Prior Authorization Review Panel
MCO Policy Submission

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Plan: Keystone First Community HealthChoices	**Submission Date**: 12/22/2022
Policy Number: CCP.1198	**Effective Date:** 1/2016 **Revision Date:** November 1, 2022
Policy Name: Genetic testing in sensorineural hearing loss	
Type of Submission – Check all that apply: ☐ **New Policy** **X Revised Policy*** ☐ **Annual Review – No Revisions** ☐ **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** Please see revisions with tracked changes below.	
Name of Authorized Individual (Please type or print): Akintayo Akinlawon, MD	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Genetic testing in sensorineural hearing loss

Clinical Policy ID: CCP.1198

Recent review date: 11/2022

Next review date: 3/2024

Policy contains: Genetic testing; genomic testing: non-syndromic hearing loss; syndromic hearing loss.

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

Coverage policy

Genetic testing for sensorineural hearing loss is clinically proven and, therefore, medically necessary in members with demonstrated hearing loss, when all of the following criteria are met (Alford, 2014; American College of Medical Genetics and Genomics, 2012; Liming, 2016):

- 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 (any of the following):
- 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 enrolled members.

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, 2015). Hearing loss is classified according to symmetry, degree of hearing loss, and stability, and when genes are implicated, inheritance pattern (Genetics Home Reference, 2020).

Genetic hearing loss may be inherited in an autosomal recessive or dominant pattern, on the X-chromosome, or through mitochondria (Koffler, 2015). 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%t 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, 2015).

Non-syndromic hearing loss may be expressed at any time from infancy to old age, depending on the subtype (Genetic Home Reference, 2020). 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.

Some early forms, referred to as non-syndromic mimics, may initially appear as isolated hearing loss (Gooch, 2021). As the patient ages, other phenotypes become apparent, which may have significant associated morbidity and mortality. One example is Jervell and Lange-Nielsen Syndrome.

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) (Genetic Testing Registry, 2021). These tests comprise sequence analysis of the entire coding region, deletion/duplication analysis, sequence analysis of select exons, and targeted variant analysis.

Findings

Identifying genetic loci and mutations that play a role in hereditary hearing loss is an active area of investigation in sensorineural hearing loss. To date, there are three different loci 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 the 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% 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 TTGCGC might be a risk factor for the normal population ($P < .001$).

Comprehensive guidelines from the International Pediatric Otolaryngology Group (Liming, 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%). Pathogenic variants were found in 49 genes, including missense variants (49%), large copy number changes (18%), small insertions and deletions (18%), nonsense variants (8%), splice-site alterations (6%), and promoter variants (< 1%). 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 complement 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%), an ophthalmology consult (39%), a genetics consult (37%), and genetic testing (20%). 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. The policy ID was changed from CP# 02.01.18 to CCP.1198.

In 2019, we identified no newly published, relevant literature to add to the policy.

In 2020, we identified no newly published, relevant literature to add to the policy.

In 2021, we identified no newly published, relevant literature to add to the policy.

In 2022, we added several studies, including:

- A review that identified at least one possibly causative genetic variant in 29 of 48 Japanese patients with late-onset sensorineural hearing loss after comprehensive genetic testing (Uehara, 2022).
- A study of 10,047 Japanese patients with sensorineural hearing loss, that found a genetic marker in 48.6% of congenital/early-onset subjects, 33.5% for juvenile/young adult-onset subjects, and 18.0% for subjects over age 40. Causative genes varied by group (Usami, 2022).

References

On August 18, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the

Centers for Medicare & Medicaid Services. Search terms were “sensorineural hearing loss” (MeSH) and “genetic testing” (MeSH). We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

10/2015: initial review date and clinical policy effective date: 1/2016

10/2016: Policy references updated.

10/2017: Policy references updated.

11/2018: Policy references updated. Coverage modified. Policy ID changed.

11/2019: Policy references updated.

11/2020: Policy references updated.

11/2021: Policy references updated.

11/2022: Policy references updated.