BlueCross BlueShield of Alabama

Name of Policy:
Genetic Testing for Hereditary Hearing Loss

Policy #: 643
Category: Laboratory

Latest Review Date: May 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries are affected by bilateral, permanent hearing loss of moderate or greater severity (≥40 db). Syndromic hearing loss refers to hearing loss associated with other medical or physical findings, including visible abnormalities of the external ear. Because syndromic hearing loss occurs as part of a syndrome of multiple clinical manifestations, it is often recognized more readily as hereditary in nature. Nonsyndromic hearing loss (NSHL) is defined as hearing loss 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.

Hereditary Hearing Loss

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.

Autosomal recessive patterns of inheritance predominate and account for 80% of congenital NSHL. A typical clinical presentation of autosomal recessive NSHL involves the following characteristics:

- Sensorineural hearing loss
- Mild-to-profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually nonprogressive
- No associated medical findings

Most of the remaining 20% of patients have an autosomal dominant inheritance pattern, with a small number having X-linked or mitochondrial inheritance. Patients with autosomal dominant inheritance typically show progressive NSHL, which begins in the second through fourth decades of life.

Diagnosis

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. 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. Delays in development of hearing treatment have been shown to delay development of communication. The primary method for identification of hearing impairment has been newborn screening with audiometry. Genetic testing has not been proposed as a primary screen for hearing loss.

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. 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*. A list of available tests for genes at the DFNA3 and DFNB1 loci is 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. The carrier rate in the general population for a recessive deafness-causing *GJB2* variant is approximately 1 in 33. Specific variants have been observed to be more common in certain ethnic populations. Variants in the *GJB2* gene will impact expression of the Cx26 connexin protein and almost always cause prelingual, but not necessarily congenital, deafness. 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 2014 systematic review of publications reporting *GJB2* variant prevalence suggested that the overall prevalence of *GJB2* variants is similar around the world, although specific variants differ.

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	*GJB2*	Prelingual	High-frequency progressive	• Sequence analysis/variant scanning • Targeted variant analysis • Deletion/duplication analysis	• Sequence variants • Specified sequence variants • Exonic or whole-gene deletions/duplications
DFNA3	*GJB6*	Prelingual	High-frequency progressive	• Sequence analysis/variant scanning • Targeted variant analysis • Deletion/duplication analysis	• Sequence variants • Specified sequence variants • Exonic or whole-gene deletions/duplications
DFNB1	*GJB2*	Prelingual	Usually stable	• Targeted variant analysis • Deletion/duplication analysis	• *GJB2* sequence variants • Exon(s) or whole-gene deletions
DFNB1	*GJB6*	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. For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported. In contrast, only 18 pathogenic copy number variants (CNVs) had been identified by 2014. CNVs, caused by insertions, deletions, or recombination, can lead to hearing loss from gene disruption or changes in the number of dose-sensitive genes. The gene most commonly associated with pathogenic CNVs in hearing loss is *STRC*, which encodes stereocilin and is the most frequent cause of autosomal recessive causes of NSHL after pathogenic variants in *GJB2*.

Because of the large number of genes associated with hereditary hearing loss, there are various genetic panels for hereditary deafness. Next-generation genetic sequencing technology allows targeted sequencing of multiple genes simultaneously, expanding the ability to examine multiple genes. These panels are alternatives to sequencing of individual genes such as *GJB6* and *GJB2*. Some examples of these panels are 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. In addition, 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. Targeted genomic enrichment

coupled with massively parallel sequencing can be used to identify both single-nucleotide variants and CNVs.

Table 2: Gene Panels for Hereditary Hearing Loss

Test	Technology	Genes Tested	Analytic Sensitivity
Partners Healthcare (OtoGenome™ Test for Hearing Loss and Related Syndromes)	NGS, followed by confirmation with Sanger sequencing or PCR	87	99%
University of Iowa Healthcare (OtoSCOPE® V8)	NGS/massive parallel sequencing	152	99%

NGS: next-generation sequencing; PCR: polymerase chain reaction

Overlap Between NSHL and Recognized Syndromes

There is overlap between hereditary NSHL and hearing loss associated with recognized syndromes. Some genetic 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 3.

Table 3: 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		• Congenital severe-to-profound HL • Abnormal vestibular function	*MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *SANS*, *CIB2*	• 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		• Congenital mild-to-severe HL • Normal vestibular function	*USH2A*, *VLGR1*, *WHRN*	
Type 3		• Progressive HL • Progressive vestibular dysfunction	*CLRN1i* *PDZD7*	
Pendred syndrome	Autosomal recessive	• Congenital sensorineural HL • Bony labyrinth	*SLC26A4* (50%)	• Goiter not present until early puberty or adulthood • Variants in *SLC26A4* may also

Syndrome	Inheritance	Clinical Description	Gene	Reason for Overlap With NSHL
		abnormalities (Mondini dysplasia or dilated vestibular aqueduct) • Euthyroid goiter		cause NSHL
Jervell and Lange-Nielsen syndrome	Autosomal recessive	• Congenital deafness • Prolongation of the QT interval	*KCNQ1* , *KCNE1*	• HL may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome)
Wolfram syndrome	Autosomal recessive	• Progressive sensorineural HL • Diabetes • Optic atrophy • Progressive neurologic abnormalities	*WFS1*	• WFS1-associated HL (DFNA6/14/38; congenital HL without associated findings) may also be caused by variants in *WFS1*

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

Policy:

Genetic testing for hereditary hearing loss genes *GJB2* and *GJB6* meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in individuals with hearing loss to confirm the diagnosis of hereditary hearing loss.

Genetic testing for hereditary hearing loss of all other hearing loss-related genes does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all other situations, including, but not limited to, testing patients without hearing loss.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through February 22, 2018.
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 Non-Syndromic Hearing Loss

Clinical Context and Test Purpose

The purpose of genetic testing of individuals with suspected hereditary nonsyndromic hearing loss (NSHL) 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 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 relevant intervention of interest is genetic testing for the genes or familial variants associated with hereditary NSHL.

Comparators

The relevant comparator of interest is 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 a 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 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 in 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 explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable;
- Clinically valid;
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

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 and to 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.

Clinical 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 NGS of two panels of deafness-associated genes, one with 80 genes and one with 129 genes, in the evaluation of NSHL for cases in which *GJB2* testing was negative. Testing with one of the two panels was performed on 30 patients from 23 families (23 probands) with hearing loss and nine 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%. In 2015, Gu et al reported results for targeted NGS 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. 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.23 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.

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

Section Summary: Clinical 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, 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%.

Clinical 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 Test 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. Therefore, a chain of evidence is considered to determine the impact on health outcomes.

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 on 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. In 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 on genetic testing are not uncommon, therefore, the utility of a negative test in discriminating between hereditary and acquired hearing loss is low.

To have clinical utility, the confirmation of the diagnosis must be accompanied by changes in clinical management that improve outcomes. No published evidence was identified to evaluate whether management changes occur, and no clinical practice guidelines were identified that

recommend these actions. However, the confirmation of a genetic basis for hereditary hearing loss may be useful in differentiating hereditary hearing loss from other causes of deafness, and thereby precluding other testing such as computed tomography or magnetic resonance imaging.

Genetic testing has also been proposed as a method to predict response to cochlear implantation. Expression of *GJB2* and *GJB6* is in the cochlea. In addition, patients with hereditary hearing loss 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.

The evidence on this question consists of 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 three patients with and four patients without variants. 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, four with genetic variants and 11 without. They reported that speech perception was higher among patients with variants than those without. In 2014, in a retrospective cohort study, Popov et al evaluated the impact of *GJB2* variants on hearing outcomes after cochlear implantation for congenital sensorineural NSHL. 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 the 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 results from a series of 41 children who received cochlear implants for severe bilateral sensorineural hearing loss treated at a single center in China, 15 of whom had *GJB2* variants and ten of whom had *SLC26A4* variants. Compared to 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.

At least two similar series have been published in the United States. In 2004, Sinnathuray et al published two articles on overlapping series of patients treated with cochlear implants. 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 (SIR) score, was used as the primary outcome measure. At 1 year, median SIR 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 2 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 ($p=0.02$).

In a second U.S. study by Connell et al (2007), these findings were not completely replicated. 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.

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. Analytic validity of the panel approaches that of direct sequencing.
4. The panel offers substantial advantages (efficiency of workup, cost) over sequential analysis of individual genes.

For NGS 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: 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 is not definitive. In addition, 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.

Summary of Evidence
For individuals who are suspected of having hereditary nonsyndromic hearing loss (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 genetic testing yield for NSHL. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic variants in mostly *GJB2* and *GJB6*, but also less so in 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 gene 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.

Practice Guidelines and Position Statement
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. The guidelines recommended obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus (CMV), imaging, or other testing based on the suspected etiology. For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories 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 (AAP) issued recommendations on early hearing detection in 2007:

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

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

U.S. Preventive Services Task Force Recommendations

Not applicable

Key Words:

Nonsyndromic hearing loss (NSHL), *GJBT, GJB6,*

Approved by Governing Bodies:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Molecular diagnostic testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81252	*GJB2* (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., Non-syndromic hearing loss) gene analysis, full gene sequence
81253	; known familial variants
81254	*GJB6* (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., Non-syndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(*GJB6*-D13S1854)]).
81430	Hearing loss (e.g., non-syndromic 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 number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes

HCPCS Codes:

S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness

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Policy History:

Medical Policy Panel, April 2017
Medical Policy Group, April 2017 **(3):** Individual policy created for genetic testing for hearing loss, pulling previous information, coding and policy statement from medical policy #136 *Genetic Testing for Non-cancerous Inheritable Diseases*; no change in policy statements; expanded panel testing continues to not be considered medically necessary; history prior to April 2017 noted on MP#136
Medical Policy Panel April 2018
Medical Policy Group, May 2018 **(6)**: Updates to Key Points and References.