Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
Current Effective Date: 08/14/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cochlear Implant is addressed separately in medical policy 00017.

Note: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders is addressed separately in medical policy 00389.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for hereditary hearing loss genes (*GJB2, GJB6* and other hereditary hearing loss-related genes) in individuals with suspected hereditary hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines section) to be **eligible for coverage.****

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider preconception genetic testing (carrier testing) for hereditary hearing loss genes (*GJB2, GJB6* and other hereditary hearing loss-related genes) in parents to be **eligible for coverage****:

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Patient Selection Criteria
Coverage eligibility will be considered when **at least ONE** of the following criteria is met:

- Offspring with hereditary hearing loss; **OR**
- One or both parents with suspected hereditary hearing loss; **OR**
- First- or second-degree relative affected with hereditary hearing loss; **OR**
- First-degree relative with offspring who is affected with hereditary hearing loss.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for hereditary hearing loss genes for all other situations, including but not limited to, testing in individuals without hearing loss to be **investigational.***

The use of genetic testing for hereditary hearing loss genes when patient selection criteria are not met is considered to be **investigational.***

Policy Guidelines

Hereditary hearing loss can be classified as syndromic or nonsyndromic. The definition of nonsyndromic hearing loss is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation. It is differentiated from syndromic hearing loss, which is hearing loss associated with other signs and symptoms characteristic of a specific syndrome. Physical signs of a syndrome often include dysmorphic changes in the maxillofacial region and/or malformations of the external ears. Malfunction of internal organs may also be part of a syndrome. The physical signs can be subtle and easily missed on physical exam; therefore, exclusion of syndromic findings is ideally done by an individual with expertise in identifying dysmorphic physical signs. The phenotypic presentation of nonsyndromic hearing loss varies, but generally involves the following features:

- Sensorineural hearing loss
- Mild-to-profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually nonprogressive

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This policy primarily focuses on the use of genetic testing to identify a cause of suspected hereditary hearing loss. The diagnosis of syndromic hearing loss can be made on the basis of associated clinical findings. However, at the time of hearing loss presentation, associated clinical findings may not be apparent. Furthermore, variants in certain genetic loci may cause both syndromic and nonsyndromic hearing loss. Given this overlap, the policy focuses on genetic testing for hereditary hearing loss more generally.

In addition to pathogenic variants in the *GJB6* and *GJB2* genes, there are many less common pathogenic variants found in other genes. They include: *ACTG1*, *CDH23*, *CLDN14*, *COCH*, *COL11A2*, *DFNA5*, *DFNB31*, *DFNB59*, *ESPN*, *EYA4*, *GJB2*, *GJB6*, *KCNQ4*, *LHFPL5*, *MT-TS1*, *MYO15A*, *MYO6*, *MYO7A*, *OTOF*, *PCDH15*, *POU3F4*, *SLC26A4*, *STRC*, *TECTA*, *TMC1*, *TMIE*, *TMPRSS3*, *TRIOBP*, *USH1C*, and *WFS1* genes.

Targeted testing for variants associated with hereditary hearing loss should be confined to known pathogenic variants. While research studies using genome-wide associations have uncovered numerous single nucleotide variants and copy number variations associated with hereditary hearing loss, the clinical significance of these findings is unclear.

For carrier testing, outcomes are expected to improve if parents alter their reproductive decision-making as a result of genetic test results. This may occur through the use of preimplantation genetic testing in combination with in vitro fertilization. Other ways that prospective parents may alter their reproductive choices are to proceed with attempts at pregnancy or to avoid attempts at pregnancy, based on carrier testing results.

Testing Strategy
Evaluation of an individual with suspected hereditary hearing loss should involve a careful physical exam and family history to assess for associated clinical findings that may point to a specific syndromic or nonsyndromic cause of hearing loss (eg, infectious, toxic, autoimmune, other causes). Consideration should also be given to temporal bone computed tomography scanning in cases of progressive hearing loss and to testing for cytomegalovirus in infants with sensorineural hearing loss.

If there is no high suspicion for a specific hearing loss etiology, ideally the evaluation should occur in a stepwise fashion. About 50% of individuals with autosomal recessive hereditary hearing loss

have pathogenic variants in the *GJB2* gene. In the remainder of individuals with apparent autosomal recessive hereditary hearing loss, numerous other genes are implicated. In autosomal dominant hereditary hearing loss, there is no single identifiable gene responsible for most cases. If there is suspicion for autosomal recessive congenital hearing loss, it would be reasonable to begin with testing of *GJB2* and *GJB6.* If this is negative, screening for the other genes associated with hearing loss using a multigene panel would be efficient. An alternative strategy for suspected autosomal recessive or autosomal dominant hearing loss would be to obtain a multigene panel that includes *GJB2* and *GJB6* as a first step. Given the extreme heterogeneity in genetic causes of hearing loss, these 2 strategies may be considered reasonably equivalent.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Hereditary Hearing Loss

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity (≥40 decibels).
Syndromic hearing loss refers to hearing loss associated with other medical or physical findings, including visible abnormalities of the external ear. Because syndromic hearing loss occurs as part of a syndrome of multiple clinical manifestations, it is often recognized more readily as hereditary.

Nonsyndromic hearing loss is defined as hearing loss not associated with other physical signs or symptoms. For nonsyndromic hearing loss, it is more difficult to determine whether the etiology is hereditary or acquired because, by definition, there are no other clinical manifestations at the time of the hearing loss presentation. Nonsyndromic hearing loss accounts for 70% to 80% of genetically determined deafness.

Autosomal recessive patterns of inheritance predominate and account for 80% of congenital nonsyndromic hearing loss. A typical clinical presentation of autosomal recessive nonsyndromic hearing loss involves the following characteristics:

- Sensorineural hearing loss
- Mild-to-profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually nonprogressive
- No associated medical findings.

Most of the remaining 20% of individuals have an autosomal dominant inheritance pattern with a small number having X-linked or mitochondrial inheritance. Individuals with autosomal dominant inheritance typically show progressive nonsyndromic hearing loss, which begins in the second through fourth decades of life.

Diagnosis

Diagnosis of nonsyndromic hearing loss requires an evaluation by appropriate core medical personnel with expertise in the genetics of hearing loss, dysmorphology, audiology, otolaryngology, genetic counseling, and communication with deaf individuals. The evaluation should include family history, as well as a physical examination consisting of otologic examination, airway examination, documentation of dysmorphisms, and neurologic evaluation. However, the clinical diagnosis of nonsyndromic hearing loss is nonspecific because there are a number of underlying etiologies, and often it cannot be determined with certainty whether a genetic cause for hearing loss exists.

Treatment

Treatment of congenital and early-onset hearing loss typically involves enrollment in an educational curriculum for hearing impaired persons and fitting with an appropriate hearing aid. In some

individuals with profound deafness, a cochlear implant can be performed. Early identification of infants with hearing impairment may be useful in facilitating early use of amplification by 6 months of age, and early intervention to achieve age-appropriate communication, speech, and language development. Delays in the development of hearing treatment have been shown to delay development of communication. The primary method for identification of hearing impairment has been newborn screening with audiometry. Genetic testing has not been proposed as a primary screen for hearing loss.

Genetics of Hereditary Hearing Loss

Genes associated with hereditary hearing loss may be associated with an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern. The genetic loci on which variants associated with hereditary hearing loss are usually found are termed DFN, and hereditary hearing loss is sometimes called DFN-associated hearing loss. DFN loci are named based on their mode of inheritance: DFNA associated with autosomal dominant inheritance; DFNB with autosomal recessive inheritance; and DFNX with X-linked inheritance.

Two DFN loci commonly associated with hereditary hearing loss are DFNA3 and DFNB1, both of which map to chromosome 13q12. DFNA3-associated hereditary hearing loss is caused by autosomal dominant pathogenic variants present in the *GJB2* or *GJB6* genes. DFNB1-associated hereditary hearing loss relates to autosomal recessive syndromes in which more than 99% of cases are caused by pathogenic variants in the *GJB2* gene, and less than 1% of remaining cases arise from pathogenic variants to GJB6. A list of available tests for genes at the DFNA3 and DFNB1 loci are provided in Table 1.

Two of the most common disease-associated genes are *GJB2* and *GJB6*. *GJB2* is a small gene with a single coding exon. Variants of this gene are most common in hereditary hearing loss, causing an estimated 50% of the cases of hereditary nonsyndromic hearing loss. The carrier rate in the general population for a recessive deafness-causing *GJB2* variant is approximately 1 in 33. Specific variants have been observed to be more common in certain ethnic populations. Variants in the *GJB2* gene will impact the expression of the Cx26 connexin protein, and almost always cause prelingual, but not necessarily congenital, deafness. Different variants of *GJB2* can present with high phenotypic variation, but it has been demonstrated that it is possible to correlate the type of associated hearing loss with findings on molecular analysis. A systematic review by Chan and Chang (2014), reporting

on *GJB2* variant prevalence, suggested the overall prevalence of *GJB2* variants is similar around the world, although specific variants differ.

Variants in the *GJB6* gene lead to similar effects on abnormal expression of connexin protein Cx30. However, *GJB6* variants are much less common than *GJB2* variants. Of all individuals with hereditary hearing loss, approximately 3% have a variant in the *GJB6* gene.

Table 1. Clinical Characteristics and Testing Methods for GJB2 and GJB6 Variants at the DFNA3 and DFNB1 Loci

Locus	Gene	Onset	Audio profile	Test Method	Variants Detected
DFNA3	*GJB2*	Prelingual	High-frequency progressive	Sequence analysis/variant scanning Targeted variant analysis Deletion/duplication analysis	Sequence variants Specified sequence variants Exonic or whole-gene deletions/duplications
DFNA3	*GJB6*	Prelingual	High-frequency progressive	Sequence analysis/variant scanning Targeted variant analysis Deletion/duplication analysis	Sequence variants Specified sequence variants Exonic or whole-gene deletions/duplications
DFNB1	*GJB2*	Prelingual	Usually stable	Targeted variant analysis Deletion/duplication analysis	GJB2 sequence variants Exon(s) or whole-gene deletions
DFNB1	*GJB6*	Prelingual	Usually stable	Deletion/duplication analysis	GJB6 deletions

Analysis for GJB6 and GJB2 variants can be performed by Sanger sequencing of individual genes. This method has a high degree of validity and reliability but is limited by the ability to sequence 1 gene at a time. With Sanger sequencing, the genes with the most common pathogenic variants are generally sequenced first, followed by sequencing of additional genes if a pathogenic variant is not found.

In addition to the most common genes associated with hereditary hearing loss (GJB6, GJB2), there are many less common disease-associated genes. Some are: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C, and WFS1 genes. Novel genetic variants continue to be identified in cases of hereditary hearing loss. For example, as of 2014, over 2000 pathogenic deafness variants in approximately 130 genes had been reported. By 2018, over 8,100 variants in over 150 genes had been reported. Copy number variants, caused by insertions, deletions, or recombination, can also lead to hearing loss from gene disruption or changes in the number of dose-sensitive genes. The gene most commonly associated with pathogenic copy number variants in hearing loss is STRC, which encodes stereocilin and is the most frequent cause of autosomal recessive causes of nonsyndromic hearing loss after pathogenic variants in GJB2.

Because a large number of genes are associated with hereditary hearing loss, there are various genetic panels for hereditary deafness. Next-generation sequencing technology allows targeted sequencing of multiple genes simultaneously, expanding the ability to examine multiple genes. These panels are alternatives to the sequencing of individual genes such as GJB6 and GJB2. These panels include the most common genes associated with nonsyndromic hearing loss. They may also include many of the less common genes associated with nonsyndromic hearing loss, as well as genes associated with syndromic hearing loss. Also, whole-exome sequencing and whole-genome sequencing have been used to identify novel variants in subjects with a history suggestive of genetic hereditary hearing loss. Targeted genomic enrichment coupled with massively parallel sequencing can be used to identify both single nucleotide variants and copy number variants.

Overlap Between Nonsyndromic Hearing Loss and Recognized Syndromes
There is overlap between hereditary nonsyndromic hearing loss and syndromic hearing loss associated with recognized syndromes. Some genetic variants may be associated with clinical

findings other than hearing loss, but they may not necessarily manifest at the time of presentation with hearing loss. For example, Jervell and Lange-Nielsen syndrome is associated with congenital deafness and prolonged QT interval, but it may present only with deafness without an apparent history to suggest cardiac dysfunction. Additionally, some genes associated with nonsyndromic hearing loss are associated with recognized syndromes. Some genetic syndromes and genes that may overlap with nonsyndromic hearing loss are shown in Table 2.

Table 2. Genes With Overlap Between Syndromic and Nonsyndromic Hearing Loss

Syndrome	Inheritance	Clinical Description	Gene	Reason for Overlap With NSHL
Usher syndrome	For all types: autosomal recessive	For all types: sensorineural HL with retinitis pigmentosa		Retinitis pigmentosa usually not apparent in first decade
Type 1		Congenital severe-to-profound HL Abnormal vestibular function	*MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *SANS*, *CIB2*	DFNB18 (nonsyndromic) may also be caused by variants in *USH1C* DFNB12 (nonsyndromic) may also be caused by variants in *CDH23* DFNB2 (nonsyndromic) and DFNA11 (nonsyndromic) may also be caused by variants in *MYO7A*
Type 2		Congenital mild-to-severe HL Normal vestibular function	*USH2A*, *VLGR1*, *WHRN*	

Syndrome	Inheritance	Clinical Description	Gene	Reason for Overlap With NSHL
Type 3		Progressive HL Progressive vestibular dysfunction	*CLRN1i*, *PDZD7*	
Pendred syndrome	Autosomal recessive	Congenital sensorineural HL Bony labyrinth abnormalities (Mondini dysplasia or dilated vestibular aqueduct) Euthyroid goiter	*SLC26A4* (50%)	Goiter not present until early puberty or adulthood Variants in *SLC26A4* may also cause NSHL
Jervell and Lange-Nielsen syndrome	Autosomal recessive	Congenital deafness Prolongation of the QT interval	*KCNQ1*, *KCNE1*	HL may present without personal or family history of cardiac symptoms (sudden death, SIDS, syncopal episodes, or long QT syndrome)
Wolfram syndrome	Autosomal recessive	Progressive sensorineural HL Diabetes Optic atrophy Progressive neurologic abnormalities	*WFS1*	WFS1-associated HL (DFNA6, DFNA4, DFNA38; congenital HL without associated findings) may also be caused by variants in *WFS1*

HL: hearing loss; NSHL: nonsyndromic hearing loss; SIDS: sudden infant death syndrome.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Molecular diagnostic testing is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Hearing loss is a common birth defect. Approximately 1 in 500 newborns in developed countries is affected by bilateral, permanent hearing loss of moderate or greater severity (≥40 decibels). Syndromic hearing loss refers to hearing loss associated with other medical or physical findings, including visible abnormalities of the external ear. Because syndromic hearing loss occurs as part of a syndrome of multiple clinical manifestations, it is often recognized more readily as hereditary. Nonsyndromic hearing loss is defined as hearing loss not associated with other physical signs or symptoms. Nonsyndromic hearing loss accounts for 70% to 80% of genetically determined deafness, and it is more difficult to determine whether the etiology is hereditary or acquired.

Summary of Evidence

For individuals who are suspected of having hereditary nonsyndromic hearing loss who receive genetic testing, the evidence includes small retrospective, single-center studies, case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and testing yield for nonsyndromic hearing loss. Relevant outcomes are test accuracy and validity, changes in reproductive decision-making, morbid events, and resource utilization. Genetic variants in *GJB2*, *GJB6*, and numerous other genes are found in a substantial percentage of individuals with hereditary hearing loss. Of all individuals with suspected hereditary hearing loss after clinical examination, a

substantial proportion will be found to have a genetic variant. The probability of finding a genetic variant is increasing as new variants are identified. False-positive results on genetic testing are expected to be very low. For diagnosis, there are a number of potential benefits of genetic testing, including a reduction in the need for alternative diagnostic tests and monitoring of individuals with genetically identified syndromic hearing loss associated with other medical conditions. Clinical guidelines have recommended a tiered genetic testing approach, starting with the most common genes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a family history of hereditary nonsyndromic hearing loss who receive preconception genetic testing to determine carrier status, the evidence is limited but includes clinical guidelines. Relevant outcomes are test accuracy and validity, changes in reproductive decision-making, morbid events, and resource utilization. Genetic variants in *GJB2*, *GJB6*, and numerous other genes are found in a substantial percentage of individuals with hereditary hearing loss. The probability of finding a genetic variant is increasing as new gene variants are identified. False-positive results on genetic testing are expected to be very low. There are several situations for which there is potential clinical utility of testing for genes associated with hereditary hearing loss. For parents at high-risk of having offspring with hereditary hearing loss, genetic testing can be useful as an aid in reproductive decision-making. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies And Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2013 Input

In response to requests, input was received from 2 physician specialty societies and 2 academic medical centers while this policy was under review in 2013. Reviewers agreed with the medically necessary indication for carrier testing, and with additional indications for carrier testing. There was support for testing the index case to confirm nonsyndromic hearing loss among most reviewers.

Reviewers in favor of genetic testing cited the ability to distinguish nonsyndromic hearing loss from other causes of hearing loss, to streamline the diagnostic workup and avoid further unnecessary testing, and to provide referrals to specialists when specific types of pathogenic variants identified are associated with disorders in other organ systems. It was considered that 2 contextual factors were present: barriers to performing high-quality trials and the potential to reduce harms by avoiding unnecessary testing.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics
In 2007, the American Academy of Pediatrics (AAP) issued recommendations on early hearing detection:

> "Every infant with confirmed hearing loss and/or middle ear dysfunction should be referred for otologic and other medical evaluation. The purpose of these evaluations is to determine the etiology of hearing loss, to identify related physical conditions, and to provide recommendations for medical/surgical treatment as well as referral for other services. Essential components of the medical evaluation include clinical history, family history of childhood-onset permanent hearing loss, identification of syndromes associated with early- or late-onset permanent hearing loss, a physical examination, and indicated radiologic and laboratory studies (including genetic testing)."
>
> "The evaluation, therefore, should include a review of family history of specific genetic disorders or syndromes, including genetic testing for gene mutations such as GJB2 (connexin-26), and syndromes commonly associated with early-onset childhood sensorineural hearing loss."
>
> "All families of children with confirmed hearing loss should be offered, and may benefit from, a genetics evaluation and counseling. This evaluation can provide families with information on etiology of hearing loss, prognosis for progression, associated disorders (eg, renal, vision,

cardiac), and likelihood of recurrence in future offspring. This information may influence parents' decision-making regarding intervention options for their child."

The 2013 supplement to the AAP 2007 position statement on early intervention after confirmation of hearing loss in a child states in its recommendations for monitoring that parents or guardians should be educated about the "importance of medical, genetic, ophthalmologic, and cardiac (EKG) evaluations on children with any type and degree of hearing loss."

Also in 2013 (reaffirmed June 2018), the AAP issued a policy statement on ethical issues in genetic testing of children. Following are some of their recommendations:

General recommendations:
"Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child."

Diagnostic testing:
"In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally and when appropriate, the assent of the child should be obtained."

Newborn screening:
"The AAP and ACMG [American College of Medical Genetics] support the mandatory offering of newborn screening for all children. After educating and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected."

Carrier testing:
"The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood."

Predictive gene testing:
"Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained."

"Predictive genetic testing for adult-onset conditions should generally be deferred unless an intervention initiated in childhood may reduce morbidity or mortality."

American College of Medical Genetics and Genomics
In 2014, the American College of Medical Genetics and Genomics issued practice guidelines for the clinical evaluation and etiologic diagnosis of hearing loss. The guidelines recommended obtaining testing for acquired hearing loss if there is clinical suspicion, including testing for cytomegalovirus, imaging, or other testing based on the suspected etiology. 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, the guidelines made the following recommendations for a tiered diagnostic approach:

- "Pretest genetic counseling should be provided, and, with individual's's informed consent, genetic testing should be ordered.
    - Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics.
    - In the absence of any specific clinical indications and for singleton cases and cases with apparent autosomal recessive inheritance, the next step should be testing for DFNB1-related hearing loss (due to mutations in GJB2 and adjacent deletions in GJB6).
    - If initial genetic testing is negative, genetic testing using gene panel tests, NGS [next-generation sequencing] technologies such as large sequencing panels targeted toward hearing loss-related genes, whole-exome sequencing, or whole-genome sequencing may be considered. Because several tests are clinically available, the clinician must be aware of the genes included in the test (panel) chosen and the performance characteristics of the platform chosen, including coverage, analytic sensitivity, and what types of mutations will be detected….

- If genetic testing reveals mutation(s) in a hearing loss-related gene, mutation-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
There were no ongoing or unpublished trials regarding this policy as of February 2023.

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Policy History

Original Effective Date: 12/18/2013
Current Effective Date: 08/14/2023

12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. New policy.
12/04/2014	Medical Policy Committee review
12/07/2014	Medical Policy Implementation Committee approval. Policy title and policy statements changed to refer to “hereditary hearing loss” (from “nonsyndromic hearing loss”) to reflect significant overlap between nonsyndromic and syndromic hearing loss.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy guidelines section added
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review

Genetic Testing for Hereditary Hearing Loss

Policy # 00379
Original Effective Date: 12/18/2013
Current Effective Date: 08/14/2023

12/20/2017	Medical Policy Implementation Committee approval. The policy is revised with updated genetics nomenclature. "Mutations" changed to "genes" in policy statements; statements otherwise unchanged. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. "Suspected hereditary" added to the first policy statement with coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/20/2022	Coding update
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Replaced "patients" with individuals" in the coverage section. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81252, 81253, 81254, 81430, 81431
HCPCS	S3844
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.