BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.87 Genetic Testing for Hereditary Hearing Loss

Annual Effective Policy Date: July 1, 2024

Original Policy Date: June 2018

Related Policies:

2.04.102 - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
7.01.05 - Cochlear Implant

Genetic Testing for Hereditary Hearing Loss

Description

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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 decibels). 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. Nonsyndromic hearing loss is defined as hearing loss not associated with other physical signs or symptoms. Nonsyndromic hearing loss accounts for 70% to 80% of genetically determined deafness, and it is more difficult to determine whether the etiology is hereditary or acquired.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals who are suspected of having hereditary nonsyndromic hearing loss.

POLICY STATEMENT

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

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.

Genetic testing for hereditary hearing loss genes is considered **investigational** for all other situations, including, but not limited to, testing individuals without hearing loss.

POLICY GUIDELINES

Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of nonsyndromic hearing loss is hearing loss 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. The phenotypic presentation of nonsyndromic hearing loss varies, but generally involves the following features:

- Sensorineural hearing loss
- Mild-to-profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually nonprogressive

This policy primarily focuses on the use of genetic testing to identify a cause of suspected hereditary hearing loss. The diagnosis of syndromic hearing loss can 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, variants in certain genetic loci may cause both syndromic and nonsyndromic hearing loss. Given this overlap, the policy focuses on genetic testing for hereditary hearing loss more generally.

In addition to pathogenic variants in the *GJB6* and *GJB2* genes, there are many less common pathogenic variants found in other genes. They include: *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.

Targeted testing for variants associated with hereditary hearing loss should be confined to known pathogenic variants. While research studies using genome-wide associations have uncovered numerous single nucleotide variants and copy number variations associated with hereditary hearing loss, the clinical significance of these findings is unclear.

For carrier testing, outcomes are expected to improve 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 an individual 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 syndromic or nonsyndromic cause of hearing loss (eg, 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 in infants with sensorineural hearing loss.

If there is no high suspicion for a specific hearing loss etiology, ideally the evaluation should occur in a stepwise fashion. About 50% of individuals with autosomal recessive hereditary hearing loss have pathogenic variants in the *GJB2* gene. In the remainder of individuals 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 with testing of *GJB2* and *GJB6.* If this is negative, screening for the other genes associated with hearing loss using 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, these 2 strategies may be considered reasonably equivalent.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). The Society"s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

RATIONALE

Summary of Evidence

For individuals who are suspected of having hereditary nonsyndromic hearing loss 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 nonsyndromic hearing loss. 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 variants are identified. False-positive results on genetic testing are expected to be very low. For diagnosis, there are a number of potential benefits of genetic testing, including a reduction in the need for alternative diagnostic tests and monitoring of patients with genetically identified syndromic hearing loss associated with other medical conditions. Clinical guidelines have recommended a tiered genetic testing approach, starting with the most common genes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a family history of hereditary nonsyndromic hearing loss 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

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics

In 2007, the American Academy of Pediatrics (AAP) 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 (eg, 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."

American College of Medical Genetics and Genomics

In 2014, the American College of Medical Genetics and Genomics issued practice guidelines for the clinical evaluation and etiologic diagnosis of hearing loss.[33,] The guidelines recommended obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus, imaging, or other testing based on the suspected etiology. For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories not suggestive of an environmental cause of hearing loss, the guidelines made the following recommendations for a tiered diagnostic approach:

- "Pretest genetic counseling should be provided, and, with patient"s informed consent, genetic testing should be ordered.
    - Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics.
    - In the absence of any specific clinical indications and for singleton cases and cases with apparent autosomal recessive inheritance, the next step should be testing for DFNB1-related hearing loss (due to mutations in *GJB2* and adjacent deletions in *GJB6*).
    - If initial genetic testing is negative, genetic testing using gene panel tests, NGS [next-generation sequencing] technologies such as large sequencing panels targeted toward hearing loss-related genes, whole-exome sequencing, or whole-genome sequencing may be considered. Because several tests are clinically available, the clinician must be aware of the genes included in the test (panel) chosen and the performance characteristics of the platform chosen, including coverage, analytic sensitivity, and what types of mutations will be detected....
    - If genetic testing reveals mutation(s) in a hearing loss-related gene, mutation-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2018	New policy	Genetic testing for hereditary hearing loss genes (GJB2, GJB6, and other hereditary hearing loss-related genes) in individuals with suspected hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines section) may be considered medically necessary.
June 2019	Replace policy	Policy updated with literature review through February 18, 2019; no references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through February 11, 2020; reference added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through February 18, 2021; reference added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through February 15, 2022; no references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through March 2, 2023; no references added. Minor editorial refinements to policy statements; intent unchanged.
June 2024	Replace policy	Policy updated with literature review through March 2, 2024; no references added. No policy statement changes and intent unchanged.