BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Autonomic Nervous System Testing

Policy #: 573
Latest Review Date: June 2022
Category: Medicine

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **autonomic nervous system testing, consisting of a battery of tests in several domains** as a **covered benefit** when 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.

Blue Advantage will treat **autonomic nervous system testing** as a **non-covered benefit** and as **investigational** in all other situations when criteria are not met, including but not limited to the evaluation of the following conditions:

- chronic fatigue syndrome;
- fibromyalgia;
- anxiety and other psychologic disorders;
- sleep apnea;
- allergic conditions;
- hypertension;
- screening of asymptomatic individuals;
- monitoring progression of disease or response to treatment.

Blue Advantage will treat **autonomic nervous system testing using portable automated devices** as a **non-covered benefit** and as **investigational** for all indications.

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 three 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 one test in each category is usually performed. More than one 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® 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 an individual with expertise in ANS testing should interpret results. Testing using automated devices with results interpreted by computer software has not been validated and thus has the potential to lead to erroneous results.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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

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 two 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 on 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.

Autonomic Nervous System Disorders

Disorders of the ANS, also called dysautonomias, are heterogeneous in etiology, clinical symptoms, and severity. Autonomic nervous system disorders can be limited and focal, such as 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, including 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. Gastrointestinal 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
- 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 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 of Autonomic Nervous System Disorders

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, 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 individual tests. Any one test may be performed individually, or the entire battery of tests may be ordered. Individual components of testing may include:

- Cardiovagal Function Testing
    - Heart Rate Variability: 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 (HRV) is a sign of autonomic dysfunction.
    - Baroreflex Sensitivity: Baroreflex sensitivity is measured by examining the change in pulse and HRV in response to changes in BP. A medication such as phenylephrine is given to induce a raise in blood pressure, and baroreflex sensitivity is calculated as the slope of the relationship between HRV and BP.
- Sudomotor Function (sweat testing): Sweat testing evaluates the structure and function of nerves that regulate the sweat glands.
    - QSART Test: The Quantitative Sudomotor Axon Reflex Test (QSART) is an example of a semiquantitative test of sudomotor function that is commercially available. The test is performed by placing a 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.

- Silastic Sweat Imprint: For the silastic sweat imprint, a 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.
- Thermoregulatory Sweat Test: A more complex approach in some centers is the use of a thermoregulatory laboratory. An individual sits for a defined period under tightly controlled temperature and humidity in this closed chamber. An indicator dye is brushed on the skin, which changes color when in contact with sweat. Digital pictures are taken and projected onto anatomic diagrams. Computer processing derives values for total area of anhidrosis, and the percent of anhidrotic areas.
- Sympathetic Skin Response: 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 the potential for false-positive results.
    - A variant of sympathetic skin response testing is electrochemical sweat conductance measured by iontophoresis (e.g., 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 Test: The protocol for this test involves the subject chewing on a pre-weighed gauze for five minutes. At the end of five 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 footrest. 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

This composite score ranging from zero to 10 is intended to estimate severity of autonomic dysfunction. Scores are based on self-reported symptoms measured by a standardized symptom survey. Scores of three or less are considered mild, scores of 3 to 7 are considered moderate, and scores greater than seven are considered severe.

KEY POINTS:

The most recent literature review was updated through May 2, 2022.

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. In addition, numerous tests are used in various conditions, making it difficult to determine values for the overall diagnostic accuracy of a battery of tests. The evidence on the reliability of individual tests raises concerns about the reproducibility of testing. 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. Among the few clinical practice guidelines from specialty societies, recommendations are primarily based on expert opinion. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Academy of Neurology et al

In 2020, a consensus statement endorsed by the AAN, American Autonomic Society, and the International Federation of Clinical Neurophysiology on assessment of the ANS was published. The consensus statement recommends that a combination of autonomic tests should be used for better accuracy compared to a single test, which should ideally assess cardiovascular adrenergic, cardiovagal, and sudomotor function. Recommended tests include continuous beat-to-beat heart rate and blood pressure responses to the Valsalva maneuver, postural changes on a tilt table, or sinusoidal deep breathing; the Valsalva ratio; quantitative sudomotor axon reflex test; and the thermoregulatory sweat test. The recommendations also outlined valid indications for autonomic testing, which are outlined in table 1.

Table 1. Valid Indications for Autonomic Testing According to the American Academy of Neurology, American Autonomic Society, and the International Federation of Clinical Neurophysiology

Diagnosis	Clinical Questions Addressed by Autonomic Testing
Autonomic failure	Evaluate its presence, severity, distribution; evaluate familial dysautonomia; distinguish from benign symptoms or syndromes.
Peripheral polyneuropathy	Evaluate its presence, severity and distribution; detect and quantitate distal small fiber neuropathy; evaluate diabetic autonomic neuropathy; evaluate amyloid autonomic neuropathy; evaluate paraneoplastic autonomic

	neuropathy; evaluate hereditary sensory and autonomic neuropathies; evaluate Guillain-Barre syndrome; evaluate chronic inflammatory demyelinating neuropathy; evaluate Lambert Eaton myasthenic syndrome; evaluate Chagas disease; evaluate leprosy.
Ganglionopathy	Evaluate the presence, severity, and distribution of autonomic failure; evaluate autoimmune autonomic ganglionopathy.
Orthostatic hypotension	Evaluate its presence, severity, and temporal profile; distinguish neurogenic orthostatic hypotension from other causes of hypotension; assess baroreflex function.
Orthostatic intolerance	Evaluate postural tachycardia syndrome; evaluate delayed orthostatic hypotension.
Syncope	Evaluate recurrent or unexplained syncope; distinguish neurally mediated syncope from psychogenic pseudo syncope.
Neurodegenerative disorders	Evaluate autonomic failure in multiple system atrophy; evaluate autonomic failure in Parkinson disease; evaluate autonomic failure in Lewy body dementia; distinguish multiple system atrophy from Parkinson disease; distinguish multiple system atrophy from other forms of cerebellar ataxia; evaluate pure autonomic failure.
Hyperadrenergic states	Evaluate baroreflex function; evaluate autonomic dysreflexia; evaluate autonomic storms; evaluate Morvan syndrome.
Heat intolerance	Evaluate the presence, severity, and distribution of anhidrosis; evaluate Ross syndrome; evaluate small fiber neuropathy in Sjogren syndrome.
Regional autonomic failure	Evaluate for the presence, severity, and distribution of more widespread autonomic failure.

The 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 retired in 2019. 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).
- 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
The AANEM (2017) published a position statement on the proper performance of autonomic function testing. The guideline 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
In 2014, the AAN published a model coverage policy on autonomic testing. 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 has published annual standards of care for treatment in diabetes. The 2022 publication contained the following statements on screening for autonomic neuropathy in diabetes:

"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.

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.

KEY WORDS:
Autonomic nervous system testing, ANS, ANX 3.0®, Bodytronic® 200, Dopplex Ability®, Neuropad®, Sudoscan® , ZYTO Hand Cradle, Finapres® Nova Noninvasive Hemodynamic Monitor

APPROVED BY GOVERNING BODIES:
Since 1976, the US Food and Drug Administration have cleared numerous autonomic nervous system testing devices for marketing through the 510(k) process. Table 2 lists examples.

The Neuropad test (TRIGOcare) is another example of a commercially available sudomotor function test. No records were identified indicating that the US FDA has cleared Neuropad for marketing.

Table 2. Autonomic Nervous System Test Devices

Device	Manufacturer	Measurement	510(k) No.	Clearance Date	FDA Product Code
ANX 3.0	Ansar Group	Respiration and heart rate variability	K941252	2004	DRT

Sudoscan®	Impeto Medical	Electrochemical sweat conductance	K100233	2010	GZO
Hrv Acquire	WR Medical Electronics Co.	Respiration and heart rate variability	K092809	2010	DRT
ZYTO Hand Cradle	ZYTO Technologies	Galvanic skin response	K111308	2011	GZO
Bodytronic® 200	Bauerfeind	Photoelectric plethysmograph	K123921	2013	JOM
Finapres® Nova Noninvasive Hemodynamic Monitor	Finapres Medical Systems B.V.	Heart rate variability and baroreflex sensitivity	K173916	2018	DRT

FDA: Food and Drug Administration.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

95921	Testing of autonomic nervous system function; cardiovagal innervation (parasympathetic function), including 2 or more of the following: heart rate response to deep breathing with recorded R-R interval, Valsalva ratio, and 30:15 ratio.
95922	Testing of autonomic nervous system function; vasomotor adrenergic innervation (sympathetic adrenergic function), including beat-to-beat blood pressure and R-R interval changes during Valsalva maneuver and at least 5 minutes of passive tilt.
95923	Testing of autonomic nervous system function; sudomotor, including 1 or more of the following: quantitative sudomotor axon reflex test (QSART), silastic sweat imprint, thermoregulatory sweat test, and changes in sympathetic skin potential.

95924	Testing of autonomic nervous system function; combined parasympathetic and sympathetic adrenergic function testing with at least 5 minutes of passive tilt.

PREVIOUS CODING:

95943	Simultaneous, independent, quantitative measures of both parasympathetic function and sympathetic function, based on time- frequency analysis of heart rate variability concurrent with time- frequency analysis of continuous respiratory activity, with mean heart rate and blood pressure measures, during rest, paced (deep) breathing, Valsalva maneuvers, and head-up postural change. (Deleted 12/31/21)

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POLICY HISTORY:

Adopted for Blue Advantage, February 2018
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Medical Policy Group, July 2019
Medical Policy Group, June 2020: Effective July 8, 2020: Active policy but no longer scheduled for regular literature reviews and updates.
Medical Policy Group, July 2021
Medical Policy Group, December, 2021: 2022 Annual Coding Update. Moved CPT code 95943 from Current coding section. Created Previous Coding section to include code 95943.
Medical Policy Group, June 2022