The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

Congenital deafness and childhood-onset hearing loss is caused by genetic mutations in a large percentage of cases. Genetic testing for hearing loss is primarily intended either to determine whether hearing loss is hereditary, or to determine carrier status of parents in order to better define the likelihood of hearing loss in their offspring.

**Background**

Description of disease. Hearing loss is a common birth defect. Approximately one of every 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. Since syndromic hearing loss occurs as part of a syndrome of multiple clinical manifestations, it is often recognized more readily as hereditary in nature.

Nonsyndromic hearing loss (NSHL) is defined as hearing loss that is not associated with other physical signs or symptoms. For NSHL, it is more difficult to determine whether the etiology is hereditary or acquired, since by definition there are no other clinical manifestations. 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

The majority 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 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 nonsyndromic hearing loss is non-specific since there are a number of underlying etiologies, and often it cannot be determined with certainty whether a genetic cause for hearing loss exists.

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 six 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.

Genetic mutations in NSHL. The genetic loci on which mutations associated with NSHL are usually found are termed DFN, and NSHL is sometimes called DFN-associated hearing loss. DFNA3-associated NSHL is caused by autosomal dominant mutations present in the \( GJB2 \) or \( GJB6 \) genes, which alters the coding sequence for the connexin proteins Cx26 or Cx30, respectively. (6) DFNB1-associated NSHL are autosomal recessive syndromes in which more than 99% of cases are caused by mutations to the \( GJB2 \) gene with less than 1% of remaining cases arising from mutations to \( GJB6 \). (7) A list of available tests for genetic mutations at the DFNA3 and DFNB1 loci is given in Table 1.

There are more than 300 individual mutations known to be associated with NSHL. (8) Two of the most commonly mutated genes are \( GJB2 \) and \( GJB6 \). \( GJB2 \) is a small gene with a single coding exon. Mutations of this gene are most common in NSHL, causing an estimated 50% of the cases on NSHL. (9) The carrier rate in the general population for a recessive deafness-causing \( GJB2 \) mutation is approximately one in 33. (1) Specific mutations have been observed to be more common in certain ethnic populations. (10, 11) Mutations in the \( GJB2 \) gene will impact expression of the Cx26 connexin protein and almost always cause pre-lingual, but not necessarily congenital, deafness. (8)

Differing mutations 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.

Mutations in the \( GJB6 \) gene are the second most common genetic defect in NSHL and lead to similar effects on abnormal expression of connexin protein Cx30. However, \( GJB6 \) mutations are much less common than mutations in \( GJB2 \). Of all the patients with NSHL, approximately 3% are found to have a mutation in the \( GJB6 \) gene.

**Table 1. Clinical Characteristics and Testing Methods for GJB2 and GJB6 Mutations 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>Mutations Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFNA3</td>
<td>( GJB2 )</td>
<td>Prelingual</td>
<td>High frequency progressive</td>
<td>Sequence Analysis/Mutation Scanning</td>
<td>Sequence Variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Targeted Mutation Analysis</td>
<td>Specified sequence variants</td>
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<td></td>
<td>Deletion/duplication analysis</td>
<td>Exonic or whole-gene deletions/duplications</td>
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</tr>
</tbody>
</table>
Mutation analysis for *GJB6* and *GJB2* mutations 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 one gene at a time. With Sanger sequencing, the gene with the most common mutations is generally sequenced first, followed by sequencing of additional genes if a pathogenic mutation is not found.

In addition to the most common mutations that are associated with NSHL, *GJB6* and *GJB2*, there are many less common pathologic mutations. Some of these are: *ACTG1*, *CDH23*, *CLDN14*, *COCH*, *COL11A2*, *DFN3*, *DFNB59*, *ESPN*, *EYA4*, *GJB2*, *GJB6*, *KCNO4*, *LHFPL5*, *MT-TS1*, *MYO15A*, *MYO6*, *MYO7A*, *OTOF*, *PCDH15*, *POU3F4*, *SLC26A4*, *STRC*, *TECTA*, *TMC1*, *TMIE*, *TMPRSS3*, *TRIOBP*, *USH1C*, and *WFS1* genes.

Because of the large number of genes associated with NSHL, there are a variety of 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 given in Table 3. 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.

**Regulatory Status**

No FDA-cleared molecular diagnostic tests were found. Thus, molecular evaluation is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (laboratory-developed tests, formerly “home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *GJB2* and *GJB6* genetic testing.

**Related Protocols**

Preimplantation Genetic Testing

Cochlear Implant

**Policy (Formerly Corporate Medical Guideline)**

Genetic testing for NSHL mutations (*GJB2*, *GJB6* and other NSHL-related mutations) in individuals with nonsyndromic hearing loss to confirm the diagnosis of hereditary nonsyndromic hearing loss (see Policy Guidelines) may be considered medically necessary.

Preconception genetic testing (carrier testing) for nonsyndromic hearing loss (NSHL) mutations (*GJB2*, *GJB6* and other NSHL-related mutations) in parents may be considered medically necessary when at least one of the following conditions has been met:

- Offspring with hereditary NSHL; OR
- One or both parents with suspected NSHL; OR
- First- or second-degree relative affected with hereditary NSHL; OR
- First-degree relative with offspring who is affected with hereditary NSHL
Genetic testing for nonsyndromic hearing loss mutations is considered **investigational** for all other situations (except as addressed in Related Protocols, e.g., Preimplantation Genetic Testing).

**Policy Guideline**

The definition of NSHL is hearing loss that is not associated with other physical signs and symptoms. 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

Genetic evaluation and counseling should be offered to all patients who are being considered for NSHL genetic testing. Genetic evaluation and counseling can help define the familial patterns of inheritance, exclude the presence of syndromic hearing loss, and provide information to patients on the future risk of NSHL in offspring.


Testing for mutations associated with NSHL should be confined to known pathologic mutations. While research studies using genome-wide associations have uncovered numerous single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs) associated with NSHL, (12, 13) 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. **For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.**

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**
References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


