Medical Policy

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Title: Genetic Testing for Hereditary Hearing Loss

Description/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 db).(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.

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

Treatment
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.(5) 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.(6) DFNB1-associated hereditary hearing loss relates to autosomal recessive syndromes in which more than 99% of cases are caused by pathogenic variants to 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 common disease-associated genes are *GJB2* and *GJB6*. *GJB2* is a small gene with a single coding exon. Variants of this gene are most common in hereditary hearing loss, causing an estimated 50% of the cases of hereditary NSHL.(8) 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.(9,10) Variants in the *GJB2* gene will impact expression of the Cx26 connexin protein and almost always cause prelingual, but not necessarily congenital, deafness.(11) Different variants of *GJB2* can present with high phenotypic variation, but it has been demonstrated that it is possible to correlate the type of associated hearing loss with findings on molecular analysis. A systematic review by

Chan and Chang (2014), reporting on *GJB2* variant prevalence suggested that the overall prevalence of *GJB2* variants is similar around the world, although specific variants differ.(12)

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 the 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* Variantsat 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 one gene at a time. With Sanger sequencing, the genes with the most common pathologic 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.(12,13) For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported.(14,15) By 2018, over 8,100 variants in over 150 genes had been reported.(16) Copy number variants (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*.(17)

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*. 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, 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 copy number variants.

Overlap Between Nonsyndromic Hearing Loss 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 may not necessarily manifest at the time of presentation with hearing loss. For example, Jervell and Lange-Nielsen syndrome is associated with congenital deafness and prolonged QT interval, but it may present only with deafness without an apparent history to suggest cardiac dysfunction. Additionally, some genes associated with NSHL are associated with recognized syndromes. A summary of some of the 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 first decade
Type 1		• Congenital severe-to-profound HL • Abnormal vestibular function	*MYO7A*, *USH1, 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 abnormalities (Mondini dysplasia or dilated vestibular aqueduct) • Euthyroid goiter	*SLC26A4* (50%)	• Goiter not present until early puberty or adulthood • Variants in SLC26A4 may also 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, DFNA4, DFNA38; congenital HL without associated findings) may also be caused by variants inWFS1

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

Regulatory Status

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.

Medical Policy Statement

The safety and effectiveness of genetic testing for hereditary hearing loss genes (*GJB2, GJB6* and other hereditary hearing loss-related genes) have been established. It may be considered a useful diagnostic option in specified situations.

Inclusionary and Exclusionary Guidelines

Inclusions

- Genetic testing for hereditary hearing loss genes (GJB2, GJB6 and other hereditary hearing loss-related genes) in individuals with hearing loss to confirm the diagnosis of hereditary hearing loss.
- Preconception (prenatal) genetic testing (carrier testing) for hereditary hearing loss genes (*GJB2, GJB6* and other hereditary hearing loss-related genes) in parents when at least one of the following conditions has been met:
  - Offspring with hereditary hearing loss; *OR*
  - One or both parents with suspected hereditary hearing loss; *OR*
  - First- or second-degree relative affected with hereditary hearing loss; *OR*
  - First-degree relative with offspring who is affected with hereditary hearing loss.

Exclusions

Patients not meeting the above criteria

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81252 81253 81254 81430 81431

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

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

- As a diagnostic test for hereditary hearing loss;
  - To confirm the diagnosis of hereditary hearing loss and distinguish from acquired hearing loss.
  - To alter management of individuals with hereditary hearing loss.
  - To direct and focus carrier testing on 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.

TESTING INDIVIDUALS WITH SUSPECTED HEREDITARY NON-SYNDROMIC HEARING LOSS

Clinical Context and Test Purpose

The purpose of genetic testing in individuals with suspected hereditary non-syndromic 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 following PICOs were used to select literature to inform this review.

Populations

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.

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

Comparators

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

Outcomes

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

Potential harmful outcomes are those resulting from 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.

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

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

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

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

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).

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

Vona et al (2014) reported test results for targeted next-generation sequencing (NGS) 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.(15) Testing with 1 of the 2 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.(21) 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.(22) Thirty-two patients had non-syndromic non-*GJB2* hearing loss, and 17 patients had syndromic hearing loss. In the patients who had

NSHL, variants were found in 5 genes (*GJB2*, *OTOF*, S*LC*26A4, *TMPRSS3*, *USH2A*). The variant detection rate was 21% in the non-syndromic non-*GJB2* patient subgroup and 47% in the syndromic patient subgroup.

Shearer et al (2014) reported on copy number variants (CNVs) in 686 patients with hearing loss using massively parallel sequencing (OtoSCOPE®).(17) Of the 686 patients studied, 15.2% (104/686) carried at least 1 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%]).

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 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.

Genetic testing in patients with suspected hereditary hearing loss can be performed to confirm the diagnosis of hereditary hearing loss, which is distinguished from acquired hearing loss. There is no direct evidence of the impact of genetic testing on outcomes when used as a diagnostic test in this manner.

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

The high analytic sensitivity indicates that if a pathogenic variant is present and included within test repertoires, it is very likely to be detected by current testing methods. The high analytic specificity indicates that if a pathogenic variant is absent, a false-positive result 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. 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, 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 and 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 that is associated with hearing loss, identification of specific pathogenic variants may prompt additional action. It has also been suggested that specific mutations

should prompt additional action. For example if a KNCQ1 pathogenic variant is found, additional cardiac workup may be warranted because pathogenic variants in this gene are also associated with cardiac rhythm abnormalities. In addition, genetic counseling can provide patients and families with further information and assistance on issues such as reproductive decision making.

Genetic testing has also been proposed as a method to predict response to cochlear implantation. Expression of *GJB2* and *GJB6* is in the cochlea. In addition, patients with hereditary hearing loss 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 those patients with other pathogenic variants or without documented pathogenic variants 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 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.(23) 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.(24) 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 NSHL.(25) 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 test ($p<0.05$), the Monosyllabic-Trochee-Polysyllabic test with 3, 6, or 12 items ($p=0.005$, $p=0.002$, and $p=0.001$, respectively). Yan et al (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. A total of 15 patients had *GJB2* variants and 10 had *SLC26A4* variants.(26) 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.

In a second U.S. study by Connell et al (2007) these findings were not completely replicated.(27) This series included 31 patients with congenital hearing loss, 12 with genetic mutations 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=not significant). The percentage of patients achieving speech perception category 6 was higher in the variant group (75% vs 53%), but statistical testing for this difference was not performed. On multivariate analysis, the variability in speech

perception was explained primarily by the length of time since cochlear implantation, and cause of hearing loss was not a significant predictor of outcomes.

Case Series
Sinnathuray et al (2004) published two articles on overlapping series of patients treated with cochlear implants.(28,29) 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). 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 mutations associated with a single condition (hearing loss), for which the following criteria apply:

1. All individual components of the panel have demonstrated clinical utility OR the tests that have not demonstrated clinical utility do not have the potential to cause harm.
2. The test is performed in a 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 associated with the need for additional subspecialist referral or additional testing; based on a chain of evidence, testing for these mutations would have demonstrated clinical utility. Testing with a panel that includes only genes that have an association with hereditary hearing loss would be associated with low potential for harm, as they would not be likely to lead to further investigations that are of unproven benefit.

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

Hereditary hearing loss can be confirmed if genetic testing reveals a pathogenic variant known to be associated with hereditary hearing loss, but a negative genetic test does not rule out hereditary hearing loss. For the individual patient, there is no evidence from literature and no specialty society guidelines that recommend specific actions or changes in management as a result of a positive genetic test. However, the use of genetic testing can streamline the

diagnostic workup, and knowledge of specific 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.

TESTING INDIVIDUALS WITH A FAMILY HISTORY OF HEREDITARY NONSYNDROMIC HEARING LOSS

Clinical Context and Test Purpose

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

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

Populations

The relevant population of interest includes individuals with a strong family history of hereditary NSHL. This population would include adults of child-bearing age.

Interventions

The test being considered is preconception testing for the genes or familial variants associated with hereditary nonsyndromic hearing loss (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 leads to a decrease in the number of affected offspring. Other outcomes of interest are test accuracy, test validity, morbid events, and resource utilization.

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

Study Selection Criteria

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

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

- Included a validation cohort separate from the development cohort.

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

Review of Evidence
See the discussion of clinical validity in the section on Testing Individuals with Suspected Hereditary Non-syndromic 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 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 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 of a genetic variant is increased; however it is still considerably less compared to parents with a child with hereditary hearing loss. For individuals without a family history of hearing loss or an offspring with hearing loss, the probability of detecting a pathogenic variant is much lower. For individuals with a low pretest likelihood of being a carrier for a hereditary hearing loss variant, the positive and negative predictive values of testing are not certain. Because the clinical specificity is not well established, it is not possible to determine the likelihood that a positive result represents a true positive versus a false positive. At a prevalence’s 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 in lieu of comprehensive genetic testing for the full range of genes associated with hereditary hearing loss. Targeted testing has a higher accuracy for confirming and excluding the presence of a pathogenic variant. It is particularly useful for excluding the presence of a pathogenic variant because comprehensive testing has suboptimal sensitivity and negative predictive value. Therefore, targeted testing can rule out a pathogenic variant with certainty whereas comprehensive testing cannot.

Panels for Carrier Testing

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

- All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated clinical utility do not have a potential to cause harm.
- Testing is performed in a CLIA-approved lab.
- The analytic validity of the panel approaches that of direct sequencing.
- Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes.
- Decision making based on genetic results is well defined.

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

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

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

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

SUMMARY OF EVIDENCE

For individuals who are suspected of having hereditary non-syndromic 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 testing yield for NSHL. 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, 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 that is associated with other medical conditions. Clinical guidelines recommend a tiered genetic testing approach, starting with the most common genes. The evidence is sufficient to determine qualitatively that the technology results in an 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. 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 having 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 an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

2013 Input

In response to requests, Blue Cross Blue Shield Association received input from 2 physician specialty societies and 2 academic medical centers while this policy was under review in 2013. Reviewers agreed with the medically necessary indication for carrier testing, and with additional indications for carrier testing. There was support for testing the index case to confirm

NSHL among a majority of reviewers. Reviewers in favor of genetic testing cited the ability to distinguish NSHL from other causes of hearing loss, to streamline the diagnostic workup and avoid further unnecessary testing and to provide referrals to specialists when specific types of mutations were identified that are associated with disorders in other organ systems. It was considered that two contextual factors were present: barriers to performing high-quality trials, and the potential to reduce harms by avoiding unnecessary testing.

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.(30) The guidelines recommend 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 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 detection:(30)

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

late-onset permanent hearing loss, a physical examination, and indicated radiologic and laboratory studies (including genetic testing).”

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

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

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

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

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

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

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

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

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

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable

Ongoing and Unpublished Clinical Trials
There are no ongoing or unpublished trials which would influence the status of this policy.

Government Regulations
National:
There is no national coverage determination on this topic.

Local:
There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Cochlear Implant
- Genetic, Molecular and Other Tests – Experimental/Investigational Status
- Genetic Testing and Counseling
- Genetic Testing – Carrier Screening for Genetic Diseases
- Genetic Testing - Preimplantation
- Genetic Testing - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 19, 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/14	10/15/13	10/25/13	Joint policy established
5/1/15	2/17/15	2/27/15	• Routine maintenance • References 3, 10-11, 17-22, 36, 37, 40-41, and 45-48 added. • Policy title, policy statement and criteria changed to refer to "hereditary hearing loss" (from "nonsyndromic hearing loss") to reflect significant overlap between nonsyndromic and syndromic hearing loss. • Added new CPT code 81430 and 81431 (Effective date 1/1/15).
7/1/16	4/19/16	4/19/16	• Routine maintenance • References and rationale updated
7/1/17	4/18/17	4/18/17	• Routine maintenance • References and rationale updated • Local Medicare information updated • Aligned with LCD
7/1/18	4/17/18	4/17/18	• Routine maintenance
7/1/19	4/16/19		• Routine maintenance • Local Medicare information updated
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance
1/1/23	10/18/22		Routine maintenance (slp)
1/1/24	10/17/23		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR HEREDITARY HEARING LOSS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.