MEDICAL POLICY – 12.04.87
Genetic Testing for Hereditary Hearing Loss

BCBSA Ref. Policy: 2.04.87
Effective Date: July 1, 2017
Last Revised: June 6, 2017
Replaces: 2.04.87

RELATED MEDICAL POLICIES:
12.04.305 Preimplantation Genetic Testing in Embryos

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POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

There are several things that can cause hearing loss. It 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.

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

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).

Preconception genetic testing (carrier testing) for variants in 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
- One or both parents with suspected hereditary hearing loss
- First- or second-degree relative affected with hereditary hearing loss
- First-degree relative with offspring who is affected with hereditary hearing loss

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></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>
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<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</td>
</tr>
</tbody>
</table>
### Related Information

Hereditary hearing loss can be classified as syndromic or non-syndromic. The definition of non-syndromic 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 NSHL. Given this overlap, the policy focuses on genetic testing for hereditary hearing loss more generally.

In addition to variants in the GJB6 and GJB2 genes, there are many less common pathologic variants found in other genes. Some of these 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.

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 syndrome or non-syndromic 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.

**Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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 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, 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 in nature.

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, 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 nonsyndromic hearing loss is non-specific 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 Table 1.

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 nonsyndromic hereditary hearing loss. The carrier rate in the general population for a recessive deafness-causing GJB2 mutation 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. Differing 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 of publications reporting GJB2 mutation prevalence suggests 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% are found to have a mutation in the GJB6 gene.
Table 1. 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/ Mutation Scanning Targeted mutation analysis Deletion/duplication analysis</td>
<td>Sequence Variants Specified sequence variants 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/ Mutation Scanning Targeted Mutation Analysis Deletion/duplication analysis</td>
<td>Sequence Variants Specified sequence variants Exonic or whole-gene deletions/duplications</td>
</tr>
<tr>
<td>DFNB1</td>
<td>GJB2</td>
<td>Prelingual</td>
<td>Usually stable</td>
<td>Targeted mutation analysis Deletion/ duplication analysis 4</td>
<td>GJB2 sequence variants 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 mutation 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 pathologic variants. Some of these genes 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. As of 2014, over 2,000 pathogenic deafness variants in approximately 130 genes had been reported. In contrast, only 18 pathogenic copy number variants (CNVs) had been identified by 2014. 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 GJB2.17

Because of the large number of genes associated with hereditary hearing loss, 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 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 that are 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.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

<table>
<thead>
<tr>
<th>Test</th>
<th>Technology</th>
<th>Genes Tested; Variants Tested</th>
<th>Analytic Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Healthcare (OtoGenome™ Test for Hearing Loss and Related Syndromes)</td>
<td>Next generation sequencing, followed by confirmation with Sanger sequencing or PCR</td>
<td>87; NA</td>
<td>99%</td>
</tr>
<tr>
<td>University of Iowa Healthcare (OtoSCOPE® V6)21</td>
<td>Next generation/Massive parallel sequencing</td>
<td>116; NA</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 present 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 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 Mutation(s)</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>USH2A VLGR1 WHRN</td>
<td>DFNB18 (nonsyndromic) may also be caused by variants in USH1C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DFNB12 (nonsyndromic) may also be caused by variants in CDH23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by variants in MYO7A</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td>Congenital mild-to-severe hearing loss Normal vestibular function</td>
<td>CLRN1i PDZD7</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td></td>
<td>Progressive hearing loss Progressive vestibular dysfunction</td>
<td></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</td>
<td>Autosomal</td>
<td>Congenital deafness</td>
<td>KCNQ1 KCNE1</td>
<td>Hearing loss may present without personal or family</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Inheritance</td>
<td>Clinical Description</td>
<td>Gene Mutation(s)</td>
<td>Reason for Overlap With NSHL</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>--------------------------------------------------------</td>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>syndrome</td>
<td>recessive</td>
<td>Prolongation of the QT interval</td>
<td></td>
<td>history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome)</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>Autosomal recessive</td>
<td>Progressive sensorineural hearing loss</td>
<td>WFS1</td>
<td>WFS1-associated hearing loss (DFNA6/14/38; 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 who are 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. The analytic validity of genetic testing for hereditary hearing loss is high. 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 analytic validity of genetic testing for hereditary hearing loss is high. 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 4.

Table 4. 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><strong>Ongoing</strong></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>Aug 2018</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01802190</td>
<td>Prevalence of POU4F3 (DFNA15) and SLC17A8 (DFNA25) Genes Mutations in Dominant Autosomal Deafness and Phenotypic Characterization of Carrier Patients</td>
<td>150</td>
<td>Terminated “no convincing results”</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 provide appropriate reviewers who collaborate with and make recommendations during this process, 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 NSHL among a majority of reviewers. Reviewers in favor of genetic testing cited the ability to distinguish NSHL 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 variants were identified that are associated with disorders in other organ systems. It was considered that two contextual factors were present: barriers to performing high-quality trials, and the potential to reduce harms by avoiding unnecessary testing.

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

In 2014, the American College of Medical Genetics and Genomics issued a practice guideline for the clinical evaluation and etiologic diagnosis of hearing loss. The guideline recommends obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus (CMV), 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 that do not suggest 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 (AAP) issued recommendations on early hearing detection in 2007\(^{36}\).

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 AAP’s 2007 position statement on early intervention after confirmation that a child is deaf or hard of hearing.\(^{37}\) Genetic testing was not addressed.
Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Molecular diagnostic testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

References


History

<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>
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<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>
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<tr>
<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. No change to policy statement. No references added.</td>
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<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>
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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). ©2017 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.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - 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
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
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)

You can also file a complaint with the Washington State Human Rights Commission, available at 800-722-1471 (TTY: 800-842-5357).

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).

Amaric (Amharic):


Oromoo (Cushite):


Français (French):


Kreyól ayisyen (Creole):


Deutsche (German):


Hmoob (Hmong):

Tsaab ntawv tshaj xno no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xno no muaj cov ntshiab lus tseem ceeb boko kaj daim ntawv thov kev pab los yog koy qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas rau hauv daim ntawm no. Tej zaum koy kaj juv yuav taa uu qee yam uas peb kom kaj uas tsip pub dhuav cov caj nyong uas teev tseg rau hauv daim ntawv no mas kaj thaj juv yuav tau baiis kev pab cuam kho mob los yog kev pab them tej qii kho mob ntawv. Kaj muaj cai kom laww muab cov ntshiab lus no uas tau mbab sau uu kaj hom lus pub dawb rau koy. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonowyen nga coverages babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramideny or nga addang sakkay dagiti partikular a na tingid nga adda aldaw tapno mapagtalaineyo nga cover age ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Premera Blue Cross.

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claves 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).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang pista o sa paunawa. Maaring magagamitin na ka na masagawa ng habak sa ilang mga talaan panahon unang unang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakauhu ng ganitong impormasyon at tungkol sa iyong wika ng walang gastos. Turnaw sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการขอรับการช่วยเหลือตามประกันสุขภาพของคุณ Premera Blue Cross และบริการที่มีอยู่ในภาษาราชการ คุณควรจด จำคำนวณในการกำหนดเวลาที่สำคัญและต้องทราบว่าการรับประกันสุขภาพของคุณขึ้นอยู่กับคุณ มีที่เพียงแค่คุณมีสิทธิ์ที่จะรับบริการและข้อมูลที่เกี่ยวข้องในภาษาราชการไม่มีปัญหาใด ๆ โปรดติดต่อ 800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Polskie (Polish):

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir data importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação ou ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている情報がある重要な日付をご確認ください。健康保険や料金サポートを維持するには、特定の日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
문서에는 중요한 정보가 들어 있습니다. 특히 문서는 한국어로 작성되어 있으며 Premera Blue Cross를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 문서에는 핵심이 되는 네이버이 있을 수 있습니다. 귀하의 관리 이름 커버리지를 제한되지거나 정보를 절약하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보는 귀하의 언어와 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하십시오.

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенному предельному сроку для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claves 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).

فارسی (Persian):
این اعلان حقوق اطلاعات مهمی می‌بهاند. این اعلان می‌تواند اطلاعات مهمی در مورد تاریخ‌های مشخصی به شما تحویل دهد که به دنبال آن نیاز به اقدامات مشخصی داشته باشید. این اعلان ممکن است به شما اجازه دهد که اطلاعات و کمک‌هایی را به طور قابل توجه دریافت نمایید. 800-722-1471 (TTY: 800-842-5357) برقرار نمایید.