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Stem Cell Therapy: A Potential Cure for Congenital Hearing Loss—A Systematic Review

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Abstract

Background: Congenital hearing loss, a prevalent permanent paediatric sensory impairment affecting multiple births globally, significantly impacts communicative and cognitive development. Due to the lack of cochlea regenerative capacity, traditional management through auditory amplification fails to achieve natural restoration. Recent advancements in stem cell therapy present a promising regenerative approach, showing potential for hair cell regeneration and auditory function restoration. **Objective:** This review provides an analysis of the efficacy and safety of stem cell intervention for congenital hearing loss, highlighting key research advancements, challenges, and future research directions, emphasising the need for interdisciplinary approaches and innovative technologies. **Methods:** A literature search was conducted across databases such as Cochrane, Google Scholar, PubMed and Web of Science. Studies were included if they were published between 2015 and 2025, in English, and focused on stem cell therapy, cochlea regeneration, hearing recovery and regenerative cell therapy. **Results:** The review included 65 studies. Significant progress is evident using stem cell therapy for cochlea hair cell regeneration and auditory nerve function restoration. Key findings include using gene therapy for cochlea cell reprogramming and using stem cells for hair cell regeneration. While preclinical models show promising results, human clinical trials indicate moderate improvements in hearing function, with challenges of cell integration, long-term efficacy, safety concerns, tumorigenesis and immune rejection noted. **Conclusion:** Stem cell therapy holds promise for potentially curing congenital hearing loss through cochlea regeneration and hearing recovery. Significant challenges and the need for optimised therapeutic protocols remain. Further research should include large-scale clinical trials, improved stem cell differentiation efficiency, refined gene editing technologies, and better delivery mechanisms, which are essential to realise the full therapeutic potential of stem cell intervention.

Keywords

Stem Cell Therapy, Congenital Hearing Loss, Sensorineural Hearing Loss, Regenerative Medicine, Regenerative Cell Therapy, Embryonic Stem Cells, Mesenchymal Stem Cells, Induced Pluripotent Stem Cells, Inner Ear Hair Cell Regeneration

1. Introduction

Congenital hearing loss is known to be one of the most prevalent chronic paediatric sensory impairments in humans and is present from birth. It can range from mild to profound hearing loss and could be either in one or both ears. According to the World Health Organization, it is estimated that around 34 million children worldwide suffer from disabling hearing loss, with approximately 1 in 1000 children from high-income countries and 3 - 4 in 1000 children from low-income countries born with profound congenital hearing loss [1]-[5]. Early detection and intervention serve to aid in the prevention of delayed speech and language development skills and the beneficial acquisition of emotional and social development. Congenital hearing loss can be attributed to various environmental and prenatal factors, particularly in low-income communities. In developed countries, congenital hearing loss is often attributed to congenital infections such as rubella and cytomegalovirus, as well as other significant genetic causes. The underlying aetiology tends to determine the therapeutic intervention including decision-making, prevention and genetic counselling. Up until recently, management options have included antimicrobial therapies, surgical intervention, and hearing amplification. Due to the lack of natural regenerative capacity in the inner ear, whilst these treatments significantly improve quality of life and address symptoms, they fail to repair the underlying cellular damage in the cochlea to achieve natural restoration of hearing [6].

Congenital hearing loss can be broadly categorised into genetic and non-genetic causes. Genetic factors account for approximately 50% - 60% of cases and may be either syndromic or non-syndromic in nature [6]. Non-genetic causes include prenatal infections (e.g., rubella, cytomegalovirus), prematurity, low birth weight, ototoxic exposure, and perinatal complications.

Among genetic causes, non-syndromic hearing loss represents approximately 70% of cases and is typically confined to auditory dysfunction without systemic involvement. Most of these cases follow an autosomal recessive inheritance pattern and are often associated with mutations in genes such as *GJB2*, *OTOF*, and *TECTA* [7]. In contrast, syndromic hearing loss, accounting for about 30% of genetic cases, occurs in conjunction with other clinical features and systemic anomalies. Significant examples include Usher syndrome, Pendred syndrome, and Waardenburg syndrome [7].

Several genes are critically implicated in the development and function of the

cochlea:

- *GJB2* encodes Connexin 26, a protein essential for potassium ion recycling via cochlear gap junctions. Mutations in *GJB2*, particularly the 35delG variant, are the most common cause of non-syndromic sensorineural hearing loss worldwide and typically result in profound hearing impairment [8].
- *MYO7A* encodes Myosin VIIA, a motor protein involved in hair cell function within the cochlea and vestibular system. Mutations in this gene are linked to Usher syndrome type 1B, characterised by congenital deafness, vestibular areflexia, and progressive retinitis pigmentosa [1].
- *SLC26A4* encodes Pendrin, an ion transporter. Mutations cause Pendred syndrome, which presents with fluctuating or progressive sensorineural hearing loss, an enlarged vestibular aqueduct, and thyroid dysfunction [1].
- *OTOF* encodes Otoferlin, a protein essential for synaptic vesicle exocytosis in inner hair cells. Mutations result in non-syndromic auditory neuropathy, characterised by normal otoacoustic emissions but disrupted auditory signal transmission, leading to poor speech discrimination [7].
- *TECTA* encodes a component of the tectorial membrane, which facilitates mechanical stimulation of cochlear hair cells. Mutations are associated with autosomal dominant, non-syndromic hearing loss of mild to moderate severity [7].

Understanding the genetic causes of congenital hearing loss, such as mutations in key genes is crucial for diagnosis and personalised intervention. Advances in genetic sequencing currently allow for earlier and more precise identification of genetic mutations, laying the ground for tailored interventions like gene therapy and stem cell therapy. By addressing the genetic foundations of hearing loss, future therapies hold the potential to restore hearing and improve the quality of life for affected individuals.

Congenital hearing loss has far-reaching consequences for both individuals and families, on education systems, and on healthcare services. Untreated hearing loss often leads to delayed speech and language development, which may impede academic achievement and socio-emotional development. Children with congenital hearing loss who fail to receive early interventions like hearing aids or cochlea implants often struggle to achieve optimal communicative ability. Furthermore, hearing loss can limit social interactions and employment opportunities in later life, placing an economic burden on both families and communities.

Current conventional treatments for congenital hearing loss include cochlea implants, hearing aids and speech therapy. Cochlea implants are surgically implanted devices that bypass an impaired inner ear and cochlea hair cells to directly stimulate the auditory nerve. These devices are commonly used in cases of severe to profound sensorineural hearing loss. Cochlea implants are beneficial in enabling sound perception in severe hearing impairment; they improve speech understanding, especially with early implantation, and they provide a pathway for auditory input, helping preserve the brain's auditory pathways. Cochlea implants are limited in that they are unable to restore natural hearing and the perceived

sound they achieve is often described as mechanical and artificial. They require intensive post-implantation auditory rehabilitation for optimal outcomes; they are not suitable for individuals with complete auditory nerve damage and may present with significant surgical risks of infection or device failure.

Hearing aids amplify sound to compensate for mild to severe hearing loss, most often useful when there is still some residual hearing. Hearing aids amplify sound waves directing them to the ear canal. Digital hearing aids are programmable and can target frequency-specific benefits based on individual audiogram presentation. Hearing aids are non-invasive and widely accessible, customisable for various degrees of hearing impairment and patient preference and are beneficial in managing mild to severe sensorineural, conductive and mixed hearing impairment. Their limitations are seen in their inability to restore natural hearing which may affect speech clarity in noisy environments. They also pose challenges in achieving optimal benefit in severe-to-profound hearing impairment or auditory nerve damage and are dependent on residual cochlea hair cells for effective function.

Speech therapy is a crucial component of auditory rehabilitation, particularly for children with congenital hearing loss and mainly focuses on improving speech, language, and auditory processing skills. Speech therapy helps children develop optimal communication skills to improve social integration, especially if speech and language are developmentally delayed due to hearing impairment. Speech therapy is highly beneficial, with effectiveness dependent on early intervention and access to supporting technologies. However, it fails to address the underlying biological cause of hearing loss.

While these conventional treatments significantly improve the quality of life for individuals with congenital hearing loss, they lack the ability of biological restoration and fail to repair damaged hair cells, supporting cells, or neural pathways in the inner ear. They work around the damage rather than address it [4] [7].

Cochlea implants and hearing aids provide artificial hearing where sound perception differs significantly from natural hearing, particularly in noisy environments and with the complexity of music. Without natural stimulation of the auditory nerve by cochlea hair cells, prolonged hearing loss can lead to neural atrophy, reducing the effectiveness of devices in the long term. Auditory amplification devices also require regular maintenance, upgrades, and replacements, posing a financial and logistical burden.

Emerging trends in stem cell therapy aim to fill the gap left by conventional intervention by addressing the root causes of hearing loss. Stem cell therapies, with their potential to regenerate hair cells, repair cochlea structures, and restore neural connections, have led to an increasing interest in the development of biological therapies that could revolutionise the management of congenital hearing loss. By addressing the root causes, these therapies promise to restore natural hearing and significantly improve quality of life [9].

The concept of stem cell therapy for hearing loss began to gain momentum in the 1990s when the regenerative capabilities of animals like birds and amphibians

were observed. These species, unlike mammals, could regenerate lost or damaged hair cells within the cochlea. Reynolds and Weiss [10] isolated pluripotent neural stem cells (NSCs) from the forebrain of adult mammals. Thomson *et al.* [11] first isolated human embryonic stem cells (hESCs). Pittenger *et al.* [12] demonstrated that bone marrow-derived human adult mesenchymal stem cells (BM-MSCs) could differentiate into multiple cell types, showing the pluripotency of adult stem cells (ASCs).

Li *et al.* [13] noted previous research in the identification of pluripotent stem cells (PSCs) in the inner ear of adult mice that could self-renew and differentiate into hair cell-like cells. Takahashi and Yamanaka [14] in a groundbreaking study transformed mouse fibroblasts into induced pluripotent stem cells (iPSCs) using four transcription factors [14] [15]. Following these findings, researchers explored the idea that stem cells might offer a potential solution to this regeneration deficit in humans, especially with the discovery of adult stem cells in the cochlea and later the reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) [16]. Over the past decade, stem cell-based therapies have gained significant attention. Recent research shows that mesenchymal stem cells (MSCs) can induce to differentiate auditory hair cells, neuronal cells, and cochlea fibrocytes, being a key milestone in hearing regeneration [17]. This highlighted the benefit of stem cells in hair cell regeneration and neural function restoration necessary for hearing.

Cochlea hair cell regeneration has been a major area of current research, with its greatest challenge being the inability of cochlea hair cells to regenerate via traditional medical treatment. Consequently, the potential of combination gene editing and stem cell therapy for genetic hearing loss correction has been of great focus in the last decade. There are notably two ways to force hair cell regeneration, namely by inducing either proliferation of the auditory epithelium or the direct transdifferentiation of stem cells into hair cells [18]. Considering that genetic hearing loss is one of the most frequent causes of irreversible hair cell spiral ganglion neuron damage, new methods of genome editing, especially the CRISPR/Cas9 technology, promote potential opportunities for better understanding the pathogenesis of human sensorineural hearing loss and novel ways to resolve this [19].

Current research shows that human-induced pluripotent cells have great potential for use in developing effective, safe, personalised restorative biological strategies for the treatment of sensorineural hearing loss. Clinical trials are ongoing focusing on genetically modified iPSCs in the use of cochlea hair cell regeneration and the promotion of spiral ganglion neuron survival, which is critical for auditory pathway integrity. Early data shows promising results in the use of these combination therapies for effective sensory and neural function restoration [20].

The refined research focus is shifting towards improving cell survival, differentiation efficiency, and cochlea integration. Exploration of biomaterial scaffolds and nanotechnology for stem cell delivery methods and proper intracochlear placement optimisation has begun, with continuing research on neural regeneration for

cochlea nerve function restoration [21].

Major advancements in genomic technologies in the 21st century led to a breakthrough in understanding the genetic basis of hearing impairment. Researchers identified that specific genetic mutations such as GJB2 which codes for Connexin 26, were a significant cause of non-syndromic congenital hearing impairment. This knowledge further prompted efforts to use stem cells for genetic correction, allowing for both regenerative therapies and gene therapies for the potential correction of underlying genetic mutations in hearing. The identification of hundreds of genes involved in hearing loss, such as MYO7A (responsible for Usher syndrome) and TMC1 (linked to autosomal dominant deafness) made the development of next-generation sequencing a possibility. These are critical insights for developing personalised stem cell interventions targeting specific genetic mutations [22].

1.1. Types of Stem Cells and Their Potential in Hearing Restoration

Embryonic Stem Cells (ESCs) are derived from the inner cell mass of a blastocyst, a stage in early embryonic development. These cells are pluripotent, being able to differentiate into any of the body's three germ layers, namely the ectoderm, mesoderm, and endoderm. This allows the potential for them to become varying types of cells, including those found in the inner ear. However, controversy surrounds this research with major ethical concerns regarding the destruction of embryos to obtain these cells.

The major potential of ESCs in hearing restoration lies in their ability to generate cochlea cells. Okano *et al.* [23] demonstrated in previous work that when treated with specific growth factors, embryonic-derived stem cells could differentiate into auditory hair cells *in vitro*. This breakthrough provided hope for the in vivo use of ESCs in the regeneration of damaged cochlea hair cells [24]. However, due to the controversial ethical challenges and concerns, the potential for tumorigenesis and possible immune suppression with donor stem cells, the hope of ESC use in clinical implementation remains dampened.

Induced Pluripotent Stem Cells (iPSCs) were introduced as an ethical and practical alternative to ESCs [14]. By reprogramming adult somatic cells like skin fibroblasts into pluripotent stem cells, iPSCs avoid ethical embryonic issues. More recent research has seen an increase in the use of iPSCs in congenital hearing loss treatment. iPSCs have the key advantage of being patient-specific, reducing the risk of immune rejection. Research in 2017 proved the successful generation of iPSC-derived auditory cells from human patients with a specific mutation linked to hearing loss. Some degree of auditory function restoration was found in animal models, hinting toward the potential for individualised treatments. However, challenges remain, such as efficient differentiation of iPSCs into cochlea cells and ensuring proper in vivo cell function. Research is ongoing with a focus on differentiation protocol optimisation and potential genetic abnormality prevention which are at risk during reprogramming [3] [25].

Adult Stem Cells (ASCs) are multipotent, being more limited in differentiation potential than ESCs and iPSCs. Regardless, certain adult stem cells especially those found within the cochlea have the potential to treat hearing loss. Supporting cells within the cochlea have the potential to transdifferentiate into hair cells under certain conditions, a natural phenomenon seen in some species like birds. An important ASC is the mesenchymal stem cells (MSCs) which are found in various tissues like bone marrow, adipose tissue and umbilical cord tissue. Due to their multidirectional differentiation potential, immunosuppressive function, low immunogenicity and migration capability, MSCs have been shown to aid in the treatment of inner ear inflammatory damage, making them suitable candidates for gene and cell therapy [26] [27]. Research has demonstrated the *in vitro* differentiation of MSCs into cochlea cells, and with cochlea implantation, they provide potential to promote healing and restore hearing. Research by Lin *et al.* [28] shows the use of MSCs in cochlea repair demonstrated that they aided in cochlea hair cell regeneration and promoted cochlea neuron growth, showing potential for combined sensory and neural regeneration.

1.2. Mechanisms of Stem Cell Action in the Cochlea

Hair Cell Regeneration: in non-mammalian species such as birds and fish, cochlea hair cells have the ability to regenerate post-injury. Mammals, including humans, lack this regenerative ability. Hence, the fundamental challenge in applying stem cell therapy to treat hearing loss is inducing hair cell regeneration in a controlled and effective manner.

Key molecular pathways have been identified recently regulating hair cell regeneration, such as the Notch signalling pathway and the Atoh1 gene [19] [29] [30]. Previous research in the last two decades showed that administration of Atoh1 gene therapy to the cochlea of embryonic animals, neonatal animals and mature animals lead to varying degrees of hair cell regeneration and improvements in vestibular function [31]. This finding prompted the investigation of combining stem cells and gene therapy, where stem cells are exposed to factors that enhance their regenerative capacity.

Gene editing technologies like CRISPR/Cas9 has successfully been used to interpret both dominant and recessive mutations as an efficient treatment for hearing impairment [32]. CRISPR/Cas9 editing is a versatile tool for genetic engineering and gene regulation, and it has been found to be beneficial in eliminating genes that inhibit hair cell regeneration and activate genes that promote it [33].

In the case of cochlea nerve regeneration, in the presence of cochlea nerve damage, independent cochlea hair cell regeneration is insufficient in hearing function restoration. Due to the lack of natural regeneration in impaired auditory nerves, cochlea nerve regeneration remains a key challenge in hearing restoration. Stem cell-based approaches to nerve regeneration focus on promoting the growth and repair of the spiral ganglion neurons in the cochlea. Neural stem cells (NSCs) and iPSCs hold some potential for regenerating auditory neurons. However, concrete

findings are still developing, and achieving full cochlea nerve function recovery remains a significant challenge [25].

Emerging new biomaterials like scaffolds and hydrogels useful in the promotion of neuronal growth and which support the survival of transplanted stem cells is crucial for integrating new cells into the cochlea structure. Stem cell-derived neurotrophic factors like BDNF and GDNF may also be used to enhance neuronal survival and connectivity [21] [34].

2. Rationale

Congenital hearing loss is a significant public health issue affecting approximately 1 to 3 per 1000 live births. Despite advancements in hearing aids and cochlea implants, these interventions effectively treat symptoms but do not restore natural hearing, and there is currently no effective cure. Stem cell therapy has gained attention as a potential means of restoring cochlea function by promoting cellular regeneration.

3. Objectives

The goal of this review is to provide a comprehensive analysis of the efficacy and safety of stem cell-based interventions to treat and potentially cure congenital hearing loss, highlighting key research advancements, challenges, and future research directions, emphasising the need for interdisciplinary approaches and innovative technologies that could lead to effective clinical intervention. It mainly focuses on studies published between 2015 and 2025 that identify key stem cell types such as ESCs, iPSCs, MSCs, and cochlea progenitor cells in cochlea function and hearing restoration for congenital hearing loss. This review aims to assess the efficacy and potential of these stem cell therapies and their methods of therapeutic differentiation and intracochlear transplantation, including their effectiveness and impact on promoting cochlea regeneration, their efficacy and safety in preclinical and clinical settings, and provide recommendations for future research in optimising stem cell therapy for congenital hearing loss.

4. Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was designed to ensure methodological transparency and reproducibility. A PRISMA flow diagram detailing the study selection process is included (**Figure 1**) [35].

A comprehensive literature search was conducted across multiple databases such as Cochrane, Google Scholar, PubMed and Web of Science of studies published between 2015 and 2025 regarding the use of stem cell therapy in the treatment of congenital hearing loss. Studies were included if they were English, and focused on stem cell therapy, cochlea regeneration, hearing recovery and regenerative cell therapy. The search was supplemented by manual reference screening

of relevant systematic reviews and key publications to identify additional studies not captured in the database searches.

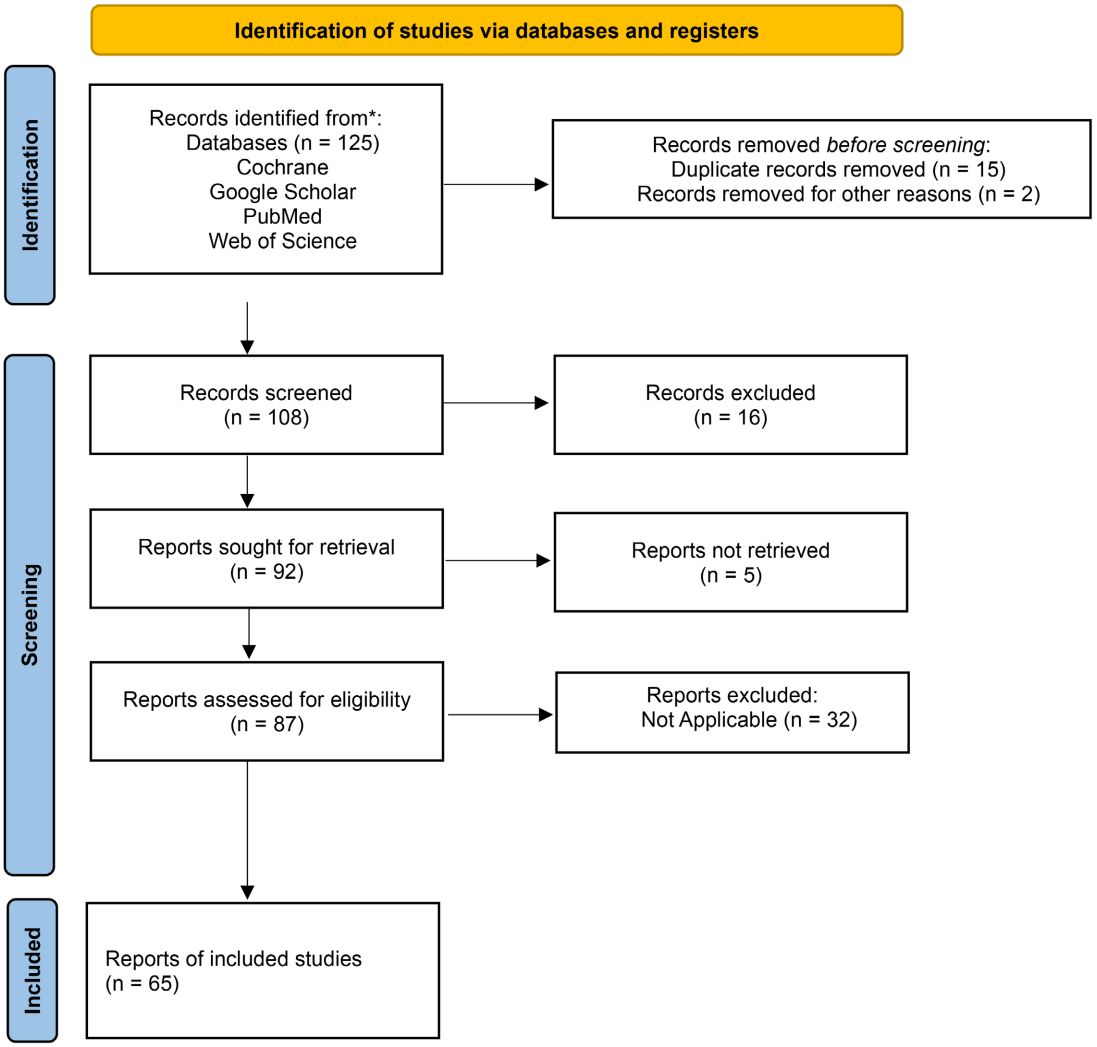

Figure 1. PRISMA flowchart [35].

4.1. Eligibility Criteria

Inclusion Criteria:

- Studies investigating stem cell or gene therapy specifically targeting congenital hearing loss.
- Utilisation of stem cell types such as induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), cochlea progenitor cells, or other relevant stem cell populations aimed at cochlea regeneration.
- Primary outcomes focused on cochlea repair or regeneration, including hair cell restoration, spiral ganglion neuron regeneration, or measurable recovery of auditory function.
- Preclinical studies involving animal models and clinical trials conducted in human participants.

- Studies reporting experimental or clinical data evaluating the efficacy and/or safety of stem cell or gene therapy interventions.
- Peer-reviewed original research articles, systematic reviews, or meta-analyses published in scientific journals.
- Studies explicitly discussing the application of regenerative medicine (stem cell or gene-based therapies) for congenital forms of hearing loss.
- Clear documentation of adherence to ethical standards, including animal welfare guidelines or ethical approval for clinical research.
- Publications dated between January 1, 2015, and January 31, 2025.

Exclusion Criteria:

- Studies not addressing stem cell or gene therapy or those evaluating alternative regenerative approaches unrelated to stem cells.
- Articles lacking defined outcomes related to cochlea repair, auditory recovery, or measurable hearing improvement.
- Research focused on hearing loss of acquired, age-related, or other non-congenital aetiologies.
- Publications not available in English.
- Studies without documented ethical approval or, where applicable, informed consent from human participants.

4.2. Information Sources

The literature search was conducted using the databases Cochrane, Google Scholar, PubMed, and Web of Science. Additional hand-searching of references from relevant review articles was performed to capture potentially missed studies.

4.3. Search Strategy

A comprehensive search was conducted in databases such as Cochrane, Google Scholar, PubMed and Web of Science from September 2024 to January 2025, and results were filtered to studies published from 2015 to 2025. The references were screened for relevance, and duplicates were removed before full-text retrieval.

Filters were applied to limit the search to peer-reviewed journal articles, reviews, clinical trials, and preclinical studies published in English and using the following Keywords: Stem cell therapy, congenital hearing loss, sensorineural hearing loss, regenerative medicine, regenerative cell therapy, embryonic stem cells, mesenchymal stem cells, induced pluripotent stem cells, inner ear hair cell regeneration.

4.4. Study Selection Process

A total of 125 records were identified through database searches and reference screening. After removal of duplicates and title/abstract screening, 87 articles were reviewed in full for eligibility. Following a full-text review, 65 studies met the inclusion criteria and were included in the qualitative synthesis.

The selection process followed the PRISMA flow chart structure and was con-

ducted independently by one reviewer.

4.5. Data Collection Process

Data was independently extracted by a single reviewer using a standardised extraction form. Extracted data included:

Data Extraction and Analysis

Data were extracted using a standardized data extraction form. A single reviewer extracted data. The following variables were collected:

- Study characteristics (authors, year, design, population)
- Stem cell type and source
- Administration method (e.g., local vs systemic)
- Outcome measures (ABR, ASSR, audiometry, histological data)
- Follow-up duration
- Adverse effects (e.g., immune response, tumorigenesis)
- Key findings and limitations

4.6. Data Synthesis

A qualitative narrative synthesis was conducted to summarize the findings. This included:

- Identification of patterns in stem cell types and administration methods
- Description of efficacy in cochlea and auditory function recovery
- Analysis of adverse effects and safety profiles
- Summary of long-term outcomes and follow-up duration

Where data were sufficiently homogeneous, subgroup trends and common findings were highlighted. Due to the heterogeneity of the study in design and outcome reporting, a quantitative meta-analysis was not conducted.

4.7. Data Items

The following key data was extracted for each study:

- Study design and characteristics
- Stem cell types and delivery administration.
- Key outcomes such as hair cell regeneration, auditory function recovery, and immune response.
- Adverse effects and safety outcomes such as tumorigenesis and immune rejection.
- Follow-up period and long-term outcomes.

4.8. Effect Measures

The primary effect measures included preclinical studies showing improvement in cochlea structure, hair cell regeneration, ABR thresholds, and cochlea histology. The clinical trials showed improved auditory function present in ABR results and better speech clarity and discrimination ability and reduced hearing aid use and reliability. The main adverse effects appeared to be the incidence of immune

rejection, tumorigenesis, and other safety concerns.

4.9. Risk of Bias Across Studies

A risk of bias across studies was assessed, considering potential publication bias and heterogeneity.

5. Results

A total of 65 studies were included, comprising preclinical studies, clinical trials, articles and reviews. Recent studies have proven significant progress in the use of stem cell therapy in cochlea hair cell regeneration and auditory nerve function restoration.

Congenital hearing loss, often caused by genetic mutations, developmental abnormalities, or infections, tends to affect the cochlea hair cells, spiral ganglion neurons, and supporting cells. Stem cell therapy, especially involving pluripotent stem cells, mesenchymal stem cells, and induced pluripotent stem cells, has shown significant promise in animal models. However, translation to clinical success remains limited.

Preclinical models, primarily in rodents and guinea pigs, have demonstrated the potential of stem cells to regenerate auditory hair cells and neurons, successfully differentiated mesenchymal stem cells into auditory hair cells in mice resulted in improved auditory brainstem response thresholds, and the enhanced synaptic connectivity between transplanted cells and existing auditory pathways was seen in guinea pigs. Most preclinical studies with animal models demonstrated some degree of cochlea regeneration, with significant improvements in hair cell and auditory function restoration, particularly with iPSCs and gene therapy [16] [24] [36].

Table 1. Stem cell therapy: potential solutions and emerging strategies.

Potential Solutions and Emerging Strategies	
Strategy	Description
Otic Organoids	Provide better preclinical models that mimic human cochlear development.
Gene-stem cell hybrids	Combine gene editing (CRISPR) with stem cells for mutation correction.
Targeted delivery	Use of nanoparticles or engineered scaffolds to localize cells precisely.
Neurotrophic factor co-therapy	Enhance integration and survival of SGNs.
Universal donor iPSCs	Gene-edited to reduce immunogenicity and allow off-the-shelf solutions.

Preclinical success is also evident in molecular pathway control, where researchers were able to successfully manipulate pathways (e.g., Notch and Wnt) to guide stem cells toward otic lineages. Additional success in microenvironment engineering is also evident, where the use of biomaterials, 3D cultures, and cochlea organoids mimicking the natural cochlea function results in improved cell integration (See Table 1).

Key findings include the successful use of gene therapy to reprogram cochlea cells and the use of induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) showed promising results with cochlea hair cell regeneration, especially in animal models. While the preclinical models have shown promising results, clinical trials have been limited. They indicate moderate improvements in hearing function, and their results are often inconclusive, with remaining challenges attributed to some significant discrepancies which may include cell integration, long-term efficacy, and safety (Table 2).

6.1. Significant Discrepancies in Clinical Trials

6.1.1. Anatomical and Functional Complexity of the Human Ear

The human cochlea is much larger and more intricate than rodent models, making precise targeting of transplanted cells to specific cochlea regions extremely difficult. It is also essential for tonotopic organization to be restored to regain meaningful hearing, which animal models may not fully replicate.

6.1.2. Immune Response and Cell Survival

Immune rejection was reported in some cases, particularly with iPSCs. Immunosuppression or genetically matched animals are often used in preclinical models, whereas in humans, immune rejection, especially with allogeneic stem cells, is a major barrier. In addition, the long-term survival and integration of transplanted cells is poor in human trials.

6.1.3. Lack of Functional Integration

Stem cells may differentiate properly *in vitro* or in animal models but fail to form functional synapses in humans, and auditory nerve integration is essential for transmitting signals to the brain, which is very rarely clinically achieved.

6.1.4. Ethical and Safety Concerns

The risk of tumorigenesis (especially with iPSCs and ESCs) remains high, particularly in those involving undifferentiated stem cells. Additionally, human trials are subject to stricter regulatory and ethical scrutiny which delays progress, long-term outcomes are poorly understood, and patients are often reluctant to register for early-phase trials.

6.1.5. Variability in Stem Cell Sources

Homogeneous cell populations are often used in preclinical studies, whereas stem cell preparations may be heterogeneous in clinical settings, with inconsistent differentiation capacity and potency and patient-specific iPSCs are expensive and

time-consuming to produce. Studies focusing on embryonic stem cells examined alternative stem cell sources, including neural stem cells and embryonic stem cells. Studies focusing on iPSCs reveal notable progress in differentiating them into cochlea progenitor cells and hair cells. Studies focusing on the effects of MSCs primarily from bone marrow, adipose tissue or umbilical cord, in cochlea regeneration, show that they contribute to the structural reorganisation of the damaged cochlea and improve incomplete hearing recovery. Studies focusing on cochlea progenitor cells explored the regenerative potential of native cochlea progenitors or reprogrammed cells within the cochlea.

6.1.6. Disease Heterogeneity

There are over 100 known genetic mutations known to cause congenital hearing loss, and preclinical studies usually model specific types of damage, not the full range of genetic variability found in human patients.

6.1.7. Outcome Measurement Disparities

ABR and histological recovery markers are mostly used in preclinical and animal models, whereas human clinical trial outcomes require subjective reports, audiograms, and speech perception tests, which may not correlate directly with animal data.

6.1.8. Ethical Constraints with Paediatric Trials

Since congenital hearing loss affects neonates and infants, clinical testing is heavily restricted due to vulnerability and consent issues and consequently most trials focus on acquired hearing loss in adults, which presents with different pathophysiology.

Table 2. Stem cell therapy: key discrepancies.

Summary of Key Discrepancies		
Area	Preclinical	Clinical
Cell survival	High	Low
Differentiation	Directed and successful	Inconsistent
Functional outcomes	ABR recovery in animals	Minimal to no improvement in patients
Integration	Demonstrated *in vitro*	Poor in vivo in humans
Immune response	Controlled	Significant challenge
Ethical approval	Less stringent	Highly regulated

Clinical trials in humans are still in the early stages, where functional hearing restoration was modest in most early-stage trials, highlighting the need for larger, long-term studies. [5] [16] [17] [20] [25] [26].

Most studies show that stem cells are found to facilitate auditory repair through their differentiation into hair cells and auditory neurons, their secretion of growth factors promoting endogenous repair and immunomodulatory effects which ap-

pear to reduce cochlea inflammation. The discrepancy between preclinical and clinical outcomes in stem cell therapy for congenital hearing loss underlines the complexity of inner ear biology, current trial limitations, and the translational barriers facing regenerative medicine. Though the science is promising, for clinical success to be achieved, a possible paradigm shift involving gene editing, tissue engineering, and personalised therapy may be required.

7. Discussion

The potential use of stem cell therapy as a curative approach for congenital hearing loss represents a significant advancement in cochlea regenerative medicine and hearing function restoration. While current interventions such as hearing aids and cochlear implants offer partial auditory perception restoration and are known to compensate for rather than restore normal auditory function, they fail to address the underlying cellular deficits. Consequently, emerging stem cell therapy potentially offers a transformative approach in the management of congenital hearing loss and promises the potential to effectively restore hearing by directly targeting the underlying biological impairment and aimed at biologically restoring auditory function through the regeneration of absent or impaired sensory cochlea hair cells and auditory cochlea neurons. This discussion explores the evolving therapeutic landscape, the implications thereof, the refinement of delivery methodologies, and the multifaceted ethical and regulatory challenges and considerations integral to clinical translation.

While the advancements in preclinical research, particularly with iPSCs and MSCs, offer promising insights, there are still considerable barriers to translating these therapies into widespread clinical applications. Recent advancements in the differentiation of iPSCs and ESCs into otic progenitor cells present a promising path for replacing lost hair cells and spiral ganglion neurons. Hair cell loss is a key pathological feature of congenital sensorineural hearing loss, and targeted cochlea regeneration promises to restore the sensory transduction capacity of the organ of Corti. The use of iPSCs and gene therapy has also shown some success in preclinical models, showing cochlea cell regeneration and some functional hearing recovery, and MSC use has been found to potentially promote tissue repair and reduce cochlea inflammation. iPSCs being patient-specific in nature, offer an exciting opportunity in the creation of personalised therapies tailored to the individual genetic profiles of patients. This could be particularly beneficial for genetic congenital hearing loss, where mutations are known and specific gene therapies may be applied [16] [36].

As of 2025, there are several ongoing clinical trials aimed at exploring the potential of stem cells for treating congenital hearing loss. To enhance the precision and efficacy of these therapies, various strategies are under investigation. While this research is still in its early stages, a few clinical trials have already begun to test the feasibility and safety of stem cell intervention. These trials mainly focus on localised delivery methods like intracochlear intratympanic stem cell injection de-

rived from iPSCs and being tested for their ability to regenerate cochlea hair cells, or mesenchymal stem cell (MSC) transplants to promote cochlea repair in patients with acquired and congenital hearing loss, with the goal of assessing their ability for cochlea tissue integration and functional hair cell regeneration. These localised delivery methods appear to minimise systemic exposure and facilitate targeted integration into cochlea tissues [20] [34] [37]-[39].

Despite early research showing improved auditory function in animal models, clinical data on human trials remain limited. Much of the current research focuses on the safety of stem cell therapies, including issues like immune rejection, tumorigenesis, and the potential for overgrowth of transplanted cells [40]. Valuable insights regarding delivery methods, cell sources, and patient selection criteria are being seen in early-phase trials and are beneficial for further studies. Future research should focus on combination therapies, where stem cells are paired with gene therapy to enhance their regenerative capacity, personalised treatments using iPSCs derived from individual patients to minimize the risk of immune rejection and developing better delivery mechanisms with the incorporation of biomimetic scaffolds, such as using nanoparticles, hydrogels, or microneedles for precise intracochlear stem cell placement, which has shown potential in supporting stem cell viability and guiding spatial organisation post-implantation [41] [42].

Gene therapy has the synergistic potential to enhance stem cell therapy in treating congenital hearing loss and is an essential tool in stem cell therapy advancement. By targeting the genetic mutations that cause hearing loss, gene therapy can correct the underlying cause of the condition prior to stem cell application for hair cell or cochlea neuron regeneration. A promising aid to these strategies is the genetic correction of patient-derived iPSCs using gene editing technologies like CRISPR/Cas9 technology correcting genetic mutations responsible for congenital hearing loss prior to differentiation and using stem cells for cochlea regeneration [33]. Atoh1 gene activation has been used to trigger the differentiation of supporting cells into hair cells. The dual approach of addressing both the genetic cause and cellular deficit and the regenerative process enhances the therapeutic specificity and long-term viability of the intervention and provides a more holistic approach to restoring hearing. Recently, CRISPR/Cas9 was used to correct the TMC1 mutation in iPSCs derived from a patient with autosomal dominant hearing loss. The corrected iPSCs were then differentiated into cochlea hair cells *in vitro*, showing improved cell function. This combination of gene editing and stem cell therapy offers a two-pronged approach to curing genetic forms of congenital hearing loss [19].

Despite the promising results in animal models of preclinical studies, clinical trials with beneficial clinical outcomes remain limited, with significant challenging concerns that require attention prior to implementation in clinical practice.

Studies show the possibility of hair cell regeneration often with the failure of proper integration into the existing auditory structures and neural network. The intricate complexity of the cochlea including its unique fluid dynamics makes suc-

cessful cell survival and effective integration a challenge, especially in ensuring accurate administration and placement of stem cells. Further research into the more conducive environment achieved through tissue engineering and biomaterial scaffolds could assist overcome this [41] [42].

Negative immune response through rejection and inflammatory reactions, tumorigenesis, and difficulties with intracochlear cell integration are still concerns. Even with iPSCs, immune rejection is still a potential concern particularly in cases where the stem cells are donor-derived rather than patient-derived. Ongoing research is currently focused on creating "universal" stem cells, where cells are genetically engineered to express proteins that prevent immune rejection. This could ensure that stem cell therapies can be used across a wide range of patients without the need for immunosuppressive intervention. The pluripotent nature of ESCs and iPSCs poses a risk of uncontrolled cell growth, leading to tumour formation. Consequently, researchers are working on improving controlled differentiation protocols and pre-differentiation strategies to reduce the risk of tumour formation by ensuring that stem cells fully differentiate into the intended cell types before transplantation. Emerging therapies such as the use of immune-modulating drugs and stem cell niche creation may ease this risk by promoting immune tolerance to transplanted cells [43].

One of the biggest barriers to the widespread use of stem cell therapy is the high cost and complexity involved in producing stem cells in large quantities for clinical implementation. Stem cell therapy remains expensive and labour-intensive. Further research is required to improve the efficiency and scalability of stem cell production, possibly with bioreactors and automated differentiation protocols that can generate large quantities of cells for clinical implementation [18] [42].

The long-term safety of stem cell intervention remains a concern. Ethical issues related to gene editing, especially in human germline cells, require further attention, especially given the potential for inheritable changes to be passed down through generations and the ethical concerns surrounding embryonic stem cell use still persistent. The use of ESCs and gene editing techniques like CRISPR/Cas9 raises ethical questions regarding the potential for "designer babies" or the unintended consequences of genetic manipulation [44].

Regardless of the promising preclinical results translation to human therapeutic intervention remains challenging, especially considering the complexity and limited regenerative capacity of the human cochlea. Hair cell loss in the cochlea is a primary cause of sensorineural hearing loss. Guided stem cell differentiation into hair cells could replenish damaged hair cells in the cochlea, which are crucial for hearing. However, immediate hearing restoration may not be achieved as the neural connections between the ear and brain must also be re-established. Though still emerging and in the early stages, stem cell therapy for congenital hearing loss may potentially transform clinical intervention paradigms in the future. For this to succeed, rigorous trials and collaborative efforts will be imperative to overcome current barriers.

Cochlea implants, which bypass damaged hair cells to provide direct electrical stimulation to the auditory nerve, are a well-established widely used technology to treat and manage severe hearing loss. Combining cochlea use with stem cell therapy could bridge the gap between biological repair and functional recovery. While stem cells regenerate the damaged auditory epithelium, cochlea implants ensure constant auditory input during the regeneration process, preventing neural atrophy and maintaining brain-auditory connections. Combining these therapies promotes the potential to restore natural hearing while also providing the necessary electrical stimulation for improved auditory processing [45] [46].

Developing and enhancing better delivery methods such as scaffold-based delivery and gene-editing techniques may further enhance cell survival to improve cell integration, retention and functionality. Emerging innovative technology like immunosuppressive treatments or gene editing such as CRISPR/Cas9 could complement stem cell therapy to enhance its efficacy and hold great promise for genetic correction prior to transplantation. Challenges still remain in ensuring precision and avoiding off-target effects. Future research should explore both gene-editing efficiency and precision tools and ensure the safe delivery of therapeutic genes to the cochlea together with the long-term effects of genetic interventions on cochlea function and overall auditory health [2] [22].

Gene therapy is being increasingly integrated into stem cell therapy to overcome the genetic mutations that cause hearing loss. Additionally, epigenetic modulation could play a role in reprogramming supporting cells into hair cells. Researchers are exploring the use of small molecules or RNA-based therapies to activate or suppress specific genes involved in hearing regeneration. Immunomodulators have the potential to prevent immune rejection of transplanted cells, while gene editing could address the genetic causes of congenital hearing loss. When combined with stem cell-based regeneration, these approaches may create a collaborative synergistic effect [21] [41].

The use of patient-specific iPSCs for congenital hearing loss is very promising holding high treatment potential. In this approach, skin fibroblasts or blood cells are reprogrammed into iPSCs, which are then differentiated into cochlea hair cells, having the advantage of eliminating immune rejection, as the stem cells are patient-derived. Ongoing research is focused on optimising the differentiation protocols to efficiently produce cochlea hair cells for seamless cochlea integration. The future of stem cell therapies could lie in personalised approaches like this and may be the key to addressing hereditary forms of congenital hearing loss, where treatments are tailored to each patient's genetic profile and specific type of hearing impairment [20] [47].

Further optimisation of stem cell differentiation protocols for cochlea cell types to produce more efficient, mature and functional cochlea hair cells and auditory neurons is required, with a better understanding of the molecular pathways that govern cochlea cell development, which is crucial for improving the functional outcomes of stem cell therapy [21] [41].

A major obstacle in translating stem cell therapies into clinical implementation is the delivery mechanism. Modulation of the cochlea microenvironment has emerged as a critical factor in the survival and functional integration of stem cells. The complex and small size of the cochlea makes effective stem cell delivery a significant challenge. Research is increasingly focused on using nanoparticles, hydrogels, or microneedle arrays to ensure precise unimpaired intracochlear delivery of stem cells and growth factors. The use of biodegradable scaffolds is another promising approach to guide stem cell differentiation and improve long-term outcomes [21] [34] [41].

Both cochlea hair cell and spiral ganglion neuron regeneration are necessary for full hearing restoration. Future therapies will probably focus on both sensory cell regeneration and neural repair. Continued research into neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), alongside immunomodulatory agents that support synaptogenesis, reduce local inflammation, and encourage cochlea neuron growth, will drive future scientific advancements. Additionally, stem cell-derived neuronal grafts may allow for auditory nerve regeneration and ensure proper communication between the hair cells and the brain [21] [34].

An additional obstacle in the translation of stem cell therapy into clinical practice is noted especially in paediatrics and congenital hearing loss where it introduces significant ethical considerations. The source of stem cells remains a topic of moral debate. While iPSCs avoid the controversies associated with ESC use, they pose risks related to genomic instability, tumorigenicity, and potential epigenetic memory. Within this context, the use of gene-editing technologies such as CRISPR further intensifies ethical scrutiny. Although current approaches target somatic cells, the proximity to germline tissues raises the potential for heritable genomic alterations, necessitating rigorous ethical oversight and transparent risk-benefit assessments. Furthermore, the ethical complexity of informed consent where parents and guardians are the decision makers introduces challenges regarding autonomy and long-term uncertainty. The nature of stem cell-based therapies being irreversible heightens the ethical imperative in ensuring robust informed consent processes and long-term post-treatment management.

The pathway from preclinical promise to clinical implementation is further complicated by substantial global regulatory barriers. Stem cell-based therapy classification may vary across regions consequently affecting trial design, approval timelines, and post-market observation requirements. This regulatory heterogeneity presents a barrier to international collaboration and streamlined clinical development. Additional challenges in manufacturing standardisation persist. Differentiation protocols often present batch-to-batch variability, and quality control systems for ensuring the safety, transparency, and efficacy of clinical-grade cell populations have yet to be universally established. These issues are heightened by the necessity for good manufacturing practice compliance, which significantly raises the production cost and complexity.

The concern of healthcare equity is also evident in high and rising development and treatment costs which may limit access to stem cell therapies, disproportionately affecting individuals in lower-income populations. This potential for inequality emphasises the necessity for clinical trial policies that are inclusive and support equitable access.

More extensive clinical trials are needed, particularly those focusing on larger sample sizes and long-term follow-up which are essential for evaluating the safety issues like tumorigenesis and immune rejection and efficacy in the durability of hearing restoration achieved from human stem cell intervention. Efforts to refine delivery systems, improve cell survival, and reduce immune rejection will be critical for successful clinical outcomes [5] [22] [36] [41].

Interdisciplinary approaches are an integral priority necessary to accelerate the safe and effective implementation of stem cell therapies for congenital hearing loss. The field of stem cell therapy for hearing loss is witnessing rapid advancements, thanks to groundbreaking technologies like bioprinting, artificial intelligence (AI), organoids and cochlea-on-a-chip platforms. These innovations offer a controlled environment for evaluating safety and efficacy prior to in vivo application and enable more precise, scalable, and personalised approaches to treating congenital hearing loss. Furthermore, the integration of bioelectronic interfaces to either guide cell growth or monitor functional restoration may enhance biological repair strategies.

Bioprinting technology is revolutionising regenerative medicine by creating complex 3D tissue structures by layering bio-inks containing cells, growth factors, and biomaterials that mimic natural tissues. In the context of hearing loss, bioprinting could allow the development of precise cochlea hair cell replicas and supporting structures. Using bio-inks made from stem cells, researchers can design custom implants that integrate seamlessly with the auditory system, potentially restoring hearing function in a highly targeted way. Biocompatible nanotechnology-based neurotrophin delivery systems such as hydrogels, nanoarticles and supraparticles are being developed for use in neurotropin therapy for hearing impairment [21] [34].

AI plays a critical role in the analysis of large datasets from stem cell research, predicting outcomes, and optimising treatment protocols, identifying optimal stem cell types, differentiation protocols, and patient-specific treatments. AI models may be used to simulate the cochlea microenvironment and predict the behaviour of transplanted stem cells, reducing trial and error in preclinical and clinical studies. Machine learning algorithms also enhance imaging techniques, thus allowing for precise visualisation of regenerated hair cells [48].

Cochlea organoids are miniaturised and simplified versions of organs derived from stem cells *in vitro* in a way that mimics their structure and function. Inner ear organoids offer a new research platform to study hair cell regeneration and test new therapies. These miniaturised, lab-grown versions of inner ear structures replicate the cellular and molecular complexity of the cochlea. Organoids are help-

ing researchers study congenital hearing loss in detail and test drug-stem cell combinations in a controlled environment. With maturity this technology may provide a direct pathway to regenerating functional cochlea structures in patients [19] [43].

The potential of independent stem cell therapy is promising, though its integration with existing and emerging treatments could maximize its therapeutic potential. Combination therapies that pair stem cell-based regeneration with technologies like cochlea implants could prove to significantly improve clinical outcomes which is exciting for future research [4] [21] [41].

Optimal success will rely on the imperative need to achieve international consensus on ethical and regulatory frameworks which will ensure responsible innovation, coherent monitoring, and equitable access. The combined efforts of a multidisciplinary network including scientists, clinicians, ethicists, policymakers, and affected communities are essential in the overall implementation and success of stem cell therapy.

8. Conclusions

This review highlights the substantial potential of stem cell therapy for congenital hearing loss, particularly in terms of cell regeneration and functional hearing recovery. The promise of stem cell therapy to cure congenital hearing loss offers an exciting glimpse into the future of regenerative medicine, offering the potential for natural hearing restoration rather than auditory amplification reliance. The potential to regenerate cochlea hair cells and restore hearing represents a breakthrough in the treatment of hearing loss, which has long been considered irreversible. The path toward curing congenital hearing loss through stem cell therapy is progressing rapidly, with significant advances made in the last decade. Gene therapy, personalised stem cell treatments, and advanced delivery systems are all contributing to a future where hearing loss can be treated at both cellular and genetic levels. While substantial progress has been made in preclinical models, the transition to human therapeutic intervention still requires overcoming significant challenges related to cell integration, clinical translation, safety and ethical concerns. Significant concerns of immune rejection, tumorigenesis, efficient cellular integration, and overcoming technical, ethical, and safety challenges remain crucial to realising the full therapeutic potential of stem cells in hearing restoration.

The future of stem cell therapy for hearing loss is incredibly promising, especially with the integration of bioprinting, AI, and organoid technologies. Moreover, the concept of combination therapies that pair stem cell-based regeneration with cochlea implants or other advanced treatments opens new frontiers in addressing the multifaceted challenges in the complexity of hearing restoration. With technological maturity, they have the potential to offer durable, scalable, and effective solutions for individuals with congenital hearing loss, improving both biological and functional outcomes.

Further research, particularly large-scale clinical trials, is essential to realise the

full therapeutic potential of stem cell-based intervention, and should focus on optimising stem cell differentiation efficiency, developing better delivery mechanisms to enhance clinical outcomes, refining gene editing technologies and ensuring the long-term safety and efficacy of treatments. Ongoing interdisciplinary research into stem cell biology, gene editing, and technological innovation is critical to realising the full potential of stem cell-based hearing restoration, thus holding the potential to offer a revolutionary cure for congenital hearing loss and transform the lives of millions of individuals born with hearing impairment. As research progresses, stem cell therapies will likely become the cornerstone of congenital hearing loss intervention, offering a path to long-term, sustainable cures that go beyond current hearing amplification interventions. The dream of restoring hearing for individuals with congenital hearing loss is fast becoming a tangible reality.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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