Clinical Policy Title: Genetic testing in sensorineural hearing loss

Clinical Policy Number: CCP.1198

Effective Date: January 1, 2016
Initial Review Date: October 16, 2015
Most Recent Review Date: October 2, 2018
Next Review Date: October 2019

Related policies:
- CCP.1060 Genetic testing for rare diseases
- CCP.1109 Brainstem auditory evoked response

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers genetic testing for sensorineural hearing loss to be clinically proven and, therefore, medically necessary in members with demonstrated hearing loss, when all of the following criteria are met (Liming, 2016; Alford, 2014; American College of Medical Genetics, 2012):

- Either clinical indication:
  - Unilateral sensorineural hearing loss with suspected syndromic genetic etiology.
  - Suspected non-syndromic bilateral hearing loss (i.e., absence of physical findings suggestive of a known syndrome and absence of medical and birth histories suggesting an environmental cause of hearing loss).

- Disease-targeted genetic testing:
  - Single-gene testing when a specific etiology is suspected.
  - Testing for DFNB1-related hearing loss (due to mutations in GJB2 and adjacent deletions in GJB6) in the absence of any suspected etiology, for singleton cases, and for cases with apparent autosomal recessive inheritance.
Comprehensive genetic testing panels using new generation sequencing technologies targeted toward hearing loss-related genes (e.g., whole-exome sequencing or whole-genome sequencing).

- The test results will directly impact care management (i.e., as a result of the test, effective treatment may be offered that will alter the course of disease or outcomes).
- The test is analytically and clinically valid (i.e., supported by peer-reviewed published research).
- The test is ordered by a trained professional (e.g., specialist in medical genetics, developmental-behavioral pediatrician, condition-specific subspecialist, obstetrician/gynecologist, maternal-fetal specialist, perinatologist, or neonatologist for neonates in the neonatal intensive care unit) who will ensure face-to-face genetic consult or counseling by appropriately trained professionals to accompany testing.
- The test results will be discussed with the patient or guardian, including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current disease management guidelines.

Limitations:

Genetic testing for sensorineural hearing loss is limited to a once-per-lifetime use.

Genetic testing for sensorineural hearing loss is not medically necessary for persons who are not members of Select Health of South Carolina health plans.

Genetic testing for unilateral hearing loss in the absence of a suspected syndrome-related hearing loss has a limited clinical role and is generally not medically necessary (Liming, 2016).

Routine prenatal genetic testing for non-syndromic sensorineural hearing loss is not medically necessary, as the risks and benefits of such testing have not been established (Lang-Roth, 2014).

Alternative covered services:

A primary care physician or a neurologic, otologic, or other qualified specialist may evaluate a patient for sensorineural hearing loss with alternative covered services, including routine office consultation and clinical investigation (i.e., laboratory, imaging, functional testing, and diagnostic procedures, specifically audiometric testing).

Background

Hearing loss is the most prevalent sensory impairment across all age groups (Koffler, 2016). Left untreated, hearing loss can result in lifelong deficits in speech and language development. Hearing loss
is classified according to symmetry, degree of hearing loss, and stability, and when genes are implicated, inheritance pattern (Genetics Home Reference, 2018).

Genetic hearing loss may be inherited in an autosomal recessive or dominant pattern, on the X-chromosome, or through mitochondria (Koffler, 2016). The majority of cases are inherited in an autosomal recessive pattern, which are often the most severe in nature and are expressed at birth or soon thereafter. In approximately half of these cases, the causes are mutations in the GJB2 or GJB6 genes that provide instructions for making the proteins Connexin 26 and Connexin 30, respectively, that are involved in hearing function.

Genetic hearing loss may indicate a genetic syndrome with (syndromic) or without (non-syndromic) involvement of other organ systems. Syndromic hearing loss comprises approximately 30 percent of all genetic cases of hearing loss. It may present with anomalies affecting organs such as the eye, kidney, and musculoskeletal and nervous systems. More than 700 genetic syndromes have been described with features of hearing impairment (Koffler, 2016).

Non-syndromic hearing loss may be expressed at any time from infancy to old age, depending on the subtype (Genetic Home Reference, 2018). Most forms of non-syndromic hearing loss are described as sensorineural associated with permanent hearing loss caused by damage to the structure and function of the inner ear or, to a lesser extent, the middle ear. More than 90 genetic abnormalities are associated with non-syndromic hearing loss.

Genetic testing for hearing loss comprises single gene sequencing and next-generation sequencing technologies (disease-targeted exon capture, whole exome sequencing, and whole genome sequencing). There are 22 molecular genetic tests for hereditary hearing loss and seven tests for non-syndromic hearing loss (Genetic Testing Registry, 2018). These tests comprise sequence analysis of the entire coding region, deletion/duplication analysis, sequence analysis of select exons, and targeted variant analysis.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on August 23, 2018. Search terms were “sensorineural hearing loss” (MeSH) and “genetic testing” (MeSH).

We included:
• **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

• **Guidelines based on systematic reviews.**

• **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Sensorineural hearing loss is an area of active investigation to identify genetic loci and mutations playing a role in hereditary hearing loss. To date, three different loci have been acknowledged: deletions in genes GJB6 (i.e., gap junction beta 6), the PDXDC1 gene located on human chromosome 16, and the MYH7B gene. These genetic sites are not typically tested in clinical settings, as the challenges of exome-sequencing and genome-wide mapping for them is considerable as of mid-decade 2010s. As such, much of our understanding of the genetic basis for sensorineural hearing loss comes from limited research directed toward families with known, pervasive penetration of auditory deficits.

Haraksingh (2014) compared two different techniques for detecting congenital sensorineural hearing loss: array comparative genomic hybridization and single nucleotide variation. Sequencing (for single nucleotide variation) was helpful but not definitive in every instance of sensorineural hearing loss; moreover, the disease-causing significance of copy number variations could not be substantiated. They concluded that resolution of the full complex of genetic polymorphisms will not be understood until an integrated study of genotypic and phenotypic auditory loss is undertaken at some point in the future.

In Germany, where newborn hearing testing is mandatory, genetic testing leads to a diagnosis of GJB6 mutational causes nearly 50 percent of the time (Lang-Roth, 2014). In the remainder of cases, the causes are heterogeneous, and genetic variability is only partially responsible for the deficit. Developments in sequencing methods and decoding of the genes involved in causing hearing disorders may be included in future routine diagnostics, but because of the risks of amniocentesis and the relative ease with which hearing disorders are managed and overcome, routine prenatal testing for these conditions is not medically indicated for non-syndromic sensorineural hearing loss.

Francey (2012) identified from a group of 659 children with known sensorineural hearing loss a group of eight in whom chromosomal deletions (i.e., involving the stereocilin or STRC locus, which is part of the GJB2 gene) were detected. They identified seven additional individuals with mild to moderate sensorineural hearing loss as a result of allelic variation of the STRC gene, and two individuals with moderate to severe (41 – 80 dB) sensorineural hearing loss. In none of the individuals was any other explainable genetic mutation detected. They posited that the STRC locus is a significant contributor to sensorineural hearing loss among those individuals with GJB2 mutations.
Nishio (2016) described advances and recent progress in molecular genetics and molecular biology of hearing and deafness. The authors identified a number of cost-effective, novel diagnostic tools tailored to specific ethnicities for genetic screening for deafness. They described their multiplex genetic screening system, “SNP scan assay,” used to screen a total of 115 known mutations in GJB2, SLC26A4, and mtDNA 12SrRNA.

A randomized controlled trial studied TGFA/TGFB3/MSX1 gene polymorphisms and haplotypes to evaluate individual differences among 343 patients with congenital non-syndromic hearing impairment and 272 normal controls, and analyzed the risk factors for non-syndromic hearing impairment (Du, 2016). The distribution of genotype frequencies and allele frequencies of TGFA rs3771494, TGFB3 rs3917201 and rs2268626, and MSX1 rs3821949 and rs62636562 were significantly different between the case and the control groups (all \( P < .05 \)). TGFA/TGFB3/MSX1 gene rs3771494, rs1058213, rs3917201, rs2268626, rs3821949, and rs62636562 haplotype analysis showed that haplotype CCGTAC and TTACGT might be protective factors (both \( P < .001 \)), while TTGCCT might be a risk factor for the normal population (\( P < .001 \)).

**Policy updates:**

Comprehensive guidelines from the International Pediatric Otolaryngology Group (2016) recommend genetic testing to diagnose the etiology of pediatric hearing loss, as targeted individualized medical care determined by the patient’s specific genetic abnormality may obviate the need for a traditional work-up (e.g., computed tomography of the head or magnetic resonance imaging). Based on these facts, they recommend genetic testing in all individuals with bilateral sensorineural hearing loss as the first step in the evaluation process.

A large trial examined the use of massively parallel sequencing on 1,119 sequentially accrued patients (Sloan-Heggen, 2016). Testing identified the underlying genetic cause for hearing loss in 440 patients (39 percent). Pathogenic variants were found in 49 genes, including missense variants (49 percent), large copy number changes (18 percent), small insertions and deletions (18 percent), nonsense variants (8 percent), splice-site alterations (6 percent), and promoter variants (< 1 percent). The diagnostic rate varied considerably based on phenotype and was highest for patients with a positive family history of hearing loss or when the loss was congenital and symmetric.

The American College of Medical Genetics and Genomics (Alford, 2014) guideline recommends pretest genetic counseling and genetic testing with the patient’s informed consent: 1) to confirm the diagnosis for individuals with findings suggestive of a syndromic genetic etiology, and 2) for individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories not suggestive of an environmental cause of hearing loss. Temporal bone imaging by computed tomography or magnetic resonance imaging may be considered as a complement to genetic testing.

A survey (Jayawardena, 2015) of clinical respondents in the field of hearing loss noted those who completed training recently are more likely to order magnetic resonance imaging and electrocardiogram
for evaluation of the condition. The most frequently ordered examinations were temporal bone computed tomography (40 percent), an ophthalmology consult (39 percent), a genetics consult (37 percent), and genetic testing (20 percent). The authors concluded that the results of the survey indicate a need for earlier genetic testing in evaluation of patients with sensorineural hearing loss.

In 2018, we added recommendations from the American College of Medical Genetics (2012) on genetic testing for congenital hearing loss. Genetic testing algorithms are prioritized around confirmed hearing loss (e.g., failed newborn screening), family history, and likelihood of a syndromal condition. If hearing loss is familial or non-syndromal, genetic testing for GJB2 (Connexin 26) and GJB6 (Connexin 30) should be performed. Changes to the coverage policy reflect the need to clarify the types of available genetic testing and medically necessary indications.

Policy ID changed from CP# 02.01.18 to CCP.1198.

Summary of clinical evidence:

<table>
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<th>Citation</th>
<th>Content, methods, recommendations</th>
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<tbody>
<tr>
<td>Sloan-Heggen (2016)</td>
<td><strong>Key points:</strong></td>
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</table>
| Comprehensive genetic testing in the clinical evaluation of 1,119 patients with hearing loss | • A large multiethnic cohort (n = 1,119) underwent targeted genomic enrichment and massively parallel sequencing. No patient was excluded based on phenotype, inheritance, or previous testing.  
• Underlying genetic cause for hearing loss was identified in 440 patients (39%).  
• Testing identified pathogenic variants in 49 genes: missense variants (49%); large copy number changes (18%); small insertions and deletions (18%); nonsense variants (8%); splice-site alterations (6%); and promoter variants (< 1%); wide ethnic variability.  
• Diagnostic rate varied based on phenotype; highest for patients with either a positive family history of hearing loss or congenital and symmetric hearing loss.  
• Authors suggest more efficient resource utilization using evidence-based algorithms for diagnosing hearing loss. |
| Liming (2016) | **Key points:** |
| Hearing loss in the pediatric patient | • For unilateral hearing loss, genetic testing has a limited role unless syndromic hearing loss is suspected (e.g., branchio-oto-renal syndrome or Waardenburg syndrome).  
• For bilateral hearing loss, after an audiogram comprehensive genetic testing that relies on next-generation sequencing methodologies should guide subsequent workup.  
  – Where comprehensive genetic testing is unavailable, directed single gene testing (e.g., for GJB2/GJB6) should be considered based on the audiometric phenotype and ethnicity. |
| Alford (2014) for the American College of Medical Genetics and Genomics | **Key points:** |
| | • Next-generation sequencing can identify genetic heterogeneity resulting in phenotypes that are not easily distinguishable.  
• Limitations of next-generation sequencing technologies may require alternative or complementary genetic testing strategies in some cases. |
Guideline for the clinical evaluation and etiologic diagnosis of hearing loss.

- Recommends for individuals with findings that suggest a syndromic genetic etiology for their hearing loss, pretest genetic counseling should be provided and, with the patient’s informed consent, genetic testing should be ordered to confirm the diagnosis if that testing is available.
- 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, pretest genetic counseling should be provided and, with the patient’s informed consent, tiered genetic testing should be ordered.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.
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<td>GJB2 (gap junction protein, beta 2 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence</td>
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