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 for 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

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

Description

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

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 FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Measurement</th>
<th>510(k) No.</th>
<th>Clearance Date</th>
<th>Product Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANX 3.0</td>
<td>Ansar Group</td>
<td>Respiration and heart rate variability</td>
<td>K941252</td>
<td>2004</td>
<td>DRT</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 Cradle</td>
<td>ZYTO Technologies</td>
<td>Galvanic skin response</td>
<td>K111308</td>
<td>2011</td>
<td>GZO</td>
</tr>
<tr>
<td>Bodytronic® 200</td>
<td>Bauerfeind</td>
<td>Photoelectric plethysmograph</td>
<td>K123921</td>
<td>2013</td>
<td>J MO</td>
</tr>
<tr>
<td>Neuropad®</td>
<td>TRIGOcare</td>
<td>Sudomotor function</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, respiration, gastrointestinal (GI) motility, thermal regulation, bladder control, and sexual function. The ANS is a complex neural regulatory network that consists of 2 complementary systems that work to maintain homeostasis: the sympathetic and the parasympathetic systems. The sympathetic nervous system is responsible for arousal, and sympathetic stimulation leads to increased pulse, increased blood pressure (BP), increased sweating, decreased GI motility, and an increase in other glandular exocrine secretions. This is typically understood as the “fight or flight” response. Activation of the parasympathetic nervous system will mostly have the opposite effects; BP and pulse will decrease, GI motility increases, and there will be a decrease in sweating and other glandular secretions.

ANS Disorders

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

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

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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**

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

**ANS Testing**

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

**Cardiovagal Function Testing**

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

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

**Sudomotor Function (Sweat Testing)**

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

For the silastic sweat imprint, silastic material is placed on the skin, and the sweat droplets form indentations on the silastic surface, allowing quantitation of the degree of sweating present. The Neuropad test is an example of a commercially available silastic sweat imprint.
A more complex approach in some centers is the use of a thermoregulatory laboratory. This is a closed chamber in which an individual sits for a defined period under tightly controlled temperature and humidity. An indicator dye is brushed on the skin, and it changes color when in contact with sweat. Digital pictures are taken and projected onto anatomic diagrams. Computer processing derives values for a total area of anhidrosis and the percent of anhidrotic areas.

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

A variant of sympathetic skin response testing is electrochemical sweat conductance measured by iontophoresis (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 the severity of autonomic dysfunction. Scores are based on self-reported symptoms measured by a standardized symptom survey. Scores of 3 or less are considered mild, scores of 3 to 7 are considered moderate and scores greater than 7 are considered severe.

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

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

**Autonomic Nervous System Testing**

**Clinical Context and Test Purpose**
The purpose of autonomic nervous system testing is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as clinical workup without autonomic nervous system testing, in patients with signs and/or symptoms of autonomic nervous system dysfunction.

The question addressed in this evidence review is: does ANS testing improve the net health outcome in patients with suspected autonomic disorder?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with signs and/or symptoms of autonomic nervous system dysfunction.

**Interventions**
The test being considered is autonomic nervous system testing.

The autonomic nervous system (ANS) controls physiologic processes that are not under conscious control. ANS testing consists of a battery of tests intended to evaluate the integrity and function of the ANS, and generally consist of 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), and sudomotor function (Quantitative Sudomotor Axon Reflex Test [QSART], quantitative sensory testing [QST], Thermoregulatory Sweat Test, silastic sweat imprint, sympathetic skin response, electrochemical sweat conductance). These tests are intended as adjuncts to the clinical examination in the diagnosis of ANS disorders.

Patients with signs and/or symptoms of autonomic nervous system dysfunction are actively managed by neurologists and primary care providers in an outpatient clinical setting.

**Comparators**
Comparators of interest include clinical workup without autonomic nervous system testing.

Comparators are actively managed by neurologists and primary care providers in an outpatient clinical setting.

**Outcomes**
The general outcomes of interest are test accuracy, symptoms, functional outcomes, and quality of life.

Much of the treatment for autonomic disorders is nonpharmacologic and supportive, but there are specific actions that can improve symptoms in patients with specific deficits and improve quality of life.

**Study Selection Criteria**
Below are selection criteria for studies to assess whether a test is clinically valid.

a. The study population represents the population of interest. Eligibility and selection are described.

b. The test is compared with a credible reference standard.

c. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.

d. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.

e. Studies should also report reclassification of diagnostic or risk category.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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

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

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

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

<table>
<thead>
<tr>
<th>Study</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 et al (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 et al (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 et al (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 et al (1999)</td>
<td>DSFN</td>
<td>Clinical sx, QSART, QST</td>
<td>EDx studies</td>
<td>495</td>
<td>80 (QSART) • 67 (QST)</td>
<td>93</td>
</tr>
<tr>
<td>Novak et al (2001)</td>
<td>Painful neuropathy</td>
<td>QSART, ART, CASS</td>
<td>Clinical exam</td>
<td>483</td>
<td>&gt;90 (ART) • 73 (QSART)</td>
<td>94</td>
</tr>
<tr>
<td>Low et al (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>Vogel et al (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>
</tbody>
</table>

Adapted from England et al (2009).art:
ART: autonomic reflex testing; BRSI: baroreflex sensitivity index; CASS: Composite Autonomic Severity Score; DSFN: distal small fiber neuropathy; EDx: electrodiagnostic studies (electromyography/nerve conduction.
velocity); HRV: heart rate variability; MSNA: muscle sympathetic nerve activity; PRT: blood pressure recovery time; QAE: quantitative autonomic evaluation; QSART: Quantitative Sudomotor Axon Reflex Test; QST: quantitative sensory testing; sx: symptoms.

Bellavere et al (2019) published an observational study comparing three types of cardiovascular autonomic tests (deep breathing [DB], lying to standing [LS], and Valsalva maneuver [VM]) for diagnosis of cardiac autonomic neuropathy. Data from 334 patients who had shown previous DB impairment were included. Test sensitivity for DB, LS, and VM were 0.667, 0.704, and 0.846, respectively, and specificity for DB, LS, and VM were 0.654, 0.726, and 0.482, respectively. No limitations to the study were reported.

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

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

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

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

**Section Summary: Clinically Valid**

It is not possible to determine the diagnostic accuracy of ANS testing. The lack of a criterion standard makes it difficult to perform high-quality research in this area. The available research has reported sensitivity in patients with clinically defined disease and specificity in health volunteers. This type of study design is known to produce inflated estimates of sensitivity and specificity; therefore, the diagnostic accuracy of testing in clinical practice is uncertain.
Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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

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

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

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

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

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 a consensus that autonomic nervous system testing should be medically necessary for some indications, and there was agreement on the proposed criteria for medical necessity.
Practice Guidelines and Position Statements
Evidence-based guidelines on autonomic nervous system (ANS) testing are lacking. Even in guidelines that involve a systematic review of the literature, such as the joint American Academy of Neurology (AAN), American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine & Rehabilitation guidelines (described below), recommendations were largely based on expert consensus.

American Academy of Neurology et al
AAN, AANEM, and American Academy of Physical Medicine & Rehabilitation (2009) issued a practice parameter,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 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
AANEM (2017) published a position statement on the proper performance of autonomic function testing.16, AANEM recommended that:

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

American Academy of Neurology
AAN published a model coverage policy on autonomic testing in 2014.2 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 (2010) published standards of care for treatment in diabetes.17 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 Society of Cardiology**
The European Society of Cardiology (2017) published a position statement on potential treatments for dysfunction of the autonomic nervous system in context of heart failure.17 The statement cited some noninvasive ANS tests, such as standing, deep breathing, and Valsalva’s maneuvers, but noted that none of these has shown “prognostic importance.”

**European Federation of Neurological Societies**
The European Federation of Neurological Societies (2011) issued a revision of its guidelines on orthostatic hypotension.18 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 3.

<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>Aug 2019 (ongoing)</td>
</tr>
<tr>
<td>NCT01568177</td>
<td>Cardiac Autonomic Function in Women With Microvascular Coronary Dysfunction</td>
<td>60</td>
<td>Feb 2021 (ongoing)</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>
<tr>
<td>NCT00608725</td>
<td>Pathophysiology of Orthostatic Intolerance</td>
<td>100</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT03156400</td>
<td>Assessment of Autonomic Function and Cardiovascular Response to Exercise Testing in Parkinson's Disease Patients</td>
<td>30</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>NCT02767037</td>
<td>SudoScan as a Biomarker of Parkinson's Disease</td>
<td>140</td>
<td>Jun 2018</td>
</tr>
</tbody>
</table>

*NCT: national clinical trial.
a 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
Autonomic Nervous System Testing

- 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 product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes 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><strong>CPT®</strong></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 |
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>
<tr>
<td>08/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2019</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.