Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cochlear Implant and Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders are addressed separately in medical policies 00017 and 00389, respectively.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for hereditary hearing loss genes (GJB2, GJB6 and other hereditary hearing loss-related genes) in individuals with hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines section) to be eligible for coverage.

Based on review of available data, the Company may consider preconception genetic testing (carrier testing) for hereditary hearing loss genes (GJB2, GJB6 and other hereditary hearing loss-related genes) in parents when at least one of the following conditions has been met to be eligible for coverage:

Patient Selection Criteria
Coverage eligibility will be considered when ANY of the following criteria is met:

- Offspring with hereditary hearing loss;
- 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.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for hereditary hearing loss genes for all other situations, including but not limited to, testing in patients without hearing loss to be investigational.*

The use of genetic testing for hereditary hearing loss genes when patient selection criteria are not met is considered to be investigational.*
Policy Guidelines

Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of nonsyndromic hearing loss (NSHL) is hearing loss 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 nonprogressive.

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 can 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 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 syndrome 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 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

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in deoxyribonucleic acid (DNA) diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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 PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. 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></td>
<td>Variant</td>
<td>Change in the DNA sequence</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>
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Table PG2. 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>
<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>

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

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.

Background/Overview

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 db). 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 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.

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.

**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. 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. 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 pathogenic variants present in the \(GJB2\) or \(GJB6\) genes. 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 \(GJB6\). A list of available tests for genes at the DFNA3 and DFNB1 loci is provided in Table 1.

Two of the most commonly disease-associated 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 hereditary 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
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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 of 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 2014 systematic review of publications 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 GJB2 variants. Of all patients with hereditary hearing loss, approximately 3% have a variant 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</th>
<th>Gene</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 scanning</td>
<td>• Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Targeted variant analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Deletion/duplication analysis</td>
<td>• Specified sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Analysis/variant scanning</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Exonic or whole-gene deletions/duplications</td>
<td></td>
</tr>
<tr>
<td>DFNA3</td>
<td>GJB6</td>
<td>Prelingual</td>
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<td>• Sequence scanning</td>
<td>• Sequence variants</td>
</tr>
<tr>
<td></td>
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<td>• Targeted variant analysis</td>
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<td></td>
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<td></td>
<td></td>
<td>• Deletion/duplication analysis</td>
<td>• Specified sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Analysis/variant scanning</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Exonic or whole-gene deletions/duplications</td>
<td></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></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Exon(s) or whole-gene deletions</td>
<td></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 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 (GJB6, 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. For example, as of 2014, over 2000 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 pathogenic variants in GJB2.
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 \textit{GJB6} and \textit{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. 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</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)</td>
<td>NGS/massive parallel sequencing</td>
<td>116</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>\textit{MYO7A}, \textit{USH1C}, \textit{CDH23}, \textit{PCDH15}, \textit{SANS}, \textit{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 HL</td>
<td>\textit{DFNB18} (nonsyndromic) may also be caused by variants in \textit{USH1C}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Abnormal vestibular function</td>
<td>\textit{DFNB12} (nonsyndromic) may also be caused by variants in \textit{CDH23}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>\textit{DFNB2} (nonsyndromic) and \textit{DFNA11} (nonsyndromic) may also be caused by variants in \textit{MYO7A}</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td>\textit{USH2A},</td>
<td></td>
</tr>
</tbody>
</table>

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Syndrome | Inheritance | Clinical Description | Gene | Reason for Overlap With NSHL
---|---|---|---|---
Type 3 | | • Normal vestibular function VLGRT1, WHRN | | 
| | • Progressive HL | | 
| | • Progressive vestibular dysfunction CLRN1i PDZD7 | | 
Pendred syndrome | Autosomal recessive | • Congenital sensorineural HL SLC26A4 (50%) | | 
| | • Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) | | 
| | • Euthyroid goiter | | 
| | • Goiter not present until early puberty or adulthood | | 
| | • Variants in SLC26A4 may also cause NSHL | | 
Jervell and Lange-Nielsen syndrome | Autosomal recessive | • Congenital deafness KCNQ1, KCNE1 | | 
| | • Prolongation of the QT interval | | 
| | • HL may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome) | | 
Wolfram syndrome | Autosomal recessive | • Progressive sensorineural HL WFS1 | | 
| | • Diabetes | | 
| | • Optic atrophy | | 
| | • Progressive neurologic abnormalities | | 
| | • WFS1-associated HL (DFNA6/14/38; congenital HL without associated findings) may also be caused by variants in WFS1 | | 

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 Amendments (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. FDA has chosen not to require any regulatory review of these tests.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Literature was sought on genetic testing for hereditary hearing loss in the following areas: analytic validity (ability to detect a variant that is known to be present and the ability to rule out variants when they are absent); clinical validity (ability to detect a variant in a patient with hereditary hearing loss, or to exclude a variant in a patient without hereditary hearing loss); and clinical utility (the impact of a variant on the management of patients and on relevant health outcomes).
TESTING INDIVIDUALS WITH SUSPECTED HEREDITARY NONSYNDROMIC HEARING LOSS

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with suspected hereditary NSHL is to establish the diagnosis of a genetic versus acquired hearing loss to inform treatment planning that may depend on hearing prognosis (e.g., early cochlear implant placement) and/or appropriate management of associated comorbidities (e.g., screening for cardiac disease consistent with established guidelines).

The question addressed in this evidence review is: In individuals with suspected hereditary NSHL, does use of genetic testing improve the efficiency of the diagnostic workup by avoiding unnecessary testing and changes in management for hearing loss or improve outcome in individuals who have a confirmed genetic etiology of hearing loss?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals with suspected hereditary NSHL.

Interventions
The relevant intervention of interest is genetic testing for the genes or familial variants associated with hereditary NSHL.

Comparators
The relevant comparator of interest is standard clinical management without genetic testing.

Outcomes
The general outcomes of interest include test accuracy and validity, changes in reproductive decision making, morbid events and resource utilization.

The potential beneficial outcomes of primary interest are avoidance of unnecessary testing and initiation management changes, including avoidance of treatments targeted for acquired hearing loss.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to lack of treatments for acquired hearing loss and failure to initiate treatments for hereditary hearing loss. False-negative test results can lead to initiation of inappropriate treatments targeting acquired hearing loss and failure to initiate treatments for hereditary hearing loss.

Timing
The time frame for outcomes measures varies from short-term development of hearing loss as well as delayed speech and language development to long-term permanent deafness.
Setting
The primary setting would be in the pediatric population where newborn hearing screening reveals deficits in hearing or in infants with delayed speech and language development. Patients may be referred from pediatrics to a pediatric neurologist, audiologist, or medical geneticist for investigation and management of hereditary NSHL. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity

Sequencing Analysis
The analytic validity of Sanger sequencing and next-generation sequencing (NGS) is known to be high. Although there is no robust evidence base for Sanger sequencing or NGS specifically for genes involved in hereditary hearing loss, it is reasonable to assume that sequencing has an analytic sensitivity and specificity that approaches 100% under ideal testing conditions.

Targeted Panel Testing
The analytic validity of targeted panels, such as microarrays for hereditary hearing loss pathogenic variants that have been described, is high. The studies identified for this review are summarized in Table 4. These data are only available for some commercially available microarray panels. In all cases where data were presented, the analytic sensitivity was greater than 99%, and in most studies it was 100%. The analytic specificity was 100% when it was reported, usually in a small number of normal individuals.

Table 4. Microarrays Testing For GJB2 and GJB6 Pathogenic Variants

<table>
<thead>
<tr>
<th>Test</th>
<th>Genes and Variants Tested</th>
<th>Analytic Sensitivity</th>
<th>Analytic Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss biochip (Murdoch Children's Institute, Australia)</td>
<td>4; 15</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Allele-specific PCR-based universal array (ASPUA; China)</td>
<td>4; 11</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>SoundGene screening panel (Pediatrix Medical Group, 2010, USA)</td>
<td>4; 15</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Invader Assay (Japan)</td>
<td>9; 41</td>
<td>&gt;99.2%</td>
<td>100%</td>
</tr>
<tr>
<td>Hereditary hearing loss arrayed primer extension microarray (APEX array) (Stanford University Medical Center, USA)</td>
<td>8; 198</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Array CGC (CGC Genetics, 2010: USA, Portugal, Spain)</td>
<td>31; 312</td>
<td>&gt;99%</td>
<td></td>
</tr>
<tr>
<td>OtoChip: oligonucleotide hybridization Affymetrix GeneChip</td>
<td>19; NA</td>
<td>99.9%</td>
<td></td>
</tr>
</tbody>
</table>

NA: not available; NR: not reported; PCR: polymerase chain reaction.

The largest of these studies was published by Abe et al (2007). This study included 338 patients from Japan with congenital or childhood-onset hearing loss before age 10 years. The population included a broad range of patients with hereditary hearing loss, including those with inheritance patterns that were autosomal dominant, autosomal recessive, mitochondrial, or sporadic. A targeted microarray panel (Invader
Assay) was used to detect pathogenic variants, which included 41 pathogenic variants in 9 different genes, one of which was GJB2.

A total of 13,858 assays were performed. The correct genotype was identified after a single Invader analysis in 13,748 (99.2%) cases. A total of 110 assays incorrectly identified the genotype. When these samples were reassayed with a larger amount of DNA, 108 of 110 were correctly genotyped. The remaining 2 assays were invalid because of insufficient DNA.

Other studies have used different patient populations and different panels of genes, but all have included the GJB2 pathogenic variants as part of the panel. Despite the heterogeneity in populations and genes examined, the analytic specificity was 100% in these other studies.

Section Summary: Analytic Validity
There is limited evidence on the analytic validity of testing for hereditary hearing loss genes and targeted variant testing using microarrays. Direct sequencing by Sanger or NGS is expected to have analytic validity approaching 100%. Targeted pathogenic variant testing using microarrays are also expected to have high analytic validity.

Clinical Validity
A number of publications have evaluated the clinical sensitivity and specificity of genetic testing for hereditary hearing loss in general and NSHL more specifically. The clinical sensitivity is reported as the percentage of patients with hereditary hearing loss who have a pathogenic variant, and the clinical specificity is reported as the percentage of patients without hereditary hearing loss who do not have a pathogenic variant. The clinical validity will vary as a function of the number of different genes examined, and by whether the population includes patients with hearing loss that is not strictly hereditary hearing loss.

Vona et al (2014) reported test results for targeted NGS of 2 panels of deafness-associated genes, 1 with 80 genes and 1 with 129 genes, in the evaluation of NSHL for cases in which GJB2 testing was negative. Testing with 1 of the 2 panels was performed on 30 patients from 23 families (23 probands) with hearing loss and 9 normal-hearing controls. Pathogenic variants in a gene associated with autosomal dominant hearing loss (ACTG1, CCDC50, EYA4, MYH14, M706, TCF21, MYO1A) or autosomal recessive hearing loss (MYO15A, MYO7A, GJB2, USH2A) were identified in 8 of 23 probands and 5 of 23 probands, respectively, for a success rate of 57%. In 2015, Gu et al reported results for targeted NGS of a panel of 131 genes related to hearing loss in 63 subjects with NSHL with negative testing for pathogenic variants in the GJB2, MT-RNR1, and SLC26A4 genes. The pathogenic variant detection rate was 12.7%, with 10 of 14 pathogenic variants detected as novel compound heterozygotes. In 2014, Shearer et al reported on CNVs in 686 patients with hearing loss using massively parallel sequencing (OtoSCOPE). Of the 686 patients studied, 15.2% (104/686) carried at least 1 CNV in a known deafness gene. The CNVs were caused by deletions (92 [64.3%]), gene conversions (3 [26.6%]), and duplications (13 [9.1%]).
Section Summary: Clinical Validity
The available studies have indicated that a substantial percentage of patients with hereditary hearing loss will have an identifiable pathogenic variant (clinical sensitivity). This rate varies widely in available studies due to differences in specific genes tested, patient population used, and the type of genetic testing performed. Clinical sensitivity increases as more genes associated with hereditary hearing loss are identified. There is limited information on the clinical specificity. Some studies with relatively small numbers of normal individuals have reported specificities approaching 100%.

Clinical Utility
There are several ways in which genetic testing for hereditary hearing loss could have clinical utility. For this evidence review, clinical utility will be considered in the following areas:

- As a diagnostic test for hereditary hearing loss
  - To confirm the diagnose of hereditary hearing loss and distinguish from acquired hearing loss
  - To alter management of individuals with hereditary hearing loss
- As preconception (carrier) testing for parents who desire to determine the risk of hereditary hearing loss in offspring
- As a screening test to identify hearing loss.

Diagnostic Test for Etiology of Hereditary Hearing Loss

Clinical Utility of Genetic Testing for Diagnosis of Hereditary Hearing Loss
Genetic testing in patients with suspected hereditary hearing loss can be performed to confirm the diagnosis of hereditary hearing loss, which is distinguished from acquired hearing loss. There is no direct evidence on the impact of genetic testing on outcomes when used as a diagnostic test in this manner. Therefore, a chain of evidence is considered to determine the impact on health outcomes.

The high analytic sensitivity indicates that if a pathogenic variant is present and included within test repertoires, it is very likely to be detected by current testing methods. The high analytic specificity indicates that if a pathogenic variant is absent, a false-positive result on genetic testing is very unlikely to occur.

Therefore, a positive genetic test with a known pathogenic variant would indicate that hereditary hearing loss is present with a high degree of certainty. In contrast, the low-to-moderate clinical sensitivity would indicate that a negative test is not definitive for ruling out hereditary hearing loss. False-negative results on genetic testing are not uncommon, therefore, the utility of a negative test in discriminating between hereditary and acquired hearing loss is low.

To have clinical utility, the confirmation of the diagnosis must be accompanied by changes in clinical management that improve outcomes. No published evidence was identified to evaluate whether management changes occur, and no clinical practice guidelines were identified that recommend these actions. However, the confirmation of a genetic basis for hereditary hearing loss may be useful in
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differentiating hereditary hearing loss from other causes of deafness, and thereby precluding other testing such as computed tomography or magnetic resonance imaging. Given that some cases of apparent NSHL may represent an initial presentation of a known syndrome associated with hearing loss, identification of specific pathogenic variants may prompt additional action. For example, if a \textit{KCNQ1} pathogenic variant is found, additional cardiac workup may be warranted because pathogenic variants in this gene are also associated with cardiac rhythm abnormalities. In addition, genetic counseling can provide patients and families with further information and assistance on issues such as reproductive decision making.

Genetic testing has also been proposed as a method to predict response to cochlear implantation. Expression of \textit{GJB2} and \textit{GJB6} is in the cochlea. In addition, patients with hereditary hearing loss pathogenic variants have been found to have intact spiral ganglion cells in the cochlea. Intact spiral ganglion cells have been associated with success following cochlear implantation. These factors lend credence to the theory that patients with \textit{GJB2} and \textit{GJB6} pathogenic variants may have a favorable prognosis following cochlear implantation and that patients with other pathogenic variants or without a documented pathogenic variant may have a less favorable prognosis.

The evidence on this question consists of several small, retrospective, single-center studies that have compared outcomes of cochlear implantation in patients with and without genetic variants. Two small series from Japan initially reported that hearing outcomes were superior in patients with variants. Fukushima et al (2002) compared 3 patients with and 4 patients without variants. Patients with \textit{GJB2} variants had a larger vocabulary (1243 words) than patients without a variant (195 words), and a higher mean developmental quotient. Matsushiro et al (2002) evaluated 15 patients with hearing loss, 4 with genetic variants and 11 without. They reported that speech perception was higher among patients with variants than those without. In 2014, in a retrospective cohort study, Popov et al evaluated the impact of \textit{GJB2} variants on hearing outcomes after cochlear implantation for congenital sensorineural NSHL. The study included 60 patients who had received a cochlear implant, 30 with \textit{GJB2} variants and 30 without, who were a subset of 71 patients included in a larger registry of cochlear implant patients evaluated at a single institution from 2009 to 2013. At 36 months of follow-up, results on several hearing test metrics were significantly better for the patients with \textit{GJB2} variants than for those without variants, including the Listening Progress Profile ($p<0.05$), and the Monosyllabic-Trochee-Polysyllabic Test with 3, 6, or 12 items ($p=0.005$, $p=0.002$, and $p=0.001$, respectively). Yan et al (2013) reported results from a series of 41 children who received cochlear implants for severe bilateral sensorineural hearing loss treated at a single center in China, 15 of whom had \textit{GJB2} variants and 10 of whom had \textit{SLC26A4} variants. Compared to patients with no variants, patients with \textit{GJB2} pathogenic variants, but not those with \textit{SLC26A4} variants, had improved outcomes on a number of hearing-related tests, including the Meaningful Auditory Integration Scale, categories of auditory performance, and speech intelligibility rating.

At least 2 similar series have been published in the United States. In 2004, Sinnathuray et al published 2 articles on overlapping series of patients treated with cochlear implants. In the larger series, 38 patients were included, 14 patients with genetic variants and 24 without. A standardized measure of speech, the Speech Intelligibility Rating (SIR) score, was used as the primary outcome measure. At 1 year, median SIR scores were higher in the patients with \textit{GJB2} variants (median, 3; range, 2-4) than patients without variants.

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(median, 2; range, 1-4), and the difference between the 2 groups was statistically significant (p=0.007). The percentage of patients achieving intelligible speech was 82% in the \( \text{GJB2} \) group and 30% in patients without variants (p=0.02).

In a second U.S. study by Connell et al (2007), these findings were not completely replicated. This series included 31 patients with congenital hearing loss, 12 with genetic variants and 19 without. The main outcome measure was speech perception category (range, 1-6). Mean speech perception category did not differ between patients with and without variants (4.1 vs 4.9, respectively, \( p=\text{NS} \)). The percentage of patients achieving speech perception category 6 was higher in the variant group (75% vs 53%), but statistical testing for this difference was not performed. On multivariate analysis, the variability in speech perception was explained primarily by the length of time since cochlear implantation, and cause of hearing loss was not a significant predictor of outcomes.

Clinical Utility of Genetic Panel Testing for Diagnosis of Hereditary Hearing Loss

Given the large quantity of genes associated with hereditary hearing loss, multiple genetic panel tests are commercially available. Panel testing for hereditary hearing loss generally falls into the category of panels containing genes associated with a single condition (hearing loss), for which the following criteria apply:

1. All individual components of the panel have demonstrated clinical utility OR the tests that have not demonstrated clinical utility do not have the potential to cause harm.
2. The test is performed in a CLIA‒approved lab.
3. Analytic validity of the panel approaches that of direct sequencing.
4. The panel offers substantial advantages (efficiency of workup, cost) over sequential analysis of individual genes.

For NGS panels for hereditary hearing loss, criteria 2, 3, and 4 generally apply. Some, but not all, of the genes evaluated in hereditary hearing loss genetic panels would be associated with the need for additional subspecialist referral or additional testing; based on a chain of evidence, testing for these genes would have demonstrated clinical utility. Testing with a panel that includes only genes that have an association with hereditary hearing loss would be associated with low potential for harm, because they would not be likely to lead to further investigations that are of unproven benefit.

Section Summary: Clinical Utility

Hereditary hearing loss can be confirmed if genetic testing reveals a pathogenic variant known to be associated with hereditary hearing loss, but a negative genetic test does not rule out hereditary hearing loss. For the individual patient, there is no evidence from the literature and no specialty society guidelines that have recommended specific actions or changes in management as a result of a positive genetic test. However, the use of genetic testing can streamline the diagnostic workup, and knowledge of specific pathogenic variants may prompt further action such as referral to specialists. Also, genetic counseling can be provided and may impact future decisions by the patient in areas such as reproductive planning.

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It is possible that the presence of a genetic variant, and/or the presence of a specific type of variant, is associated with the degree of response to cochlear implantation. This evidence is from small case series and therefore is not definitive. In addition, no treatment guidelines have recommended genetic testing as part of the decision to perform a cochlear implant. Therefore it is not possible to conclude that genetic testing has clinical utility in predicting response to cochlear implantation.

TESTING INDIVIDUALS WITH A FAMILY HISTORY OF HEREDITARY NSHL

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with a family history of hereditary NSHL is to determine the risk of hereditary hearing loss in offspring.

The question addressed in this evidence review is: Does carrier screening in individuals with a strong family history of hearing loss aid in reproductive decision making?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals with a strong family history of hereditary NSHL.

Interventions
The relevant intervention of interest is genetic testing for the genes or familial variants associated with hereditary NSHL.

Comparators
The relevant comparator of interest is standard preconception counseling without genetic testing.

Outcomes
The general outcomes of interest include test accuracy and validity, changes in reproductive decision making, morbidity events and resource utilization. The potential beneficial outcome of primary interest is changes in reproductive decision making that lead to a decrease in the number of affected offspring.

Timing
The time frame for outcome measures varies from short-term changes reproductive decision making with preimplantation genetic testing to long-term decreases in the number of affected offspring.

Setting
The primary setting would be in the adults of child-bearing age with a strong family history of hereditary NSHL receiving care in a primary care or obstetrics setting. Patients may be referred to medical geneticist for further investigation of hereditary NSHL. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.3
Analytic Validity
See the discussion of analytic validity in the section on Testing Individuals with Suspected Hereditary Nonsyndromic Hearing Loss.

Clinical Validity
See the discussion of clinical validity in the section on Testing Individuals with Suspected Hereditary Nonsyndromic Hearing Loss.

Clinical Utility
Individuals who are contemplating having children may desire to know the probability of hereditary hearing loss. This is most relevant when parents have had a previous child with hearing loss, or when there is a strong family history of hereditary hearing loss. In this situation, testing of the index case for a genetic variant can first be performed. If a pathogenic variant is found, then targeted testing for that specific pathogenic variant (familial variant) can be performed in the parents to confirm the presence of the carrier state, and to determine the risk of hereditary hearing loss in future offspring. The specific familial variant identified will give substantial information on the usual inheritance patterns, and the probability of a future offspring being affected.

Carrier testing can also be performed in people who do not have an offspring with hereditary hearing loss. If there is a strong family history of hearing loss, the likelihood a genetic variant is increased, but is still considerably less than for parents with a child who has hereditary hearing loss. For individuals without a family history of hearing loss or an offspring with hearing loss, the probability of detecting a pathogenic variant is much lower. For individuals with a low pretest likelihood of being a carrier for a hereditary hearing loss variant, the positive and negative predictive values of testing are not certain. Because the clinical specificity is not well established, it is not possible to determine the likelihood that a positive result represents a true positive or a false positive. At prevalences that approach the population rate, it is possible that a substantial number of positive results are false positives, even in the presence of a low false-positive rate.

Carrier testing has clinical utility if it aids in reproductive decision making. Parents may decide to change their plans for attempting pregnancy based on results of genetic testing. Carrier testing, combined with preimplantation genetic testing and in vitro fertilization, may be effective in reducing the number of infants born with hereditary hearing loss. While there is no direct evidence that carrier testing leads to a higher percentage of live births without hereditary hearing loss, there is evidence from other disorders (e.g., Tay-Sachs disease, cystic fibrosis) that carrier testing can result in a decrease in offspring with those disorders. Theoretically, a similar decrease should be expected with carrier testing for hereditary hearing loss.

Carrier testing is most accurate when the pathogenic variant in the index case with hereditary hearing loss is known. In those cases, targeted familial variant testing for a single pathogenic variant can be performed in lieu of comprehensive genetic testing for the full range of genes associated with hereditary hearing loss. Targeted testing has a higher accuracy for confirming and excluding the presence of a pathogenic variant. It is particularly useful for excluding the presence of a pathogenic variant, because comprehensive testing has
a suboptimal sensitivity and negative predictive value. Therefore, targeted testing can rule out a pathogenic variant with certainty whereas comprehensive testing cannot.

**Panels for Carrier Testing**
The following criteria apply for the use of panel testing for carrier testing in hereditary hearing loss:

1. All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated clinical utility do not have a potential to cause harm.
2. Testing is performed in a CLIA-approved lab.
3. The analytic validity of panel approaches that of direct sequencing.
4. Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes.
5. Decision making based on genetic results is well-defined.

In line with the reasoning for the clinical utility of panel testing for diagnosis of hereditary hearing loss, panel testing for hearing loss for carrier testing can be considered to meet these criteria for individuals who will make reproductive decisions based on the test results.

**Section Summary: Clinical Utility**
Carrier testing can be performed in parents who are planning offspring to determine their likelihood of a child with hereditary hearing loss. If there is a previous child with hereditary hearing loss, there is a high likelihood of subsequent offspring having hereditary hearing loss. In other situations, a family history of hereditary hearing loss is sufficient to conclude that the likelihood of an offspring with hereditary hearing loss is increased. Examples of these situations are when a first- or second-degree relative has hereditary hearing loss. Carrier testing has clinical utility in these high-risk situations when used as an aid in reproductive decision making. Carrier testing is most useful when the specific pathogenic variant causing hereditary hearing loss in the family is known, because targeted familial variant testing is more accurate than comprehensive testing, and can confirm or exclude the presence of a pathogenic variant with higher certainty.

Because of the low prevalence of pathogenic variants in unselected populations, the positive predictive value of finding a pathogenic variant is not known in unselected populations and the value of carrier testing is uncertain for these individuals.

**SUMMARY OF EVIDENCE**
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 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.

**References**

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12/12/2013 Medical Policy Committee review
12/18/2013 Medical Policy Implementation Committee approval. New policy.
12/04/2014 Medical Policy Committee review
12/07/2014 Medical Policy Implementation Committee approval. 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.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy guidelines section added
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017 Medical Policy Committee review
12/20/2017 Medical Policy Implementation Committee approval. The policy is revised with updated genetics nomenclature. “Mutations” changed to “genes” in policy statements; statements otherwise unchanged. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2018

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| ICD-10 Diagnosis | All related diagnoses |

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