Clinical Policy Title: Genomic tests in sensorineural hearing loss

Clinical Policy Number: 02.01.18

Effective Date: January 1, 2016
Initial Review Date: October 16, 2015
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:

CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.03 Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.09 Genetic testing, rare diseases
CP# 04.01.02 Genetic testing for long QT syndrome (LQTS)
CP# 11.04.02 Genetic testing for autism spectrum disorder
CP# 13.01.01 Genetic testing for prostate cancer prognosis

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’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 Keystone First 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. Keystone First’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. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers genomic testing in sensorineural hearing, done either alone or in combination, to be investigational and, therefore, not medically necessary.

Limitations:

Keystone First considers all other genomic tests in sensorineural hearing loss to be medically unnecessary and clinically unproven, except as delineated in the related policies cited above.
Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:
81252 - GJB2 (gap junction protein, beta 2 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence

81254 - GJB2 (gap junction protein, beta 2 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; with known variants

**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**

The merits of definitive genome testing for sensorineural hearing loss are several. Contemporary estimates of prevalence have one in 500 newborns afflicted by this condition nationwide, and almost all of those cases (80 percent) are inherited nonsyndromic, mild to moderate (26 – 60 dB), bilateral hearing loss. Over 400 genetic syndromes have been identified, as well, in which hearing loss is a prominent impairment. Prenatal diagnosis may lead to greater awareness of hearing deficits in the very young child, and reduction in aural comorbidities such as delayed speech and language development, impaired socialization, and educational deficiencies.

Unfortunately, there is much genetic heterogeneity associated with the derangement: approximately 133 autosomal non-syndromic loci have been mapped to date, with 78 more suspected but not substantiated sites known. Additionally, most cases of sensorineural hearing loss in humans do not have an identifiable genetic cause (though admittedly we are at the beginning of our understanding of this condition, not the end, and that number may change in time).

Of these many possible etiologies for auditory decrement there are a few under intense investigation. They are the DFNB1A/B locus, which contains the GJB2 and GJB6 genes (these play a role in nearly 50 percent of cases of autosomal recessive transmission of hearing loss); the MYH7B mutations, which have been identified to date in an exclusive group of five individuals, all of whom are family members; and the chromosomal deletions of human chromosome number 16 that makes up the PDXDC1 gene.

**Searches**

Keystone First 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 (CMS).

We conducted searches on September 28, 2016. Search terms were: "sensorineural hearing loss (MeSH)," "genome (MeSH)," and "test (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) has compared two different techniques for detecting congenital sensorineural hearing loss: array comparative genomic hybridization (aCGH) and single nucleotide variation (SNV). They found sequencing (for SNV type variations) was helpful but not definitive in every instance of sensorineural hearing loss; moreover, the disease-causing significance of copy number variations (CNVs, as identified by aCGH) 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. The authors go on to say that because of the huge developments in sequencing methods and decoding of the genes involved in causing hearing disorders, as of 2014, it is expected that in the future routine diagnostics will include molecular genetic methods. They acknowledge, however, that 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.
Francy (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 Sterocilin or STRC locus, which is part of the GJB2 gene) were detected. They subsequently 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 mutations detected. They posited that the STRC locus is a significant contributor to sensorineural hearing loss among those individuals with GJB2 mutations.

Policy updates:

Nishio (2016) offered a narrative review of advances and recent progress in molecular genetics and molecular biology of hearing and deafness. The authors identified a number of novel diagnostic tools tailored to specific ethnicities as a cost-effective genetic screening for deafness and described their multiplex genetic screening system, “SNPscan assay,” used to screen a total of 115 known mutations in GJB2, SLC26A4, and mtDNA 12SrRNA.

A randomized controlled trial (RCT) studied TGFA/TGFB3/MSX1 gene polymorphisms and haplotypes to evaluate individual differences between 343 congenital non-syndromic hearing impairment (NSHI) patients and 272 normal controls, and analyzed the risk factors for NSHI (Jhang 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 < 0.05). 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 < 0.001), while TTGCGC might be a risk factor for the normal population (P < 0.001).

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
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<tbody>
<tr>
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<td>Genetics and the Molecular</td>
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</table>

**Glossary**

**Array comparative genomic hybridization (aCGH)** — A molecular technique to detect chromosome gain or loss by hybridizing DNA from a target cell and a normal cell.

**Sensorineural hearing loss** — An otologic condition in which there is damage to the cochlea or to the auditory nerve from the brain to the inner ear. This is the most common type of permanent hearing loss.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs 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.

<table>
<thead>
<tr>
<th>CPT Code</th>
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<th>ICD 10 Code</th>
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<tr>
<td>HCPCS Code</td>
<td>Description</td>
<td>Comments</td>
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<tr>
<td>H90.3</td>
<td>Sensorineural hearing loss, bilateral</td>
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<tr>
<td>H90.41</td>
<td>Sensorineural hearing loss, unilateral, right ear</td>
<td></td>
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<tr>
<td>H90.42</td>
<td>Sensorineural hearing loss, unilateral, left ear</td>
<td></td>
</tr>
<tr>
<td>H90.5</td>
<td>Sensorineural hearing loss, unspecified</td>
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**Appendix A**

**Commonwealth of Pennsylvania genetic framework document:**

Genetic testing encompasses a large number of tests for a variety of indications, including diagnosis, carrier state, predisposition to a specific disease and therapeutic decision-making. There are also different types of genetic tests, such as looking at single mutations or multiple mutations. Each managed care organization (MCO) has a variety of policies for genetic testing. Some are disease- or condition-specific, and some are more general. It may make more sense for an MCO to make one general policy statement or to have multiple policies, some of which are disease-specific. Some of these policies may already have been reviewed and approved, but we are requesting that all guidelines and policies be reviewed and resubmitted to be sure the following guidelines are followed in all policies:

- The MCO may require some form of genetic counseling for each test, but it does not have to be performed by a geneticist or genetic counselor. Such specialists may not be readily accessible to consumers in certain areas of the state. It can be a requirement that the genetic counseling done by a specialist or other physician be equivalent to that provided by a genetic counselor, but it should also be appropriate for the test being requested. For example, genetic testing for a mutation that directs cancer treatment for acute lymphoblastic leukemia (ALL) is probably appropriately done by the oncologist ordering the test.
- A genetic test is considered medically necessary if the results are expected to make a difference in the recipient’s care or his or her treatment plan, or the recipient (or a responsible family member or legal guardian) intends to use the information in making decisions about his or her care or treatment plan. An example would be family-planning decisions or the planning of other indicated testing in light of the diagnosis.
- Genetic testing is medically necessary if it is a currently accepted method of diagnosis of a condition or disease. (You can still require that the preceding two guidelines apply.) Examples are the evaluation of global developmental delay, recurrent fetal loss or multiple congenital anomalies without an obvious etiology.
- Genetic testing is medically necessary if, by the current guidelines, it is consistent with the accepted standards for disease predisposition testing or screening. (You can still require that the
first two guidelines above apply.) Examples would be testing for cystic fibrosis carrier state in women of reproductive age and breast cancer (BRCA) testing.

- Genetic testing is medically necessary if it is needed to determine appropriate medication or treatment. (You can still require that the first two guidelines above apply.) An example would be for non-small cell lung cancer treatment (first-line) Tarceva and Gilotrif. An FDA-approved epidermal growth factor receptor (EGFR) mutation test is required.
- All requests should be considered individually, even if the above guideline criteria are not met.
- All terms referring to genetic testing should be used correctly. Be careful when using the terms microarray, CGH and SNP.