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REVIEW ARTICLE

Precision Medicine Shows Promise to Advance the Care of Individuals with Hearing Loss

Michelle Pei, MD[1], Brett M. Colbert[1,2], Molly R. Smeal, AuD[1], Susan H. Blanton, PhD[1,3], Xue Zhong Liu*, MD, PhD[1,3,4]

[1]Department of Otolaryngology – Head and Neck Surgery, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[2]Department of Biochemistry, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[3]John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami FL 33136, USA
[4]Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Miami, FL 33136, USA

*x.liu1@med.miami.edu

ABSTRACT

Hearing loss (HL) is the most common sensory disorder worldwide and arises from a heterogeneous set of genetic and environmental etiologies. Currently, therapy for sensorineural HL is non-specific and limited to amplification devices and implanted neuroprosthetics. Recent advances in the burgeoning field of precision medicine focused on individualizing disease diagnosis and tailoring treatment to each patient's own biology hold great promise to provide tailored care for hearing loss patients. In this review, we discuss the current diagnostic algorithm and treatment options for hearing loss, the advances in using precision medicine tools to identify specific genetic variants that predispose to or result in hearing loss, the role of genetics in determining surgical outcomes following cochlear implantation, recent advances in gene and stem cell therapies for treating hearing loss, and patient-specific disease modeling using induced pluripotent stem cells. All of these precision medicine techniques will result in improved care for patients based on the precise etiology of their hearing loss.

1. Introduction

In recent years, 'precision medicine (PM)' initiatives have garnered increasing attention for their individualized approach to the prevention, diagnosis, and treatment of diseases. While patient-centric care has always been a core tenant of medicine, scientific progress over the last century has made deep phenotyping of patients and individually tailored treatment approaches possible and attainable. Instead of the traditional model of fitting a patient within a stereotypical disease schema with a blanket diagnosis and limited treatment options, PM involves high-resolution disease diagnosis, sometimes down to the specific genetic variant and its phenotypical manifestation. Specific subgroups of patients can be isolated and more targeted therapies can be developed and given.

Personalized medical care has existed for many years. For centuries, eye specialists have diagnosed individual refractive disorders and dispensed the appropriate corrective lenses. Every patient in need of blood transfusions within the last century was individually tested and precisely matched to donor blood of the same type. The identification of subtypes of breast cancer have directed the breakthrough development of receptor-specific antineoplastic drugs like Herceptin. The first drug to target the underlying cause of cystic fibrosis, lumacaftor/ivacaftor, was developed for patients homozygous for the most common cystic fibrosis variant, *F508del-CFTR*.

With the increasing accessibility of existing sequencing technologies, more accurate genetic testing, and a rapidly expanding library of genetic knowledge and research, there is great potential in the coming years for advancements in PM. The field of hearing loss (HL), a common condition with a wide array of heterogeneous etiologies, is particularly well-positioned to benefit from incorporating PM strategies to improve individual disease diagnosis and treatment.

2. Hearing loss: epidemiology, etiology, and diagnosis

Hearing loss is the most common sensory disorder in humans, affecting an estimated 1.5 billion people globally; roughly one in five people worldwide experience some degree of HL [1]. Because of the heterogeneity in its etiology, severity, and disease progression, HL may be classified in many ways. The most straightforward classification is based on the severity of auditory impairment as assessed by audiometric testing, ranging from mild to profound degrees of HL. HL may be further classified physiologically as conductive, sensorineural, or mixed types. Conductive hearing loss (CHL) is HL due to pathologies within the sound conduction pathway. Often, CHL is due to an anatomical obstruction to sound conduction, such as absence or malformation of the outer and middle ear structures, cerumen impaction, and perforation or sclerosis of the tympanic membrane. As such, many CHL cases are curable with medication, surgery, amplification, and assistive devices [2]. On the other hand, sensorineural hearing loss (SNHL) is HL due to pathologies of the inner ear, vestibulocochlear nerve, or the sound processing centers in the brain. Because irreversible cell death of the sensory hair cells, spiral ganglion neurons, or central nervous system is often involved, SNHL cannot currently be cured, and existing treatments aim to improve symptoms by amplifying signals to remaining healthy hair cells (HCs) or bypassing the damaged sections of the auditory pathway entirely. Lastly, mixed hearing loss (MHL) is HL due to a combination of both conductive and sensorineural pathologies within the same ear.

Hearing loss may also be classified by its etiology, such as genetic or non-genetic. Non-genetic causes of HL may be infectious, toxic, traumatic, neurologic, neoplastic, endocrinologic, systemic, psychological, or idiopathic in nature. Genetic HL may be further categorized into disorders that are syndromic (SHL) or nonsyndromic (NSHL). Genetic HL accounts for over half of congenital HL cases in developed countries [3] and roughly 80% of pre-lingual deafness [4]. Congenital HL affects one in every 500-1000 newborns, and of the genetic congenital HL cases, 30% are syndromic and 70% are non-syndromic [3]. More than 400 genetic syndromes associated with HL have been identified ([5]), and may be autosomal dominant (e.g., Waardenburg, Brachio-oto-renal, CHARGE, Treacher-Collins), autosomal recessive (e.g., Usher, Pendred, Jervell and Lange-Nielsen), X-linked (e.g., Alport, Otopalatodigital, Stapes gusher), or mitochondrially inherited. NSHL is extremely heterogeneous with 124 genes and more than 6,000 causative variants identified to date (*hereditaryhearingloss.org*). The inheritance of NSHL is 75-80% autosomal recessive, 20% autosomal dominant, 2-5% X-linked, and 1% mitochondrial [6].

2.1. Diagnosis of hearing loss

Since the widespread adoption of newborn hearing screen (NHS) in parts of Europe and the United States in the late 1990s to early 2000s, many cases of congenital HL have been identified in the neonatal period, leading to earlier

intervention and improved patient outcomes [7]. In current practice in the US, a neonate should undergo physiologic screening of otoacoustic emission (OAE) and/or auditory brainstem response (ABR) tests by 1 month of age. If the neonate 'refers' (i.e., fails) the screen, they are referred to audiologists for a diagnostic ABR to be done by 3 months of age. Infants diagnosed with HL should begin intervention by 6 months of age.

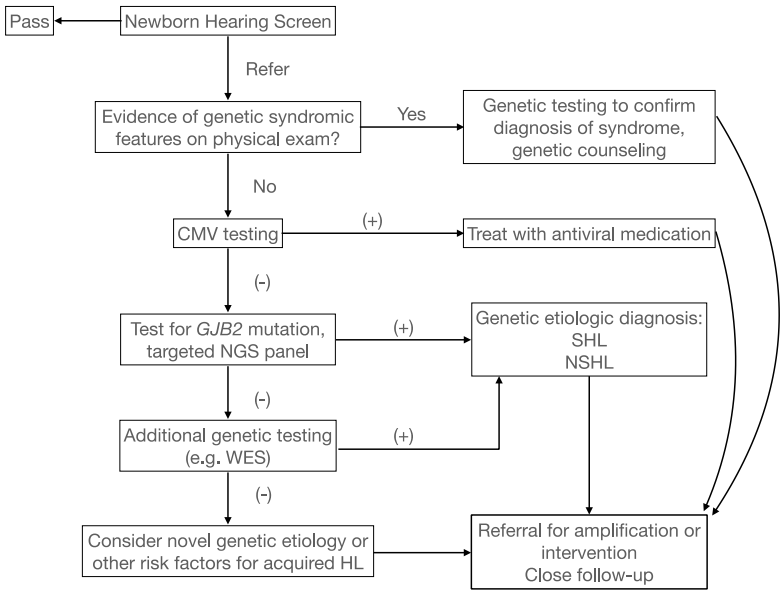
Hearing loss with onset past the neonatal period may be due to genetic factors, such as syndromes and variants associated with progressive hearing loss, and/or environmental insults, such as antibiotic use, noise exposure, and birth trauma. Because children with later-onset pre-lingual HL often have intact hearing at birth and may pass their NHS, there is often a delay in their HL diagnosis. In these cases, caregivers are usually first to notice the HL. In all patients presenting with HL the diagnosis is usually made using age-appropriate audiometric testing, a complete history and physical exam, and imaging. Follow-up testing for the etiology of HL include CMV tests (in neonates) and genetic screening.

2.2. Current genetic testing

Genetic factors are a common cause of hearing loss in all age groups, and genetic testing plays an important role in identifying the etiology of each patient's HL. Genetic testing is indicated for neonates who refer on the NHS, who do not have obvious syndromic features, and who test negative for CMV. If there is a family history of a particular HL disease, the neonate should first undergo single gene testing for the inherited disease. Otherwise, the next step should be *GJB2* testing (Figure 1). *GJB2* encodes Connexin 26 and its mutations have been shown to be causative for DFNB1. Variants in *GJB2* are the most common cause of hereditary, congenital, non-syndromic HL, and account for roughly 50% of severe-to-profound congenital, autosomal recessive NSHL [8].

If single gene testing based on a familial history of *GJB2* mutations is negative, patients should consider undergoing a targeted, next-generation sequencing (NGS) panel (Figure 1). Targeted NGS panels will be discussed in detail in a later section of this review. Given genetic factors are involved in more than half of congenital HL cases, there are increasing calls to adopt a concomitant genetic HL screen to the current NHS guidelines[15].

Figure 1: HL diagnosis algorithm



3. Current genetic tools for precision medicine in Hearing Loss

Significant genomic advances within the last several decades have greatly propelled advances in the field of precision medicine. Genetic testing for HL began in the late 1990s, with the discovery of the first gene implicated in non-syndromic human deafness: *GJB2* [11,17]. At that time, genetic testing using variant detection assays and single-gene Sanger sequencing were low-throughput, time-intensive, and expensive. In 2003, after roughly 13 years and $3 billion, the Human Genome Project

gave us the first complete human reference genome that played a foundational role in the shift from single gene sequencing to high-throughput next generation sequencing (NGS). Over the last two decades, the meteoric advancement in sequencing technology has led to a burgeoning new era of HL-related genetic discoveries. The following sections aim to provide an overview of several key tools crucial to improving PM by finding underlying causes, optimizing treatments, and ultimately improving patient outcomes. As we progress in the era of PM, an early and accurate diagnosis of the genetic etiology of each patient's HL will aid in directing individual prevention and treatment plans, improving genetic counseling, and steering the direction of future research. In the published literature, NGS panels have proven to be quite effective, consistently yielding genetic diagnoses in study patients [12,13]. Considering the utility and increasing affordability of NGS testing for genetic etiologies of HL, the 2014 practice guidelines by the American College of Medical Genetics supports the use of NGS tests for a comprehensive evaluation of HL patients [14].

3.1. Targeted next-generation sequencing panels

One of the most popular current methods for genetic testing for HL, targeted next-generation sequencing (NGS) panels can sequence up to hundreds of genes in parallel, producing faster results at lower costs than earlier generation sequencing methods. These panels efficiently analyze the exomes of all previously reported HL-related genes, giving researchers and clinicians a quick and reliable tool to study and diagnose genetic HL. Recently, X. Yu and colleagues (2020) used a custom NGS panel to identify separate causes for HL in one deaf family in Shanghai. Many panels have been developed over the last decade.

Otological Sequence Capture of Pathogenic Exons (OtoSCOPE) was the first clinically available genetic HL panel. Developed at the University of Iowa Molecular Otolaryngology and Renal Research Labs [15], it is currently on its 9th version and tests for 224 genes known to cause syndromic and non-syndromic HL (https://morl.lab.uiowa.edu/genes-included-otoscope-v9). It has a diagnostic sensitivity and specificity of greater than 99% [15]. The test has since been used in the clinic for etiologic diagnosis and in numerous studies to identify novel pathogenic HL variants (Table 1). Since its inception, OtoSCOPE has been used in studies of patients from various ethnic backgrounds, validating its suitability for use globally.

The OtoGenome test for Hearing Loss was developed at the Laboratory for Molecular Medicine. It tests for genes known to be related to syndromic and non-syndromic HL and is reported to be >99% sensitive to SNP variants and 97% sensitive to insertion and deletion variants. It does not test for variants in non-coding regions. (http://personalizedmedicine.partners.org/Laboratory-For-Molecular-Medicine/Tests/Hearing-Loss/OtoGenome.aspx).

Other targeted NGS panels for HL include, but are not limited to: OtoSeq (Cincinnati Children's Hospital) which tests for 23 of the most common HL genes and can identify approximately 80% of genetic causes of early onset SNHL (https://www.cincinnatichildrens.org/service/g/genetics-genomics-diagnostic-lab); MiamiOtoGenes (Miami Otogenetics Program) tests for 180 HL-associated genes and has been used to study both small families and broad multiethnic populations across 4 continents to discover novel gene variants [16]; Otogenetics Corporation offers a HL gene panel that tests for 129 HL genes and has been used to find novel pathologic gene variants (https://www.otogenetics.com/); LabCorp Comprehensive HL panel (LabCorp) tests for 264 genes and has a turnaround time of 28 days (https://www.labcorp.com/tests/630628/comprehensive-hearing-loss-ngs-panel-mtdna); Fulgent NSHL panel (Fulgent Genetics) tests for 100 NSHL genes (https://www.fulgentgenetics.com/hearing-loss-nonsyndromic); Blueprint Genetics Comprehensive HL and Deafness panel (Blueprint Genetics) tests for 288 genes with >99% sensitivity and specificity in detecting SNP, insertion, deletion, indels, and CNV variants (https://blueprintgenetics.com/tests/panels/ear-nose-throat/comprehensive-hearing-loss-and-deafness-panel/).

Custom, population-specific gene panels have also been developed and utilized in research studies to identify common variants and uncover new variants. A non-exhaustive assembly of such studies can be found in Table 1.

Table 1: Recently published studies using custom gene-panels

Study	*HL subjects*	Ethnic/geographic background(s)	Gene panel used	Gene	Novel variant
[17]	686 patients		OtoSCOPE	*ALMS1, MYO6, PDZD7, PNPT1, SERPINB6, TRIOBP, USH2A*	Copy number variants (CNVs)
[18]	1 consanguineous family, 3 probands AR NSHL	Pakistani, European, Middle-eastern, 1 unknown	OtoSCOPE	*COCH*	c.271C>G c.439A>T c.571_572delinsAG c.631G>T c.1093_1101del
[19]	26 patients from 10 families AR NSHL	Sub-Saharan African	OtoSCOPE	*MYO7A* *CDH23* *LOXHD1*	c.5809_5811delCTC c.6399C>A c.8720T>C c.3371G>A c.3979T>A
[20]	3 generational patients from 1 family with Baraitser-Winter Syndrome	N/a	OtoSCOPE	*ACTG1*	p.Ala58Val
[21]	Generational patients from 1 family with BL AD NSHL	European	OtoSCOPE	*TBC1D24*	C.533C>T
[22]	1314 unrelated individuals with NSHL	Japanese	OtoSCOPE	*LOXHD1*	c.879+1G>A c.5869G>T c.4480C>T
[23]	220 unrelated individuals with SNHL	Japanese	OtoSCOPE	*PTPRQ*	c.1261C>T c.166C>G or T c.6453+3delA
[24]	302 *GJB2*-negative families with AR NSHL	Iran	OtoSCOPE	Many; see reference	113 novel variants
[25]	18 unrelated patients, 1 from a consanguineous family	Mostly White, 1 White Egyptian, 1 mixed, 1 Hispanic/Latino	OtoGenome	*TMPRSS3*	Deletion of exons 1-5 and 13
[26]	1 family	Ashkenazi Jew	OtoGenome	*OTOF*	c.5332GG>T
[27]	23 unrelated consanguineous families	Iranian	MiamiOtoGenes	*MYO7A* *GIPC3* *STRC*	c.1190C>T c.6438 + 1G>T c.245A>G c.4012C>T
[28]	342 *GJB2* mutation-negative probands	South Africa, Nigeria, Tunisia, Turkey, Iran, India, Guatemala, USA	MiamiOtoGenes	Many; see reference	31 novel variants

29	5 families	Iranian	MiamiOtoGenes	*TRIOBP* *LHFPL5* *CDH23* *PCDH15* *MYO7A*	c.3089delC c.269C>G c.2432G>A c.9389_9390delCT c.2758C>T c.2361C>A
30	1 family	Arab	OtoGenetics	*GIPC3*	c.472G>A
31	20 families with AR NSHL	Iranian	OtoGenetics	*MARVELD2*	c.1555delinsAA
32	44 patients with Usher syndrome	Spanish	Custom 10 Usher or Usher-related gene panel	Many; see reference	24 novel variants
33	1 non-consanguineous family	Chinese	Custom 127 gene panel	*ILDR1*	c.427delT
34	4 conganguineous and 2 multiplex families without *GJB2, SLC26A4, MT-RNR1* mutations	Uyghur	Custom 97 gene panel	*TMC1* *MYO7A* *PCDH15* *MYO15A*	p.L416R/p.A438T p.V1880E c.1238delT c.9690+1G>A
35	29 probands with consanguineous parents or had affected relatives	Turkish	Custom 102 gene panel	Many; see reference	8 novel variants
36	6 generational patients form 1 family	Italian	Custom 59 gene panel	*EYA4*	c.1154C>T
37	1 family	Spanish	Custom 117 gene panel	*HOMER2*	c.832_836delCCTCA
38	131 unrelated NSHL patients	Chinese	Custom 227 gene panel	*MYO15A* *OTOF* *RDX*	c.3866dupC c.10251_10253del c.1274G>C c.129_130del c.76_79del
39	128 patients from 118 families	Spanish	Custom 59 gene panel	Many; see reference	14 novel varients
40	1 6-generation family with AD SNHL	Chinese	Custom 129 gene panel	*KCNQ4*	c.887G>A
41	1 consanguineous family	Iranian	Custom 127 gene panel	*ESRRB*	c.499G>A

4.2. Whole Exome Sequencing

Whole exome sequencing (WES) targets most of the protein-coding regions of the genome. Because exomes only account for 1.5% of the entire genome, and with most single-gene pathogenic mutations located in the exome, WES has the advantage of being dramatically more time- and cost-efficient than whole genome sequencing (WGS). WES has been used to identify novel HL gene variants in many studies, including novel variants in *MITF* by Thongpradit et al.; in *WFS1* by Mohammadi-Asl et al.; *MYO15A, COL11A2, and CDH23* by Liang et al.; *GRM7* in 30 British patients by Lewis et al.; *CDH23, GJB2, MYO15A, OTOG,* and *SLC26A4* in a large consanguineous Muslim Family in India by Fareed et al.; *TMPRSS3,*

MYO15A, TMC1, ADGRV1 and *PTPRQ* in 33 Chinese families by Sang et al.; and many more [42–46,12].

Not only can WES reveal novel variants of known HL genes (https://hereditaryhearingloss.org/), it can also be used to identify new candidate genes, which will ultimately improve our understanding of HL and increase the catchment of targeted gene panels [45,47]. *TPRN* was among the first gene to be identified using WES methods and was found to be the causative gene in NSHL DFNB79 [47]. Since then, a number of new deafness candidate genes have been found. Lewis et al. identified 4 new candidate HL genes in a group of 30 NSHL patients: *NEDD4, ZAN, DNAH2,* and *NEFH* [45]. Wonkam et al. found 7 novel candidate HL genes (*INPP4B, CCDC141, MYO19, DNAH11, POTEI, SOX9,* and *PAX8)* in 184 Ghana patients from 51 families with at least 2 hearing-impaired members [48].

5. Pharmacogenomics and Hearing Loss

Pharmacogenomics, perhaps the earliest application of precision medicine, is the study of how an individual's genetic profile influences their response to pharmaceuticals, and is a crucial component of PM [49]. In brief, pharmacogenomics aims to study positive and adverse responses to medications, profile genetic variations between affected and unaffected individuals, and use the compiled data to direct future clinical decisions and streamline drug development [50,51].

More than 200 drugs are known or suspected to cause ototoxicity [52]. Depending on the structures affected, ototoxicity may manifest as cochleotoxicity (tinnitus, HL), vestibulotoxicity (dizziness, imbalance), or a combination of both. Because there is the potential for physiologic compensation for vestibular damage, the irreversible hair cell damage due to cochleotoxicity is generally considered the more serious problem [53]. The aminoglycoside antibiotic class and the anticancer drug cisplatin are of specific interest for the purposes of this review since they are two indispensable, widely used, first-line medications that are known to cause permanent SNHL. It has been estimated up to 50% of aminoglycoside-treated and 75-100% of cisplatin-treated patients developed some degree of HL [54–56]. Both drugs damage cochlear HCs, with the initial insult primarily affecting the physiologically sensitive basal outer hair cells (OHCs), resulting in high-frequency HL. Continued exposure to the inciting mediations will lead to hair cell damage further along the organ of Corti. Because individual susceptibility to aminoglycoside- and cisplatin-induced ototoxicity varies widely within the population, there has been great interest in identifying the relevant genetic and non-genetic risk factors.

Aminoglycosides are the most well-studied class of ototoxic drugs. Within the drug class, there is variable cochleotoxicity and vestibulotoxicity: gentamicin, streptomycin, and tobramycin are primarily vestibulotoxic, whereas amikacin, dihydrosterptomycin, kanamycin, and neomycin are primarily cochleotoxic [53]. Currently, the most effective preventative measure to ototoxicity is avoiding exposure altogether and using an alternative, possibly less effective, antibiotic [57]. Aminoglycoside-induced cochleotoxicity occur both in a dose-dependent and idiosyncratic fashion, with the latter being the more common and related to genetic predispositions [58]. Aminoglycosides are bactericidal antibiotics that work by binding bacterial rRNA and inhibiting protein synthesis. Since human mitochondrial ribosomes are structurally more related to bacterial ribosomes than eukaryotic cytosolic ribosomes, aminoglycosides have an affinity to bind to mitochondrial rRNA. This explains why cochlear hair cells, rich in mitochondria, are more susceptible to aminoglycoside-related toxicities. As such, most of the reported variants associated with aminoglycoside-induced HL are in mitochondrial genome, specifically within the mitochondrial 12S rRNA gene. In fact, the 12S rRNA gene has been shown to be a hotspot for both non-syndromic and aminoglycoside-induced HL [58]. Of the reported 12S rRNA mutations, the most common is A1555G, with a 0.2% overall prevalence and is found in 17% of caucasian and 10-33% of Asian patients with aminoglycoside-induced HL [59–62]. There is also high frequency of A1555G in non-syndromic SNHL patients without a history of aminoglycoside exposure but not in controls [62–66]. Other 12S rRNA mtDNA variants with associated risk for aminoglycoside-induced deafness that have been identified and validated in replication studies include C1494T, delT961insC, A827G, T1095C, and multiple variants at position 961 [67–73].

Comparatively, whether or not there is genetic predisposition to cisplatin-induced ototoxicity remains unclear. The mechanism of cisplatin-related ototoxicity is multifactorial, involving long-term cisplatin retention in the inner ear, inflammation, and dysfunction of various antioxidant defenses [74,75]. In brief, cisplatin increases the generation of reactive oxygen species (ROS) and induces DNA damage within a cell. Theoretically, any variation in the cell's ability to modulate ROS via antioxidant enzymes or ROS

scavengers may lead to either otoprotective or ototoxic effects. Reported genetic variants pertaining to cisplatin-induced ototoxicity have been primarily in the megalin, glutathione-S-transferase (GST), thiopurine-S-methyltransferase (TPMT), and catechol-O-methyltransferase (COMT) genes. Studying patients with a history of cisplatin therapy, Riedemann et. al. reported a higher frequency of the A-allele at megalin rs2075252 in the HL group than the intact hearing group [76]; however, a repeat study by Ross et al. was not able replicate this finding [77]. Some GST variants, including GSTM3*B, GSTP1 rs1695 G-G genotype, and the GSTM1 deletion, have been reported to be otoprotective from cisplatin-induced ototoxicity [78,79], but the findings were not replicated by [77]. Ross et al, using high-throughput screening tools to screen for SNPs in hundreds of genes, found that the SNP rs12201199 in TPMT and the SNP rs9332377 in COMT to be highly associated with cisplatin-induced HL [77]; subsequent studies designed to validate these findings have reported inconsistent results [80–82]. Currently, with inconsistent findings from different groups, it is not yet clear whether these reported gene variants play a significant role in cisplatin-induced ototoxicity. Because it is difficult to control for study methods such as cumulative cisplatin exposure, concurrent therapies, type of cancer, ototoxicity grading criteria, and ethnic makeup of study subjects, future work to elucidate genetic contributions to cisplatin-induced ototoxicity should include larger and more diverse cohorts and focus on standardizing study criteria [56,83].

There is a wide variability in drug-induced HL amongst individual patients. As such, there is great potential to be more precise in preventing and reversing drug-induced HL, from screening for high-risk alleles to developing targeted otoprotective therapies. High-throughput screens and genome-wide association studies have replaced targeted gene approaches to identifying potential genetic markers for drug-induced ototoxicity. Therapeutic models for generally preventing drug-induced ototoxic hair cell death, such as small molecular antioxidative and anti-inflammatory agents and neurotropic growth factors, have been proposed with investigations currently underway [84–86]. Further elucidating individual susceptibilities to ototoxicity, whether genetic or other factors, will improve potential interventions.

6. The role of genetics in determining cochlear implant outcomes

Since the first cochlear implant by William House and John Doyle in 1961, an estimated 800,000 registered devices have been implanted worldwide in patients with moderate-to-severe SNHL ([87], nidcd.nih.gov). Though cochlear implantation (CI) technology and surgical techniques have continued to improve over the years [88,89], post-implant functional performance has remained widely variable. Historically, outcome variation has largely been attributed to clinical and patient-specific factors, such as variable duration of deafness prior to implantation, general etiology of HL, nonverbal IQ, and familial background [90,91]. Some recent studies, however, have shown that the genetic makeup of the CI recipient may possibly contribute to the variability of post-operative outcomes [92]. HL due to genes with high intra-cochlear expressions tend to benefit greatly from CI whereas HL due to genes with predominantly extra-cochlear expression tend to have poor post-CI performance. Studying two of the most common genetic causes of NSHL, Wu et al. compared outcomes in CI patients with and without pathogenic variants in *GJB2* or *SLC26A4* and found those with variants had better post-implant outcomes if they received their CI prior to age 3.5 years and equivalent outcomes if they received their CI later [93]. Similar studies by multiple authors [28,94–100] reported good post-CI outcomes for patients with *GJB2* related HL. As thoroughly reviewed by [92], variants in *GJB2, SLC26A4, CDH23, MYO7A, MYO15A, ACTG1, OTOF, LOXHD1,* and mt12SrRNA have been found to be associated with good post-CI outcomes. Patients with *DFNB59* and *PCDH15* as the cause of their HL tend to have poor post-CI outcomes [93,99]. There are conflicting results in the post-CI outcomes for *TMPRSS3* and *COCH*, with some reports of benefit and others reporting no hearing improvement post-implant, possibly due to the role of these genes in affecting healthy SGN function [101,102]). A subsequent study showed CI patients with variants causing abnormal SGN function (e.g., *AIFM1, DIAPH3, DFNB59, OPA1*) had significantly worse post-implant outcomes than patients with variants in genes confined to the cochlea [103].

7. Personalized therapy for Hearing Loss

Currently, treatments for SNHL patients are non-specific and mostly limited to amplification devices and surgical implants, which provide patients with functional improvements but are have no effect on curing their specific underlying disease. With the ever-expanding field of knowledge in HL research and promising preclinical advances in gene and cell-based therapies, we are inching towards the day where HL patients may benefit

from personalized disease modeling and individualized therapeutics.

7.1. Gene therapy research in Hearing Loss

Gene therapy is the genetic modification of pathogenic variants via the delivery of exogenous nucleic acids or gene-editing agents to treat or prevent disease. The cochlea is an ideal organ for gene therapy as its surgical accessibility and anatomical isolation allows precise delivery of therapeutics with minimal off-target effects. There are several gene therapy methods currently being investigated in animal models with promising results.

Gene replacement

Gene replacement therapy is the technique in which dysfunctional genes are replaced by the normal functioning version in affected cells. Recessive conditions benefit most from gene replacement, as most are due to loss-of-function variants. A popular method of delivering normal genes to replace abnormal genes is via viral vectors. Several viruses have been developed into viral vectors for gene replacement, including adenovirus, adeno-associated virus (AAV), helper-dependent adenovirus, lentivirus, herpes simplex virus, vaccinia virus, and sendai virus [104]. Of these, AAV is generally preferred due to its low immunogenicity and pathogenicity, few off-target effects, wide host-cell range, and high transduction efficiency [105,106]. Akil et al. reported the first successful inner ear gene therapy study in mice, in which cochlear delivery of *Vglut3* using AAV-1 to congenitally deaf *Vglut3*-KO mice led to transgene expression in inner hair cells (IHC), normalized ABR thresholds, and rescue of the deafness phenotype [107]. Similar results were achieved by Zhao et al. using an AAV8 vehicle for *Vglut3* delivery, with exogenous expression mediated in all IHCs and restored auditory function that remained stable for at least 3 months [108]. AAV-mediated delivery of *Otof* to profoundly deaf *Otof-/-* mice has been achieved by various groups using dual-AAV vectors and overloaded AAV vectors [109–111], resulting in full-length *Otof* expression in IHCs and restoration of hearing as evident on ABR and behavioral assays. Askew et al. used AAV2/1 to induce exogenous *Tmc1* and *Tmc2* expression in the IHC of *Tmc1*-mutated deaf mice, and found it was sufficient in partially restoring ABR and acoustic startle reflexes [112].

Conventional AAVs have two major disadvantages: low viral capacity (4.7 kb) and limited transduction of OHCs and supporting cells. The former has been overcome by the successful development of dual injection methods [109,113–116]. The latter has ushered in the emergence of synthetic AAVs [117]. Nist-Lund et al. showed the synthetic AAV Anc80L65 could transduce IHC and OHC with high efficiency, restore auditory function, and improve hair cell survival, in addition to improved breeding and growth rates of the mouse model [114]. Wu et al. showed single and dual vector delivery of exogenous *Tmc1* using synthetic AAV9-PHP.B promoted both IHC and OHC survival in dominant and recessive forms of *Tmc1*-related HL mouse models [116]. Taiber et al. used the synthetic AAV9-PHP.B to deliver *Syne4* into *Syne4-/-* mice (a model of DFNB76) and demonstrated the restoration of hair cell morphology and near complete recovery of auditory function[115].

Other gene replacement studies using both conventional and synthetic AAVs have shown also promising results in restoring normal gene function and reversing the HL phenotypes in mouse models of *Gjb2* [118,119], Usher syndrome 1C [120], Usher syndrome 2D [121,122], Usher syndrome 3A [123–125], Jervell and Lange-Nielsen Syndrome [126,127], and more.

Gene silencing

Gene silencing aims to knock down abnormal gene expression. The three main methods of gene silencing are antisense oligonucleotides (ASOs), RNA interference (RNAi), and clustered regularly interspaced short palindromic repeats (CRISPR).

Short interfering RNA (siRNA) and microRNA (miRNA) are short duplex noncoding RNA molecules ~20-24 bp in length that act as the main facilitators of RNAi. Both function by binding to target messenger RNA (mRNA) and promoting mRNA degradation and prohibiting translation; siRNAs are highly specific to one mRNA target while miRNAs may have multiple targets [128]. Maeda et al. showed siRNA could suppress the expression of an autosomal dominant variant of *GJB2,* R75W, and prevent HL [129]. Shibata et al. used a single intracochlear injection of miRNA carried by an AAV vector to restore hearing in the *Bth* mutant mouse, which had a dominant missense change in *Tmc1* that modeled the human autosomal dominant NSHL DFNA36 [130]. Mukherjea et al. showed the siRNA-mediated suppression of NOX3, a cochlea-specific isoform of NADPH oxidase that is the primary generator of ROS, reduced apoptosis in cisplatin-exposed cochlea and reduced cisplatin-induced ototoxicity [131].

ASOs are ~20-30 bp sequences that are delivered as single strands to bind to target mRNA molecules to promote mRNA degradation and splicing interference [132]. Lentz et al. was the first to successfully use ASOs to restore cochlear and vestibular function in a mouse model of type 1 Usher

syndrome [133]. ASOs were delivered systemically in the initial study but have since been successfully delivered locally to the auditory system via inner ear injection, trans-tympanic membrane injection, and topical tympanic membrane application [134]. An in-depth review of ASO therapy for hearing loss was recently published [135].

Gene editing and CRISPR/Cas9

Faster, cheaper, simpler, and more accurate than traditional gene editing techniques, the CRISPR/Cas9 system has revolutionized gene editing. Briefly, the system works as follows: a ~20 bp guide RNA (gRNA) specifically binds to its intended DNA target. The Cas9 enzyme then follows the RNA to the same location on the genome and enzymatically cleaves the DNA. Scientists can then use the cell's innate DNA repair mechanisms to add, delete, or change the DNA sequence at the breakage site [136]. Though Cas9 is most often used, other Cas enzymes exist, each with slightly different properties.

The CRISPR/Cas (CRISPR-associated protein) gene editing system has recently been shown to knockdown altered gene expression in dominant conditions. Gao et al. used a cationic lipid mediated CRISPR/Cas9 complex to disrupt the altered gene expression in *Tmc1*$^{Bth/+}$ mice and significantly reduced the progression of HL [137]. Targeting the same allele variant, György et al. used an AAV-mediated SaCas9-KKH delivery system, and showed it prevented deafness in *Bth* mice for up to one year following injection without toxicity [138]. Gu et al. used an AAV-delivered CRISPR/Cas9 system to target the proapoptotic gene *Htra2*, which has been shown to be involved in aminoglycoside-induced ototoxicity in mice and found there were significant improvements in ABR thresholds for at least 4 weeks following neomycin exposure [139].

Gene therapy clinical trials

Though preclinical animal studies have been encouraging, the human auditory system differs from animal auditory systems in many ways, from anatomical differences to physiologic sturdiness against insults [140,141]. As such, human clinical trials are the necessary next step in the advancement of cochlear gene therapy. Recently, a 22-patient phase 1 and 2 trial studying the safety and effect of the drug CGF166 on severe-to-profound HL was completed (*https://clinicaltrials.gov/ct2/show/results/NCT02132130*). CGF166 is a recombinant adenovirus (Ad) vector containing the human *ATOH1* which codes for HATH1, a transcription factor with key roles in human HC differentiation. The study participants received a single dose of CGF166, delivered via an intra-labyrinthine infusion, at one of four assigned dosages. In preclinical studies using a guinea pig HL model, Ad-delivered Hath1 (also known as Atoh1) induced stereocilia regeneration in damaged hair cells following noise exposure and was shown to significantly improved post-treatment hearing [142]. Though there has yet to be a published report of the recently-concluded clinical trial, a preliminary review of the available data showed no study participants had ABR threshold improvements or clinically significant speech recognition improvements following CGF166 treatment while there were 46 adverse events reported for all of the 22 participants, although none were considered to be serious (*https://clinicaltrials.gov/ct2/show/results/NCT02132130*).

7.2. Using stem cells for precision research in Hearing Loss

Unlike other non-mammalian vertebrate hair cells, mammalian cochlear hair cells cannot regenerate [143,144]; as such, there is great interest in cochlear hair cell regeneration. There are three main approaches to hair cell regeneration: transdifferentiation of supporting cells, promotion of existing support cells, and stem cell transplantation [145]. In birds and zebrafish, spontaneous regeneration following hair cell death involves a combination of supporting cell proliferation and transdifferentiation of progenitor supporting cells into HCs [146–148]. Though utilizing endogenous cells for regeneration has its advantages, a number of issues including difficulty controlling the cell cycle and temporal limitations are still currently being investigated.

Comparatively, there have been tremendous strides in stem cell transplantation research. Stem cells, with their ability to continually self-renewal and differentiate into any cell type, hold great therapeutic potential for reversing SNHL. There are three main types of stem cells used for hair cell regeneration research: embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs). ESCs are collected from the inner cell mass of the human blastocyst and have pluripotent potential, or the ability to form all cell types of the body [149]. ESCs have significant research and therapeutic potential, but their use is significantly restricted by ethical concerns and limited availability. ASCs exist to continually replenish somatic cells and can be found throughout the body but have very limited differentiation potential. iPSCs are cells artificially induced from somatic cells and, as its name implies, have

pluripotent potential like that of ESCs while avoiding the ethical, harvesting, and immunologic issues [150,151].

Current studies using iPSCs have focused on developing patient-specific disease models and HC regeneration. Significant progress has been made in both realms in the last decade, raising the possibility of personalized disease modeling and stem cell therapies for HL [152]. With regards to HC regeneration, Chen et al. reprogrammed human donor urinary epithelial cells to form iPSCs that were then successfully differentiated into otic epithelial progenitors (OEPs), HC-like cells, and spiral ganglion neuron (SGN)-like cells. OEPs transplanted into mouse cochlea via round window injection localized to the organ of Corti, differentiated into HC-like cells, and formed synaptic connections with native SGNs [153]. Lopez-Juarez et al. transplanted OPCs derived from human iPSCs into an adult guinea pig model of ototoxicity and showed the OPCs migrated to and engrafted in damaged sites within the cochlea, and partially differentiated into HC-like cells [154]. Other iPSC models of variant-specific HL have been achieved for a number of pathologic variants: *MYO15A* [155], *MYO7A* [156(p20)], *Barh11* [157(p),158]), *pendrin* [159].

8. Conclusion

Hearing loss is a vastly heterogeneous disease with a diverse set of etiologies and phenotypes. It deserves a set of diagnostic and therapeutic tools that can accurately identify subtypes and precisely target the underlying pathology. Significant work in recent years have broadened our understanding of pathologic variants, shown the utility of genetic testing, and laid the foundational groundwork for individualized disease modeling and tailored therapies. Though preliminary efforts have been promising, many scientific and translational hurdles lay ahead.

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