Medical Policy

Genetic Testing for Nonsyndromic Hearing Loss

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 452
BCBSA Reference Number: 2.04.87

Related Policies
- Preimplantation Genetic Testing, #088
- Cochlear Implant, #478

Policy

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

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 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.

Prior Authorization Information

Commercial Members: Managed Care (HMO and POS)
Prior authorization is NOT required.

Commercial Members: PPO, and Indemnity
Prior authorization is NOT required.
Medicare Members: HMO Blue℠
Prior authorization is NOT required.

Medicare Members: PPO Blue℠
Prior authorization is NOT required.

CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. 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.

CPT Codes

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

HCPCS Codes

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

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 2nd through 4th 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 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.

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 \textit{GJB2} or \textit{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 \textit{GJB2} gene with less than 1% of remaining cases arising from mutations to \textit{GJB6}. (7) A list of available tests for genetic mutations at the DFNA3 and DFNB1 loci is given in Table1.

There are more than 300 individual mutations known to be associated with NSHL. (8) Two of the most commonly mutated genes are \textit{GJB2} and \textit{GJB6}. \textit{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 \textit{GJB2} mutation is approximately 1 in 33. (1) Specific mutations have been observed to be more common in certain ethnic populations. (10, 11) Mutations in the \textit{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 \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.

Mutations in the \textit{GJB6} gene are the second most common genetic defect in NSHL and lead to similar effects on abnormal expression of connexin protein Cx30. However, \textit{GJB6} mutations are much less common than mutations in \textit{GJB2}. Of all the patients with NSHL, approximately 3% are found to have a mutation in the \textit{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</td>
<td>Sequence Analysis/Mutation Scanning</td>
<td>Sequence Variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>progressive</td>
<td>Targeted Mutation 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</td>
<td>Sequence Analysis/Mutation Scanning</td>
<td>Sequence Variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>progressive</td>
<td>Targeted Mutation 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>Sequence analysis 2</td>
<td><em>GJB2</em> sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/ duplication analysis 4</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>Targeted Mutation Analysis</td>
<td><em>GJB6</em> deletions</td>
</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*, *DFNA5*, *DFNB31*, *DFNB59*, *ESPN*, *EYA4*, *GJB2*, *GJB6*, *KCNQ4*, *LHFPFL5*, *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*.

**Summary**

Genetic mutations in *GJB2*, *GJB6*, and numerous other genes are found in a substantial percent of patients with nonsyndromic hearing loss (NSHL). The analytic validity of genetic testing for NSHL is high. Of all patients with suspected NSHL after clinical examination, a substantial minority, in the range of 30-60% will be found to have a genetic mutation. False-positive results on mutation testing are expected to be very low.

There are several situations for which there is potential clinical utility of testing for NSHL mutations. For diagnosis alone, there is a lack of evidence from the literature or from clinical practice guidelines on specific management changes that result from genetic testing. The results of clinical vetting demonstrated...
support for genetic testing to differentiate NSHL from other causes of hearing loss, and to improve the
efficiency of the diagnostic workup by avoiding unnecessary testing. Clinical vetting also suggested that
knowledge of specific mutations may lead to further management changes, such as referral to specialists.
Therefore, genetic testing to confirm the diagnosis of hereditary NSHL may be considered medically
necessary.

For parents at high risk of an offspring with NSHL, genetic testing can be useful as an aid in reproductive
decision making. Parents may alter their attempts at pregnancy following testing, or can increase the
likelihood of a birth free of genetic mutations through preimplantation genetic testing followed by in vitro
fertilization. Based on the available evidence and results of clinical vetting, genetic testing for NSHL
carrier status may be considered medically necessary when one of the following is present: 1) an
offspring with hereditary NSHL, 2) one or both parents with suspected hereditary NSHL, 3) A first-degree
relative with an offspring who has hereditary NSHL, 4) a first- or second-degree relative with NSHL, and
the parents desire to have further offspring and wish to know the likelihood of another offspring with
NSHL. Therefore, carrier testing of parents for mutations associated with NSHL may be considered
medically necessary in these populations.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
</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