



Louisiana

Genetic Testing for Neurofibromatosis

Policy # 00502

Original Effective Date: 04/20/2016

Current Effective Date: 07/13/2020

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.

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 neurofibromatosis (NF) to be **eligible for coverage**** when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing.

Based on review of available data, the Company may consider genetic testing for neurofibromatosis in at-risk relatives with no signs of disease to be **eligible for coverage**** when a definitive diagnosis cannot be made without genetic testing AND at least one of the following criteria is met:

- A close relative (ie, first-, second-, or third-degree relative) has a known *NF* variant; or
- A close relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable.

When Services Are Considered Investigational

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

Genetic testing for neurofibromatosis for all other situations and when patient selection criteria are not met is considered to be **investigational.***

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Policy Guidelines

Testing Strategy

For evaluation of neurofibromatosis type 1 (NF1), testing for a variety of pathogenic variants of *NF1*, preferably through a multistep variant detection protocol, is indicated. If no *NF1* pathogenic variants are detected in patients with suspected NF1, testing for *SPRED1* variants is reasonable.

Definitions

Mutation Scanning

Mutation scanning is a process by which a particular segment of DNA is screened to identify sequence variants. Variant gene regions are then further analyzed (eg, by sequencing) to identify the sequence alteration. Mutation scanning allows for screening of large genes and novel sequence variants.

Schwann Cells

Schwann cells cover the nerve fibers in the peripheral nervous system and form the myelin sheath.

Simplex Disease

Simplex disease is a single occurrence of a disease in a family.

Somatic Mosaicism

Somatic mosaicism is the occurrence of 2 genetically distinct populations of cells within an individual, derived from a postzygotic variant. Unlike inherited variants, somatic mosaic variants may affect only a portion of the body and are not transmitted to progeny.

Genetic Counseling

Genetic counseling is primarily aimed at patients 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.

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Background/Overview

Neurofibromatosis

There are three major clinically and genetically distinct forms of neurofibromatosis (NF): NF type 1 (NF1; also known as von Recklinghausen disease), NF type 2 (NF2), and schwannomatosis.

Neurofibromatosis Type 1

NF1 is one of the most common dominantly inherited genetic disorders, with an incidence at birth of 1 in 3000 individuals.

Clinical Characteristics

The clinical manifestations of NF1 show extreme variability, between unrelated individuals, among affected individuals within a single-family, and within a single person at different times in life.

NF1 is characterized by multiple café-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. Segmental NF1 is limited to one area of the body. Many individuals with NF1 only develop cutaneous manifestations of the disease and Lisch nodules.

Cutaneous Manifestations

Café-au-lait macules occur in nearly all affected individuals, and intertriginous freckling occurs in almost 90%. Café-au-lait macules are common in the general population, but when more than six are present, NF1 should be suspected. Café-au-lait spots are often present at birth and increase in number during the first few years of life.

Neurofibromas

Neurofibromas are benign tumors of Schwann cells that affect virtually any nerve in the body and develop in most people with NF1. They are divided into cutaneous and plexiform types. Cutaneous neurofibromas, which develop in almost all people with NF1, are discrete, soft, sessile, or pedunculated tumors. Discrete cutaneous and subcutaneous neurofibromas are rare before late childhood. They may vary from a few to hundreds or thousands, and the rate of development may vary greatly from year to year. Cutaneous neurofibromas do not carry a risk of malignant transformation but may be a major cosmetic problem in adults.

Plexiform neurofibromas, which occur in about half of individuals with NF1, are more diffuse growths that may be locally invasive. They can be superficial or deep and, therefore, the extent

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cannot be determined by clinical examination alone; magnetic resonance imaging (MRI) is the method of choice for imaging plexiform neurofibromas.¹ Plexiform neurofibromas represent a major cause of morbidity and disfigurement in individuals with NF1. They tend to develop and grow in childhood and adolescence and stabilize throughout adulthood.¹ Plexiform neurofibromas can compress the spinal cord or airway and can transform into malignant peripheral nerve sheath tumors. Malignant peripheral nerve sheath tumors occur in approximately 10% of affected individuals.¹

Central Nervous System Tumors

Optic gliomas, which can lead to blindness, develop in the first six years of life. Symptomatic optic gliomas usually present before six years of age with loss of visual acuity or proptosis, but they may not become symptomatic until later in childhood or adulthood.

While optic pathway gliomas are particularly associated with NF1, other central nervous system tumors occur at higher frequency in NF1, including astrocytomas and brainstem gliomas.

Other Findings

Other findings in NF1 include:

- Intellectual disability occurs at a frequency of about twice that in the general population, and features of autism spectrum disorder occur in up to 30% of children with NF1.
- Musculoskeletal features include dysplasia of the long bones, most often the tibia and fibula, which is almost always unilateral. Generalized osteopenia is more common in people with NF1 and osteoporosis is more common and occurs at a younger age than in the general population.
- Cardiovascular involvement includes the common occurrence of hypertension. Vasculopathies may involve major arteries or arteries of the heart or brain and can have serious or fatal consequences. Cardiac issues include valvar pulmonic stenosis, and congenital heart defects and hypertrophic cardiomyopathy may be especially frequent in individuals with NF1 whole gene deletions. Adults may develop pulmonary hypertension, often in association with parenchymal lung disease.
- Lisch nodules are innocuous hamartomas of the iris.

Diagnosis

Although the clinical manifestations of NF1 are extremely variable and some are age-dependent, the diagnosis can usually be made on clinical findings, and genetic testing is rarely needed.¹

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The clinical diagnosis of NF1 should be suspected in individuals with the diagnostic criteria for NF1 developed by the National Institute of Health (NIH). The criteria are met when an individual has two or more of the following features:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in post pubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (raised, tan-colored hamartomas of the iris)
- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
- A first-degree relative with NF1 as defined by the above criteria.

In adults, the clinical diagnostic criteria are highly specific and sensitive for a diagnosis of NF1.1, Approximately half of the children with NF1 and no known family history of NF1 meet NIH criteria for the clinical diagnosis by age one year. By eight years of age, most meet NIH criteria because many features of NF1 increase in frequency with age. Children who have inherited NF1 from an affected parent can usually be diagnosed within the first year of life because the diagnosis requires one diagnostic clinical feature in addition to a family history of the disease. This feature is usually multiple café-au-lait spots, present in infancy in more than 95% of individuals with NF1.

Young children with multiple café-au-lait spots and no other features of NF1 who do not have a parent with signs of NF1 should be suspected of having NF1 and should be followed clinically as if they do. A definitive diagnosis of NF1 can be made in most children by four years of age using the NIH criteria.

Genetics

NF1 is caused by dominant loss-of-function variants in the NF1 gene, which is a tumor suppressor gene located at chromosome 17q11.2 that encodes neurofibromin, a negative regulator of RAS activity. About half of affected individuals have a de novo NF1 variant. Penetrance is virtually complete after childhood though expressivity is highly variable.

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The variants responsible for NF1 are heterogeneous and include nonsense and missense single nucleotide changes, single-base insertions or deletions, splicing variants ($\approx 30\%$ of cases), whole gene deletions ($\approx 5\%$ of cases), intragenic copy number variants, and other structural rearrangements. Several thousand pathogenic NF1 variants have been identified and none is frequent.

Management

Patient management guidelines for NF1 have been developed by the American Academy of Pediatrics, the National Society of Genetic Counselors, and other expert groups.

After an initial diagnosis of NF1, the extent of the disease should be established, with a personal medical history and physical examination and particular attention to features of NF1, ophthalmologic evaluation including slit-lamp examination of the irides, developmental assessment in children, and other studies as indicated on the basis of clinically apparent signs or symptoms.

Surveillance recommendations for an individual with NF1 focus on regular annual visits for skin examination for new peripheral neurofibromas, signs of plexiform neurofibroma or progression of existing lesions, checks for hypertension, other studies (eg, MRI) as indicated based on clinically apparent signs or symptoms, and monitoring of abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist. In children, recommendations include annual ophthalmologic examination in early childhood (less frequently in older children and adults) and regular developmental assessment.

Long-term care goals for individuals with NF1 are early detection and treatment of symptomatic complications.

It is recommended that radiotherapy is avoided because radiotherapy in individuals with NF1 may be associated with a high-risk of developing a malignant peripheral nerve sheath tumor within the field of treatment.

Legius Syndrome

Clinical Characteristics

A few clinical syndromes may overlap clinically with NF1. In most cases, including Proteus syndrome, Noonan syndrome, McCune-Albright syndrome, and LEOPARD syndrome, patients will be missing key features or will have features of the other disorder. However, Legius syndrome is a

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rare autosomal-dominant disorder characterized by multiple café-au-lait macules, intertriginous freckling, macrocephaly, lipomas, and potential attention-deficit/hyperactivity disorder. Misdiagnosis of Legius syndrome as NF1 might result in overtreatment and psychological burden on families about potential serious NF-related complications.

Genetics

Legius syndrome is associated with pathogenic loss-of-function variants in the *SPRED1* gene on chromosome 15, which is the only known gene associated with Legius syndrome.

Management

Legius syndrome typically follows a benign course and management generally focuses on the treatment of manifestations and prevention of secondary complications. Treatment of manifestations include behavioral modification and/or pharmacologic therapy for those with attention-deficit/hyperactivity disorder; physical, speech, and occupational therapy for those with identified developmental delays; and individualized education plans for those with learning disorders.

Neurofibromatosis Type 2

NF2 (also known as bilateral acoustic neurofibromatosis and central neurofibromatosis) is estimated to occur in 1 in 33000 individuals.

Clinical Characteristics

NF2 is characterized by bilateral vestibular schwannomas and associated symptoms of tinnitus, hearing loss, and balance dysfunction. The average age of onset is 18 to 24 years, and almost all affected individuals develop bilateral vestibular schwannomas by age 30 years. Affected individuals may also develop schwannomas of other cranial and peripheral nerves, ependymomas, meningiomas, and, rarely, astrocytomas. The most common ocular finding, which may be the first sign of NF2, is posterior subcapsular lens opacities which rarely progress to visually significant cataracts.

Most patients with NF2 present with hearing loss, which is usually unilateral at the onset. Hearing loss may be accompanied or preceded by tinnitus. Occasionally, features such as dizziness or imbalance are the first symptom. A significant proportion of cases (20%-30%) present with an intracranial meningioma, spinal, or cutaneous tumor. The presentation in pediatric populations may

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differ from adult populations as vestibular schwannomas may account for only 15% to 30% of initial symptoms.

Diagnosis

The diagnosis of NF2 is usually based on clinical findings, with diagnosis depending on the presence of one of the following modified NIH diagnostic criteria:

- Bilateral vestibular schwannomas
- A first-degree relative with NF2 AND
 - Unilateral vestibular schwannoma OR
 - Any two of meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities.
- Multiple meningiomas AND
 - Unilateral vestibular schwannoma OR
 - Any two of schwannoma, glioma, neurofibroma, cataract.

Genetics

NF2 is inherited in an autosomal-dominant manner; approximately 50% of individuals have an affected parent, and the other 50% have NF2 as a result of a de novo variant.

Between 25% and 33% of individuals with NF2 caused by a de novo variant have somatic mosaicism. Variant detection rates are lower in simplex cases and in an individual in the first generation of a family to have NF2 because they are more likely to have somatic mosaicism. Somatic mosaicism can make clinical recognition of NF2 difficult and results in lower variant detection rates. Clinical recognition of NF2 in these patients may be more difficult because these individuals may not have bilateral vestibular schwannomas. Variant detection rates may also be lower because molecular genetic test results may be normal in unaffected tissue (eg, lymphocytes), and molecular testing of tumor tissue may be necessary to establish the presence of somatic mosaicism.

Management

In an individual diagnosed with NF2, it is recommended that an initial evaluation establishes the extent of the disease, typically using cranial MRI, hearing evaluation, and ophthalmologic and cutaneous examinations.

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Counseling is recommended for insidious problems with balance and underwater disorientation, which can result in drowning.

Hearing preservation and augmentation are part of the management of NF2, as is early recognition and management of visual impairment from other manifestations of NF2. Therefore, routine hearing and eye examination should be conducted.

Surveillance measures for affected or at-risk individuals include annual MRI beginning at around age ten and continuing until at least the fourth decade of life.

Treatment of manifestations includes surgical resection of small vestibular schwannomas, which may often be completely resected with preservation of hearing and facial nerve function. Larger tumors are often managed expectantly with debulking or decompression when brain stem compression, deterioration of hearing, and/or facial nerve dysfunction occur.

Radiotherapy should be avoided, because radiotherapy of NF2-associated tumors, especially in childhood, may induce, accelerate, or transform tumors.

Evaluation of At-Risk Relatives

Early identification of relatives who have inherited the family-specific NF2 variant allows for appropriate screening using MRI for neuroimaging and audiologic evaluation, which results in earlier detection and improved outcomes. Identification of at-risk relatives who do not have the family-specific *NF2* variant eliminates the need for surveillance.

Schwannomatosis

Schwannomatosis is a rare condition defined as multiple schwannomas without vestibular schwannomas that are diagnostic of NF2. Individuals with schwannomatosis may develop intracranial, spinal nerve root, or peripheral nerve tumors. Familial cases are inherited in an autosomal-dominant manner, with highly variable expressivity and incomplete penetrance. Clinically, schwannomatosis is distinct from NF1 and NF2, although some individuals eventually fulfill diagnostic criteria for NF2. *SMARCB1* variants have been shown to cause 30% to 60% of familial schwannomatosis but only a small number of simplex disease.

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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. Lab tests for NF are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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

Neurofibromatoses are autosomal dominant genetic disorders associated with tumors of the peripheral and central nervous systems. There are three clinically and genetically distinct forms: neurofibromatosis (NF) type 1, NF type 2, and schwannomatosis. The potential benefit of genetic testing for NF is to confirm the diagnosis in an individual with suspected NF who does not fulfill clinical diagnostic criteria or to determine future risk of NF in asymptomatic at-risk relatives.

For individuals who have suspected NF who receive genetic testing for NF, the evidence includes clinical validation studies of a multistep diagnostic protocol and genotype-phenotype correlation studies. The relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. A multistep variant testing protocol identifies more than 95% of pathogenic variants in NF type 1; for NF type 2, the variant detection rate approaches more than 70% in simplex cases and exceeds 90% for familial cases. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic, with a close relative(s) with an NF diagnosis, who receive genetic testing for NF, there is no direct evidence. The relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. For individuals with a known pathogenic variant in the family, testing of at-risk relatives will confirm or exclude the variant with high certainty. While direct evidence on the clinical utility of genetic testing for NF is lacking, a definitive diagnosis resulting from genetic testing can direct patient care according to established clinical management guidelines, including referrals to the proper specialists, treatment of manifestations, and surveillance. Testing of at-risk relatives will lead to initiation or avoidance of

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management and/or surveillance. Early surveillance may be particularly important for patients with NF type 2 because early identification of internal lesions by imaging is expected to improve outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

The American Academy of Pediatrics (2019) published diagnostic and health supervision guidance for children with neurofibromatosis type 1 (NF1). The guidance makes the following statements related to genetic testing:

" NF1 genetic testing may be performed for purposes of diagnosis or to assist in genetic counseling and family planning. If a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. For a young child who presents only with [café-au-lait macules], NF1 genetic testing can confirm a suspected diagnosis before a second feature, such as skinfold freckling, appears. Some families may wish to establish a definitive diagnosis as soon as possible and not wait for this second feature, and genetic testing can usually resolve the issue" and "Knowledge of the NF1 [pathogenic sequence variant] can enable testing of other family members and prenatal diagnostic testing."

The guidance includes the following summary and recommendations about genetic testing:

- can confirm a suspected diagnosis before a clinical diagnosis is possible;
- can differentiate NF1 from Legius syndrome;
- may be helpful in children who present with atypical features;
- usually does not predict future complications; and
- may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity

U.S. Preventive Services Task Force Recommendations

Not applicable.

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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 ongoing and unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
	Prevalence of Constitutional Mismatch-repair Deficiency Among Suspected Neurofibromatosis Type 1/Legius Syndrome Children Without a Malignancy and Without an NF1 or SPRED1 Mutation	670	Jan 2021
<i>Unpublished</i>			
NCT03210285	Whole Exome Sequencing (WES) of NF2-associated in Comparison to Sporadic Vestibular Schwannomas - Correlation With Clinical Data	70	Jul 2018

NCT: national clinical trial.

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Louisiana

Genetic Testing for Neurofibromatosis

Policy # 00502

Original Effective Date: 04/20/2016

Current Effective Date: 07/13/2020

Policy History

Original Effective Date: 04/20/2016

Current Effective Date: 07/13/2020

04/07/2016 Medical Policy Committee review

04/20/2016 Medical Policy Implementation Committee approval. New policy.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

04/06/2017 Medical Policy Committee review

04/19/2017 Medical Policy Implementation Committee approval. No change to coverage.

06/07/2018 Medical Policy Committee review

06/20/2018 Medical Policy Implementation Committee approval. No change to coverage.

06/06/2019 Medical Policy Committee review

06/19/2019 Medical Policy Implementation Committee approval. No change to coverage.

06/04/2020 Medical Policy Committee review

06/10/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2021

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 2019 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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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	81405, 81406, 81408
HCPCS	No codes
ICD-10 Diagnosis	Q85.00-Q85.09

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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****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.

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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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