



# Louisiana

## Autonomic Nervous System Testing

Policy # 00591

Original Effective Date: 11/15/2017

Current Effective Date: 12/14/2020

*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 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 autonomic nervous system (ANS) testing, consisting of a battery of tests in several domains (see Policy Guidelines section) to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility may be considered for autonomic nervous system (ANS) testing, consisting of a battery of tests in several domains (see Policy Guidelines section) when ALL of the following criteria are met:

- Signs and/or symptoms of autonomic dysfunction are present; AND
- A definitive diagnosis cannot be made from clinical examination and routine laboratory testing alone; AND
- Diagnosis of the suspected autonomic disorder will lead to a change in management or will eliminate the need for further testing.

### 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 autonomic nervous system (ANS) testing, to be **investigational\*** in all other situations when criteria are not met, including but not limited to the evaluation of the following conditions:

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- Chronic fatigue syndrome; OR
- Fibromyalgia; OR
- Anxiety and other psychologic disorders; OR
- Sleep apnea; OR
- Allergic conditions; OR
- Hypertension; OR
- Screening of asymptomatic individuals; OR
- Monitoring progression of disease or response to treatment.

Autonomic nervous system (ANS) testing using portable automated devices for all indications (see Policy Guidelines section) is considered to be **investigational**.\*

### **Policy Guidelines**

Although there is no standard battery of tests for autonomic nervous system (ANS) testing, a full battery generally consists of individual tests in 3 categories.

- Cardiovascular function (heart rate variability, heart rate response to deep breathing and Valsalva maneuver)
- Vasomotor adrenergic function (blood pressure response to standing, Valsalva maneuver, and hand grip, tilt table testing)
- Sudomotor function (Quantitative Sudomotor Axon Reflex Test, quantitative sensory test, Thermoregulatory Sweat Test, silastic sweat imprint, sympathetic skin response, electrochemical sweat conductance).

At least 1 test in each category is usually performed. More than 1 test from a category will often be included in a battery of tests, but the incremental value of using multiple tests in a category is unknown.

There is little evidence on the comparative accuracy of different ANS tests, but the following tests are generally considered to have uncertain value in ANS testing:

- Pupillography
- Pupil edge light cycle
- Gastric emptying tests

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- Cold pressor test
- Quantitative direct and indirect testing of sudomotor function test
- Plasma catecholamine levels
- Skin vasomotor testing
- The ANSAR<sup>®‡</sup> test

ANS testing should be performed in a dedicated ANS testing laboratory. Testing in a dedicated laboratory should be performed under closely controlled conditions, and results should be interpreted by an individual with expertise in ANS testing. Testing using automated devices with results interpreted by computer software has not been validated and thus has the potential to lead to erroneous results.

## **Background/Overview**

### **Autonomic Nervous System**

The autonomic nervous system (ANS) has a primary role in controlling physiologic processes not generally under conscious control. They include heart rate, respirations, gastrointestinal (GI) motility, thermal regulation, bladder control, and sexual function. The ANS is a complex neural regulatory network that consists of 2 complementary systems that work to maintain homeostasis: the sympathetic and the parasympathetic systems. The sympathetic nervous system is responsible for arousal, and sympathetic stimulation leads to increased pulse, increased blood pressure (BP), increased sweating, decreased GI motility, and an increase in other glandular exocrine secretions. This is typically understood as the "fight or flight" response. Activation of the parasympathetic nervous system will mostly have the opposite effects; BP and pulse will decrease, GI motility increases, and there will be a decrease in sweating and other glandular secretions.

### **ANS Disorders**

ANS disorders, also called dysautonomias, are heterogeneous in etiology, clinical symptoms, and severity. ANS disorders can be limited and focal, such as patients with isolated neurocardiogenic syncope or idiopathic palmar hyperhidrosis. At the other extreme, some ANS disorders can be widespread and severely disabling, such as multiple systems atrophy, which leads to widespread and severe autonomic failure.

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Symptoms of autonomic disorders can vary, based on the etiology and location of dysfunction. Cardiovascular manifestations are often prominent. Involvement of the cardiovascular system causes abnormalities in heart rate control and vascular dynamics. Orthostatic hypotension and other manifestations of BP lability can occur, causing weakness, dizziness, and syncope. Resting tachycardia and an inability to appropriately increase heart rate in response to exertion leads to exercise intolerance. There is a 2- to 3-fold higher incidence of major cardiac events in patients with diabetic autonomic neuropathy (myocardial infarction, heart failure, resuscitation from ventricular arrhythmia, angina, or the need for revascularization). There is also an increase in sudden cardiac death and overall mortality for these patients.

Many other organ systems can be affected by autonomic neuropathy. Involvement of the bladder can lead to incomplete emptying, resulting in urinary retention and possible overflow incontinence. GI involvement is commonly manifested as gastroparesis, which is defined as slowed gastric emptying and can cause nausea, vomiting, and a decreased tolerance for solid food and large meals. Constipation may also occur if the lower GI tract is involved. Impairment of sexual function in males can manifest as erectile dysfunction and ejaculatory failure. Dysfunction of thermal regulation and sweating can lead to anhidrosis and heat intolerance. Paradoxically, excessive sweating can also occur as a compensatory mechanism in unaffected regions.

A classification of the different types of autonomic dysfunction, adapted from Freeman (2005) and Macdougall and McLeod (1996), can be made as follows:

- Diabetic autonomic neuropathy
- Amyloid neuropathy
- Immune-mediated neuropathy
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren syndrome
- Paraneoplastic neuropathy
- Inflammatory neuropathy
  - Guillain-Barré syndrome
  - Chronic inflammatory demyelinating polyneuropathy
  - Crohn disease
  - Ulcerative colitis

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- Hereditary autonomic neuropathies
- Autonomic neuropathy secondary to infectious disease
  - HIV disease
  - Lyme disease
  - Chagas disease
  - Diphtheria
  - Leprosy
- Acute and subacute idiopathic autonomic neuropathy
- Toxic neuropathies

Other chronic diseases may involve an ANS imbalance, without outright dysfunction of the nerves themselves. Approximately 40% of individuals with essential hypertension will show evidence of excess sympathetic activity. Sympathetic over activity is also a prominent feature of generalized anxiety, panic disorder, and some types of depression, as well as certain cardiac disorders such as chronic heart failure. These types of ANS imbalances are not usually classified as ANS disorders.

### **Treatment**

Much of the treatment for autonomic disorders is non pharmacologic and supportive. However, there are specific actions that can improve symptoms in patients with specific deficits. For patients with orthostatic hypotension, this involves adequate intake of fluids and salt, moving to an upright position slowly and deliberately, use of lower-extremity compression stockings, and keeping the head of the bed elevated 4 to 6 inches (10-15. cm). In severe cases, treatment with medications that promote salt retention, such as fludrocortisone, is often prescribed. Patients with symptoms of hyperhidrosis may benefit from cooling devices and potent antiperspirants such as Drysol, and patients with decreased tearing and dry mucous membranes can use over-the-counter artificial tears or other artificial moisturizers.

### **Autonomic Nervous System Testing**

ANS testing consists of a battery of tests. Any single test may be performed individually, or the entire battery of tests may be ordered. Individual components of testing may include cardiovascular function testing, sudomotor function, salivation testing, and tilt table testing.

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### **Cardiovascular Function Testing**

Beat-to-beat variability in the heart rate can be measured at rest, or in response to provocative measures, such as deep breathing or the Valsalva maneuver. Reduced, or absent, heart rate variability is a sign of autonomic dysfunction.

Baroreflex sensitivity is measured by examining the change in pulse and heart rate variability in response to changes in BP. A medication such as phenylephrine is given to induce a raise in BP, and baroreflex sensitivity is calculated as the slope of the relation between heart rate variability and BP.

### **Sudomotor Function (Sweat Testing)**

Sweat testing evaluates the structure and function of nerves that regulate the sweat glands.

The Quantitative Sudomotor Axon Reflex Test is an example of a commercially available semiquantitative test of sudomotor function. The test is performed by placing the color-sensitive paper on the skin, which changes color on contact with sweat. Measurement of the amount of color change is a semiquantitative measure of sudomotor function.

For the silastic sweatimprint, silastic material is placed on the skin, and the sweat droplets form indentations on the silastic surface, allowing quantitation of the degree of sweating present. The Neuropad test is an example of a commercially available silastic sweat imprint.

A more complex approach in some centers is the use of a thermoregulatory laboratory. This is a closed chamber in which an individual sits for a defined period under tightly controlled temperature and humidity. An indicator dye is brushed on the skin, and it changes color when in contact with sweat. Digital pictures are taken and projected onto anatomic diagrams. Computer processing derives values for a total area of anhidrosis and the percent of anhidrotic areas.

Sympathetic skin response tests use an electric current to stimulate sympathetic nerves. The tests measure the change in electrical resistance, which is altered in the presence of sweat. In general, these tests are considered to be sensitive but have high variability and potential for false-positive results.

A variant of sympathetic skin response testing is electrochemical sweat conductance measured by iontophoresis (eg, SudoScan). In this test, a low-level current is used to attract chloride ions from

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sweat glands. The chloride ions interact with stainless-steel plate electrodes to measure electrochemical resistance.

### **Salivation Testing**

The protocol for salivation testing involves the subject chewing on a pre weighed gauze for 5 minutes. At the end of 5 minutes, the gauze is removed and reweighed to determine the total weight of saliva present.

### **Tilt Table Testing**

Tilt table testing is intended to evaluate for orthostatic intolerance. The patient lies on the table and is strapped in with a foot rest. The table is then inclined to the upright position, with monitoring of the pulse and BP. Symptoms of lightheadedness or syncope in conjunction with changes in pulse or BP constitute a positive test. A provocative medication, such as isoproterenol, can be given to increase the sensitivity of the test.

### **Composite Autonomic Severity Score**

The Composite Autonomic Severity Score, which ranges from 0 to 10, is intended to estimate the severity of autonomic dysfunction. Scores are based on self-reported symptoms measured by a standardized symptom survey. Scores of 3 or less are considered mild, scores of 3 to 7 are considered moderate and scores greater than 7 are considered severe.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Since 1976, numerous ANS testing devices have been cleared for marketing by the US Food and Drug Administration through the 510(k) process. Table 1 lists examples.

The Neuropad<sup>®‡</sup> test (TRIGOCare) is another example of a commercially available sudomotor function test. No records were identified indicating that Neuropad<sup>®‡</sup> has been cleared for marketing by the US FDA, however.

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**Table 1. Autonomic Nervous System Test Devices**

Device	Manufacturer	Measurement	510(k) No.	Clearance Date	Product Code
ANX 3.0	Ansar Group	Respiration and heart rate variability	K941252	1995	DRT
Sudoscan <sup>®</sup> †	Impeto Medical	Electrochemical sweat conductance	K100233	2010	GZO
ZYTO Hand Cradle	ZYTO Technologies	Galvanic skin response	K111308	2011	GZO
Bodytronic <sup>®</sup> † 200	Bauerfeind	Photoelectric plethysmograph	K123921	2013	JOM

## **Rationale/Source**

The autonomic nervous system (ANS) controls physiologic processes that are not under conscious control. ANS testing consists of a battery of tests intended to evaluate the integrity and function of the ANS. These tests are intended as adjuncts to the clinical examination in the diagnosis of ANS disorders.

For individuals who have signs and symptoms of ANS dysfunction who receive ANS testing, the evidence includes studies of diagnostic accuracy. Relevant outcomes are test accuracy, symptoms, functional outcomes, and quality of life. The evidence base is limited. There is a lack of a criterion standard for determining autonomic dysfunction, which limits the ability to perform high-quality research on diagnostic accuracy. Also, numerous tests are used in various conditions, making it difficult to determine values for the overall diagnostic accuracy of a battery of tests. Scattered reports of diagnostic accuracy are available for certain tests, most commonly in the diabetic population, but these reports do not specify estimates of accuracy for the entire battery of tests. Reported sensitivities and specificities are high for patients with clinically defined distal symmetric polyneuropathy using a symptom-based score as a reference standard, but these estimates are likely biased by study designs that used patients with clinically diagnosed disease and a control group of healthy volunteers. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2014 has strongly supported the use of ANS testing as a diagnostic aid in situations of suspected ANS disorders. ANS testing should be performed in the setting of a dedicated ANS testing laboratory. Portable, automated testing intended for office use has not been sufficiently validated and has a greater potential to lead to erroneous results. Also, despite the limitations in the evidence base, ANS tests provide information that cannot be obtained by other methods, given the limitations of clinical examination. Information from ANS testing can improve diagnostic accuracy in some patients, and in others may obviate the need for further diagnostic testing.

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### **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.

In response to requests, input was received from 1 physician specialty society and 7 academic medical centers while this policy was under review in 2014. There was a consensus that autonomic nervous system testing should be medically necessary for some indications, and there was agreement on the proposed criteria for medical necessity.

#### **Practice Guidelines and Position Statements**

Evidence-based guidelines on autonomic nervous system (ANS) testing are lacking. Even in guidelines that involve a systematic review of the literature, such as the joint American Academy of Neurology (AAN), American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine & Rehabilitation guidelines (described below), recommendations were largely based on expert consensus.

#### **American Academy of Neurology et al**

AAN, AANEM, and American Academy of Physical Medicine & Rehabilitation (2009) issued a practice parameter, on the evaluation of distal symmetric polyneuropathy. This parameter was reaffirmed in July 2013, and an update is currently in progress. This document addressed the use of autonomic testing in the evaluation of patients with distal symmetric polyneuropathy. The following conclusion and recommendations were made:

"Autonomic testing is probably useful in documenting autonomic nervous system involvement in polyneuropathy (Class II and Class III). The sensitivity and specificity vary with the particular test. The utilization of the combination of autonomic reflex screening tests in the CASS [Composite Autonomic Severity Score] probably provides the highest sensitivity and specificity for documenting autonomic dysfunction (Class II).

- Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system involvement (Level B).

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- Autonomic testing should be considered in the evaluation of patients with suspected autonomic neuropathies (Level B) and may be considered in the evaluation of patients with suspected distal SFSN [small fiber sensory neuropathy] (Level C).
- The combination of autonomic screening tests in the CASS should be considered to achieve the highest diagnostic accuracy (Level B)."

### **American Association of Neuromuscular and Electrodiagnostic Medicine**

AANEM (2017) published a position statement on the proper performance of autonomic function testing. AANEM recommended that:

- "Autonomic testing procedures be performed by physicians with comprehensive knowledge of neurologic and autonomic disorders to ensure precise interpretation and diagnosis at completion of testing," and that
- "The same physician should directly supervise and interpret the data on-site...", and
- "It is inappropriate to interpret autonomic studies without obtaining a relevant history to understand the scope of the problem, obtaining a relevant physical examination to support a diagnosis, and providing the necessary oversight in the design and performance of testing."

### **American Academy of Neurology**

AAN published a model coverage policy on autonomic testing in 2014. The document addressed:

- The qualifications of physicians who perform ANS testing.
- Techniques used in ANS testing.
- The types of patients who will benefit from ANS testing.
- The clinical indications for testing.
- Diagnoses where testing is indicated.
- Indications for which data are limited.

### **American Diabetes Association**

The American Diabetes Association published standards of care for treatment in diabetes. This 2020 publication contained the following statements on autonomic neuropathy in diabetes:

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- "All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **(B)**
- Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **(B)**
- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **(E)**"

Recommendation ratings B: supportive evidence from well conducted cohort studies.

Recommendation ratings E: expert consensus or clinical experience.

### **European Society of Cardiology**

The European Society of Cardiology (2017) published a position statement on potential treatments for dysfunction of the autonomic nervous system in context of heart failure. The statement cited some noninvasive ANS tests, such as standing, deep breathing, and Valsalva's maneuvers, but noted that none of these has shown "prognostic importance."

### **European Federation of Neurological Societies**

The European Federation of Neurological Societies (2011) issued a revision of its guidelines on orthostatic hypotension. The guidelines made a level C recommendation that ANS screening tests with other appropriate investigations should be considered depending on the possible etiology of the underlying disorder.

### **National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence issued guidance (2018) on Neuropad for detecting preclinical diabetic peripheral neuropathy (MTG38). The guidance states "The case for adopting Neuropad to detect preclinical diabetic peripheral neuropathy is not supported by the evidence".

### **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 unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02985710	Assessment of Small Fiber Neuropathy in Rare Diseases Using Sudoscan	100	Aug 2019 (ongoing)
NCT03990142	Study of Abnormalities of the Vegetative Nervous System in the Occurrence of Intradialytic Arterial Hypotension (Intervention: SudoScan)	300	Jun 2020
NCT01568177	Cardiac Autonomic Function in Women With Microvascular Coronary Dysfunction	60	Feb 2021 (ongoing)

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NCT03043768 <sup>a</sup>	Cutaneous Autonomic Pilomotor Testing to Unveil the Role of Neuropathy Progression in Early Parkinson's Disease (CAPTURE PD)	104	Dec 2019 (unknown)
NCT04071535	Application of Skin Biopsy in the Early Diagnosis of Small Fiber Neuropathy in Chinese Patients With Diabetes (Intervention: SudoScan)	100	Jul 2021
NCT00608725	Pathophysiology of Orthostatic Intolerance	100	Dec 2021
<i>Unpublished</i>			
NCT03156400	Assessment of Autonomic Function and Cardiovascular Response to Exercise Testing in Parkinson's Disease Patients	30	Jun 2018
NCT02767037	SudoScan as a Biomarker of Parkinson's Disease	140	Jun 2018

NCT: national clinical trial. <sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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# Louisiana

## Autonomic Nervous System Testing

Policy # 00591

Original Effective Date: 11/15/2017

Current Effective Date: 12/14/2020

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## **Policy History**

Original Effective Date: 11/15/2017

Current Effective Date: 12/14/2020

11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. New policy.
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
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2021

## **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*

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*descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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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	
CPT	95921, 95922, 95923, 95924, 95943
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses codes

\*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

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- 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.

**\*\*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.

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**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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