Test Specific Guidelines

Nonsyndromic Hearing Loss and Deafness Genetic Testing

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
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

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

What Is Nonsyndromic Hearing Loss and Deafness?

Definition

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 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 20% 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 80% of cases are thought to be genetic, either as part of a recognized genetic syndrome, or as isolated, nonsyndromic hearing loss (NSHL).[3]

Inheritance

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

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

X-Linked Inheritance

In X-linked inheritance, the mutation is carried on the X chromosome. Females have two X chromosomes, and males have one. Males typically have more severe symptoms than females. A female with a mutation has a 50% chance to pass that mutation to her children. A male with a mutation cannot pass the mutation to any sons, but will pass it to all daughters. A process called X-inactivation in females results in random inactivation of expression of one X-chromosome in each cell of the body. For females with one mutation, the percentage and distribution of cells with expression of the X chromosome carrying the mutation can influence the degree of severity.

Mitochondrial Inheritance

MtDNA mutations may be de novo (not inherited) or follow maternal inheritance. This means that a female who carries the mtDNA mutation at a high mutation load will typically pass it on to all of her children. However, due to the meiotic bottleneck, the heteroplasmy level may vary significantly between generations. A male who carries the mtDNA mutation cannot pass it on to his children. Clinical expressivity of mtDNA mutations depends on the degree of heteroplasmy and the organs and tissues most affected by the mutation.

Diagnosis

In the United States, 95% 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, single gene analysis, or multigene panel testing.

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 patient 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 patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

Single Gene Analysis

Under certain circumstances, technologies used in multi-gene 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 multi-gene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.

NSHL and deafness multi-gene panels include a wide variety of genes associated with nonsyndromic hearing loss and deafness. Multi-gene 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

Introduction

This section includes relevant guidelines and evidence pertaining to genetic testing for nonsyndromic hearing loss and deafness.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2014) stated:[4]

A genetic evaluation is recommended for all cases of congenital deafness or hearing loss with onset in childhood or early adulthood. While the usefulness of ancillary testing (e.g. electrocardiogram, renal ultrasound, temporal bone imaging and ophthalmology examination) was mentioned, it was acknowledged that genetic testing via NGS panels would soon become more cost-effective. Cytomegalovirus (CMV) testing is important for cases of congenital hearing loss, but only accurate in the first 6 weeks of life.

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: If the personal and family history is suggestive of a particular gene, single gene testing should be performed first. For simplex cases and cases with apparent autosomal recessive inheritance, the next step should be testing of GJB2 and GJB6. If single-gene testing is not diagnostic, testing via NGS panels, whole exome sequencing, or whole genome sequencing should be considered.

The statement stopped short of endorsing the use of NGS panels as a first-tier test, but noted they are “rapidly replacing” sequencing of the GJB2 and GJB6 loci and would soon be a more cost-effective alternative.

International Pediatric Otolaryngology Group

The International Pediatric Otolaryngology Group (IPOG, 2016) stated:[9]

"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 state:

"A comprehensive deafness-specific genetic panel that includes all genes implicated in nonsyndromic hearing loss and nonsyndromic hearing loss mimics is recommended as the initial genetic test."[6]

"Performing sequence analysis of GJB2 alone is not cost-effective unless it is limited to persons with severe-to-profound congenital nonsyndromic hearing loss. Offering single-gene testing of GJB2 reflexively to everyone with congenital hearing loss without regard to the degree of hearing loss is not evidence based and not cost effective." [6]

Multi-gene testing is recommended for apparent nonsyndromic hearing loss, while individuals with features of syndromic hearing loss should be diagnosed with targeted genetic testing. Ancillary cardiac, ophthalmologic and renal evaluations are only recommended on the basis of genetic test results or clinical findings.[3]

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."

If these tests fail to confirm a diagnosis, mitochondrial genome sequencing can be considered. Mitochondrial genome sequencing should be performed prior to a multigene panel if there is a clear mitochondrial inheritance pattern.

An alternative strategy is to perform a multi-gene panel that includes both MT-RNR1 and MT-TS1, plus other genes of interest.

Criteria

Known Familial Mutation Analysis

Previous testing:

Member has not previously had testing for the requested mutation(s), AND

Member has a 1st, 2nd, or 3rd degree biologic relative with a pathogenic mutation(s) in a gene associated with nonsyndromic hereditary hearing loss or deafness, AND

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 biologic 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 biologic 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 biologic 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 biologic 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 biologic 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

When a multi-gene panel is being requested and will be billed with a panel CPT code (e.g. 81430, 81431, 81479), the panel 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 biologic 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.

When separate procedure codes will be billed for individual hearing loss genes (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), the entire panel will be approved if the above criteria are met. However, the laboratory will be redirected to use an appropriate panel CPT code for billing purposes (e.g. 81430, 81431, 81479).

Billing and Reimbursement Considerations

The billed amount should not exceed the list price of the test.

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.

Genetic testing is only necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.

If the laboratory will not accept redirection to a single code, the medical necessity of each billed component procedure will be assessed independently, and only the individual panel components that meet medical necessity criteria as a first tier of testing will be reimbursed. The remaining individual 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.

If a single hearing loss/deafness gene test is billed simultaneously with a panel code (e.g. 81430), only the billed procedure that meets medical necessity criteria as a first tier of testing will be reimbursed.

Panel testing will generally be the most appropriate first-tier test, except when the history is strongly suggestive of the individual genetic disorder requested

(e.g. congenital, severe-to-profound deafness for GJB2 analysis or history of aminoglycoside exposure for MT-RNR1 analysis).

References

Introduction

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