

2.04.87	Genetic Testing for Hereditary Hearing Loss		
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Policy Statement

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**.

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:

- Offspring with hereditary hearing loss
- One or both parents with suspected hereditary hearing loss
- First- or second-degree relative affected with hereditary hearing loss
- First-degree relative with offspring who is affected with hereditary hearing loss

Genetic testing for hereditary hearing loss genes is considered **investigational** for all other situations, including, but not limited to, testing patients without hearing loss (except as addressed in related policies, e.g., Blue Shield of California Medical Policy: Preimplantation Genetic Testing).

Policy Guidelines

Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of nonsyndromic hearing loss (NSHL) is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation. It is differentiated from syndromic hearing loss, which is hearing loss associated with other signs and symptoms characteristic of a specific syndrome. Physical signs of a syndrome often include dysmorphic changes in the maxillofacial region and/or malformations of the external ears. Malfunction of internal organs may also be part of a syndrome. The physical signs can be subtle and easily missed on physical exam, therefore, exclusion of syndromic findings is ideally done by an individual with expertise in identifying dysmorphic physical signs. The phenotypic presentation of 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 be improved if parents alter their reproductive decision making as a result of genetic test results. This may occur through the use of preimplantation genetic testing in combination with in vitro fertilization. Other ways that prospective parents may alter their reproductive choices are to proceed with attempts at pregnancy, or to avoid attempts at pregnancy, based on carrier testing results.

Testing Strategy

Evaluation of a patient with suspected hereditary hearing loss should involve a careful physical exam and family history to assess for associated clinical findings that may point to a specific syndrome or nonsyndromic cause of hearing loss (e.g., infectious, toxic, autoimmune, other causes). Consideration should also be given to temporal bone computed tomography scanning in cases of progressive hearing loss and to testing for cytomegalovirus in infants with sensorineural hearing loss.

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

Genetics Nomenclature Update

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	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

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

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

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

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

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:** 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)])

There is a CPT code for a genomic sequencing procedure 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, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1

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 (≥ 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 (NSHL) is defined as hearing loss not associated with other physical signs or symptoms. NSHL 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

- Cochlear Implant
- Preimplantation Genetic Testing
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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. Molecular diagnostic testing is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 (≥ 40 decibels).¹

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

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.³

Diagnosis

Diagnosis of NSHL requires an evaluation by appropriate core medical personnel with expertise in the genetics of hearing loss, dysmorphology, audiology, otolaryngology, genetic counseling, and communication with deaf patients. The evaluation should include a family history, as well as a physical examination consisting of otologic examination, airway examination, documentation of dysmorphisms, and neurologic evaluation.⁴ However, the clinical diagnosis of NSHL is nonspecific because there are a number of underlying etiologies, and often it cannot be determined with certainty whether a genetic cause for hearing loss exists.

Treatment

Treatment of congenital and early-onset hearing loss typically involves enrollment in an educational curriculum for hearing impaired persons and fitting with an appropriate hearing aid. In some patients with profound deafness, a cochlear implant can be performed. Early identification of infants with hearing impairment may be useful in facilitating early use of amplification by 6 months of age and early intervention to achieve age-appropriate communication, speech, and language development.⁴ 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.⁵ 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*.⁷ A list of available tests for genes at the DFNA3 and DFNB1 loci are provided in Table 1.

Two of the most commonly disease-associated genes are *GJB2* and *GJB6*. *GJB2* is a small gene with a single coding exon. Variants of this gene are most common in hereditary hearing loss, causing an estimated 50% of the cases of hereditary NSHL.⁶ The carrier rate in the general population for a recessive deafness-causing *GJB2* variant is approximately 1 in 33.¹ Specific variants have been observed to be more common in certain ethnic populations.^{7,8} Variants in the *GJB2* gene will impact the expression of the Cx26 connexin protein, and almost always cause prelingual but not necessarily congenital, deafness.⁹ Different variants of *GJB2* can present high phenotypic variation but it has been demonstrated that it is possible to correlate the type of associated hearing loss with findings on molecular analysis. A 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.¹⁰

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	Audioprofile	Test Method	Variants Detected
DFNA3	<i>GJB2</i>	Prelingual	High-frequency progressive	<ul style="list-style-type: none"> · Sequence analysis/variant scanning · Targeted variant analysis · Deletion/duplication analysis 	<ul style="list-style-type: none"> · Sequence variants · Specified sequence variants · Exonic or whole-gene deletions/duplications
DFNA3	<i>GJB6</i>	Prelingual	High-frequency progressive	<ul style="list-style-type: none"> · Sequence analysis/variant scanning · Targeted variant analysis · Deletion/duplication analysis 	<ul style="list-style-type: none"> · Sequence variants · Specified sequence variants · Exonic or whole-gene deletions/duplications
DFNB1	<i>GJB2</i>	Prelingual	Usually stable	<ul style="list-style-type: none"> · Targeted variant analysis · Deletion/duplication analysis 	<ul style="list-style-type: none"> · <i>GJB2</i> sequence variants · Exon(s) or whole-gene deletions
DFNB1	<i>GJB6</i>	Prelingual	Usually stable	<ul style="list-style-type: none"> · Deletion/duplication analysis 	<ul style="list-style-type: none"> · <i>GJB6</i> 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 one 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.^{11,12} For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported.^{13,14} In contrast, only 18 pathogenic copy number variants (CNVs) had been identified by 2014.¹⁵ CNVs, caused by insertions, deletions, or recombination, can lead to hearing loss from gene disruption or changes in the number of dose-sensitive genes. The gene most commonly associated with pathogenic CNVs in hearing loss is *STRC*, which encodes stereocilin and is the most frequent cause of autosomal recessive causes of NSHL after pathogenic variants in *GJB2*.¹⁵

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*. Some examples of these panels are shown in Table 2. These panels include the most common genes associated with NSHL. They may also include many of the less common genes associated with NSHL, as well as genes associated with syndromic hearing loss. 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.¹⁸⁻²⁰ Targeted genomic enrichment coupled with massively parallel sequencing can be used to identify both single nucleotide variants and CNVs.

Overlap Between NSHL and Recognized Syndromes

There is overlap between hereditary NSHL and syndromic hearing loss associated with recognized syndromes. Some genetic variants may be associated with clinical findings other than hearing loss but they are not necessarily manifest at the time of presentation with hearing loss. For example, Jervell and Lange-Nielsen syndrome is associated with congenital deafness

and prolonged QT interval, but it may present only with deafness without an apparent history to suggest cardiac dysfunction. Additionally, some genes associated with NSHL are associated with recognized syndromes. Some genetic syndromes and genes that may overlap with NSHL are shown in Table 2.

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

Syndrome	Inheritance	Clinical Description	Gene	Reason for Overlap With NSHL
Usher syndrome	For all types: autosomal recessive	For all types: sensorineural HL with retinitis pigmentosa		Retinitis pigmentosa usually not apparent in 1st decade
Type 1		<ul style="list-style-type: none"> · Congenital severe-to-profound HL · Abnormal vestibular function 	<i>MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2</i>	<ul style="list-style-type: none"> · DFNB18 (nonsyndromic) may also be caused by variants in USH1C · DFNB12 (nonsyndromic) may also be caused by variants in CDH23 · DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by variants in MYO7A
Type 2		<ul style="list-style-type: none"> · Congenital mild-to-severe HL · Normal vestibular function 	<i>USH2A, VLGR1, WHRN</i>	
Type 3		<ul style="list-style-type: none"> · Progressive HL · Progressive vestibular dysfunction 	<i>CLRN1; PDZD7</i>	
Pendred syndrome	Autosomal recessive	<ul style="list-style-type: none"> · Congenital sensorineural HL · Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) · Euthyroid goiter 	<i>SLC26A4</i> (50%)	<ul style="list-style-type: none"> · Goiter not present until early puberty or adulthood · Variants in <i>SLC26A4</i> may also cause NSHL
Jervell and Lange-Nielsen syndrome	Autosomal recessive	<ul style="list-style-type: none"> · Congenital deafness · Prolongation of the QT interval 	<i>KCNQ1, KCNE1</i>	<ul style="list-style-type: none"> · HL may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome)
Wolfram syndrome	Autosomal recessive	<ul style="list-style-type: none"> · Progressive sensorineural HL · Diabetes · Optic atrophy · Progressive neurologic abnormalities 	<i>WFS1</i>	<ul style="list-style-type: none"> · 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.

Testing Individuals with Suspected Hereditary Nonsyndromic Hearing Loss

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

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

Comparators

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

Outcomes

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

Potential harmful outcomes are those resulting from 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.

Timing

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

Setting

The primary setting would be in the pediatric population where newborn hearing screening reveals deficits in hearing or infants with delayed speech and language development. Patients may be referred from pediatrics to a pediatric neurologist, audiologist, or medical geneticist for investigation and management of hereditary NSHL. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for hereditary hearing loss, methodologically credible studies were selected using the following principles:

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 development cohort.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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

Vona et al (2014) reported test results for targeted 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.¹⁴ 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*, *M7O6*, *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 NSHL with negative testing for pathogenic variants in the *GJB2*, *MT-RNR1*, and *SLC26A4* genes.¹⁹ 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.²⁰ Thirty-two patients had nonsyndromic non-*GJB2* hearing loss, and 17 patients had syndromic hearing loss. Within patients who had NSHL, 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).¹⁵ 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%]).

Section Summary: Clinically Valid

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%.

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

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

- As a diagnostic test for hereditary hearing loss
 - To confirm the diagnose of hereditary hearing loss and distinguish from acquired hearing loss
 - To alter management of individuals with hereditary hearing loss
 - 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 Testing for Etiology of Hereditary Hearing Loss

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.

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. Given that some cases of apparent NSHL may represent an initial presentation of a known syndrome associated with hearing loss, identification of specific pathogenic variants may prompt additional action. 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.²¹ 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.²² 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 NSHL.²⁶ 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 ($p < 0.05$), and the Monosyllabic-Trochee-Polysyllabic Test with 3, 6, or 12 items ($p = 0.005$, $p = 0.002$, and $p = 0.001$, respectively). Yan et al (2013) reported 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, 15 of who had *GJB2* variants and 10 of who had *SLC26A4* variants.²³ 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 SpeechIntelligibilityRating.

In a second U.S. study by Connell et al (2007), these findings were not completely replicated.²⁴ This series included 31 patients with congenital hearing loss, 12 with genetic variants

and 19 without. The main outcome measure was speech perception category (range, 1-6). Mean speech perception category did not differ between patients with and without variants (4.1 vs 4.9, respectively, $p=NS$). The percentage of patients achieving speech perception category 6 was higher in the variant group (75% vs 53%) but statistical testing for this difference was not performed. On multivariate analysis, the variability in speech perception was explained primarily by the length of time since cochlear implantation, and cause of hearing loss was not a significant predictor of outcomes.

Case Series: Meaningful Auditory Integration Scale; Infants and Toddlers

At least two similar series have been published in the U. S. Sinnathuray et al (2004) published 2 articles on overlapping series of patients treated with cochlear implants.^{25,26} 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 one year, median Speech Intelligibility Rating scores were higher in the patients with GJB2 variants (median, 3; range, 2-4) than patients without variants (median, 2; range, 1-4), and the difference between the two groups was statistically significant ($p=0.007$). The percentage of patients achieving intelligible speech was 82% in the GJB2 group and 30% in patients without variants ($p=0.02$).

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-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 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: Clinically Useful

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 NSHL

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

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

Comparators

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

Outcomes

The potential beneficial outcome of primary interest is changes in reproductive decision making that lead to a decrease in the number of affected offspring.

Timing

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

Setting

The primary setting would be for adults of child-bearing age with a strong family history of hereditary NSHL receiving care in a primary care or obstetrics setting. Patients may be referred to a medical geneticist for further investigation of hereditary NSHL. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

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

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

Carrier testing is most accurate when the pathogenic variant in the index case with hereditary hearing loss is known. In those cases, targeted familial variant testing for a single pathogenic variant can be performed 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 a suboptimal sensitivity and negative predictive value. Therefore, targeted testing can rule out a pathogenic variant with certainty whereas comprehensive testing cannot.

Panels for Carrier Testing

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

1. All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated clinical utility do not have a potential to cause harm.
2. Testing is performed in a Clinical Laboratory Improvement Amendments-approved lab.

3. The analytic validity of panel approaches that of direct sequencing.
4. Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes.
5. Decision making based on genetic results is well-defined.

In line with the reasoning for the clinical utility of panel testing for the 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: Clinically Useful

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

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

Summary of Evidence

For individuals who are suspected of having hereditary NSHL who receive genetic testing, the evidence includes small retrospective, single-center studies, case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and testing yield for NSHL. The relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic variants in *GJB2*, *GJB6*, and numerous other genes are found in a substantial percentage of patients with hereditary hearing loss. Of all patients with suspected hereditary hearing loss after clinical examination, a substantial proportion, in the range of 30% to 60%, will be found to have a genetic variant. The probability of finding a genetic variant is increasing as new variants are identified. False-positive results on genetic testing are expected to be very low. For diagnosis, there are a number of potential benefits of genetic testing, including a reduction in the need for alternative diagnostic tests and monitoring of patients with genetically identified syndromic hearing loss associated with other medical conditions. Clinical guidelines have recommended a tiered genetic testing approach, starting with the most common genes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a family history of hereditary NSHL who receive preconception genetic testing to determine carrier status, the evidence is limited but includes clinical guidelines. The relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic variants in *GJB2*, *GJB6*, and numerous other genes are found in a substantial percentage of patients with hereditary hearing loss. The probability of finding a genetic variant is increasing as new gene variants are identified. False-positive results on genetic testing are expected to be very low. There are several situations for which there is potential clinical utility of testing for genes associated with hereditary hearing loss. For parents at high-risk of an offspring with hereditary hearing loss, genetic testing can be useful as an aid in reproductive decision making. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION**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.

In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 2 academic medical centers 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 two 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**American College of Medical Genetics and Genomics**

The American College of Medical Genetics and Genomics (2014) issued practice guidelines for the clinical evaluation and etiologic diagnosis of hearing loss.²⁷ 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”

American Academy of Pediatrics

The American Academy of Pediatrics (2007) issued recommendations on early hearing detection²⁸:

“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, medical/surgical 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), making and likelihood of recurrence in future offspring. This information may influence parents' decision- regarding intervention options for their child."

There is a 2013 supplement to the Academy's (2007) position statement on early intervention after confirmation that a child is deaf or hard of hearing.²⁹ Genetic testing was not addressed.

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

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02082431	Long QT & Hearing Loss Prospective Study Registry	600	Dec 2018

NCT: national clinical trial

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - Clinical findings (i.e., pertinent symptoms and duration)
 - Comorbidities
 - Activity and functional limitations
 - Family history if applicable
 - Reason for procedure/test/device, when applicable
 - Pertinent past procedural and surgical history
 - Past and present diagnostic testing and results
 - Prior conservative treatments, duration, and response
 - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service

- Results/reports of tests performed
- Procedure report(s)

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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be 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.

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
HCPCS	None	
ICD-10 Procedure	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	Reason
01/30/2015	BCBSA Medical Policy adoption	Medical Policy Committee
07/01/2016	Policy revision without position change	Medical Policy Committee
06/01/2017	Policy revision without position change	Medical Policy Committee
06/01/2018	Policy revision without position change	Medical Policy Committee
07/01/2019	Policy revision without position change	Medical Policy Committee

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 (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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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

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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.