Autonomic Testing / Sudomotor Tests

Aetna considers autonomic testing such as quantitative sudomotor axon reflex test (QSART), silastic sweat imprint, and thermoregulatory sweat test (TST) medically necessary for use as a diagnostic tool for any of the following conditions/disorders:

A. Amyloid neuropathy
B. Diabetic autonomic neuropathy
C. Distal small fiber neuropathy
D. Idiopathic neuropathy
E. Multiple system atrophy
F. Postural tachycardia syndrome
G. Pure autonomic failure
H. Recurrent, unexplained syncope
I. Reflex sympathetic dystrophy or causalgia (sympathetically maintained pain)
J. Sjogren’s syndrome.

Aetna considers autonomic testing experimental and

Policy History

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Definitions

Additional Information

Clinical Policy Bulletin Notes
investigational for all other indications (e.g., chronic fatigue syndrome/myalgic encephalomyelitis, concussion, Raynaud phenomenon, traumatic brain injury, and predicting foot ulcers) because its effectiveness for indications other than the ones listed above has not been established.

II. Aetna considers sympathetic skin response testing experimental and investigational for any indications because it has a relatively low sensitivity and uncertain specificity, and the peer-reviewed medical literature does not support its effectiveness.

III. Aetna considers the use of quantitative direct and indirect reflex testing (QDIRT) of sudomotor function experimental and investigational because its clinical value has not been established.

IV. Aetna considers quantitative pilomotor axon reflex test (QPART) for evaluating pilomotor function experimental and investigational because its clinical value has not been established.

V. Aetna considers autonomic testing using automated devices, in which software automatically generates an interpretation (e.g., ANSAR, Medeia QANS/QHRV System), experimental and investigational in the evaluation of gastro-esophageal reflux disease, hypertension, irritable bowel syndrome, paradoxical parasympathetic syndrome, and all other indications because its clinical value has not been established.

VI. Aetna considers measurement of cardiac baroreflex sensitivity for assessing autonomic nervous system dysfunction after stroke, cognitive function experimental and investigational because its clinical value for this indication has not been established.

VII. Aetna considers ambulatory autonomic nervous system monitors (e.g., BioHarness) experimental and investigational
because their clinical value has not been established.

VIII. Aetna considers the SudoScan experimental and investigational because its effectiveness has not been established.

Background
Sudomotor testing is used in the clinical setting to evaluate and document neuropathic disturbances that may be associated with pain. The quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test (TST), sympathetic skin responses, and silastic sweat imprints are tests of sympathetic cholinergic sudomotor function. All of these tests measure only post-ganglionic sudomotor function.


& Berlit, 1995; Abbott, et al., 1996; Baron & Maier, 1996; Magerl, et al., 1996; Shivji, et al., 1999; Illigens & Gibbons, 2008). Widely used in the past, sympathetic skin response measures change in skin resistance following a random electric stimulation, and provides an index of sweat production. However, this is non-thermoregulatory sweat that occurs on the palms and soles, is of different pharmacological and physiologic properties, and involves somatic afferents. The medical literature proves that this test is of relatively low sensitivity and uncertain specificity, as compared to QSART.

The thermoregulatory sweat test (TST) is another widely used clinical test for evaluating sudomotor function (Hilz & Dutch, 2006; Nolano, et al., 2006; Illigens & Gibbons, 2009; Cheshire & Freeman, 2003; Lipp, et al., 2009; Stewart, et al., 1992; Jacobson & Hiner, 1998; Birklein, et al., 2001; Atkinson & Fealey, 2003; Schiffmann, et al., 2003; Nakazato, et al., 2004; Kimpinski, et al., 2009). The TST evaluates the distribution of sweating by a change in color of an indicator powder. The test is sensitive, and its specificity for delineating the site of lesion is greatly enhanced when used in conjunction with QSART.

Quantitative direct and indirect reflex testing (QDIERT) and silastic sweat imprint methods are also widely used, but do not have the same level of clinical data supporting their use (Kihara, et al., 1993; Illigens & Gibbons, 2009; Gibbons, et al., 2001; Perretti, et al., 2003; Berghoff, et al., 2006; Manganelli, et al., 2007). Sweat imprints are formed by the secretion of active sweat glands into a plastic (silastic) imprint. The test can determine sweat gland density, a histogram of sweat droplet size and sweat volume per area.

Presently, post-ganglionic sudomotor function is assessed by means of QSART or silicone impressions. Quantitative direct and indirect reflex testing is a technique for assessing post-ganglionic sudomotor function. This technique combines some of the advantages of silicone impressions and QSART by providing data on droplet number, droplet topographic
Gibbons et al (2008) described their findings on the use of QDIRT for evaluating sudomotor function. In this study, sweating in 10 healthy subjects (3 women and 7 men) was stimulated on both forearms by iontophoresis of 10% acetylcholine. Silicone impressions were made and topical indicator dyes were digitally photographed every 15 seconds for 7 minutes after iontophoresis. Sweat droplets were quantified by size, location, and percent surface area. Each test was repeated eight times in each subject on alternating arms over 2 months. Another 10 subjects (5 women and 5 men) had silicone impressions, QDIRT, and QSART performed on the dorsum of the right foot. The percent area of sweat photographically imaged correlated with silicone impressions at 5 minutes on the forearm \((r = 0.92, p < 0.01)\) and dorsal foot \((r = 0.85, p < 0.01)\). The number of sweat droplets assessed with QDIRT correlated with the silicone impression, although the droplet number was lower \((162 +/- 28\) versus \(341 +/- 56, p < 0.01, r = 0.83, p < 0.01)\). The sweat response and sweat onset latency assessed by QDIRT correlated with QSART measured at the dorsum of the foot \((r = 0.63, p < 0.05; r = 0.52, p < 0.05)\). The authors concluded that QDIRT measured both the direct and the indirect sudomotor response with spatial resolution similar to that of silicone impressions, and with temporal resolution similar to that of QSART. They noted that QDIRT provides a novel tool for the evaluation of post-ganglionic sudomotor function. Furthermore, they stated that more research is needed to ascertain the utility of QDIRT in disease states that alter sudomotor structure or function.

One limitation of QDIRT is that ambient room temperature and humidity need to be controlled to prevent cool dry air from causing evaporation of sweat production. Furthermore, normative values for QDIRT need to be established to avoid over-diagnosis of sudomotor dysfunction.

Sudomotor testing has data to suggest it may be the most
sensitive means to detect a peripheral small fiber neuropathy (Low, et al., 2006). Hoitsma et al (2003) reported that sympathetic skin responses testing appeared to be of little value in diagnosing small-fiber neuropathy in patients with sarcoidosis. On the other hand, Hoitsma et al (2004) noted that QSART is useful for diagnosing small fiber neuropathy.

Sudomotor testing is also the only way to detect isolated damage to sudomotor nerves in a number of different disease states such as Ross Syndrome, Harlequin Syndrome, diabetes, multiple system atrophy, Parkinson’s disease, autoimmune autonomic ganglionopathy, and pure autonomic failure (Low, et al., 1983; Kennedy, et al, 1984; Low, et al., 1990; Kihara, et al., 1991; Kihara, et al., 1993; Sandroni, et al., 1998; O'Suilleabhan, et al., 1998; Low, 2003; Bickel, et al., 2004; Low, 2004; Low, et al., 2006; Niahan & Harati, 1998; Baser, et al., 1991; Illigen & Gibbons, 2009; Cheshire & Freeman, 2003; Stewart, et al., 1992; Ross, 1958; Petagan, et al., 1965; Schondorf & Low, 1993; Kihara, et al., 1993; Wolfe, et al., 1995; Rex, et al., 1998). The clinical implications of testing and outcomes are reviewed in detail in a number of different studies across different diseases (Cheshire & Freeman, 2003).

Autonomic testing (including sudomotor testing) is recommended for all patients with type 2 diabetes at the time of diagnosis and 5 years after diagnosis in individuals with type 1 diabetes (Boulton, et al., 2005; Tesfaye, et al., 2010; Spallone, et al., 2011a; Bernardi, et al., 2011; Spallone, et al., 2011b; Spallone, et al., 2011c). Individuals with diabetes that have autonomic neuropathy have a significantly higher mortality, and guidelines for anesthesia, surgery and medical therapies to affect outcomes have been established (Boulton, et al., 2005; Spallone, et al., 2011a; Vinik & Ziegler, 2007).

Argiana et al (2011) noted that diabetic foot ulcers affect almost 5 % of the patients with diabetes and carry a huge physical, emotional, and financial burden. Almost 80 % of amputations in patients with diabetes are preceded by a foot ulcer. Simple tests (e.g., monofilament, tuning fork, vibration perception
threshold determination, ankle reflexes, and pinprick sensation), alone or in combination, have been studied prospectively and can be used for identification of patients at risk. Newer tests examining sudomotor dysfunction and skin dryness have been introduced in recent years. In cross-sectional studies, sudomotor dysfunction assessed by either sympathetic skin response or Neupad (Miro Verbandstoffe GmbH, Wiehl-Drabenderhöhe, Germany) testing has been consistently associated with foot ulceration. The authors concluded that prospective studies are needed to establish if sudomotor dysfunction can predict foot ulcers and if simple methods assessing sudomotor dysfunction (e.g., Neupad testing) can be included in the screening tests for the prevention of this complication.

Peltier and colleagues (2010) stated that postural tachycardia syndrome (POTS) is a heterogeneous disorder characterized by excessive orthostatic tachycardia in the absence of orthostatic hypotension and by sympathetic nervous system activation. Post-ganglionic sudomotor deficits have been used to define a neurogenic POTS subtype. Norepinephrine levels above 600 pg/ml have also been used to delineate patients with a hyperadrenergic state. These researchers determined the relationship of sudomotor abnormalities to other aspects of dysautonomia in POTS. Autonomic function was quantified in 30 women through tests of cardio-vagal, adrenergic, and sudomotor function including QSART and spectral indices. Differences between patients with and without sudomotor dysfunction as defined by QSART and between patients with and without hyperadrenergic POTS were assessed with Mann-Whitney U test and Mantel-Haenszel Chi-Square test using a p value of 0.01 for significance. Spearman correlation coefficients were used to test raw sweat volume correlations with other variables. Of 30 women (aged 20 to 58), 17 patients (56%) had an abnormal QSART that was typically patchy and involved the lower extremity, while 13 patients had normal QSART results. Other autonomic tests, catecholamines or spectral indices did not correlate with QSART results. No differences in autonomic tests or spectral indices were
observed between hyperadrenergic and non-hyperadrenergic POTS. The authors concluded that these findings confirmed that a large subset of POTS patients have sudomotor abnormalities that are typically patchy in distribution but do not correlate with other tests of autonomic function. They stated that further studies are needed to determine the best method of endophenotyping patients with POTS.

Manek and associates (2011) stated that the pathophysiological factors of primary Raynaud phenomenon (RP) are unknown. Preliminary evidence from skin biopsy suggests small-fiber neuropathy (SFN) in primary RP. In a pilot study, these investigators aimed to quantitatively assess SFN in patients with primary RP. Consecutive subjects with an a priori diagnosis of primary RP presenting to the authors' outpatient rheumatology clinic over a 6-month period were invited to participate. Cases of secondary RP were excluded. All participants were required to have normal results on nail-fold capillary microscopy. Assessment for SFN was performed with autonomic reflex screening, which includes QSART, and cardiovagal and adrenergic function testing, TST, and quantitative sensory test (QST) for vibratory, cooling, and heat-pain sensory thresholds. A total of 9 female subjects with a median age of 38 years (range of 21 to 46 years) and a median symptom duration of 9 years (range of 5 months to 31 years) were assessed. Three participants had abnormal results on QSART, indicating peripheral sudomotor autonomic dysfunction; 2 participants had evidence of large-fiber involvement with heat-pain thresholds on QST. Heart rate and blood pressure responses to deep breathing, Valsalva maneuver, and 70-degree tilt were normal for all participants. Furthermore, all participants had normal TST results. In total, 3 of the 9 participants had evidence of SFN. The presence of SFN raises the possibility that a subset of patients with primary RP have an underlying, subclinical small-fiber dysfunction. The authors concluded that these data open new avenues of research and therapeutics for this common condition. The findings of this small, pilot study need to be validated by well-designed studies.
Guidelines from the American College of Occupational and Environmental Medicine (2008) make no recommendation for use of Quantitative Sudomotor Axon Reflex Test (QSART) to assist in the diagnostic confirmation of CRPS because of insufficient evidence.

An International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis’s practice guideline on “Chronic fatigue syndrome/myalgic encephalomyelitis” (2012) stated that “No specific diagnostic laboratory test is currently available for ME/CFS, although potential biomarkers are under investigation”.

Siepmann et al (2012) noted that although piloerector muscles are innervated by the sympathetic nervous system, there are at present no methods to quantify pilomotor function. In a pilot study, these researchers quantified piloerection using phenylephrine hydrochloride in humans. A total of 22 healthy volunteers (18 males, 4 females) aged 24 to 48 years participated in 6 studies. Piloerection was stimulated by iontophoresis of 1% phenylephrine. Silicone impressions of piloerection were quantified by number and area. The direct and indirect responses to phenylephrine iontophoresis were compared on both forearms after pre-treatment to topical and subcutaneous lidocaine and iontophoresis of normal saline. Iontophoresis of phenylephrine induced piloerection in both the direct and axon reflex-mediated regions, with similar responses in both arms. Topical lidocaine blocked axon reflex-mediated piloerection post-iontophoresis (mean [SD], 66.6 [19.2] for control impressions versus 7.2 [4.3] for lidocaine impressions; p < 0.001). Subcutaneous lidocaine completely blocked piloerection. The area of axon reflex-mediated piloerection was also attenuated in the lidocaine-treated region post-iontophoresis (mean [SD], 46.2 [16.1] cm² versus 7.2 [3.9] cm²; p < 0.001). Piloerection was delayed in the axon reflex region compared with the direct region. Normal saline did not cause piloerection. The authors concluded that phenylephrine provoked piloerection directly and indirectly through an axon reflex-mediated response that is attenuated by...
Piloerection is not stimulated by iontophoresis of normal saline alone. They stated that the quantitative pilomotor axon reflex test (QPART) may complement other measures of cutaneous autonomic nerve fiber function.

Quattrini et al (2007) measured foot skin vasodilator responses to acetylcholine (Ach) and sodium nitroprusside (SNP) and vasoconstrictor responses to sympathetic stimulation in 5 healthy control subjects, 10 non-neuropathic diabetic (NND) patients, 10 diabetic patients with painless neuropathy (PLDN), and 8 diabetic patients with painful diabetic neuropathy (PDN). In PDN, there were significantly reduced responses to Ach (ANOVA, p = 0.003) and vasoconstrictor inspiratory gasp (ANOVA, p < 0.001) but not to SNP (not significant). Post-hoc analysis showed significant differences in Ach-induced vasodilation between PDN and non-diabetic control subjects (p < 0.05) as well as between PDN and NND (p < 0.05) but not PDN and PLDN (not significant). There were no significant differences for SNP-induced vasodilation. However, there were significant differences in the vasoconstrictor response between PDN and control, NND, and PLDN (p < 0.01). This study found an impairment of cutaneous endothelium-related vasodilation and C-fiber-mediated vasoconstriction in PDN. Inappropriate local blood flow regulation may have a role in the pathogenesis of pain in diabetic neuropathy. The authors stated that prospective studies are needed to determine the temporal relationship of these changes in relation to the emergence of neuropathic pain.

The use of autonomic nervous system function testing for cardiovagal innervation has clinical data supporting its use. It is the only way to measure the function of the parasympathetic, or cardiovagal, nervous system (O'Suilleabhain, et al., 1998; Low, 2003; Singer, et al., 2004; Low, et al., 2004; Low & Opfer-Gehrking, 1993; Salo, et al., 1996; Novak, et al., 1996; Low, et al., 1997; Wright, et al., 1999; Benarroch, 2002; Goldstein, et al., 2003; Thaisetthawatkul, et al., 2004; Sanya, et al., 2005; Benarrach, et al., 2006; Wang, et al., 2008; Goldstein, et al., 2010).
Autonomic testing (including cardiovagal testing) is recommended for all patients with type 2 diabetes at the time of diagnosis and 5 years after diagnosis in individuals with type 1 diabetes (Boulton, et al., 2005; Tesfaye, et al., 2010; Spallone, et al., 2011a; Bernardi, et al., 2011; Spallone, et al., 2011b; Spallone, et al., 2011c). Individuals with diabetes that have cardiac autonomic neuropathy have a significantly higher mortality, and guidelines for anesthesia, surgery and medical therapies to affect outcomes have been established (Boulton, et al., 2005; Spallone, et al., 2011a; Vinik & Ziegler, 2007). Cardiovagal testing has been demonstrated in a number of disease states as an early marker of autonomic parasympathetic dysfunction (O'Suilleabhain, et al., 1998; Low, et al., 2004; Novak, et al., 1996; Thaisetthawatkur, et al., 2004; Beske, et al., 2002; Gibbons & Freeman, 2006; Goldstein, et al., 2009). Some disorders preferentially affect autonomic nerve fibers, such as amyloidosis and autoimmune autonomic ganglionopathy, and do not exhibit abnormalities of somatic nerve fiber tests (Low, et al., 2003). Heart rate variability is a simple and reliable test of cardiovagal function. It has a sensitivity of 97.5% for detection of parasympathetic dysfunction in diabetes when age related normative values are used (Low, et al., 1997; Dyck, et al., 1992). The heart rate response to deep breathing, tilt table test and the heart rate response to the Valsalva maneuver are considered standard clinical tests of autonomic function and are sensitive, specific and reproducible methods for grading the degree of autonomic dysfunction (Low, 1993).

Freeman and Chapleau (2013) stated that autonomic testing is used to define the role of the autonomic nervous system in diverse clinical and research settings. Because most of the autonomic nervous system is inaccessible to direct physiological testing, in the clinical setting the most widely used techniques entail the assessment of an end-organ response to a physiological provocation. The non-invasive measures of cardiovascular parasympathetic function involve the assessment of heart rate variability while the measures of cardiovascular sympathetic function assess the blood pressure...
response to physiological stimuli. Tilt-table testing, with or without pharmacological provocation, has become an important tool in the assessment of a predisposition to neurally mediated (vasovagal) syncope, the postural tachycardia syndrome, and orthostatic hypotension. Distal, post-ganglionic, sympathetic cholinergic (sudomotor) function may be evaluated by provoking axon reflex mediated sweating, e.g., the quantitative sudomotor axon reflex test (QSART) or the quantitative direct and indirect axon reflex test (QDIRT). The thermoregulatory sweat test provides a non-localizing measure of global pre- and post-ganglionic sudomotor function. Frequency domain analyses of heart rate and blood pressure variability, microneurography, and baroreflex assessment are currently research tools but may find a place in the clinical assessment of autonomic function in the future.

Siepmann et al (2013) noted that among the few well-established techniques to diagnose autonomic dysfunction are head-up-tilt table testing, heart rate variability measurement and axon-reflex based sudomotor testing. Recent research focused on the development of novel techniques to assess autonomic function based on axon-reflex testing in both vasomotor and pilomotor nerve fibers. However, these techniques are clinically not widely used due to technical limitations and the lack of data on their utility to detect autonomic dysfunction in patients with neuropathy.

In a community-based cross-sectional study, Saint Martin et al (2013) evaluated the role of the cardiac autonomic nervous system (ANS), as measured according to spontaneous cardiac baroreflex sensitivity (BRS), in the type and degree of cognitive performance in healthy young-elderly individuals, taking into account the presence of other vascular risk factors. A subset of participants, aged 66.9 ± 0.9, from a prospective study that aimed to assess the influence of ANS activity on cardiovascular and cerebrovascular morbidity and mortality (n = 916) were included in this study. All subjects underwent a clinical interview, neuropsychological testing, and autonomic and vascular measurements. Three cognitive domains were
defined: (i) attentional (Trail-Making Test Part A, (ii) Stroop code and parts I & II), and (iii) executive (Trail-Making Test Part B, Stroop part III, verbal fluency and similarity tests), and memory (Benton visual retention test, Grober and Buschke procedure). Subjects were stratified according to their scores into normal, low, and impaired performers. After adjustments to demographic and vascular data, participants with moderate autonomic dysregulation (3 < BRS ≤ 6) were determined to be 1.82 times as likely to have memory impairment (odds ratio (OR) = 1.82, 95% confidence interval (CI): 1.13 to 3.17, p = 0.02) and those with severe autonomic dysregulation (BRS ≤ 3) to be 2.65 as likely (OR = 2.65, 95% CI: 1.40 to 5.59, p = 0.006) as participants with normal BRS (> 6). The authors concluded that in older individuals without dementia, autonomic dysregulation seems to have a direct, gradual, and independent effect on memory. Moreover, they stated that future studies are needed to evaluate the long-term effects of BRS and other markers of the ANS on cognitive decline.

Autonomic testing (including adrenergic testing) is recommended for all patients with type 2 diabetes at the time of diagnosis and 5 years after diagnosis in individuals with type 1 diabetes (Boulton, et al., 2005; Tesfaye, et al., 2010; Spallone, et al., 2011a; Bernardi, et al., 2011; Spallone, et al., 2011b; Spallone, et al., 2011c). Individuals with diabetes that have cardiac autonomic neuropathy have a significantly higher mortality, and guidelines for anesthesia, surgery and medical therapies to affect outcomes have been established (Boulton, et al., 2005; Spallone, et al., 2011a; Vinik & Ziegler, 2007).

There are studies that support the role of autonomic testing in improving clinical outcomes (Low, et al., 2006; Nolano, et al., 2006; Illigens & Gibbons, 2009; Gibbons & Freeman, 2006; Low, 1993; Mathias, et al., 2001; Gibbons, et al., 2001; Gibbons, et al., 2008; Gibbons & Freeman, 2010; Gibbons & Freeman, 2005, Maguire, et al., 20008; Schurmann, et al., 2000; Donadio, et al., 2008). One of the longest running and most detailed examples includes the DCCT trial of diabetic autonomic neuropathy where cardiovagal function was better in individuals with tight glycemic control even 13 years after the end of the study (Pop-Busui, et al., 2009). This data strongly supports the utility of autonomic testing to impact clinical outcomes. Patients with cardiac autonomic neuropathy have an increased risk of silent myocardial ischemia (Vinik, et al., 2003), major cardiac events (Vinik & Ziegler, 2007) and is a predictor of cardiovascular mortality (Vinik & Ziegler, 2007; Maser, et al., 2003).

There are studies of the impact of autonomic testing on clinical treatment. A few examples of the many situations where autonomic testing is of clinical use include:

I. Patients with syncope – autonomic testing is necessary to differentiate neurally mediated syncope from neurogenic
orthostatic hypotension and other causes of syncope

II. Patients with diabetes – all patients with diabetes are recommended to have autonomic testing (sudomotor, cardiovagal and adrenergic) at diagnosis (type 1 diabetes) or 5 years after diagnosis (type 2 diabetes) (Boulton, et al., 2005; Tesfaye, et al., 2010; Spallone, et al., 2011a; Bernardi, et al., 2011; Spallone, et al., 2011b; Spallone, et al., 2011c). In diabetes there is a high prevalence of cardiovascular autonomic neuropathy in this population (Low, et al., 1983; Kennedy, et al., 1984). The relationship between autonomic dysfunction and cardiovascular risk has been well documented and is important to monitor for patients planning major surgical procedures or considering moderate to high intensity physical exercise. This is the reason that the ADA recommends autonomic testing for all patients with type 2 diabetes at the time of diagnosis, and all patients with type 1 diabetes 5 years after diagnosis. The perioperative mortality in cardiovascular autonomic neuropathy is linked to greater blood pressure instability and hypothermia (Low, et al., 1985; Cohen, et al., 1987; Fealey, et al., 1989; Maselli, et al., 1989). This information may prompt high-risk patients to forgo an elective procedure or allow the anesthesiologist to prepare for potential hemodynamic changes, thereby reducing morbidity and mortality (Kennedy, et al., 1984; Low, et al., 1985; Cohen, et al., 1987; Fealey, et al., 1989; Maselli, et al., 1989).

III. Patients with orthostatic dizziness – patients with recurrent dizziness with standing may have autonomic dysfunction, postural tachycardia syndrome or other autonomic neuropathy that can be treated if a diagnosis is made (Singer, et al., 2004; Gibbons, et al., 2011; Baker, et al., 2001; Iodice, et al., 2009; Vernino, et al., 1998; Vernino, et al., 2000; Low, et al., 1995; Gordon, et al., 2000; Sandvani, et al., 2000; Low, et al., 2001; Thieben, et al., 2007). All autonomic tests (sudomotor, cardiovagal and adrenergic) are
appropriate to use in forming a differential diagnosis.

IV. Patients with disorders of sweating – autonomic testing can provide a diagnosis which can lead to treatment of the underlying disorder and improvements in clinical outcomes (Fealey, et al., 1989; Nolano, et al., 2006; Cheshire & Freeman 2003; Kimpinski, et al., 2009; Fisher & Maibach, 1970; Spector & Bachman, 1984; Kang, et al., 1987; Mitchell, et al., 1987; Weller, et al., 1992; Gibbons & Freeman, 2009). Although sudomotor testing will provide specific information about the problem with sweating, cardiovagal and adrenergic testing will narrow the differential diagnosis and are therefore integral parts of the autonomic test (i.e. is this an autonomic ganglionopathy, an isolated autonomic neuropathy such as Ross syndrome, is this a peripheral neuropathy causing distal anhidrosis and proximal hyperhidrosis etc).

V. Patients with peripheral neuropathy from a number of different causes such as (but not limited to) amyloidosis, Fabry’s disease, sjogren’s syndrome, autoimmune neuropathies (Wang, et al., 2008; Low, et al., 2003; Kang, et al., 1987; Sung, 1979; Kaye, et al., 1988; Mutoh, et al., 1988; Kovacs, et al., 2004; Sakakibora, et al., 2004; Mori, et al., 2005; Lopate, et al., 2006; Seldin, et al., 2004; Delanaye, et al., 2006; Shimojima, et al., 2008). All tests of autonomic function (sudomotor, cardiovagal and adrenergic) can provide utility in making a diagnosis, defining the severity of autonomic dysfunction and aiding in treatment of the underlying disorder. The autonomic phenotype can be relatively specific for some neuropathies such as amyloid (Wang, et al., 2008)) and autoimmune autonomic neuropathy (Kimpinski, et al., 2009; Sandroni, et al., 2004; Manganelli, et al., 2011).

VI. In Parkinson’s disease (or other synucleinopathies): Many patients are on a variety of medications that may exacerbate, or cause, autonomic dysfunction (such as levodopa). Patients may be having falls for a variety of reasons, and it is important to distinguish the underlying cause before major injury occurs. Autonomic testing can quickly help distinguish whether there is a primary
underlying autonomic disorder that is causing the problem (and therefore result in a change in diagnosis or management) or the medication is actually causing the problem thereby leading to a change in pharmacotherapy.

VII. Patients with neurogenic orthostatic hypotension, especially if due to a treatable etiology such as drug-induced or autoimmune. Testing, for instance in autoimmune autonomic ganglionopathy, can help the clinician evaluate response to therapy (Manganelli, et al., 2011; Gibbons, et al., 2011; Gibbons, et al., 2008; Gibbons & Freeman, 2009).

There are several devices on the market (e.g., ANSAR, Critical Care Assessment) that state that they offer complete autonomic assessment in 10-15 minutes. In contrast to standard autonomic testing (as described above), the use of “autonomic testing” by these automated devices has not been validated, nor is there data to show they are clinically meaningful. This testing is typically performed without a 5 minute tilt table test and beat-to-beat blood pressure monitoring. These automated testing devices have been promoted for use by physicians with little or no training in autonomic testing, and little understanding of autonomic nervous system physiology.

Many of the references to ANSAR testing offered by the manufacturer are in abstract form or are published in journals that are not indexed by the National Library of Medicine's PubMed database of peer-reviewed medical publications. Of the full-length articles that were published in peer-reviewed journals indexed in PubMed, three are to animal studies, one is a case report, four are to review articles and not primary research studies, and two are to studies that observe autonomic activity following trauma. One of the references is to a study that reports on changes in management of subjects with ANSAR testing; however, there is no comparison group managed without ANSAR testing.

None of the articles in peer-reviewed publications index in PubMed are of clinical studies proving the value of ANSAR
testing. Of the peer-reviewed published evidence, one of the references is to a case report (Turner & Colombo, 2004); case reports do not provide high quality evidence.


A study by Arora, et al. (2008) documents changes in alpha-1 agonist (midodrine) with ANSAR testing in persons with diabetes; however, there is no comparison group of subjects managed without ANSAR testing. Thus, this study does not provide evidence that clinical outcomes were improved with ANSAR testing compared to management without ANSAR testing in persons with diabetes.

Two of the studies of ANSAR testing in peer-reviewed publications indexed by the National Library of Medicine (PubMed) are to observations of autonomic activity following trauma. A study by Fathizadeh, et al. (2004) reports on cardiovascular changes and autonomic activity (by ANSAR testing) in trauma subjects. However, ANSAR testing results were not used in managing patients in this study. A study by Colombo, et al. (2008) is also a descriptive study, reporting on changes in autonomic activity in trauma subjects.

Several of the ANSAR references are to review articles, and not primary clinical studies. A reference from Vinik & Ziegler, et al. (2007) is a review of diabetic cardiovascular autonomic neuropathy. The authors mention ANSAR testing as a method of autonomic nervous system functioning; however, the article was not a clinical study of ANSAR testing. An additional reference from Akselrod, et al. (1988) is a review article and is not primary research. An editorial from Vinik (2010) reviews the relationships between neuropathy and cardiovascular disease in diabetes; this is not a clinical study, and no specific reference is made to ANSAR testing. The reference to Vinik (2003) is also a review article and not a clinical study.
Several references to ANSAR testing are abstracts, rather than full-length peer-reviewed publications: Waheed, et al., 2006; Arora, et al., 2008; Aysin & Aysin, 2006; Aysin, et al., 2007; Vinik, et al., 2004; Boyd, et al., 2010; Boyd, et al., 2010; Nemechek, et al., 2009; Nemechek, et al., 2009; Pereira, et al., 2011, Baker, et al., 2011; Rothstein, et al., 2011. Abstracts do not undergo the level of peer-review as full-length publications, and provide insufficient information to adequately evaluate the clinical study.

Several of the references to ANSAR are to the Touchpoint Briefings in *U.S. Cardiology, U.S. Neurology, and U.S. Endocrinology*; these journals are not of sufficient quality to be indexed by the National Library of Medicine in the PubMed database of peer-reviewed published medical literature: Vinik & Murray, 2008; Vinik, et al., 2007; Tobias, et al., 2010; Nanavanti, et al., 2010. An article by Vinik & Murray (2008) is a review article that includes case reports. An article by Vinik, et al. (2007) is also a review article, and is not a clinical study. An article by Nanavanti, et al. (2010) described a study where therapies in atrial fibrillation were changed based upon ANSAR testing; however, there is no comparison group of subjects managed without ANSAR testing, so no conclusions about the benefits of ANSAR testing can be drawn from this study. A study by Tobias, et al. (2010) reports on observations regarding a large number of subjects who underwent ANSAR testing at six primary care ambulatory clinics, and those with parasympathetic excess were treated according to certain protocols; this study did not include a comparison group of subjects managed without ANSAR testing, so no conclusions can be drawn on the effectiveness of ANSAR testing in improving clinical outcomes.

Siepmann et al (2014) stated that axon-reflex-based tests of peripheral small nerve fiber function, including techniques to quantify vasomotor and sudomotor responses following acetylcholine iontophoresis, are used in the assessment of autonomic neuropathy. However, the established axon-reflex-based techniques, laser Doppler flowmetry (LDF) to
assess vasomotor function and QSART to measure sudomotor function, are limited by technically demanding settings as well as inter-individual variability and are therefore restricted to specialized clinical centers. New axon-reflex tests are characterized by quantification of axon responses with both temporal and spatial resolution and include "laser Doppler imaging (LDI) axon-reflex flare area test" to assess vasomotor function, the QDIRT to quantify sudomotor function, as well as the quantitative pilomotor axon-reflex test (QPART), a technique to measure pilomotor nerve fiber function using adrenergic cutaneous stimulation through phenylephrine iontophoresis. The effectiveness of new axon-reflex tests in the assessment of neuropathy is currently being investigated in clinical studies.

**SudoScan**

SudoScan purportedly measures electrochemical skin conductance of hands and feet through reverse iontophoresis. High conductances correlate with normal sweat function and healthy nerve innervation (small C-fibers). Low conductances may represent peripheral or autonomic neuropathy. There is a lack of published evidence on the effectiveness of the SudoScan.

**BioHarness**

The BioHarness allows ambulatory measurement of the following parameters: heart rate, r-r interval, breathing rate, posture, activity level, peak acceleration, speed and distance, and GPS. The BioHarness is held against the chest using a chest strap, compression shirt, or a BioModule holder. There is a lack of peer-reviewed studies demonstrating improvement in clinical outcomes with ambulatory measurement of these parameters and use of this device.

*Autonomic Testing for Evaluation of Concussion/Traumatic Brain Injury:*
In a systematic review, Blake and colleagues (2016) evaluated the evidence regarding the effect of concussion on cardiac autonomic function (CAF). Original research; available in English; included participants with concussion or mild traumatic brain injury (mTBI) and a comparison group; included measures of heart rate (HR) and/or heart rate variability (HRV) as outcomes. Studies of humans (greater than 6 years old) and animals were included. Critical appraisal tools: The Downs and Black (DB) criteria and Structured Effectiveness Quality Evaluation Scale (SEQES). A total of 9 full-length articles and 4 abstracts were identified. There is conflicting evidence regarding CAF at rest following concussion. There is evidence of elevated HR and reduced HRV with low-intensity, steady-state exercise up to 10 days following concussion. There was no significant difference in HRV during isometric handgrip testing or HR while performing cognitive tasks following concussion. The validity of current literature is limited by small sample sizes, lack of female or pediatric participants, methodological heterogeneity and lack of follow-up. The authors concluded that while there is some evidence to suggest CAF is altered during physical activity following concussion, methodological limitations highlighted the need for further research. They stated that understanding the effect of concussion on CAF will contribute to the development of more comprehensive concussion management strategies.

Furthermore, UpToDate reviews on “Concussion and mild traumatic brain injury” (Evans, 2016a) and “Postconcussion syndrome” (Evans, 2016b) do not mention autonomic testing as a management tool.

Measurement of Cardiac Baroreflex Sensitivity for Assessing Autonomic Nervous System Dysfunction after Stroke:

Yperzeele et al (2015) stated that ANS dysfunction is common after acute stroke and is associated with elevated risk of cardiac arrhythmia and mortality. Heart rate variability and baroreceptor sensitivity have been investigated as parameters of ANS dysfunction for the prediction of stroke outcome. These
researchers performed a systematic literature review on HRV and baroreceptor sensitivity as parameters for autonomic nervous function in acute stroke. A total of 22 studies were included; associations between HRV or baroreceptor sensitivity and stroke severity, early and late complications, dependency and mortality were reported. However, interpretability of most studies and extrapolation to general stroke population were limited due to many confounding factors such as varying methodology, small sample sizes, survival selection, and exclusion of patients with frequently occurring co-morbidities in stroke. Key issues, such as the effect of thrombolytic therapy on autonomic function, ANS dysfunction in the hyper-acute phase of stroke, and correlation with the risk of recurrent stroke have not been investigated. Furthermore, non-linear techniques have remained largely unexplored in this domain, in spite of their advantage to provide more solid evaluation in the occurrence of arrhythmia. The authors concluded that cardiac autonomic dysfunction, represented by reduced HRV or impaired baroreceptor sensitivity, is associated with stroke severity, early and late complications, dependency, and mortality. Moreover, they stated that large-scale prospective studies applying internationally accepted standards of measures for analysis of HRV and baroreceptor sensitivity are needed in patients with acute stroke.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
</tr>
<tr>
<td><strong>CPT codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td>95921</td>
</tr>
<tr>
<td>Code</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>95922</td>
</tr>
<tr>
<td>95923</td>
</tr>
<tr>
<td>95924</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95943</td>
<td>Simultaneous, independent, quantitative measures of both parasympathetic function and sympathetic function, based on time-frequency analysis of heart rate variability concurrent with time-frequency analysis of continuous respiratory activity, with mean heart rate and blood pressure measures, during rest, paced (deep) breathing, Valsalva maneuvers, and head-up postural change</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.42</td>
<td>Polyneuropathy in diabetes</td>
</tr>
<tr>
<td>E09.42</td>
<td></td>
</tr>
<tr>
<td>E10.40</td>
<td>Diabetes with neurological manifestations</td>
</tr>
<tr>
<td>E10.49</td>
<td></td>
</tr>
<tr>
<td>E11.40</td>
<td></td>
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<td>E13.40</td>
<td></td>
</tr>
<tr>
<td>E13.49</td>
<td></td>
</tr>
<tr>
<td>E85.0</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>E85.9</td>
<td></td>
</tr>
<tr>
<td>G60.3</td>
<td>Idiopathic progressive neuropathy</td>
</tr>
<tr>
<td>G60.8</td>
<td>Other hereditary and idiopathic neuropathies</td>
</tr>
<tr>
<td>G60.9</td>
<td>Hereditary and idiopathic neuropathy, unspecified</td>
</tr>
<tr>
<td>ICD-10 Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>G63</td>
<td>Polyneuropathy in diseases classified elsewhere</td>
</tr>
<tr>
<td>G90.50 - G90.59</td>
<td>Complex regional pain syndrome I (CRPS I)</td>
</tr>
<tr>
<td>G90.9</td>
<td>Disorder of the autonomic nervous system, unspecified [postural tachycardia syndrome] [not covered for paradoxical parasympathetic syndrome]</td>
</tr>
<tr>
<td>M35.00 - M35.09</td>
<td>Sicca syndrome [Sjegren]</td>
</tr>
<tr>
<td>R00.0</td>
<td>Tachycardia, unspecified [postural tachycardia syndrome]</td>
</tr>
<tr>
<td>R55</td>
<td>Syncope and collapse</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>G04.90</td>
<td>Encephalitis and encephalomyelitis, unspecified</td>
</tr>
<tr>
<td>I10</td>
<td>Essential (primary) hypertension</td>
</tr>
<tr>
<td>I63.00 - I63.9</td>
<td>Cerebral infarction, unspecified</td>
</tr>
<tr>
<td>I73.00 - I73.01</td>
<td>Raynaud's syndrome</td>
</tr>
<tr>
<td>K21.9</td>
<td>Gastro-esophageal reflux disease without esophagitis</td>
</tr>
<tr>
<td>K58.0 - K58.9</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>R53.82</td>
<td>Chronic fatigue, unspecified</td>
</tr>
<tr>
<td>S06.2X0 - S06.310</td>
<td>Diffuse traumatic brain injury</td>
</tr>
</tbody>
</table>

**The above policy is based on the following references:**


9. Amoiridis G, Tzagournissakis M, Christodoulou P, et al. Patients with horizontal gaze palsy and progressive scoliosis due to ROBO3 E319K mutation have both
uncrossed and crossed central nervous system pathways and perform normally on neuropsychological testing. J Neurol Neurosurg Psychiatry. 2006;77(9):1047-1053.


42. Fagius J, Wallin BG. Sympathetic reflex latencies and


68. 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.


212. Evans RE. Postconcussion syndrome. UpToDate Inc., Waltham, MA. Last reviewed March 2016b.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0485
Autonomic Testing/Sudomotor Tests

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 05/201