Genetic Testing for Hereditary Hearing Loss

BCBSA Ref. Policy: 2.04.87
Effective Date: July 1, 2018
Last Revised: June 22, 2018
Replaces: 2.04.87

RELATED MEDICAL POLICIES:
12.04.305 Preimplantation Genetic Testing in Embryos

Introduction

Hearing loss can be caused by illness, injuries, or even certain medications. A baby who is born too soon or who needs to use a breathing machine (ventilator) after birth may develop hearing loss. Complicating this even more is that hearing loss can be “syndromic.” This means that a person has other symptoms in addition to hearing loss. “Nonsyndromic” hearing loss means a person doesn’t have any other symptoms.

Genetic changes are the root cause of some hearing loss. If more than one person in a family has hearing loss, it is called familial hearing loss. Even in families with genetic hearing loss, it may not be caused by changes to any of the genes known to be associated with hearing. This policy describes when genetic testing for hearing loss may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Genetic Testing

| Variants in hereditary hearing loss genes | Genetic testing for hereditary hearing loss genes (GJB2, GJB6, and other hereditary hearing loss-related genes) in individuals with suspected hearing loss in order to confirm the diagnosis of hereditary hearing loss (see Related Information) may be considered medically necessary. |

| Preconception genetic testing for hereditary hearing loss variants | Preconception genetic testing (carrier testing) for hereditary hearing loss gene (GJB2, GJB6, and other hereditary hearing loss-related genes) in parents may be considered medically necessary when at least one of the following conditions has been met:  
• Offspring with hereditary hearing loss  
OR  
• One or both parents with suspected hereditary hearing loss  
OR  
• First- or second-degree relative affected with hereditary hearing loss  
OR  
• First-degree relative with offspring who is affected with hereditary hearing loss |

### Investigational

| Variants in hereditary hearing loss genes | Genetic testing for hereditary hearing loss variants is considered investigational for all other situations, including, but not limited to, testing in patients without hearing loss (except as addressed in Related Policies). |

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis, full gene sequence</td>
</tr>
<tr>
<td>81252</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis, full gene sequence</td>
</tr>
<tr>
<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis, full gene sequence</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>81254</td>
<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)(eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])</td>
</tr>
<tr>
<td>81430</td>
<td>Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1</td>
</tr>
<tr>
<td>81431</td>
<td>Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of nonsyndromic hearing loss (NSHL) is hearing loss that is not associated with other physical signs and symptoms at the time of hearing loss presentation. It is differentiated from syndromic hearing loss, which is hearing loss associated with other signs and symptoms characteristic of a specific syndrome. Physical signs of a syndrome often include dysmorphic changes in the maxillofacial region and/or malformations of the external ears. Malfunction of internal organs may also be part of a syndrome. The physical signs can be subtle and easily missed on physical exam, therefore exclusion of syndromic findings is ideally done by an individual with expertise in identifying dysmorphic physical signs. The phenotypic presentation of NSHL varies, but generally involves the following features:

- Sensorineural hearing loss
- Mild to profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually non-progressive

This policy primarily focuses on the use of genetic testing to identify a cause of suspected hereditary hearing loss. The diagnosis of syndromic hearing loss may be able to be made on the
basis of associated clinical findings. However, at the time of hearing loss presentation, associated clinical findings may not be apparent; furthermore, variants in certain genetic loci may cause both syndromic and nonsyndromic hearing loss. Given this overlap, the policy focuses on genetic testing for hereditary hearing loss more generally.

In addition to pathogenic variants in the GJB6 and GJB2 genes, there are many less common pathogenic variants found in other genes. They include: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes.

Targeted testing for variants associated with hereditary hearing loss should be confined to known pathogenic variants. While research studies using genome-wide associations have uncovered numerous single nucleotide variants and copy number variations associated with hereditary hearing loss, the clinical significance of these findings is unclear.

For carrier testing, outcomes are expected to be improved if parents alter their reproductive decision making as a result of genetic test results. This may occur through the use of preimplantation genetic testing in combination with in vitro fertilization. Other ways that prospective parents may alter their reproductive choices are to proceed with attempts at pregnancy, or to avoid attempts at pregnancy, based on carrier testing results.

**Testing Strategy**

Evaluation of a patient with suspected hereditary hearing loss should involve a careful physical exam and family history to assess for associated clinical findings that may point to a specific syndromic or nonsyndromic cause of hearing loss (e.g., infectious, toxic, autoimmune, other causes). Consideration should also be given to temporal bone computed tomography scanning in cases of progressive hearing loss and to testing for cytomegalovirus (CMV) in infants with sensorineural hearing loss.

If there is no high suspicion for a specific hearing loss etiology, ideally the evaluation should occur in a step-wise fashion. About 50% of individuals with autosomal recessive hereditary hearing loss have pathogenic variants in the GJB2 gene. In the remainder of patients with apparent autosomal recessive hereditary hearing loss, numerous other genes are implicated. In autosomal dominant hereditary hearing loss, there is no single identifiable gene responsible for most cases. If there is suspicion for autosomal recessive congenital hearing loss, it would be reasonable to begin with testing of GJB2 and GJB6. If this is negative, screening for the other genes associated with hearing loss with a multigene panel would be efficient. An alternative
strategy for suspected autosomal recessive or autosomal dominant hearing loss would be to obtain a multigene panel that includes GJB2 and GJB6 as a first step. Given the extreme heterogeneity in genetic causes of hearing loss, these 2 strategies may be considered reasonably equivalent.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
</tbody>
</table>
### Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

### Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Evidence Review

### Background

**Hereditary Hearing Loss**

Hearing loss is a common birth defect. Approximately 1 of 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity (≥40 db).¹

Syndromic hearing loss refers to hearing loss associated with other medical or physical findings, including visible abnormalities of the external ear. Because syndromic hearing loss occurs as part of a syndrome of multiple clinical manifestations, it is often recognized more readily as hereditary.

Nonsyndromic hearing loss (NSHL) is defined as hearing loss not associated with other physical signs or symptoms. For NSHL, it is more difficult to determine whether the etiology is hereditary or acquired, because, by definition, there are no other clinical manifestations at the time of the hearing loss presentation. NSHL accounts for 70% to 80% of genetically determined deafness.²
Autosomal recessive patterns of inheritance predominate and account for 80% of congenital NSHL. A typical clinical presentation of autosomal recessive NSHL involves the following characteristics:

- Sensorineural hearing loss
- Mild to profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually non-progressive
- No associated medical findings

Most of the remaining 20% of patients have an autosomal dominant inheritance pattern, with a small number having X-linked or mitochondrial inheritance. Patients with autosomal dominant inheritance typically show progressive NSHL, which begins in the second through fourth decades of life.³

**Diagnosis**

Diagnosis of nonsyndromic hearing loss requires an evaluation with appropriate core medical personnel with expertise in the genetics of hearing loss, dysmorphology, audiology, otolaryngology, genetic counseling, and communication with deaf patients. The evaluation should include a family history, as well as a physical examination consisting of otologic examination, airway examination, documentation of dysmorphisms, and neurologic evaluation.⁴ However, the clinical diagnosis of NSHL is nonspecific because there are a number of underlying etiologies, and often it cannot be determined with certainty whether a genetic cause for hearing loss exists.

**Treatment**

Treatment of congenital and early-onset hearing loss typically involves enrollment in an educational curriculum for hearing impaired persons and fitting with an appropriate hearing aid. In some patients with profound deafness, a cochlear implant can be performed. Early identification of infants with hearing impairment may be useful in facilitating early use of amplification by 6 months of age and early intervention to achieve age-appropriate communication, speech, and language development.⁵ Delays in development of hearing treatment have been shown to delay development of communication. The primary method for
identification of hearing impairment has been newborn screening with audiometry. Genetic testing has not been proposed as a primary screen for hearing loss.

**Genetics of Hereditary Hearing Loss**

Genes associated with hereditary hearing loss may be associated with an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern. The genetic loci on which variants associated with hereditary hearing loss are usually found are termed DFN, and hereditary hearing loss is sometimes called DFN-associated hearing loss. DFN loci are named based on their mode of inheritance: DFNA associated with autosomal dominant inheritance; DFNB with autosomal recessive inheritance; and DFNX with x-linked inheritance.

Two DFN loci commonly associated with hereditary hearing loss are DFNA3 and DFNB1, both of which map to chromosome 13q12. DFNA3-associated hereditary hearing loss is caused by autosomal dominant variants present in the GJB2 or GJB6 genes. DFNB1-associated hereditary hearing loss are autosomal recessive syndromes in which more than 99% of cases are caused by variants to the GJB2 gene with less than 1% of remaining cases arising from variants to GJB6. A list of available tests for genetic variants at the DFNA3 and DFNB1 loci is given in Table3.

Two of the most commonly mutated genes are GJB2 and GJB6. GJB2 is a small gene with a single coding exon. Variants of this gene are most common in hereditary hearing loss, causing an estimated 50% of the cases of NSHL. The carrier rate in the general population for a recessive deafness-causing GJB2 variant is approximately 1 in 33. Specific variants have been observed to be more common in certain ethnic populations. Variants in the GJB2 gene will impact expression of the Cx26 connexin protein and almost always cause prelingual, but not necessarily congenital, deafness. Different variants to GJB2 can present high phenotypic variation, but it has been demonstrated that it is possible to correlate the type of associated hearing loss with findings on molecular analysis. A systematic review by Chan and Chang (2014), reporting GJB2 variant prevalence, suggested that the overall prevalence of GJB2 variants is similar around the world, although specific variants differ.

Variants in the GJB6 gene lead to similar effects on abnormal expression of connexin protein Cx30. However, GJB6 variants are much less common than variants in GJB2. Of all the patients with hereditary hearing loss, approximately 3% have a variant in the GJB6 gene.
Table 3. Clinical Characteristics and Testing Methods for GJB2 and GJB6 Variants at the DFNA3 and DFNB1 Loci

<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Gene Symbol</th>
<th>Onset</th>
<th>Audioprofile</th>
<th>Test Method</th>
<th>Variants Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFNA3</td>
<td>GJB2</td>
<td>Prelingual</td>
<td>High-frequency progressive</td>
<td>Sequence analysis/ variant scanning</td>
<td>Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Targeted variant analysis</td>
<td>Specified sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/duplication analysis</td>
<td>Exonic or whole-gene deletions/duplications</td>
</tr>
<tr>
<td>DFNA3</td>
<td>GJB6</td>
<td>Prelingual</td>
<td>High-frequency progressive</td>
<td>Sequence analysis/ variant scanning</td>
<td>Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Targeted variant analysis</td>
<td>Specified sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/ duplication analysis</td>
<td>Exonic or whole-gene deletions/duplications</td>
</tr>
<tr>
<td>DFNB1</td>
<td>GJB2</td>
<td>Prelingual</td>
<td>Usually stable</td>
<td>Targeted variant analysis</td>
<td>GJB2 sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/ duplication analysis</td>
<td>Exon(s) or whole-gene deletions</td>
</tr>
<tr>
<td>DFNB1</td>
<td>GJB6</td>
<td>Prelingual</td>
<td>Usually stable</td>
<td>Deletion/ duplication analysis</td>
<td>GJB6 deletions</td>
</tr>
</tbody>
</table>

Analysis for GJB6 and GJB2 variants can be performed by Sanger sequencing analysis of individual genes. This method has a high degree of validity and reliability but is limited by the ability to sequence 1 gene at a time. With Sanger sequencing, the gene with the most common variants is generally sequenced first, followed by sequencing of additional genes if a pathogenic variant is not found.

In addition to the most common variants in genes that are associated with hereditary hearing loss (GJB6 and GJB2) there are many less common disease-associated genes. Some are: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes. Novel genetic variants continue to be identified in cases of hereditary hearing loss.\(^\text{13,14}\) For example, as of 2014, over 2,000 pathogenic deafness variants in approximately 130 genes had been reported.\(^\text{15,16}\) In contrast, only 18 pathogenic copy number variants (CNVs) had been identified by 2014.\(^\text{17}\) CNVs, caused by insertions, deletions, or recombination, can lead to hearing loss from gene disruption or changes in the number of dose-sensitive genes. The gene most commonly associated with
pathogenic CNVs in hearing loss is STRC, which encodes stereocilin and is the most frequent cause of autosomal recessive causes of NSHL after variants in GJB2.\textsuperscript{17}

Because of the large number of genes associated with hereditary hearing loss, there are various genetic panels for hereditary deafness. Next-generation sequencing technology allows targeted sequencing of multiple genes simultaneously, expanding the ability to examine multiple genes. These panels are alternatives to sequencing of individual genes such as GJB6 and GJB2. Some examples of these panels are given in Table 4. These panels include the most common genes associated with NSHL. They may also include many of the less common genes associated with NSHL, as well as genes that are associated with syndromic hearing loss. Also, whole exome sequencing and whole genome sequencing have been used to identify novel variants in subjects with a history suggestive of genetic hereditary hearing loss.\textsuperscript{18-20} Targeted genomic enrichment coupled with massively parallel sequencing can be used to identify both single nucleotide variants and CNVs.

### Table 4. Gene Panels for Hereditary Hearing Loss

<table>
<thead>
<tr>
<th>Test</th>
<th>Technology</th>
<th>Genes Tested</th>
<th>Analytic Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Healthcare (OtoGenome™ Test for Hearing Loss and Related Syndromes)</td>
<td>NGS, followed by confirmation with Sanger sequencing or PCR</td>
<td>87</td>
<td>99%</td>
</tr>
<tr>
<td>University of Iowa Healthcare (OtoSCOPE® V8)\textsuperscript{21}</td>
<td>NGS/massive parallel sequencing</td>
<td>152</td>
<td>99%</td>
</tr>
</tbody>
</table>

Adapted from Linden Phillips et al (2013)\textsuperscript{11}

NGS: next-generation sequencing; PCR: polymerase chain reaction

### Overlap Between NSHL and Recognized Syndromes

There is overlap between hereditary NSHL and hearing loss associated with recognized syndromes. Some genetic variants may be associated with clinical findings other than hearing loss, but they are not necessarily manifest at the time of presentation with hearing loss. For example, Jervell and Lange-Nielsen syndrome is associated with congenital deafness and prolonged QT interval, but it may present only with deafness without an apparent history to suggest cardiac dysfunction. Additionally, some of the genes associated with NSHL are also associated with recognized syndromes. A summary of some of the genetic syndromes and variants that may have overlap with NSHL is shown in Table 5.
# Table 5. Genes With Overlap Between Syndromic and Nonsyndromic Hearing Loss

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Clinical Description</th>
<th>Gene</th>
<th>Reason for Overlap With NSHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usher syndrome</td>
<td>For all types: autosomal recessive</td>
<td>For all types: sensorineural hearing loss with retinitis pigmentosa</td>
<td>MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2</td>
<td>Retinitis pigmentosa usually not apparent in 1st decade</td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td>Congenital severe-to-profound hearing loss Abnormal vestibular function</td>
<td>MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2, DFNB18 (nonsyndromic) may also be caused by variants in USH1C, DFNB12 (nonsyndromic) may also be caused by variants in CDH23, DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by variants in MYO7A</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td>Congenital mild-to-severe hearing loss Normal vestibular function</td>
<td>USH2A, VLGR1 WHRN</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td></td>
<td>Progressive hearing loss Progressive vestibular dysfunction</td>
<td>CLRN1i, PDZD7</td>
<td></td>
</tr>
<tr>
<td>Pendred syndrome</td>
<td>Autosomal recessive</td>
<td>Congenital sensorineural hearing loss Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) Euthyroid goiter</td>
<td>SLC26A4 (50%)</td>
<td>Goiter not present until early puberty or adulthood Variants in SLC26A4 may also cause NSHL</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen syndrome</td>
<td>Autosomal recessive</td>
<td>Congenital deafness Prolongation of the QT interval</td>
<td>KCNQ1, KCNE1</td>
<td>Hearing loss may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT)</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Inheritance</td>
<td>Clinical Description</td>
<td>Gene</td>
<td>Reason for Overlap With NSHL</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>Autosomal</td>
<td>Progressive sensorineural hearing loss, Diabetes, Optic atrophy, Progressive neurologic abnormalities</td>
<td>WFS1</td>
<td>WFS1-associated hearing loss (DFNA6, DFNA4, DFNA38; congenital hearing loss without associated findings) may also be caused by variants in WFS1</td>
</tr>
</tbody>
</table>

SIDS: sudden infant death syndrome.

**Summary of Evidence**

For individuals with suspected of having hereditary nonsyndromic hearing loss (NSHL) who receive genetic testing, the evidence includes small retrospective, single-center studies, case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and genetic testing yield for NSHL. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic variants in GJB2, GJB6, and numerous other genes are found in a substantial percentage of patients with hereditary hearing loss. Of all patients with suspected hereditary hearing loss after clinical examination, a substantial proportion, in the range of 30% to 60%, will be found to have a genetic variant. The probability of finding a genetic variant is increasing as new gene variants are identified. False-positive results on genetic testing are expected to be very low. For diagnosis, there are a number of potential benefits of genetic testing, including a reduction in the need for alternative diagnostic tests and monitoring of patients with genetically identified syndromic hearing loss associated with other medical conditions. Clinical guidelines have recommended a tiered genetic testing approach, starting with the most common genes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a family history of hereditary NSHL who receive preconception genetic testing to determine carrier status, the evidence is limited but includes clinical guidelines. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic variants in GJB2, GJB6, and numerous other genes are found in a substantial percentage of patients with hereditary hearing loss. The probability of finding a genetic variant is increasing as new gene variants are identified. False-positive results on genetic testing are expected to be very low. There are several situations for
which there is potential clinical utility of testing for genes associated with hereditary hearing loss. For parents at high risk of an offspring with hereditary hearing loss, genetic testing can be useful as an aid in reproductive decision making. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02082431</td>
<td>Long QT &amp; Hearing Loss Prospective Study Registry</td>
<td>600</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from two physician specialty societies and 2 academic medical centers while this policy was under review in 2013. Reviewers agreed with the medically necessary indication for carrier testing, and with additional indications for carrier testing. There was support for testing the index case to confirm nonsyndromic hearing loss among a most reviewers. Reviewers in favor of genetic testing cited the ability to distinguish nonsyndromic hearing loss from other causes of hearing loss, to streamline the diagnostic workup and avoid further unnecessary testing, and to provide referrals to specialists when specific types of pathogenic variants identified are associated with disorders in other organ systems. It was considered that 2 contextual factors were present: barriers to performing high-quality trials, and the potential to reduce harms by avoiding unnecessary testing.
In 2014, the American College of Medical Genetics and Genomics issued practice guidelines for the clinical evaluation and etiologic diagnosis of hearing loss. The guidelines recommend obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus, imaging, or other testing based on the suspected etiology. For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories not suggestive of an environmental cause of hearing loss, the guidelines make the following recommendations for a tiered diagnostic approach:

- “Pretest genetic counseling should be provided, and, with patient’s informed consent, genetic testing should be ordered.
  - Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics.
  - In the absence of any specific clinical indications and for singleton cases and cases with apparent autosomal recessive inheritance, the next step should be testing for DFNB1-related hearing loss (due to mutations in GJB2 and adjacent deletions in GJB6).
  - If initial genetic testing is negative, genetic testing using gene panel tests, NGS technologies such as large sequencing panels targeted toward hearing loss-related genes, whole exome sequencing, or whole genome sequencing may be considered. Because several tests are clinically available, the clinician must be aware of the genes included in the test (panel) chosen and the performance characteristics of the platform chosen, including coverage, analytic sensitivity, and what types of mutations will be detected.
  - If genetic testing reveals mutation(s) in a hearing loss–related gene, mutation-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals.”
**American Academy of Pediatrics**

The American Academy of Pediatrics issued recommendations on early hearing detection in 2007:

Every infant with confirmed hearing loss and/or middle ear dysfunction should be referred for otologic and other medical evaluation. The purpose of these evaluations is to determine the etiology of hearing loss, to identify related physical conditions, and to provide recommendations for medical/surgical treatment as well as referral for other services. Essential components of the medical evaluation include clinical history, family history of childhood-onset permanent hearing loss, identification of syndromes associated with early- or late-onset permanent hearing loss, a physical examination, and indicated radiologic and laboratory studies (including genetic testing).

The evaluation, therefore, should include a review of family history of specific genetic disorders or syndromes, including genetic testing for gene mutations such as GJB2 (connexin-26), and syndromes commonly associated with early-onset childhood sensorineural hearing loss....

All families of children with confirmed hearing loss should be offered, and may benefit from, a genetics evaluation and counseling. This evaluation can provide families with information on etiology of hearing loss, prognosis for progression, associated disorders (eg, renal, vision, cardiac), and likelihood of recurrence in future offspring. This information may influence parents' decision-making regarding intervention options for their child.

There is a 2013 supplement to the Academy’s 2007 position statement on early intervention after confirmation that a child is deaf or hard of hearing. Genetic testing was not addressed.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must
be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/11/13</td>
<td>New Policy. Policy created with literature search through June 30, 2013 and clinical input reviewed; may be considered medically necessary for confirmation of the diagnosis of hereditary nonsyndromic hearing loss, and for carrier testing in parents under certain conditions.</td>
</tr>
<tr>
<td>11/20/14</td>
<td>Annual Review. Policy title and policy statements changed to refer to “hereditary hearing loss” (from “nonsyndromic hearing loss”) to reflect significant overlap between nonsyndromic and syndromic hearing loss. Added related policy 12.04.92 General Approach to Evaluating the Utility of Genetic Panels. Added Table 2 - a summary of some of the genetic syndromes and variants that may have overlap with NSHL. Replaced the word “proband” with “index patient”. Policy updated with literature review through July 29, 2014. References 3, 10-11, 17-22, 36, 37, 40-41, 45-48 added. Policy statements changed as noted. New CPT code 81430 added effective 1/15.</td>
</tr>
<tr>
<td>01/14/15</td>
<td>Coding update. New CPT code 81431, effective 1/1/15, added to policy. Update related policy title 7.01.105.</td>
</tr>
<tr>
<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. No change to policy statement. No references added.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Annual Review, approved June 6, 2017. Policy moved into new format. Policy updated with literature review through February 23, 2017; no references added, references 35-36 removed due to unselected pediatric population for genetic testing. The policy is revised with updated genetics nomenclature. “Mutations” changed to “variants” in policy statements; statements otherwise unchanged.</td>
</tr>
<tr>
<td>07/01/18</td>
<td>Annual Review, approved June 22, 2018. Policy updated with literature review through February 2018; reference 23 added; reference 21 updated; reference 1 updated. “Suspected” added to the first policy statement; statements otherwise unchanged.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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Premera:
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  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
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Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.
Call 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要的日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmong (Hmongo):

Ilokano (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaa mabalina nga adda ket naglaon iti napateg nga impormasion maiyagan nga iti aplikasyonño wenni coverage babaen iti Premera Blue Cross. Daytoy ket mabalina dagiti importante a petsa iti daytoy a pakdaar. Mabalina nga adda rumbeng nga aramideng nga adda sakkab dagiti partikular a naituding nga adda alaww tapon mapagtalainey nga coverage iti salay-ayno wenni tulong kadagitir gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong niti bukodyo a pagasagao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

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Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

وتالوگ (Tagalog): Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagpako sa pamamagitan ng Premera Blue Cross. Maaaring magaangalang ka na nagmagsagot sa kabaw sa ilang mga itinakdang klase o tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon.

ไทย (Thai): ประกาศนี้มีข้อมูลสําคัญ คุณอาจต้องดำเนินการในวันที่ระบุในประกาศนี้เพื่อให้รักษาสิทธิการประกันสุขภาพของคุณหรือการคืนค่าใช้จ่ายที่คุณมีสิทธิได้ โปรดติดต่อกับ 800-722-1471 (TTY: 800-842-5357).