BSC_CON_2.16	Genetic Testing: Hearing Loss		
Original Policy Date:	February 1, 2024	**Effective Date:**	February 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 7

Example Test Table

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Hereditary Hearing Loss		
Known Familial Variant Analysis for Hereditary Hearing Loss	*GJB2* Targeted Mutation Analysis	81253
	GJB6 Targeted Mutation Analysis	81403
GJB2 and *GJB6* Sequencing and/or Deletion/ Duplication Analysis or Multigene Panel Analysis	*GJB2* Gene Sequencing (GeneDx)	81252
	GJB2 Deletion/Duplication Analysis (GeneDx)	81479
	GJB6 Common Variant Analysis	81254
	GJB6 Sequencing Analysis	81479
	Hearing Loss Panel (GeneDx)	81430, 81431

Policy Statement

Hereditary Hearing Loss

Known Familial Variant Analysis for Hereditary Hearing Loss

I. Targeted variant analysis for a known familial variant(s) to establish a diagnosis of hereditary hearing loss (81253, 81403) may be considered **medically necessary** when:
   A. The member has a close relative with pathogenic or likely pathogenic variant(s) in *GJB2*, *GJB6*, or another gene known to cause hereditary hearing loss.

II. Targeted variant analysis for a known familial variant (81253, 81403) for hereditary hearing loss is considered **investigational** for all other indications.

***GJB2* and *GJB6* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel Analysis**

III. *GJB2* sequencing and/or deletion/duplication (81252, 81479) and/or *GJB6* sequencing and/or deletion/duplication analysis (81254, 81479) or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss may be considered **medically necessary** when **both** of the following are met:
   A. The member has hearing loss
   B. There is no known acquired cause of the hearing loss (i.e., TORCH infections [Toxoplasma gondii, other agents, rubella, cytomegalovirus, and herpes simplex virus], bacterial infection, age-related or noise-related hearing loss).

IV. *GJB2* sequencing and/or deletion/duplication (81252, 81479) and/or *GJB6* sequencing and/or deletion/duplication analysis (81254, 81479) or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss is considered **investigational** for all other indications.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Notes And Definitions

1. Close relatives include first, second, and third degree **blood** relatives:
   a. **First-degree relatives** are parents, siblings, and children
   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

Clinical Considerations

If there is not a 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 other 50% of patients with apparent autosomal recessive hereditary hearing loss, numerous other genes are implicated. There is no single identifiable gene responsible for most cases of autosomal dominant hereditary hearing loss.

If there is suspicion for autosomal recessive congenital hearing loss, it would be reasonable to begin with testing of *GJB2* and *GJB6* and if testing is negative, screening for the other genes associated with hearing loss with a multigene panel would be efficient. An alternative strategy for suspected autosomal recessive or autosomal dominant hearing loss would be to obtain a multigene panel that includes GJB2 and GJB6 as a first step.

Given the extreme heterogeneity in genetic causes of hearing loss, these 2 strategies may be considered reasonably equivalent.

Description

Hereditary hearing loss can be classified as syndromic or nonsyndromic. 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.

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.

Related Policies

This policy document provides coverage criteria for genetic testing for hereditary hearing loss. Please refer to:

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to carrier screening for hereditary hearing loss.

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems ***(to be published)***
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to genetic testing for hearing loss that is not specifically discussed in this or another non-general policy.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

- N/A

Rationale

Known Familial Variant Analysis for Hereditary Hearing Loss

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on genetic testing says the following about testing for familial pathogenic variants:
Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

GJB2 and *GJB6* Sequencing and/or Deletion Duplication Analysis or Multigene Panel Analysis

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (ACMG) published guidelines in 2022 to guide genetics evaluation for individuals with hearing loss: "For individuals lacking physical findings suggestive of a known syndrome, a tiered diagnostic approach should be implemented. Unless clinical and/or family history suggests a specific genetic etiology, comprehensive HL gene panel testing should be initiated." (p. 9)

The guidelines also state the following: "Although nonsyndromic HL [hearing loss] demonstrates high genetic heterogeneity, 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 HL and 15% to 40% of all deaf individuals in a variety of populations." (p. 3)

GeneReviews: Hereditary Hearing Loss and Deafness Overview
GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. In the section that discusses possible differential diagnosis for hereditary hearing loss and deafness, it states:
In developed countries approximately 80% of prelingual hearing loss is due to genetic causes, with 70% of prelingual genetic hearing loss being nonsyndromic. The remainder of cases are due to environmental (acquired) causes, which should be differentiated from genetic causes to inform the evaluation and required ancillary testing. Acquired hearing loss in children commonly results from prenatal infections from 'TORCH' organisms...or postnatal infections (such as CMV). Acquired hearing loss in adults is most often attributed to environmental factors.

GeneReviews also states that molecular genetic testing includes the use of multigene hearing loss panels and/or genomic testing. Single-gene testing (sequence analysis of a given gene, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

References

1. 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.
2. Shearer AE, Hildebrand MS, Smith RJH. Hereditary Hearing Loss and Deafness Overview. 1999 Feb 14 [Updated 2023 April 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1434/
3. Genetic Support Foundation. Genetics 101 Genetic Testing: Familial Pathogenic Variant. Accessed 10/4/2022. https://geneticsupportfoundation.org/genetics-101/#

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants
	81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81430	Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
	81431	Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2024	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**Genetic Testing: Hearing Loss BSC_CON_2.16** **Policy Statement:** **Hereditary Hearing Loss** **Known Familial Variant Analysis for Hereditary Hearing Loss** I. Targeted variant analysis for a known familial variant(s) to establish a diagnosis of hereditary hearing loss (81253, 81403) may be considered **medically necessary** when: A. The member has a close relative with pathogenic or likely pathogenic variant(s) in *GJB2*, *GJB6*, or another gene known to cause hereditary hearing loss. II. Targeted variant analysis for a known familial variant (81253, 81403) for hereditary hearing loss is considered **investigational** for all other indications. ***GJB2* and *GJB6* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel Analysis** III. *GJB2* sequencing and/or deletion/duplication (81252, 81479) and/or *GJB6* sequencing and/or deletion/duplication analysis (81254, 81479) or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss may be considered **medically necessary** when **both** of the following are met: A. The member has hearing loss B. There is no known acquired cause of the hearing loss (i.e., TORCH infections [Toxoplasma gondii, other agents, rubella, cytomegalovirus, and herpes simplex virus], bacterial infection, age-related or noise-related hearing loss). IV. *GJB2* sequencing and/or deletion/duplication (81252, 81479) and/or *GJB6* sequencing and/or deletion/duplication analysis (81254, 81479) or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss is considered **investigational** for all other indications.