

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319
CLINICAL	☐ MINIMIZE SAFETY RISK OR CONCERN.
BENEFIT	☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS.
	☐ ASSURE APPROPRIATE LEVEL OF CARE.

□ Assure appropriate duration of service for interventions.
 ☑ Assure that recommended medical prerequisites have been met.

☐ **A**SSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.

POLICYPRODUCT VARIATIONSDESCRIPTION/BACKGROUNDRATIONALEDEFINITIONSDISCLAIMERCODING INFORMATIONREFERENCESPOLICY HISTORY

I. POLICY

Effective Date:

Genetic testing for hereditary hearing loss mutations (*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) may be considered **medically necessary**.

Preconception genetic testing (carrier testing) for hereditary hearing loss–related genes (*GJB2*, *GJB*,6 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

11/1/2025

- 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 (except as addressed in related policies, e.g., **MP 7.009 Preimplantation Genetic Testing**). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

This policy primarily focuses on the use of genetic testing to identify a cause of suspected hereditary hearing loss. Hereditary hearing loss can be classified as syndromic or nonsyndromic. Nonsyndromic hearing loss is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation. Syndromic hearing loss is hearing loss associated with other signs and symptoms characteristic of a specific syndrome. 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.



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

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 (SNHL)
- Mild to profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually non-progressive

In addition to pathogenic variants in the *GJB6* and *GJB2* genes, there are many less common pathologic variants 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.

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 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 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 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 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 with a multigene panel would be efficient. An alternative strategy



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

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 (HGVS) 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 (see 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 (ACMG) and the Association for Molecular Pathology (AMP) 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	Change in DNA sequence with uncertain effects on disease	
significance		
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

Experts recommend formal genetic counseling for individuals who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-Reference:

MP 7.009 Preimplantation Genetic Testing

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-quidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

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 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. For nonsyndromic hearing loss, 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. Nonsyndromic hearing loss accounts for 70% to 80% of genetically determined deafness.

Autosomal recessive patterns of inheritance predominate and account for 80% of congenital nonsyndromic hearing loss. A typical clinical presentation of autosomal recessive nonsyndromic hearing loss 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



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

inheritance typically show progressive nonsyndromic hearing loss, which begins in the second through fourth decades of life.

Diagnosis

Diagnosis of nonsyndromic hearing loss 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 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

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.

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 in the *GJB2* gene, and less than 1% of remaining cases arise from pathogenic variants to *GJB6*. A list of available tests for genes at the DFNA3 and DFNB1 loci are provided in **Table 1**.

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 hereditary nonsyndromic 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



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

ethnic populations. Variants in the *GJB2* gene will impact the expression of the Cx26 connexin protein, and almost always cause prelingual but not necessarily congenital, deafness. Different variants of *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 by Chan and Chang (2014), reporting on *GJB2* variant prevalence, suggested the overall prevalence of *GJB2* variants is similar around the world, although specific variants differ.

Table 1. Clinical Characteristics and Testing Methods for GJB2 and GJB6 Variants

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 wholegene deletions/duplication s
DFNA3	GJB6	Prelingual	High- frequency progressive	 Sequence analysis/variant scanning Targeted variant analysis Deletion/duplication analysis 	 Sequence variants Specified sequence variants Exonic or wholegene deletions/duplication s
DFNB1	GJB2	Prelingual	Usually stable	Targeted variant analysisDeletion/duplication analysis	 GJB2 sequence variants Exon(s) or whole- gene deletions
DFNB1	GJB6	Prelingual	Usually stable	 Deletion/duplication analysis 	GJB6 deletions

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 patients with hereditary hearing loss, approximately 3% have a variant 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 genes 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, 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,



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes. Novel genetic variants continue to be identified in cases of hereditary hearing loss. For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported. By 2018, over 8,100 variants in over 150 genes had been reported. In contrast, only 18 pathogenic copy number variants had been identified by 2014. Copy number variants, 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 copy number variants in hearing loss is STRC, which encodes stereocilin and is the most frequent cause of autosomal recessive causes of nonsyndromic hearing loss after pathogenic variants in GJB2.

Because a large number of genes are associated with hereditary hearing loss, there are various genetic panels for hereditary deafness. Next-generation sequencing technology allows targeted sequencing of multiple genes simultaneously, expanding the ability to examine multiple genes. These panels are alternatives to the sequencing of individual genes such as GJB6 and GJB2. These panels include the most common genes associated with nonsyndromic hearing loss. They may also include many of the less common genes associated with nonsyndromic 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. 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 nonsyndromic hearing loss and syndromic hearing loss associated with recognized syndromes. Some genetic variants may be associated with clinical findings other than hearing loss, but they are 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 nonsyndromic hearing loss are associated with recognized syndromes. Some genetic syndromes and genes that may overlap with nonsyndromic hearing loss 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 hearing loss (HL) with retinitis pigmentosa		Retinitis pigmentosa, usually not apparent in 1st decade
Type 1		Congenital severe-to-profound HLAbnormal	MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2	DFNB18 (nonsyndromic) may also be caused by



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

		vestibular function		variants in USH1C DFNB12 (nonsyndromic may also be caused by variants in CD DFNB2 (nonsyndromic and DFNA11 (nonsyndromic may also be caused by variants in MYO7A	H23
Type 2		 Congenital mild- to-severe HL Normal vestibular function 	USH2A, VLGR1, WHRN		
Type 3		Progressive HLProgressive vestibular dysfunction	CLRN1i, PDZD7		
Pendred syndrome	Autosomal recessive	 Congenital SNHL Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) Euthyroid goiter 	SLC26A4 (50%)	 Goiter not presuntil early pub or adulthood Variants in SLC26A4 may also cause nonsyndromic hearing loss 	erty ⁄
Jervell and Lange- Nielsen syndrome	Autosomal recessive	 Congenital deafness Prolongation of the QT interval 	KCNQ, KCNE1	HL may prese without persor or family historicardiac symptome (sudden death SIDS, syncopal episodes, or long QT Syndrome)	nal ry of oms I, al ong
Wolfram syndrome	Autosomal recessive	Progressive SNHLDiabetesOptic atrophyProgressive neurological	WFS1	WFS1-associa HL (DFNA6/14/38 congenital HL without	ated



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

abnormalities	associated findings) may also
	been caused by
	variants in WFS1

HL: hearing loss; SNHL: sensorineural 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.

IV. RATIONALE TOP

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 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.



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

V. DEFINITIONS TOP

NONSYNDROMIC HEARING LOSS is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation

SYNDROMIC HEARING LOSS is hearing loss associated with other signs and symptoms characteristic of a specific syndrome

VI. DISCLAIMER TOP

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedu	re Codes						
S3844	81252	81253	81254	81430	81431		

ICD-10- CM Diagnosis Codes	Description
H90.3	Sensorineural hearing loss, bilateral
H90.41	Sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.42	Sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H90.5	Unspecified sensorineural hearing loss



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

ICD-10- CM Diagnosis Codes	Description
H90.6	Mixed conductive and sensorineural hearing loss, bilateral
H90.71	Mixed conductive and sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.72	Mixed conductive and sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H91.8X1	Other specified hearing loss, right ear
H91.8X2	Other specified hearing loss, left ear
H91.8X3	Other specified hearing loss, bilateral
Z31.438	Encounter for other genetic testing of female for procreative management
Z31.448	Encounter for other genetic testing of male for procreative management
Z82.2	Family history of deafness and hearing loss

VIII. REFERENCES TOP

1. Shearer AE, Hildebrand MS, Smith RJH. Deafness and Hereditary Hearing Loss Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington: 2017.

- 2. Morton CC, Nance WE. Newborn hearing screening--a silent revolution. N Engl J Med. May, 18 2006; 354(20): 2151-64. PMID 16707752
- 3. Matsunaga T. Value of genetic testing in the otological approach for sensorineural hearing loss. Keio J Med. Dec 2009; 58(4): 216-22. PMID 20037285
- 4. ACMG. Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss. Genetic Evaluation of Congenital Hearing Loss Expert Panel. ACMG statement. Genet Med. May-Jun 2002; 4(3): 162-71. PMID 12180152
- 5. Milunsky JM, Maher TA, Yosunkaya E, et al. Connexin-26 gene analysis in hearingimpaired newborns. Genet Test. 2000; 4(4): 345-9. PMID 11216657
- 6. Smith RJH, Ranum PT. Nonsyndromic Hearing Loss and Deafness, DFNA3. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington: 2016.
- 7. Smith RJH, Jones MKN. Nonsyndromic Hearing Loss and Deafness, DFNB1. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2016.
- 8. Apps SA, Rankin WA, Kurmis AP. Connexin 26 mutations in autosomal recessive deafness disorders: a review. Int J Audiol. Feb 2007; 46(2): 75-81. PMID 17365058
- Green GE, Scott DA, McDonald JM, et al. Carrier rates in the midwestern United States for GJB2 mutations causing inherited deafness. JAMA. Jun 16 1999; 281(23): 2211-6. PMID 10376574
- 10. Bitner-Glindzicz M. Hereditary deafness and phenotyping in humans. Br Med Bull. 2002; 63: 73-94. PMID 12324385



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

- 11. Linden Phillips L, Bitner-Glindzicz M, Lench N, et al. The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. Int J Audiol. Feb 2013; 52(2): 124-33. PMID 23131088
- 12. Chan DK, Chang KW. GJB2-associated hearing loss: systematic review of worldwide prevalence, genotype, and auditory phenotype. Laryngoscope. Feb 2014; 124(2): E34-53. PMID 23900770
- 13. Azaiez H, Booth KT, Bu F, et al. TBC1D24 mutation causes autosomal-dominant nonsyndromic hearing loss. Hum Mutat. Jul 2014; 35(7): 819-23. PMID 24729539
- 14. Goncalves AC, Matos TD, Simoes-Teixeira HR, et al. WFS1, and non-syndromic low-frequency sensorineural hearing loss: a novel mutation in a Portuguese case. Gene. Apr 01 2014; 538(2): 288-91. PMID 24462758
- 15. Shearer AE, Eppsteiner RW, Booth KT, et al. Utilizing ethnic-specific differences in minor allele frequency to recategorize reported pathogenic deafness variants. Am J Hum Genet. Oct 02 2014; 95(4): 445-53. PMID 25262649
- 16. Vona B, Muller T, Nanda I, et al. Targeted next-generation sequencing of deafness genes in hearing-impaired individuals uncovers informative mutations. Genet Med. Dec 2014; 16(12): 945-53. PMID 24875298
- 17. Azaiez H, Booth KT, Ephraim SS, et al. Genomic Landscape and Mutational Signatures of Deafness-Associated Genes. Am J Hum Genet. Oct 04 2018; 103(4): 484-497. PMID 30245029
- 18. Shearer AE, Kolbe DL, Azaiez H, et al. Copy number variants are a common cause of non-syndromic hearing loss. Genome Med. 2014; 6(5): 37. PMID 24963352
- 19. Choi BY, Kim J, Chung J, et al. Whole-exome sequencing identifies a novel genotypephenotype correlation in the entactin domain of the known deafness gene TECTA. PLoS One. 2014; 9(5): e97040. PMID 24816743
- 20. Kim HJ, Won HH, Park KJ, et al. SNP linkage analysis and whole exome sequencing identify a novel POU4F3 mutation in autosomal dominant late-onset nonsyndromic hearing loss (DFNA15). PLoS One. 2013; 8(11): e79063. PMID 24260153
- 21. Bademci G, Diaz-Horta O, Guo S, et al. Identification of copy number variants through whole-exome sequencing in autosomal recessive nonsyndromic hearing loss. Genet Test Mol Biomarkers. Sep 2014; 18(9): 658-61. PMID 25062256
- 22. Gu X, Guo L, Ji H, et al. Genetic testing for sporadic hearing loss using targeted massively parallel sequencing identifies 10 novel mutations. Clin Genet. Jun 2015; 87(6): 588-93. PMID 24853665
- 23. Likar T, Hasanhodzic M, Teran N, et al. Diagnostic outcomes of exome sequencing in patients with syndromic or non-syndromic hearing loss. PLoS One. 2018; 13(1): e0188578. PMID 29293505
- 24. Fukushima K, Sugata K, Kasai N, et al. Better speech performance in cochlear implant patients with GJB2-related deafness. Int J Pediatr Otorhinolaryngol. Feb 01 2002; 62(2): 151-7. PMID 11788148
- 25. Matsushiro N, Doi K, Fuse Y, et al. Successful cochlear implantation in prelingual profound deafness resulting from the common 233delC mutation of the GJB2 gene in the Japanese. Laryngoscope. Feb 2002; 112(2): 255-61. PMID 11889380



POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

- 26. Popov TM, Stancheva I, Kachakova DL, et al. Auditory outcome after cochlear implantation in patients with congenital nonsyndromic hearing loss: influence of the GJB2 status. Otol Neurotol. Sep 2014; 35(8): 1361-5. PMID 24691507
- 27. Yan YJ, Li Y, Yang T, et al. The effect of GJB2 and SLC26A4 gene mutations on rehabilitative outcomes in pediatric cochlear implant patients. Eur Arch Otorhinolaryngol. Nov 2013; 270(11): 2865-70. PMID 23296490
- 28. Connell SS, Angeli SI, Suarez H, et al. Performance after cochlear implantation in DFNB1 patients. Otolaryngol Head Neck Surg. Oct 2007; 137(4): 596-602. PMID 17903576
- 29. Sinnathuray AR, Toner JG, Clarke-Lyttle J, et al. Connexin 26 (GJB2) gene-related deafness and speech intelligibility after cochlear implantation. Otol Neurotol. Nov 2004; 25(6): 935-42. PMID 15547423
- 30. Sinnathuray AR, Toner JG, Geddis A, et al. Auditory perception and speech discrimination after cochlear implantation in patients with connexin 26 (GJB2) generalated deafness. Otol Neurotol. Nov 2004; 25(6): 930-4. PMID 15547422
- 31. Alford RL, Arnos KS, Fox M, et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med. Apr 2014; 16(4): 347-55. PMID 24651602
- 32. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. Pediatrics. Oct 2007; 120(4): 898-921. PMID 17908777
- 33. Muse C, Harrison J, Yoshinaga-Itano C, et al. Supplement to the JCIH 2007 position statement: principles and guidelines for early intervention after confirmation that a child is deaf or hard of hearing. Pediatrics. Apr 2013; 131(4): e1324-49. PMID 23530178
- 34. COMMITTEE ON BIOETHICS. Ethical and policy issues in genetic testing and screening of children. Pediatrics. Mar 2013; 131(3): 620-2. PMID 23428972
- 35. Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1392-1406. doi:10.1016/j.gim.2022.03.018 PMID: 35802133

IX. POLICY HISTORY TOP

MP 2.319	08/10/2020 Consensus Review. Policy statement unchanged. Added FEP
	variation. References added.
	05/12/2021 Consensus Review. Policy statement unchanged. References,
	and rationale updated. Coding reviewed.
	05/05/2022 Consensus Review. No change to policy statement.
	References reviewed and updated.
	04/12/2023 Consensus Review. No change to policy statement.
	References and coding reviewed. Background updated.
	05/23/2024 Consensus Review. No change to policy statement. New
	references.
	6/23/2025 Consensus Review. No change to policy statement. Reviewed
	and updated references.



POLICY TITLE	E GENETIC TESTING FOR HEREDITARY HEARING LOSS	
POLICY NUMBER	MP 2.319	
	09/23/2025 Administrative Update. Removed Benefit Variations Section	

Top

Health care benefit programs issued or administered by Capital Blue Cross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company®, and Keystone Health Plan® Central. Independent licensees of the Blue Cross BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.