

(20487)

Medical Benefit		Effective Date: 01/01/15	Next Review Date: 11/17
Preauthorization	Yes	Review Dates: 01/14, 11/14, 11/15, 11/16	

Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are suspected of having hereditary nonsyndromic hearing loss 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing 	Comparators of interest are: <ul style="list-style-type: none"> Standard diagnostic workup 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Changes in reproductive decision making Morbid events Resource utilization

Description

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

Summary of Evidence

The evidence for genetic testing in individuals who are suspected of having hereditary NSHL includes studies on analytic validity, test accuracy, and test validity. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Genetic mutations in *GJB2*, *GJB6*, and numerous other genes are found in a substantial percent of patients with hereditary hearing loss. The analytic validity of genetic testing for hereditary hearing loss is high. Of all patients with suspected hereditary hearing loss after clinical examination, a substantial proportion, in the range of 30% to 60%, will be found to have a genetic mutation. The probability of finding a genetic mutation is increasing as new gene mutations are identified. False-positive results on mutation testing are expected to be very low. There are several situations for which there is potential clinical utility of testing for hereditary hearing loss mutations. For diagnosis, 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 mutations. For parents at high risk of an offspring with hereditary hearing loss, genetic testing can be useful as an aid in reproductive decision making. Although genetic testing for hereditary hearing loss has been investigated as an adjunct to audiologic testing for screening of congenital hearing loss, no studies demonstrate that such testing is associated with incremental improvement in outcomes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Policy

Genetic testing for hereditary hearing loss mutations (*GJB2*, *GJB6* and other hereditary hearing loss-related mutations) in individuals with hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines) may be considered **medically necessary**.

Preconception genetic testing (carrier testing) for hereditary hearing loss mutations (*GJB2*, *GJB6* and other hereditary hearing loss-related mutations) in parents may be considered **medically necessary** when at least 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.

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

Policy Guidelines

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

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

Genetic evaluation and counseling should be offered to all patients who are being considered for hereditary hearing loss genetic testing. Genetic evaluation and counseling can help define the familial patterns of inheritance, exclude the presence of syndromic hearing loss, and provide information to patients on the future risk of hereditary hearing loss in offspring.

In addition to mutations in the *GJB6* and *GJB2* genes, there are many less common pathologic mutations found in other genes. Some of these are: *ACTG1*, *CDH23*, *CLDN14*, *COCH*, *COL11A2*, *DFNA5*, *DFNB31*, *DFNB59*, *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.

Testing for mutations associated with hereditary hearing loss should be confined to known pathologic mutations. While research studies using genome-wide associations have uncovered numerous single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs) associated with hereditary hearing loss the clinical significance of these findings is unclear.

For carrier testing, outcomes are expected to be improved if parents alter their reproductive decision-making as a result of genetic test results. This may occur through the use of preimplantation genetic testing in combination with in vitro fertilization. Other ways that prospective parents may alter their reproductive choices are to proceed with attempts at pregnancy, or to avoid attempts at pregnancy, based on carrier testing results.

Testing Strategy

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

If there is not high suspicion for a specific hearing loss etiology, ideally the evaluation should occur in a step-wise fashion. About 50% of individuals with autosomal recessive hereditary hearing loss have mutations in *GJB2* gene. In the remainder of patients with apparent autosomal recessive hereditary hearing loss, numerous other genes are implicated. In autosomal dominant hereditary hearing loss, there is no single identifiable gene responsible for most cases. If there is suspicion for autosomal recessive congenital hearing loss, it would be reasonable to begin testing with testing of *GJB2* and *GJB6*. If this is negative, screening for the other genetic mutations associated with hearing loss with a multigene panel would be efficient. An alternative strategy for suspected autosomal recessive or autosomal dominant hearing loss would be to obtain a multigene panel that includes *GJB2* and *GJB6* as a first step. Given the extreme heterogeneity in genetic causes of hearing loss, either strategy may be reasonably equivalent to the other.

Genetic Counseling

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

Background

Description of Disease

Hearing loss is a common birth defect. Approximately one of every 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 in nature.

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

Treatment 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 six 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.

Genetic Mutations in Hereditary Hearing Loss

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

Two DFN loci commonly associated with hereditary hearing loss are DFNA3 and DFNB1, both of which map to chromosome 13q12. DFNA3-associated hereditary hearing loss is caused by autosomal dominant mutations present in the *GJB2* or *GJB6* genes.⁶ DFNB1-associated hereditary hearing loss are autosomal recessive syndromes in which more than 99% of cases are caused by mutations to the *GJB2* gene and less than 1% of remaining cases arising from mutations to *GJB6*.⁷ A list of available tests for genetic mutations at the DFNA3 and DFNB1 loci is given in Table 1.

Two of the most commonly mutated genes are *GJB2* and *GJB6*. *GJB2* is a small gene with a single coding exon. Mutations of this gene are most common in hereditary hearing loss, causing an estimated 50% of the cases of hereditary NSHL.⁸ The carrier rate in the general population for a recessive deafness-causing *GJB2* mutation is approximately one in 33.¹ Specific mutations have been observed to be more common in certain ethnic populations.^{9,10} Mutations in the *GJB2* gene will impact expression of the Cx26 connexin protein and almost always cause prelingual, but not necessarily congenital, deafness.¹¹ Differing mutations to *GJB2* can present high phenotypic variation, but it has been demonstrated that it is possible to correlate the type of associated hearing loss

with findings on molecular analysis. A systematic review of publications reporting *GJB2* mutation prevalence suggests that the overall prevalence of *GJB2* mutations is similar around the world, although specific mutations differ.¹²

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

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

Locus	Gene	Onset	Audioprofile	Test Method	Mutations Detected
DFNA3	<i>GJB2</i>	Prelingual	High-frequency progressive	<ul style="list-style-type: none"> Sequence analysis/mutation scanning Targeted mutation analysis Deletion/duplication analysis 	<ul style="list-style-type: none"> Sequence variants Specified sequence variants Exonic or whole-gene deletions/duplications
DFNA3	<i>GJB6</i>	Prelingual	High-frequency progressive	<ul style="list-style-type: none"> Sequence analysis/mutation scanning Targeted mutation analysis Deletion/duplication analysis 	<ul style="list-style-type: none"> Sequence variants Specified sequence variants Exonic or whole-gene deletions/duplications
DFNB1	<i>GJB2</i>	Prelingual	Usually stable	<ul style="list-style-type: none"> Targeted mutation analysis Deletion/duplication analysis 	<ul style="list-style-type: none"> <i>GJB2</i> sequence variants Exon(s) or whole-gene deletions
DFNB1	<i>GJB6</i>	Prelingual	Usually stable	<ul style="list-style-type: none"> Deletion/duplication analysis 	<ul style="list-style-type: none"> <i>GJB6</i> deletions

Analysis for *GJB6* and *GJB2* mutations 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 gene with the most common mutations is generally sequenced first, followed by sequencing of additional genes if a pathogenic mutation is not found.

In addition to the most common mutations associated with hereditary hearing loss (*GJB6*, *GJB2*), there are many less common pathologic mutations. 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 mutations continue to be identified in cases of hereditary hearing loss.^{13,14} As of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported.^{15,16} In contrast, only 18 pathogenic copy number variants (CNVs) had been identified by 2014.¹⁷ 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 mutations 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*. Some examples of these panels are given 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 mutations in subjects with a history suggestive of genetic hereditary hearing loss.¹⁸⁻²⁰ Targeted genomic enrichment coupled with massively parallel sequencing can be used to identify both single-nucleotide variants and CNVs.

Table 2. Genomic Mutations Panels for Hereditary Hearing Loss¹¹

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® V6) ²¹	NGS/massiveparallel sequencing	116	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 mutations may be associated with clinical findings other than hearing loss, but they are not necessarily present at the time of presentation with hearing loss. For example, Jervell and Lange-Nielsen syndrome is associated with congenital deafness and prolonged QT interval, but it may present only with deafness without an apparent history to suggest cardiac dysfunction. Additionally, some of the genes associated with NSHL are associated with recognized syndromes. Some of the genetic syndromes and mutations that may overlap with NSHL is shown in Table 3.

Table 3. Genetic Mutations With Overlap Between Syndromic and NSHL

Syndrome	Inheritance	Clinical Description	Gene Mutations	Reason for Overlap With NSHL
Usher syndrome	For all types: autosomal recessive	For all types: sensorineural hearing loss with retinitis pigmentosa		<ul style="list-style-type: none"> Retinitis pigmentosa usually not apparent in 1st decade
Type 1		<ul style="list-style-type: none"> Congenital severe-to-profound hearing loss Abnormal vestibular function 	<i>MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2</i>	<ul style="list-style-type: none"> DFNB18 (nonsyndromic) may also be caused by mutations in USH1C DFNB12 (nonsyndromic) may also be caused by mutations in CDH23 DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by mutations in MYO7A
Type 2		<ul style="list-style-type: none"> Congenital mild-to-severe hearing loss Normal vestibular function 	<i>USH2A, VLGR1, WHRN</i>	
Type 3		<ul style="list-style-type: none"> Progressive hearing loss Progressive vestibular dysfunction 	<i>CLRN1, PDZD7</i>	
Pendred syndrome	Autosomal recessive	<ul style="list-style-type: none"> Congenital sensorineural hearing loss Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) Euthyroid goiter 	<i>SLC26A4 (50%)</i>	<ul style="list-style-type: none"> Goiter not present until early puberty or adulthood. Mutations in SLC26A4 may also cause NSHL
Jervell and Lange-Nielsen syndrome	Autosomal Recessive	<ul style="list-style-type: none"> Congenital deafness Prolongation of the QT interval 	<i>KCNQ1, KCNE1</i>	<ul style="list-style-type: none"> Hearing loss may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome)
Wolfram syndrome	Autosomal Recessive	<ul style="list-style-type: none"> Progressive sensorineural hearing loss Diabetes mellitus Optic atrophy 	<i>WFS1</i>	<ul style="list-style-type: none"> WFS1-associated hearing loss (DFNA6/14/38; congenital hearing loss without associated findings) may also be caused by mutations in

Syndrome	Inheritance	Clinical Description	Gene Mutations	Reason for Overlap With NSHL
		<ul style="list-style-type: none"> Progressive neurologic abnormalities 		WFS1

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 Act (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.

Related Protocols

Cochlear Implant

Preimplantation Genetic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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