Autonomic Nervous System Testing

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Autonomic Nervous System Testing when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Autonomic nervous system testing, consisting of a battery of tests in several domains (see Considerations section) may be considered medically necessary 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.

When Policy Topic is not covered
Autonomic nervous system testing is considered 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.

Autonomic nervous system testing using portable automated devices is considered investigational for all indications (see Considerations section).
Considerations
Although there is not a standard battery of tests that are part of ANS testing, a full battery of testing generally consists of individual tests in 3 domains.

- Cardiovagal function (heart rate [HR] variability, HR response to deep breathing and Valsalva)
- Vasomotor adrenergic function (blood pressure [BP] response to standing, Valsalva, and hand grip, tilt table testing)
- Sudomotor function (QSART, QST, TST, silastic sweat test)

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 not known.

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
- QDIRT test
- Plasma catecholamine levels
- Skin vasomotor testing
- The ANSAR® test

Autonomic nervous system testing should be performed in a dedicated autonomic nervous system 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 autonomic nervous system 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 of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Autonomic nervous system testing</td>
<td>Clinical workup without autonomic nervous system testing</td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td>With signs and/or symptoms of autonomic nervous system dysfunction</td>
<td></td>
<td></td>
<td>Symptoms</td>
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<td></td>
<td></td>
<td></td>
<td>Functional outcomes</td>
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<td></td>
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<td>Quality of life</td>
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</table>

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.
For individuals who have signs and symptoms of ANS dysfunction who receive ANS testing, the evidence includes studies of diagnostic accuracy. Relevant outcomes are diagnostic accuracy, symptoms, functional outcomes, and quality of life. The evidence base is limited by a number of factors. 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 individual tests, most commonly in the diabetic population, but these reports do not provide estimates of accuracy for the entire battery of tests. Reported sensitivities and specificities were 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 the study designs that use patients with clinically diagnosed disease and a control group of healthy volunteers. There are also few clinical practice guidelines from specialty societies; the available recommendations are primarily based on expert opinion. The evidence is insufficient to determine the effects of the technology on health outcomes.

Despite the deficiencies in the evidence base, these tests provide information that cannot be obtained by other methods, given the limitations of clinical examination. This will lead to improved ability to make a diagnosis in some patients, and in others may avoid the need for further diagnostic testing. In addition, clinical input strongly supports the use of ANS testing as a diagnostic aid in situations of suspected ANS disorders. ANS testing should be performed in the setting of a dedicated ANS testing laboratory. Portable, automated testing that is intended for office use has not been sufficiently validated and has a greater potential to lead to erroneous results.

**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.\(^1\)\(^2\) 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 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
  - 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.\(^2\) 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).\(^1\) 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.\(^1\)

**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.\(^8\)
  - **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.\(^8\)

- **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.\(^8\) 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 (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 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.

### 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></td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Sudoscan®</td>
<td>Impeto Medical</td>
<td>Electrochemical sweat conductance</td>
<td>K100233</td>
<td>2010</td>
<td>GZO</td>
</tr>
<tr>
<td>ZYTO Hand</td>
<td>ZYTO Technologies</td>
<td>Galvanic skin response</td>
<td>K111308</td>
<td>2011</td>
<td>GZO</td>
</tr>
<tr>
<td>Cradle</td>
<td>Bauerfeind</td>
<td>Photoelectric plethysmograph</td>
<td>K123921</td>
<td>2013</td>
<td>JMO</td>
</tr>
<tr>
<td>Bodytronic® 200</td>
<td>TRIGOCare</td>
<td>Sudomotor function</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.

Rationale

This evidence review was originally created in August 2014 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through April 25, 2017.

AUTONOMIC NERVOUS SYSTEM TESTING

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical performance (test-retest reliability or interrater 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).

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: whether there evidence 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 populations of interest are 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 that are part of ANS testing, a full battery of testing generally consists of individual tests in 3 domains.

- Cardiovagal function (heart rate variability [HRV], 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], [TST], silastic sweat test, sympathetic skin response, electrochemical sweat conductance)

**Comparators**
The following tools, tests, rules, and practices are currently being 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 interrater reliability. The relevant outcomes for diagnostic accuracy are sensitivity, specificity, predictive values, and related measures of diagnostic accuracy. Effects on health outcomes include aiding in diagnosis of disease and guiding management.

Beneficial outcomes: Much of the treatment of autonomic disorders is nonpharmacologic and supportive, but there are specific actions that can be taken to 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 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 autonomic nervous system testing.

**Technical Performance**
ANS testing is essentially the only laboratory method available to evaluate dysfunction of the ANS. 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 about 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,(10) but reliability over longer time periods is less certain. A systematic review of published studies on the reliability of HRV was published in 2005.(11) Reviewers identified 8 studies (total N=183 patients) that reported on the reliability of short-term recordings (ie, excluding studies that used 24-hour monitoring). Four studies included healthy patients, 3 included patients with cardiac disease, and 1 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 2 studies the CV was much higher, 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 of reliability were identified. (12,13) Berger et al (2013) evaluated the reliability of the Quantitative Sudomotor Axon Reflex Test (QSART) measure in 20 healthy individuals. (12) They reported intraclass 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 evaluated both QSART and the QST measures in 23 patients with impaired glucose regulation and neuropathy. (13) The ICCs were high for both measures, ranging from 0.52 to 0.80. The QST measure 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 the study in patients with an initial positive test. An example of this type of study was published by Kochiadakis et al in 1998. (14) This study evaluated 35 patients with syncope and a positive tilt table test with a repeat tilt table test. The study also included a comparison group of 15 healthy volunteers who 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 some individual tests, mostly test-retest reproducibility. The available evidence is incomplete, and there is a lack of high-quality studies reporting on reliability. The research that is available is variable, but in most cases does not show high reproducibility. Therefore, there is a concern that these tests are not reliable, although further research is needed to evaluate this with more certainty.

**Diagnostic Accuracy**

There are a number of challenges in 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 the 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 these 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 were available, but high-quality research on the diagnostic accuracy of testing is lacking. The most rigorous evaluation of diagnostic accuracy identified was in the systematic review by the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPM&R), which focused on the accuracy of autonomic testing for distal symmetric polyneuropathy. (8)

Table 2 summarizes the results on diagnostic accuracy from this study. While reported sensitivity and specificity 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 AAN Practice Parameters, 20138)

<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 neuropathy</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>67% (QST)</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% (QSART)</td>
</tr>
<tr>
<td>Low (1993)</td>
<td>Diabetic neuropathy</td>
<td>CASS</td>
<td>Clinical exam EDx studies</td>
<td>428</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Schrezenmairer (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, multisystem atrophy</td>
<td>PRT, CASS</td>
<td>Clinical exam</td>
<td>194</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Singer (2004)</td>
<td>DSFN, diabetic and idiopathic neuropathy</td>
<td>CASS</td>
<td>Neurologic exam</td>
<td>49</td>
<td>95%</td>
<td>90%</td>
</tr>
</tbody>
</table>

AAN: American Academy of Neurology; 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: BP recovery time; QAE: quantitative autonomic evaluation; QSART: quantitative sudomotor axon reflex testing; QST: quantitative sensory testing; sx: symptoms.

In 2016, Franca da Silva et al reported a systematic review of the accuracy of HRV for the diagnosis and prognosis of cardiac autonomic neuropathy in individuals with diabetes.(15) 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 RR intervals every 5 minutes for a period of time, expressed in milliseconds), HF (high frequency component), and slope of TFC 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, the Neuropad device was identified. Kamenov et al (2010) enrolled 264 inpatients with diabetes.(16) 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.(17) 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.(18) This study 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. When 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%.

A 2013 publication, Casselini et al evaluated the accuracy of the Sudoscan electrochemical sweat conductance test, compared with other available tests of sudomotor function.(19) 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±3), intermediate for patients with diabetes without neuropathy (75.9±5.5) and highest for normal volunteers (84.4±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 with a Spearman correlation coefficient, ranging from 0.24 to 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 results of these studies probably do not reflect the diagnostic accuracy of testing in clinical practice.

Clinical Utility
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 autonomic 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 as well. In those cases, determining that autonomic dysfunction is the cause of symptoms may end the need for further testing.

SUMMARY OF EVIDENCE
The evidence for the diagnostic accuracy of autonomic nervous system (ANS) testing for patients who have signs and symptoms of ANS dysfunction includes studies of diagnostic accuracy. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, functional outcomes, and quality of life. The evidence base is limited by a number of factors. 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 individual tests, most commonly in the diabetic population, but this does not provide estimates of accuracy for the entire battery of tests. Reported sensitivities and specificities were 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 the study designs that use patients with clinically diagnosed disease and a control group of healthy volunteers. There are also few clinical practice guidelines from specialty societies; the available 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, input was received from 7 academic medical centers and 1 physician specialty society while this policy was under review 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
There is a 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, American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine & Rehabilitation guidelines, the recommendations are 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 societies convened a Polyneuropathy Task Force, consisting of 19 physician representatives from the 3 societies. All had expertise in polyneuropathy, in addition 4 had expertise in evidence-based methodology and practice parameter development. Each subcommittee performed a systematic review of the literature for their key question. 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 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 (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 an autonomic testing model coverage policy in 2014.(1) 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 is limited.

American Diabetes Association
The American Diabetes Association published standards of care for treatment in diabetes in 2010.(21) This document contained the following statement about autonomic neuropathy in diabetes:

- 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 (Expert opinion).
- Medications for the relief of specific symptoms related to DPN and autonomic neuropathy are recommended, as they improve the quality of life of the patient (Expert opinion).

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>NCT No.</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.

a Denotes industry-sponsored or cosponsored trial.

**References**


Billing Coding/Physician Documentation Information

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
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

**ICD-10 Codes**

- **E10.40** - Type 1 diabetes mellitus with neurological complications code range
- **E10.49**
- **E85.1;** - Neuropathic heredofamilial amyloidosis; other amyloidosis
- **E85.8**
- **G61.0-**
- **G61.9** - Inflammatory polyneuropathy code range
- **G90.01-**
- **G90.9** - Disorders of autonomic nervous system code range
- **M32.0-**
- **M32.9** - Systemic lupus erythematosus (SLE) code range
- **M35.00-**
- **M35.09** - Sicca syndrome [Sjögren]
- **R55** - Syncope and collapse

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- **8/1/15** - New Policy, Autonomic nervous system (ANS) testing may be considered medically necessary when criteria are met. ANS testing using portable, automated devices is considered investigational.
- **8/1/16** - No policy statement changes.
- **8/1/17** - No policy statement changes.
- **8/1/18** - No policy statement changes.

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