MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEARING LOSS
POLICY NUMBER	MP 2.319

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**11/1/2024**

I. POLICY

Genetic testing for hereditary hearing loss mutations (*GJB2, GJB6,* and other hereditary hearing loss-related genes) in individuals with suspected hearing loss to confirm the diagnosis of hereditary hearing loss (see Policy Guidelines) may be considered **medically necessary**.

Preconception genetic testing (carrier testing) for hereditary hearing loss–related genes (*GJB2, GJB,6* and other hereditary hearing loss related genes) in parents may be considered **medically necessary** when at least one of the following conditions has been 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

Genetic testing for hereditary hearing loss genes is considered **investigational** for all other situations, including, but not limited to, testing individuals without hearing loss (except as addressed in related policies, e.g., **MP 7.009** Preimplantation Genetic Testing). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

This policy primarily focuses on the use of genetic testing to identify a cause of suspected hereditary hearing loss. Hereditary hearing loss can be classified as syndromic or nonsyndromic. Nonsyndromic hearing loss is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation. Syndromic hearing loss is hearing loss associated with other signs and symptoms characteristic of a specific syndrome. 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.

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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 (SNHL)
- Mild to profound (more commonly) degree of hearing impairment
- Congenital onset
- Usually non-progressive

In addition to pathogenic variants in the *GJB6* and *GJB2* genes, there are many less common pathologic variants found in other genes. Some of these 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.

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 be improved 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 syndrome or nonsyndromic cause of hearing loss (e.g., 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 (CMV) 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 with 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 (HGVS) 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 (see 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 (ACMG) and the Association for Molecular Pathology (AMP) 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

Experts recommend formal genetic counseling for individuals who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could

have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:
MP 7.009 Preimplantation Genetic Testing

II. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND TOP

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 patients have an autosomal dominant inheritance pattern with a small number having X-linked or mitochondrial inheritance. Patients 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 patients. 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 patients 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 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 commonly 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 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.

Table 1. Clinical Characteristics and Testing Methods for *GJB2* and *GJB6* Variants

Locus	Gene	Onset	Audioprofile	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

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 patients with hereditary hearing loss, approximately 3% have a variant in the *GJB6* gene.

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. In contrast, only 18 pathogenic copy number variants had been identified by 2014. Copy number variants, caused by insertions, deletions, or recombination, can 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 are 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 hearing loss (HL) with retinitis pigmentosa		• Retinitis pigmentosa, usually not apparent in 1st decade
Type 1		• Congenital severe-to-profound HL • Abnormal	*MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2*	• *DFNB18* (nonsyndromic) may also be caused by

		vestibular function		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*	
Type 3		• Progressive HL • Progressive vestibular dysfunction	*CLRN1i, PDZD7*	
Pendred syndrome	Autosomal recessive	• Congenital SNHL • 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 nonsyndromic hearing loss
Jervell and Lange-Nielsen syndrome	Autosomal recessive	• Congenital deafness • Prolongation of the QT interval	*KCNQ, 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 SNHL • Diabetes • Optic atrophy • Progressive neurological	*WFS1*	• *WFS1*-associated HL (DFNA6/14/38; congenital HL without

		abnormalities		associated findings) may also been caused by variants in *WFS1*

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

Regulatory Status

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

IV. RATIONALE

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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 patients with hereditary hearing loss. Of all patients 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 patients 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 patients 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 an 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 a meaningful improvement in the net health outcome.

V. DEFINITIONS

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NONSYNDROMIC HEARING LOSS is hearing loss not associated with other physical signs and symptoms at the time of hearing loss presentation

SYNDROMIC HEARING LOSS is hearing loss associated with other signs and symptoms characteristic of a specific syndrome

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
S3844	81252	81253	81254	81430	81431			

ICD-10-CM Diagnosis Codes	Description
H90.3	Sensorineural hearing loss, bilateral
H90.41	Sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.42	Sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H90.5	Unspecified sensorineural hearing loss
H90.6	Mixed conductive and sensorineural hearing loss, bilateral
H90.71	Mixed conductive and sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.72	Mixed conductive and sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H91.8X1	Other specified hearing loss, right ear
H91.8X2	Other specified hearing loss, left ear
H91.8X3	Other specified hearing loss, bilateral
Z31.438	Encounter for other genetic testing of female for procreative management
Z31.448	Encounter for other genetic testing of male for procreative management
Z82.2	Family history of deafness and hearing loss

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X. POLICY HISTORY

TOP

MP 2.319	**08/10/2020 Consensus Review.** Policy statement unchanged. Added FEP

	variation. References added.
	05/12/2021 Consensus Review. Policy statement unchanged. References, and rationale updated. Coding reviewed.
	05/05/2022 Consensus Review. No change to policy statement. References reviewed and updated.
	04/12/2023 Consensus Review. No change to policy statement. References and coding reviewed. Background updated.
	05/23/2024 Consensus Review. No change to policy statement. New references.

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