Nonsyndromic Hearing Loss and Deafness Genetic Testing

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Introduction

Nonsyndromic hearing loss and deafness genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
GJB2 gene analysis	S3844
GJB2 known familial mutation analysis	81253
GJB2 sequencing	81252
GJB6 common variant analysis	81254
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	81430
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	81431

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Procedures addressed by this guideline	Procedure codes
Hearing loss and deafness gene tests	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
MT-RNR1 sequencing	81403
MT-RNR1 targeted mutation analysis	81401
MT-TS1 sequencing	81403
MT-TS1, MT-RNR1 targeted mutation analysis	81401

Criteria

Introduction

Requests for nonsyndromic hearing loss and deafness testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Previous testing:
  - Member has not previously had testing that would detect the known familial mutation(s), AND
- Member has a 1st, 2nd, or 3rd degree biological relative with a pathogenic mutation(s) in a gene associated with nonsyndromic hereditary hearing loss or deafness, AND

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- Member is at risk of inheriting the pathogenic mutation based on the family history and the inheritance pattern associated with the mutation, AND
- Diagnostic testing:
  - Member has nonsyndromic hearing loss or deafness that is consistent with the mutation in the family, OR
- Carrier testing:
  - Member is of reproductive age, and
  - Member has ability and intention to reproduce, or
  - Member is currently pregnant.

GJB2 Sequencing

- Previous testing:
  - Member has not previously had GJB2 sequencing, and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - Prelingual onset of hearing loss (prior to speech development), and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  - Member's family history is consistent with autosomal recessive inheritance (including simplex cases), OR
- Carrier screening
  - Member is of reproductive age, and
  - Has potential and intention to reproduce, and
  - Has a reproductive partner who is a carrier of a GJB2/GJB6 mutation, or
  - Has a reproductive partner with GJB2/GJB6-related deafness.

GJB6 Common Variant Analysis for 309kb and 232kb Deletions

- Previous testing:
  - Member has not previously had GJB6 common variant analysis or deletion/duplication analysis, AND
- Diagnostic Testing:
  - Member meets criteria for GJB2 sequencing, and

- No mutation or only one mutation identified on GJB2 sequencing, OR
- Carrier screening
  - Member is of reproductive age, and
  - Has potential and intention to reproduce, and
  - Has a 1st, 2nd, or 3rd-degree biological relative with a GJB6 variant, or
  - Member meets criteria for GJB2 sequencing, and
  - No mutation identified on GJB2 sequencing.

MT-RNR1 Targeted Mutation Analysis for m.1555A>G Mutation

- Previous testing:
  - Member has not previously had MT-RNR1 targeted mutation analysis, and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  - Member has at least one of the following risk factors for MT-RNR1 related deafness:
    - History of aminoglycoside antibiotic exposure (gentamycin, tobramycin, amikacin, kanamycin, or streptomycin), or
    - Member's family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

MT-RNR1 Sequencing

- Previous testing:
  - Member has not previously had MT-RNR1 sequencing, and
  - No mutations detected in any previous MT-RNR1 testing (targeted m.1555A>G mutation analysis), and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and

- Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
- Member has at least one of the following risk factors for MT-RNR1 related deafness:
  - Aminoglycoside antibiotic exposure (gentamycin, tobramycin, amikacin, kanamycin, or streptomycin) prior to hearing loss onset, or
  - Member's family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

MT-TS1 Sequencing

- Previous testing:
  - Member has not previously had MT-TS1 analysis, and
  - No mutations detected in any previous MT-TS1 testing (targeted variant analysis), and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a formal diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies, or other signs of syndromic hearing loss, and
  - Member's family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

Nonsyndromic Hearing Loss and Deafness Multigene Panel Testing

Multigene panels will be considered medically necessary when the following criteria are met:

- Previous testing:
  - Member has not previously had a hearing loss panel, and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and

- Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss.

Other considerations

Broad hearing loss and deafness panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multigene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81430 to represent a sequencing panel and 81431 to represent a deletion/duplication panel)*.
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
    - If appropriate first-tier tests cannot be determined on the basis of clinical and family histories, only the following genes may be considered for reimbursement: GJB2, STRC, SLC26A4, TECTA, MYO15A, MYO7A.

Note: *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is nonsyndromic hearing loss and deafness?

Nonsyndromic hearing loss (NSHL) is defined as partial or total hearing loss that does not occur with other medical conditions or symptoms.[1]

Prevalence

It is estimated that up to 3/1000 children are born with hearing loss in one or both ears.[1] About 15% of adults in America have some level of hearing loss.[2]

Symptoms

Approximately 70-80% of genetic hearing loss is nonsyndromic, with no related systemic findings.[3,4] Some syndromic forms of hearing loss and deafness may masquerade as nonsyndromic in infancy and early childhood, before additional symptoms emerge. For example, goiter does not develop until puberty or adulthood in Pendred syndrome; retinitis pigmentosa emerges in adolescence in Usher syndrome; and males with Deafness-Dystonia-Optic Neuronopathy (Mohr-Tranebjaerg) Syndrome begin having progressive neurological symptoms in their teens.[3,5]

Cause

Approximately 35% of cases of prelingual hearing loss are attributed to environmental causes, including viral (cytomegalovirus) or bacterial (meningitis) infection, trauma, prenatal exposure to certain drugs, and other environmental factors.[3] The remaining 65% of cases are thought to be genetic, either as part of a recognized genetic syndrome, or as isolated, nonsyndromic hearing loss (NSHL).[3]

GJB2-related autosomal recessive hearing loss is the most common cause of congenital severe-to-profound non-progressive sensorineural hearing loss.[6] Carrier frequency for GJB2-related hearing loss is dependent on population. Based on current available data, the highest carrier rate (~8%) is reported in the East Asian population.[6]

According to a large study of individuals with nonsyndromic hearing loss tested with multigene panels, the following genes were most often implicated: GJB2, STRC, SLC26A4, TECTA, MYO15A, and MYO7A.[5]

Inheritance

NSHL can exhibit autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns.[3,6,7] Autosomal recessive inheritance accounts for 80% of NSHL, while 15-19% is autosomal dominant, and ~1% is mitochondrial or X-linked.

Diagnosis

In the United States, >98% of newborns have hearing screening which can identify congenital hearing loss.[3] Diagnosis of hearing loss may involve physiologic testing (including auditory brainstem response or ABR/BAER) and/or audiometry.[3]

Management

Management of congenital hearing loss or deafness may include hearing aids, cochlear implants, and appropriate educational interventions[1]. Uncovering the genetic etiology of the hearing loss may also identify (or allay concerns about) comorbidities that may require referral for specialty care.[3,4]

Survival

NSHL is not associated with decreased survival.

Test information

Introduction

Testing for NSHL may include known familial mutation analysis, targeted mutation analysis, multigene panel testing, or single gene analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Single Gene Analysis

Under certain circumstances, technologies used in multigene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion remains for a particular syndrome after negative multigene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.

NSHL and deafness multigene panels include a wide variety of genes associated with nonsyndromic hearing loss and deafness. Multigene nonsyndromic hearing loss and deafness panels may also include genes for syndromes that mimic nonsyndromic hearing loss (e.g. Usher syndrome, Pendred syndrome, Jervell and Lange-Nielsen syndrome, etc.).

A study of 440 individuals with genetic hearing loss found mutations in ~40% of cases tested with a multigene panel. The only feature with an adverse effect on test yield was unilateral hearing loss, for which the panel only identified mutations in 1% of cases.[5] In another study, the mutation detection rate was ~60% via multigene panel; multigene panel testing was noted to be more cost-effective than single gene testing.[8]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2022) stated:[4]

- A comprehensive genetic evaluation is recommended for all cases of congenital deafness or hearing loss with onset in childhood or early adulthood. Cytomegalovirus (CMV) testing is important for cases of congenital hearing loss (HL). The testing should be completed within the first three weeks of life if possible. Ancillary testing (e.g. electrocardiogram, renal ultrasound, temporal bone imaging and ophthalmology examination) remains important, as results may support genetic testing selection or interpretation of variants. The clinical utility of these tests should be evaluated on a case-by-case basis since genetic testing via NGS panels may soon become more cost-effective.
- Genetic testing to confirm a diagnosis of suspected syndromic hearing loss is recommended based on clinical findings. For apparently nonsyndromic hearing loss, a tiered approach was recommended: "Unless clinical and/or family history suggests a specific etiology, comprehensive HL [hearing loss] gene panel testing should be initiated. If panel testing is negative, genome-wide testing, such as ES [exome sequencing] or GS [genome sequencing], may be considered. However, issues related to genomic testing, such as the likelihood of incidental or secondary findings, will have to be addressed."
- Hearing loss panels should include those genes recommended by the ClinGen Hearing Loss Gene Curation Expert Panel.[9]

- "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 for a patient's HL, the possibility of a genetic 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."

International Pediatric Otolaryngology Group

The International Pediatric Otolaryngology Group (IPOG, 2016) stated:[10]

- "In the setting of unilateral hearing loss, genetic testing has a limited role unless syndromic hearing loss is suspected."
- "After and [sic] audiogram and physical exam, comprehensive genetic testing (CGT) that relies on next generation sequencing (NGS) methodologies should guide subsequent workup in children with bilateral sensorineural hearing loss."
- "Diagnostic rates for single gene testing for GJB2/GJB6 vary significantly based on the patient's ethnicity, and do not outperform the diagnostic rates for comprehensive genetic testing. In cases where CGT is unavailable, single gene testing can be directed by the audiometric phenotype and ethnicity."
- The general consensus of the authors was that temporal bone imaging "should not be a routine part of the diagnostic algorithm for bilateral symmetric sensorineural hearing loss."

Selected Relevant Publications

Expert-authored reviews of nonsyndromic hearing loss stated:

- "A hearing loss multigene panel that includes all genes implicated in nonsyndromic hearing loss and disorders that mimic nonsyndromic hearing loss including GJB2and other genes of interest … is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."[6]
- "Analytic methods used for this panel must include the detection of deletions of GJB2, either intragenic or whole gene, and deletions that include sequences upstream of GJB2 (comprising either GJB6 and portions of CRYL1or just portions of CRYL1) that delete cis-regulatory regions of GJB2, thereby abolishing GJB2 expression."[6]
- Regarding mitochondrial NSHL, the diagnosis should be suspected in individuals with moderate-to-profound hearing loss and a family history suggestive of maternal inheritance (e.g. no transmission through a male), or onset of hearing loss after exposure to an aminoglycoside antibiotic.[7]

- "In individuals with hearing loss following aminoglycoside exposure, molecular testing for the pathogenic variants m.1555A>G and m.1494C>T in MT-RNR1 and m.7445A>C/T/G in MT-TS1 can be done first."
- An alternative strategy is to perform multigene panel testing that includes both MT-RNR1 and MT-TS1, plus other genes of interest.
- If targeted mtDNA testing and/or multigene panel testing including these mtDNA genes fail to confirm a diagnosis, mitochondrial genome sequencing can be considered. Mitochondrial genome sequencing should be performed prior to multigene panel testing if there is a clear mitochondrial inheritance pattern.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for nonsyndromic hearing loss and deafness genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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