CONCERT GENETIC TESTING: HEARING LOSS

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Date of Last Revision 12/23

Coding implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

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.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis.

Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Hereditary Hearing Loss				
Known Familial Variant Analysis for Hereditary Hearing Loss	*GJB2* Targeted Mutation Analysis	81253*	H90-H90.8, H90.A-90.A3, H91.3- H91.93	3
	GJB6 Targeted Mutation Analysis	81403*		
GJB2 and *GJB6* Sequencing and/or Deletion/ Duplication Analysis or Multigene Panel Analysis	*GJB2* Gene Sequencing (GeneDx)	81252*		1, 2
	GJB2 Deletion/Duplication Analysis (GeneDx)	81479		
	GJB6 Common Variant Analysis	81254*		
	GJB6 Sequencing Analysis	81479		
	Hearing Loss Panel (GeneDx)	81430*, 81431*		
	Comprehensive Hearing Loss NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)			
	Hearing Loss and Deafness - Comprehensive (PreventionGenetics, part of Exact Sciences)			

OTHER RELATED POLICIES

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

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to carrier screening for hereditary hearing loss.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to genetic disorders that affect multiple organ systems

- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to genetic testing for hearing loss that is not specifically discussed in this or another non-general policy.

CRITERIA

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*) is considered **medically necessary** when:

   A. The member/enrollee has a close relative with pathogenic or likely pathogenic variant(s) in *GJB2*, *GJB6*, or another gene known to cause hereditary hearing loss.

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

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

I. *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 **medically necessary** when:

   A. The member/enrollee has hearing loss, **AND**

   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).

II. *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.

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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

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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.

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BACKGROUND AND 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.

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	09/23	11/27/23
Semi-annual review. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table: changed "Sequencing Analysis" to "Gene Sequencing"; added "GeneDx" to "GJB2 Deletion/Duplication Analysis; added "part of Exact Sciences" to "Hearing Loss and Deafness…". For Other Related Policies: added "and Molecular" to "Genetic Testing: General Approach…". For Hereditary Hearing Loss I.A. added "Targeted variant analysis for a known…". For Background and Rationale: replaced "inheritance patterns" to "genetic testing". For GJB2 and GJB6 Sequencing and/or Deletion Duplication Analysis or Multigene Panel Analysis: replaced "congenital" with "prelingual"; replaced "and the remainder" with "with 70% of prelingual…"; removed "Acquired cases"; added "which"; added statement "GeneReviews also states…".	12/23	2/27/24

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/#

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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