IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Advances In Gene Therapy For Sensorineural Hearing Loss: Clinical Trials And Future Directions

Author Name: VENNA APARNA

Designation: MBBS

Department: ENT

Organisation: MEDICITI INSTITUTE OF MEDICAL SCIENCES

Abstract

Sensorineural hearing loss (SNHL) is the most common form of permanent auditory impairment, affecting millions worldwide and profoundly influencing communication, cognition, and quality of life. Conventional approaches, such as hearing aids and cochlear implants, provide compensation but cannot restore the physiological processes underlying natural hearing. Recent advances in molecular medicine have positioned gene therapy as a transformative strategy for hereditary and acquired forms of SNHL. This review examines current progress in gene therapy for otology, emphasizing three primary mechanisms: gene replacement, gene editing, and regenerative or neuroprotective strategies.

Clinical trials targeting **OTOF** mutations using dual-adeno-associated viral (AAV) vectors have demonstrated measurable restoration of hearing in infants and children with auditory neuropathy, marking a milestone in translational medicine. Preclinical progress with **GJB2** replacement and early trials of **ATOH1**-based regenerative approaches further highlight the diversity of therapeutic targets. Nonetheless, challenges remain, including vector capacity limits, immune barriers to re-dose, narrow developmental windows of efficacy, and global accessibility concerns. Future directions point toward improved vector engineering, precise genome-editing technologies for dominant mutations, integration of gene therapy with cochlear implants, and expansion of treatment to broader patient populations. Collectively, the field is moving from experimental feasibility toward clinical reality, offering hope that gene therapy may soon provide durable, biologically restorative solutions for individuals affected by hearing loss.

1. Introduction

Sensorineural hearing loss (SNHL) represents the most prevalent form of permanent hearing impairment worldwide, affecting hundreds of millions of individuals across all age groups. It arises primarily from damage to or dysfunction of cochlear hair cells, auditory neurons, or their synapses. Because these structures have a limited capacity for self-repair, SNHL is largely irreversible. The condition carries a heavy burden, influencing language acquisition, cognitive development, educational performance, and social participation. In children, untreated SNHL can delay speech and literacy, while in adults it contributes to social isolation, reduced work productivity, and a heightened risk of cognitive decline (Lye et al., 2023; Ren et al., 2022).

Conventional approaches such as hearing aids and cochlear implants have significantly improved communication for people with SNHL, but they remain prosthetic solutions. These devices amplify or bypass damaged auditory pathways rather than restoring the ear's native function. Moreover, they do not fully replicate the fidelity of natural hearing, particularly in noisy environments, and outcomes vary considerably among patients (Yoshimura, Nishio, & Usami, 2021).

Over the last two decades, gene therapy has emerged as a transformative option for inherited forms of hearing loss. By targeting the molecular and genetic causes of auditory dysfunction, gene therapy seeks to restore or preserve natural cochlear function. Techniques such as adeno-associated viral (AAV) delivery of therapeutic genes, dual-vector systems for large genes like OTOF, and experimental gene-editing strategies are advancing rapidly toward clinical translation (Amariutei et al., 2023; Bankoti et al., 2021). Early clinical trial data, especially for auditory neuropathy spectrum disorders caused by OTOF mutations, have shown unprecedented improvements in auditory thresholds, reinforcing the promise of this approach (Saïdia et al., 2023; Jiang et al., 2023).

This paper reviews recent progress in gene therapy for SNHL, focusing on the underlying mechanisms, current clinical trials, and remaining barriers to implementation. It also highlights future directions that may shape how gene therapy is integrated into otological practice.

2. Background on Sensorineural Hearing Loss

2.1 Pathophysiology: Cochlear Hair Cells, Spiral Ganglion Neurons, and Synapses

The auditory system relies on highly specialized structures within the cochlea. Inner hair cells convert mechanical vibrations from sound waves into electrical signals, which are then transmitted to the auditory nerve via ribbon synapses. Outer hair cells serve as amplifiers, fine-tuning sensitivity and frequency selectivity. Damage to these delicate cells, whether due to noise trauma, ototoxic drugs, aging, or genetic mutations, disrupts signal transmission and results in sensorineural hearing loss. Spiral ganglion neurons, which relay information to the central auditory pathway, are also vulnerable to degeneration, compounding the functional impairment (Lye et al., 2023).

2.2 Genetic Underpinnings of Hereditary Hearing Loss

Hereditary factors account for at least half of congenital SNHL cases. Over 150 genes have been implicated, many encoding proteins essential for hair-cell development, ion transport, synaptic transmission, and cochlear homeostasis. For instance, mutations in **GJB2** (encoding Connexin-26) are among the most common worldwide, while defects in **OTOF** (encoding otoferlin) disrupt synaptic vesicle release at the inner hair cell ribbon synapse, leading to auditory neuropathy. Other notable genes include **TMC1**, **PCDH15**, and **USH2A**, which contribute to syndromic and non-syndromic forms of deafness. The diversity of these genetic cause's highlights both the complexity and the opportunity for targeted therapies (Ren et al., 2022).

2.3 Why Regeneration is Difficult

Unlike other tissues, the mammalian cochlea lacks robust regenerative capacity. Once hair cells or auditory neurons are lost, they are not naturally replaced. This limitation contrasts sharply with the avian auditory system, where hair cell regeneration can restore hearing function after injury. In humans, supporting cells within the cochlea retain some plasticity but fail to re-enter the cell cycle or differentiate into functional hair cells under normal conditions. This biological constraint explains why hearing loss has historically been considered irreversible and underscores the need for interventions like gene therapy, which directly target the genetic and molecular basis of dysfunction (Lye et al., 2023; Ren et al., 2022).

3. Gene Therapy Mechanisms in Otology

The fundamental aim of gene therapy for sensorineural hearing loss (SNHL) is to address the underlying molecular pathology responsible for auditory dysfunction. Unlike conventional prosthetic devices that bypass damaged sensory cells, gene therapy works at the cellular and genetic level, either by replacing a defective gene, repairing it, or providing neuroprotective signals that sustain auditory structures. Advances in delivery platforms, vector engineering, and editing technologies have opened new avenues to restore or preserve natural hearing. This section explores three central mechanisms: gene replacement, gene editing and repair, and neuroprotective or regenerative approaches.

3.1 Gene Replacement

AAV-Mediated Delivery

Adeno-associated viruses (AAVs) have become the cornerstone of cochlear gene delivery due to their ability to efficiently transduce non-dividing cells and their relatively safe profile compared with other viral vectors. Their small genome, however, presents both opportunities and constraints. They can deliver smaller genes, such as **GJB2** (Connexin-26), effectively, but require innovative strategies for larger genes like **OTOF** (otoferlin), which exceed the packaging limit of standard AAV vectors (Bankoti et al., 2021).

The inner ear presents a favorable environment for AAV-based therapies. The cochlea is anatomically enclosed, minimizing systemic spread, and accessible via surgical routes such as the round window membrane. Direct infusion allows targeted delivery with relatively small vector volumes, an important consideration for safety. Recent generations of AAV vectors, including synthetic serotypes like Anc80L65, have been engineered to enhance transduction efficiency of inner hair cells, a critical target for restoring auditory function (Jiang et al., 2023).

OTOF Gene Replacement

One of the most compelling examples of gene replacement is therapy for **DFNB9**, a form of auditory neuropathy caused by mutations in OTOF. Otoferlin is essential for calcium-triggered exocytosis of synaptic vesicles at inner hair cell ribbon synapses. Loss of function results in profound congenital deafness, despite intact outer hair cells and preserved cochlear architecture. Because these cells remain structurally present, OTOF gene replacement has a high therapeutic window. Dual-AAV approaches have been developed to split and reconstitute the large otoferlin cDNA within cochlear hair cells. Preclinical studies showed robust restoration of synaptic function and hearing in mouse and primate models, and early human clinical trials have reported measurable improvements in auditory thresholds (Jiang et al., 2023).

GJB2 and Other Targets

GJB2 mutations account for a substantial proportion of hereditary SNHL globally. The gene encodes Connexin-26, a protein critical for potassium recycling in the cochlea. AAV-based replacement strategies have shown promise in preclinical work, restoring gap junction function and preserving hearing in animal models. Because GJB2 is small enough to fit into a single AAV, it circumvents the technical hurdles faced with larger genes, making it an attractive near-term candidate for clinical application (Bankoti et al., 2021). Other genes under investigation for replacement therapies include **TMC1**, which encodes a mechanotransduction channel essential for hair cell function, and **CLRN1**, linked to Usher syndrome type 3.

In summary, AAV-mediated gene replacement has already moved from proof-of-concept to clinical testing, particularly for OTOF-related auditory neuropathy. As vector design continues to improve, additional monogenic forms of hearing loss are likely to become treatable.

3.2 Gene Editing and Repair

While gene replacement is suitable for loss-of-function mutations, not all hereditary deafness results from absent proteins. Some cases involve dominant-negative mutations, where the defective protein interferes with normal cellular function. In these situations, gene replacement alone may be insufficient, and direct gene correction or silence is required.

CRISPR-Cas9 Technology

CRISPR-Cas9 has revolutionized the prospects for correcting pathogenic mutations directly within the genome. Preclinical studies in auditory models have demonstrated the feasibility of using CRISPR-mediated disruption of dominant mutations in **TMC1**, effectively halting progressive hearing loss. This approach offers the advantage of permanent correction, reducing the need for repeat treatments (Simons & Trapani, 2023).

Base Editing and Prime Editing

More refined tools, such as base editors and prime editors, extend the precision of gene editing. Base editors allow single-nucleotide substitutions without generating double-strand breaks, which lowers the risk of off-target effects. Prime editing expands this capacity further, enabling targeted insertions or deletions. These tools are particularly valuable for SNHL, where many pathogenic variants involve single-based substitutions. Early-stage research has demonstrated correction of point mutations in auditory genes in vitro, with ongoing work exploring delivery to cochlear tissues in vivo (Hahn & Avraham, 2023).

Challenges of Gene Editing in the Cochlea

Despite its promise, gene editing faces hurdles in the auditory system. Efficient delivery to inner ear cells is still a bottleneck, as large CRISPR systems often exceed AAV capacity. Strategies include using smaller Cas variants (e.g., Cas12f) or split-Cas9 systems, though these approaches must balance efficiency and fidelity. Another concern is the permanency of edits; while this can be advantageous, it also raises risks of unintended mutations. Ethical considerations regarding germline versus somatic editing are especially salient in congenital hearing loss, given that interventions would often be performed in children (Simons & Trapani, 2023).

3.3 Neuroprotection and Regenerative Strategies

Not all cases of SNHL stem from genetic mutations amenable to replacement or editing. Environmental insults, aging, and acquired injuries also contribute substantially. Gene therapy in this context can aim to preserve residual function or stimulate regeneration of lost cells.

Neurotrophic Factor Delivery

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) are critical for the survival and connectivity of spiral ganglion neurons. Viral-mediated delivery of these factors into the cochlea has shown potential to promote neuronal survival and improve the performance of cochlear implants. By enhancing the health of auditory neurons, these approaches may extend the therapeutic window for other interventions and provide combined benefits when used with prosthetic devices (Yoshimura et al., 2021).

Supporting Cell Reprogramming

The mammalian cochlea contains non-sensory supporting cells that share lineage with hair cells. Unlike birds, where these cells can regenerate hair cells after injury, mammalian supporting cells remain quiescent. Gene therapy approaches aim to reprogram these cells by manipulating transcription factors such as ATOH1, which can induce hair cell-like phenotypes. Although early clinical trials with ATOH1 delivery (e.g., CGF166) demonstrated limited efficacy, they validated the feasibility of vivo reprogramming strategies. Ongoing research seeks to optimize reprogramming by combining transcription factor delivery with pathways that regulate cell cycle re-entry and differentiation (Amariutei et al., 2023).

Combined Regenerative Approaches

Future regenerative strategies may involve multi-modal approaches, combining gene delivery with pharmacological modulation or biomaterials that support cell growth. The goal is to recreate a permissive environment within the cochlea where new hair cells or neurons can form and integrate into existing circuitry. While this remains in early preclinical stages, it represents an exciting frontier for reversing acquired as well as hereditary SNHL (Amariutei et al., 2023).

3.4 Summary of Mechanisms

Gene therapy for SNHL currently spans three overlapping strategies: replacement, editing, and regeneration. Replacement therapies, particularly AAV-based OTOF and GJB2 delivery, are closest to clinical translation. Editing approaches offer future potential for dominant mutations and precision correction. Regenerative therapies, though less advanced, provide a pathway to address acquired losses and broaden therapeutic applicability. Collectively, these approaches underscore the versatility of gene therapy in tackling the diverse etiologies of hearing loss.

4. Advances in Clinical Trials

Clinical trials in otological gene therapy represent the transition from theoretical promise to tangible human outcomes. While preclinical models provided proof of concept, recent first-in-human trials have begun demonstrating that genetic correction in the inner ear can restore auditory function. These trials provide critical insights into efficacy, safety, and feasibility, and highlight the remaining challenges in translating laboratory success into durable clinical practice.

4.1 OTOF Gene Therapy (Auditory Neuropathy Spectrum Disorder)

Clinical Rationale

Mutations in the **OTOF** gene, encoding the protein otoferlin, are among the most well-characterized causes of auditory neuropathy spectrum disorder (ANSD). Otoferlin is essential for synaptic vesicle release at inner hair cell ribbon synapses, enabling neurotransmission to spiral ganglion neurons. In its absence, outer hair cells and general cochlear architecture remain intact, but signal transduction to the auditory nerve fails. This unique pathology makes OTOF-associated ANSD particularly attractive for gene therapy because the target cells are present and structurally preserved, creating a receptive environment for genetic rescue (Saïdia et al., 2023).

Vector Design and Delivery

The OTOF cDNA is larger than the packaging capacity of standard AAV vectors, necessitating **dual-AAV systems**. These vectors split the gene into two fragments that reconstitute into a functional transcript inside the host cell. Delivery is typically performed via round-window membrane injection, a minimally invasive approach that allows local targeting while minimizing systemic exposure (Jiang et al., 2023).

Human Clinical Outcomes

The most significant advances to date come from early-phase clinical trials of OTOF gene therapy. In these trials, children with profound congenital hearing loss underwent unilateral cochlear administration of dual-AAV vectors. Follow-up assessments using auditory brainstem responses (ABR) and behavioral audiometry revealed measurable improvements in auditory thresholds, in some cases approaching near-normal sensitivity for speech frequencies. Parents and clinicians also reported functional gains in language perception and environmental sound awareness, suggesting real-world impact beyond laboratory measures (Saïdia et al., 2023).

Jiang et al. (2023) highlighted that improvements were observed across multiple age groups, though younger children tended to exhibit more robust recovery, consistent with greater neural plasticity. These findings underscore the importance of early diagnosis and intervention, ideally within critical language acquisition windows. Safety profiles from these trials were favorable, with no major immune or inflammatory responses detected.

Implications

The success of OTOF trials demonstrates that **congenital deafness caused by synaptic dysfunction is reversible** with targeted gene therapy. This marks the first clear human evidence that natural hearing can be restored at the molecular level. These trials also establish important principles for future programs: the feasibility of dual-AAV delivery, the safety of cochlear injection, and the importance of developmental timing.

4.2 GJB2 and Connexin-related Therapies

Clinical Relevance

Mutations in **GJB2**, which encode Connexin-26, are the most frequent genetic cause of hereditary SNHL worldwide. Connexin-26 is a gap junction protein critical for potassium recycling in the cochlea. Loss of function leads to a breakdown of the ionic environment required for hair cell transduction.

Preclinical Achievements

Hahn and Avraham (2023) note that GJB2 gene therapy has shown strong preclinical momentum. Because the GJB2 gene is small enough to fit within a single AAV vector, it avoids the technical limitations encountered with larger genes like OTOF. Animal studies have demonstrated that AAV-mediated GJB2 delivery can restore intercellular coupling, preserve hair cell integrity, and rescue auditory function when administered at early developmental stages.

Translational Potential

While human trials for GJB2 therapy have not yet commenced, regulatory discussions and preclinical successes suggest that **first-in-human studies may begin within the coming years**. The widespread prevalence of GJB2 mutations makes this target particularly impactful, with the potential to benefit a large global patient population. However, several translation barriers remain, including identifying the optimal delivery window and ensuring that therapy can reverse, rather than merely halt, hearing loss in cases where degeneration has already occurred (Hahn & Avraham, 2023).

Implications

The trajectory of GJB2 therapy illustrates the expanding scope of cochlear gene therapy. Unlike OTOF, which affects synaptic machinery, GJB2 mutations disrupt cochlear homeostasis, a different biological mechanism. Demonstrating therapeutic benefit in GJB2-related hearing loss would validate gene therapy across multiple pathogenic pathways, reinforcing the adaptability of this approach.

4.3 ATOH1 and Other Early Trials

CGF166 and the First Wave of Trials

The earliest attempts at cochlear gene therapy involved **ATOH1**, a transcription factor required for hair cell differentiation. Novartis developed **CGF166**, an adenoviral vector delivering ATOH1, with the aim of reprogramming supporting cells in the cochlea to regenerate hair cells. This approach targeted a broad patient population, not just those with monogenic hearing loss, by attempting to restore sensory cells lost due to diverse etiologies (Yoshimura et al., 2021).

Phase I/II trials of CGF166, however, yielded limited clinical benefit. Although the therapy was safe and demonstrated the feasibility of direct cochlear delivery in humans, auditory outcomes were inconsistent and modest. In most participants, no significant improvement in hearing thresholds was recorded, and durable recovery of function was not achieved. These results led to the discontinuation of the CGF166 program (Yoshimura et al., 2021).

Lessons Learned

The CGF166 trial was nevertheless an important milestone. It confirmed that gene therapy vectors can be safely delivered to human cochlea and established critical surgical and regulatory pathways for future studies. Moreover, it highlighted the limitations of single-factor regenerative strategies, underscoring that inducing hair cell-like morphology alone is insufficient. Functional integration into the existing cochlear circuitry, synaptic formation, and neural survival are equally essential.

Implications

While CGF166 did not provide clinical efficacy, it paved the way for more targeted and biologically informed approaches. Modern regenerative strategies now combine transcription factor delivery with additional molecular cues to drive functional maturation, and gene replacement for monogenic causes has become the dominant paradigm. Thus, ATOH1 trials serve as a reminder that feasibility is not the same as success, but each setback sharpens the field's understanding of what is required for durable restoration.

4.4 Broader Clinical Landscape

Expanding Global Progress

Beyond OTOF and ATOH1, several clinical and preclinical programs are advancing across different regions. Guthrie (2025) provides a historical overview of the field, emphasizing how gene therapy for hearing loss has transitioned from a conceptual framework in the 1990s to first-in-human applications in the 2010s and tangible hearing restoration in the 2020s. The field is now characterized by global collaboration, with trials being launched in the United States, Europe, and Asia.

Lye et al. (2023) highlights the broader spectrum of targets under investigation. These include **TMC1**, a Mechan transduction channel essential for hair cell function; **PCDH15**, implicated in Usher syndrome type 1F; and **CLRN1**, associated with Usher syndrome type 3. While most remain in preclinical stages, they represent the next wave of clinical innovation.

Trial Design Principles

The structure of auditory gene therapy trials has evolved significantly. Early trials focused narrowly on safety and vector delivery feasibility. Contemporary designs now incorporate comprehensive auditory endpoints, including pure-tone audiometry, speech recognition in quiet and noise, auditory brainstem responses, and parent-reported developmental outcomes in children. Longitudinal follow-up is emphasized, as long-term durability of effect remains unknown (Lye et al., 2023).

Safety remains the cornerstone of trial design. Unilateral delivery is often employed in initial cohorts to reduce risk, with contralateral treatment considered after safety confirmation. Dosing regimens are carefully escalated, balancing efficacy with concerns about potential immunogenicity. Importantly, these trials increasingly recognize the role of age and neuroplasticity, prioritizing younger patients for early-phase enrollment.

Broader Implications

The global clinical landscape reflects a field that is rapidly maturing. Whereas a decade ago gene therapy for SNHL was speculative, today it is a proven clinical reality for certain genetic subtypes. The next decade will likely see expansion to more genes, refinement of editing technologies, and integration of gene therapy into newborn screening and pediatric otology practice (Guthrie, 2025; Lye et al., 2023).

4.5 Summary of Clinical Progress

The trajectory of clinical trials in otology illustrates both dramatic breakthroughs and instructive setbacks. OTOF therapy has provided the first definitive proof of auditory restoration through gene therapy, offering hope to families with congenital deafness. GJB2 therapies represent the next frontier, with strong preclinical support and the potential to address the most common form of hereditary hearing loss. The ATOH1/CGF166 experience, though limited in efficacy, validated key delivery strategies and clarified the complexity of functional regeneration. Taking together, these efforts paint a landscape of cautious optimism: gene therapy for SNHL is no longer an abstract promise but a tangible clinical strategy, poised to reshape otological care in the coming years.

5. Challenges and Limitations

Despite remarkable progress, several challenges limit the widespread adoption and long-term efficacy of gene therapy for sensorineural hearing loss (SNHL). These barriers span technical, biological, ethical, and accessibility domains.

5.1 Vector Capacity: Large Genes and Dual-AAV Issues

Adeno-associated viruses (AAVs) remain the most widely used vectors for inner-ear gene delivery due to their safety and efficiency in transducing non-dividing cells. However, AAV vectors can only accommodate genes up to ~4.7 kilobases. Many genes implicated in hearing loss, such as **OTOF**, exceed this size, necessitating dual-AAV or alternative strategies. While dual-AAV approaches have enabled partial success by splitting large genes into two halves that recombine within the cell, the efficiency of reconstitution is inconsistent. This can lead to variability in therapeutic outcomes and limits scalability (Bankoti et al., 2021).

Ongoing research into split-inteins and hybrid vectors offers potential solutions, but these approaches remain in early stages.

5.2 Immune Responses and Re-Dosing Barriers

Although cochlea is partially immune-privileged, systemic and local immune responses to viral vectors remain a concern. Neutralizing antibodies against AAV capsids can prevent re-dosing, which is particularly problematic for therapies requiring staged bilateral delivery. Even low levels of pre-existing immunity, potentially from natural AAV exposure, may reduce transduction efficiency. Strategies such as capsid engineering, immunosuppression, or non-viral delivery systems are being explored, but no consensus solution has yet been established (Amariutei et al., 2023).

5.3 Timing of Intervention: Critical Developmental Windows

The efficacy of gene therapy is closely linked to the timing of intervention. For conditions like **OTOF-related auditory neuropathy**, earlier treatment in infancy leads to superior outcomes because neural plasticity facilitates integration of restored signals into language acquisition pathways. Delays in treatment risk diminished benefit, as prolonged sensory deprivation reduces central auditory responsiveness. This makes newborn screening and early genetic diagnosis essential for effective deployment. However, in many regions, such screening infrastructure is limited, and patients are often diagnosed too late to benefit fully (Ren et al., 2022).

5.4 Ethical and Accessibility Concerns

The high cost, surgical expertise required, and limited number of specialized centers pose accessibility challenges. Most early-phase trials are confined to high-income countries, raising concerns about global equity. Ethical debates also surround the application of gene therapy in children, who cannot provide informed consent, even though early intervention is most effective. Parents and clinicians must weigh the risks of invasive procedures against the promise of long-term auditory benefits. Finally, there is the challenge of managing expectations: while gene therapy can restore some auditory function, outcomes vary, and therapy may not eliminate the need for cochlear implants or assistive devices (Amariutei et al., 2023).

6. Future Directions

While challenges remain, rapid advances in molecular technologies, vector design, and clinical strategies point toward a transformative future for otological gene therapy.

6.1 Improved AAV Engineering and Delivery Systems

Next-generation AAVs are being engineered for higher efficiency, lower immunogenicity, and broader tropism across cochlear cell types. Capsids such as Anc80L65 have demonstrated exceptional transduction of inner hair cells, and synthetic variants may expand access to outer hair cells and supporting cells. Non-viral systems, such as lipid nanoparticles, are also being investigated for safer repeat dosing (Jiang et al., 2023). Advances in surgical techniques, including precision cochlear infusion and intraoperative monitoring, are expected to improve safety and efficacy.

6.2 Gene Editing for Dominant Mutations

CRISPR-based systems are likely to play a larger role in treating dominant-negative mutations where simple replacement is insufficient. For instance, CRISPR-Cas9 or base editing could silence pathogenic alleles or precisely correct single-nucleotide variants. Early preclinical studies suggest the feasibility of editing mutations in **TMC1** and related loci, with long-term potential for durable correction (Simons & Trapani, 2023). Prime editing, though still in its infancy, may expand the editing toolbox for SNHL by enabling versatile genomic changes with fewer off-target effects.

6.3 Integration with Cochlear Implants

Rather than competing, gene therapy and cochlear implants may evolve as complementary approaches. In patients with partial restoration of auditory thresholds through gene therapy, cochlear implants could provide additional benefits by enhancing speech perception in noisy environments. Conversely, gene therapy targeting neural survival could improve implant outcomes by preserving or regenerating spiral ganglion neurons. This combinatorial model has the potential to maximize hearing rehabilitation outcomes across diverse patient populations (Guthrie, 2025).

6.4 Expanding Patient Age Range and Global Accessibility

Future trials are expected to broaden inclusion criteria to older patients, provided that sufficient cochlear structures remain intact. The success of OTOF therapy in older children and even young adults in recent studies suggests that gene therapy may not be limited exclusively to infants. However, maximizing benefit still depends on timely intervention. Global accessibility remains a pressing issue: to achieve widespread impact, gene therapy must extend beyond specialized centers in high-income countries. This will require cost reduction, capacity building in surgical expertise, and integration into newborn screening programs worldwide (Jiang et al., 2023).

7. Conclusion

Gene therapy for sensorineural hearing loss is moving from theoretical aspiration to clinical reality. Replacement strategies, particularly for **OTOF** mutations, have already shown measurable restoration of hearing in children, representing a landmark achievement in otology. Other targets, including **GJB2** and transcription factor-based regenerative strategies, are rapidly advancing through preclinical pipelines. However, significant challenges persist, including limitations in vector capacity, immune barriers to re-dosing, the need for early intervention, and questions of ethical application and accessibility (Bankoti et al., 2021; Amariutei et al., 2023; Ren et al., 2022).

Looking forward, advances in AAV engineering, the adoption of CRISPR and base editing for dominant mutations, and the integration of gene therapy with cochlear implant technology are likely to expand the therapeutic landscape. As clinical experience accumulates, and as global systems adapt to support genetic screening and specialized delivery, gene therapy could become a standard of care for selected forms of hereditary deafness.

The next decade will be decisive. If current trends continue, gene therapy may evolve from isolated trials to mainstream otological practice, offering not just prosthetic compensation but genuine biological restoration of hearing. For patients and families affected by SNHL, this represents not only a medical breakthrough but a profound shift in how hearing loss is understood and treated (Simons & Trapani, 2023; Jiang et al., 2023; Guthrie, 2025).

References

1. Amariutei, A. E., Jeng, J. Y., Safieddine, S., & Marcotti, W. (2023). Recent advances and future challenges in gene therapy for hearing loss. *Royal Society Open Science, 10*(6), 230644.
2. Bankoti, K., Generotti, C., Hwa, T., Wang, L., O'Malley, B. W., & Li, D. (2021). Advances and challenges in adeno-associated viral inner-ear gene therapy for sensorineural hearing loss. *Molecular Therapy – Methods & Clinical Development, 21*, 209–236.
3. Guthrie, O. N. W. (2025). Gene therapy: An historical overview for familial hearing loss. *International Journal of Molecular Sciences, 26*(4), 1469.
4. Hahn, R., & Avraham, K. B. (2023). Gene therapy for inherited hearing loss: Updates and remaining challenges. *Audiology Research, 13*(6), 952–966.
5. Jiang, L., Wang, D., He, Y., & Shu, Y. (2023). Advances in gene therapy hold promise for treating hereditary hearing loss. *Molecular Therapy, 31*(4), 934–950.
6. Lye, J., Delaney, D. S., Leith, F. K., Sardesai, V. S., McLenachan, S., Chen, F. K., ... & Wong, E. Y. (2023). Recent therapeutic progress and future perspectives for the treatment of hearing loss. *Biomedicines, 11*(12), 3347.
7. Ren, H., Hu, B., & Jiang, G. (2022). Advancements in prevention and intervention of sensorineural hearing loss. *Therapeutic Advances in Chronic Disease, 13*, 20406223221104987.
8. Saïdia, A. R., Ruel, J., Bahloul, A., Chaix, B., Venail, F., & Wang, J. (2023). Current advances in gene therapies of genetic auditory neuropathy spectrum disorder. *Journal of Clinical Medicine, 12*(3), 738.
9. Simons, E. J., & Trapani, I. (2023). The opportunities and challenges of gene therapy for treatment of inherited forms of vision and hearing loss. *Human Gene Therapy, 34*(17–18), 808–820.
10. Yoshimura, H., Nishio, S. Y., & Usami, S. I. (2021). Milestones toward cochlear gene therapy for patients with hereditary hearing loss. *Laryngoscope Investigative Otolaryngology, 6*(5), 958–967.