Medical Policy
Genetic Testing for Hereditary Hearing Loss

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- Coding Information
- Policy: Medicare
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Policy Number: 452
BCBSA Reference Number: 2.04.87
NCD/LCD: N/A

Related Policies
- Preimplantation Genetic Testing, #088
- Cochlear Implant, #478
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders, #457

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing for hereditary hearing loss genes (GJB2, GJB6, and other hereditary hearing loss-related genes) in individuals with suspected hearing loss to confirm the diagnosis of hereditary hearing loss may be considered MEDICALLY NECESSARY.

Preconception genetic testing (carrier testing) for hereditary hearing loss genes (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.

Genetic testing for hereditary hearing loss genes is considered INVESTIGATIONAL for all other situations, including, but not limited to, testing patients without hearing loss (except as addressed in related policies, eg, policy #088 [preimplantation genetic testing]).

Prior Authorization Information
Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED if the procedure is performed inpatient.
Outpatient

- For services described in this policy, see below for situations where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Prior authorization is <strong>not required</strong>.</td>
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<tr>
<th>Commercial PPO and Indemnity</th>
<th>Outpatient</th>
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<td>Prior authorization is <strong>not required</strong>.</td>
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<tr>
<th>Medicare HMO BlueSM</th>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria **MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81252</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence</td>
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<tr>
<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants</td>
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<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>
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<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>
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</table>

HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>S3844</td>
<td>DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness</td>
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Description

**HEREDITARY HEARING LOSS**

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity (≥40 decibels).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 nonprogressive
- 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 NSHL requires an evaluation by 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 the 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 pathogenic variants present in the *GJB2* or *GJB6* genes.⁶ DFNB1-associated hereditary hearing loss relates to autosomal recessive syndromes in which more than 99% of cases are caused by pathogenic variants in the *GJB2* gene, and less than 1% of remaining cases arise from pathogenic variants to *GJB6*.⁷ A list of available tests for genes at the DFNA3 and DFNB1 loci are provided in Table 1.
Two of the most commonly disease-associated genes are \textit{GJB2} and \textit{GJB6}. \textit{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 hereditary NSHL.\textsuperscript{8} The carrier rate in the general population for a recessive deafness-causing \textit{GJB2} variant is approximately 1 in 33.\textsuperscript{1} Specific variants have been observed to be more common in certain ethnic populations.\textsuperscript{9,10} Variants in the \textit{GJB2} gene will impact the expression of the Cx26 connexin protein and almost always cause prelingual, but not necessarily congenital, deafness.\textsuperscript{11} Different variants of \textit{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 on \textit{GJB2} variant prevalence, suggested that the overall prevalence of \textit{GJB2} variants is similar around the world, although specific variants differ.\textsuperscript{12}

Variants in the \textit{GJB6} gene lead to similar effects on abnormal expression of connexin protein Cx30. However, \textit{GJB6} variants are much less common than \textit{GJB2} variants. Of all patients with hereditary hearing loss, approximately 3\% have a variant in the \textit{GJB6} gene.

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

Analysis for \textit{GJB6} and \textit{GJB2} variants can be performed by Sanger sequencing 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 genes with the most common pathogenic variants are generally sequenced first, followed by sequencing of additional genes if a pathogenic variant is not found.

In addition to the most common genes associated with hereditary hearing loss (\textit{GJB6}, \textit{GJB2}), there are many less common disease-associated genes. Some are: \textit{ACTG1}, \textit{CDH23}, \textit{CLDN14}, \textit{COCH}, \textit{COL11A2},
DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMRPSS3, TRIOBP, USH1C, and WFS1 genes. Novel genetic variants continue to be identified in cases of hereditary hearing loss.\textsuperscript{13,14} For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported.\textsuperscript{15,16} In contrast, only 18 pathogenic copy number variants (CNVs) had been identified by 2014.\textsuperscript{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 pathogenic 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 genetic 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 shown in Table 2. 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 associated with syndromic hearing loss. In addition, 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 2. Gene Panels for Hereditary Hearing Loss\textsuperscript{11}

<table>
<thead>
<tr>
<th>Test (Gene Panel)</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® V6)\textsuperscript{21}</td>
<td>NGS/massive parallel sequencing</td>
<td>152</td>
<td>99%</td>
</tr>
</tbody>
</table>

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 genes associated with NSHL are associated with recognized syndromes. Some genetic syndromes and genes that may overlap with NSHL are shown in Table 3.

### Table 3. 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 HL 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></td>
<td>MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2</td>
<td>DFNB18 (nonsyndromic) may also be caused by variants in USH1C; DFNB12 (nonsyndromic) may also be caused by variants in CDH23</td>
</tr>
</tbody>
</table>
| Type 2 | • Congenital mild-to-severe HL  
• Normal vestibular function | USH2A, VLGR1, WHRN |
| Type 3 | • Progressive HL  
• Progressive vestibular dysfunction | CLRN1i PDZD7 |
| Pendred syndrome | • Congenital sensorineural HL  
• Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct)  
• Euthyroid goiter | SLC26A4 (50%) |
| Jervell and Lange-Nielsen syndrome | • Congenital deafness  
• Prolongation of the QT interval | KCNQ1, KCNE1 |
| Wolfram syndrome | • Progressive sensorineural HL  
• Diabetes  
• Optic atrophy  
• Progressive neurologic abnormalities | WFS1 |

| • DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by variants in MYO7A |
| • Goiter not present until early puberty or adulthood  
• Variants in SLC26A4 may also cause NSHL |
| • HL may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome) |
| • WFS1-associated HL (DFNA6/14/38; congenital HL without associated findings) may also be caused by variants in WFS1 |

HL: hearing loss; NSHL: nonsyndromic hearing loss; SIDS: sudden infant death syndrome.

**Summary**

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity (≥40 decibels). 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. NSHL accounts for 70% to 80% of genetically determined deafness, and it is more difficult to determine whether the etiology is hereditary or acquired.

For individuals who are suspected of having hereditary 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 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 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.

Input obtained in 2013 has demonstrated support for genetic testing to differentiate hereditary hearing loss from other causes of hearing loss, and to improve the efficiency of the diagnostic workup by avoiding unnecessary testing. Input has also suggested that knowledge of specific pathogenic variants may lead to further management changes, such as referral to specialists. Therefore, genetic testing to confirm the diagnosis of hereditary hearing loss may be considered medically necessary.

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 \textit{GJB2}, \textit{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.

Based on the available evidence and clinical input obtained in 2013, genetic testing for hereditary hearing loss carrier status may be considered medically necessary when one of the following is present: (1) an offspring with suspected hereditary hearing loss, (2) 1 or both parents with suspected hereditary hearing loss, (3) a first-degree relative with an offspring who has hereditary hearing loss, or (4) a first- or second-degree relative with hereditary hearing loss and the parents desire to have further offspring and want to know the likelihood of another offspring with hereditary hearing loss.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>6/2018</td>
<td>BCBSA National medical policy review. First policy statement clarified to add suspected; statements otherwise unchanged.</td>
</tr>
<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2015</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>11/2014</td>
<td>BCBSA National medical policy review. Policy title and policy statements clarified to refer to hereditary hearing loss (from nonsyndromic hearing loss) to reflect overlap between nonsyndromic and syndromic hearing loss.</td>
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</tbody>
</table>

### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


