or blood is analyzed.

PRE-SURGICAL CARE

- Corticosteroids are typically delivered before the injection to weaken the immune system. This prevents the immune system from attacking or preventing the treatment from being successful. Steroids are continued for a few weeks.

SURGERY

- Duration is ~2 hours
- Children may stay in the hospital a few days to monitor for any adverse event (inflammation, systemic reactions, such as fever or fatigue, etc.) as this can impact the safety and effectiveness of the gene therapy.

- *Images: https://www.canva.com/photos/MAFlNrjUNPY-happy-parents-with-baby-talking-to-pediatric-nurse-at-medical-clinic-/*
- *Image: https://www.pexels.com/photo/surgeon-performing-an-operation-6291248/*

Post Surgical Timeline

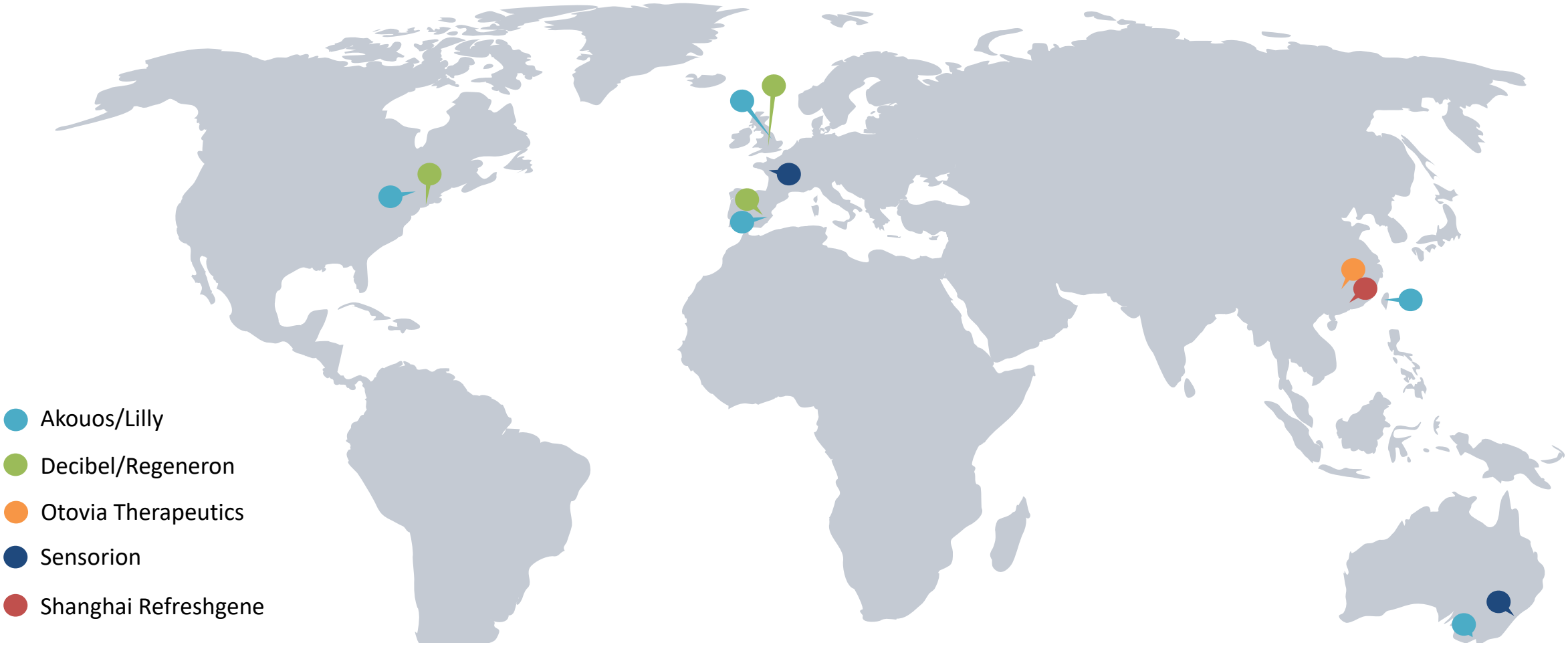
- Several visits mandatory for at least 1 year
- In general, an initial response may be observed within 30 – 90 days.
- Variables which may contribute to different outcomes and timeline:
  - the product (AAV serotype, promoter, manufacturing process)
  - the population (prior CI, contralateral CI + gene therapy, etc)
  - residual cell function

- *Image: https://www.canva.com/photos/MAERLRhT5ho-a-mom-watching-her-child-play-music/*

Clinical Trials & Current Outcomes

Otoferlin Gene Therapy: First Indication in Clinical Trial

Clinical Trial Locations



- https://clinicaltrials.gov/study/NCT05788536?term=db-oto&rank=1
- Https://clinicaltrials.gov/study/NCT06370351?term=sens-501&rank=1
- https://clinicaltrials.gov/study/NCT05821959?term=ak-otof&rank=3
- https://clinicaltrials.gov/study/NCT05901480?term=otovia&rank=1
- *Lv J, Wang H, Cheng X, et al. AAV1-hOTOF gene therapy for autosomal recessive deafness 9: a single-arm trial [published correction appears in Lancet. 2024 May 25;403(10441):2292. doi: 10.1016/S0140-6736(24)01040-7]. Lancet. 2024;403(10441):2317-2325. doi:10.1016/S0140-6736(23)02874-X*

Summary of Outcomes

These studies suggest:

- **Safety and Side Effects**
  - Good safety with mostly mild side effects.
  - Ongoing monitoring is necessary to comment on long-term safety with the gene therapy.
- **Hearing Sensitivity and Auditory Skill Improvement**
  - Improvement in hearing thresholds, both by ABR and pure tone audiometry, are seen over the months following surgery.
  - Progress in auditory development and speech perception.
  - Bilateral treatment suggests improvement in localization though further data is needed.
- **Limitations and Future Research Needs**
  - Current outcomes are limited to a short time duration, and all measures warrant ongoing monitoring to determine further progress.
  - Measures such as speech recognition in varying scenarios, language development, etc. are more widely needed to better understand the amount of benefit.
  - Improvement in hearing sensitivity may not occur for all children.

An Introductory Guide to Genetic Hearing Loss, Genetic Testing, & Gene Therapy

Clinical Trial Results: What We Know So Far

Safety and Side Effects

- So far, the treatment has been well tolerated, with only possible mild side effects, such as a mild fever.
- Children will be monitored to better understand long-term safety and hearing progress.

Changes in Hearing and Listening

- Initial hearing improvements may be seen within 30 – 90 days after surgery.
- These changes happen gradually, and the amount of improvement can differ from one child to another.
- Variables such as the surgical approach, the child's age, the residual inner ear function, or the components of the gene therapy may contribute to timing and the amount of improvement in hearing.
- Some children may still need a hearing aid or cochlear implant after gene therapy to help them ensure access to sound.

Progress in Listening Skills

- For some children, whether treated in one or both ears, progress in auditory development and understanding of speech has been shown. More long-term research is needed to understand what outcomes to expect for each child.

What Parents Can Do to Support Their Child's Development

Don't Delay Access to Sound

- Early sound input is essential for brain development and spoken language. If the brain does not receive sound in the first years of life, some areas may not fully develop. Gene therapy for hearing loss holds real promise, but it's still in clinical trials. In the meantime, it's important to ensure a child gets the best possible access to sound as early as possible.

Develop Early Communication Skills

- Obtain support to develop early parent – child interaction to encourage communication and spoken language.

Track Progress Over Time

- Regularly monitor a child's hearing and language development to ensure they're getting the right support and to make changes, if needed.

Explore Genetic Testing

- Results may offer insight into the cause of hearing loss and how hearing may change over time and whether future treatments, like gene therapy, may be an option. A genetic counsellor can also help explain the results.

Connect with Other Families

- Sharing experiences and resources with other parents can be really helpful and can help decision-making and in managing expectations.

Stay Updated on New Research

- Stay up to date about research and clinical trials, including gene therapy, to keep informed about current and future treatment options.

This leaflet developed by:

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sensorion.com

2025

An Introductory Guide to

Genetic Hearing Loss, Genetic Testing, & Gene Therapy

Newborn hearing screening identifies hearing loss early, enabling children to receive timely access to sound amplification, and family support.

For many children, genetic testing can help identify the cause of hearing loss - if it's hereditary, part of a broader condition, or due to other factors.

There is growing interest in gene therapy, which aims to improve hearing by targeting specific genetic causes of hearing loss in the inner ear.

Genes and Genetic Testing

- In about 80% of children born with hearing loss, the cause is genetic.
- Genes contain the genetic code that directs how the body develops and functions. If a gene changes, it can affect how the body functions - including hearing.
- Genetic testing may help identify if a child's hearing loss is caused by a change in a gene.
- Knowing the cause helps parents and the child's care team make more informed choices for the child.
- While genetic testing is not yet available everywhere, it is important to think about future options for a child, including potential gene therapy.

...eted Treatment Based on Genetics:

...Therapy

- ...50 genes are known to cause hearing loss on ...vn, and more than 400 genetic conditions ...hearing loss as one of their features.
- ...apy must target the specific gene ...ene therapy developed for one gene ...r other genetic causes of hearing loss.
- ...gene therapy is being studied in humans ...e gene: OTOF.
- The OTOF gene produces otoferlin, a protein which is essential for sending sound signals from the ear to the brain. OTOF-related hearing loss is rare, accounting for only 3–8% of cases in children born with hearing loss that is not part of another medical condition.
- Gene therapy for OTOF is still only available through research trials in several countries.
- Gene therapy for OTOF only targets the inner ear. It does not change your child's entire genetic code, so the genetic condition can still be inherited by future generations.
- Researchers are developing gene therapies for other causes of genetic hearing loss, but these are still experimental.

FROM TESTING TO TREATMENT: THE GENE THERAPY PROCESS

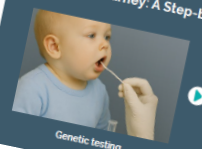
Genetic Testing

- A sample of a child's saliva or blood is taken and sent to a lab to look for changes in genes that are known to cause hearing loss.
- If results indicate a genetic cause of deafness, gene therapy may be an option. The child's doctor or genetic counsellor will explain the results to the family and help guide the next steps.

Eligibility and Timing of Gene Therapy

- Currently, children of various ages are being included in clinical trials. However, the greatest possible benefit is expected to be in the youngest, when the brain can develop hearing and spoken language more easily from sound input.
- While the current gene therapy trials in children are focused on the OTOF gene, there is ongoing research to explore gene therapy in adults targeting other genes associated with hearing loss.
- Gene therapy is likely to only be possible in ears that do not already have a cochlear implant. This is because after a cochlear implant is inserted, the inner ear forms scar tissue which may block the gene therapy from working.
- In the future, gene therapy is likely to be considered as the first step for some children.
- The use of hearing aids before gene therapy will be considered by the care team.

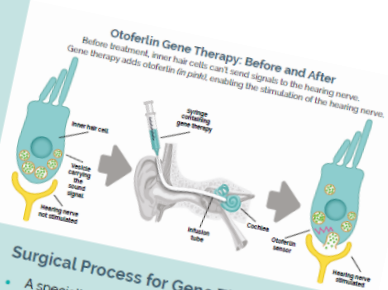
A Child's Journey: A Step-by-Step Overview


Genetic testing


Gene therapy injection


Monitoring health after surgery


Monitoring hearing progress after surgery



Surgical Process for Gene Therapy

- A specially trained ear surgeon places the treatment directly into the cochlea under general anaesthesia.
- Corticosteroids are usually given for a short time before and after surgery to lower the body's immune response to gene therapy. This helps the gene therapy be more effective.
- During surgery, the doctor creates a pathway to the cochlea to deliver the gene therapy directly to where it is needed.
- Using a special tool, the doctor places the gene therapy into the cochlea. The healthy copies of the gene are transported by a tiny virus that safely carries them to the right place, allowing the ear to make proteins needed for hearing.
- Surgery typically takes two hours, followed by a short hospital stay for monitoring. As with any surgery, there are risks, but these are generally low and will be discussed by the child's care team with the family. Follow-up visits will check healing and how well the treatment is working.
- Gene therapy is designed to be a single treatment. Once the specific cells receive the correct gene, they can continue working for life.

THANK YOU

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