Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
Current Effective Date: 12/21/2016

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 mutations (GJB2, GJB6 and other hereditary hearing loss-related mutations) in individuals with hearing loss to confirm the diagnosis of hereditary hearing loss to be eligible for coverage.

Based on review of available data, the Company may consider preconception genetic testing (carrier testing) for hereditary hearing loss mutations (GJB2, GJB6 and other hereditary hearing loss-related mutations) 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; OR
- One or both parents with suspected hereditary hearing loss; OR
- First- or second-degree relative affected with hereditary hearing loss; OR
- First-degree relative with offspring who is affected with hereditary hearing loss.

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 mutations 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 mutations when patient selection criteria are not met is considered to be investigational.*
Genetic Testing for Hereditary Hearing Loss

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Policy Guidelines
Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of nonsyndromic 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 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 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, mutations 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.

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

In addition to mutations in the GJB6 and GJB2 genes, there are many less common pathologic mutations 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.

Testing for mutations associated with hereditary hearing loss should be confined to known pathologic mutations. While research studies using genome-wide associations have uncovered numerous single-nucleotide polymorphisms 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.
Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
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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 (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 mutations in \textit{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 \textit{GJB2} and \textit{GJB6}. If this is negative, screening for the other genetic mutations 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 \textit{GJB2} and \textit{GJB6} as a first step. Given the extreme heterogeneity in genetic causes of hearing loss, either strategy may be considered reasonably equivalent to the other.

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
Description of Disease
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). 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.

Nonsyndromic hearing loss (NSHL) is defined as hearing loss that is not associated with other physical signs or symptoms. For NSHL, it is more difficult to determine whether the etiology is hereditary or acquired, because by definition, there are no other clinical manifestations at the time of the hearing loss presentation. Nonsyndromic hearing loss 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:
Genetic Testing for Hereditary Hearing Loss

Policy #: 00379
Original Effective Date: 12/18/2013
Current Effective Date: 12/21/2016

- Sensorineural hearing loss
- Mild to profound (more commonly) degree of hearing impairment
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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 of NSHL 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. 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 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.

Genetic Mutations in 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 mutations associated with hereditary hearing loss are usually found are termed DFN, and hereditary hearing loss is sometimes called DFNA-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 mutations 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 mutations to the GJB2 gene with less than 1% of remaining cases arising from mutations to GJB6. A list of available tests for genetic mutations 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. Mutations of this gene are most common in hereditary hearing loss, causing an estimated 50% of the
cases of NSHL. The carrier rate in the general population for a recessive deafness-causing GJB2 mutation is approximately 1 in 33. Specific mutations have been observed to be more common in certain ethnic populations. Mutations in the GJB2 gene will impact expression of the Cx26 connexin protein and almost always cause prelingual, but not necessarily congenital, deafness. Differing mutations to GJB2 can present high phenotypic variation, but it has been demonstrated that it is possible to correlate the type of associated hearing loss with findings on molecular analysis. A systematic review of publications reporting GJB2 mutation prevalence suggests that the overall prevalence of GJB2 mutations is similar around the world, although specific mutations differ.

Mutations in the GJB6 gene lead to similar effects on abnormal expression of connexin protein Cx30. However, GJB6 mutations are much less common than mutations in GJB2. Of all the patients with 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 Mutations 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>Mutations Detected</th>
</tr>
</thead>
</table>
| DFNA3 | GJB2 | Prelingual  | High-frequency progressive | • Sequence analysis/mutation scanning  
• Targeted mutation analysis  
• Deletion/duplication analysis | • Sequence variants  
• Specified sequence variants  
• Exonic or whole-gene deletions/duplications |
|      | GJB6 | Prelingual  | High-frequency progressive | • Sequence analysis/mutation scanning  
• Targeted mutation analysis  
• Deletion/duplication analysis | • Sequence variants  
• Specified sequence variants  
• Exonic or whole-gene deletions/duplications |
| DFNB1 | GJB2 | Prelingual  | Usually stable      | • Targeted mutation analysis  
• Deletion/duplication analysis | • GJB2 sequence variants  
• Exon(s) or whole-gene deletions |
|      | GJB6 | Prelingual  | Usually stable      | • Deletion/duplication analysis | • GJB6 deletions |

Mutation analysis for GJB6 and GJB2 mutations can be performed by Sanger sequencing analysis of individual genes. This method has a high degree of validity and reliability but is limited by the ability to sequence 1 gene at a time. With Sanger sequencing, the gene with the most common mutations is generally sequenced first, followed by sequencing of additional genes if a pathogenic mutation is not found.

In addition to the most common mutations that are associated with hereditary hearing loss, GJB6 and GJB2, there are many less common pathologic mutations. Some of these are: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POUSF4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TROBP, USH1C, and WFS1 genes. Novel genetic mutations continue to be identified in cases of hereditary hearing loss. 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 mutations in GJB2.

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 mutations 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. Genomic Mutations 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 mutations 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 mutations that may have overlap with NSHL is shown in Table 3.

### Table 3. Genetic Mutations with Overlap Between Syndromic and NSHL

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Clinical Description</th>
<th>Gene Mutations</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</td>
<td></td>
<td>DFNB18 (nonsyndromic) may also be caused by mutations in USH1C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal vestibular function</td>
<td></td>
<td>DFNB12 (nonsyndromic) may also be caused by mutations in CDH23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by mutations in MYO7A</td>
</tr>
</tbody>
</table>
Genetic Testing for Hereditary Hearing Loss

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Clinical Description</th>
<th>Gene Mutations</th>
<th>Reason for Overlap With NSHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td></td>
<td>• Congenital mild-to-severe hearing loss</td>
<td>USH2A, VLGR1, WHRN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Normal vestibular function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td></td>
<td>• Progressive hearing loss</td>
<td>CLRN1i PDZD7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progressive vestibular dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pendred syndrome</td>
<td>Autosomal recessive</td>
<td>• Congenital sensorineural hearing loss</td>
<td>SLC26A4 (50%)</td>
<td>• Goiter not present until early puberty or adulthood.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct)</td>
<td></td>
<td>• Mutations in SLC26A4 may also cause NSHL</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen</td>
<td>Autosomal recessive</td>
<td>• Congenital deafness</td>
<td>KCNQ1, KCNE1</td>
<td>• Hearing loss may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncope episodes, or long QT syndrome)</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td>• Prolongation of the QT interval</td>
<td></td>
<td></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 mutations in WFS1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Optic atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progressive neurologic abnormalities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSHL: nonsyndromic 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 (laboratory-developed tests, formerly "home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD).

Rationale/Source
The evidence review was created in 2013 and has been updated periodically with literature reviews, most recently through September 17, 2015.

Literature was sought on genetic testing for hereditary hearing loss in the following areas: analytic validity (ability to detect a mutation that is known to be present and the ability to rule out mutations when they are absent); clinical validity (ability to detect a mutation in a patient with hereditary hearing loss, or to exclude a mutation in a patient without hereditary hearing loss); and clinical utility (the impact of a mutation on the management of patients and on relevant health outcomes).
Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
Current Effective Date: 12/21/2016

Analytic Validity

Sequencing Analysis
The analytic validity of Sanger sequencing is known to be high. Although there is not a robust evidence base for Sanger sequencing 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.

Panel Testing
The analytic validity of targeted panels, such as the available microchips for hereditary hearing loss mutations that have been described, is less certain. The studies identified for this review are summarized in Table 4. These data are only available for some of the panels that are commercially available. 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. Mutation Chips Including GJB2 and GJB6 Genes

<table>
<thead>
<tr>
<th>Test</th>
<th>Genes and Mutations 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 array, 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</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. 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 genetic mutations, which included 41 mutations 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 cases (99.2%). 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 used different patient populations and different panels of genes, but all included the GJB2 mutations 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 mutations. When performed by direct sequencing, the analytic validity approaches 100%. When performed as part of a next generation testing panel, the error rate is expected to be higher than for direct sequencing. However, the available evidence reports high sensitivity and specificity for available next generation genetic panels, and the difference in accuracy between direct sequencing and targeted panels is not well defined in the literature.

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 percent of patients with hereditary hearing loss who have a pathologic genetic mutation, and the clinical specificity is reported as the percent of patients without hereditary hearing loss who do not have a pathologic genetic mutation. The clinical validity will vary as a function of the number of different genes examined, and also by whether the population includes patients with hearing loss that is not strictly hereditary hearing loss.

Vona et al reported testing results for targeted next generation sequencing 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 mutations in a gene associated with autosomal dominant hearing loss (ACTG1, CCDC50, EYA4, MYH14, M7O6, TCF21, MYO1A) or autosomal recessive hearing loss (MYO15A, MYO7A, GJB2, USH2A) were identified in 8/23 probands and 5/23 probands, respectively, for a success rate of 57%. Gu et al reported results for targeted next generation sequencing of a panel of 131 genetic mutations related to hearing loss in 63 subjects with NSHL with negative testing for mutations in the GJB2, MT-RNR1, and SLC26A4 genes. The mutation detection rate was 12.7%, with 10 of 14 mutations detected as novel compound heterozygotes. In 2014, Shearer et al reported on copy number variants (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 indicate that a substantial percentage of patients with hereditary hearing loss will have an identifiable pathologic mutation (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
Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
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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 potential ways in which genetic testing for hereditary hearing loss may have clinical utility. For this policy review, Clinical utility will be considered in the following areas:

- As a diagnostic test for hereditary hearing loss
  o To confirm the diagnosis of hereditary hearing loss and distinguish from acquired hearing loss
  o To alter management of individuals with hereditary hearing loss
  o To direct and focus carrier testing in relatives who are considering pregnancy
- 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, an indirect chain of evidence is considered to determine the impact on health outcomes.

The high analytic sensitivity indicates that if a genetic mutation 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 genetic mutation is absent, a false-negative result on genetic testing is very unlikely to occur.

Therefore, a positive genetic test with a known pathologic mutation indicates that hereditary hearing loss is present with a high degree of certainty. In contrast, the low to moderate clinical sensitivity indicates 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 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, in reality, represent an initial presentation of a known syndrome that is associated with hearing loss, identification of specific mutations may prompt additional action. For example if a \textit{KCNQ1} mutation is found, additional cardiac workup may be warranted because mutations 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 \( GJB2 \) and \( GJB6 \) is in the cochlea. In addition, patients with hereditary hearing loss mutations 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 \( GJB2 \) and \( GJB6 \) mutations may have a favorable prognosis following cochlear implantation and that patients with other mutations or without a documented mutation may have a less favorable prognosis.

The evidence on this question consists of several small, retrospective, single center studies that compared outcomes of cochlear implantation in patients with and without genetic mutations. Two small series from Japan initially reported that hearing outcomes were superior in patients with genetic mutations. Fukushima et al compared 3 patients with genetic mutation with 4 patients without mutations. Patients with \( GJB2 \) mutations had a larger vocabulary compared with patients without a mutation (1243 words vs 195 words), and a higher mean developmental quotient. Matsushiro et al evaluated 15 patients with hearing loss, 4 with genetic mutations and 11 without. These authors reported that speech perception was higher among patients with mutations compared with those without. In 2014, in a retrospective cohort study, Popov et al evaluated the impact of \( GJB2 \) mutations on hearing outcomes after cochlear implantation for congenital nonsyndromic sensorineural hearing loss. The study included 60 patients who had received a cochlear implant, 30 with \( GJB2 \) mutations 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 \( GJB2 \) mutations than for those without mutations, including the Listening Progress Profile test \((p<0.05)\), the Monosyllabic-Trochee-Polysyllabic test with 3, 6, or 12 items \((p=0.005, p=0.002, \text{and } p=0.001, \text{respectively})\). Yan et al 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 \( GJB2 \) mutations and 10 of whom had \( SLC26A4 \) mutations. Compared with patients with no mutation, patients with \( GJB2 \) mutations but not those with \( SLC26A4 \) mutations, 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 U.S. Sinnathuray et al published 2 articles on overlapping series of patients who were treated with cochlear implants. In the larger series, 38 patients were included, 14 patients with genetic mutations and 24 without. A standardized measure of speech, the Speech Intelligibility Rating (SIR) score, was used as the primary outcome measure. At 1 year, the median SIR scores were higher in the patients with \( GJB2 \) mutations \((\text{median, 3; range, 2-4})\) compared with patients without mutations \((\text{median, 2; range, 1-4})\), and the difference between the 2 groups was statistically significant \((p=0.007)\). The percent of patients achieving intelligible speech was 82% in the \( GJB2 \) group compared with 30% in patients without mutations \((p=0.02)\).

In a second U.S. study by Connell et al, these findings were not completely replicated. This series included 31 patients with congenital hearing loss, 12 with genetic mutations and 19 without. The main outcome measure was speech perception category ranging from 1 to 6. The mean speech perception category was not different between patients with and without mutations \((4.1 \text{ vs } 4.9 \text{ respectively, } p=\text{NS})\). The percent of
patients achieving speech perception category 6 was higher in the mutation 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. Blue Cross Blue Shield Association’s Medical Policy Reference Manual (MPRM) Policy No. 2.04.92, General Approach to Evaluating the Utility of Genetic Panels, outlines criteria that can be used to evaluate the clinical utility of panel testing for hereditary or genetic conditions. Panel testing for hereditary hearing loss generally falls into the category of panels containing mutations 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 next generation sequencing panels for hereditary hearing loss, criteria 2 to 4 generally apply. Some, but not all, of the mutations evaluated in hereditary hearing loss genetic panels would be associated with the need for additional subspecialist referral or additional testing; based on an indirect chain of evidence, testing for these mutations 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, as they would not be likely to lead to further investigations that are of unproven benefit.

Section Summary: Diagnostic Test for Etiology of Hereditary Hearing Loss

Hereditary hearing loss can be confirmed if genetic testing reveals a pathologic mutation 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 literature and no specialty society guidelines that recommend 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 mutations 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.

It is possible that the presence of a genetic mutation, and/or the presence of a specific type of mutation, is associated with the degree of response to cochlear implantation. This evidence is from small case series and therefore is not definitive. In addition, there are not treatment guidelines that recommend 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.
Carrier Testing

Clinical Utility of Genetic Testing for Carrier Testing for Hereditary Hearing Loss in High-Risk Individuals

People 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 mutation can first be performed. If a pathologic mutation is found, then targeted testing for that specific mutation 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 mutation 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 of a genetic mutation is increased, but is still considerably less than for parents with a child who has hereditary hearing loss. For individuals with neither a family history of hearing loss nor an offspring with hearing loss, the probability of detecting a pathologic mutation is much lower. For individuals with a low pretest likelihood of being a carrier for a hereditary hearing loss mutation, the positive and negative predictive values of testing is 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 versus 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, such as Tay-Sachs disease and 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 mutation in the index case with hereditary hearing loss is known. In those cases, targeted mutation testing for a single mutation can be performed in lieu of comprehensive genetic testing for the full range of mutations associated with hereditary hearing loss. Targeted testing has a higher accuracy for confirming and excluding the presence of a pathologic mutation. It is particularly useful for excluding the presence of a mutation, because comprehensive testing has a suboptimal sensitivity and negative predictive value. Therefore, targeted testing can rule out a genetic mutation with certainty whereas comprehensive testing cannot.
Clinical Utility of Genetic Panel Testing for Carrier Testing for Hereditary Hearing Loss in High-Risk Individuals

The evidence review “General Approach to Evaluating the Utility of Genetic Panels” outlines criteria that can be used to evaluate the clinical utility of reproductive panel testing for at-risk individuals. 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. 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: Carrier Testing

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 mutation causing hereditary hearing loss in the family is known, because targeted mutation testing is more accurate than comprehensive testing, and can confirm or exclude the presence of a mutation with higher certainty.

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

Genetic Testing to Screen for Hearing Loss

Routine screening of newborns for congenital hearing loss via audiometric testing is standard of care and has been recognized to be associated with improved outcomes. However, audiometric testing does not identify all newborns with congenital hearing loss. As a result, genetic testing has been investigated as a way to identify early-onset hearing loss.

Several studies have evaluated the use of genetic testing, either by itself or as a complement to audiometric screening, in the detection of congenital hearing loss. Lim et al reported results from genetic panel testing for 14 genetic mutations associated with hearing loss (SoundGene panel) of 3806 infants without major congenital malformations. Thirty-five subjects (0.95%) had a positive panel test; of those, 3 patients (8.6%) had persistent hearing loss compared with 5 (0.21%) of 2398 subjects with no report of a mutation (p<0.01).
Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
Current Effective Date: 12/21/2016

Two of the 35 (6%) subjects with a positive genetic panel test panel had a positive newborn audiometric screen. Han et al demonstrated the feasibility of testing newborns for mutations related to hereditary hearing loss on a large scale using the types of filter paper blood samples that are used for routine newborn screening, using a PCR-based panel test designed to detect high-risk deafness-associated mutations, including GJB2 c.235delC, SLC26A4 c.919-2A>G, mtDNA 12S rRNA mt.1555A>G and mt.1494C>T. Among 1181 newborns tested, 29 had 1 or 2 mutant alleles, for a carrier rate of 2.46% (29/1181).

Section Summary: Genetic Testing to Screen for Hearing Loss

Although a few studies have demonstrated the feasibility of genetic testing to screen for congenital hearing loss, the positive and negative predictive values of genetic testing for hereditary hearing loss in unselected populations is not well-defined. There are no studies that demonstrate that such testing is associated with incremental improvement in outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5.

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<th>NCT No.</th>
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<td>Unpublished</td>
<td>Prevalence of POU4F3 (DFNA15) and SLC17A8 (DFNA25) Genes Mutations in Dominant Autosomal Deafness and Phenotypic Characterization of Carrier Patients</td>
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<td>Terminated (no convincing results)</td>
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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 collaborate with and make recommendations during this process through the provision of appropriate reviewers, 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 2 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 mutations were identified that are associated with disorders in other organ systems. It was considered that 2 contextual factors were present: barriers to performing high-quality trials, and the potential to reduce harms by avoiding unnecessary testing.
Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
Current Effective Date: 12/21/2016

Summary of Evidence
The evidence for genetic testing in individuals who are suspected of having hereditary NSHL includes studies on analytic validity, test accuracy, and test validity. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic mutations in GJB2, GJB6, and numerous other genes are found in a substantial percent 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 mutation. The probability of finding a genetic mutation is increasing as new gene mutations are identified. False-positive results on mutation testing are expected to be very low. There are several situations for which there is potential clinical utility of testing for hereditary hearing loss mutations. 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 that is associated with other medical conditions. Clinical guidelines recommend a tiered genetic testing approach, starting with the most common mutations. For parents at high risk of an offspring with hereditary hearing loss, genetic testing can be useful as an aid in reproductive decision making. Although genetic testing for hereditary hearing loss has been investigated as an adjunct to audiologic testing for screening of congenital hearing loss, no studies demonstrate that such testing is associated with incremental improvement in outcomes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

References

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Genetic Testing for Hereditary Hearing Loss

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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
Next Scheduled Review Date: 12/2017

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Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
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<th>Code Type</th>
<th>Code</th>
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C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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