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Genetic Testing for Hereditary Hearing Loss

Policy Number: AHS - G2148 – Genetic Testing for Hereditary Hearing Loss	Prior Policy Name and Number, as applicable: • AHS-G2148 Genetic Testing for Nonsyndromic Hereditary Hearing Loss
Initial Presentation Date: 4/26/2017 Revision Date: 06/02/2021	

I. Policy Description

Hearing loss is among the most etiologically heterogeneous disorders. More than 400 genetic syndromes include hearing loss as a feature; additionally, more than 100 genes are associated with nonsyndromic genetic hearing loss, and a number of non-genetic causes can also result in hearing loss. Genes associated with syndromic and nonsyndromic genetic hearing loss encode a variety of proteins involved in the development and function of the auditory system, including transcription factors, structural proteins, gap junction proteins, and ion channels (Alford et al., 2014). The genes may be associated with an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern (A Eliot Shearer, 2017).

II. Related Policies

Policy Number	Policy Title
AHS-M2145	General Genetic Testing, Germline Disorders
AHS-M2146	General Genetic Testing, Somatic Disorders

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx or the manual website

1. Genetic counseling **MEETS COVERAGE CRITERIA** and is recommended in patients considered for genetic testing for nonsyndromic hereditary hearing loss.

2. Genetic testing for the two most common mutations for nonsyndromic hereditary hearing loss (gap junction protein beta 2 (*GJB2*) and gap junction protein beta 6 (*GJB6*))**MEETS COVERAGE CRITERIA** in individuals to confirm the diagnosis of

hereditary hearing loss where other causes of nonsyndromic acquired hearing loss (infection, injury, age-related) have been excluded.

3. Genetic testing using gene panel tests or next-generation sequencing (NGS) technologies for additional hereditary hearing loss-related mutations **MEETS COVERAGE CRITERIA** if ALL of the following are met:

    a. ONLY AFTER initial testing for common mutations (*GJB2* and *GJB6*) is negative

    b. Syndrome is not suspected based on individual's clinical presentation

4. Genetic testing **MEETS COVERAGE CRITERIA** for individuals with a known familial mutation variant.

5. Genetic testing using gene panel tests or NGS technologies for suspected syndromic hearing loss **MEETS COVERAGE CRITERIA.**

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

6. Genetic testing for hereditary hearing loss-related mutations **DOES NOT MEET COVERAGE CRITERIA**

    a. If more than once per lifetime

    b. For all other situations, including, but not limited to, testing in individuals without hearing loss

Note: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

IV. Scientific Background

Approximately one in every 500 children born in the United States is deaf or has a hearing loss significant enough to affect speech and language development. Ninety-five percent of newborns with hearing loss identified by newborn hearing screening programs are born to hearing parents, obscuring the fact that the majority of newborns have a hereditary cause for their hearing loss (Alford et al., 2014). Approximately 80 percent of cases of hereditary hearing loss are inherited in an autosomal recessive pattern, 19 percent are autosomal dominant, and the remaining cases X-linked (mainly recessive) or mitochondrial (A Eliot Shearer, 2017).

Hearing loss is typically described in terms related to its clinical presentation. In general, it is categorized as either syndromic or nonsyndromic. Syndromic hearing loss is associated with other medical or physical findings, including malformations of the external ear or other organs, or with medical problems involving other organ systems. An estimated 30% of hereditary hearing loss is syndromic. Nonsyndromic hearing loss (NSHL) is defined as hearing loss that is not associated with visible abnormalities of the external ear or any related medical problems. For NSHL, it is more difficult

to determine whether the etiology is hereditary or acquired because there are no other clinical manifestations at the time of the hearing loss presentation. NSHL accounts for an estimated 70% of genetically determined hearing loss (Angeli, Lin, & Liu, 2012), and it is frequently congenital and sensorineural (Sloan-Heggen et al., 2016).

The genetic loci on which mutations associated with nonsyndromic hereditary hearing loss are usually found are termed DFN. 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 (A Eliot Shearer, 2017). 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 hearing loss and 15–40% of all deaf individuals in a variety of populations (Alford et al., 2014).

GJB2 is a small gene with a single coding exon, which codes for the Cx26 connexin protein (OMIM, 2016). At least 83 deafness-causing variants have been identified in *GJB2*, but a few common mutations account for a large percentage of alleles in several populations. Probands with this mutation generally have congenital hearing loss (A Eliot Shearer, 2017). Mutations in the *GJB6* gene lead to similar effects on abnormal expression of connexin protein Cx30 (OMIM, 2014). *GJB6* deletions have been observed in multiple populations, although they appear to be a relatively uncommon explanation for hearing loss in the United States (Alford et al., 2014).

In addition to mutations in the *GJB6* and *GJB2* genes, many less common pathologic mutations are found in other genes. Some of these are: *ACTG1, BSND, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, ESRRB, EYA4, GRXCR1, HGF, KCNQ4, LHFPL5, MARVELD2, MT-TS1, MYO15A, MYO6, MYO7A, OTOA, OTOF, PCDH15, POU3F4, PTPRQ, RDX, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, WFS1*, and *WHRN* genes (A Eliot Shearer, 2017). Several gene panels exist for assessment of hereditary hearing loss. For example, Shang et al evaluated the "MiamiOtoGenes" panel, which consists of 180 genes. The investigators examined 5 unrelated probands with varying degrees of hearing loss onset and severity and found 7 different genetic variants (Shang et al., 2018). Other entities offering proprietary genetic panels include BluePrint (239 genes), GeneDx (146 genes), OtoSCOPE by the University of Iowa (152 genes), The Comprehensive Hearing Loss Panel by Sema4 (92 genes), Otogenetics Gx (167 genes), OtoGenome™ Test (84 genes), Hearing Loss Advanced Sequencing and CNV Evaluation by Athena Diagnostics (183 genes), Invitae Comprehensive Deaf Panel (203 genes), and AudioloGene Hereditary Hearing Loss Panel by Mayo Clinic Laboratories (160 genes) (BluePrint, 2021; GeneDx, 2018; Invitae, 2021; Iowa, 2020; Mayo_Clinic, 2021; Otogenetics, 2021; Partners_Healthcare, 2021; Sema4, 2021).

Clinical Validity and Utility

Shearer et al performed a meta-analysis focusing on the current genetic tests used to evaluate hearing loss. 20 studies were included, containing 426 controls and 603 patients with idiopathic hearing loss. Several genetic panels such as OtoGenetics Deafness Test and OtoGenome were used. Overall, the controls showed good sensitivity and specificity (over 99%), and the diagnostic rate was found to be 41% (with a range of 10%-83%). The authors concluded that "comprehensive genetic testing should form the cornerstone of a tiered approach to clinical evaluation of patients with hearing loss along with history, physical exam, and audiometry and can determine further testing that may be required, if any (Shearer & Smith, 2015)."

Sloan-Heggen et al performed parallel sequencing on 1119 “sequentially accrued” patients. 440 (39%) of these patients were found to have a genetic etiology for hearing loss. Pathogenic variants were found in 49 genes, and various alterations such as missense variants (49% of the alterations), copy number variants (18%), insertions or deletions (13%), and nonsense variants (8%) were found. The authors noted the wide variety of the genetic spectrum of hearing loss (Sloan-Heggen et al., 2016).

D’Aguillo et al examined the role of genetic screening as an adjunct to universal newborn hearing screening. The authors evaluated 16 studies and identified the rate of children that passed the universal newborn hearing screening but who also tested positive on a genetic screening. Of the 137895 infants included in the studies, pathogenic mutations were detected in 8.66% of them. Of this cohort, 545 infants passed the universal screening, but also tested positive on a genetic screening (1.4%) (D'Aguillo et al., 2019).

(Costales et al., 2020) studied the application of Otogenetics, a Next Generation Sequencing panel, in 27 patients diagnosed with sensorineural hearing loss (SNL) within a childhood hearing loss unit. A genetic diagnosis of SNL was made in 56% (15/27) of the patients whereas 44% (12/27) had pathogenic variants in genes associated with isolated SNL, syndromic SNL, and non-syndromic SNL. According to the authors, this study demonstrated that "it is possible to implement genetic diagnosis in the daily routine (Costales et al., 2020)."

(Yang et al., 2021) developed a multiplex PCR sequencing assay to sequence the *GJB2*, *SLC26A4*, and *MT-RNR1* genes and demonstrated that genetic screening can play an important role in newborn hearing screening. To validate the assay, 103 samples with known genotypes were analyzed using the multiplex PCR, which accurately identified all the variants with a 100% sensitivity and specificity. In the pilot study, 300 samples were analyzed and 12.3% were found to carry at least one pathogenic variant in the *GJB2, SLC26A4*, and *MT-RNR1* genes. The study also revealed that pathogenic variants in the *GJB2* gene had an 8% carrier rate in the newborn population. The authors concluded that "the assay is an accurate and reliable test and can be used to screen genetic hearing loss in newborns (Yang et al., 2021)."

V. Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG) (ACMG, 2018)

In 2014, the ACMG issued the following guidelines for the clinical evaluation and diagnosis of hearing loss. For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories that do not suggest an environmental cause of hearing loss, ACMG recommends that a tiered diagnostic approach should be implemented.

- “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 technologies such as large sequencing panels targeted toward hearing loss–related genes, WES, or WGS 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. It should be noted that the cost of these new genetic sequencing technologies is decreasing so rapidly that a tiered approach to testing may soon no longer be cost effective. In particular, for large sequencing panels targeted toward hearing loss– related genes, it may, in some cases, already be more cost effective to use NGS technologies as the initial test in the evaluation of hearing loss. However, issues related to genomic testing, such as the likelihood of incidental findings, will have to be addressed."
- "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."
- "If genetic testing fails to identify an etiology for a patient's hearing loss, the possibility of a genetic or acquired etiology remains. This point must be emphasized because it can be misunderstood by clinicians and by patients and their families. For interested patients and families, further genetic testing may be pursued on a research basis."
- "CMV testing should be done at the same time as genetic testing for infants with congenital hearing loss. For later-onset or progressive hearing loss, CMV testing can be obtained, but the likelihood that a positive test is due to postnatal exposure increases with age".

For individuals with findings that suggest a syndromic genetic etiology for their hearing loss:

- "Pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing, if available, should be ordered to confirm the diagnosis—this testing may include single-gene tests, hearing loss sequencing panels, WES, WGS, chromosome analysis, or microarray-based copy-number analysis, depending on clinical findings"
- "Appropriate studies should be undertaken to determine whether other organs are involved; and
- "Appropriate near-term and long-term screening and management should be arranged, including referrals to specialists, as indicated by the associated manifestations of the particular syndrome" (Alford et al., 2014).

The ACMG also published an algorithm stating to "consider" *GJB2*, *GJB6* or other gene specific testing if familial or nonsyndromic hearing loss was suspected. If nonsyndromic and mitochondrial inheritance was suspected, the ACMG recommended testing for the A1555G mutation (ACMG, 2018).

Joint Commission on Infant Hearing (JCIH) (JCIH, 2007, 2019)

In 2007, the JCIH recommended that evaluation of infants with confirmed hearing loss 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 (JCIH, 2007). In 2013, a supplement by the ASHA was added to the JCIH. The 2013 supplement also stated that medical providers must "understand atypical

development etiologies and diagnoses, and refer for medical-genetic evaluation" and that families must be educated on the "importance of medical, genetic, ophthalmologic, and cardiac (EKG) evaluations on children with any type and degree of hearing loss" (ASHA, 2013).

In 2019, the JCIH published an updated position statement. They note that the American College of Medical Genetics and Genomics recommends offering genetic counseling and testing to all infants who are deaf or hard of hearing and their families. A geneticist's evaluation should include "a review of family history of specific genetic disorders or syndromes, genetic testing for gene mutations such as *GJB2* (connexin-26), and syndromes commonly associated with early-onset hearing loss" (JCIH, 2019).

The **American Academy of Otolaryngology-Head and Neck Surgery** has adopted the 2007 position statement of the Joint Committee on Infant Hearing (AAO, 2014).

International Pediatric Otolaryngology Group (IPOG) (Liming et al., 2016)

In 2016, the IPOG released their guidelines on hearing loss in the pediatric patient. Concerning which children should be offered comprehensive genetic testing they recommend the following:

- "Nonsyndromic children with unilateral hearing loss should not be offered genetic testing as part of initial workup."
- "Comprehensive genetic testing is not universally available."
- "A negative test does not rule out a genetic cause."
- "Comprehensive genetic testing should be offered to children with bilateral ANSD, or unilateral ANSD if imaging for cochlear nerve dysplasia is negative and no obvious acquired cause exists."
- "After an audiogram, comprehensive genetic testing has the highest diagnostic yield of any single test for bilateral sensorineural hearing loss."

In addressing the question "Should single gene or directed genetic testing be used?", they make the following consensus recommendation statements:

- "In the setting of comprehensive genetic testing, single gene testing is of low diagnostic yield and should not be offered as part of an initial workup unless a known family history exists."
- "Directed genetic testing for *GJB2*/*GJB6* should be considered if comprehensive genetic testing is unavailable."
- "Directed genetic testing may be considered in consultation with a geneticist if comprehensive genetic testing is negative but suspicion for a genetic cause still exists (Liming et al., 2016)."

American Academy of Pediatrics (AAP)

The AAP also recommends genetic testing for evaluation of hearing loss. Testing protocol typically tests *GJB2*/*6* first, then applies targeted next generation sequencing of gene panels for recessive, dominant, x-linked patterns or syndromic hearing loss (AAP). AAP also notes that It is important to note that genetic testing "cannot identify 100% of genetic hearing loss; negative genetic testing does not rule out a genetic form of hearing loss (AAP)."

VI. State and Federal Regulations, as applicable

A. FDA

A search for "hearing loss" on the FDA website on March 29, 2021 did not yield any genetic results (FDA, 2021). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

B. CMS

N/A

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
81252	*GJB2* (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	*GJB2* (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	*GJB6* (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(*GJB6*-D13S1830)] and 232kb [del(*GJB6*-D13S1854)])
81430	Hearing loss (eg, 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 (eg, 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
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

A Eliot Shearer, M. S. H., and Richard JH Smith. (2017). Hereditary Hearing Loss and Deafness Overview. In.

AAO. (2014). Position Statement: Infant Hearing. Retrieved from https://www.entnet.org/content/infant-hearing

AAP. Genetics Testing and Early Childhood Hearing Loss – Why is it medically necessary? . Retrieved from https://www.aap.org/en-us/Documents/ehdi/ehdi_geneticshl.pdf

ACMG. (2018). Hearing Loss Retrieved from https://www.acmg.net/PDFLibrary/Hearing-Loss-Algorithm.pdf

Alford, R. L., Arnos, K. S., Fox, M., Lin, J. W., Palmer, C. G., Pandya, A., . . . Yoshinaga-Itano, C. (2014). American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. *Genet Med, 16*(4), 347-355. doi:10.1038/gim.2014.2

Angeli, S., Lin, X., & Liu, X. Z. (2012). Genetics of hearing and deafness. *Anat Rec (Hoboken), 295*(11), 1812-1829. doi:10.1002/ar.22579

ASHA. (2013). Supplement to the JCIH 2007 position statement: principles and guidelines for early intervention following confirmation that a child is deaf or hard of hearing [Position Statement]. Retrieved from https://www.asha.org/policy/ps2013-00339/

BluePrint. (2021). Comprehensive Hearing Loss and Deafness Panel. Retrieved from https://blueprintgenetics.com/tests/panels/ear-nose-throat/comprehensive-hearing-loss-and-deafness-panel/

Costales, M., Diñeiro, M., Cifuentes, G. Á., Capín, R., Otero, A., Viejo-Díaz, M., . . . Cabanillas, R. (2020). Clinical Utility of Next-generation Sequencing in the Aetiological Diagnosis of Sensorineural Hearing Loss in a Childhood Hearing Loss Unit. *Acta Otorrinolaringologica (English Edition), 71*(3), 166-174. doi:https://doi.org/10.1016/j.otoeng.2019.05.005

D'Aguillo, C., Bressler, S., Yan, D., Mittal, R. A.-O. X., Fifer, R., Blanton, S. H., & Liu, X. (2019). Genetic screening as an adjunct to universal newborn hearing screening: literature review and implications for non-congenital pre-lingual hearing loss. (1708-8186 (Electronic)).

FDA. (2021). Devices@FDA. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm

GeneDx. (2018). Hearing Loss Panel. Retrieved from https://www.genedx.com/test-catalog/available-tests/hearing-loss-test/

Invitae. (2021). Invitae Comprehensive Deafness Panel. Retrieved from https://www.invitae.com/en/physician/tests/55009/#info-panel-assay_information

Iowa, U. o. (2020). OtoSCOPE Genetic Testing. Retrieved from https://morl.lab.uiowa.edu/clinical-diagnostics/deafness-otoscope/otoscope-genetic-testing

JCIH. (2007). Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs. *Pediatrics, 120*(4), 898. doi:10.1542/peds.2007-2333

JCIH. (2019). Year 2019 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs. *Journal of Early Hearing Detection and Intervention, 4*(2), 1-44. doi:https://doi.org/10.15142/fptk-b748

Liming, B. J., Carter, J., Cheng, A., Choo, D., Curotta, J., Carvalho, D., . . . Smith, R. J. (2016). International Pediatric Otolaryngology Group (IPOG) consensus recommendations: Hearing loss in the pediatric patient. *Int J Pediatr Otorhinolaryngol, 90*, 251-258. doi:10.1016/j.ijporl.2016.09.016

Mayo_Clinic. (2021). AudioloGene Hereditary Hearing Loss Panel. Retrieved from https://www.mayocliniclabs.com/test-catalog/Overview/606144

OMIM. (2014). GAP JUNCTION PROTEIN, BETA-6; GJB6. Retrieved from https://www.omim.org/entry/604418

OMIM. (2016). GAP JUNCTION PROTEIN, BETA-2; GJB2. Retrieved from https://www.omim.org/entry/121011

Otogenetics. (2021). Hearing Loss & Molecular Screening of Congenital Hearing Loss. Retrieved from https://www.otogenetics.com/products/clinical-genetic-testing/hearing-loss/

Partners_Healthcare. (2021). OtoGenome™ Test for Hearing Loss and Related Syndromes (110 Genes) Details. Retrieved from https://personalizedmedicine.partners.org/Laboratory-For-Molecular-Medicine/Tests/Hearing-Loss/OtoGenome.aspx

Sema4. (2021). Comprehensive Hearing Loss Panel. Retrieved from https://sema4.com/products/test-catalog/comprehensive-hearing-loss-panel/

Shang, H., Yan, D., Tayebi, N., Saeidi, K., Sahebalzamani, A., Feng, Y., . . . Liu, X. (2018). Targeted Next-Generation Sequencing of a Deafness Gene Panel (MiamiOtoGenes) Analysis in Families Unsuitable for Linkage Analysis. *Biomed Res Int, 2018*, 3103986. doi:10.1155/2018/3103986

Shearer, A. E., & Smith, R. J. (2015). Massively Parallel Sequencing for Genetic Diagnosis of Hearing Loss: The New Standard of Care. *Otolaryngol Head Neck Surg, 153*(2), 175-182. doi:10.1177/0194599815591156

Sloan-Heggen, C. M., Bierer, A. O., Shearer, A. E., Kolbe, D. L., Nishimura, C. J., Frees, K. L., . . . Smith, R. J. (2016). Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. *Hum Genet, 135*(4), 441-450. doi:10.1007/s00439-016-1648-8

Yang, H., Luo, H., Zhang, G., Zhang, J., Peng, Z., & Xiang, J. (2021). A multiplex PCR amplicon sequencing assay to screen genetic hearing loss variants in newborns. *BMC Medical Genomics, 14*(1), 61. doi:10.1186/s12920-021-00906-1