Genetic Counseling Training Guide for Genetic Hearing Loss

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Introduction

The purpose of this Genetic Counseling Training Guide for Genetic Hearing Loss is:

1. To describe in detail the genetic counseling process
2. To provide general guidance on important information to discuss with the patient/family
3. To provide additional resources and support needed to counsel patients with hearing loss before and after genetic testing

Of note, this guide was tailored for providers ordering a comprehensive hearing loss gene panel. Broader tests that include genes not associated with hearing loss (e.g., exome or genome sequencing) may have additional clinical implications that are not within the scope of this guide.

The Role of Genetic Counseling

Genetic counseling for hearing loss can be performed by a variety of healthcare providers including clinical geneticists, genetic counselors, or hearing healthcare providers with appropriate understanding of the process. Pre-test genetic counseling provides education and support to enable patients/families to make informed decisions about genetic testing for hearing loss. Post-test genetic counseling explains results and implications. The genetic counseling process aims to meet the patient's educational and psychosocial needs.

Special Considerations for Genetic Testing of Children

Genetic testing of children requires specific considerations:

- **Informed Consent:** Parents/guardians provide consent. Involve the child when appropriate.
- **Results Disclosure:** Encourage parents to share information with the child at an appropriate developmental stage. Address potential implications for family members.
- **Confidentiality:** Protect the child's privacy and future autonomy.
- **Psychological Impact:** Advise parents about potential emotional burdens and the child's right to know results when appropriate.

Pre-test Genetic Counseling

Pre-test counseling addresses the psychological impact of potential test results and prepares patients for possible outcomes. It includes reviewing the patient's personal and family history, providing education about hearing loss genetics, and discussing the elements of informed consent, including the potential results and implications.

Family History and Risk Assessment

The process of taking the family history provides an opportunity to solicit the individual's personal and family experience with hearing loss and provides an opportunity to develop rapport with the patient. A geneticist or genetic counselor will typically obtain a 3-generation pedigree using standardized nomenclature documenting known and suspected hearing loss diagnoses, including age at diagnosis and laterality and the results of genetic testing in family members, if available. For a hearing healthcare provider, family history collection should involve a review of the family history and results of a physical exam to determine if there is a potential genetic etiology or syndromic condition.

Guidelines recommend using a comprehensive hearing loss gene panel unless a specific syndrome or family history indicates otherwise. Hundreds of genes have been associated with hearing loss; some of the most common include: *GJB2*, *STRC*, *SLC26A4*, *MYO15A*, and *OTOF*. A risk assessment can be provided to the patient based on family history which may indicate an inheritance pattern in the family.

Explain that it is possible that genetic testing could suggest that the family history of hearing loss is caused by one of the known genes associated with hearing loss, by an undiscovered gene, or due to multifactorial (genetic and environmental) risk factors.

In families with a known disease-causing gene variant, review the likelihood to test positive for the familial variant given the family history and inheritance pattern which could be autosomal dominant, autosomal recessive, or X-linked (described in the following section).

Education about the Genetics of Hearing Loss

Provide a brief introduction to genetics vocabulary that may be used during the appointment. Example language may include:

- Genes are the instructions that tell the body how to develop and function. Humans have approximately 30,000 genes. A complete set of our genes is located in the nucleus (or center) of almost every cell in the body. Genes are organized on structures called chromosomes. Humans have 23 pairs of chromosomes. Chromosomes are made of DNA (deoxyribonucleic acid). DNA is a chemical arranged in a linear sequence. Genes are DNA sequences, which may serve as templates to make proteins that carry out each gene's function.

- Genetic testing is an analysis of the DNA sequence of a gene, looking for variations that might contribute to conditions such as hearing loss. Some variations may be harmful because they can disrupt the gene's ability to make a functional protein. These harmful variations are called disease-causing variants (formerly called mutations). Other variants may be rare, but not harmful.

Then provide an overview of the genetics of hearing loss. Talking points include, but are not limited to:

- Every year, thousands of children are born with hearing loss in the United States and 95% of newborns with hearing loss are born to hearing parents. More than 60% of congenital hearing loss is due to an underlying genetic cause. The majority of congenital hearing loss is isolated (nonsyndromic), however, approximately 20% is associated with an underlying genetic syndrome.

- Genetic testing is required to confirm a genetic hearing loss diagnosis. Testing may identify specific genetic variants responsible for hearing loss and help determine the most appropriate management strategies.

- Inheritance patterns for genetic hearing loss vary:

  Autosomal recessive hearing loss: occurs when an individual inherits two copies of a disease-causing genetic variant (one from each parent). This is the most common genetic cause of hearing loss. Carriers of a single variant typically do not show symptoms but can pass the variant to their children. Typically, neither parent has hearing loss.

  Autosomal dominant hearing loss: occurs when only one disease-causing genetic variant is necessary to cause the condition. Individuals with autosomal dominant hearing loss typically have a 50% chance of passing the condition to their offspring. Typically, one parent is affected by hearing loss.

  X-linked hearing loss: involves genes located on the X chromosome, and the patterns of inheritance differ between males and females due to their differing sex chromosome compositions. It predominantly affects males, who have only one X chromosome, meaning that a single disease-causing genetic variant can result in hearing loss. Females, with two X chromosomes, are usually carriers but can exhibit symptoms if the variant is present on both X chromosomes. Affected males cannot pass the condition to male offspring but all female offspring will be carriers. Male offspring of a carrier mother have a 50% chance of being affected.

  Mitochondrial DNA (mtDNA) hearing loss: inherited in a maternal manner. Most mtDNA hearing loss is syndromic. Of note, nonsyndromic hearing loss associated with the MT-RNR1 and MT-TS1 genes is likely due to increased sensitivity to cellular damage

caused by aminoglycoside antibiotics and other ototoxic drugs. Typically, the mother is affected, and all of her children are affected.

Components of Informed Consent for Genetic Testing

These core components should be discussed during the pre-test counseling appointment to ensure informed consent for genetic testing:

1. **What test is recommended:** Clearly state the condition being tested and why. In this case, it is to attempt to identify a genetic form of hearing loss, which may enable prognostication, treatment selection (e.g., hearing aids or cochlear implants), exploration of surveillance or preventative options, recurrence risk calculation, identification of carrier/risk status in family members, and research guidance.

2. **Genetic test results and implications:** Discuss possible results (positive, negative, uncertain). The section on post-test genetic counseling includes more information about test results and their potential implications for the individual and family members. While genetic testing may provide valuable insights into health risks, it also carries psychological implications for individuals and families that must be understood to provide comprehensive support and ensure ethical and effective use of testing.

3. **Test limitations and next steps:** Certain genetic tests are not able to detect all disease-causing variants, and additional testing may be recommended. Genetic testing cannot tell you everything about inherited conditions like genetic hearing loss. For example, depending on the particular variant, a positive result does not always mean a patient will develop a condition, and it is hard to predict how severe symptoms may be.

4. **Genetic discrimination and legal protections:** Genetic discrimination is the unequal and negative treatment of an individual relative to others based on their genetic information. Genetic information can include an individual's genetic test results, their family members' genetic test results, family health history, genetic services obtained, or data derived from genetic research. Genetic counseling providers should help individuals understand the risk of genetic discrimination and discuss with them existing laws and regulations specific to their region that may protect them from some forms of genetic discrimination.

   In the United States, patient health information (including genetic testing and family history) is protected under the Health Insurance Portability and Accountability Act (HIPAA). Within HIPAA there is a federal privacy rule that provides federal protection for individually identifiable health information, including information about genetic testing. This includes information in patient records and allows disclosures for purposes of treatment, care, and payment. Under HIPAA, a patient's genetic testing information may not be disclosed without prior patient consent.

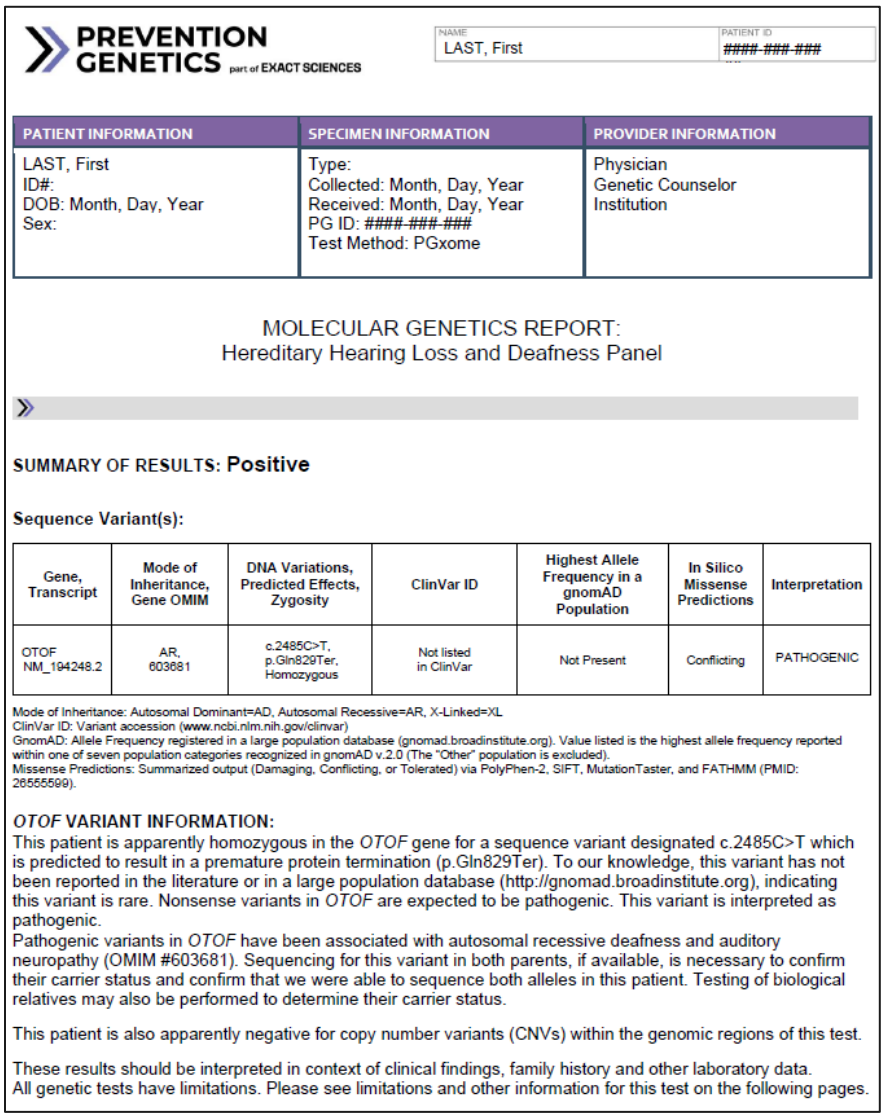
   The Genetic Information Nondiscrimination Act (GINA) protects against discrimination by health insurers and employers. Title I of GINA prohibits health insurers from using genetic

information to determine health insurance eligibility or premiums. Health insurers also may not request that person undergo genetic testing or provide the results of past genetic testing for making decisions about underwriting. Title II of GINA prohibits employers from using genetic information to make employment decisions such as hiring, firing, promotions, or any other terms of employment. Employers cannot request, require, or acquire genetic information about an employee or their family members. Importantly, GINA does not apply to long-term care insurance, life insurance, or disability insurance. GINA also does not apply to the U.S. Military or employers with fewer than 15 employees. Additional protections are afforded through the Americans with Disabilities Act, the Affordable Care Act, and state laws.

Post-test Genetic Counseling

The genetic test results are disclosed to the individual in the post-test genetic counseling appointment. While genetic testing may provide valuable information for managing health and understanding genetic risks, it also has potential psychological implications. Genetic counseling is essential to help individuals and families navigate these implications effectively and make informed, balanced decisions.

The genetic test result will be classified as positive, negative, or uncertain. Here is an example of a positive test report:



PREVENTION GENETICS part of EXACT SCIENCES

NAME: LAST, First | PATIENT ID: #### ### ###

PATIENT INFORMATION	SPECIMEN INFORMATION	PROVIDER INFORMATION
LAST, First ID#: DOB: Month, Day, Year Sex:	Type: Collected: Month, Day, Year Received: Month, Day, Year PG ID: #### ### ### Test Method: PGxome	Physician Genetic Counselor Institution

MOLECULAR GENETICS REPORT:
Hereditary Hearing Loss and Deafness Panel

SUMMARY OF RESULTS: Positive

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
OTOF NM_194248.2	AR, 603681	c.2485C>T, p.Gln829Ter, Homozygous	Not listed in ClinVar	Not Present	Conflicting	PATHOGENIC

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.0 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555599).

***OTOF* VARIANT INFORMATION:**
This patient is apparently homozygous in the *OTOF* gene for a sequence variant designated c.2485C>T which is predicted to result in a premature protein termination (p.Gln829Ter). To our knowledge, this variant has not been reported in the literature or in a large population database (http://gnomad.broadinstitute.org), indicating this variant is rare. Nonsense variants in *OTOF* are expected to be pathogenic. This variant is interpreted as pathogenic.
Pathogenic variants in *OTOF* have been associated with autosomal recessive deafness and auditory neuropathy (OMIM #603681). Sequencing for this variant in both parents, if available, is necessary to confirm their carrier status and confirm that we were able to sequence both alleles in this patient. Testing of biological relatives may also be performed to determine their carrier status.

This patient is also apparently negative for copy number variants (CNVs) within the genomic regions of this test.

These results should be interpreted in context of clinical findings, family history and other laboratory data.
All genetic tests have limitations. Please see limitations and other information for this test on the following pages.

The post-test genetic counseling process includes the following steps:

Result Disclosure and Implications

Directly state the genetic test result at the beginning of the appointment. Discuss relevant result-specific considerations detailed in the Genetic Test Results and Implications section.

Positive genetic test result: Indicates the patient has a pathogenic or likely pathogenic variant in a gene associated with hearing loss. Implications for receiving a positive result might include clarifying a diagnosis (syndromic or isolated) and prognosis (stable or progressive), informing decisions about surveillance (especially for a syndromic diagnosis), providing information about recurrence risks (inheritance pattern), indicating preventive or therapeutic interventions (e.g., an individual that receives a genetic diagnosis of riboflavin transporter deficiency would be treated with riboflavin supplementation), and allowing an individual to participate in research opportunities like registries and clinical trials.

Negative genetic test result: Indicates the patient does not have a pathogenic or likely pathogenic variant detected in a gene associated with hearing loss. The experience of receiving a negative genetic test result should not be underestimated. There may be tremendous relief in learning one is negative for the gene variant responsible for hearing loss in their family. Others may be frustrated that they did not receive a causative explanation for their hearing loss and are not eligible to participate in gene therapy clinical trials. Additional testing may be recommended if a small panel of genes was used for testing or if clinically indicated.

Uncertain genetic test result: The lab identified a variant of uncertain significance (VUS) in a gene associated with hearing loss. There is no definitive evidence the variant is associated with hearing loss. This classification may change in the future if more data become available. Individuals who receive a VUS result may have feelings of sadness and disappointment to not have a clear answer. Conversely, some people may feel relief and optimism. Others may have mixed feelings about a VUS result, experiencing both worry about the VUS and hope that it may be benign. Gene-specific clinical trials often do not enroll participants with a VUS, so consult trial eligibility criteria. A VUS should also be considered in the context of the complete clinical picture of an individual when considering ultimate diagnosis and treatment decisions.

Other types of potential results: The International Pediatric Otolaryngology Group (IPOG) and the American College of Medical Genetics and Genomics (ACMG) recommend a comprehensive hearing loss gene panel for bilateral sensorineural hearing loss (SNHL). Use of a comprehensive hearing loss gene panel reduces the possibility of secondary/incidental findings (e.g., detecting a condition other than the one for which testing was originally indicated). If genetic testing is done using exome or genome sequencing, secondary and/or incidental findings may be detected.

Psychological Considerations

A range of psychological responses may arise in a post-test counseling session. Depending on results, some patients may need to be referred to mental health providers or certified genetic counselors.

Uncertainty and ambiguity: Genetic testing can yield uncertain results, such as a VUS, causing stress and frustration. Individuals may struggle to interpret these results and their impact on health decisions.

Guilt and responsibility: Positive results for conditions that can be passed to offspring may lead to feelings of guilt, even if the individual was unaware of their carrier status.

Deaf Culture and identity: There is a noted difference between the medical model of deafness, which focuses on a deaf individual's altered auditory capacity and use of assisted hearing devices, and the cultural model signified as Deaf (with a capital "D"), which incorporates other communication modalities and incorporates deafness as a component of cultural identity.

Family relationships: Genetic testing can impact family dynamics, especially when results reveal hereditary conditions affecting multiple members. This can lead to tension or conflict.

Medical Documentation

Share the test report with the patient and provide a written summary of the verbal communication after the post-test genetic counseling appointment.

Follow-up

The information presented during the post-test genetic counseling appointment can be overwhelming from a volume and emotional standpoint. The patient may need time to digest the information and have additional questions later. You should offer to refer to a genetic counselor, if additional genetic counseling is needed, to provide patients with the information and support they need to navigate the implications of the results of genetic testing for hearing loss. If the test results indicate the patient has an isolated form of hearing loss, the patient should continue their regular otolaryngology and audiology follow-up. If a syndromic diagnosis is made, the patient may need other multispecialty referrals and care. Identification of a specific gene variant associated with hearing loss may allow an individual to participate in research opportunities, such as registries and clinical trials. These trials can be found at www.clinicaltrials.gov.

Identify what support resources the patient currently has and provide additional resources as needed. Does the patient have a support system (family, friend, religious community)? Does the patient or family need help navigating school, work, government services? Here are some resources that may be helpful:

- Hands & Voices- handsandvoices.org
- Alexander Graham Bell Association for the Deaf and Hard of Hearing- agbell.org

- HearingFirst.org- hearingfirst.org
- BabyHearing.org- babyhearing.org
- Parent Guides to Hearing Loss- cdc.gov/hearing-loss-children-guide/parents-guide-genetics/about-the-types-of-hearing-loss.html
- American Speech-Language-Hearing Association (ASHA)- asha.org
- Find a Genetic Counselor- findageneticcounselor.nsgc.org
- Find a Mental Health Provider- psychologytoday.com
- MedlinePlus- medlineplus.gov/genetics/condition/nonsyndromic-hearing-loss

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