Medical Coverage Policy

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Coverage Policy Number 0506

Autonomic Nerve Function Testing

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Related Coverage Resources

Electrodiagnostic Testing (EMG/NCV)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses autonomic nerve function testing. The tests for autonomic nerve function can be grouped into three main categories which include sudomotor, cardiovagal, and adrenergic tests, with at least one test from each category being performed.

Coverage Policy

Autonomic nerve function testing is considered medically necessary to evaluate autonomic nerve function and aid in the diagnosis of ANY of the following conditions:

- Distal small fiber neuropathy
- Postural tachycardia syndrome
- Reflex sympathetic dystrophy (e.g., sympathetically maintained pain, causalgia)
- Recurrent, unexplained syncope
- Any of the following progressive autonomic neuropathies:
  - Diabetic autonomic neuropathy
  - Amyloid neuropathy
  - Sjogren's syndrome

- Idiopathic neuropathy
- Pure autonomic failure
- Multiple system atrophy (Shy-Drager syndrome)

Autonomic nerve function testing to aid in the diagnosis of ANY other condition is considered experimental, investigational or unproven.

Autonomic nerve function testing using portable, automated device is considered experimental, investigational or unproven.

General Background

The autonomic nervous system controls the internal organs of the body regulating and maintaining physiologic processes such as blood pressure, heart rate, body temperature, metabolism, sweating, urination, and fluid and electrolyte balance. The autonomic nervous system is controlled by two nerve systems, the parasympathetic nervous system and sympathetic nervous system. Stimulus to the sympathetic nervous system activates what is commonly referred to as the "fight or flight response" involving redistribution of blood flow from the viscera to skeletal muscle, increased cardiac function, sweating, and pupillary dilatation. Stimulation of the parasympathetic nervous system is associated with maintenance of function and conserving energy. Most of the body organs are innervated by both systems although some organs are innervated by only one. When innervated by both systems the two systems work together allowing the body to respond appropriately to various stimuli.

Disorders of the autonomic nervous system can affect any body system. They can be classed as either structural or functional disorders. Structural disorders (i.e., autonomic failure), such as multiple system atrophy (MSA) or diabetic autonomic neuropathy, exert a direct effect on autonomic nerve function whereas functional disorders do not. Functional disorders are less specific in cause and effect and are generally defined by the symptoms that an individual displays as part of a "syndrome", such as postural tachycardia syndrome or complex regional pain syndrome.

Clinical symptoms that are associated with autonomic impairment typically include lightheadedness resulting from postural changes, dry mouth, dry eyes, impotence, gastroparesis, bowel or urinary incontinence and neuropathies, to name a few. When symptoms suggest autonomic nerve dysfunction autonomic nerve function testing may be recommended to aid with the diagnosis of a condition. Treatment is then aimed at correction of the underlying disease and/or management of the specific symptoms.

Sudomotor testing (i.e, sweat testing) is invasive and is used to test nerve fibers associated with sweating and aids in the assessment of neuropathy. Cardiovagal and adrenergic testing, which are both noninvasive, use blood pressure and heart rate to obtain waveforms and measurements and are performed to evaluate conditions such as tachycardia and orthostatic hypotension.

Autonomic Sudomotor Function Tests (Sweat Testing) (CPT code 95923)
Tests that are established and commonly used to assess sudomotor function include the thermoregulatory sweat test, quantitative sudomotor axon reflex test, silastic sweat imprint test and sympathetic skin response test.

Thermoregulatory Sweat Test (TST): The TST assesses the sympathetic nerves that supply the skin and evaluates both pre and post ganglionic pathways. A color indicator in the form of powder is applied to the skin. A heat cabinet is used to raise the patients' temperature, the elevated temperature induces sweating and the presence of sweating causes a change in the indicator. Digital photography is used to document sweat distribution. The test can be used to diagnose neuropathy, ganglionopathy, or generalized autonomic failure. This test has also been helpful in assessing the status of dysautonomias over time.

Quantitative Sudomotor Axon Reflex Test (QSART): QSART involves stimulation of the sympathetic nerve fibers using iontophoresis of acetylcholine (ACh) and then measuring an evoked sweat response. The QSART specifically evaluates the functional status of the postganglionic sympathetic axons. The sweat response is

recorded from four distinct body areas to assess for deficits: one on the forearm and three located on the lower extremities. An absent response indicates a lesion of the postganglionic axon.

Quantitative Direct and Indirect Reflex test (QDIRT): Another test for evaluating postganglionic sudomotor function is the quantitative direct and indirect reflex test (QDIRT) (Illigens, Gibbons, 2009). This is a new technique being proposed that combines some of the advantages of silicone impressions and QSART by providing data on droplet number, droplet topographic distribution, and temporal resolution in direct and axon reflex-mediated regions. Sweat glands are stimulated by acetylcholine iontophoresis and sweat is displayed via an activator dye followed by digital photographs over time. QDIRT has been associated with some limitations which include the ability to control the room temperature and humidity when and where testing is conducted. Temperature and humidity control prevents cool, dry air from causing evaporation of sweat production, which could affect the validity of test results.

Quantitative Pilomotor Axon Reflex Test (QPART): The piloerector muscles generally react to mechanical, thermal, electrical or pharmacological stimuli by way of an axon reflex (Siepmann, et al., 2012). While sudomotor axon tests and vasomotor axon tests are commonly used to evaluate small nerve fiber function the QPART is under investigation as a method to evaluate pilomotor nerve and muscle function, which in theory can be used to complement the axon mediated tests (Siepmann, et al., 2012). Published scientific evidence supporting the clinical utility of QPART however is still being gathered.

Sympathetic Skin Response Test (SSR): The SSR test measures a change in skin resistance following a random electric stimulation and provides an index of sweat production. Sympathetic peripheral autonomic potentials are evoked by electrical stimulation producing sweat with recordings taken over the palms and soles. The SSR is recorded as being present or absent in the hand and in the foot.

Silastic Sweat Imprint Test: Sweat imprints are formed by the secretion of active sweat glands into a plastic/silastic imprint. This test is used to determine sweat gland density, sweat droplet size and sweat volume per area.

Cardiovagal Innervation (CPT code 95921)
Cardiovagal testing provides a standardized quantitative assessment of vagal innervation to the heart and evaluates heart rate response to deep breathing, a Valsalva ratio, and/or heart rate response to standing. Changes in heart rate response are recorded and interpreted; when the autonomic nervous system is intact variation of heart rate occurs with the specific maneuver. These tests have high sensitivity and specificity, and are standardized established tests of autonomic function (American Academy of Neurology [AAN], 1996). Impairment may be seen as a result of diabetic neuropathy, Shy-Drager syndrome, idiopathic hypotension or other neuropathies affecting the autonomic nerves**.**

Vasomotor Adrenergic Innervation (CPT code 95922)
Vasomotor adrenergic testing evaluates a beat-to-beat blood pressure response to tilt-testing, a Valsalva maneuver or standing (e.g., Valsalva maneuver analysis). Tilt-testing results in a shift of blood to dependent body areas causing reflex responses while Valsalva maneuvers result in increased intrathoracic pressure decreasing venous return and causing changes to blood pressure and reflex vasoconstriction. When performed these tests enhance the sensitivity and specificity of adrenergic function and are considered established methods of testing (AAN, 1996). Similar to cardiovagal testing impairment may be seen with conditions such as Shy-Drager syndrome, idiopathic orthostatic hypotension, and diabetic or other neuropathies affecting autonomic nerves.

Combined Parasympathetic and Sympathetic With Tilt Table (CPT codes 95924)
Combined testing of autonomic function may also be conducted and may be appropriate when there is a need to differentiate sympathetic from parasympathetic cardiovascular function. One method that is well established involves testing parasympathetic function and vasomotor adrenergic function using at least a 5-minute tilt with a passive tilt table.

Combined Parasympathetic and Sympathetic without Tilt Table and/or Beat to Beat (CPT code 95943)

Devices have also been developed that allow for combined testing without the use of beat-to-beat recordings or tilt table. These devices are referred to as "automated autonomic nerve function testing" and represent a simplified method of ANS testing which has not been validated in the scientific literature therefore results may be erroneous. According to the AAN (2014) these devices do not measure or control for expiratory pressures or beat-to-beat blood pressure measurements. In the absence of expiratory pressure and blood pressure measurements in response to a Valsalva maneuver, interpretation of heart rate cannot be validated (AAN, 2014).

U.S. Food and Drug Administration (FDA)
Various monitoring devices have been FDA approved for autonomic nerve function testing. Some of these devices are able to assess both branches of the nervous system, some employ automation of results and others require physician review and interpretation. Examples of automated testing devices include but are not limited to the ANX 3.0™ (Autonomic Nervous System and Respiration [ANSAR]) (Ansar Medical Technology, Philadelphia, PA) and the VitalScan ANS (Medeia Inc, Santa Barbara, CA).

Literature Review
The results of clinical trials evaluating the clinical utility of autonomic nerve testing in the peer-reviewed published scientific literature are mixed, and consist of both retrospective and prospective case series, observational studies and few randomized controlled trials. Some studies demonstrate that autonomic nervous system testing impacts treatment strategies and clinical outcomes while some studies show no impact (Chelimsky, et al., 1995; Hoitsma, et al., 2004; Huang, et al., 2004; Low, et al., 2004; Strickberger, et al., 2006; Wang, et al., 2008; Chen, et al., 2008; Illigens, Gibbons, 2009; England, et al., 2009/2019; Lipp, et al., 2009; Gibbons, et al., 2010; Peltier, et al, 2010; Keet, et al., 2011; Kimpinsky, et al., 2012; Iodice, et al., 2012; Jones, Gibbons, 2014). However, autonomic nerve function tests have been used extensively, are considered established tests that are safe and effective, and have shown clinical utility for a specific subset of conditions (AAN, 1996; England, et al., 2009/2019).

According to the AAN (1996) assessment of autonomic nerve function tests, (which summarizes sensitivity, specificity, reproducibility, safety and clinical utility), scientific evidence, textbook, and expert opinion support that autonomic nervous system testing may be clinically useful for the following indications:

- To diagnose progressive autonomic neuropathy and determine severity and distribution (i.e., diabetic neuropathy, amyloid neuropathy, Sjogren's syndrome, immune-mediated neuropathy, pure autonomic failure, and multiple system dystrophy)
- 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 a patient with distressing symptoms where there is suspicion 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 diagnose sympathetically maintained pain, as in reflex sympathetic dystrophy or causalgia.
- To evaluate and treat patients with recurrent unexplained syncope.

Professional Societies/Organizations
Various professional societies have published recommendations supporting the performance of autonomic nerve function testing for various conditions.

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) published a recommended policy for electrodiagnostic medicine (AANEM, 1999, updated 2012). Within this policy the AANEM states autonomic nervous system function testing is employed to determine the presence of autonomic dysfunction, to determine the site of autonomic function and to identify various autonomic systems that are

disordered. The recommended policy includes testing of cardiovagal innervation, vasomotor innervation, and evaluation of sudomotor function for various conditions, such as Shy-Drager syndrome, idiopathic orthostatic hypotension, Diabetic neuropathy, progressive autonomic disorders, and other neuropathies affecting autonomic function.

The American Heart Association/American College of Cardiology Foundation (AHA/ACC) scientific statement on the evaluation of syncope (Strickberger, et al., 2006) includes autonomic testing to confirm the presence of a dysautonomia, to distinguish central from peripheral causes, and to guide patient management. Autonomic tests included in the recommendations are tilt table testing, cardiac responses to deep breathing and the Valsalva maneuver, and sweat testing.

According to the American Academy of Neurology (AAN) practice parameter "Diagnosis and Prognosis of New Onset Parkinson Disease (PD)" autonomic nerve function testing is not considered useful to distinguish Parkinson Disease from other forms of Parkinsonism (Suchowersky, 2006).

A 2009 Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of Autonomic Testing, Nerve Biopsy and Skin Biopsy by the AAN (England, 2009, reaffirmed 2019) states autonomic nerve testing can document autonomic system dysfunction in polyneuropathy with a high degree of accuracy. In particular, QSART can detect small fiber loss with a high degree of sensitivity. The authors of this publication noted however that sensitivity and specificity varies among the tests and additional research is necessary to determine whether the documentation of autonomic abnormalities is an important factor in modifying the evaluation and treatment of polyneuropathy.

The American Diabetes Association (2010) recommendations on neuropathy screening and treatment state 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 mellitus; special testing is rarely needed and may not affect management outcomes. According to the guidelines, the recommendation rating was "E", is considered low quality and corresponds to expert consensus/clinical experience.

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN, 1996) published a clinical assessment of autonomic testing, which concluded the following:

- Cardiovagal heart rate tests (heart rate response to deep breathing, Valsalva ratio, heart rate response to standing) have high sensitivity and specificity, are safe, valuable, cost-effective, well-standardized.
- Adrenergic tests (beat-to-beat blood pressure recordings of the Valsalva maneuver, blood pressure and heart rate response to standing) are established tests that enhance sensitivity and specificity of laboratory evaluation of adrenergic function.
- Sudomotor tests:
    - Quantitative sudomotor axon reflex testing (QSART) is an established test, has been used for decades, has a high sensitivity, specificity and reproducibility; confounding variables are well-known.
    - Thermoregulatory sweat test (TST) is an established test, has been used for at least four decades, has a high sensitivity, and when combined with QSART has better specificity.
    - Sympathetic skin response test is an established test, has relatively low sensitivity and uncertain specificity, and habituates, as a result this test is being replaced by better tests, such as QSART or sweat imprint.
    - Sweat imprint test is an established test that appears to be sensitive and quantitative.

Use Outside of the US: No relevant information

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	No National Coverage Determination	
LCD	First Coast Service Options, Inc.	Local Coverage Determination (LCD): Autonomic Function Tests (L33609)	1/2021
LCD	Novitas Solutions, Inc.	Local Coverage Determination (LCD): Autonomic Function Tests (L35395)	11/2019
LCD	Wisconsin Physicians Service Insurance Corporation	Local Coverage Determination (LCD): Autonomic Function Testing (L35124)	11/2019
LCD	National Government Services, Inc.	Local Coverage Determination (LCD): Autonomic Function Testing (L36236)	9/2019

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
95921	Testing of autonomic nervous system function; cardiovagal innervation (parasympathetic function), including 2 or more of the following: heart rate response to deep breathing with recorded R-R interval, Valsalva ratio, and 30:15 ratio
95922	Testing of autonomic nervous system function; vasomotor adrenergic innervation (sympathetic adrenergic function), including beat-to-beat blood pressure and R-R interval changes during Valsalva maneuver and at least 5 minutes of passive tilt
95923	Testing of autonomic nervous system function; sudomotor, including 1 or more of the following: quantitative sudomotor axon reflex test (QSART), silastic sweat imprint, thermoregulatory sweat test, and changes in sympathetic skin potential
95924	Testing of autonomic nervous system function; combined parasympathetic and sympathetic adrenergic function testing with at least 5 minutes of passive tilt
95943†	Simultaneous, independent, quantitative measures of both parasympathetic function and sympathetic function, based on time-frequency analysis of heart rate variability concurrent with time-frequency analysis of continuous respiratory activity, with mean heart rate and blood pressure measures, during rest, paced (deep) breathing, Valsalva maneuvers, and head-up postural change

†**Note: Considered Experimental, Investigational, or Unproven when used to report testing using portable, automated devices.**

ICD-10-CM Diagnosis Codes	Description
A50.43	Late congenital syphilitic polyneuropathy
A52.15	Late syphilitic neuropathy

ICD-10-CM Diagnosis Codes	Description
E08.40	Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified
E08.41	Diabetes mellitus due to underlying condition with diabetic mononeuropathy
E08.42	Diabetes mellitus due to underlying condition with diabetic polyneuropathy
E08.43	Diabetes mellitus due to underlying condition with diabetic autonomic (poly)neuropathy
E08.49	Diabetes mellitus due to underlying condition with other diabetic neurological complication
E09.40	Drug or chemical induced diabetes mellitus with neurological complications with diabetic neuropathy, unspecified
E09.41	Drug or chemical induced diabetes mellitus with neurological complications with diabetic mononeuropathy
E09.42	Drug or chemical induced diabetes mellitus with neurological complications with diabetic polyneuropathy
E09.43	Drug or chemical induced diabetes mellitus with neurological complications with diabetic autonomic (poly)neuropathy
E09.49	Drug or chemical induced diabetes mellitus with neurological complications with other diabetic neurological complication
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication
E13.40	Other specified diabetes mellitus with diabetic neuropathy, unspecified
E13.41	Other specified diabetes mellitus with diabetic mononeuropathy
E13.42	Other specified diabetes mellitus with diabetic polyneuropathy
E13.43	Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy
E13.49	Other specified diabetes mellitus with other diabetic neurological complication
G13.0	Paraneoplastic neuromyopathy and neuropathy
G13.1	Other systemic atrophy primarily affecting central nervous system in neoplastic disease
G23.0	Hallervorden-Spatz disease
G23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]
G23.2	Striatonigral degeneration
G23.8	Other specified degenerative diseases of basal ganglia
G23.9	Degenerative disease of basal ganglia, unspecified
G58.8	Other specified mononeuropathies
G58.9	Mononeuropathy, unspecified
G59	Mononeuropathy in diseases classified elsewhere
G60.3	Idiopathic progressive neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified
G61.0	Guillain-Barre syndrome
G63	Polyneuropathy in diseases classified elsewhere
G65.0	Sequelae of Guillain-Barre syndrome
G65.1	Sequelae of other inflammatory polyneuropathy
G65.2	Sequelae of toxic polyneuropathy
G90.09	Other idiopathic peripheral autonomic neuropathy
G90.2	Horner's syndrome
G90.3	Multi-system degeneration of the autonomic nervous system

ICD-10-CM Diagnosis Codes	Description
G90.50	Complex regional pain syndrome I, unspecified
G90.511	Complex regional pain syndrome I of right upper limb
G90.512	Complex regional pain syndrome I of left upper limb
G90.513	Complex regional pain syndrome I of upper limb, bilateral
G90.519	Complex regional pain syndrome I of unspecified upper limb
G90.521	Complex regional pain syndrome I of right lower limb
G90.522	Complex regional pain syndrome I of left lower limb
G90.523	Complex regional pain syndrome I of lower limb, bilateral
G90.529	Complex regional pain syndrome I of unspecified lower limb
G90.59	Complex regional pain syndrome I of other specified site
G90.8	Other disorders of autonomic nervous system
G90.9	Disorder of the autonomic nervous system, unspecified
G99.0	Autonomic neuropathy in diseases classified elsewhere
I49.8	Other specified cardiac arrhythmias
M34.83	Systemic sclerosis with polyneuropathy
M35.00	Sjögren syndrome, unspecified
M35.01	Sjögren syndrome with keratoconjunctivitis
M35.02	Sjögren syndrome with lung involvement
M35.03	Sjögren syndrome with myopathy
M35.04	Sjögren syndrome with tubulo-interstitial nephropathy
M35.05	Sjögren syndrome with inflammatory arthritis (Code effective 10/01/2021)
M35.06	Sjögren syndrome with peripheral nervous system involvement (Code effective 10/01/2021)
M35.07	Sjögren syndrome with central nervous system involvement (Code effective 10/01/2021)
M35.08	Sjögren syndrome with gastrointestinal involvement (Code effective 10/01/2021)
M35.09	Sjögren syndrome with other organ involvement
M35.0A	Sjögren syndrome with glomerular disease (Code effective 10/01/2021)
M35.0B	Sjögren syndrome with vasculitis (Code effective 10/01/2021)
M35.0C	Sjögren syndrome with dental involvement (Code effective 10/01/2021)
R55	Syncope and collapse

Experimental/Investigational/Unproven:

ICD-10-CM Diagnosis Codes	Description
	All other codes

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