### Genetic Testing for Nonsyndromic Hearing Loss and Deafness

**Procedures addressed**

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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**What is nonsyndromic hearing loss and deafness**

**Definition**

Prelingual hearing loss affects about 1 out of every 500 individuals.\(^1\) Approximately 20% of cases are attributed to environmental causes, including viral (cytomegalovirus) or bacterial (meningitis) infection, trauma, prenatal exposure to certain drugs, and other environmental factors.\(^1\) The remaining 80% of cases are thought to be genetic, either as part of a recognized genetic syndrome, or as isolated, nonsyndromic hearing loss (NSHL).\(^1\)

- 95% of congenital hearing loss is detected by newborn screening. Diagnosis of hearing loss may involve physiologic testing (including auditory brainstem response or ABR/BAER) and/or audiometry.\(^1\)

- 70-80% of genetic hearing loss is nonsyndromic, with no related systemic findings.\(^1,2\) Some syndromic forms of hearing loss and deafness may masquerade as nonsyndromic in infancy and early childhood, before additional symptoms emerge. For example, goiter does not develop until puberty or adulthood in Pendred syndrome; retinitis pigmentosa emerges in adolescence in Usher syndrome; and males with Deafness-Dystonia-Optic Neuroneopathy (Mohr-Tranebjaerg) Syndrome begin having progressive neurological symptoms in their teens.\(^3\)

- Many inheritance patterns are possible in NSHL; 80% is autosomal recessive, 15-19% is autosomal dominant, and ~1% is mitochondrial or X-linked.\(^1,2\)
• A study of 440 individuals with genetic hearing loss found mutations in ~40% of cases tested with a multigene panel. The only feature with an adverse effect on test yield was unilateral hearing loss, for which the panel only identified mutations in 1% of cases. In another study, the mutation detection rate was ~60% via multigene panel; multigene panel testing was noted to be more cost-effective than single gene testing.

• While the most common cause of severe-to-profound autosomal recessive NSHL in most populations is mutation of GJB2 (DFNB1 locus), there is ethnic variability. Approximately 1% of DFNB1 is due to compound heterozygous mutations in GJB2 and GJB6. The most common cause of mild-to-moderate autosomal recessive hearing loss is mutations of STRC.

• Mitochondrial NSHL is caused by mutations in MT-RNR1 (~71%), MT-TS1 (~29%), and rarely by mutations in other mitochondrial encoded genes (less than 1%). MT-RNR1 pathogenic variants, particularly the m.1555A>G allele, are associated with a predisposition to aminoglycoside ototoxicity, with ~100% penetrance after exposure to aminoglycosides. Without aminoglycoside exposure, penetrance is ~80% by age 65 years.

• Management of congenital hearing loss or deafness may include hearing aids, cochlear implants, and appropriate educational interventions. Uncovering the genetic etiology of the hearing loss may also identify (or allay concerns about) comorbidities that may require referral for specialty care.

Test information

• There are various methods used to test for mutations in genes which can cause hearing loss and deafness.
  
  o Single gene analysis
  
  o Panel testing using next generation sequencing

• Until recently, most sequencing tests used the Sanger sequencing methodology that was originally developed in the 1970s. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.

• Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, has been developing since about 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence.

• The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions, making it difficult to reliably narrow down likely causes. As a result, several laboratories have begun to combine genes involved in certain conditions.
conditions, which often have both of those characteristics. However, NGS may not perform as well as Sanger sequencing in some applications. Results may also be obtained that cannot be adequately interpreted based on the current knowledgebase. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.

• Nonsyndromic hearing loss and deafness multi-gene panels include a wide variety of genes associated with nonsyndromic hearing loss and deafness. Multi-gene nonsyndromic hearing loss and deafness panels may also include genes for syndromes that mimic nonsyndromic hearing loss (e.g. Usher syndrome, Pendred syndrome, Jervell and Lange-Nielsen syndrome, etc.).

• Under certain circumstances, technologies used in multi-gene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion remains for a particular syndrome after negative multi-gene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.

• Multi-gene tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

• Since genes can be easily added or removed from multi-gene tests over time by a given lab, medical records must document which genes were included in the specific multi-gene test used from each patient, and in which labs they were performed.

• Additionally, tests should be chosen that maximize the likelihood of identifying mutations in the genes of interest and that will alter patient management.

Guidelines and evidence

• In 2016, the International Pediatric Otolaryngology Group (IPOG) stated: 7
  o "In the setting of unilateral hearing loss, genetic testing has a limited role unless syndromic hearing loss is suspected."
  o "After an audiogram and physical exam, comprehensive genetic testing (CGT) that relies on next generation sequencing (NGS) methodologies should guide subsequent workup in children with bilateral sensorineural hearing loss."
  o "Diagnostic rates for single gene testing for GJB2/GJB6 vary significantly based on the patient's ethnicity, and do not outperform the diagnostic rates for comprehensive genetic testing. In cases where CGT is unavailable, single gene testing can be directed by the audiometric phenotype and ethnicity."
  o The general consensus of the authors was that temporal bone imaging “should not be a routine part of the diagnostic algorithm for bilateral symmetric sensorineural hearing loss.”
• In 2014, the American College of Medical Genetics and Genomics (ACMG) made the following recommendations:\(^2\)
  
  o A genetic evaluation is recommended for all cases of congenital deafness or hearing loss with onset in childhood or early adulthood. While the usefulness of ancillary testing (e.g. electrocardiogram, renal ultrasound, temporal bone imaging and ophthalmology examination) was mentioned, it was acknowledged that genetic testing via NGS panels would soon become more cost-effective. Cytomegalovirus (CMV) testing is important for cases of congenital hearing loss, but only accurate in the first 6 weeks of life.
  
  o Genetic testing to confirm a diagnosis of suspected syndromic hearing loss is recommended based on clinical findings. For apparently nonsyndromic hearing loss, a tiered approach was recommended: If the personal and family history is suggestive of a particular gene, single gene testing should be performed first. For simplex cases and cases with apparent autosomal recessive inheritance, the next step should be testing of GJB2 and GJB6. If single-gene testing is not diagnostic, testing via NGS panels, whole exome sequencing, or whole genome sequencing should be considered.
  
  o The statement stopped short of endorsing the use of NGS panels as a first-tier test, but noted they are “rapidly replacing” sequencing of the GJB2 and GJB6 loci and would soon be a more cost-effective alternative.

• An expert-authored review of nonsyndromic hearing loss states:\(^3\)
  
  o “A comprehensive deafness-specific genetic panel that includes all genes implicated in nonsyndromic hearing loss and nonsyndromic hearing loss mimics is recommended as the initial genetic test.”
  
  o “Performing sequence analysis of GJB2 alone is not cost-effective unless it is limited to persons with severe-to-profound congenital nonsyndromic hearing loss. Offering single-gene testing of GJB2 reflexively to everyone with congenital hearing loss without regard to the degree of hearing loss is not evidence based and not cost effective.”

• An expert-authored review on hereditary hearing loss and deafness\(^1\) likewise states that a multi-gene test is recommended for apparent nonsyndromic hearing loss, while individuals with features of syndromic hearing loss should be diagnosed with targeted genetic testing. Ancillary cardiac, ophthalmologic and renal evaluations are only recommended on the basis of genetic test results or clinical findings.

• An expert-authored review on mitochondrial NSHL\(^6\) states that the diagnosis should be suspected in individuals with moderate-to-profound hearing loss and a family history suggestive of maternal inheritance (e.g. no transmission through a male), or onset of hearing loss after exposure to an aminoglycoside antibiotic.
  
  o To confirm the diagnosis: MT-RNR1 testing, beginning with targeted analysis for the m.1555A>G mutation, is recommended following aminoglycoside exposure. In the absence of aminoglycoside exposure, testing of both MT-RNR1 and MT-
TS1 is recommended. If these tests fail to confirm a diagnosis, mitochondrial genome sequencing can be considered.

- An alternative strategy is to perform a multi-gene panel that includes both MT-RNR1 and MT-TS1, plus other genes of interest.

### Criteria

#### Known Familial Mutation Analysis

- **Previous testing:**
  - Member has not previously had testing for the requested mutation(s), AND
  - Member has a 1st, 2nd, or 3rd degree biologic relative with a pathogenic mutation(s) in a gene associated with nonsyndromic hereditary hearing loss or deafness, AND
  - Member is at risk of inheriting the pathogenic mutation based on the family history and the inheritance pattern associated with the mutation, AND
- **Diagnostic testing:**
  - Member has nonsyndromic hearing loss or deafness that is consistent with the mutation in the family

#### GJB2 Sequencing

- **Previous testing:**
  - Member has not previously had GJB2 sequencing, and
  - No known pathogenic hearing loss/deafness gene variants in a biologic relative, AND
- **Diagnostic Testing:**
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - Prelingual onset of hearing loss (prior to speech development), and
  - No known cause for the member’s hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  - Member’s family history is consistent with autosomal recessive inheritance (including simplex cases)
GJB6 Common Variant Analysis for 309kb and 232kb Deletions

- Previous testing:
  - Member has not previously had GJB6 common variant analysis or deletion/duplication analysis, AND
- Diagnostic Testing:
  - Member meets criteria for GJB2 sequencing, and
  - No mutation or only one mutation identified on GJB2 sequencing

MT-RNR1 Targeted Mutation Analysis for m.1555A>G Mutation

- Previous testing:
  - Member has not previously had MT-RNR1 targeted mutation analysis, and
  - No known pathogenic hearing loss/deafness gene variants in a biologic relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member’s hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  - Member has one of the following risk factors for MT-RNR1 related deafness:
    - History of aminoglycoside antibiotic exposure (gentamycin, tobramycin, amikacin, kanamycin, or streptomycin), or
    - Member’s family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

MT-RNR1 Sequencing

- Previous testing:
  - Member has not previously had MT-RNR1 sequencing, and
  - No mutations detected in any previous MT-RNR1 testing (targeted m.1555A>G mutation analysis), and
  - No known pathogenic hearing loss/deafness gene variants in a biologic relative, AND
• Diagnostic Testing:
  o Member has a diagnosis of bilateral sensorineural hearing loss, and
  o No known cause for the member’s hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  o Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  o Member has one of the following risk factors for MT-RNR1 related deafness:
    ▪ Aminoglycoside antibiotic exposure (gentamycin, tobramycin, amikacin, kanamycin, or streptomycin) prior to hearing loss onset, or
    ▪ Member’s family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

MT-TS1 Sequencing

• Previous testing:
  o Member has not previously had MT-TS1 analysis, and
  o No mutations detected in any previous MT-TS1 testing (targeted variant analysis), and
  o No known pathogenic hearing loss/deafness gene variants in a biologic relative, AND

• Diagnostic Testing:
  o Member has a formal diagnosis of bilateral sensorineural hearing loss, and
  o No known cause for the member’s hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  o Absence of significant dysmorphism, congenital anomalies, or other signs of syndromic hearing loss, and
  o Member’s family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

Hearing Loss and Deafness Multigene Panel Testing

When a multi-gene panel is being requested and will be billed with a panel CPT code (e.g. 81430, 81431, 81479), the panel will be considered medically necessary when the following criteria are met:

• Previous testing:
  o Member has not previously had a hearing loss panel, and
o No known pathogenic hearing loss/deafness gene variants in a biologic relative, AND

• Diagnostic Testing:
  o Member has a diagnosis of bilateral sensorineural hearing loss, and
  o No known cause for the member’s hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  o Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss.

When separate procedure codes will be billed for individual hearing loss genes (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), the entire panel will be approved if the above criteria are met. However, the laboratory will be redirected to use an appropriate panel CPT code for billing purposes (e.g. 81430, 81431, 81479).

Billing and reimbursement considerations

• The billed amount should not exceed the list price of the test.
• Broad hearing loss and deafness panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.
• Genetic testing is only necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
• If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
• If the laboratory will not accept redirection to a single code, the medical necessity of each billed component procedure will be assessed independently, and only the individual panel components that meet medical necessity criteria as a first tier of testing will be reimbursed. The remaining individual components will not be reimbursable.
  o If appropriate first-tier tests cannot be determined on the basis of clinical and family histories, only the following genes may be considered for reimbursement: GJB2, STRC, SLC26A4, TECTA, MYO15A, MYO7A.
• If a single hearing loss/deafness gene test is billed simultaneously with a panel code (e.g. 81430), only the billed procedure that meets medical necessity criteria as a first tier of testing will be reimbursed.
Panel testing will generally be the most appropriate first-tier test, except when the history is strongly suggestive of the individual genetic disorder requested (e.g. congenital, severe-to-profound deafness for GJB2 analysis or history of aminoglycoside exposure for MT-RNR1 analysis).

**Benefit exclusion**

**Exclusions and other considerations**

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

**References**


