



Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206

Original Effective Date: 09/20/2006

Current Effective Date: 11/13/2023

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: Gene Expression Profiling for Cutaneous Melanoma is addressed separately in medical policy 00622.

Note: Germline Genetic Testing for Pancreatic Cancer Susceptibility Gene is addressed separately in medical policy 00706.

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 once per lifetime germline testing for *p16/CDKN2A* variant in individuals considered at high risk for cutaneous melanoma to be **eligible for coverage**.**

Patient Selection Criteria

The Company may consider once per lifetime germline testing for *CDKN2A (p16)* variant in individuals considered at high risk for cutaneous melanoma when ANY of the following criteria are met:

- An affected individual diagnosed with 3 or more invasive cutaneous melanomas; OR
- An affected individual or close family relative diagnosed with a combination of invasive melanoma, pancreatic cancer, and/or astrocytoma (when testing of affected patient is not available); OR
- An affected individual with invasive cutaneous melanoma who has a first-degree relative diagnosed with pancreatic cancer (see medical policy 00706).

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Note:

Individuals eligible for CDKN2A testing with family history of multiple invasive cutaneous melanomas, and pancreatic, renal and/or breast cancer, astrocytoma, uveal melanoma, and/or mesothelioma may be considered for once per lifetime germline mutation or polymorphism testing also for other genes predisposing to melanoma (e.g., CDK4, MC1R, BRCA2, BAP1 [especially for uveal melanoma], TERT, MITF, PTEN). In this situation and when applicable, procedure code representing small panel (e.g., 81479) should be reported rather than multiple codes representing individual or sequential gene testing.

When known, testing of an unaffected (asymptomatic) individual should focus on the pathogenic or likely pathogenic variant found in the affected patient.

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 genes associated with familial cutaneous malignant melanoma (CMM) or associated with susceptibility to cutaneous malignant melanoma (CMM) in all other situations to be **investigational**.*

When Services Are Considered Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

Note: *Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders.*

Policy Guidelines

Genetics Nomenclature Update

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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 is being 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 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

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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 patients 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.

Background/Overview

Genetics of Cutaneous Malignant Melanoma

A genetic predisposition to cutaneous malignant melanoma cutaneous malignant melanoma is suspected in specific clinical situations: (1) melanoma has been diagnosed in multiple family members; (2) multiple primary melanomas have been identified in a single patient; and (3) early age of onset. A positive family history of melanoma is the most significant risk factor; it is estimated that approximately 10% of melanoma cases report a first- or second-degree relative with melanoma. Although some of the familial risk may be related to shared environmental factors, 3 principal genes involved in cutaneous malignant melanoma susceptibility have been identified. Cyclin-dependent kinase inhibitor 2A (*CDKN2A*), located on chromosome 9p21, encodes proteins that act as tumor suppressors. Variants in this gene can alter the tumor suppressor function. The second gene, cyclin-dependent kinase 4 (*CDK4*), is an oncogene located on chromosome 12q13 and has been identified in about 6 families worldwide. A third gene, not fully characterized, maps to chromosome 1p22.

The incidence of *CDKN2A* disease-associated variants in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a *CDKN2A* disease-associated variant. Variants

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are also infrequent in those with an early age of onset or those with multiple primary melanomas. However, the incidence of *CDKN2A* disease-associated variants increases with a positive family history; *CDKN2A* disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20% to 40% in patients with 3 or more affected first-degree relatives. Variant detection rates of the *CDKN2A* gene are generally estimated to be 20% to 25% in hereditary cutaneous malignant melanoma but can vary between 2% and 50%, depending on the family history and population studied. Validated clinical risk prediction tools to assess the probability that an affected individual carries a germline *CDKN2A* disease-associated variant are available.

Familial cutaneous malignant melanoma has been described in families in which either 2 first-degree relatives are diagnosed with melanoma or a family with 3 melanoma patients, irrespective of the degree of relationship. Others have defined familial cutaneous malignant melanoma as having at least 3 (first-, second-, or third-degree) affected members or 2 affected family members in which at least 1 was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative or 1 member had multiple primary melanomas. Other malignancies associated with familial cutaneous malignant melanoma, specifically those associated with *CDKN2A* variants, have been described. The most pronounced associated malignancy is pancreatic cancer. Other associated malignancies include other gastrointestinal malignancies, breast cancer, brain cancer, lymphoproliferative malignancies, and lung cancer. It is also important to recognize that other cancer susceptibility genes may be involved in these families. In particular, germline *BRCA2* gene variants have been described in families with melanoma and breast cancer, gastrointestinal cancer, pancreatic cancer, or prostate cancer.

Some common allele(s) are associated with increased susceptibility to cutaneous malignant melanoma but have low-to-moderate penetrance. One gene of moderate penetrance is the melanocortin 1 receptor gene (*MC1R*). Variants in this gene are relatively common and have low penetrance for cutaneous malignant melanoma. This gene is associated with fair complexion, freckles, and red hair, all risk factors for cutaneous malignant melanoma. Variants in *MC1R* also modify the cutaneous malignant melanoma risk in families with *CDKN2A* variants.

Cutaneous malignant melanoma can occur either with or without a family history of multiple dysplastic nevi. Families with both cutaneous malignant melanoma and multiple dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome. This syndrome is difficult to define because there is no agreement on a standard phenotype, and dysplastic nevi

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occur in up to 50% of the general population. Atypical or dysplastic nevi are associated with an increased risk for cutaneous malignant melanoma. Initially, the phenotypes of atypical nevi and cutaneous malignant melanoma were thought to co-segregate in familial atypical multiple mole and melanoma syndrome families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that, in families with *CDKN2A* variants, some family members with multiple atypical nevi were noncarriers of the *CDKN2A* familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of cutaneous malignant melanoma susceptibility in these families.

In 2012, Ward et al reviewed the literature on germline melanoma susceptibility and concluded that in addition to the 2 rare, high-penetrance variants (*CDKN2A* and *CDK4*), there are potentially many single nucleotide polymorphisms which have small effects and low penetrance.

Management

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist. In 2012, Badenas et al suggested several parameters to guide genetic testing for melanoma: in countries with a low to medium incidence of melanoma, genetic testing should be offered to families with 2 cases of melanoma or to an individual with 2 primary melanomas (the rule of 2); in countries with a high incidence of melanoma, genetic testing should be offered to families with 3 cases of melanoma, or to an individual with 3 primary melanomas (the rule of 3). In 2017, Delaunay et al suggested a modification to the recommendations by Badenas et al (2012). In countries with a low to medium incidence of melanoma, Delaunay et al (2017) proposed that the rule of 2 should guide genetic testing only if there is an individual with melanoma before the age of 40, otherwise the rule of 3 should apply.

In general, individuals with increased risk of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

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). Melaris®[‡] (Myriad Genetics) and other *CDKN2A*

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tests are 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. FDA 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.

Cutaneous melanoma is the third most common type of skin cancer, but the most lethal. Some cases of cutaneous malignant melanoma are familial. Potential genetic markers for this disease are being evaluated in affected individuals with a family history of the disease and in unaffected individuals in a high-risk family.

For individuals who have cutaneous malignant melanoma and a family history of this disease who receive genetic testing for genes associated with familial cutaneous malignant melanoma, the evidence includes genetic association studies measuring prevalence of variants in certain genes among those with cutaneous malignant melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual risk with a benign variant. Currently, management of melanoma patients, which involves surveillance and education on sun avoidance behaviors, does not change based on genetic variants identified in genes associated with familial cutaneous malignant melanoma; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and in a family at high-risk of developing cutaneous malignant melanoma who receive genetic testing for genes associated with familial cutaneous malignant melanoma, the evidence includes genetic association studies correlating variants in certain genes and the risk of developing cutaneous malignant melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual

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risk with a benign variant. Currently, management of patients considered high-risk for cutaneous malignant melanoma focuses on the reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. It is unclear how genetic testing for variants associated with increased risk of cutaneous malignant melanoma would alter these management recommendations; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

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 Society of Clinical Oncology

In an American Society of Clinical Oncology (ASCO) publication, Kefford et al (2002) noted that the sensitivity and specificity of tests for *CDKN2A* variants are not fully known. Because interpreting genetic tests is difficult and because test results do not alter patient management, ASCO recommended that *CDKN2A* genetic testing should be performed only in clinical trials, for several reasons, including a low likelihood of finding disease-associated variants in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression of the trait among disease-associated variant carriers, and lack of proven melanoma prevention and surveillance strategies. Additionally, it was noted that all individuals with risk factors for cutaneous melanoma should follow programs of sun protection and skin surveillance, not just those considered high-risk due to family history.

In 2003, and 2010, the ASCO issued policy statements on genetic and genomic testing for cancer susceptibility. Both statements recommended that, outside of a research setting, genetic testing for cancer susceptibility should only be offered when the following 3 criteria are met: (1) the individual being tested has a personal or family history suggestive of an underlying hereditary component; (2) the genetic test can be adequately interpreted; and (3) test results will guide diagnosis and management.

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In 2010, the ASCO updated its policy statement on genetic and genomic testing for cancer susceptibility. The ASCO recommended that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

In 2015, the ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility. The ASCO “affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history.”

American Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma. Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma was recommended for consideration with a level IIIC grade of evidence. The Work Group explained that “there is no strong evidence that genetic evaluation is either harmful or helpful.” Criteria for cancer risk genetic counseling with possible multigene testing for patients with cutaneous melanoma include:

- A family history of invasive cutaneous melanoma or pancreatic cancer (≥ 3 affected members on 1 side of the family)
- Multiple primary invasive cutaneous melanomas (≥ 3), including 1 early-onset tumor (at age < 45 years)
- A family history of mesothelioma, meningioma, and/or uveal melanoma and ≥ 1 melanocytic BAP1-mutated atypical intradermal tumor (MBAIT)
- ≥ 2 MBAITs

These 2019 guidelines are similar to standards previously established by the International Melanoma Genetics Consortium in 2009.

National Comprehensive Cancer Network

Current (v.1.2023) National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma include the following follow-up recommendations:

- “Consider genetic counseling referral for *p16/CDKN2A* mutation [variant] testing in the presence of 3 or more invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family.”

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- "Multigene panel testing that includes *CDKN2A* is recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer."
- "Testing for other genes that can harbor melanoma-predisposing mutations [e.g., *MC1R*, *CDK4*, *TERT*, *MITF*, *PTEN*, *BRCA2*, and *BAP1*] may be warranted."

Current (v.2.2023) NCCN guidelines for genetic/familial high-risk assessment in breast, ovarian, and pancreatic cancer state that for *CDKN2A* mutation carriers 'Comprehensive skin examination by a dermatologist, supplemented with total body photography and dermoscopy is recommended biannually'.

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

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT00040352	Clinical, Laboratory, and Epidemiologic Characterization of Individuals and Families at High Risk of Melanoma	3000	NR (recruiting)
NCT00849407	Genetic Risk Factors and Acquired Oncogenic Mutations of Melanoma	2000	Dec 2020 (unknown)
NCT00450593	Studies of Familial Melanoma	5000	Dec 2020 (unknown)

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NCT00445783	Melanoma Family Case-Control Study Protocol	3700	Dec 2020 (unknown)
NCT00591500	A Model for Genetic Susceptibility: Melanoma	4082	Jul 2023 (ongoing)
NCT02645149 ^a	Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma (MatchMel)	1000	Dec 2028 (recruiting)
<i>Unpublished</i>			
NCT00339222	Family Study of Melanoma in Italy	1708	Jun 2020 (completed)

NCT: national clinical trial; NR: not reported.

^a Denotes industry-sponsored or cosponsored trial.

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Policy History

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09/06/2006	Medical Director review
09/20/2006	Medical Policy Committee approval
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee review
10/14/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Added “familial” to the policy title. Replaced “hereditary” with “familial” in the investigational statement and throughout the policy.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review

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11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/11/2020	Coding update
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage went from investigational to eligible with criteria. Senate bill review.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. Added When services are not covered section for repeat germline testing and a note to the policy.

Next Scheduled Review Date: 10/2024

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	81167, 81216, 81217, 81345, 81404, 81479 Delete code effective 1/1/2023: 81529
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses Z12.83, Z80.8

*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;

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- 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.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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.

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