GENETIC TESTING: HEARING LOSS

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

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Hereditary Hearing Loss				
Known Familial Variant Analysis	GJB2 Targeted Mutation Analysis	81253	H90.0-H90.8, H91.8X1-H91.8X9	1, 2, 3
	GJB6 Targeted Mutation Analysis	81403		

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GJB2 and GJB6 Sequencing and/or Deletion Duplication Analysis or Multigene Panel Analysis	GJB2 Sequencing Analysis	81252, S3844		
	GBJ6 Targeted Mutation Analysis; Common Variants	81254		
	GJB6 Sequencing Analysis	81479		
	Hearing Loss Panel (GeneDX) PGXome Custom - Hereditary Hearing Loss and Deafness - Comprehensive (PreventionGenetics) Comprehensive Hearing Loss NGS Panel + mtDNA (LabCorp) Comprehensive Hearing Loss NGS Panel (Sequencing & Deletion/Duplication) (Fulgent)	81430, 81431		

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

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COVERAGE CRITERIA

HEREDITARY HEARING LOSS

Known Familial Variant Analysis

I. Targeted variant analysis for known familial variant(s) to establish a diagnosis of hereditary hearing loss (81253, 81403) is 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.

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

I. *GJB2* (81252, S3844) and/or *GJB6* (81254, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss is considered **medically necessary** when:

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

   B. There is no known acquired cause of the hearing loss (e.g., TORCH, bacterial infection, age-related or noise-related hearing loss).

II. *GJB2* (81252, S3844) and/or *GJB6* (81254, 81479) sequencing and/or deletion/duplication analysis 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

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (2014) issued practice guidelines for the clinical evaluation and etiologic diagnosis of hearing loss which stated, that 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 pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing should be ordered.

American Academy of Pediatrics

The American Academy of Pediatrics (2007) issued recommendations on early hearing detection which stated that infants with confirmed hearing loss and/or middle ear dysfunction should be referred for otologic and other medical evaluation to determine the etiology of hearing loss.

In regard to recommended components of the evaluation and test, the AAP states, "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."

The recommendations also stated, "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."

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REFERENCES

1. 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*. 2014;16(4):347-355. doi:10.1038/gim.2014.2
2. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. Pediatrics. 2007;120(4):898-921. doi:10.1542/peds.2007-2333
3. Shearer AE, Hildebrand MS, Smith RJH. Hereditary Hearing Loss and Deafness Overview. 1999 Feb 14 [Updated 2017 Jul 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1434/

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