

Corporate Medical Policy

Genetic Testing for Hereditary Hearing Loss AHS – G2148

File Name: genetic_testing_for_hereditary_hearing_loss
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Description of Procedure or Service

Hearing loss is among the most etiologically heterogeneous disorders. More than 400 genetic syndromes that include hearing loss as a feature, more than 100 genes associated with nonsyndromic genetic hearing loss, and a number of non-genetic causes. Genes associated with syndromic and nonsyndromic genetic hearing loss encode a variety of proteins involved in the development and function of the auditory system, including transcription factors, structural proteins, gap junction proteins, and ion channels (Alford et al., 2014). The genes may be associated with an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern (A Eliot Shearer, 2017).

Related Policies

General Genetic Testing, Germline Disorders AHS-M2145

General Genetic Testing, Somatic Disorders AHD -M2146

******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 the medical criteria and reimbursement 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

1. Reimbursement is allowed for genetic counseling and is recommended in patients considered for genetic testing for nonsyndromic hereditary hearing loss.
2. Reimbursement is allowed for genetic testing for the two most common mutations for nonsyndromic hereditary hearing loss (GJB2 and GJB6) in individuals to confirm the diagnosis of hereditary hearing loss where other causes of nonsyndromic acquired hearing loss (infection, injury, age-related) have been excluded.

Genetic Testing for Hereditary Hearing Loss AHS – G2148

3. Reimbursement is allowed for genetic testing using gene panel tests or NGS technologies for additional hereditary hearing loss-related mutations if ALL of the following are met:
 - a. ONLY AFTER initial testing for common mutations (GJB2 and GJB6) is negative
 - b. Syndrome is not suspected based on individual's clinical presentation
4. Reimbursement is allowed for genetic testing for individuals with a known familial mutation variant.
5. Reimbursement is allowed for genetic testing using gene panel tests or NGS technologies for suspected syndromic hearing loss.

When Genetic Testing for Hereditary Hearing Loss is not covered

Reimbursement is not allowed for genetic testing for hereditary hearing loss-related mutations

- a. For all other situations, including but not limited to, testing in individuals without hearing loss.

Policy Guidelines

Background

Approximately one in every 500 children born in the United States is deaf or has a hearing loss significant enough to affect speech and language development. Ninety-five percent of newborns with hearing loss identified by newborn hearing screening programs are born to hearing parents, obscuring the fact that the majority of newborns have a hereditary cause for their hearing loss (Alford et al., 2014). Approximately 80 percent of cases of hereditary hearing loss are inherited in an autosomal recessive pattern, 19 percent are autosomal dominant, and the remaining cases X-linked (mainly recessive) or mitochondrial (A Eliot Shearer, 2017).

Hearing loss is typically described in terms related to its clinical presentation. In general, it is categorized as either syndromic or nonsyndromic. Syndromic hearing loss is associated with other medical or physical findings, including malformations of the external ear or other organs, or with medical problems involving other organ systems. An estimated 30% of hereditary hearing loss is syndromic. Nonsyndromic hearing loss (NSHL) is defined as hearing loss that is not associated with visible abnormalities of the external ear or any related medical problems. For NSHL, it is more difficult to determine whether the etiology is hereditary or acquired because there are no other clinical manifestations at the time of the hearing loss presentation. NSHL accounts for an estimated 70% of genetically determined hearing loss (Angeli, Lin, & Liu, 2012), and it is frequently congenital and sensorineural (Sloan-Heggen et al., 2016).

The genetic loci on which mutations associated with nonsyndromic hereditary hearing loss are usually found are termed DFN. 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 (A Eliot Shearer, 2017). The DFNB1 locus, which includes the GJB2 gene encoding the gap junction protein connexin 26 and the GJB6 gene encoding the gap junction protein connexin 30, accounts for an estimated 50% of all autosomal recessive nonsyndromic hearing loss and 15–40% of all deaf individuals in a variety of populations (Alford et al., 2014).

GJB2 is a small gene with a single coding exon, which codes for the Cx26 connexin protein (OMIM, 2016). At least 83 deafness-causing variants have been identified in GJB2, but a few common mutations account for a large percentage of alleles in several populations. Probands with

Genetic Testing for Hereditary Hearing Loss AHS – G2148

this mutation generally have congenital hearing loss (A Eliot Shearer, 2017). Mutations in the *GJB6* gene lead to similar effects on abnormal expression of connexin protein Cx30 (OMIM, 2014). *GJB6* deletions have been observed in multiple populations, although they appear to be a relatively uncommon explanation for hearing loss in the United States (Alford et al., 2014).

In addition to mutations in the *GJB6* and *GJB2* genes, many less common pathologic mutations are found in other genes. Some of these are: *ACTG1*, *BSND*, *CDH23*, *CLDN14*, *COCH*, *COL11A2*, *DFNA5*, *DFNB31*, *DFNB59*, *ESPN*, *ESRRB*, *EYA4*, *GRXCRI*, *HGF*, *KCNQ4*, *LHFPL5*, *MARVELD2*, *MT-TS1*, *MYO15A*, *MYO6*, *MYO7A*, *OTOA*, *OTOF*, *PCDH15*, *POU3F4*, *PTPRQ*, *RDX*, *SLC26A4*, *STRC*, *TECTA*, *TMC1*, *TMIE*, *TMPRSS3*, *TRIOBP*, *USH1C*, *WFS1*, and *WHRN* genes (A Eliot Shearer, 2017). Several gene panels exist for assessment of hereditary hearing loss. For example, Shang et al evaluated the “MiamiOtoGenes” panel, which consists of 180 genes. The investigators examined 5 unrelated probands with varying degrees of hearing loss onset and severity and found 7 different genetic variants (Shang et al., 2018). Other entities offering proprietary genetic panels include BluePrint (230 genes), GeneDx (146 genes), and the University of Iowa (152 genes) (BluePrint, 2020; GeneDx, 2018; Iowa, 2020).

Clinical Validity and Utility

Shearer et al performed a meta-analysis focusing on the current genetic tests used to evaluate hearing loss. 20 studies were included, containing 426 controls and 603 patients with idiopathic hearing loss. Several genetic panels such as OtoGenetics Deafness Test and OtoGenome were used. Overall, the controls showed good sensitivity and specificity (over 99%), and the diagnostic rate was found to be 41% (with a range of 10%-83%). The authors concluded that “comprehensive genetic testing should form the cornerstone of a tiered approach to clinical evaluation of patients with hearing loss along with history, physical exam, and audiometry and can determine further testing that may be required, if any (Shearer & Smith, 2015).”

Sloan-Heggen et al performed parallel sequencing on 1119 “sequentially accrued” patients. 440 (39%) of these patients were found to have a genetic etiology for hearing loss. Pathogenic variants were found in 49 genes, and various alterations such as missense variants (49% of the alterations), copy number variants (18%), insertions or deletions (13%), and nonsense variants (8%) were found. The authors noted the wide variety of the genetic spectrum of hearing loss (Sloan-Heggen et al., 2016).

D’Aguillo et al examined the role of genetic screening as an adjunct to universal newborn hearing screening. The authors evaluated 16 studies and identified the rate of children that passed the universal newborn hearing screening but who also tested positive on a genetic screening. Of the 137895 infants included in the studies, pathogenic mutations were detected in 8.66% of them. Of this cohort, 545 infants passed the universal screening, but also tested positive on a genetic screening (1.4%) (D’Aguillo et al., 2019).

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG)

In 2014, the ACMG issued the following guidelines for the clinical evaluation and diagnosis of hearing loss. For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories that do not suggest an environmental cause of hearing loss, ACMG recommends that a tiered diagnostic approach should be implemented.

- “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

Genetic Testing for Hereditary Hearing Loss AHS – G2148

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, WES, or WGS 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. It should be noted that the cost of these new genetic sequencing technologies is decreasing so rapidly that a tiered approach to testing may soon no longer be cost effective. In particular, for large sequencing panels targeted toward hearing loss-related genes, it may, in some cases, already be more cost effective to use NGS technologies as the initial test in the evaluation of hearing loss. However, issues related to genomic testing, such as the likelihood of incidental findings, will have to be addressed.”
- “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.”
- “If genetic testing fails to identify an etiology for a patient’s hearing loss, the possibility of a genetic or acquired etiology remains. This point must be emphasized because it can be misunderstood by clinicians and by patients and their families. For interested patients and families, further genetic testing may be pursued on a research basis.”
- “CMV testing should be done at the same time as genetic testing for infants with congenital hearing loss. For later-onset or progressive hearing loss, CMV testing can be obtained, but the likelihood that a positive test is due to postnatal exposure increases with age.”

For individual with findings that suggest a syndromic genetic etiology for their hearing loss:

- “Pretest genetic counseling should be provided, and, with patient’s informed consent, genetic testing, if available, should be ordered to confirm the diagnosis – this testing may include single-gene tests, hearing loss sequencing panels, WES, WGS, chromosome analysis, or microarray-based copy-number analysis, depending on clinical findings.”
- “Appropriate studies should be undertaken to determine whether other organs are involved; and
- “Appropriate near-term and long-term screening and management should be arranged, including referrals to specialists, as indicated by the associated manifestation of the particular syndrome” (Alford et al., 2014).

The ACMG also published an algorithm stating to “consider” *GJB2*, *GJB6* or other gene specific testing if familial or nonsyndromic hearing loss was suspected. If nonsyndromic and mitochondrial inheritance was suspected, the ACMG recommended testing for the A1555G mutation (ACMG, 2018).

Joint Commission on Infant Hearing (JCIH)

In 2007, the JCIH recommended that evaluation of infants with confirmed hearing loss 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 (JCIH, 2007). In 2013, a supplement by the ASHA was added to the JCIH. The 2013 supplement also stated that medical providers must “understand atypical development etiologies and diagnoses, and refer for medical-genetic

Genetic Testing for Hereditary Hearing Loss AHS – G2148

evaluation” and that families must be educated on the “importance of medical, genetic, ophthalmologic, and cardiac (EKG) evaluations on children with any type and degree of hearing loss” (ASHA, 2013).

In 2019, the JCIH published an updated position statement. They note that the American College of Medical Genetics and Genomics recommends offering genetic counseling and testing to all infants who are deaf or hard of hearing and their families. A geneticist’s evaluation should include “a review of family history of specific genetic disorders or syndromes, genetic testing for gene mutations such as *GJB2* (connexin-26), and syndromes commonly associated with early-onset hearing loss” (JCIH, 2019).

The **American Academy of Otolaryngology-Head and Neck Surgery** has adopted the 2007 position statement of the Joint Committee on Infant Hearing (AAO, 2014).

International Pediatric Otolaryngology Group (IPOG)

In 2016, the IPOG released their guidelines on hearing loss in the pediatric patient. Concerning which children should be offered comprehensive genetic testing they recommend the following:

- “Nonsyndromic children with unilateral hearing loss should not be offered genetic testing as part of initial workup.”
- “Comprehensive genetic testing is not universally available.”
- “A negative test does not rule out a genetic cause.”
- “Comprehensive genetic testing should be offered to children with bilateral ANSD, or unilateral ANSD if imaging for cochlear nerve dysplasia is negative and no obvious acquired cause exists.”
- “After an audiogram, comprehensive genetic testing has the highest diagnostic yield of any single test for bilateral sensorineural hearing loss.”

In addressing the question “Should single gene or directed genetic testing be used?”, they make the following consensus recommendation statements:

- “In the setting of comprehensive genetic testing, single gene testing is of low diagnostic yield and should not be offered as part of an initial workup unless a known family history exists.”
- “Directed genetic testing for *GJB2*/*GJB6* should be considered if comprehensive genetic testing is unavailable.”
- “Directed genetic testing may be considered in consultation with a geneticist if comprehensive genetic testing is negative but suspicion for a genetic cause still exists (Liming et al., 2016).”

American Academy of Pediatrics (AAP)

The AAP also recommends genetic testing for evaluation of hearing loss. Testing protocol typically tests *GJB2/6* first, then applies targeted next generation sequencing of gene panels for recessive, dominant, x-linked patterns or syndromic hearing loss (AAP).

Applicable Federal Regulations

A search for “hearing loss” on the FDA website on March 6, 2020 did not yield any genetic results (FDA, 2020). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug

Genetic Testing for Hereditary Hearing Loss AHS – G2148

Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

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 service codes: 81252, 81253, 81254, 81430, 81431, 96040, S0265

Note: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to Laboratory Procedures Reimbursement Policy AHS - R2162.

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 policy titled: Genetic Testing For Nonsyndromic Hereditary Hearing Loss:

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Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Genetic Testing for Hereditary Hearing Loss AHS – G2148

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Genetic Testing for Hereditary Hearing Loss AHS – G2148

Policy Implementation/Update Information

For policy titled: Genetic Testing for Nonsyndromic Hereditary Hearing Loss

- 1/1/2019 BCBSNC will provide coverage for genetic testing for nonsyndromic hereditary hearing loss when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
- 8/13/19 When Not Covered section revised; removed item “a. If more than once per lifetime”. Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)

For policy titled: Genetic Testing for Hereditary Hearing Loss

- 9/10/2019 Reviewed by Avalon 2nd Quarter 2019 CAB with title change. Added Related Policies to the Description section. The following were added to the When Covered section: Item 1, “**and is recommended**” regarding genetic counseling; item 3, removed reference to Table 1-3 in background section and added “**ALL of the following are met**”: for items a and b; added item 5. Added “If more than once per lifetime” to When Not Covered section. Policy guidelines and references updated. Removed the following codes from the Billing/Coding section: 96040, S0265, along with the code table. Medical Director review 8/2019. (jd)
- 7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Wording changed to reimbursement language in policy statement, When Covered section, and When Not Covered section. Policy guidelines and references updated. The following codes were added to the Billing/Coding section: 96040, S0265, along with the Note regarding testing five or more genes being tested on same platform to reference the Laboratory Procedures Reimbursement Policy AHS R2162. Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (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.