Genetic Testing for Nonsyndromic 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.

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

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

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 nonsyndromic hearing loss mutations for all other situations to be investigational.*

The use of genetic testing for nonsyndromic hearing loss mutations when patient selection criteria are not met is considered to be investigational.*

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

Description of disease. Hearing loss is a common birth defect. Approximately one of every 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity (≥40
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db). Syndromic hearing loss refers to hearing loss associated with other medical or physical findings. Since syndromic hearing loss occurs as part of a syndrome of multiple clinical manifestations, it is often recognized more readily as hereditary in nature.

Nonsyndromic hearing loss (NSHL) is defined as hearing loss that is not associated with other physical signs or symptoms. For NSHL, it is more difficult to determine whether the etiology is hereditary or acquired, since by definition there are no other clinical manifestations. NSHL accounts for 70% to 80% of genetically-determined deafness.

Autosomal recessive patterns of inheritance predominate and account for 80% of congenital NSHL. A typical clinical presentation of autosomal recessive NSHL involves the following characteristics:
- Sensorineural hearing loss
- Mild to profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually non-progressive
- No associated medical findings

The majority of the remaining 20% of patients have an autosomal dominant inheritance pattern, with a small number having X-linked or mitochondrial inheritance. Patients with autosomal dominant inheritance typically show progressive NSHL which begins in the 2nd through 4th decades of life.

Diagnosis of nonsyndromic hearing loss requires an evaluation with appropriate core medical personnel with expertise in the genetics of hearing loss, dysmorphology, audiology, otolaryngology, genetic counseling, and communication with deaf patients. The evaluation should include a family history, as well as a physical examination consisting of otologic examination, airway examination, documentation of dysmorphisms and neurolologic evaluation. However, the clinical diagnosis of nonsyndromic hearing loss is non-specific since there are a number of underlying etiologies, and often it cannot be determined with certainty whether a genetic cause for hearing loss exists.

Treatment of congenital and early-onset hearing loss typically involves enrollment in an educational curriculum for hearing impaired persons and fitting with an appropriate hearing aid. In some patients with profound deafness, a cochlear implant can be performed. Early identification of infants with hearing impairment may be useful in facilitating early use of amplification by 6 months of age and early intervention to achieve age-appropriate communication, speech and language development. Delays in development of hearing treatment have been shown to delay development of communication. The primary method for identification of hearing impairment has been newborn screening with audiometry. Genetic testing has not been proposed as a primary screen for hearing loss.

Genetic mutations in NSHL. The genetic loci on which mutations associated with NSHL are usually found are termed DFN, and NSHL is sometimes called DFN-associated hearing loss. DFNA3-associated NSHL is caused by autosomal dominant mutations present in the GJB2 or GJB6 genes, which alters the coding sequence for the connexin proteins Cx26 or Cx30, respectively. DFNB1-associated NSHL are autosomal recessive syndromes in which more than 99% of cases are caused by mutations to the GJB2 gene with less
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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 Table1.

There are more than 300 individual mutations known to be associated with NSHL. Two of the most commonly mutated genes are GJB2 and GJB6. GJB2 is a small gene with a single coding exon. Mutations of this gene are most common in NSHL, causing an estimated 50% of the cases on NSHL. 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 pre-lingual, 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.

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

Table 1. Clinical Characteristics and Testing Methods for GJB2 and GJB6 Mutations at the DFNA3 and DFNB1 Loci

<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Gene Symbol</th>
<th>Onset</th>
<th>Audioprofile</th>
<th>Test Method</th>
<th>Mutations Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFNA3</td>
<td>GJB2</td>
<td>Prelingual</td>
<td>High frequency progressive</td>
<td>Sequence Analysis/ Mutation Scanning</td>
<td>Sequence Variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Targeted Mutation Analysis</td>
<td>Specified sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/ duplication analysis</td>
<td>Exonic or whole-gene deletions/ duplications</td>
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<td>Specified sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/ duplication analysis</td>
<td>Exonic or whole-gene deletions/ duplications</td>
</tr>
<tr>
<td>DFNB1</td>
<td>GJB2</td>
<td>Prelingual</td>
<td>Usually stable</td>
<td>Sequence analysis 2</td>
<td>GJB2 sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deletion/ duplication</td>
<td>Exon(s) or whole-gene</td>
</tr>
</tbody>
</table>
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Mutation analysis for GJB6 and GJB2 mutations can be performed by Sanger sequencing analysis of individual genes. This method has a high degree of validity and reliability, but is limited by the ability to sequence one gene at a time. With Sanger sequencing, the gene with the most common mutations is generally sequenced first, followed by sequencing of additional genes if a pathogenic mutation is not found. In addition to the most common mutations that are associated with NSHL, GJB6 and GJB2, there are many less common pathologic mutations. Some of these are: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes.

Because of the large number of genes associated with NSHL, there are a variety of genetic panels for hereditary deafness. Next generation genetic sequencing technology allows targeted sequencing of multiple genes simultaneously, expanding the ability to examine multiple genes. These panels are alternatives to sequencing of individual genes such as GJB6 and GJB2. Some examples of these panels are given in Table 3. These panels include the most common genes associated with NSHL. They may also include many of the less common genes associated with NSHL, as well as genes that are associated with syndromic hearing loss.

FDA or Other Governmental Regulatory Approval

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

Rationale/Source

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).
Analytic validity

Sequencing analysis. The analytic validity of Sanger sequencing is known to be high. Although there is not a robust evidence base, it is reasonable to assume that sequencing has an analytic sensitivity and specificity that approaches 100% under ideal testing conditions.

The analytic validity of targeted panels, such as the available microchips for NSHL mutations that have been described, is less certain. The studies identified for this review are summarized in Table 3. 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 >99%, and in the majority of studies it was 100%. The analytic specificity was 100% when it was reported, usually in a small number of normal individuals. Table 3 summarizes some of the commercially available targeted panels for hereditary hearing loss.

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 re-assayed with a larger amount of DNA, 108/110 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. There is limited evidence on the analytic validity of testing for NSHL 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.

Table 2. Mutation Chips Including GJB2 and GJB6 Genes

<table>
<thead>
<tr>
<th>Test</th>
<th>Genes Tested; 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>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Test</th>
<th>Technology</th>
<th>Genes Tested; Mutations Tested</th>
<th>Analytic Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Healthcare (OtoGenome™)‡</td>
<td>Resequencing microarray</td>
<td>63 genes*; NA</td>
<td>99%</td>
</tr>
<tr>
<td>University of Iowa Healthcare (OtoSCOPE®)‡</td>
<td>Massive parallel sequencing</td>
<td>80 ; NA</td>
<td>99%</td>
</tr>
<tr>
<td>Stanford University (Hereditary Hearing Loss APEX)</td>
<td>Single-basepair primer extension</td>
<td>8 ; 198</td>
<td>100%</td>
</tr>
</tbody>
</table>

*This result is for version 1 of the OtoGenome Test; an additional 52 genes will be added to the panel to increase clinical sensitivity

Clinical validity
A number of publications have evaluated the clinical sensitivity and specificity of genetic testing for NSHL. The clinical sensitivity is reported as the percent of patients with NSHL who have a pathologic genetic mutation, and the clinical specificity is reported as the percent of patients without NSHL 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 NSHL.

A representative sample of articles on clinical validity is given in Table 4. Studies were selected that were published within the past 10 years, had populations of primarily NSHL. Mixed populations that included patients with syndromic hearing loss, or with non-hereditary hearing loss were not included.

Table 4: Clinical Validity of Genetic Testing for Hereditary Hearing Loss

<table>
<thead>
<tr>
<th>Study/Yr</th>
<th>Testing Method/ (Genes tested)</th>
<th>N</th>
<th>Clinical Sensitivity</th>
<th>Clinical Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalamon 2010</td>
<td>Sanger sequencing (GJB2, GJB6)</td>
<td>252</td>
<td>34%</td>
<td>94%</td>
</tr>
<tr>
<td>De Oliveira 2007</td>
<td>Sanger sequencing (6 genes, including GJB2 and GJB6)</td>
<td>207</td>
<td>35.7%</td>
<td>NR</td>
</tr>
<tr>
<td>Duman 2011</td>
<td>Targeted microarray (38 genes)</td>
<td>49</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Green 1999</td>
<td>Sanger sequencing (GJB2)</td>
<td>32</td>
<td>31%</td>
<td>100%</td>
</tr>
<tr>
<td>Joseph 2009</td>
<td>PCR/sequencing (GJB2)</td>
<td>86</td>
<td>37%</td>
<td>NR</td>
</tr>
<tr>
<td>Siemering 2006</td>
<td>Targeted microarray (15 mutations)</td>
<td>250</td>
<td>32%</td>
<td>100%</td>
</tr>
</tbody>
</table>

In general, these studies indicate that the clinical sensitivity is low to moderate and the clinical specificity is high. There is a high degree of variability among these studies in the type of sequencing used and the number of genes examined. For example, the study with the highest sensitivity (62%), Duman et al. 2011, tested for mutations on 38 different genes, which was the highest number examined in any of these studies. The other studies generally tested for one or several genes, and reported lower sensitivities in the range of 30-40%.

Section summary. There is some data on clinical validity, but it is incomplete. The available studies indicate that a substantial percent of patients with NSHL will have a 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. As a result, the clinical sensitivity is not well-defined. 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 potential ways in which genetic testing for NSHL may have clinical utility. For this policy review, clinical utility will be considered in the following areas:

- As a diagnostic test for hereditary NSHL
  - To confirm the diagnosis of hereditary NSHL and distinguish from acquired hearing loss
  - To alter management of individuals with NSHL
  - 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 NSHL in offspring

Diagnostic test for etiology of NSHL. Genetic testing in patients with NSHL 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-positive 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.

In order 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 NSHL may be useful in differentiating NSHL from other causes and deafness, and thereby precluding other testing such as computed tomography (CT) or magnetic resonance imaging (MRI). It has also been suggested that specific mutations should prompt additional action. For example if a KNCQ1 mutation is found, additional cardiac workup may be warranted since 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 NSHL 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.
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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 to 4 patients without mutations. Patients with GJB2 mutations had a larger vocabulary compared to patients without a mutation (1,243 words versus 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 to those without.

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 (median 3, range 2-4) compared to patients without mutations (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 to 30% in patients without mutations (p=0.02).

In a second U.S. study by Connell et al., the above 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 versus 4.9 respectively, p NS). The percent of patients achieving speech perception category 6 was higher in the mutation group (75% versus 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.

Section summary. Hereditary hearing loss can be confirmed if genetic testing reveals a pathologic mutation known to be associated with NSHL, but a negative genetic test does not rule out hereditary NSHL. 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. Parents 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 NSHL. 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 NSHL 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 parents 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 pre-test likelihood of being a carrier for a NSHL mutation, the positive and negative predictive values of testing is not certain. Since 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 NSHL. While there is no direct evidence that carrier testing leads to a higher percentage of live births without NSHL, 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 NSHL.

Carrier testing is most accurate when the mutation in the index case with NSHL 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 NSHL. 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, since 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.

Section summary. Carrier testing can be performed in parents who are planning offspring to determine their likelihood of a child with NSHL. If there is a previous child with NSHL, there is a high likelihood of subsequent offspring having NSHL. In other situations, a family history of NSHL is sufficient to conclude that the likelihood of an offspring with NSHL is increased. Examples of these situations are when a first- or second-degree relative has NSHL, or when a first-degree relative has an offspring with NSHL. 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 NSHL in the family is known, since targeted mutation testing is more accurate than comprehensive testing, and can confirm or exclude the presence of a mutation with higher certainty.
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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.

Clinical Input Received through 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 two contextual factors were present: barriers to performing high-quality trials, and the potential to reduce harms by avoiding unnecessary testing.

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

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

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

References

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81252, 81253, 81254</td>
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<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>All diagnoses</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>No codes</td>
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Policy History

Original Effective Date:  12/18/2013
Current Effective Date:  12/18/2013
12/12/2013  Medical Policy Committee review
12/18/2013  Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date:  12/2014
Genetic Testing for Nonsyndromic Hearing Loss

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

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;

B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.