Protocol

Autonomic Nervous System Testing

(20196)

Medical Benefit		**Effective Date**: 04/01/16	**Next Review Date**: 01/18
Preauthorization	No	**Review Dates**: 01/15, 01/16, 01/17	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With signs and/or symptoms of autonomic nervous system dysfunction	Interventions of interest are: • Autonomic nervous system testing	Comparators of interest are: • Clinical workup without autonomic nervous system testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Symptoms • Functional outcomes • Quality of life

Description

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

Summary of Evidence

The evidence for the diagnostic accuracy of ANS testing for patients who have signs and symptoms of ANS dysfunction includes studies of diagnostic accuracy. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, functional outcomes, and quality of life. The evidence base is limited by a number of factors. There is a lack of a criterion standard for determining autonomic dysfunction, which limits the ability to perform high-quality research on diagnostic accuracy. Also, numerous tests are used in various conditions, making it difficult to determine values for overall diagnostic accuracy of a battery of tests. The evidence on the reliability of individual tests raises concerns about the reproducibility of testing. Scattered reports of diagnostic accuracy are available for certain individual tests, most commonly in the diabetic population, but this does not provide estimates of accuracy for the entire battery of tests. Reported sensitivities and specificities were high for patients with clinically defined distal symmetric polyneuropathy using a symptom-based score as a reference standard, but these estimates are likely biased by the study designs that use patients with clinically diagnosed disease and a control group of healthy volunteers. There are also few clinical practice guidelines from specialty societies; the available recommendations are primarily based on expert opinion. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

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

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

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

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

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

Policy Guidelines

Although there is not a standard battery of tests that are part of ANS testing, a full battery of testing generally consists of individual tests in three domains.

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

At least one test in each category is usually performed. More than one test from a category will often be included in a battery of tests, but the incremental value of using multiple tests in one domain is not known.

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

- Pupillography
- Pupil edge light cycle
- Gastric emptying tests
- Cold pressor test

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

Autonomic nervous system testing should be performed in a dedicated autonomic nervous system testing laboratory. Testing in a dedicated laboratory should be performed under closely controlled conditions, and interpretation of the results should be performed by an individual with expertise in autonomic nervous system testing. Testing using automated devices with interpretation of the results performed by computer software has not been validated and thus has the potential to lead to erroneous results.[1]

Medicare Advantage

For Medicare Advantage autonomic function testing is considered **medically necessary** when used as a diagnostic tool to evaluate symptoms indicative of vasomotor instability and the ANS testing is directed at establishing a more accurate or definitive diagnosis or contributing to clinically useful and relevant medical decision making for one of the following indications:

- To diagnose the presence of autonomic neuropathy in a patient with signs or symptoms suggesting a progressive autonomic neuropathy.
- To evaluate the severity and distribution of a diagnosed progressive autonomic neuropathy.
- To differentiate the diagnosis between certain complicated variants of syncope from other causes of loss of consciousness.
- To evaluate inadequate response to beta blockade in vasodepressor syncope.
- To evaluate distressing symptoms in a patient with a clinical picture suspicious for distal small fiber neuropathy in order to diagnose the condition.
- To differentiate the cause of postural tachycardia syndrome.
- To evaluate change in type, distribution or severity of autonomic deficits in patients with autonomic failure.
- To evaluate the response to treatment in patients with autonomic failure who demonstrate a change in clinical exam.
- To diagnose axonal neuropathy or suspected autonomic neuropathy in the symptomatic patient.
- To evaluate and treat patients with recurrent unexplained syncope or demonstrate autonomic failure, after more common causes have been excluded by other standard testing.

The following indications are considered **investigational** and will not be covered:

- Screening patients without signs or symptoms of autonomic dysfunction, including patients with diabetes, hepatic or renal disease.
- Testing for the sole purpose of monitoring disease intensity or treatment efficacy in diabetes, hepatic or renal disease.
- Testing results that are not used in clinical decision-making or patient management.
- Testing performed by physicians who do not have evidence of training, and expertise to perform and interpret these tests.

- General professional standards with FDA clearance apply for all equipment used in ANS testing.
- Testing with ANSAR ANX 3.0 or a similar machine is considered investigational for screening.

Background

The ANS has a primary role in controlling physiologic processes that are not generally under conscious control. These include heart rate, respirations, gastrointestinal (GI) motility, thermal regulation, bladder control, and sexual function.[1, 2] It is a complex neural regulatory network that consists of two complementary systems that work together to maintain homeostasis. The sympathetic nervous system is responsible for arousal, and sympathetic stimulation leads to increased pulse, increased blood pressure (BP), increased sweating, decreased GI motility and an increase on other glandular exocrine secretions. This is typically understood as the "fight or flight" response. Activation of the parasympathetic nervous system will mostly have the opposite effects; BP and pulse will decrease, GI motility increases, and there will be a decrease in sweating and other glandular secretions.

ANS Disorders

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

Symptoms of autonomic disorders can be varied, 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 an approximately two- to three-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).[4] There is also an increase in cardiac sudden 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. 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.[5]

A classification of the different types of autonomic dysfunction, adapted from Freeman et al[5] and Macdougall et al,[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 disease
  - Lyme disease
  - Chagas disease
  - Diphtheria
  - Leprosy
- Acute and subacute idiopathic autonomic neuropathy
- Toxic neuropathies

A variety of other chronic diseases may involve an imbalance of the ANS, 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.

Much of the treatment of autonomic disorders is nonpharmacologic and supportive. However, there are specific actions that can be taken to 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 four to six inches.[2] 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.[2]

ANS Testing

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

- Cardiovagal function testing
  - Heart rate variability. Beat-to-beat variability in the heart rate can be measured at rest, or in response to provocative measures, such as deep breathing or the Valsalva maneuver. Reduced, or absent, heart rate variability (HRV) is a sign of autonomic dysfunction.[8]
  - Baroreflex sensitivity**.** Baroreflex sensitivity is measured by examining the change in pulse and HRV in response to changes in BP. A medication such as phenylephrine is given to induce a raise in blood pressure, and baroreflex sensitivity is calculated as the slope of the relationship between HRV and BP.[8]

- Sudomotor function (sweat testing). Sweat testing evaluates the structure and function of nerves that regulate the sweat glands.
    - QSART test. The Quantitative Sudomotor Axon Reflex Test (QSART) is an example of a semiquantitative test of sudomotor function that is commercially available.[8] The test is performed by placing a color sensitive paper on the skin, which changes color on contact with sweat. Measurement of the amount of color change is a semiquantitative measure of sudomotor function.
    - Silastic Sweat test. In this test, a silastic material is placed on the skin, and the sweat droplets form indentations on the silastic surface, allowing quantitation of the degree of sweating present. The Neuropad® test is an example of a commercially available silastic sweat test.
    - Thermoregulatory Sweat test. 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 of time under tightly controlled temperature and humidity. An indicator dye is brushed on the skin, which changes color when in contact with sweat. Digital pictures are taken and projected onto anatomic diagrams. Computer processing derives values for total area of anhidrosis, and the percent of anhidrotic areas.
    - Sympathetic skin response. These tests use an electric current to stimulate sympathetic nerves. The tests measure the change in electrical resistance, which is altered in the presence of sweat. In general these tests are considered to be sensitive, but have high variability and the potential for false-positive results.[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 test. The protocol for this test involves the subject chewing on a preweighed gauze for five minutes. At the end of five minutes, the gauze is removed and reweighed to determine the total weight of saliva present.
- Tilt table testing. Tilt table testing is intended to evaluate for orthostatic intolerance. The patient lies on the table and is strapped in with a 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

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

Regulatory Status

Since 1976, numerous ANS testing devices have been cleared for marketing by the US Food and Drug Administration (FDA) through the 510(k) process. A hydraulic, pneumatic, or photoelectric plethysmograph is a noninvasive device to estimate blood flow to a region of the body using hydraulic, pneumatic, or photoelectric measurement techniques. The ANX 3.0® system (Ansar Group) measures both branches of the ANS (sympathetic and parasympathetic) independently and simultaneously in real time. The ANX 3.0 performs respiratory-based digital testing of the ANS and heart rate variability measurements. FDA approval for the ANX 3.0 was received in

2004. In 2010, Sudoscan® (Impeto Medical), a device measuring electrochemical sweat conductance, was cleared for marketing. FDA product code GZO. Most recently, in 2013, the following ANS measurement devices were cleared for marketing by FDA through the 510(k) process: the Bodytronic® 200 (Bauerfeind AG) and the Dopplex Ability® (Huntleigh Healthcare). FDA product code: JOM.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. American Academy of Neurology (AAN). Model Coverage Policy: Autonomic Nervous System Testing. 2014; https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/3.Practice_Management/1.Reimbursement/1.Billing_and_Coding/5.Coverage_Policies/14%20Autonomic%20Testing%20Policy%20v001.pdf. Accessed October 28, 2014.
2. Klein CM. Evaluation and management of autonomic nervous system disorders. Semin Neurol. Apr 2008; 28(2):195-204. PMID 18351521
3. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. Jan 23 2007; 115(3):387-397. PMID 17242296
4. Valensi P, Sachs RN, Harfouche B, et al. Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. Diabetes Care. Feb 2001; 24(2):339-343. PMID 11213889
5. Freeman R. Autonomic peripheral neuropathy. Lancet. Apr 2-8 2005; 365(9466):1259-1270. PMID 15811460
6. McDougall AJ, McLeod JG. Autonomic neuropathy, II: Specific peripheral neuropathies. J Neurol Sci. Jun 1996; 138(1-2):1-13. PMID 8791232
7. Goldstein DS, Robertson D, Esler M, et al. Dysautonomias: clinical disorders of the autonomic nervous system. Ann Intern Med. Nov 5 2002; 137(9):753-763. PMID 12416949
8. American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. Practice parameter: evaluation of distal symmentric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review) 2013; http://www.neurology.org/content/72/2/177.full.html#ref-list-1. Accessed July, 2014.
9. Low PA. Testing the autonomic nervous system. Semin Neurol. Dec 2003; 23(4):407-421. PMID 15088262
10. Umetani K, Singer DH, McCraty R, et al. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol. Mar 1 1998; 31(3):593-601. PMID 9502641
11. Sandercock GR, Bromley PD, Brodie DA. The reliability of short-term measurements of heart rate variability. Int J Cardiol. Sep 1 2005; 103(3):238-247. PMID 16098384
12. Berger MJ, Kimpinski K. Test-retest reliability of quantitative sudomotor axon reflex testing. J Clin Neurophysiol. Jun 2013; 30(3):308-312. PMID 23733097

13. Peltier A, Smith AG, Russell JW, et al. Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. Muscle Nerve. Apr 2009; 39(4):529-535. PMID 19260066
14. Kochiadakis GE, Kanoupakis EM, Rombola AT, et al. Reproducibility of tilt table testing in patients with vasovagal syncope and its relation to variations in autonomic nervous system activity. Pacing Clin Electrophysiol. May 1998; 21(5):1069-1076. PMID 9604238
15. Kamenov ZA, Petrova JJ, Christov VG. Diagnosis of diabetic neuropathy using simple somatic and a new autonomic (neuropad) tests in the clinical practice. Exp Clin Endocrinol Diabetes. Apr 2010; 118(4):226-233. PMID 20200815
16. Quattrini C, Jeziorska M, Tavakoli M, et al. The Neuropad test: a visual indicator test for human diabetic neuropathy. Diabetologia. Jun 2008; 51(6):1046-1050. PMID 18368386
17. Ponirakis G, Petropoulos IN, Fadavi H, et al. The diagnostic accuracy of Neuropad for assessing large and small fibre diabetic neuropathy. Diabet Med. Dec 2014; 31(12):1673-1680. PMID 24975286
18. Casellini CM, Parson HK, Richardson MS, et al. Sudoscan, a noninvasive tool for detecting diabetic small fiber neuropathy and autonomic dysfunction. Diabetes Technol Ther. Nov 2013; 15(11):948-953. PMID 23889506
19. American Diabetes Association. Standards of medical care in diabetes--2010. Diabetes Care. Jan 2010; 33 Suppl 1:S11-61. PMID 20042772
20. European Federation of Neurological Societies. Guideline: Orthostatic Hypotention. 2011; http://www.guideline.gov/content.aspx?id=34904&search=autonomic+nervous+system+testing. Accessed July, 2014.
21. National Government Services, Inc. Local Coverage Determination (LCD): AUTONOMIC Function TESTing (L36236), Revision Effective Date for services performed on or after 10/01/2015.