**Policy Statement**

Autonomic nervous system testing, consisting of a battery of tests in several domains (see Policy Guidelines section), may be considered **medically necessary** when all the following criteria are met:

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

Autonomic nervous system testing is considered **investigational** in all other situations when criteria are not met, including but not limited to the evaluation of any of the following conditions:

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

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

**Policy Guidelines**

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

- Cardiovagal function (heart rate [HR] variability, heart rate [HR] response to deep breathing and Valsalva maneuver)
- Vasomotor adrenergic function (blood pressure [BP] response to standing, Valsalva maneuver, and hand grip, tilt table testing)
- Sudomotor function (Quantitative Sudomotor Axon Reflex Test [QSART], Quantitative Sensory Test [QST], Thermoregulatory Sweat Test [TST], 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:

- Cold pressor test
- Gastric emptying tests
- Plasma catecholamine levels
- Pupil edge light cycle
- Pupillography
- Quantitative direct and indirect testing of sudomotor function test (QDIRT)
- Skin vasomotor testing
- The ANSAR® test
Autonomic Nervous System Testing

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

**Description**

The autonomic nervous system (ANS) controls physiologic processes that are not under conscious control. ANS testing consists of a battery of tests that are 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.

**Related Policies**

- Neural Therapy

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of the FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

Since 1976, numerous autonomic nervous system 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**

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Measurement</th>
<th>510(k) No.</th>
<th>Clearance Date</th>
<th>FDA Product Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANX 3.0</td>
<td>Ansar Group</td>
<td>Respiration and heart rate variability</td>
<td>K100233</td>
<td>2004</td>
<td>GZO</td>
</tr>
<tr>
<td>Sudoscan®</td>
<td>Impeto Medical</td>
<td>Electrochemical sweat conductance</td>
<td>K111308</td>
<td>2011</td>
<td>GZO</td>
</tr>
<tr>
<td>ZYTO Hand Cradle</td>
<td>ZYTO Technologies</td>
<td>Galvanic skin response</td>
<td>K123921</td>
<td>2013</td>
<td>JMO</td>
</tr>
<tr>
<td>Bodytronic® 200</td>
<td>Bauerfeind</td>
<td>Photoelectric plethysmograph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropad®</td>
<td>TRIGOcare</td>
<td>Sudomotor function</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.
Rationale

Background

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 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.

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 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
  - 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

A variety of 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
    • 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 BP, and baroreflex sensitivity is calculated as the slope of the relation 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 commercially available semiquantitative test of sudomotor function. The test is performed by placing 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, 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. This is a closed chamber in which an individual sits for a defined period of time 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 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 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 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 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.

### Literature Review

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical performance (test-retest reliability or inter-rater reliability); (2) diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

### 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.

**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:

- Cardiovagal 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 [TST], silastic sweat imprint, sympathetic skin response, electrochemical sweat conductance)

Comparators
The following tools, tests, rules, and practices are currently used to make decisions about the diagnosis signs and/or symptoms of ANS: standard clinical diagnostic workup without ANS testing.

Outcomes
The outcomes of interest for technical performance are test-retest reliability or inter-rater reliability. The relevant outcomes for diagnostic accuracy are sensitivity, specificity, predictive values, and related measures of diagnostic accuracy. The outcomes for clinical validity include aiding in diagnosis of disease and guiding management. Much of the treatment for autonomic disorders is non-pharmacologic 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 or to provide additional information for diagnosis.

Setting
ANS testing should be performed in a dedicated ANS testing laboratory. Interpretation of the results should be performed by an individual with expertise in ANS testing.

Technical Performance
ANS testing is essentially the only laboratory method available to evaluate ANS dysfunction. Because of the lack of a true criterion standard of autonomic dysfunction, the validity of results of ANS testing cannot be determined.

Some evidence was identified on the reliability of ANS testing, particularly for HRV. A number of studies have reported that the test-retest reliability of ANS is high over short periods of time, but reliability over longer time periods is less certain. A systematic review of published studies on the reliability of HRV was published in 2005. Reviewers identified 8 studies (total N=183 patients) that reported on the reliability of short-term recordings (i.e., excluding studies that used 24-hour monitoring). Four studies included healthy patients, 3 included patients with cardiac disease, and one included both healthy and cardiac patients. Studies used different measures of HRV, and reviewers performed a qualitative synthesis of the results. For 3 of the 5 studies that included healthy individuals, the reliability was high, with coefficients of variation (CVs) ranging from 6% to 15%. However, in the other 2 studies, the CV was much higher at 20% in one and 45% in the other. For patients with cardiac disease, the reliability was lower, with CVs being higher and reaching 100% in 1 study.

Less evidence was available for other specific tests. For sudomotor testing, 2 small studies assessing reliability were identified. Berger et al (2013) evaluated the reliability of the QSART in 20 healthy individuals. They reported intra-class correlation coefficients (ICCs) at 3 different body sites ranging from 0.49 to 0.75, indicating moderate reliability, and standard error of measurements ranging from 0.273 to 0.978, indicating large standard errors. Peltier et al (2009) evaluated both the QSART and QST in 23 patients with impaired glucose regulation and neuropathy. The ICCs were high for both measures, ranging from 0.52 to 0.80. QST was more reliable (ICC range, 0.75-0.80) than the QSART (ICC =0.52), indicating suboptimal reliability.

Some studies have evaluated the reproducibility of tilt testing, usually by repeating a study in patients with an initial positive test. An example of this type of study was published by...
Kochiadakis et al in 1998.\textsuperscript{14} It evaluated 35 patients with syncope and a positive tilt table test using a repeat tilt table test. The study also included a comparison group (15 healthy volunteers) that underwent 2 tilt table tests. In conjunction with tilt table testing, the study also recorded HRV. Twenty-one (60\%) of the 35 patients had a second positive test, while none of the healthy controls had any positive test. HRV results showed that high parasympathetic predicted a second positive test.

**Section Summary: Technical Performance**

The main evidence on the technical performance of ANS testing is on the reliability of individual tests, mostly test-retest reproducibility. The available evidence is incomplete, and there is a lack of high-quality reporting on reliability. The available research is variable and, in most cases, does not show high reproducibility. Therefore, the reliability of these tests is currently uncertain.

**Diagnostic Accuracy**

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 individual test or for 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 was in the systematic review by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation, which focused on the accuracy of autonomic testing for distal symmetric polyneuropathy.\textsuperscript{8} 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 for the Diagnosis of Distal Symmetric Polyneuropathy (Adapted from England et al, 2013)\textsuperscript{8}

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Disorder Studied</th>
<th>Test(s) Used</th>
<th>Reference Standard</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart (1992)</td>
<td>DSFN</td>
<td>HRV, QST, QSART</td>
<td>Clinical exam, EDx studies</td>
<td>169</td>
<td>80%</td>
<td>72%</td>
</tr>
<tr>
<td>Dyck (1992)</td>
<td>Diabetic polyneuropathy</td>
<td>QAE</td>
<td>EDx studies</td>
<td>737</td>
<td>97%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Low (1997)</td>
<td>Parkinson, multisystem atrophy</td>
<td>QSART</td>
<td>Older scale for autonomic neuropathy</td>
<td>575</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Tobin (1999)</td>
<td>DSFN</td>
<td>Clinical sx, QSART, QST</td>
<td>EDx studies</td>
<td>495</td>
<td>80% (QSART)</td>
<td>93%</td>
</tr>
<tr>
<td>Novak (2001)</td>
<td>Painful neuropathy</td>
<td>QSART, ART, CASS</td>
<td>Clinical exam</td>
<td>483</td>
<td>93% (ART)</td>
<td>73% (Q SART)</td>
</tr>
<tr>
<td>Low (1993)</td>
<td>Diabetic polyneuropathy</td>
<td>CASS</td>
<td>Clinical exam, EDx studies</td>
<td>428</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Schrenzenmaier (2007)</td>
<td>Adrenergic failure</td>
<td>BRSI</td>
<td>MSNA</td>
<td>113</td>
<td>86%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Vogel (2005)</td>
<td>Polyneuropathy,</td>
<td>PRT, CASS</td>
<td>Clinical exam</td>
<td>194</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>
### Study/Year | Disorder Studied | Test(s) Used | Reference Standard | N | Sensitivity | Specificity
--- | --- | --- | --- | --- | --- | ---
Singer (2004) | multisystem atrophy, diabetic and idiopathic neuropathy | CASS | Neurologic exam | 49 | 95% | 90%


In 2016, da Silva et al reported on a systematic review of 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, SD1/SD2 indices (standard deviation of the instantaneous variability and long-term variability), SDANN (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 sensitivity ranging from 72% to 100% and specificity 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 in 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%.

In 2013, Casselini et al 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, SEM = 3), intermediate for patients with diabetes without neuropathy (75.9, SEM = 5.5), and highest for normal volunteers (84.4, SEM = 0.9, p < 0.001 for group differences). Using clinically defined neuropathy as the criterion standard, sensitivity was 78% and specificity was 92%. Results of the test 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 ρ range, 0.24-0.47).

**Section Summary: Diagnostic Accuracy**

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 design is known to produce inflated estimates of sensitivity and specificity; therefore, the diagnostic accuracy of testing in clinical practice is uncertain.
Clinical Utility
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. It is likely that these tests provide information beyond that obtainable from the clinical exam alone, given the limitations of 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 autonomic nervous system (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 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 use 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.

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 from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 7 academic medical centers in 2014. There was 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
We lack of evidence-based guidelines on autonomic nervous system (ANS) testing. 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 (AAPM&R) guidelines, the recommendations were largely based on expert consensus.

American Academy of Neurology et al
AAN, AANEM, and AAPM&R issued a 2009 practice parameter,8 affirmed in July 2013, on the evaluation of distal symmetric polyneuropathy. This document addressed the use of autonomic testing in the evaluation of patients with distal symmetric polyneuropathy. The following conclusion and recommendation was 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
AANEM published a position statement in 2017 on the proper performance of autonomic
function testing.20 AANEM recommends 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 2014.2 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 in
2010.21 This document contained the following statements on autonomic neuropathy in diabetes
(where E is expert opinion):
• “Screening for signs and symptoms of cardiovascular autonomic neuropathy should be
instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1
diabetes. Special testing is rarely needed and may not affect management or outcome
(E).
• Medications for the relief of specific symptoms related to DPN [distal polyneuropathy]
and autonomic neuropathy are recommended, as they improve the quality of life of the
patient (E).”

European Federation of Neurological Societies
The European Federation of Neurological Societies issued a 2011 revision of its guidelines on
orthostatic hypotension.22 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.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, 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 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02985710</td>
<td>Assessment of Small Fiber Neuropathy in Rare Diseases Using Sudoscan</td>
<td>100</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02767037</td>
<td>SudoScan as a Biomarker of Parkinson's Disease</td>
<td>140</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT03043768a</td>
<td>Cutaneous Autonomic Pilomotor Testing to Unveil the Role of Neuropathy Progression in Early Parkinson's Disease (CAPTURE PD)</td>
<td>104</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>

NCT: National Clinical Trial.
* Denotes industry-sponsored or cosponsored trial.

References


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
  - Consultation and medical clearance report(s), when applicable
  - Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
  - Laboratory results
  - Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

**Post Service**

- Results/reports of tests performed
- Procedure report(s)
Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>95921</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>95922</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>95923</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>95924</td>
<td>Testing of autonomic nervous system function; combined parasympathetic and sympathetic adrenergic function testing with at least 5 minutes of passive tilt</td>
</tr>
<tr>
<td></td>
<td>95943</td>
<td>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</td>
</tr>
</tbody>
</table>

HCPCS | None |
ICD-10 Procedure | None |
ICD-10 Diagnosis | All Diagnoses |

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01/2016</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Review</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.