



# Louisiana

## Autonomic Nervous System Testing

**Policy #** 00591

**Original Effective Date:** 11/15/2017

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*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:

- 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\***.

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### **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.

- Cardiovagal 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
- 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

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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.

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
  - o Rheumatoid arthritis
  - o Systemic lupus erythematosus
  - o Sjögren syndrome
- Paraneoplastic neuropathy
- Inflammatory neuropathy
  - o Guillain-Barré syndrome
  - o Chronic inflammatory demyelinating polyneuropathy
  - o Crohn disease

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- o Ulcerative colitis
- Hereditary autonomic neuropathies
- Autonomic neuropathy secondary to infectious disease
  - o HIV disease
  - o Lyme disease
  - o Chagas disease
  - o Diphtheria
  - o 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 overactivity 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 nonpharmacologic 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.

### ***ANS 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 cardiovagal function testing, sudomotor function, salivation testing, and tilt table testing.

#### *Cardiovagal 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.

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### *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 sweat imprint, 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 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 preweighed 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

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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.

**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	2004	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	JMO
Neuropad <sup>®†</sup>	TRIGOCare	Sudomotor function			

#### **Centers for Medicare and Medicaid Services (CMS)**

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.

### **Rationale/Source**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

## **AUTONOMIC NERVOUS SYSTEM TESTING**

### **Clinical Context and Test Purpose**

The purpose of autonomic nervous system (ANS) testing in patients who have signs and/or symptoms of ANS dysfunction is to aid in the diagnosis of disease and guide treatment.

The question addressed in this evidence review is: Does the evidence indicate that ANS testing improves health outcomes in patients who have signs and/or symptoms of ANS without a definitive diagnosis.

The following PICOTS were used to select literature to inform this review.

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### **Patients**

The relevant population of interest is patients who have signs and/or symptoms of ANS without a definitive diagnosis.

### **Interventions**

ANS testing is performed to evaluate the integrity and function of the ANS. Although there is no standard battery of tests for ANS testing, a full battery generally consists of individual tests in 3 domains.

- Cardiovascular function (heart rate variability [HRV], 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 [QSART], quantitative sensory testing [QST], Thermoregulatory Sweat Test, silastic sweat imprint, sympathetic skin response, electrochemical sweat conductance).

### **Comparators**

The following practice is currently used to make decisions about the diagnosis signs and/or symptoms of ANS: standard clinical diagnostic workup without ANS testing.

### **Outcomes**

The outcomes for clinical validity include aiding in the diagnosis of disease and guiding management. Much of the treatment for autonomic disorders is nonpharmacologic and supportive, but there are specific actions that can improve symptoms in patients with specific deficits and improve quality of life.

### **Timing**

ANS tests are typically performed following clinical evaluation to confirm a diagnosis of ANS or to provide additional information for diagnosis.

### **Setting**

ANS testing should be performed in a dedicated ANS testing laboratory. Results should be interpreted by an individual with expertise in ANS testing.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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There are a number of challenges when evaluating the diagnostic accuracy of ANS testing:

- There is a lack of a true criterion standard for determining autonomic dysfunction. Comparisons with imperfect criterion standards, such as clinical examination or nerve conduction studies, may lead to biased estimates of accuracy.
- Most of the ANS is inaccessible to testing, and available tests are measures of end-organ response rather than direct measures of ANS function.
- There are numerous individual tests of ANS function, and a combination of them is typically used in ANS testing. Diagnostic accuracy could be reported for each test or the package of testing performed.
- Different types of equipment may be used for testing, and the accuracy of different systems may vary.

Scattered reports of diagnostic accuracy for specific tests in specific patient groups are available, but high-quality research is lacking. The most rigorous evaluation of diagnostic accuracy identified is in the 2009 systematic review by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine & Rehabilitation, which focused on the accuracy of autonomic testing for distal symmetric polyneuropathy. Table 2 summarizes the results on diagnostic accuracy from this review. While reported sensitivities and specificities are high, the populations in these studies include patients with known disease and healthy volunteers. These populations are not optimal for determining diagnostic accuracy and are known to lead to inflated estimates of both sensitivity and specificity.

**Table 2. Diagnostic Accuracy of Autonomic Nervous System Testing to Diagnose Distal Symmetric Polyneuropathy**

Study	Disorder Studied	Test(s) Used	Reference Standard	N	Sensitivity, %	Specificity, %
Stewart et al (1992)	DSFN	HRV, QST, QSART	• Clinical exam • EDx studies	169	80	72
Dyck et al (1992)	Diabetic polyneuropathy	QAE	EDx studies	737	97	>90
Low et al (1997)	Parkinson, multisystem atrophy	QSART	Older scale for autonomic neuropathy	575	>90	>90
Tobin et al (1999)	DSFN	Clinical sx, QSART, QST	EDx studies	495	• 80 (QSART) • 67 (QST)	93
Novak et al (2001)	Painful neuropathy	QSART, ART, CASS	Clinical exam	483	• 93 (ART) • 73 (QSART)	94
Low et al (1993)	Diabetic polyneuropathy	CASS	• Clinical exam • EDx studies	428	>90	>90
Schrezenmaier et al (2007)	Adrenergic failure	BRSI	MSNA	113	86	>90
Vogel et al (2005)	Polyneuropathy, multisystem atrophy	PRT, CASS	Clinical exam	194	>90	>90
Singer et al (2004)	DSFN, diabetic and idiopathic neuropathy	CASS	Neurologic exam	49	95	90

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Adapted from England et al (2009).

ART: autonomic reflex testing; BRSI: baroreflex sensitivity index; CASS: Composite Autonomic Severity Score; DSFN: distal small fiber neuropathy; EDx: electrodiagnostic studies (electromyography/nerve conduction velocity); HRV: heart rate variability; MSNA: muscle sympathetic nerve activity; PRT: blood pressure recovery time; QAE: quantitative autonomic evaluation; QSART: Quantitative Sudomotor Axon Reflex Test; QST: quantitative sensory testing; sx: symptoms.

Da Silva et al (2016) reported on a systematic review evaluating the accuracy of HRV for the diagnosis and prognosis of cardiac autonomic neuropathy in individuals with diabetes. Reviewers included 8 studies, finding that HRV is useful to discriminate cardiac autonomic neuropathy. Measures of sample entropy, standard deviation of the instantaneous variability and long-term variability, standard deviation of mean of normal relative risk intervals every 5 minutes for a period of time, expressed in milliseconds, high-frequency component, and slope of heart rate turbulence had the best discriminatory power, with sensitivities ranging from 72% to 100% and specificities ranging from 71% to 97%.

Evidence on the sensitivity and specificity of a silastic sweat testing device (Neuropad) was identified. Kamenov et al (2010) enrolled 264 inpatients with diabetes. Patients with autonomic neuropathy were identified by the Neuropathy Disability Score, with a cutoff of 5 indicating autonomic neuropathy. An abnormal silastic sweat test had a sensitivity of 76%, a specificity of 56%, a positive predictive value of 86%, and a negative predictive value of 40%. In a similar study, Quattrini et al (2008) evaluated 57 diabetic patients with several autonomic tests, including the Neuropad device. The sensitivity of silastic sweat testing in this study was 85%, the specificity was 45%, the positive predictive value was 69%, and the negative predictive value was 71%.

Another diagnostic accuracy study of the Neuropad device was published by Ponirakis et al (2014). It included 38 patients with diabetic peripheral neuropathy and 89 patients without neuropathy. The diagnostic performance of Neuropad was compared with a number of other measures of nerve function. Compared with other measures of large fiber dysfunction, the Neuropad had a sensitivity ranging from 70% to 83% and a specificity ranging from 50% to 54%. Compared with a measure of small fiber function (corneal nerve fiber length), the sensitivity was 83%, and the specificity was 80%.

Casselini et al (2013) compared the accuracy of the SudoScan test with other available tests of sudomotor function. This study evaluated 83 patients with diabetes (60 with peripheral neuropathy, 20 without peripheral neuropathy) and 210 normal controls. Electrochemical skin conductance of the feet was lowest for patients with diabetes and neuropathy (56.3), intermediate for patients with diabetes without neuropathy (75.9), and highest for normal volunteers (84.4,  $p < 0.001$  for group differences). Using clinically defined neuropathy as the criterion standard, sensitivity was 78%, and specificity was 92%. Test results correlated significantly with a number of other measures, including symptom scores, QST, and measures of HRV. The correlations were in the low-to-moderate range (Spearman  $\rho$  range, 0.24-0.47).

### **Section Summary: Clinically Valid**

It is not possible to determine the diagnostic accuracy of ANS testing. The lack of a criterion standard makes it difficult to perform high-quality research in this area. The available research has reported sensitivity in patients with clinically defined disease and specificity in health volunteers. This type of study

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design is known to produce inflated estimates of sensitivity and specificity; therefore, the diagnostic accuracy of testing in clinical practice is uncertain.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

The use of ANS testing will improve outcomes if the test has incremental diagnostic accuracy over clinical exam alone, and if establishing the diagnosis leads to changes in management that improves outcomes. There is a lack of direct evidence on the impact of ANS testing on changes in management or health outcomes.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

It is likely that these tests provide information beyond that obtainable from the clinical exam alone, given the limitations of the physical exam for assessing physiologic processes. Some autonomic disorders have specific treatments, such as medications to retain salt and preserve hydration status. In other cases, the use of autonomic testing may limit the need for further diagnostic testing, when symptoms are possibly autonomic related, but may be due to other pathology. In those cases, determining whether autonomic dysfunction is the cause of symptoms may end the need for further testing.

### **SUMMARY OF EVIDENCE**

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.

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### Policy History

Original Effective Date: 11/15/2017

Current Effective Date: 11/21/2018

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.

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# Louisiana

## Autonomic Nervous System Testing

Policy # 00591  
Original Effective Date: 11/15/2017  
Current Effective Date: 11/21/2018

Next Scheduled Review Date: 11/2019

### **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 2017 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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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	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
- 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;

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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.

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

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