Sentara Health Plans

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
Policy Revision Date: 12/01/2024 Initial Policy Effective Date: 12/01/2024	

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 several 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 channel (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). Genetic counseling is strongly recommended for individuals pursuing genetic testing for nonsyndromic hereditary hearing loss.

For guidance on prenatal screening and preconception screening for hereditary hearing loss, please see AHS-M2179-Prenatal Screening (Genetic).

II. Related Policies

Policy Number	Policy Title
AHS-M2179	Prenatal Screening Genetic

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. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals who are in a family with a deleterious familial hearing loss gene mutation, the following genetic testing **MEETS COVERAGE CRITERIA**:
   a) Testing restricted to the known familial mutation.
   b) Comprehensive genetic testing using multi-gene panel testing when the specific familial mutation is unknown.

2) For individuals diagnosed with hearing loss (when hearing loss due to nonhereditary causes [e.g., infection, injury, age-related] has been excluded), multi-gene panel testing (panel must include *GJB2* and *GJB6*) **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 an individual's illness.

3) Genetic testing for hereditary hearing loss-related mutations more than once per lifetime **DOES NOT MEET COVERAGE CRITERIA**.

4) For all other situations not described above, genetic testing for hearing loss **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

IV. Table of Terminology

Term	Definition
AAO	American Academy of Otolaryngology
AAP	American Academy of Pediatrics
ACMG	American College of Medical Genetics and Genomics
ACTG1	*Actin gamma 1*
ANSD	Auditory neuropathy spectrum disorder
ASHA	American Speech-Language-Hearing Association
BSND	*Barttin CLCNK type accessory subunit beta*
CDH23	*Cadherin related 23*
CLDN14	*Claudin 14*
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CLRN1	*Clarin 1*
CMS	Centers For Medicare and Medicaid
CMV	Cytomegalovirus

CNV	Contingent negative variation
COCH	*Cochlin*
COL11A2	*Collagen type Xl alpha 2 chain*
DFN	Different gene loci for nonsyndromic deafness
DFNA	Autosomal dominant inherited deafness
DFNA5	*Nonsyndromic hearing impairment protein 5*
DFNB	Autosomal recessive inherited deafness
DFNB1	*Nonsyndromic hearing loss and deafness*
DFNB31	*Deafness autosomal recessive 31 - Whirlin*
DFNB59	*Deafness autosomal recessive 59*
DFNX	X-linked Inheritance
DNA	*Deoxyribonucleic acid*
EKG	Electrocardiogram
ESPN	*Espin*
ESRRB	*Estrogen related receptor beta*
EYA4	*Transcriptional coactivator and phosphatase 4*
FDA	Food And Drug Administration
GJB2	Gap junction protein, beta 2
GJB6	Gap junction protein, beta 6
GPR98	*G-protein coupled receptor 98*
GRXCR1	*Glutaredoxin and cysteine rich domain containing 1*
HGF	*Hepatocyte growth factor*
IPOG	International Pediatric Otolaryngology Group
JCIH	Joint Commission on Infant Hearing
KCNQ4	*Potassium voltage-gated channel subfamily Q member 4*
LDTs	Laboratory-developed tests
LHFPL5	*LHFPL tetraspan subfamily member 5*
MARVELD2	*MARVEL domain containing 2*
MT-RNR1	*Mitochondrially encoded 12S ribosomal ribonucleic acid*
MT-TS1	*Mitochondrially encoded transfer ribonucleic acid-SER*
MYO15A	*Myosin XVA*
MYO6	*Myosin VI*
MYO7A	*Myosin VIIA*
NGS	Next-generation sequencing
NSHL	Nonsyndromic hearing loss
OMIM	Online Mendelian Inheritance in Man
OTOA	*Otoancorin*
OTOF	*Otoferlin*
PCDH15	*Protocadherin related 15*
PCR	Polymerase chain reaction

POU3F4	*POU class 3 homeobox 4*
PTPRQ	*Protein tyrosine phosphatase receptor type Q*
RDX	*Radixin*
SLC26A4	*Solute carrier family 26 member 4*
SNL	Sensorineural hearing loss
STRC	*Stereocilin*
TECTA	*Tectorin alpha*
TMC1	*Transmembrane channel like 1*
TMIE	*Transmembrane inner ear*
TMPRSS3	*Transmembrane serine protease 3*
TRIOBP	*TRIO and F-actin binding protein*
USH1C	*Usher syndrome type 1 protein component harmonin*
WES	Whole exome sequencing
WFS1	*Wolframin ER transmembrane glycoprotein*
WGS	Whole genome sequencing
WHRN	*Whirlin*

V. 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 most 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 et al., 2012), and it is frequently congenital and sensorineural (Sloan-Heggen et al., 2016).

The genetic loci where mutations associated with nonsyndromic hereditary hearing loss are commonly 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 five unrelated probands with varying degrees of hearing loss onset and severity and found seven 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), 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, 2023; GeneDx, 2024; Invitae, 2024; Iowa, 2020; Mayo Clinic, 2024; Otogenetics, 2021; Partners Healthcare, 2021).

Clinical Utility and Validity

Shearer and Smith (2015) performed a meta-analysis focusing on the current genetic tests used to evaluate hearing loss. A total of 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. (2016) performed parallel sequencing on 1119 "sequentially accrued" patients. A total of 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. (2019) 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).

Liao et al. (2022) put together a retrospective cohort study of 2075 patients who were seen at the Children's Communications Clinic; 517 patients completed a hearing loss testing with a GeneDx panel. Researchers gathered sociodemographic characteristics, hearing loss characteristics, and medical variables of hearing loss. On univariable analysis, those who received a genetic diagnosis were younger than those who did not receive a genetic diagnosis (OR, 0.92; 95% CI, 0.88-0.96). Twenty-four diagnostic genes were found in the study cohort, the most common diagnostic gene being *GJB2*, which encodes for connexin 26, a major protein found in gap junction protein in the cochlea. Additionally, the most prevalent diagnostic variant was different across races and ethnicities, that is, Asian patients were more likely to have the C.109 G>A variant and white patients were more likely to have the C.35del, and Hispanic patients were "almost equally" likely to have the c.35del variant as any other variant (aside from c.109 G>A) (Liao et al., 2022).

VI. Guidelines and Recommendations

The American College of Medical Genetics and Genomics (ACMG)

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).

In 2021, ACMG released an updated guideline for screening for autosomal recessive and X-linked conditions during pregnancy and preconception. Their practice resource aims to recommend "a consistent and equitable approach for offering carrier screening to all individuals during pregnancy and preconception" and replaces any earlier ACMG position statements on prenatal/preconception expanded carrier screening and provide the following recommendations:

- "Carrier screening enables those screened to consider their reproductive risks, reproductive options, and to make informed decisions."
- "The phrase "expanded carrier screening" be replaced by "carrier screening"."
- "Adopting a more precise tiered system based on carrier frequency:
  - Tier 4: <1/200 carrier frequency (includes Tier 3) genes/condition will vary by lab
  - Tier 3: ≥ 1/200 carrier frequency (includes Tier 2) includes X-linked conditions
  - Tier 2: ≥1/100 carrier frequency (includes Tier 1)
  - Tier 1: *CF* [Cystic Fibrosis] + *SMA* [spinal muscular atrophy] + Risk Based Screening
    - "Tier 1 screening conveys the recommendations previously adopted by ACMG and ACOG" and "adopts an ethnic and population neutral approach when screening for cystic fibrosis and spinal muscular atrophy. Beyond these two conditions, additional carrier screening is determined after risk assessment, which incorporates personal medical and family history as well as laboratory and imaging information where appropriate"
    - "Tier 2 carrier screening stems from an ACOG recommendation for conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100." However, "data demonstrate that carrier screening for two common conditions using a carrier frequency threshold of 1/100 may not be equitable across diverse populations. Others have shown that limiting the carrier frequency to ≥1/100 creates missed opportunities to identify couples at risk for serious conditions."
    - "We define Tier 3 screening as carrier screening for conditions with a carrier frequency ≥1/200 . . . Tier 2 and Tier 3 screening prioritize carrier frequency as a way to think about conditions most appropriate for screening in the general population. However, when ACOG proposed this level, they did not specify whether it was thinking about carrier frequency in terms of the global population or subpopulations. We use "carrier frequency" to mean in any ethnic group with reasonable representation in the United States."
    - "Tier 4 includes genes less common than those in Tier 3 and can identify additional at-risk couples. Tier 4 has no lower limit carrier screening frequency and can

> greatly extend the number of conditions screened . . . the clinical validity at this level of carrier screening may be less compelling, therefore we suggest reserving this level of screening for consanguineous pregnancies (second cousins or closer) and in couples where family or medical history suggests Tier 4 screening might be beneficial . . . Importantly, patients should understand that their chance of being a carrier for one or more conditions increases as the number of conditions screened is increased."

- "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening.
- Tier 4 screening should be considered:
  - When a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer);
  - When a family or personal medical history warrants.
- ACMG does NOT recommend:
  - Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups.
  - Routine offering of Tier 4 panels.
- "Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion."
- "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive [Table 1] . . . conditions."
- "Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions [Table 1] when carrier screening is performed simultaneously with their partner."
- "When Tier 1 or Tier 2 carrier screening was performed in a prior pregnancy, Tier 3 screening should be offered" (Gregg et al., 2021).

Table 1. Autosomal recessive genes for screening with carrier frequency ≥1/50.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
141900	*HBB*	0.119837	603903	Sickle cell anemia β-thalassemia
			613985	
613208	*XPC*	0.050885	278720	Xeroderma pigmentosum
606933	*TYR*	0.049337	203100	Oculocutaneous albinism type 1A and 1B
			606952	
613815	*CYP21A2*	0.048459	201910	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency
612349	*PAH*	0.046068	261600	Phenylketonuria
602421	*CFTR*	0.040972	219700	Cystic fibrosis
600985	*TNXB*	0.035134	606408	Ehlers–Danlos-like syndrome due to tenascin-X deficiency
606869	*HEXA*	0.033146	272800	Tay–Sachs disease
121011	*GJB2*	0.026200	220290	Nonsyndromic hearing loss recessive 1A
			601544	Nonsyndromic hearing loss dominant 3A
602858	*DHCR7*	0.023709	270400	Smith–Lemli–Opitz syndrome
277900	*ATP7B*	0.021983	606882	Wilson disease
608034	*ASPA*	0.019856	271900	Canavan disease
607008	*ACADM*	0.016583	201450	Medium-chain acyl-coenzyme A dehydrogenase deficiency
602716	*NPHS1*	0.015994	256300	Finnish congenital nephrotic syndrome
601785	*PMM2*	0.015877	212065	Carbohydrate-deficient glycoprotein syndrome type Ia
607440	*FKTN*	0.015660	611615	Cardiomyopathy, dilated, 1X
			253800	Walker–Warburg congenital muscular dystrophy
605646	*SLC26A4*	0.015422	600791	Deafness autosomal recessive 4
			274600	Pendred syndrome
126340	*ERCC2*	0.015255	610756	Cerebrooculofacioskeletal syndrome 2
			601675	Trichothiodystrophy 1, photosensitive
603297	*DYNC2H1*	0.014817	613091	Short-rib thoracic dysplasia 3 with or without polydactyly

OMIM Online Mendelian Inheritance in Man.[55]
[a]Values round to ≥ 0.02 (two decimal places).

(Gregg et al., 2021)

In 2022, the ACMG released updated guidelines for clinical evaluation and etiologic diagnosis of hearing loss. The updated guideline suggests the following recommendations:

1. "All newborns and infants with confirmed HL should undergo a comprehensive evaluation in which patient-focused medical and birth histories, a 3-generation pedigree, and family medical history are obtained, and a physical examination that focuses on dysmorphic physical findings is performed. Evaluation of children and young adults with HL should follow a similar approach. Evaluation of deaf or hard-of-hearing adults should be customized based on the age of onset and other characteristics of HL."
    - "The medical and birth histories may be helpful in differentiating between acquired vs inherited causes of HL."
2. "For individuals with findings that suggest a syndromic genetic etiology for their HL:
    - "Pretest genetic counseling should be provided, and, with patient's or caregiver's informed consent, genetic testing should be ordered to confirm the diagnosis. This testing may include single-gene tests, HL multigene panels, ES, GS, chromosome

analysis, or microarray- or NGS-based copy number analysis, depending on clinical findings."

- "Appropriate studies should be undertaken to determine whether other organs are involved."
- "Appropriate near-term and long-term screening and management should be arranged, including referrals to specialists, as indicated by the associated manifestations of the syndrome."

3. "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. If panel testing is negative, genome-wide testing, such as ES or GS, may be considered.
     - The HL panel should include the genes recommended by the HL Gene Curation Expert Panel [https://search.clinicalgenome.org/kb/affiliate/10007?page=1&size=25&search=].
     - If genetic testing reveals variant(s) in an HL-related gene, gene-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals.
     - If genetic testing fails to identify an etiology fora patient's HL, the possibility of a genetic etiology remains."
   - "Temporal bone imaging by computed tomography or magnetic resonance imaging should be considered as a complement to genetic testing, particularly if the diagnosis remains unclear; if cochlear im-plantation is being considered; if auditory neuropathy is noted, in cases of progressive HL; or if other clinical concerns exist. The anticipated clinical utility of imaging studies should be balanced against the risks associated with radiation exposure and sedation."
   - "CMV testing should be done as soon as possible after birth but within the first 3 weeks of life for infants with congenital HL. For later-onset or progressive HL, CMV testing can be obtained, but the likelihood that a positive test is caused by postnatal exposure increases with age."
4. "Referral to a multidisciplinary care center, when available, is recommended."
   - "A team approach that includes otolaryngologists, clinical geneticists, genetic counselors, audiologists, speech and language specialists, early hearing intervention and family support specialists and other appropriate specialists offers optimal opportunity to provide ongoing management and support of deaf and hard-of-hearing individuals and their families as their needs change over time."
   - "For cases in which the genetic evaluation failed to identify an underlying cause, periodic follow-up care every 3 years with a geneticist may be appropriate for several reasons. First, subtle features of syndromic forms of HL may not be apparent at birth or early in childhood but may appear as deaf or hard-of-hearing individuals grow into adulthood. These may prompt additional medical tests or referrals for specialty care. Second, follow-up visits offer the opportunity to inform individuals about new genetic tests that may have become available or changes in the interpretation of previous test results as medical knowledge advances. Finally, follow-up visits may also help identify

clinical concerns unrelated to HL, for which referral for specialty care may be appropriate."

"Regardless of whether genetic test results are positive, negative, or inconclusive, results should be communicated through the process of genetic counseling and potential risks to other family members should be conveyed" (Li et al., 2022).

The Joint Committee on Infant Hearing (JCIH)

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).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	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
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.

IX. Evidence-based Scientific References

A Eliot Shearer, M. S. H., and Richard JH Smith. (2017). Hereditary Hearing Loss and Deafness Overview. In. https://www.ncbi.nlm.nih.gov/books/NBK1434/

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X. Review/Revision History

Effective Date	Summary
12/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following changes were made for clarity and consistency: Note was updated to reflect changes to Avalon's definition of a genetic panel within R2162. Now reads: "Note: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy."
12/01/2024	Initial Policy Implementation