2.01.96	Autonomic Nervous System Testing		
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Section:	2.0 Medicine	**Page:**	Page 1 of 19

Policy Statement

I. Autonomic nervous system testing, consisting of a battery of tests in several domains (see Policy Guidelines section), may be considered **medically necessary** when **all** of the following criteria are met:
   A. Signs and/or symptoms of autonomic dysfunction are present.
   B. A definitive diagnosis cannot be made from clinical examination and routine laboratory testing alone.
   C. Diagnosis of the suspected autonomic disorder will lead to a change in management or will eliminate the need for further testing.

II. 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:
   A. Allergic conditions
   B. Anxiety and other psychologic disorders
   C. Chronic fatigue syndrome
   D. Fibromyalgia
   E. Hypertension
   F. Monitoring progression of disease or response to treatment
   G. Screening of asymptomatic individuals
   H. Sleep apnea,

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

- Cardiovagal function (heart rate variability, heart rate response to deep breathing, and Valsalva maneuver)
- Vasomotor adrenergic function (blood pressure response to standing, Valsalva maneuver, hand grip, and tilt table testing)
- Sudomotor function (Quantitative Sudomotor Axon Reflex Test, quantitative sensory test, Thermoregulatory Sweat Test, silastic sweat imprint, sympathetic skin response, and electrochemical sweat conductance).

At least 1 test in each category is usually performed. More than 1 test from a category will often be included in a battery of tests, but the incremental value of using multiple tests in a category is unknown.

There is little evidence on the comparative accuracy of different ANS tests, but the following tests are generally considered to have uncertain value in ANS testing:

- Pupillography,
- Pupil edge light cycle,

- Gastric emptying tests,
- Cold pressor test,
- Quantitative direct and indirect testing of sudomotor function test,
- Plasma catecholamine levels,
- Skin vasomotor testing, and
- The ANSAR® test

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 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.

Coding
See the Codes table for details.

Description

The autonomic nervous system (ANS) controls physiologic processes that are not under conscious control. Autonomic nervous system testing consists of a battery of tests intended to evaluate the integrity and function of the ANS. These tests are intended as adjuncts to 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 U.S. Food and Drug Administration (FDA) through the 510(k) process. Table 1 lists examples.

The Neuropad test (TRIGOcare) is another example of a commercially available sudomotor function test.[10,] No records were identified indicating that Neuropad has been cleared for marketing by the U.S. FDA.

Table 1. Autonomic Nervous System Test Devices

Device	Manufacturer	Measurement	510(k) No.	Clearance Date	Product Code
ANX 3.0	Ansar Group	Respiration and heart rate variability	K941252	1995	DRT
Sudoscan	Impeto Medical	Electrochemical sweat conductance	K100233	2010	GZO
Hrv Acquire	WR Medical Electronics Co.	Respiration and heart rate variability	K092809	2010	DRT
ZYTO Hand Cradle	ZYTO Technologies	Galvanic skin response	K111308	2011	GZO
Bodytronic® 200	Bauerfeind	Photoelectric plethysmograph	K123921	2013	JOM
Finapres® Nova Noninvasive Hemodynamic Monitor	Finapres Medical Systems B.V.	Heart rate variability and baroreflex sensitivity	K173916	2018	DRT
VitalScan® ANS	Medeia, Inc.	Heart rate variability	K191266	2020	JOM

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.[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 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 decrease, GI motility increases, and decreased sweating and other glandular secretions.

Autonomic Nervous System Disorders

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

Symptoms of autonomic disorders can vary based on the etiology and location of dysfunction. Cardiovascular manifestations are often prominent. Involvement of the cardiovascular system causes abnormalities in heart rate control and vascular dynamics.[3,] Orthostatic hypotension and other manifestations of BP lability can occur, causing weakness, dizziness, and syncope. Resting tachycardia and an inability to appropriately increase heart rate in response to exertion leads to exercise intolerance. There is a 2- to 3-fold higher incidence of major cardiac events in patients with diabetic autonomic neuropathy, including myocardial infarction, heart failure, resuscitation from ventricular arrhythmia, angina, or the need for revascularization.[4,] There is also an increase in sudden cardiac death and overall mortality for these patients.[3,]

Many other organ systems can be affected by autonomic neuropathy. Involvement of the bladder can lead to incomplete emptying, resulting in urinary retention and possible overflow incontinence. Gastrointestinal involvement is commonly manifested as gastroparesis, which is defined as slowed gastric emptying and can cause nausea, vomiting, and a decreased tolerance for solid food and large meals. Constipation may also occur if the lower GI tract is involved. Impairment of sexual

function in males can manifest as erectile dysfunction and ejaculatory failure. Dysfunction of thermal regulation and sweating can lead to anhidrosis and heat intolerance. Paradoxically, excessive sweating can also occur as a compensatory mechanism in unaffected regions.[5,]

A classification of the different types of autonomic dysfunction, adapted from Freeman (2005)[5,] and Macdougall and McLeod (1996),[6,] 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,
    - Lyme disease,
    - Chagas disease,
    - Diphtheria,
    - Leprosy;
- Acute and subacute idiopathic autonomic neuropathy; and
- 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.[7,] Sympathetic overactivity is also a prominent feature of generalized anxiety, panic disorder, and some types of depression, as well as certain cardiac disorders such as chronic heart failure. These types of ANS imbalances are not usually classified as ANS disorders.

Treatment of Autonomic Nervous System Disorders

Much of the treatment for autonomic disorders is nonpharmacologic and supportive. However, there are specific actions that can improve symptoms in patients with specific deficits. For patients with orthostatic hypotension, this involves adequate intake of fluids and salt, moving to an upright position slowly and deliberately, use of lower-extremity compression stockings, and keeping the head of the bed elevated 4 to 6 inches (i.e., 10 to 15 cm).[1,] In severe cases, medications that promote salt retention, such as fludrocortisone, are 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,]

Autonomic Nervous System Testing

Autonomic nervous system 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.[8,]

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.[8,]

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.[8,] 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.[9,] 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.[9,]
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. Autonomic nervous system testing consists of tests in 3 categories:

- Cardiovagal function (heart rate variability, heart rate response to deep breathing, and Valsalva maneuver).
- Vasomotor adrenergic function (blood pressure response to standing, Valsalva maneuver, hand grip, and tilt table testing).
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- Quantitative direct and indirect testing of sudomotor function test,
- Plasma catecholamine levels,
- Skin vasomotor testing, and
- The ANSAR test.

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Autonomic Nervous System Testing

Clinical Context and Test Purpose

The purpose of autonomic nervous system (ANS) testing is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as clinical workup without ANS testing, in individuals with signs and/or symptoms of ANS dysfunction.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with signs and/or symptoms of ANS dysfunction.

Interventions
The test being considered is ANS testing.

The ANS controls physiologic processes that are not under conscious control. Autonomic nervous system 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, hand grip, and 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, and electrochemical sweat conductance). These tests are intended as adjuncts to the clinical examination in the diagnosis of ANS disorders.

Comparators
Comparators of interest include clinical workup without ANS testing.

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 actions that can improve symptoms in individuals with specific deficits and improve quality of life.

Study Selection Criteria
For the evaluation of clinical validity of ANS testing, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

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).

Review of Evidence
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.

Diagnostic Accuracy of Various Tests
Systematic Review
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.[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 to Diagnose Distal Symmetric Polyneuropathy

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

Adapted from England et al (2009).[8,]
ART: autonomic reflex testing; BRSI: baroreflex sensitivity index; CASS: Composite Autonomic Severity Score; DSFN: distal small fiber neuropathy; EDx: electrodiagnostic studies (electromyography/nerve conduction velocity); HRV: heart rate variability; MSNA: muscle sympathetic nerve activity; PRT: blood pressure recovery time; QAE: quantitative autonomic evaluation; QSART: quantitative sudomotor axon reflex test; QST: quantitative sensory testing; sx: symptoms.

da Silva et al (2016) reported on a systematic review evaluating the accuracy of HRV for the diagnosis and prognosis of cardiac autonomic neuropathy in individuals with diabetes.[11,] 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 the mean of normal relative risk (RR) intervals every 5 minutes for a period of time expressed in milliseconds (i.e., intervals between heartbeats), 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%.

Observational and Noncomparative Studies

Bellavere et al (2019) published an observational study comparing 3 types of cardiovascular autonomic tests (deep breathing, lying to standing, and Valsalva maneuver) for diagnosis of cardiac autonomic neuropathy. Data from 334 patients who had shown previous deep breathing impairment were included.[12,] Test sensitivity for deep breathing, lying to standing, and Valsalva maneuver were 0.667, 0.704, and 0.846, respectively, and specificity for deep breathing, lying to standing, and Valsalva maneuver were 0.654, 0.726, and 0.482, respectively. No limitations to the study were reported.

A study by Park et al (2019) investigated the usefulness of various quantitative fractionalized autonomic indexes in distinguishing between idiopathic Parkinson disease (IPD) and multiple system atrophy-Parkinson type (MSA-P) in 36 individuals with Parkinson disease (PD) treated at Soonchunhyang University Bucheon Hospital from February 2014 to June 2015.[13,] This study also evaluated the correlations between these autonomic test indexes and functional status. This study found that among the test indices evaluated, use of a cut-off value of 5.5 seconds for pressure recovery time stood out as distinguishing between the 2 diagnoses and had a sensitivity of 71.4% and a specificity of 72.7%. Additionally, Valsalva ratio (r=-0.455, p=.009) and adrenergic baroreflex sensitivity (r=-0.356, p=.036) demonstrated significant correlations with the Unified Multiple System Atrophy Rating Scale and the Hoehn and Yahr score less than or equal to 3.

Neuropad

Systematic Reviews

The National Institute of Health and Care Excellence (NICE) (2017) published an evidence review on the Neuropad test for the early detection of diabetic neuropathy.[14,] This review included 17 studies that evaluated the diagnostic accuracy of Neuropad against a reference standard, most commonly the Neuropathy Disability Score. In their meta-analysis of 5 diagnostic accuracy studies using a Neuropathy Disability Score of 5 or greater as a reference standard, NICE reported that Neuropad had a pooled sensitivity and specificity of 89.4% and 60.3%, respectively. However, NICE reviewers noted that high heterogeneity limited interpretation of these findings. Additionally, the NICE review reported that, in 2 published studies that assessed the diagnostic accuracy of Neuropad against the 10 g monofilament (MONO) test, results indicated that, overall, the Neuropad has a higher sensitivity, but a much lower specificity than the monofilament. Finally, the NICE review reported that evidence was insufficient to evaluate the performance of Neuropad against vibration perception threshold testing. NICE concluded that "no clear or conclusive evidence was found for the use of Neuropad as a screening test for early neuropathy" and also noted that "while Neuropad may theoretically be able to detect earlier stage neuropathy, in the current pathway this is of limited benefit, as action is only triggered when moderate or advanced neuropathy is detected."

Observational Study

Subsequent to the 2017 NICE review, Didangelos et al (2019) published a study of 174 patients with diabetes that evaluated the diagnostic accuracy of Neuropad compared with the Michigan Neuropathy Screening Instrument Questionnaire and Examination (MNSIQ and MNSIE, respectively), application of 10 g MONO, and measurement of vibration perception threshold with biothesiometer (BIO).[15,] Sensitivity of Neuropad testing was 95% versus MONO, 73% versus BIO, 73% versus MNSIE, and 75% versus MNSIQ. Specificity was 69%, 81%, 90%, and 92%, respectively.

Sudoscan

Systematic Review

Rajan et al (2019) reported on the results of a systematic review of 37 studies of Sudoscan published between 2010 and 2018 and spanned several types of conditions, including types 1 and 2 diabetes, pre-diabetes or metabolic syndrome, rheumatoid arthritis, ankylosing spondylitis, small fiber neuropathy, distal symmetric polyneuropathy, Fabry's disease, amyloidosis, cystic fibrosis, and chronic kidney disease.[16,] Review authors reported that the studies typically compared the test performance of Sudoscan to various other physiologic parameters, such as nerve function, kidney function, metabolic function, disease state, and/or cardiovascular risk. These studies found significant, but variable and modest correlations (0.4 to 0.7). However, review authors raised 4 key concerns about the Sudoscan evidence that raise serious questions about the clinical utility of the device: (1) due to a failure to detect age-, gender-, and disease-appropriate variability, the published results violate biological plausibility; (2) inadequate information is available to determine the exact method by which the Sudoscan device calculates electrochemical skin conductance; (3) the majority of the studies have been funded by the device manufacturer; and (4) there is important inconsistency across publication in the device's normative values. Due to these limitations and the lack of evidence

with detailed comparisons to standard sudomotor testing with longitudinal follow-up, the review authors concluded that they could not recommend the clinical use of Sudoscan.

Observational Studies

A number of additional studies of Sudoscan have been published since the systematic review by Rajan et al (2019). These include studies in transthyretin familial amyloid polyneuropathy, diabetes, and PD. However, none of these studies addressed the limitations identified by the systematic review by Rajan et al (2019) discussed above.

A study by Fortanier et al (2020) evaluated the performance of Sudoscan in differentiating transthyretin familial amyloid polyneuropathy from chronic inflammatory demyelinating polyneuropathy and found that feet electrochemical skin conductance less than 64 µS had a 89% sensitivity and a 96% specificity to differentiate between the 2 types.[17,]

In diabetes, a study by Lai et al (2021) evaluated the combination of Sudoscan and HRV, measured as the standard deviation of the RR interval, in diagnosing cardiovascular autonomic neuropathy in 90 patients with type 2 diabetes.[18,] When combined, the specificity increased from 56.2% (HRV) and 40.6% (Sudoscan) to 70%, and the specificity remained relatively unchanged at 79.4% from 76.1% (HRV) and 82.6% (Sudoscan). A study by D'Amato et al (2020) evaluated the combined use of composite autonomic symptom score (COMPASS) 31 questionnaire and electrochemical skin conductance using Sudoscan to diagnose diabetic cardiovascular autonomic neuropathy and diabetic polyneuropathy in 102 participants with diabetes.[19,] When the tests were combined, the sensitivity for cardiovascular autonomic neuropathy increased from 75% to 83%, to 100%; and the specificity increased from 65% to 67%, to 89%, for diabetic polyneuropathy. In a study by Carbajal-Ramirez et al (2019), the performance of Sudoscan in detecting small fibers neuropathy was compared to the Michigan Neuropathy Screening Instrument in 221 individuals with type 2 diabetes in Mexico.[20,] Compared to the Michigan Neuropathy Screening Instrument, abnormal hands or feet electrochemical skin conductance as measured by Sudoscan (<60 µS and 70 µS respectively) has a sensitivity of 97% in patients with diabetes duration of 5 years or more and 91% in patients with a diabetes duration of less than 5 years. Lin et al (2022) evaluated the use of Sudoscan in 515 patients with type 2 diabetes and found a sensitivity of 79% and specificity of 65% when evaluating the feet for peripheral neuropathy.[21,] García-Ulloa et al (2023) evaluated the diagnostic accuracy of Sudoscan compared with MONO and tuning fork tests (N=2243) for detecting diabetic peripheral neuropathy.[22,] Sudoscan detected 619 patients (27.6%) with sudomotor dysfunction, while MONO or tuning fork identified 650 patients (28.9%) with diabetic peripheral neuropathy. The area under the curve for Sudoscan was 0.495 (95% confidence interval, 0.469 to 0.522), with sensitivity and specificity of 24% and 71%, respectively, for detecting neuropathy.

The use of Sudoscan has also been studied for its ability to identify autonomic neuropathy in people with PD. Two similar studies identified had conflicting results. A study by Xu et al (2019) compared Sudoscan's predictive ability to detect PD-related autonomic neuropathy among 43 hospitalized patients in the later stages of PD with 42 healthy controls.[23,] Authors of the study reported that, in individuals with PD, Sudoscan detected lower electrochemical skin conductance in both the hands (-28%) and the feet (-19.1%). However, in another study by Pepescu et al (2019), no significant reduction in electrochemical skin conductance measured by Sudoscan was found in 67 individuals with PD compared with 66 age-matched controls.[24,]

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 healthy 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, more effective therapy, or avoid unnecessary therapy or 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.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

2014 Input
In response to requests, input was received from 1 physician specialty society and 7 academic medical centers while this policy was under review 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
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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

In 2020, a consensus statement endorsed by the AAN, American Autonomic Society, and the International Federation of Clinical Neurophysiology on assessment of the ANS was published.[25,] The consensus statement recommends that a combination of autonomic tests should be used for better accuracy compared to a single test, which should ideally assess cardiovascular adrenergic, cardiovagal, and sudomotor function. Recommended tests include: continuous beat-to-beat heart rate and blood pressure responses to the Valsalva maneuver, postural changes on a tilt table, or sinusoidal deep breathing; the Valsalva ratio; quantitative sudomotor axon reflex test; and the thermoregulatory sweat test. The recommendations also outlined valid indications for autonomic testing, which are outlined in Table 3.

Table 3. Valid Indications for Autonomic Testing According to the American Academy of Neurology, American Autonomic Society, and the International Federation of Clinical Neurophysiology

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

The AAN, AANEM, and American Academy of Physical Medicine & Rehabilitation (2009) issued a practice parameter on the evaluation of distal symmetric polyneuropathy.[8,] This parameter was reaffirmed in July 2013 and retired in 2019. This document addressed the use of autonomic testing in the evaluation of patients with distal symmetric polyneuropathy. The following conclusion and recommendations were made:

"Autonomic testing is probably useful in documenting autonomic nervous system involvement in polyneuropathy (Class II and Class III). The sensitivity and specificity vary with the particular test. The utilization of the combination of autonomic reflex screening tests in the CASS [Composite Autonomic Severity Score] probably provides the highest sensitivity and specificity for documenting autonomic dysfunction (Class II).

- Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system involvement (Level B).
- Autonomic testing should be considered in the evaluation of patients with suspected autonomic neuropathies (Level B) and may be considered in the evaluation of patients with suspected distal SFSN [small fiber sensory neuropathy] (Level C).
- The combination of autonomic screening tests in the CASS should be considered to achieve the highest diagnostic accuracy (Level B)."

American Association of Neuromuscular and Electrodiagnostic Medicine

In 2023, the AANEM updated its recommended policy for electrodiagnostic medicine.[26,] The policy states that the purpose of ANS function testing is "to determine the presence of autonomic dysfunction, the site of autonomic dysfunction, and the various autonomic systems which may be disordered." The policy includes testing of cardiovagal innervation; vasomotor adrenergic innervation; and evaluation of sudomotor function (specifically, the quantitative sudomotor axon reflex test, silastic sweat imprint, thermoregulatory sweat test, and sympathetic skin response). Conditions for which testing may be appropriate include idiopathic orthostatic hypotension, diabetic neuropathy, and other neuropathies affecting autonomic nerves.

In 2021, the AANEM published a revised position statement on the proper performance of autonomic function testing.[27,] The statement 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 in real time collected in various autonomic procedures including those performed by a technician.

The statement recommended the following series of tests as reliable and reproducible:

- Evaluation of sudomotor function: quantitative sudomotor axon reflex testing, thermoregulatory sweat testing, induced silastic skin imprints, sympathetic skin response.
- Evaluation of cardiovagal function: heart rate response to deep breathing, Valsalva ratio, postural change.
- Evaluation of vasomotor adrenergic function: continuous beat-to-beat heart rate and blood pressure response to a Valsalva maneuver, tilt table test, active standing.

American Academy of Neurology

In 2014, the AAN published a model coverage policy on autonomic testing.[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 publishes annual standards of care for treatment of diabetes.[28,] The 2024 publication contained the following statements on screening for autonomic neuropathy in diabetes:

- "All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter." (B)

- "Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation." (B)
- "Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin." (E)

Recommendation ratings B: supportive evidence from well conducted cohort studies.

Recommendation ratings E: expert consensus or clinical experience.

National Institute for Health and Care Excellence

The NICE published guidance in 2018 on Neuropad for detecting preclinical diabetic peripheral neuropathy (MTG38).[29,] The guidance was updated in 2022 and maintained that: "The case for adopting Neuropad to detect preclinical diabetic peripheral neuropathy is not supported by the evidence".

U.S. Preventive Services Task Force Recommendations

Not applicable.

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 and ongoing trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04927832	Detection of Small Fiber Neuropathies by the Non-invasive SUDOSCAN Method During Chronic Autoimmune Pathologies and/or Unexplained Pain Syndromes	150	Dec 2022 (ongoing)
NCT01568177	Cardiac Autonomic Function in Women with Microvascular Coronary Dysfunction	105	Feb 2024 (ongoing)
NCT00608725	Pathophysiology of Orthostatic Intolerance	100	Dec 2025
Unpublished			
NCT03156400	Assessment of Autonomic Function and Cardiovascular Response to Exercise Testing in Parkinson's Disease Patients	30	Jun 2018
NCT02767037	SudoScan as a Biomarker of Parkinson's Disease	150	Jun 2018
NCT02985710	Assessment of Small Fiber Neuropathy in Rare Diseases Using Sudoscan	102	Aug 2020

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- 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 (in addition to the above, please include the following):

- 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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
HCPCS	None	

Policy History

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

Effective Date	Action
04/01/2016	BCBSA Medical Policy adoption
08/01/2017	Policy revision without position change
08/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
08/01/2023	Policy reactivated. Previously archived from 07/01/2020 to 07/31/2023.
08/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 and Feedback (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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Autonomic Nervous System Testing 2.01.96 **Policy Statement:** I. Autonomic nervous system testing, consisting of a battery of tests in several domains (see Policy Guidelines section), may be considered **medically necessary** when **all** of the following criteria are met: A. Signs and/or symptoms of autonomic dysfunction are present. B. A definitive diagnosis cannot be made from clinical examination and routine laboratory testing alone. C. Diagnosis of the suspected autonomic disorder will lead to a change in management or will eliminate the need for further testing. II. 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: A. Allergic conditions B. Anxiety and other psychologic disorders C. Chronic fatigue syndrome D. Fibromyalgia E. Hypertension F. Monitoring progression of disease or response to treatment G. Screening of asymptomatic individuals H. Sleep apnea, III. Autonomic nervous system testing using portable automated devices is considered **investigational** for all indications (see Policy Guidelines section).	**Autonomic Nervous System Testing 2.01.96** **Policy Statement:** I. Autonomic nervous system testing, consisting of a battery of tests in several domains (see Policy Guidelines section), may be considered **medically necessary** when **all** of the following criteria are met: A. Signs and/or symptoms of autonomic dysfunction are present. B. A definitive diagnosis cannot be made from clinical examination and routine laboratory testing alone. C. Diagnosis of the suspected autonomic disorder will lead to a change in management or will eliminate the need for further testing. II. 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: A. Allergic conditions B. Anxiety and other psychologic disorders C. Chronic fatigue syndrome D. Fibromyalgia E. Hypertension F. Monitoring progression of disease or response to treatment G. Screening of asymptomatic individuals H. Sleep apnea, III. Autonomic nervous system testing using portable automated devices is considered **investigational** for all indications (see Policy Guidelines section).