

Oscar Clinical Guideline: Autonomic Testing (CG026 Ver. 9)

# **Autonomic Testing**

#### Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

#### Summary

The autonomic nervous system (ANS) regulates parts of the body that are not consciously controlled. such as blood pressure, heart rate, body temperature, and many others. It includes sympathetic nerves (e.g., the "fight-or-flight" system) and parasympathetic nerves (e.g., the "rest-and-digest" system). Certain diseases, injuries, and medications can impair the ANS, resulting in "autonomic dysfunction". Because the autonomic nervous system is widespread throughout the body, clinical manifestations can vary depending on the underlying process. Some signs of dysfunction include impaired blood pressure and heart autoregulation, abnormal sweat production, heat or cold intolerance, digestive problems, erectile dysfunction, or problems with urination and bowel movements. There are a number of tests to evaluate the autonomic nervous system. These are generally performed by applying a stimulus to the affected organ system and measuring for the appropriate autonomic response (or lack thereof). This guideline outlines the clinical criteria and exclusions for autonomic testing.

This guideline does not describe the clinical criteria, exclusions, or benefit details for testing of the somatosensory nervous system, which is also part of the peripheral nervous system, but is responsible for sensory feedback, balance, and position.

#### **Definitions**

"Autonomic Nervous System (ANS)" is a division of the peripheral nervous system (i.e., nerves and ganglia outside of the brain and spinal cord). It controls involuntary actions such as, but not limited to,

blood pressure, urination/defecation, sexual function, digestion, pupillary light reflex, and glandular secretion (sweat, saliva, tears, etc.).

"Dysautonomia," or autonomic dysfunction, occurs when the ANS is damaged or impaired by some disease, injury, or medication.

- 1. Signs of dysautonomia include, but are not limited to:
  - Orthostatic hypotension or other blood pressure fluctuations
  - Urinary incontinence or retention
  - Bradycardia, tachycardia, or other fluctuations in heart rate/rhythm
  - Changes in vision
  - Dizziness
  - Syncope
  - Digestive issues
- 2. Dysautonomia can be seen in the diseases or conditions that may include, but are not limited to:
  - Parkinson's disease and associated parkinsonian syndromes
  - Diabetes mellitus and other neuropathies
  - Surgical or iatrogenic injury
  - Autoimmune diseases such as SLE or Sjogren's disease
  - HIV and AIDS
  - Multiple sclerosis
  - Toxicity from medications and drugs
  - Amyloidosis
- 3. The diagnosis of dysautonomia relies on four autonomic functions:
  - Cardiovagal, which is the parasympathetic response in heart rate to breathing and valsalva maneuvers (e.g., holding your breath and bearing down);
  - Vasomotor or adrenergic, which refers to the sympathetic-mediated constriction of blood vessels to increase blood pressure;
  - Sudomotor, which is sweat production in response to sympathetic stimuli
  - Pupillary constriction to light, which is a parasympathetic function

"Somatosensory Nervous System" is also a division of the peripheral nervous system. It controls sensory input and reflexes. Testing of the somatosensory nervous system differs from the ANS and is usually performed through various nerve conduction studies. It also differs from testing of the central nervous system and associated nerves, which is often performed through evoked potential or evoked response testing.

"Sympathetic" nerves are a part of the ANS responsible for the "fight-or-flight" response, which diverts blood away from nonessential organs, increases heart rate and contractility, and dilates the pupils, among other functions. It is counteracted by the parasympathetic system.

"Parasympathetic" nerves are part of the ANS responsible for the "rest-and-digest" response, which activates digestion and peristalsis while decreasing cardiac and respiratory rates, among other functions.

"Sudomotor" refers to a branch of the sympathetic nervous system that controls sweat glands. The sudomotor system is a frequent surrogate for testing for evidence of autonomic dysfunction as it is easily stimulated and accessible for measurement of response (i.e., sweat production). Various tests for sudomotor function are defined below.

"QSART (Quantitative Sudomotor Axon Reflex Test)" is a test used to diagnose autonomic dysfunction by evaluating the postganglionic sudomotor nerves. To perform this test, an electric current is used to draw acetylcholine (which stimulates sweat excretion) to the sweat glands, and the sweat response is recorded.

"QDIRT (Quantitative Direct and Indirect Testing of Sudomotor Function)" is similar to QSART, but also adds temporal and volumetric data on the sweat production. QDIRT is more variable than QSART and normative values have yet to be clearly established.

"QPART" (Quantitative Pilomotor Axon Reflex Test) is a test of piloerection (e.g., "goose bumps"), which is an alternative expression of autonomic function. The clinical role of QPART has not yet been established in the literature.

"TST" (Thermoregulatory Sweat Test) tests sudomotor function from the pre- and postganglionic nerves. The test is conducted by applying an indicator dye over the skin surface, and then placing the patient in a heated enclosure to increase the core body temperature. The indicator will change color in areas where sweat is produced and remain unchanged in areas of autonomic dysfunction.

"Silastic Sweat Imprinting" is a technique like QSART, however the sweat drops are recorded as imprints in a silastic material to quantify the response.

"SSR" (Sympathetic Skin Response) is a test to measure changes in skin electrical potential in response to an arousing stimulus. SSR is difficult to reproduce accurately and may lack the sensitivity and specificity for broad clinical application.

"Tilt-Table Test" is used to assess adrenergic sympathetic activity (e.g., the vasomotor response). Patients are positioned supine on a table and allowed to acclimate. The table is then tilted to an upright position to mimic standing for 20-45 minutes. Blood pressure, heart rate, and sometimes EKG tracings are recorded for each position at set time points. In a normal physiologic response, the blood vessels should constrict to maintain cerebral perfusion. In autonomic dysfunction, there is a failure of the body's response to adjust for blood pressure and heart rate, resulting in multiple symptoms including but not limited to dizziness and potential syncope.

"Syncope" is the temporary loss of consciousness and muscle tone due to inadequate brain perfusion. It is typically self-limited and resolves quickly without significant intervention, depending on the underlying cause.

#### Clinical Indications

#### Tilt-Table Testing

Tilt-table testing, alone or with provocative agents (e.g., isoproterenol), is considered medically necessary when ALL of the following criteria are met:

- 1. The patient has a history of syncope or recurrent syncopal episodes, with further testing indicated for at least ONE of the following:
  - a. Suspected carotid sinus hypersensitivity; or
  - b. Evaluation is needed for a patient returning to high-risk work (i.e., commercial driving, operating machinery, etc.) or a leisure activity that may place the patient at risk; or
  - c. Neurally mediated syncope is suspected, including:
    - i. Vasovagal syncope, except when this is the first episode of suspected vasovagal syncope; or
    - ii. Carotid sinus dysfunction; or
    - iii. Situational syncope.
  - d. Postural orthostatic tachycardia syndrome (POTS); or
  - e. For other conditions where the results of the tilt-table test would change medical management (i.e., medications or further workup would be indicated).
- 2. Cardiac causes of syncope have been excluded via the appropriate non-invasive tests and workup (e.g., history and physical exam, EKG, stress test, and/or cardiac echocardiogram); and
- 3. Comorbid conditions that may have contributed have been diagnosed, adequately treated, and/or ruled out (e.g., hypovolemia, bleeding, shock, seizures, infections, anemia, etc); and
- 4. Medications that may contribute to autonomic dysfunction and/or syncopal episodes have been adjusted or discontinued; *and*
- 5. There are NOT contraindications to tilt-table testing, including but not limited to:
  - a. Critical aortic and/or mitral valvular stenosis
  - b. Left ventricular outflow tract obstruction
  - c. Severe proximal cerebral artery stenosis or coronary artery disease
- 6. Testing is ordered ONCE when used to exclude specific autonomic diseases, or no more than once annually for patients who have already been diagnosed with autonomic dysfunction in whom repeat testing is indicated for new or worsening symptoms meeting the above criteria.

#### Sudomotor Testing

Sudomotor testing is considered medically necessary when ALL of the following criteria are met:

- 1. Testing is ordered for QSART, silastic sweat imprint, or TST; and
- 2. The testing is conducted by physicians with the appropriate expertise and training to perform and interpret the tests results; *and*

- 3. Testing is ordered ONCE when used to exclude specific autonomic diseases, or no more than once annually for patients who have already been diagnosed with autonomic dysfunction in whom repeat testing is indicated for new or worsening symptoms meeting the above criteria; and
- 4. Testing is ordered for one of the following:
  - a. To diagnose an appropriate condition, specified as any one or more of the following:
    - i. Peripheral neuropathies:
      - Amyloid neuropathy; or
      - Diabetic autonomic neuropathy; or
      - Distal small fiber neuropathy; or
      - Idiopathic neuropathy.
    - ii. Multiple systems atrophy; or
    - iii. Sjogren's disease; or
    - iv. Pure autonomic failure; or
    - v. Postural orthostatic hypotension or postural orthostatic tachycardia syndrome (POTS); *or*
    - vi. Reflex sympathetic dystrophy or causalgia; or
    - vii. Recurrent syncope without a known cause despite appropriate workup.
  - b. To evaluate any one or more of the following:
    - i. The severity and/or distribution of a previous diagnosed autonomic neuropathy that is progressing; *or*
    - ii. The change in severity, distribution, or type of autonomic dysfunction in a patient who has previously exhibited signs of autonomic failure but does not yet have a diagnosis; *or*
    - iii. The response to treatment in a patient with autonomic dysfunction who had recent changes in symptoms and clinical exam findings; *or*
    - iv. To evaluate inadequate response to beta blocker therapy in vasodepressor syncope.

### Experimental or Investigational / Not Medically Necessary

#### Tilt-Table Testing

Tilt-table testing is considered investigational and/or experimental, and thus NOT medically necessary, in the following situations:

- Any indication not meeting the above Tilt-Table Testing criteria in the Clinical Indications section;
   or
- 2. Solely for following the effectiveness or response to treatment for syncope; or
- 3. To evaluate dizziness, near syncope, or vertigo; or
- 4. To evaluate post-concussive syndrome; or
- 5. To evaluate chronic fatigue syndrome; or

- 6. Suspected vasovagal syncope with a single episode or when the diagnosis of vasovagal syncope has already been established through history and physical exam; *or*
- 7. To differentiate convulsive syncope from epilepsy in a patient with recurrent loss of consciousness associated with tonic-clonic movements; *or*
- 8. To evaluate for unexplained recurrent falls when there is no sign of cardiovagal instability; or
- 9. To evaluate patients with recurrent transient ischemic attacks (TIAs).

# **Sudomotor Testing**

Sudomotor testing is considered investigational and/or experimental, and thus NOT medically necessary, in the following situations:

- 1. Any condition or test not meeting the Sudomotor Testing criteria in the *Clinical Indications* section, such as chronic fatigue syndrome, myalgia, encephalomyelitis, Raynaud phenomenon, traumatic brain injury or predicting foot ulcers; *or*
- 2. Screening for patients without signs or symptoms of autonomic dysfunction, regardless of their current diagnoses; *or*
- 3. Testing solely performed to monitor disease intensity or treatment efficacy, unless otherwise specified above; *or*
- 4. Testing when the results will not impact clinical management; or
- 5. Clearly diagnosed somatosensory neuropathies that have not changed in severity and/or distribution of symptoms, including but not limited to the demyelinating neuropathies (e.g., Guillain-Barre, CIDP, etc.); or
- 6. The following sudomotor testing methods are NOT indicated for any condition as there is insufficient evidence to support clinical effectiveness in the existing literature:
  - a. SSR; or
  - b. QDIRT; or
  - c. QPART; or
  - d. Any ambulatory and/or automatic measuring device for autonomic function, including but not limited to:
    - i. Sudoscan; or
    - ii. ANSAR and Medeia QANS/QHRV System; or
    - iii. Zephyr Bioharness or Biopatch.

### Applicable Billing Codes

Autonomic Testing		
CPT/HCPCS Codes considered medically necessary if criteria are met:		
Code	Description	
95921	Testing of autonomic nervous system function; cardiovagal innervation (parasympathetic function), including two or more of the following: heart rate	

	response to deep breathing with recorded R-R interval, Valsalva ratio, and 30:15 ratio
95922	Vasomotor adrenergic innervation (sympathetic adrenergic function), including beat-to beat blood pressure and R-R interval changes during Valsalva maneuver and at least five minutes of passive tilt
95923	Sudomotor, including one 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
ICD-10 codes consi	dered medically necessary if criteria are met:
Code	Description
E08.42; E09.42	Polyneuropathy in diabetes
E10.40 - E10.49; E11.40 - E11.49; E13.40 - E13.49	Diabetes with neurological manifestations
E85.1	Amyloid heredofamilial amyloidosis [amyloid polyneuropathy]
G56.40 - G56.43	Causalgia of upper limb
G57.70 - G57.73	Causalgia of lower limb
G60.3	Idiopathic progressive neuropathy
G60.8	Other hereditary and idiopathic neuropathies [distal small fiber neuropathy]
G63	Polyneuropathy in diseases classified elsewhere [when coded with E85.1]
G90.0 - G90.09	Idiopathic peripheral autonomic neuropathy
G90.3	Multi-system degeneration of the autonomic nervous system
G90.50 - G90.59	Complex regional pain syndrome I (CRPS I) [Reflex sympathetic dystrophy]
G90.8	Other disorders of autonomic nervous system [when used for pure autonomic failure]
G90.A	Postural orthostatic tachycardia syndrome [POTS]
L	

<del>G90.9</del>	Disorder of the autonomic nervous system, unspecified	
G99.0	Autonomic neuropathy in diseases classified elsewhere [when coded with E85.0 - E85.9]	
M35.00 - M35.09	Sjögren syndrome	
R00.0	Tachycardia, unspecified [postural tachycardia syndrome]	
R55	Syncope and collapse	
ICD-10 codes considered experimental, investigational, or <i>not</i> medically necessary:		
Code	Description	
A8	Unspecified viral encephalitis	
F07.81	Postconcussional syndrome	
G04.00 - G04.02	Acute disseminated encephalitis and encephalomyelitis (ADEM)	
G04.81; G04.90	Other and unspecified encephalitis and encephalomyelitis	
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere	
G45.8 - G45.9	Transient cerebral ischemic attacks and related syndromes	
173.00 - 173.01	Raynaud's syndrome	
M79.10 - M79.18	Myalgia	
R53.82	Chronic fatigue, unspecified	
S06.2x0A - S06.309S	Diffuse traumatic brain injury	

## References

- American Academy of Neurology (AAN); Gibbons CH, Cheshire WP, Fife TD. Autonomic Testing. Model Coverage Policy. September 2014. Accessed March 16, 2017. Available at URL address:<a href="https://www.aan.com/uploadedFiles/Website\_Library\_Assets/Documents/3.Practice\_M">https://www.aan.com/uploadedFiles/Website\_Library\_Assets/Documents/3.Practice\_M</a> anagement/1.Reimbursement/1.Billing\_and\_Coding/5.Coverage\_Policies/14%20Autonomic%20 Testing%20Policy%20v0 01.pdf
- 2. Benditt DG, Ferguson DW, Grubb BP, et al. Tilt table testing for assessing syncope. American College of Cardiology. J Am Coll Cardiol. 1996;28(1):263-275.

- 3. Brignole M, Alboni P, Benditt D, et al. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J. 2001;22(15):1256-1306.
- 4. Brignole M, Moya A, Lange FJD, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *European Heart Journal*. 2018; 39(21):1883-1948.

  Doi:https://doi.org/10.1093/eurheartj/ehy037
- 5. Carmona-Torre, F., Mínguez-Olaondo, A., López-Bravo, A., Tijero, B., Grozeva, V., Walcker, M., ... & Gómez-Esteban, J. C. (2022). Dysautonomia in COVID-19 patients: a narrative review on clinical course, diagnostic and therapeutic strategies. Frontiers in Neurology, 13, 761.
- 6. Chahal, S., Vohra, K., & Syngle, A. (2017). Association of sudomotor function with peripheral artery disease in type 2 diabetes. Neurological Sciences, 38, 151-156.
- 7. Chao, C. C., Tseng, M. T., Hsieh, P. C., Lin, C. H. J., Huang, S. L., Hsieh, S. T., & Chiang, M. C. (2022). Brain mechanisms of pain and dysautonomia in diabetic neuropathy: connectivity changes in thalamus and hypothalamus. The Journal of Clinical Endocrinology & Metabolism, 107(3), e1167-e1180.
- 8. Chen, Z., Li, G., & Liu, J. (2020). Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. Neurobiology of Disease, 134, 104700.
- 9. Colombo J, Shoemaker WC, Belzberg H, et al. Noninvasive monitoring of the autonomic nervous system and hemodynamics of patients with blunt and penetrating trauma. J Trauma. 2008 Dec;65(6):1364-73.
- D'Sa S, Kersten MJ, Castillo JJ. Investigation and management of IgM and Waldenstr€om-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel. British Journal of Haematology, 2017,176,728–742. doi: 10.1111/bjh.14492
- 11. Fathizadeh P, Shoemaker WC, Woo CCJ, Colombo J. Autonomic activity in trauma patients based on variability of heart rate and respiratory rate. Crit Care Med. 2004;32(5):1300-5.
- 12. Fisher DA, Maibach HI. Postural hypotension and anhidrosis. The autonomic insufficiency syndrome. Arch Dermatol. 1970;102(5):527-531.
- 13. Fouad FM, Sitthisook S, Vanerio G, et al. Sensitivity and specificity of the tilt table test in young patients with unexplained syncope. Pacing Clin Electrophysiol. 1993;16(3 Pt 1):394-400.
- 14. Fortanier E, Delmont E, Verschueren A, Attarian S. Quantitative sudomotor test helps differentiate transthyretin familial amyloid polyneuropathy from chronic inflammatory demyelinating polyneuropathy. Clin Neurophysiol. 2020;131(5):1129-1133.
- 15. Freeman R, Chapleau MW. Testing the autonomic nervous system. Handb Clin Neurol. 2013;115:115-136.
- 16. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neutrally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72.
- 17. Freeman R. Assessment of cardiovascular autonomic function. Clin Neurophysiol. 2006;117(4):716-730.
- 18. Gibbons CH, Centi J, Vernino S, Freeman R. Autoimmune autonomic ganglionopathy with reversible cognitive impairment. Arch Neurol. 2012r;69(4):461-466.

- 19. Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. Auton Neurosci. 2009;146(1-2):8-12.
- 20. Gibbons CH, Freeman R. Delayed orthostatic hypotension: A frequent cause of orthostatic intolerance. Neurology. 2006;67(1):28-32.
- 21. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Ann Neurol. 2010; 67(4):534-541.
- 22. Gibbons CH, Illigens BM, Centi J, Freeman R. QDIRT: quantitative direct and indirect test of sudomotor function. Neurology. 2008; 70(24):2299-2304.
- 23. Gibons CH, Vernino SA, Freeman R. Combined immunomodulatory therapy in autoimmune autonomic ganglionopathy. Arch Neurol. 2008;65(2):213-217.
- 24. Gierelak G, Makowski K, Guzik P, et al. Effects of therapy based on tilt testing results on the long-term outcome in patients with syncope. Kardiol Pol. 2005;63(7):1-16; discussion 17-19.
- 25. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008; 71(9):670–676.
- 26. Gin H, Baudoin R, Raffaitin CH, et al. Non-invasive and quantitative assessment of sudomotor function for peripheral diabetic neuropathy evaluation. Diabetes Metab. 2011; 37(6):527-532.
- 27. Goldstein DS, Pechnik S, Holmes C, et al. Association between supine hypertension and orthostatic hypotension in autonomic failure. Hypertension. 2003;42(2):136-142.
- 28. Goldstein DS, Sewell L, Holmes C. Association of anosmia with autonomic failure in Parkinson disease. Neurology. 2010;74(3):245-251.
- 29. Goldstein DS, Sharabi Y, Karp BI, et al. Cardiac sympathetic denervation preceding motor signs in Parkinson disease. Cleve Clin J Med. 2009;76 Suppl 2:S47-S50.
- 30. Gordon VM, Opfer-Gehrking TL, Novak V, Low PA. Hemodynamic and symptomatic effects of acute interventions on tilt in patients with postural tachycardia syndrome. Clin Auton Res. 2000;10(1):29-33.
- 31. Grubb BP, Gerard G, Roush K, et al. Differentiation of convulsive syncope and epilepsy with head-up tilt testing. Ann Intern Med. 1991;115(11):871-876.
- 32. Grubb BP, Kosinski D. Current trends in etiology, diagnosis, and management of neurocardiogenic syncope. Curr Opin Cardiol. 1996;11(1):32-41.
- 33. Heyer, G. L., Fischer, A., Wilson, J., MacDonald, J., Cribbs, S., Ravindran, R., ... & Cuff, S. (2016). Orthostatic intolerance and autonomic dysfunction in youth with persistent postconcussion symptoms: a head-upright tilt table study. Clinical Journal of Sport Medicine, 26(1), 40-45.
- 34. Huang YN, Jia ZR, Shi X, Sun XR. Value of sympathetic skin response test in the early diagnosis of diabetic neuropathy. Chin Med J (Engl). 2004;117(9):1317-1320.
- 35. Humm AM, Mathias CJ. Unexplained syncope--is screening for carotid sinus hypersensitivity indicated in all patients aged >40 years? J Neurol Neurosurg Psychiatry. 2006;77(11):1267-1270.
- 36. Illigens BM, Gibbons CH. Sweat testing to evaluate autonomic function. Clin Auton Res. 2009;19(2):79-87.
- 37. Iodice V, Kimpinski K, Vernino S, et al. Immunotherapy for autoimmune autonomic ganglionopathy. Auton Neurosci. 2009;146(1-2):22-25.

- 38. Iodice V, Lipp A, Ahlskog JE, et al. Autopsy confirmed multiple system atrophy cases: Mayo experience and role of autonomic function tests. J Neurol Neurosurg Psychiatry. 2012; 83(4):453-459.
- 39. Jacobson DM, Hiner BC. Asymptomatic autonomic and sweat dysfunction in patients with Adie's syndrome. J Neuroophthalmol. 1998;18(2):143-147.
- 40. Jaradeh SS, Prieto TE. Evaluation of the autonomic nervous system. Phys Med Rehabil Clin N Am. 2003;14(2):287-305.
- 41. Kang WH, Chun SI, Lee S. Generalized anhidrosis associated with Fabry's disease. J Am Acad Dermatol. 1987;17(5 Pt 2):883-887.
- 42. Kapoor WN. Using a tilt table to evaluate syncope. Am J Med Sci. 1999;317(2):110-116.
- 43. Keet SW, Bulte CS, Sivanathan A, et al. Cardiovascular autonomic function testing under non-standardised and standardised conditions in cardiovascular patients with type-2 diabetes mellitus. Anaesthesia. 2014; 69(5):476-483.
- 44. Kimpinski K, Figueroa JJ, Singer W, et al. A prospective, 1-year follow-up study of postural tachycardia syndrome. Mayo Clin Proc. 2012b; 87(8):746-752.
- 45. Kimpinski K, lodice V, Burton DD, et al. The role of autonomic testing in the differentiation of Parkinson's disease from multiple system atrophy. J Neurol Sci. 2012a; 317(1-2):92-96.
- 46. Linzer M, Yang EH, Estes NA 3rd, et al. Diagnosing syncope. Part 2: Unexplained syncope. Ann Intern Med. 1997;127(1):76-86.
- 47. Lipp A, Sandroni P, Ahlskog JE, et al. Prospective differentiation of multiple system atrophy from Parkinson disease, with and without autonomic failure. Arch.Neurol. 2009; 66(6):742-750.
- 48. Low PA, Benrud-Larson LM, Sletten DM, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care. 2004; 27(12):2942-2947.
- 49. Low PA, Tomalia VA, Park KJ. Autonomic function tests: some clinical applications. J Clin Neurol. 2013; 9(1):1-8.
- 50. Luria DM, Shen WK. Syncope in the elderly: New trends in diagnostic approach and nonpharmacologic management. Am J Geriatr Cardiol. 2001;10(2):91-96.
- 51. Lykke JA, Tarnow L, Parving HH, Hilsted J. A combined abnormality in heart rate variation and QT corrected interval is a strong predictor of cardiovascular death in type 1 diabetes. Scand J Clin Lab Invest. 2008; 68(7):654–659.
- 52. Miller TH, Kruse JE. Evaluation of syncope. Am Fam Physician. 2005;72(8):1492-1500.
- 53. Morillo CA, Klein GJ, Gersh BJ. Can serial tilt testing be used to evaluate therapy in neurally mediated syncope? Am J Cardiol. 1996;77(7):521-523.
- 54. Nanavanti SH, Bulgarelli RJ, Vazquez-Tanus J, et al. Altered autonomic activity with atrial fibrillation as demonstrated by non-invasive autonomic monitoring. US Cardiol. 2010;7(1):47-50.
- 55. Nemechek P, Gosh Dastidar S, Colombo J. Early autonomic dysfunction is associated with secondary hypertension in HIV/AIDS patients. American Autonomic Society, St. Thomas, Virgin Islands, 31 Oct 3 Nov 2009.
- 56. Nemechek P, Gosh Dastidar S, Colombo J. HIV/AIDS leads to early cardiovascular autonomic neuropathy. American Autonomic Society, St. Thomas, Virgin Islands, 31 Oct 3 Nov, 2009.

- 57. Parry SW, Kenny RA. Tilt table testing in the diagnosis of unexplained syncope. QJM. 1999;92(11):623-629.
- 58. Quattrini C, Harris ND, Malik RA, Tesfaye S. Impaired skin microvascular reactivity in painful diabetic neuropathy. Diabetes Care. 2007;30(3):655-659.
- 59. Rajan, S., Campagnolo, M., Callaghan, B., & Gibbons, C. H. (2019). Sudomotor function testing by electrochemical skin conductance: does it really measure sudomotor function?. Clinical Autonomic Research, 29, 31-39.
- 60. Raviele A, Gasparini G, Di Pede F, et al. Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study. Am J Cardiol. 1990;65(20):1322-1327.
- 61. Rex L, Claes G, Drott C, et al. Vasomotor and sudomotor function in the hand after thoracoscopic transection of the sympathetic chain: Implications for choice of therapeutic strategy. Muscle Nerve. 1998;21(11):1486-1492.
- 62. Rothstein M, Pereira E, Baker S, et al. Parasympathetic and Sympathetic Involvement in Obstructive Sleep Apnea. Accepted abstract, Autonomic Society, 2011.
- 63. Ruiz GA, Scaglione J, Gonzalez-Zuelgaray J. Reproducibility of head-up tilt test in patients with syncope. Clin Cardiol. 1996;19(3):215-220.
- 64. Saint Martin M, Sforza E, Thomas-Anterion C, et al. Baroreflex sensitivity, vascular risk factors, and cognitive function in a healthy elderly population: The PROOF cohort. J Am Geriatr Soc. 2013;61(12):2096-2102.
- 65. Sakakibara R, Hirano S, Asahina M, et al. Primary Sjogren's syndrome presenting with generalized autonomic failure. Eur J Neurol. 2004;11(9):635-638.
- 66. Smith AG, Gibson S. Skin biopsy for the evaluation of peripheral nerve disease. UpToDate.com. Last updated Feb 25, 2022. Retrieved from https://www.uptodate.com/contents/skin-biopsy-for-the-evaluation-of-peripheral-nerve-disease? search=skin%20biopsy%20for%20small%20fiber%20neuropathy%20dysautonomia&source=sear ch\_result&selectedTitle=1~150&usage\_type=default&display\_rank=1
- 67. Steinberg LA, Knilans TK. Syncope in children: Diagnostic tests have a high cost and low yield. J Pediatr. 2005;146(3):355-358.
- 68. Sundkvist G, Almér LO, Lilja B. A sensitive orthostatic test on tilt table, useful in the detection of diabetic autonomic neuropathy. Acta Med Scand Suppl. 1981;656:43-45.
- 69. Sundkvist G. Autonomic nervous function in asymptomatic diabetic patients with signs of peripheral neuropathy. Diabetes Care. 1981;4(5):529-534.
- 70. Sutton R, Bloomfield DM. Indications, methodology, and classification of results of tilt-table testing. Am J Cardiol. 1999;84(8A):10Q-19Q.
- 71. Tesfaye S, Boulton AJ, Dyck PJ, et al.; Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285-2293.
- 72. Thaisetthawatkul P, Boeve BF, Benarroch EE, et al. Autonomic dysfunction in dementia with Lewy bodies. Neurology. 2004;62(10):1804-1809.

- 73. Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: The Mayo clinic experience. Mayo Clin Proc. 2007;82(3):308-313.
- 74. Thilenius OG, Quinones JA, Husayni TS, Novak J. Tilt test for diagnosis of unexplained syncope in pediatric patients. Pediatrics. 1991;87(3):334-338.
- 75. Tobias H, Vinitsky A, Bulgarelli RJ, et al. Autonomic nervous system monitoring of patients with excess parasympathetic responses to sympathetic challenges clinical observations. US Neurol. 2010;5(2):62-66.
- 76. Turkka JT, Tolonen U, Myllylä VV. Cardiovascular reflexes in Parkinson's disease. Eur Neurol. 1987;26(2):104-112.
- 77. Uncini A, Pullman SL, Lovelace RE, Gambi D. The sympathetic skin response: Normal values, elucidation of afferent components and application limits. J Neurol Sci. 1988;87(2-3):299-306.
- 78. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26:1553-1579.
- 79. Vlahos AP, Tzoufi M, Katsouras CS, et al. Provocation of neurocardiogenic syncope during head-up tilt testing in children: Comparison between isoproterenol and nitroglycerin. Pediatrics. 2007;119(2):e419-e425.
- 80. Voice RA, Lurie KG, Sakaguchi S, et al. Comparison of tilt angles and provocative agents (edrophonium and isoproterenol) to improve head-upright tilt-table testing. Am J Cardiol. 1998;81(3):346-351.
- 81. Ziemssen, T., & Siepmann, T. (2019). The investigation of the cardiovascular and sudomotor autonomic nervous system—a review. Frontiers in neurology, 10, 53.
- 82. CGS Administrators LLC. CMS Local Coverage Determination (LCD): AUTONOMIC Function TESTING (L36236). Accessed on March 17, 2017.
- 83. Moya A, Sutton R, et al. Guidelines for the diagnosis and management of syncope (version 2009): the Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Eur Heart J. 2009 Nov. 30(21):2631-71.
- 84. Ang L, Jaiswal M, Callaghan B, Raffel D, B Brown M, Pop-Busui R. Sudomotor dysfunction as a measure of small fiber neuropathy in type 1 diabetes. Auton Neurosci. 2017;205:87-92.
- 85. Brown TP. Pure autonomic failure. Pract Neurol. 2017;17:341-348.
- 86. Cheshire WP Jr, Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. Clin Auton Res. 2019;29:215-230.
- 87. Dineen J, Freeman R. Autonomic Neuropathy. Semin Neurol. 2015;35:458-468.
- 88. Goodman BP. Evaluation of postural tachycardia syndrome (POTS). Auton Neurosci. 2018;215:12-19.
- 89. Iodice V, Sandroni P. Autonomic neuropathies. Continuum (Minneap Minn). 2014;20(5 Peripheral Nervous System Disorders):1373-1397.
- 90. Jones PK, Gibbons CH. Autonomic function testing: an important diagnostic test for patients with syncope. Pract Neurol. 2015;15:346-351.
- 91. Sopacua M, Hoeijmakers JGJ, Merkies ISJ, Lauria G, Waxman SG, Faber CG. Small-fiber neuropathy: Expanding the clinical pain universe. J Peripher Nerv Syst. 2019;24:19-33.

- 92. Sutton R. The Value of Tilt Testing and Autonomic Nervous System Assessment. Cardiol Clin. 2015;33:357-360.
- 93. Terkelsen AJ, Karlsson P, Lauria G, Freeman R, Finnerup NB, Jensen TS. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. Lancet Neurol. 2017;16:934-944.
- 94. Vinik A, Casellini C, Nevoret ML. Diabetic Neuropathies. [Updated 2018 Feb 5]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279175/.

# Clinical Guideline Revision / History Information

Original Date: 8/21/2017

Reviewed/Revised: 1/18/2018, 7/31/2018, 7/23/2019, 7/21/2020, 08/04/2021, 12/01/2021, 07/26/2022,

07/19/2023