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 minority, in the range of 30% to 60% will be found to have a genetic mutation. False positive results on mutation testing are expected to be very low.

Preconception genetic testing (carrier testing) for hereditary hearing loss mutations (GJB2, GJB6 and other hereditary hearing loss-related mutations) in parents may be considered medically necessary when at least 1 of the following conditions has been 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

Genetic testing for hereditary hearing loss mutations is considered investigational for all other situations, including, but not limited to, testing in patients without hearing loss (except as addressed in related policies, e.g., 4.02.05 Preimplantation Genetic Testing)

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, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MTS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMEM1, 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.

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 not 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 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 not a single identifiable gene that is responsible for most cases. If there is suspicion for autosomal recessive congenital hearing loss, it would be reasonable to begin testing with testing of GJB2 and GJB6. If this is negative, screening for other genetic causes of hearing loss with a multigene panel would be reasonable. 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, either strategy may be considered reasonable.3

There are specific CPT codes for some of this testing:

- 81252: GJB2 (gap junction protein, beta 2, 26kDa; connexin 26)(e.g., nonsyndromic hearing loss) gene analysis, full gene sequence
- 81253: known familial variants
- 81254: GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)(e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])

There is a CPT code for a genomic sequencing procedure (GSP) panel for hereditary hearing loss:

- 81430: Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, YO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1.

There is a CPT code for a genomic sequence analysis panel for hereditary colon cancer syndromes. This panel must include at least 7 genes which are listed in the code:

- 81431: Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

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.

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

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 of nonsyndromic hearing loss requires 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 nonsyndromic hearing loss 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 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. Dozens of deafness-associated loci have been identified. There are more than 300 individual mutations known to be associated with NSHL.

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 nonsyndromic hereditary hearing loss. The carrier rate in the general population for a recessive deafness-causing GJB2 mutation is approximately 1 in 33.6 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 are the second most common genetic defect in hereditary hearing loss 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 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 Name</th>
<th>Gene Symbol</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 |
| DFNA3      | GJB6        | Prelingual| High-frequency progressive | • Sequence analysis/mutation scanning  
• Targeted mutation analysis | • Sequence variants  
• Specified sequence variants  
• Exonic or whole-gene deletions/duplications |
**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, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes. Novel genetic mutations continue to be identified in cases of hereditary.18,19

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 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. 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.20-22

### 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 2.

See Table 3 below.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetics</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jervell and Lange-Nielsen syndrome</td>
<td>A variety of genes associated with clinical findings other than hearing loss</td>
<td>Associated with congenital deafness and prolonged QT interval, may present only with deafness without an apparent history to suggest cardiac dysfunction</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Inheritance</td>
<td>Clinical Description</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>For all types:</td>
<td>For all types: sensorineural hearing loss with retinitis pigmentosa.</td>
</tr>
<tr>
<td></td>
<td>autosomal recessive</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td>• Congenital severe-to-profound hearing loss.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Abnormal vestibular function.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td>• Congenital mild-to-severe hearing loss.</td>
</tr>
<tr>
<td>Type 3</td>
<td></td>
<td>• Progressive hearing loss.</td>
</tr>
<tr>
<td>Pendred syndrome</td>
<td>Autosomal recessive</td>
<td>• Congenital sensorineural hearing loss.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct).</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen</td>
<td>Autosomal recessive</td>
<td>• Congenital deafness</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td>• Prolongation of the QT interval.</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>Autosomal recessive</td>
<td>• Progressive sensorineural hearing loss.</td>
</tr>
</tbody>
</table>
Medical Policy

Optic atrophy.
Progressive neurologic abnormalities.

findings) may also be caused by mutations in WFS1

SIDS, sudden infant death syndrome

Regulatory Status

No U.S. Food and Drug Administration (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

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 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 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 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 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 reassayed 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.²⁴-²⁶

**Section Summary**

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.

**Table 3. 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)²⁶</td>
<td>4; 15</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Allele-specific PCR-based universal array (ASPUA), China²⁵</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, Japan²³</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)²⁴</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 CustomSeq sequencing microarray (Harvard Medical School/Cincinnati Children's Hospital, USA)²⁷</td>
<td>19; NA</td>
<td>99.9</td>
<td></td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction

**Table 4. Genomic Mutations Panels for Hereditary Hearing Loss¹¹**

<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™ Test for Hearing Loss and Related Syndromes)</td>
<td>Next generation sequencing, followed by confirmation with Sanger sequencing or PCR</td>
<td>70; NA</td>
<td>99</td>
</tr>
<tr>
<td>University of Iowa Healthcare (OtoSCOPE®)³⁰</td>
<td>Massive parallel sequencing</td>
<td>80; NA</td>
<td>99</td>
</tr>
<tr>
<td>Stanford University (Hereditary)</td>
<td>Single-base pair</td>
<td>8; 198</td>
<td>100</td>
</tr>
</tbody>
</table>
Clinical Validity

A number of publications have evaluated the clinical sensitivity and specificity of genetic testing for hereditary hearing loss in general and nonsyndromic hearing loss (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.

A representative sample of articles on clinical validity is given in Table 5. 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 nonhereditary hearing loss were not included.

Table 5: Clinical Validity of Genetic Testing for Hereditary Hearing Loss

<table>
<thead>
<tr>
<th>Study/Year</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>

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, MTRNR1, and SLC26A4 genes. The mutation detection rate was 12.7%, with 10 of 14 mutations detected as novel compound heterozygotes.

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 1 or several genes, and reported lower sensitivities in the range of 30% to 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 hereditary hearing loss 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 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
  - To confirm the diagnosis of hereditary hearing loss and distinguish from acquired hearing loss
  - To alter management of individuals with hereditary hearing loss
  - 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 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.

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 (CT) or magnetic resonance imaging. Given that some cases of
apparent NSHL may, in actuality, 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 KNCQ1 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, and p=0.001, 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 (median, 3; range, 2-4) compared with 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 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 vs 4.9 respectively, p 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. Medical Policy Reference Manual 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 [Clinical Laboratory Improvement Amendments]-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**

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

Medical Policy Reference Manual 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 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 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). 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

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

A search of online database ClinicalTrials.gov in July 2014 found several ongoing trials related to genetic testing for hereditary hearing loss:

- **Prevalence of POU4F3 and SLC17A8 Mutations** (NCT01802190) – This is a prospective, observational study to determine the prevalence of POU4F3 and SLC17A8 mutations in patients with deafness with suspected autosomal dominant transmission. Enrollment is planned for 150 subjects; the planned study completion date was February 2014, but no results have been posted.

- **Long QT and Hearing Loss Registry** (NCT02082431) – This is a prospective, observational study to identify the prevalence of long QT interval in infants with sensorineural hearing loss and to determine the incidence of genetic mutations consistent with long QT syndrome (regardless of ECG findings) in infants with sensorineural hearing loss. Enrollment is planned for 600 subjects; the planned study completion date is April 2016.

Summary

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 minority, in the range of 30% to 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 hereditary hearing loss 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. Clinical input received from physician specialty societies and academic medical centers 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 input 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 hearing loss may be considered medically necessary.

For parents at high risk of an offspring with hereditary hearing loss, 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 hereditary hearing loss carrier status may be considered medically necessary when 1 of the following is present: 1) an offspring with hereditary hearing loss, 2) 1 or both parents with suspected hereditary hearing loss, 3) A first-degree relative with an offspring who has hereditary hearing loss, 4) a first- or second-degree relative with hereditary hearing loss, and the parents desire to have further offspring and wish to know the likelihood of another offspring with hereditary hearing loss.
Although genetic testing for hereditary hearing loss has been investigated as an adjunct to audiologic testing for identification of congenital hearing loss, there are no studies that demonstrate that such testing is associated with incremental improvement in outcomes. Therefore, genetic testing for hereditary hearing loss in patients without identified hearing loss is considered investigational.

Supplemental Information

Practice Guidelines and Position Statements

In 2014, the American College of Medical Genetics and Genomics issued a practice guideline for the clinical evaluation and etiologic diagnosis of hearing loss. The guideline recommends obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus (CMV), imaging, or other testing based on the suspected etiology. For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories that do not suggest an environmental cause of hearing loss, the guidelines make the following recommendations for a tiered diagnostic approach:

- Pretest genetic counseling should be provided, and, with patient’s informed consent, genetic testing should be ordered.
  - Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics.
  - In the absence of any specific clinical indications and for singleton cases and cases with apparent autosomal recessive inheritance, the next step should be testing for DFNB1-related hearing loss (due to mutations in GJB2 and adjacent deletions in GJB6).
  - If initial genetic testing is negative, genetic testing using gene panel tests, NGS technologies such as large sequencing panels targeted toward hearing loss–related genes, whole exome sequencing, or whole genome sequencing may be considered. Because several tests are clinically available, the clinician must be aware of the genes included in the test (panel) chosen and the performance characteristics of the platform chosen, including coverage, analytic sensitivity, and what types of mutations will be detected.
  - If genetic testing reveals mutation(s) in a hearing loss–related gene, mutation-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals.

The Joint Committee on Infant Hearing (JCIH) issued recommendations in 2007:

- Every infant with confirmed hearing loss and/or middle ear dysfunction should be referred for otologic and other medical evaluation. The purpose of these evaluations is to determine the etiology of hearing loss, to identify related physical conditions, and to provide recommendations for medical/surgical treatment as well as referral for other services. Essential components of the medical evaluation include clinical history, family history of childhood-onset permanent hearing loss, identification of syndromes associated with early- or late-onset permanent hearing loss, a physical examination, and indicated radiologic and laboratory studies (including genetic testing).

- Evaluation should include a review of family history of specific genetic disorders or syndromes, including genetic testing for gene mutations such as
GJB2 (connexin-26), and syndromes commonly associated with early-onset childhood sensorineural hearing loss.

- All families of children with confirmed hearing loss should be offered and may benefit from a genetics evaluation and counseling. This evaluation can provide families with information on etiology of hearing loss, prognosis for progression, associated disorders (e.g., renal, vision, cardiac), and likelihood of recurrence in future offspring. This information may influence parents’ decision making regarding intervention options for their child.

There is a 2013 supplement to the JCIH 2007 position statement on early intervention after confirmation that a child is deaf or hard of hearing. Genetic testing was not addressed.

**U.S. Preventive Services Task Force Recommendations**

Genetic testing is not a preventive service under normal circumstances.

**Medicare National Coverage**

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

**References**


Documentation Required for Clinical Review

Please provide the following documentation:

- History and physical including:
  - Consultation report(s)
  - Laboratory report including:
    - Confirmation of the diagnosis of hereditary hearing loss
    - Preconception genetic testing for hereditary hearing loss mutation in parents

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when policy criteria are met. Services are considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<th>Code</th>
<th>Description</th>
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<td>CPT®</td>
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<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence</td>
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<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants</td>
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<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis; common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])</td>
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### Policy History

This section provides a chronological history of the activities, updates, and changes that have occurred with this Medical Policy.

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<th>Effective Date</th>
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<tr>
<td>01/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).
For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.