

<b>2.04.87</b>	<b>Genetic Testing for Hereditary Hearing Loss</b>		
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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 22

### Policy Statement

- I. Genetic testing for hereditary hearing loss genes (*GJB2*, *GJB6*, and other hereditary hearing loss-related genes) in individuals with suspected hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines section) may be considered **medically necessary**.
- II. Preconception genetic testing (carrier testing) for hereditary hearing loss genes (*GJB2*, *GJB6*, and other hereditary hearing loss-related genes) in parents may be considered **medically necessary** when **at least one** of the following conditions has been met:
  - A. Offspring with hereditary hearing loss
  - B. One or both parents with suspected hereditary hearing loss
  - C. First- or second-degree relative affected with hereditary hearing loss
  - D. First-degree relative with offspring who is affected with hereditary hearing loss
- III. Genetic testing for hereditary hearing loss genes is considered **investigational** for all other situations, including, but not limited to, testing individuals without hearing loss (except as addressed in related policies, e.g., Blue Shield of California Medical Policy: Genetic Testing: Preimplantation Genetic Testing).

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

### Policy Guidelines

Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of non-syndromic hearing loss is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation. It is differentiated from syndromic hearing loss, which is hearing loss associated with other signs and symptoms characteristic of a specific syndrome. Physical signs of a syndrome often include dysmorphic changes in the maxillofacial region and/or malformations of the external ears. Malfunction of internal organs may also be part of a syndrome. The physical signs can be subtle and easily missed on physical exam; therefore, exclusion of syndromic findings is ideally done by an individual with expertise in identifying dysmorphic physical signs. The phenotypic presentation of nonsyndromic hearing loss varies, but generally involves the following features:

- Sensorineural hearing loss
- Mild-to-profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually nonprogressive

This policy primarily focuses on the use of genetic testing to identify a cause of suspected hereditary hearing loss. The diagnosis of syndromic hearing loss can be made on the basis of associated clinical findings. However, at the time of hearing loss presentation, associated clinical findings may not be apparent. Furthermore, variants in certain genetic loci may cause both syndromic and nonsyndromic hearing loss. Given this overlap, the policy focuses on genetic testing for hereditary hearing loss more generally.

In addition to pathogenic variants in the *GJB6* and *GJB2* genes, there are many less common pathogenic variants found in other genes. They include: *ACTG1*, *CDH23*, *CLDN14*, *COCH*, *COL11A2*, *DFNA5*, *DFNB31*, *DFNB59*, *ESPN*, *EYA4*, *GJB2*, *GJB6*, *KCNQ4*, *LHFPL5*, *MT-TS1*, *MYO15A*, *MYO6*,

MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes.

Targeted testing for variants associated with hereditary hearing loss should be confined to known pathogenic variants. While research studies using genome-wide associations have uncovered numerous single nucleotide variants and copy number variations associated with hereditary hearing loss, the clinical significance of these findings is unclear.

For carrier testing, outcomes are expected to improve 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 an individual 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 syndromic or nonsyndromic cause of hearing loss (e.g., infectious, toxic, autoimmune, other causes). Consideration should also be given to temporal bone computed tomography scanning in cases of progressive hearing loss and to testing for cytomegalovirus in infants with sensorineural hearing loss.

If there is no high suspicion for a specific hearing loss etiology, ideally the evaluation should occur in a stepwise fashion. About 50% of individuals with autosomal recessive hereditary hearing loss have pathogenic variants in the *GJB2* gene. In the remainder of individuals with apparent autosomal recessive hereditary hearing loss, numerous other genes are implicated. In autosomal dominant hereditary hearing loss, there is no single identifiable gene responsible for most cases. If there is suspicion for autosomal recessive congenital hearing loss, it would be reasonable to begin with testing of *GJB2* and *GJB6*. If this is negative, screening for the other genes associated with hearing loss using a multigene panel would be efficient. An alternative strategy for suspected autosomal recessive or autosomal dominant hearing loss would be to obtain a multigene panel that includes *GJB2* and *GJB6* as a first step. Given the extreme heterogeneity in genetic causes of hearing loss, these 2 strategies may be considered reasonably equivalent.

### Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
<b>Mutation</b>	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives
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**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
<b>Pathogenic</b>	Disease-causing change in the DNA sequence
<b>Likely pathogenic</b>	Likely disease-causing change in the DNA sequence
<b>Variant of uncertain significance</b>	Change in DNA sequence with uncertain effects on disease
<b>Likely benign</b>	Likely benign change in the DNA sequence
<b>Benign</b>	Benign change in the DNA sequence

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

### Genetic Counseling

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

### Description

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity ( $\geq 40$  decibels). 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. Nonsyndromic hearing loss is defined as hearing loss not associated with other physical signs or symptoms. Nonsyndromic hearing loss accounts for 70% to 80% of genetically determined deafness, and it is more difficult to determine whether the etiology is hereditary or acquired.

### Related Policies

- Genetic Testing: Preimplantation Genetic Testing

### 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]) prohibits 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.

### Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical

Laboratory Improvement Amendments (CLIA). Molecular diagnostic testing is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## Rationale

### Background

#### Hereditary Hearing Loss

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity ( $\geq 40$  decibels).<sup>1</sup>

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.

Nonsyndromic hearing loss is defined as hearing loss not associated with other physical signs or symptoms. For nonsyndromic hearing loss, it is more difficult to determine whether the etiology is hereditary or acquired because, by definition, there are no other clinical manifestations at the time of the hearing loss presentation. Nonsyndromic hearing loss accounts for 70% to 80% of genetically determined deafness.<sup>2</sup>

Autosomal recessive patterns of inheritance predominate and account for 80% of congenital nonsyndromic hearing loss. A typical clinical presentation of autosomal recessive nonsyndromic hearing loss 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 nonsyndromic hearing loss, which begins in the second through fourth decades of life.<sup>3</sup>

### Diagnosis

Diagnosis of nonsyndromic hearing loss requires an evaluation by appropriate core medical personnel with expertise in the genetics of hearing loss, dysmorphology, audiology, otolaryngology, genetic counseling, and communication with deaf patients. The evaluation should include family history, as well as a physical examination consisting of otologic examination, airway examination, documentation of dysmorphisms, and neurologic evaluation.<sup>4</sup> 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

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.<sup>5</sup> Delays in the development of hearing treatment have been shown to delay development of communication. The primary method for identification of hearing impairment has been newborn

screening with audiometry. Genetic testing has not been proposed as a primary screen for hearing loss.

### Genetics of Hereditary Hearing Loss

Genes associated with hereditary hearing loss may be associated with an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern. The genetic loci on which variants associated with hereditary hearing loss are usually found are termed DFN, and hereditary hearing loss is sometimes called DFN-associated hearing loss. DFN loci are named based on their mode of inheritance: DFNA associated with autosomal dominant inheritance; DFNB with autosomal recessive inheritance; and DFNX with X-linked inheritance.

Two DFN loci commonly associated with hereditary hearing loss are DFNA3 and DFNB1, both of which map to chromosome 13q12. DFNA3-associated hereditary hearing loss is caused by autosomal dominant pathogenic variants present in the *GJB2* or *GJB6* genes.<sup>6</sup> DFNB1-associated hereditary hearing loss relates to autosomal recessive syndromes in which more than 99% of cases are caused by pathogenic variants in the *GJB2* gene, and less than 1% of remaining cases arise from pathogenic variants to *GJB6*.<sup>6</sup> A list of available tests for genes at the DFNA3 and DFNB1 loci are provided in Table 1.

Two of the most common disease-associated genes are *GJB2* and *GJB6*. *GJB2* is a small gene with a single coding exon. Variants of this gene are most common in hereditary hearing loss, causing an estimated 50% of the cases of hereditary nonsyndromic hearing loss.<sup>7</sup> The carrier rate in the general population for a recessive deafness-causing *GJB2* variant is approximately 1 in 33.<sup>1</sup> Specific variants have been observed to be more common in certain ethnic populations.<sup>8,9</sup> Variants in the *GJB2* gene will impact the expression of the Cx26 connexin protein, and almost always cause prelingual, but not necessarily congenital, deafness.<sup>10</sup> Different variants of *GJB2* can present with 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 by Chan and Chang (2014), reporting on *GJB2* variant prevalence, suggested the overall prevalence of *GJB2* variants is similar around the world, although specific variants differ.<sup>11</sup>

Variants in the *GJB6* gene lead to similar effects on abnormal expression of connexin protein Cx30. However, *GJB6* variants are much less common than *GJB2* variants. Of all patients with hereditary hearing loss, approximately 3% have a variant in the *GJB6* gene.

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

Locus	Gene	Onset	Audio profile	Test Method	Variants Detected
DFNA3	<i>GJB2</i>	Prelingual	High-frequency progressive	Sequence analysis/variant scanning	Sequence variants
				Targeted variant analysis	Specified sequence variants
				Deletion/duplication analysis	Exonic or whole-gene deletions/duplications
DFNA3	<i>GJB6</i>	Prelingual	High-frequency progressive	Sequence analysis/variant scanning	Sequence variants
				Targeted variant analysis	Specified sequence variants
				Deletion/duplication analysis	Exonic or whole-gene deletions/duplications
DFNB1	<i>GJB2</i>	Prelingual	Usually stable	Targeted variant analysis	GJB2 sequence variants
DFNB1	<i>GJB6</i>	Prelingual	Usually stable	Deletion/duplication analysis	Exon(s) or whole-gene deletions
DFNB1	<i>GJB6</i>	Prelingual	Usually stable	Deletion/duplication analysis	GJB6 deletions

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

In addition to the most common genes associated with hereditary hearing loss (*GJB6*, *GJB2*), there are many less common disease-associated genes. Some are: *ACTG1*, *CDH23*, *CLDN14*, *COCH*, *COL11A2*, *DFNA5*, *DFNB31*, *DFNB59*, *ESPN*, *EYA4*, *GJB2*, *GJB6*, *KCNQ4*, *LHFPL5*, *MT-TS1*, *MYO15A*, *MYO6*, *MYO7A*, *OTOF*, *PCDH15*, *POU3F4*, *SLC26A4*, *STRC*, *TECTA*, *TMC1*, *TMIE*, *TMPRSS3*, *TRIOBP*, *USH1C*, and *WFS1* genes. Novel genetic variants continue to be identified in cases of hereditary hearing loss.<sup>12,13</sup> For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported.<sup>14,15</sup> By 2018, over 8,100 variants in over 150 genes had been reported.<sup>16</sup> Copy number variants, caused by insertions, deletions, or recombination, can also lead to hearing loss from gene disruption or changes in the number of dose-sensitive genes. The gene most commonly associated with pathogenic copy number variants in hearing loss is *STRC*, which encodes stereocilin and is the most frequent cause of autosomal recessive causes of nonsyndromic hearing loss after pathogenic variants in *GJB2*.<sup>17</sup>

Because a large number of genes are associated with hereditary hearing loss, there are various genetic panels for hereditary deafness. Next-generation sequencing technology allows targeted sequencing of multiple genes simultaneously, expanding the ability to examine multiple genes. These panels are alternatives to the sequencing of individual genes such as *GJB6* and *GJB2*. These panels include the most common genes associated with nonsyndromic hearing loss. They may also include many of the less common genes associated with nonsyndromic hearing loss, as well as genes associated with syndromic hearing loss. Also, whole-exome sequencing and whole-genome sequencing have been used to identify novel variants in subjects with a history suggestive of genetic hereditary hearing loss.<sup>18,19,20</sup> Targeted genomic enrichment coupled with massively parallel sequencing can be used to identify both single nucleotide variants and copy number variants.

### Overlap Between Nonsyndromic Hearing Loss and Recognized Syndromes

There is overlap between hereditary nonsyndromic hearing loss and syndromic hearing loss associated with recognized syndromes. Some genetic variants may be associated with clinical findings other than hearing loss, but they may not necessarily manifest at the time of presentation with hearing loss. For example, Jervell and Lange-Nielsen syndrome is associated with congenital deafness and prolonged QT interval, but it may present only with deafness without an apparent history to suggest cardiac dysfunction. Additionally, some genes associated with nonsyndromic hearing loss are associated with recognized syndromes. Some genetic syndromes and genes that may overlap with nonsyndromic hearing loss are shown in Table 2.

**Table 2. Genes With Overlap Between Syndromic and Nonsyndromic Hearing Loss**

Syndrome	Inheritance	Clinical Description	Gene	Reason for Overlap With NSHL
<b>Usher syndrome</b>	For all types: autosomal recessive	For all types: sensorineural HL with retinitis pigmentosa		Retinitis pigmentosa usually not apparent in first decade
<b>Type 1</b>		Congenital severe-to-profound HL Abnormal vestibular function	<i>MYO7A</i> , <i>USH1C</i> , <i>CDH23</i> , <i>PCDH15</i> , <i>SANS</i> , <i>CIB2</i>	<i>DFNB18</i> (nonsyndromic) may also be caused by variants in <i>USH1C</i> <i>DFNB12</i> (nonsyndromic) may also be caused by variants in <i>CDH23</i> <i>DFNB2</i> (nonsyndromic) and <i>DFNA11</i> (nonsyndromic) may also be caused by variants in <i>MYO7A</i>
<b>Type 2</b>		Congenital mild-to-severe HL	<i>USH2A</i> , <i>VLGR1</i> , <i>WHRN</i>	

Syndrome	Inheritance	Clinical Description	Gene	Reason for Overlap With NSHL
		Normal vestibular function		
<b>Type 3</b>		Progressive HL Progressive vestibular dysfunction	<i>CLRN1i, PDZD7</i>	
<b>Pendred syndrome</b>	Autosomal recessive	Congenital sensorineural HL Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) Euthyroid goiter	<i>SLC26A4</i> (50%)	Goiter not present until early puberty or adulthood Variants in <i>SLC26A4</i> may also cause NSHL
<b>Jervell and Lange-Nielsen syndrome</b>	Autosomal recessive	Congenital deafness Prolongation of the QT interval	<i>KCNQ1, KCNE1</i>	HL may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome)
<b>Wolfram syndrome</b>	Autosomal recessive	Progressive sensorineural HL Diabetes Optic atrophy Progressive neurologic abnormalities	<i>WFS1</i>	WFS1-associated HL (DFNA6, DFNA4, DFNA38; congenital HL without associated findings) may also be caused by variants in <i>WFS1</i>

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

### Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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

- As a diagnostic test for hereditary hearing loss;
  - To confirm the 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

### **Testing Individuals with Suspected Hereditary Nonsyndromic Hearing Loss**

#### **Clinical Context and Test Purpose**

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

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest is individuals with suspected hereditary nonsyndromic hearing loss.

#### ***Interventions***

The test being considered is testing for the genes or familial variants associated with hereditary nonsyndromic hearing loss.

Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

#### ***Comparators***

The following practice is currently being used: standard clinical management without genetic testing.

#### ***Outcomes***

The potential beneficial outcomes of primary interest are improving the efficiency of the diagnostic workup by avoiding unnecessary testing and initiating management changes, including avoiding treatments targeted for acquired hearing loss.

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

Other outcomes of interest are test accuracy, test validity, changes in reproductive decision-making, morbid events, and resource utilization.

The time frame for outcome measures varies from short-term development of hearing loss as well as delayed speech and language development to long-term permanent deafness.



### Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.
- Included a validation cohort separate from the development cohort.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### Review of Evidence

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

Vona et al (2014) reported test 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 nonsyndromic hearing loss for cases in which *GJB2* testing was negative.<sup>15</sup> Testing with 1 of the 2 panels was performed on 30 patients from 23 families (23 probands) with hearing loss and 9 normal-hearing controls. Pathogenic variants in a gene associated with autosomal dominant hearing loss (*ACTG1*, *CCDC50*, *EYA4*, *MYH14*, *MTO6*, *TCF21*, *MYO1A*) or autosomal recessive hearing loss (*MYO15A*, *MYO7A*, *GJB2*, *USH2A*) were identified in 8 of 23 probands and 5 of 23 probands, respectively, for a success rate of 57%. Gu et al (2015) reported on results for targeted next-generation sequencing of a panel of 131 genes related to hearing loss in 63 subjects with nonsyndromic hearing loss with negative testing for pathogenic variants in the *GJB2*, *MT-RNR1*, and *SLC26A4* genes.<sup>21</sup> The pathogenic variant detection rate was 12.7%, with 10 of 14 pathogenic variants detected as novel compound heterozygotes. Likar et al (2018) reported on results of exome sequencing among 56 patients (49 probands) with hearing loss.<sup>22</sup> Thirty-two patients had nonsyndromic non-*GJB2* hearing loss, and 17 patients had syndromic hearing loss. In the patients who had nonsyndromic hearing loss, variants were found in 5 genes (*GJB2*, *OTOF*, *SLC26A4*, *TMPRSS3*, *USH2A*). The variant detection rate was 21% in the nonsyndromic non-*GJB2* patient subgroup and 47% in the syndromic patient subgroup.

Shearer et al (2014) reported on copy number variants in 686 patients with hearing loss using massively parallel sequencing (OtoSCOPE®).<sup>17</sup> Of the 686 patients studied, 15.2% (104/686) carried at least 1 copy number variant in a known deafness gene. The copy number variants were caused by deletions (92 [64.3%]), gene conversions (3 [26.6%]), and duplications (13 [9.1%]).

### Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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 of the impact of genetic testing on outcomes when used as a diagnostic test in this manner.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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

Therefore, a positive genetic test with a known pathogenic variant would indicate that hereditary hearing loss is present with a high degree of certainty. By contrast, the low-to-moderate clinical sensitivity would indicate that a negative test is not definitive for ruling out hereditary hearing loss. False-negative results in 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, confirmation of the diagnosis must be accompanied by changes in clinical management that improve outcomes. No published evidence was identified to evaluate whether management changes occur, and no clinical practice guidelines were identified that recommend these actions. However, the confirmation of a genetic basis for hereditary hearing loss may be useful in differentiating hereditary hearing loss from other causes of deafness and thereby precluding other testing such as computed tomography or magnetic resonance imaging (MRI). Given that some cases of apparent nonsyndromic hearing loss may represent an initial presentation of a known syndrome associated with hearing loss, identification of specific pathogenic variants may prompt additional action. Also, 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. Also, patients with hereditary hearing loss pathogenic variants have been found to have intact spiral ganglion cells in the cochlea. Intact spiral ganglion cells have been associated with success following cochlear implantation. These factors lend credence to the theory that patients with *GJB2* and *GJB6* pathogenic variants may have a favorable prognosis following cochlear implantation and that patients with other pathogenic variants or without a documented pathogenic variant may have a less favorable prognosis.

**Nonrandomized Controlled Trials**

The evidence regarding whether patients with *GJB2* and *GJB6* pathogenic variants could have a more favorable prognosis following cochlear implantation than those with other variants is limited to several small, retrospective, single-center studies that have compared outcomes of cochlear implantation in patients with and without genetic variants. Two small series from Japan initially reported that hearing outcomes were superior in patients with variants. Fukushima et al (2002) compared 3 patients with and 4 patients without variants.<sup>23</sup> Patients with *GJB2* variants had a larger vocabulary (1243 words) than patients without a variant (195 words), and a higher mean developmental quotient. Matsushiro et al (2002) evaluated 15 patients with hearing loss, 4 with genetic variants and 11 without.<sup>24</sup> They reported that speech perception was higher among patients

with variants than those without. In a retrospective cohort study, Popov et al (2014) evaluated the impact of *GJB2* variants on hearing outcomes after cochlear implantation for congenital sensorineural nonsyndromic hearing loss.<sup>25</sup> The study included 60 patients who had received a cochlear implant, 30 with *GJB2* variants and 30 without, who were a subset of 71 patients included in a larger registry of cochlear implant patients evaluated at a single institution from 2009 to 2013. At 36 months of follow-up, results on several hearing test metrics were significantly better for patients with *GJB2* variants than for those without variants, including the Listening Progress Profile ( $p < .05$ ), and the Monosyllabic-Trochee-Polysyllabic Test with 3, 6, or 12 items ( $p = .005$ ,  $p = .002$ , and  $p = .001$ , respectively). Yan et al (2013) reported on results from a series of 41 children who received cochlear implants for severe bilateral sensorineural hearing loss treated at a single center in China. A total of 15 patients had *GJB2* variants and 10 had *SLC26A4* variants.<sup>26</sup> Compared with patients with no variants, patients with *GJB2* pathogenic variants, but not those with *SLC26A4* variants, had improved outcomes on a number of hearing-related tests, including the Meaningful Auditory Integration Scale, categories of auditory performance, and Speech Intelligibility Rating.

In a second U.S. study by Connell et al (2007), these findings were not completely replicated.<sup>27</sup> This series included 31 patients with congenital hearing loss, 12 with genetic variants and 19 without. The main outcome measure was speech perception category (range, 1 to 6). Mean speech perception category did not differ between patients with and without variants (4.1 vs. 4.9, respectively,  $p = \text{not significant}$ ). The percentage of patients achieving speech perception category 6 was higher in the variant group (75% vs. 53%) but statistical testing for this difference was not performed. On multivariate analysis, the variability in speech perception was explained primarily by the length of time since cochlear implantation, and cause of hearing loss was not a significant predictor of outcomes.

### Case Series

Sinnathuray et al (2004) published 2 articles on overlapping series of patients treated with cochlear implants.<sup>28,29</sup> In the larger series, 38 patients were included, 14 patients with genetic variants and 24 without. A standardized measure of speech, the Speech Intelligibility Rating score, was used as the primary outcome measure. At 1 year, median Speech Intelligibility Rating scores were higher in the patients with *GJB2* variants (median, 3; range, 2 to 4) than patients without variants (median, 2; range, 1 to 4). The difference between the 2 groups was statistically significant ( $p = .007$ ). The percentage of patients achieving intelligible speech was 82% in the *GJB2* group and 30% in patients without variants ( $p = .02$ ).

### Panel Testing for Diagnosis of Hereditary Hearing Loss

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

1. All individual components of the panel have demonstrated clinical utility OR the tests that have not demonstrated clinical utility do not have the potential to cause harm.
2. The test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved lab.
3. The analytic validity of the panel approaches that of direct sequencing.
4. Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes.

For next-generation sequencing panels for hereditary hearing loss, criteria 2, 3, and 4 generally apply. Some, but not all, of the genes evaluated in hereditary hearing loss genetic panels would be associated with the need for additional subspecialist referral or additional testing; based on a chain of evidence, testing for these genes would have demonstrated clinical utility. Testing with a panel that includes only genes that have an association with hereditary hearing loss would be associated

with low potential for harm because they would not be likely to lead to further investigations that are of unproven benefit.

### **Section Summary: Testing Individuals with Suspected Hereditary Nonsyndromic Hearing Loss**

The available studies have indicated that a substantial percentage of patients with hereditary hearing loss will have an identifiable pathogenic variant (clinical sensitivity). This rate varies widely in available studies due to differences in specific genes tested, the patient population used, and the type of genetic testing performed. Clinical sensitivity increases as more genes associated with hereditary hearing loss are identified. There is limited information on the clinical specificity. Some studies with relatively small numbers of normal individuals have reported specificities approaching 100%.

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

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

### **Testing Individuals With a Family History of Hereditary Nonsyndromic Hearing Loss**

#### **Clinical Context and Test Purpose**

The purpose of preconception genetic testing to determine carrier status in individuals with a family history of hereditary nonsyndromic hearing loss is to determine the risk of hereditary hearing loss in offspring.

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest is individuals with a strong family history of hereditary nonsyndromic hearing loss. This population would include adults of child-bearing age.

#### ***Interventions***

The test being considered is preconception testing for the genes or familial variants associated with hereditary nonsyndromic hearing loss.

Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

#### ***Comparators***

The following practice is currently being used: standard preconception counseling without genetic testing.

#### ***Outcomes***

The potential beneficial outcome of primary interest is change in reproductive decision-making that leads to a decrease in the number of affected offspring. Other outcomes of interest are test accuracy, test validity, morbid events, and resource utilization.

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

### **Study Selection Criteria**

For the evaluation of clinical validity of genetic testing for hereditary hearing loss, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.
- Included a validation cohort separate from the development cohort.

### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### **Review of Evidence**

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

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No randomized trials were identified on managing patients with or without testing.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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

Carrier testing can also be performed in people who do not have offspring with hereditary hearing loss. If there is a strong family history of hearing loss, the likelihood of a genetic variant is increased; however, it is still considerably less compared to parents with a child with hereditary hearing loss. For individuals without a family history of hearing loss or an offspring with hearing loss, the probability of detecting a pathogenic variant is much lower. For individuals with a low pretest likelihood of being a

carrier for a hereditary hearing loss variant, the positive and negative predictive values of testing are not certain. Because the clinical specificity is not well established, it is not possible to determine the likelihood that a positive result represents a true-positive or a false-positive. At a prevalence that approaches the population rate, it is possible that a substantial number of positive results are false-positives, even in the presence of a low false-positive rate.

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

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

### **Panels for Carrier Testing**

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

- 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.
- Testing is performed in a CLIA-approved lab.
- The analytic validity of the panel approaches that of direct sequencing.
- Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes.
- Decision-making based on genetic results is well-defined.

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

### **Section Summary: Testing Individuals With a Family History of Hereditary Nonsyndromic Hearing Loss**

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

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

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **Clinical Input From Physician Specialty Societies And Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### **2013 Input**

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 nonsyndromic hearing loss among most reviewers. Reviewers in favor of genetic testing cited the ability to distinguish nonsyndromic hearing loss 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 pathogenic variants identified are associated with disorders in other organ systems. It was considered that 2 contextual factors were present: barriers to performing high-quality trials and the potential to reduce harms by avoiding unnecessary testing.

### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### **American Academy of Pediatrics**

In 2007, the American Academy of Pediatrics (AAP) issued recommendations on early hearing detection<sup>30</sup>:

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

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

"All families of children with confirmed hearing loss should be offered, and may benefit from, a genetics evaluation and counseling. This evaluation can provide families with information on etiology of hearing loss, prognosis for progression, associated disorders (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."

The 2013 supplement to the AAP 2007 position statement on early intervention after confirmation of hearing loss in a child states in its recommendations for monitoring that parents or guardians should be educated about the "importance of medical, genetic, ophthalmologic, and cardiac (EKG) evaluations on children with any type and degree of hearing loss."<sup>31</sup>

Also in 2013 (reaffirmed June 2018), the AAP issued a policy statement on ethical issues in genetic testing of children.<sup>32</sup> Following are some of their recommendations:

**General recommendations:**

"Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child."

**Diagnostic testing:**

"In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally and when appropriate, the assent of the child should be obtained."

**Newborn screening:**

"The AAP and ACMG [American College of Medical Genetics] support the mandatory offering of newborn screening for all children. After educating and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected."

**Carrier testing:**

"The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood."

**Predictive gene testing:**

"Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained."

"Predictive genetic testing for adult-onset conditions should generally be deferred unless an intervention initiated in childhood may reduce morbidity or mortality."

**American College of Medical Genetics and Genomics**

In 2014, the American College of Medical Genetics and Genomics issued practice guidelines for the clinical evaluation and etiologic diagnosis of hearing loss.<sup>33</sup> The guidelines recommended obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus, 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 not suggestive of an environmental cause of hearing loss, the guidelines made 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 [next-generation sequencing] 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.”

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

Not applicable.

### Medicare National Coverage

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

### Ongoing and Unpublished Clinical Trials

There were no ongoing or unpublished trials regarding this policy as of February 2023.

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## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Activity and functional limitations
  - Family history if applicable
  - Reason for test
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results including but not limited to hearing test results
  - Prior conservative treatments, duration, and response
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT) if applicable
- Laboratory results if applicable

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; 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)])
	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, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
	81431	Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy

Type	Code	Description
		number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
HCPCS	None	

## Policy History

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

Effective Date	Action
01/30/2015	BCBSA Medical Policy adoption
07/01/2016	Policy revision without position change
06/01/2017	Policy revision without position change
06/01/2018	Policy revision without position change
07/01/2019	Policy revision without position change
06/01/2023	Policy reactivated. Previously archived from 06/01/2020 to 05/31/2023. Coding update.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

**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 and Feedback (as applicable to your plan)

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 be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT	
BEFORE	AFTER <u>Blue font: Verbiage Changes/Additions</u>
<p><b>Reactivated Policy</b></p> <p><b>Policy Statement:</b> N/A</p>	<p><b>Genetic Testing for Hereditary Hearing Loss 2.04.87</b></p> <p><b>Policy Statement:</b></p> <ol style="list-style-type: none"> <li>I. Genetic testing for hereditary hearing loss genes (<i>GJB2</i>, <i>GJB6</i>, and other hereditary hearing loss–related genes) in individuals with suspected hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines section) may be considered <b>medically necessary</b>.</li> <li>II. Preconception genetic testing (carrier testing) for hereditary hearing loss genes (<i>GJB2</i>, <i>GJB6</i>, and other hereditary hearing loss-related genes) in parents may be considered <b>medically necessary</b> when <b>at least one</b> of the following conditions has been met:                         <ol style="list-style-type: none"> <li>A. Offspring with hereditary hearing loss</li> <li>B. One or both parents with suspected hereditary hearing loss</li> <li>C. First- or second-degree relative affected with hereditary hearing loss</li> <li>D. First-degree relative with offspring who is affected with hereditary hearing loss.</li> </ol> </li> <li>III. Genetic testing for hereditary hearing loss genes is considered <b>investigational</b> for all other situations, including, but not limited to, testing individuals without hearing loss (except as addressed in related policies, e.g., Blue Shield of California Medical Policy: Genetic Testing: Preimplantation Genetic Testing).</li> </ol>