Genetic Testing for Hereditary Hearing Loss

Hearing loss is a common birth defect. Approximately 1 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. 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 of nonsyndromic hearing loss 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. However, the clinical diagnosis of nonsyndromic hearing loss is nonspecific because there are a number of underlying etiologies, and often it cannot be determined with certainty whether a genetic cause for hearing loss exists.

Treatment 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.
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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 to the GJB2 gene with less than 1% of remaining cases arising from pathogenic variantsto GJB6.

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 nonsyndromic hereditary hearing loss. 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. Differing variants 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 variant prevalence suggests 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 the patients with hereditary hearing loss, approximately 3% are found to have a variants in the GJB6 gene. 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 gene 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 and GJB2, there are many less common disease-associated genes. Some of these are: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MTS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POUSF4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes. Novel genetic variants continue to be identified in cases of hereditary hearing loss. 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 mutations in GJB2.

Because of the large number of genes associated with hereditary hearing loss, there are a variety of 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 that are associated with syndromic hearing loss. In addition, whole exome sequencing and whole genome sequencing have been used to identify novel variants in
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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.

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 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 also associated with recognized syndromes.

***Note: This Medical Policy is complex and technical. For questions concerning the technical
language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Genetic Testing for Hereditary Hearing Loss when it is
determined to be medically necessary because the medical criteria and guidelines shown below
are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the
Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit
design; therefore member benefit language should be reviewed before applying the terms of this
medical policy.

When Genetic Testing for Hereditary Hearing Loss is covered

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

Preconception genetic testing (carrier testing) for hereditary hearing loss genes (GJB2, GJB6 and other
hereditary hearing loss-related genes) in parents may be considered medically necessary when at least
one of the following conditions has been met:

- Offspring with hereditary hearing loss; 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

When Genetic Testing for Hereditary Hearing Loss is not covered

Genetic testing for hereditary hearing loss genes is considered investigational for all other conditions
not listed above.

Policy Guidelines

The evidence for genetic testing in individuals who are suspected of having hereditary
nonsyndromic hearing loss (NSHL) 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 GJB2,

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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 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. There are several situations for which there is potential clinical utility of testing for hereditary hearing loss variants. 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 that the technology results in a meaningful improvement in the net health outcome.

The evidence for preconception genetic testing in individuals with a family history of hereditary NSHL to determine carrier status 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 analytic validity of genetic testing for hereditary hearing loss is high. The probability of finding a genetic variant is increasing as new gene variants are identified. False-positive results on genetic testing are expected to be very low. There are several situations for which there is potential clinical utility of testing for genes associated with hereditary hearing loss. For parents at high risk of an offspring with hereditary hearing loss, genetic testing can be useful as an aid in reproductive decision making. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81252, 81253, 81254, 81430, 81431

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Evidenced Based Guideline titled, “Genetic Testing for Nonsyndromic Hearing Loss”


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3545543/


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841091/
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Medical Director review 10/2013

Specialty Matched Consultant Advisory Panel review 8/2014

Medical Director review 8/2014

For Evidenced Based Guideline titled, “Genetic Testing for Hereditary Hearing Loss”


Specialty Matched Consultant Advisory Panel review 8/2015

Medical Director review 8/2015


Medical Director review 7/2016


Medical Director review 4/2017

Specialty Matched Consultant Advisory Panel review 7/2017

Medical Director review 7/2017

Policy Implementation/Update Information

For Evidenced Based Guideline titled, “Genetic Testing for Nonsyndromic Hearing Loss”

10/29/13 New Evidence Based Guideline developed. Genetic testing to confirm the diagnosis of hereditary nonsyndromic hearing loss (NSHL) may be recommended to distinguish NSHL from other etiologies of hearing loss and facilitate the diagnostic workup. Preconception testing of parents (carrier testing) may be recommended under certain conditions. Medical Director review 9/2013. (mco)

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For Evidenced Based Guideline titled, “Genetic Testing for Hereditary Hearing Loss”

11/25/14 References updated. EBG retitled from “Genetic Testing for Nonsyndromic Hearing Loss” to “Genetic Testing for Hereditary Hearing Loss”. Description section updated. Billing/Coding section updated to include CPT codes: 81430, 81431 which are effective 1/1/2015. Removed fifth bullet which stated “Parents are planning future offspring and desire to determine the likelihood of deafness” from the Evidence Based Guideline for Genetic Testing for Hereditary Hearing Loss section. No changes to Guideline statements. (td)


12/30/15 Description section updated. Policy Guidelines section extensively revised. References updated. (td)

8/30/16 Minor edit to When Covered section; added word “suspected” as recommended by External Physician Consultant. Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)

5/26/17 Minor edits with updated genetic nomenclature, “mutations” replaced with “variants”, no change to policy intent. References updated. Medical Director review 4/2017. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.