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Autonomic Testing / Sudomotor Tests

Number: 0485

Policy

I. Autonomic testing

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 investigational for all other indications (e.g., chronic fatigue syndrome/myalgic encephalomyelitis, concussion, Raynaud phenomenon, traumatic brachial plexus injury, traumatic brain injury, and

Policy History

Last Review

07/17/2018

Effective: 08/21/2001

Next

Review: 05/09/2019

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

predicting foot ulcers) because its effectiveness for indications other than the ones listed above has not been established.

II. **Sympathetic skin response testing**

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. **Quantitative direct and indirect reflex testing (QDIRT)**

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. **Quantitative pilomotor axon reflex test (QPART)**

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

V. **Automated devices**

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. **Cardiac baroreflex sensitivity**

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. **Ambulatory autonomic nervous system monitors**

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

VIII. Sudoscan

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

IX. EZSCAN

Aetna considers EZSCAN experimental and investigational for diagnosis of type 2 diabetes mellitus and all other indication 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.

The QSART device was first reported in detail in 1983 and its clinical use has spread since that time for the evaluation of autonomic dysfunction (Low, et al., 1983; Kennedy, et al., 1984; Low, et al., 1985; Cohen, et al., 1987; Fealey, et al., 1989; Maselli, et al., 1989; Low, et al., 1990; Kahara, et al., 1991; Levy, et al., 1992; Kihara, et al., 1983; Crandall, et al., 1995; Lang, et al., 1995; Sandroni, et al., 1998; O'Suilleabhain, et al., 1998; Birklein, et al., 1998; Hoeldtke et al., 2001; Vinik, et al., 2003; Low, 2003; Bickel, et al., 2004; Singer, et al., 2004; Low, 2004; Low, et al., 2004; Hilz, et al., 2006; Smith, et al., 2006; Low, et al., 2006; Nolano, et al., 2006). The QSART measures axon reflex-mediated sudomotor responses quantitatively and evaluates post-ganglionic sudomotor function. Recording is usually carried out from the forearm and 3 lower extremity skin sites to assess the distribution of post-ganglionic deficits. Normative values for QSART have been established.

The sympathetic skin response is another test of sudomotor function (Maselli, et al., 1989; Levy, et al., 1992; Fagias & Wallin, 1980a; Fagias & Wallin, 1980b; Lidberg & Wallin, 1981; Shahani, et al., 1984; Soliven, et al., 1987; Uncini, et al., 1988; Niakan & Harati, 1988; Dellantonio, et al., 1989; Elie & Guihaneus, 1990; Baser, et al., 1991; Caccia, et al., 1991; Berne, et al., 1992; Drory & Korczyn, 1993; Paresi, et al., 1995; Linden & 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 (QDIRT) 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 distribution, and temporal resolution in direct and axon reflex-mediated regions.

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 Neuropad (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., Neuropad 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 reseachers 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 lidocaine. 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 patients with painless diabetic 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.

Testing sympathetic adrenergic function is the primary method for evaluating patients with syncope, orthostatic hypotension, postural tachycardia syndrome and postural dizziness (Gibbons & Freeman, 2006; Faraji, et al., 2011; Sundkvist, 1981; Sundkvist, et al., 1981; Abraham, et al., 1986; Kenny, et al., 1986; Turkka, et al., 1987; Bergstrom, et al., 1987; Abi Samra, 1988; Ruviele, et al., 1990; Thilenius, et al., 1991; Grubb, et al., 1991; Sra, et al., 1991; Benditt, et al., 1991; Navarro, et al., 1991; Kupoor, 1992; Fouad, et al., 1993; Calkins, et al., 1993; Mathias, et al., 2001; Lahrmann, et al., 2006). Testing is sensitive, specific, and is useful across diseases to diagnose patients with autonomic dysfunction. Sympathetic adrenergic testing (in conjunction with cardiovagal and sudomotor function testing) has been shown to aid in diagnosis, management and outcomes in patients with autonomic dysfunction or syncope of unexplained cause(Gibbons & Freeman, 2006; Faraji, et al., 2011; Sundkvist, 1981; Sundkvist, et al., 1981; Abraham, et al., 1986; Kenny, et al., 1986; Turkka, et al., 1987; Bergstrom, et al., 1987; Abi Samra, 1988; Ruviele, et al., 1990; Thilenius, et al., 1991; Grubb, et al., 1991; Sra, et al., 1991; Benditt, et al., 1991; Navarro, et al., 1991; Kupoor, 1992; Fouad, et al., 1993; Calkins, et al., 1993; Mathias, et al., 2001; Lahrmann, et al., 2006' Freeman, 2006; Oka, et al., 2007; Low, 2008; Gibbons, et al., 2011).

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 (Lahrmann, et al., 2006; Abi-Samra, et al, 1988; Kaufmann, 1997; Kochiadakis, et al., 1997; Stewart, 2000; Karas, et al., 2000; Freeman, et al., 2011; Baker, et al., 2009; Iodice, et al., 2009).

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.

Three of the ANSAR references in peer-reviewed publications indexed in PubMed are to animal studies: Akselrod, et al., 1981; Akselrod, et al., 1985; Akselrod, et al., 1987.

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 (Vinik et al, 2015). High conductances correlate with normal sweat function and healthy nerve innervation (small C-fibers). Low conductances may represent peripheral or autonomic neuropathy.

Casellini et al (2013) sought to evaluate the efficacy of Sudoscan in detecting diabetic neuropathy (DN), in comparison with other standardized tests, in patients with diabetes mellitus (DM). The investigators evaluated 83 DM patients with and without DN and 210 healthy controls (HCs). Neuropathy Impairment Score-Lower Legs (NIS-LL), quantitative autonomic function testing (QAFT), and quantitative sensory testing (QST) were performed. Symptomatic pain was recorded using a visual analog scale. Receiver-operator characteristic (ROC) curves were calculated to evaluate the efficacy of Sudoscan in detecting DN compared with traditional modalities. Diabetes patients with DN had significantly worse electrochemical skin conductances (ESCs) of feet and hands than DM patients without DN and HCs (respectively, 56.3±3 vs. 75.9±5.5 and 84.4±0.9 [$P<0.0001$] for feet and 51.9±2.4 vs. 67.5±4.3 and 73.1±0.8 [$P<0.0001$] for hands). Increasing NIS-LL scores were associated with decreasing ESC values. ESCs correlated significantly with clinical (NIS-LL), somatic (QST), and autonomic (QAFT) measures of neuropathy and with pain scores. ROC curve analysis showed significant results for both hands and feet ESC (area under the curve of 0.86 and 0.88, respectively; $P<0.0001$) with sensitivity of 78% and specificity of 92% for feet to detect DN.

Casellini et al (2016) evaluated the impact of bariatric surgery on cardiac and sudomotor autonomic C-fiber function in obese subjects with and without Type 2 diabetes mellitus (T2DM), using Sudoscan sudorimetry and heart rate variability (HRV) analysis. Patients were evaluated at baseline, 4, 12 and 24 weeks after vertical sleeve gastrectomy or Roux-en-Y gastric bypass. All subjects were assessed using Sudoscan to measure electrochemical skin conductance (ESC) of hands and feet, time and frequency domain analysis of HRV, Neurologic Impairment Scores of lower legs (NIS-LL), quantitative sensory tests (QST) and sural nerve conduction studies. Seventy subjects completed up to 24-weeks of follow-up (24 non-T2DM, 29 pre-DM and 17 T2DM). ESC of feet improved significantly towards normal in T2DM subjects (Baseline = 56.71±3.98 vs 12-weeks = 62.69±3.71 vs 24-weeks = 70.13±2.88, $p<0.005$). HRV improved significantly in T2DM subjects (Baseline sdNN (sample difference of the beat to beat (NN) variability) = 32.53±4.28 vs 12-weeks = 44.94±4.18 vs 24-weeks = 49.71±5.19, p<0,001 and baseline rmsSD (root mean square of the difference of successive R-R intervals) = 23.88±4.67 vs 12-weeks = 38.06±5.39 vs 24-weeks = 43.0±6.25, $p<0.0005$). Basal heart rate (HR) improved significantly in all groups, as did weight, body mass index (BMI), percent body fat, waist circumference and high-density lipoprotein (HDL). Glycated hemoglobin (HbA1C), insulin and HOMA2-IR (homeostatic model assessment) levels improved significantly in pre-DM and T2DM subjects. On multiple linear regression analysis, feet ESC improvement was independently associated with A1C, insulin and HOMA2-IR levels at baseline, and improvement in A1C at 24 weeks, after adjusting for age, gender and ethnicity. Sudomotor function improvement was not associated with baseline weight, BMI, % body fat or lipid levels. Improvement in basal HR was also independently associated with A1C, insulin and HOMA2-IR levels at baseline.

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an axonal sensory-motor and autonomic neuropathy. Castro, et al. (2016) assessed the diagnostic value of Sudoscan sudomotor test in TTR-FAP. One hundred and thirty-three TTR-FAP Val30Met carriers, divided in asymptomatic and symptomatic stage 1, were compared with 37 healthy controls. The investigators analyzed the right sural sensory nerve action potential (SNAP), the plantar sympathetic skin response (SSR) and the electrochemical skin conductance (ESC) measured by Sudoscan in both hands and feet. All neurophysiological measures were significantly worse in the symptomatic group. However, feet ESC was the only test distinguishing symptomatic patients with autonomic dysfunction from those without autonomic dysfunction, and both groups from asymptomatic subjects and healthy controls. Feet ESC was a significant independent predictor for the presence of symptoms and autonomic

Novak et al (2016) conducted a prospective, blinded study assessing the correlation between ESC at the feet measured by Sudoscan and results of skin biopsies including epidermal nerve fiber density (ENFD) and sweat gland nerve fiber density (SGNFD) at the distal leg. ESC, ENFD, and SGNFD data were normalized by adjusting for weight. The secondary outcome measures were the correlation between ESC and the following variables: quantitative sudomotor axon reflex test (QSART) and symptom scales (neuropathy, pain and autonomic). Eighty-one patients (mean ± sd): age = 53.3 ± 17.3, men/women = 25/56 were enrolled in the study. ESC was reduced in subjects with abnormally low ENFD (ENFD normal/abnormal, ESC = 1.17 ± 0.27/0.87 ± 0.34 μSiemens/kg, $p < 0.0008$) and abnormally low SGNFD (SGNFD normal/abnormal ESC = 1.09 ± 0.34/0.78 ± 0.3 μSiemens/kg, $p < 0.0003$). ESC correlated with ENFD ($\rho = 0.73$, $p = 0.0001$) and SGNFD ($\rho = 0.64$, $p = 0.0001$). ESC did not correlate with symptom scales.

Smith et al (2014) evaluated Sudoscan's diagnostic utility for distal symmetric polyneuropathy (DSP). Fifty-five patients with suspected DSP (22 with diabetes, 2 prediabetes, 31 idiopathic) and 42 controls underwent the Utah Early Neuropathy Scale (UENS) and Sudoscan. Each was offered skin biopsy. DSP participants underwent quantitative sudomotor axon reflex testing (QSART) and nerve conduction study (NCS). Feet and hands ESCs were reduced among DSP participants compared to controls (64±22 vs. 76±14 μS $p<0.005$, and 58±19 vs. 66±18 μS p<0.04). There was no difference between diabetic and idiopathic DSP. Receiver operating characteristic curve analysis revealed feet ESC and IENFD had similar areas under the curve (0.761 and 0.752). ESC correlated with Sural amplitude (0.337, p<0.02), UENS (-0.388, p<0.004), and MNSI (-0.398, p<0.005).

Noting that shear stresses have been implicated in the formation of diabetes-related foot ulcers, Wrobel, et al. (2014) evaluated the effect of a novel shear-reducing insole on the thermal response to walking, balance, and gait. Twenty-seven diabetes peripheral neuropathy patients were enrolled and asked to take 200 steps in both intervention and standard insoles. Thermal foot images of the feet were taken at baseline (i) following a 5-minute temperature acclimatization and (ii) after walking. Testing order was randomized, and a 5-minute washout period was used between testing each insole condition. Sudomotor function was also assessed with Sudoscan. Gait and balance were measured under single and dual task conditions using a validated body worn sensor system. The mean age was 65.1 years, height was 67.3 inches, weight was 218 pounds, and body mass index was 33.9, 48% were female, and 82% had type 2 diabetes. After walking in both insole conditions, foot temperatures increased significantly in standard insoles. The intervention insole significantly reduced forefoot and midfoot temperature increases (64.1%, P = .008; 48%, P = .046) compared to standard insoles. There were significant negative correlations with sudomotor function and baseline temperatures (r = .53-.57). The intervention demonstrated 10.4% less gait initiation double support time compared to

standard insoles (P = .05). There were no differences in static balance measures. The investigators found significantly lower forefoot and midfoot temperature increases following walking with shear-reducing insoles compared to standard insoles. They also found improvements in gait. The investigators concluded that these findings merit future study for the prevention of foot ulcer.

Vinik et al (2016) sought to establish reference values in healthy subjects of different ethnic groups, age, and gender, to define factors potentially affecting results, and to provide standardization of the methodology. Data from 1,350 generally healthy study participants who underwent sudomotor function testing were collected and analyzed. The relationship between age, height, weight, gender, glycemic and lipid profiles, ethnicity, and hand and foot electrochemical skin conductance (ESC) was assessed among subgroups of participants. Lower mean hands and feet ESC values were observed in African American, Indian, and Chinese subjects (P < 0.0001). No participant discomfort or safety concern was reported in 1,376 tests. No significant difference in ESC was observed between women and men at the hands (75 [57-87] vs. 76 [56-89] μS; P = 0.35) or feet (83.5 [71-90] vs. 82.5 [70-91] μS; P = 0.12). The coefficient of correlation between right and left side ESC was r = 0.96, P < 0.0001 for hands and r = 0.97, P < 0.0001 for feet. A significant but weak correlation was observed between ESC and age: for hands, r = -0.17, P < 0.0001; for feet, r = -0.19, P < 0.0001. The authors concluded that a normative reference range was established in whites showing that there was no effect of sex or body mass index and a slight decrease in ESC with age. The authors noted that ethnicity influenced ESC scores, but additional studies are necessary to validate this effect and determine its mechanism and impact on nerve function.

Saad and colleagues (2016) stated that chemotherapy-induced peripheral neurotoxicity (CIPN) is a common, potentially severe and dose-limiting adverse effect; however, it is poorly investigated at an early stage due to the lack of a simple assessment tool. As sweat glands are innervated by small autonomic C-fibers, sudomotor function testing has been suggested for early screening of peripheral neuropathy. These investigators evaluated the use of SudoScan in the detection and follow-up of CIPN. A total of 88 patients receiving at least 2 infusions of oxaliplatin only (45.4 %), paclitaxel only (14.8 %), another drug only (28.4 %) or 2 drugs (11.4 %) were enrolled in the study. At each chemotherapy infusion the accumulated dose of chemotherapy was calculated and the Total Neuropathy Score clinical version (TNSc) was carried out. Small fiber neuropathy was assessed using SudoScan (a 3-min test). The device measures the ESC of the hands and feet expressed in microSiemens (μS). For patients receiving oxaliplatin mean hands ESC changed from 73 ± 2 to 63 ± 2 and feet ESC from 77 ± 2 to 66 ± 3 μS ($p < 0.001$) while TNSc changed from 2.9 ± 0.5 to 4.3 ± 0.4. Similar results were observed in patients receiving paclitaxel or another neurotoxic chemotherapy. During the follow-up, ESC values of both hands and feet with a corresponding TNSc of less than 2 were 70 ± 2 and 73 ± 2 μS, respectively, while they were 59 ± 1.4 and 64 ± 1.5 μS with a corresponding TNSc of greater than or equal to 6 ($p < 0.0001$ and $p = 0.0003$, respectively). The authors concluded that the findings of this preliminary study suggested that SFN could be screened and followed using SudoScan in patients receiving chemotherapy.

Zhu and co-workers (2016) noted that there is still a lack of simple methods and instruments for the early assessment of autonomic dysfunction in metabolic syndrome patients. Assessment of sudomotor function has been proposed to explore autonomic function, and could be used as an early biomarker for metabolic syndrome. In the present study, these researchers used a quick and non-invasive method to (i) measure sudomotor function, and (ii) to evaluate its effectiveness to identify metabolic syndrome in a Chinese population. Information on the 1,160 Chinese participants involved in the study, such as age, sex, blood pressure, waist circumference, BMI, fasting plasma glucose and lipid profile, and SudoScan, was recorded. During the sudomotor test, patients were asked to place their bare hands and feet on large electrodes. The test took 2 minutes to carry out, was painless and no participant preparation was required. A total of 567 participants were diagnosed with metabolic syndrome. The prevalence of metabolic syndrome correlated significantly with increasing SudoScan cardiac risk score (p for trend < 0.0001). Furthermore, an increase in cardiac risk score value was associated with an increase in the number of metabolic syndrome components (p for trend < 0.0001). Compared with the no-risk group (cardiac risk score < 20), participants in the high-risk group (cardiac risk score greater than or equal to 30) had a 2.83-fold increased risk of prevalent metabolic syndrome (p < 0.0001), and 1.51-fold increased risk (p = 0.01) after adjustments. The authors concluded that autonomic dysfunction was correlated to components of metabolic syndrome; and they stated that the role of SudoScan in the screening of at-risk populations for metabolic syndrome has to be confirmed by further studies.

Sahuc and associates (2016) stated that hypohidrosis is a frequent and early symptom in patients with Fabry disease (FD). Studies have reported improved sweating in patients treated with enzyme-replacement therapy. In a case-control study, these researchers examined the SudoScan as a tool to evaluate sudomotor dysfunction in patients with FD. Consecutive patients were prospectively recruited who had a diagnosis of FD, which had been confirmed genetically and/or by measurement of α-galactosidase activity in leukocytes. Healthy controls, matched (1:1) for age and sex, were also enrolled. Test results were expressed immediately as ESC (μS) for hands and feet. Sudomotor dysfunction was considered absent, moderate, or severe if the ESC measured on the feet was greater than 60 μS, between 60 and 40 μS, or less than 40 μS, respectively. Among the 18 patients, 11 had hypohidrosis or anhidrosis. Hand and feet ESCs were significantly lower in patients compared to their controls (p = 0.0015 and p = 0.0047, respectively). Among patients, 8/18 (44.5 %) had a sudomotor dysfunction, moderate in 3, and severe in 5 cases. Hand and feet ESCs were significantly lower in those with hypohidrosis/anhidrosis compared to those without (p = 0.0014 and p = 0.0056, respectively). This study showed that SudoScan provided a quick, non-invasive, and quantitative measurement of sudomotor function in FD patients. Moreover, they stated that additional studies in larger cohorts of patients are needed to evaluate its potential use to monitor treatment responses of patients with FD both in clinical practice and in clinical trials where objective and non-invasive surrogate markers are needed

This study had several drawbacks: (i) the small number of patients (n = 18) tested precluded subgroup analyses according to treatment received or correlations with extra-neurological involvements. Notably, SFN has been reported in the context of renal dysfunction; however, the lack of correlation of ESC with renal function in this cohort suggested that its decrease in FD is not just secondary to renal dysfunction, (ii) this preliminary study was not designed to test diagnostic performance of SudoScan for SFN. This would have required comparison to gold standard for the diagnosis of SFN such as skin biopsy. In the absence of such gold standard, the authors provided data according to the presence (or not) of hypohidrosis/anhidrosis. Importantly, a lack of such neurologic symptoms cannot be considered as synonym of preserved sudomotor function. Indeed, discrepancies between

ESC and neurologic symptoms could correspond to the detection of early altered (i.e., patients with no reported hypohydrosis but already low ESC) or improved (i.e., delay between ESC and clinical improvement in some treated patients) sudomotor function by SudoScan. Of note, these researchers were not able to study the possible relation between ESC and residual enzymatic activity, and (iii) no longitudinal assessment of ESC was planned in this first study.

Mao and colleagues (2017) noted that SudoScan is a non-invasive method of measuring peripheral small fiber and autonomic nerve activity by detection of abnormal sweat gland function through electrochemical skin conductance. It has been reported to be an effective screening tool in early detection of microvascular T2DM complications including DN and nephropathy in recent studies. However, previous studies used estimated glomerular filtration rate (eGFR) as the golden standard, which has a 90 % chance of being within 30 % of the measured GFR at best. No relevant study has been performed in the Chinese population concerning SudoScan in the screening of diabetic nephropathy in comparison with GFR. In this cross-sectional study, SudoScan was performed in 176 Chinese patients with T2DM between September 2014 and September 2015. It was found that the SudoScan test had a sensitivity of 57.8% and a specificity of 100 % to detect chronic kidney disease (CKD) at a cut-off SudoScan-diabetic nephropathy score of 59.5. The area under receiver operating characteristic curve (AUC) for diabetic nephropathy was 0.85 [95 % CI: 0.76 to 0.93] compared with 0.84 for eGFRMDRD (MDRD, modification of diet in renal disease; 95 % CI: 0.71 to 0.98) and 0.77 for eGFREPI (EPI, epidemiology collaboration; 95 % CI: 0.68 to 0.87). Patients with diabetic nephropathy score of less than 59.5 had a significantly lower GFR level ($p < 0.001$) and significantly older age ($p < 0.001$), longer duration of T2DM ($p < 0.001$) and higher risk of diabetic complications, including DN ($p < 0.001$) and peripheral vascular disease ($p < 0.05$). The authors concluded that these findings suggested that SudoScan may be useful for detecting patients at risk of impaired renal function as part of a screening program in the Chinese population with T2DM.

The authors stated that this study had some drawbacks. The sample size of this cross-sectional cohort (n = 176) was not large enough to analyze the correlation between kidney function with all associated clinical characteristics. The possibility of selection bias could not be excluded in drawing the conclusion of high specificity of SudoScan-diabetic nephropathy score in detecting CKD. They stated that further studies with larger sample sizes are needed to confirm the clinical use of SudoScan for diagnosing risk of CKD.

Chae and associates (2017) examined if patients with lumbosacral (LS) radiculopathy and peripheral polyneuropathy (PPNP) exhibit sudomotor abnormalities and whether SudoScan can complement NCS and electromyography (EMG). Out-patients with lower extremity dysesthesia underwent electrophysiological studies and SudoScan. They were classified as normal (group A; n = 34), LS radiculopathy (group B; n = 18), or PPNP (group C; n = 21). Pain severity was measured by the Michigan Neuropathy Screening Instrument (MNSI) and visual analog scale (VAS). Demographic features, ESC values on hands and feet, and SudoScan-risk scores were analyzed. There were no statistical differences in MNSI and VAS among the 3 groups. Feet-ESC and hands-ESC values in group C were lower than group A and B. SudoScan-risk score in group B and C was higher than group A. With a cut-off at 48 microSiemens of feet-ESC, PPNP was detected with 57.1 % sensitivity and 94.2 % specificity (AUC = 0.780; 95 % CI]: 0646 to 0.915). With a SudoScan-risk score cut-off at 29 %, NCS and EMG abnormalities related to LS radiculopathy and PPNP were detected with 64.1 % sensitivity and 84.2 % specificity (AUC = 0.750; 95 % CI: 0.674 to 0.886). The authors concluded that this cross-sectional study was the first report of the usefulness of SudoScan in out-patients with lower extremities dysesthesia including those with lumbar lesions and PPNP. Results obtained from preliminary SudoScan evaluation may help complement NCS and EMG testing. Abnormal ESC and SudoScan-risk scores indicated not only involvement of sudomotor in these patients but may also reflect the need of additional NCS and EMG to further confirm the presence of LS radiculopathy or PPNP. Normal ESC and SudoScan-risk scores increased the probability of normal NCS and EMG results. They stated that subsequent studies that expand the application of sudomotor dysfunction using SudoScan testing and how this new assessment tool could complement with current NCS and EMG evaluations are needed.

The authors stated that this study had several drawbacks. First, this study was limited by its small size (n = 73), despite statistically reliable and meaningful results. Small sample sizes could produce statistically unintentional errors because of heterogeneous patient populations. Second, group B with LS radiculopathy included uneven involved levels of distribution. Almost all subjects in group B were diagnosed as lower LS radiculopathy involving L4, L5 or/and S1, except for 1 involving L2 nerve root with 55 μS on feet ESC, which was lower by 10 points than the average in the LS radiculopathy group. Thus, further study of sudomotor dysfunction using SudoScan for LS radiculopathy undoubtedly needs to be done with a large population including upper lumbar radiculopathy. Third, patients with lower extremity dysesthesia may have the sudomotor abnormality even if they are not diagnosed with peripheral neuropathy or radiculopathy in NCS and EMG. Also, SudoScan may not detect subtle sudomotor changes depending on the severity of radiculopathic lesions. Since group A as a control group did not exclude other causes of pain, it is necessary to compare group B with the healthy control group without pain symptom and patients with herniated disc lesion or spinal stenosis of group A.

In a longitudinal study, Ang and colleagues (2017) examined if measuring the ESC may be also a reliable surrogate for early cardiovascular autonomic neuropathy (CAN). This trial included 37 type 1 diabetes (T1D) subjects (mean age of 38 ± 13years, duration of 15 ± 7 years, hemoglobin

A1C (HbA1C) 7.9 ± 1.1 %, no known complications at baseline), and 40 age-matched healthy control (HC) subjects. Mean hands ESC (ESChands) and feet (ESCfeet) were measured with the SudoScan; CAN was assessed with heart rate variability (HRV) studies, cardiovascular autonomic reflex tests (deep-breathing, Valsalva, postural test), and positron emission tomography with sympathetic analogue [11C]meta-hydroxyephedrine. Associations between measures of CAN and ESC were estimated using Spearman correlations. Longitudinal changes were analyzed using paired t-test. At baseline, there were no differences between T1D and HC in ESChands (69 ± 14 versus 69 ± 13 μS; p = 0.84) or ESCfeet (82 ± 8 versus 78 ± 9 μS; p = 0.12), while some indices of HRV and Valsalva ratio were significantly lower in T1D versus HC. Subjects with T1D experienced a significant decline in both ESChands and ESCfeet at 12months (mean change of -7.2 ± 11.6 μS, p = 0.0006; -2.8 ± 7.3 μS, p = 0.023, respectively). No significant correlations were consistently found between ESC and measures of CAN at baseline or at 12 months. The authors concluded that comparing patients with T1D to controls, no differences in ESC were observed at baseline. The associations between ESC and established measures of CAN were inconsistent, which did not support ESC as a reliable surrogate for CAN. Moreover, they stated that while both hands and feet ESC declined over time, the significance of this finding was unclear and warranted further reliability testing.

In an observational, cross-sectional study, Zhu and co-workers (2017) examined the possible relationship between vibration perception threshold (VPT) and CAN values produced by SudoScan. A total of 920 Chinese patients with T2DM were enrolled in the study. Spearman correlation analysis and multivariate regression analysis were performed to determine the relation between CAN and VPT values. Mean VPT values across the CAN value tertiles were analyzed stratified by HbA1c status. In the study, these researchers found a relatively high correlation between CAN value and both VPT values from dorsal feet and toes. Multi-variate regression analyses also showed a significant relation between VPT and CAN values after adjusting all co-variates. The mean value of VPT decreased across the SudoScan-CAN value quartiles in both groups, and it was higher in patients with HbA1C greater than 9 % than in patients with HbA1C less than 9 % across all quartiles of the SudoScan-CAN except for the VPT mean in the low quartile of the SudoScan-CAN value. The authors concluded that all these results suggested that SudoScan-CAN result was associated with VPT value that indicated a probable link between VPT value and cardiovascular autonomic dysfunction. Moreover, they stated that further tests are needed to confirm the findings of this study.

The authors stated that this study had several drawbacks. First, these investigators simply provided the evidence of possible correlation between CAN score with VPT value in this cross-sectional study whereas they did not perform the confirmatory tests of DPN such as electromyography test. Secondly, this observational study simply provided a hint that VPT might predict diabetic cardiovascular disease. However, there is still a need to perform a longitudinal study to validate this possibility.

Lefaucheur (2017) examined the value of ESC measurement at penile level using SudoScan for the diagnosis of neurogenic impotence in diabetics. The following neurophysiological parameters were assessed in 25 male diabetics who complained of impotence and 25 age-matched normal male subjects without erectile dysfunction (ED; age range of 29 to 70 years): ESC, SSR, warm detection thresholds (WDT), and cold detection thresholds (CDT) for the penis and the feet, vibration detection thresholds (VDT) for the penis, and sensory nerve conduction study of the dorsal nerve of the penis (DNP) with SNAP recording. Diabetic patients with impotence differed from controls with regard to most neurophysiological results at both penile and foot levels. Among penile innervation variables in the group of impotent diabetics, penile ESC was found to be the most frequently abnormal (80 % of patients), followed by penile WDT, CDT, and DNP-SNAP amplitude (52 % of patients), and then penile SSR amplitude and VDT (44 % of patients). Various combinations of abnormalities were observed: penile ESC was the only abnormal test in 2 patients, while all tests were abnormal in 2 patients and remained normal in only 1 patient. The author concluded that ED is common in diabetic men, but the diagnosis of a neurogenic origin is challenging. This study showed that ESC measurement using SudoScan was feasible and more sensitive than SSR recordings to show penile sympathetic innervation impairment; this new test should be further studied to better define its diagnostic accuracy and clinical correlates.

Ma and colleagues (2017) evaluated the clinical value of SudoScan in diagnosis of diabetic distal symmetrical peripheral neuropathy. According to the diagnostic criteria for multiple diabetic distal symmetrical peripheral neuropathy, a total of 130 patients with T2DM were divided into 2 groups: DPN group (50 cases) and non-DPN group (NDPN group, 80 cases). Additional 80 healthy volunteers were selected as healthy control group (NC group). SudoScan was employed to detect ESC (the unit was μS) of subjects' hands and feet, and the correlation between sensory nerve conduction velocity (SCV) and ESC was analyzed as well. The average hands ESC in NC and T2DM group were (79.1 ± 10.4) μS and (59.7 ± 18.1) μS, respectively; the average feet ESC were (82.0 ± 8.2) μS and (62.1 ± 21.8) μS, respectively (both $p < 0.01$). The average hands ESC in DPN and NDPN group were (53.2 ± 18.9) μS and (63.7 ± 16.5) μS; the average feet ESC were (53.5 ± 24.4) μS and (67.4 ± 18.2) μS, respectively (both $p < 0.05$). The hands and feet ESC were positively correlated with SCV, and the correlation coefficient were 0.425 and 0.445, respectively (both $p < 0.01$). The area under the receiver operating characteristic curve (ROC) of hands and feet ESC to evaluate diabetic symmetrical peripheral polyneuropathy were 0.785 and 0.768, respectively (both $p < 0.01$). The authors concluded that SudoScan is a promising tool for the diagnosis of diabetic symmetrical peripheral polyneuropathy.

BioHarness:

The BioHarness allows ambulatory measurement of the following parameteres: 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.

Autonomic Testing for Diagnosis of Traumatic Brachial Plexus Injury:

Baruah and colleagues (2017) documented autonomic dysfunction in the affected arm with traumatic brachial plexus injury (TBPI) using QSART. Patients with TBPI were included in the study (n = 20; age ranged from 15 to 50 years). The QSART was administered to each patient with prior informed consent detailing the procedure. The age, sex, mode of injury, date of injury, side of injury, and type of injury (pan brachial plexus versus preserved distal function) were recorded. The presence of any pain was also recorded. The injuries were also grouped as pre-ganglionic and post-ganglionic injuries based on clinical, electroneuromyography (ENMG) and magnetic resonance imaging (MRI) findings. The results of the test for the affected and normal magnetic resonance imaging (MRI) findings. The results of the test for the affected and normal limb were recorded and analyzed with appropriate statistical tests to determine any significant differences. Out of the 20 patients, 1 was female and the rest 19 were males; 7 (35 %) of the injuries were complete (pan brachial plexus) and 13 (65 %) were incomplete (preserved distal function). All patients had pre-ganglionic TBPI. There was no evidence of any statistically significant difference between the affected and normal arm for total sweat volume (p = 0.20) and latency period (p = 0.42). However, the average mean values for the same were lower in the affected arm as compared to the normal. The baseline sweat output (p = 0.010), however, was significantly lower in the affected arm as compared to the normal arm. The authors concluded that QSART has demonstrated reduced baseline sweat output in the affected arm in patients with TBPI indicating the presence of autonomic dysfunction in the injured arm.

The authors stated that the main drawback of this study was its small sample size (n = 20). They stated that further studies with a larger sample size are required to confirm the findings. The other limitation was the difference in duration after injury between the patients.

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.

EZSCAN for Diagnosis of Type 2 Diabetes Mellitus:

Bernabe-Ortiz and colleagues (2017) noted that the EZSCAN is a non-invasive device that, by evaluating sweat gland function, may detect subjects with T2DM. These investigators performed a systematic review and meta-analysis including studies assessing the performance of the EZSCAN for detecting cases of undiagnosed T2DM. They searched for observational studies including diagnostic accuracy and performance results assessing EZSCAN for detecting cases of undiagnosed T2DM. OVID (Medline, Embase, Global Health), CINAHL and SCOPUS databases, plus secondary resources, were searched until March 29, 2017. The following keywords were utilized for the systematic searching: type 2 diabetes mellitus, hyperglycemia, EZSCAN, SudoScan, and sudomotor function. Two investigators extracted the information for meta-analysis and assessed the quality of the data using the Revised Version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) check-list. Pooled estimates were obtained by fitting the logistic-normal random-effects model without covariates but random intercepts and using the Freeman-Tukey Arcsine Transformation to stabilize variances. Heterogeneity was also assessed using the I2 measure. A total of 4 studies (n = 7,720) were included, 3 of them used oral glucose tolerance test as the gold standard. Using Hierarchical Summary Receiver Operating Characteristic model, summary sensitivity was 72.0 % (95 % CI: 60.0 % to 83.0 %), whereas specificity was 56.0 % (95 % CI: 38.0 % to 74.0 %). Studies were very heterogeneous (I2 for sensitivity: 79.2 % and for specificity: 99.1 %) regarding the inclusion criteria and bias was present mainly due to participants selection. The authors concluded that the sensitivity of EZSCAN for detecting cases of undiagnosed T2DM appeared to be acceptable, however, evidence of high heterogeneity and participant selection bias was detected in most of the studies included. They stated that the performance of the EZSCAN needs confirmation in different populations, using the appropriate gold standard, and population-based samples. Moreover, they noted that adequate report of findings and longitudinal utility of the EZSCAN is also compulsory.

The authors stated that one of the limitations of this review was the representativeness of the results characterized by bias in participants' selection as well as the lack of a true gold standard in some of the studies (i.e., fasting glucose was used in 1 study instead of oral glucose tolerance test). In addition, characteristics of the study population were poorly reported and this was reflected in the quality assessment. As all the studies assessing EZSCAN were recently published (from 2010 and onwards); authors should have been utilized the Standards for Reporting Diagnostic Accuracy Studies (STARD) to guide their manuscripts' writing. They stated that future studies should follow these guidelines to guarantee an appropriate reporting of diagnostic studies.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	**Code Description**
CPT codes covered if selection criteria are met:	
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 [not covered for Sudoscan]
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 [not covered for Sudoscan]
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 [not covered for Sudoscan]
95924	Testing of autonomic nervous system function; combined parasympathetic and sympathetic adrenergic function testing with at least 5 minutes of passive tilt [not covered for Sudoscan]

CPT codes not covered for indications listed in the CPB:	
EZSCAN - no specific code:	
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
ICD-10 codes covered if selection criteria are met:	
E08.42, E09.42	Polyneuropathy in diabetes
E10.40 - E10.49, E11.40 - E11.49, E13.40 - E13.49	Diabetes with neurological manifestations
E85.0 - E85.9	Amyloidosis
G60.3	Idiopathic progressive neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified

Code	Code Description
G60.9	Hereditary and idiopathic neuropathy, unspecified
G63	Polyneuropathy in diseases classified elsewhere
G90.09	Other idiopathic peripheral autonomic neuropathy
G90.50 - G90.59	Complex regional pain syndrome I (CRPS I)
G90.9	Disorder of the autonomic nervous system, unspecified [postural tachycardia syndrome] [not covered for paradoxical parasympathetic syndrome]
M04.1 - M04.9	Autoinflammatory syndromes
M35.00 - M35.09	Sicca syndrome [Sjogren]
R00.0	Tachycardia, unspecified [postural tachycardia syndrome]
R55	Syncope and collapse
ICD-10 codes not covered for indications listed in the CPB:	
E11.00 - E11.9	Type 2 diabetes mellitus
G04.90	Encephalitis and encephalomyelitis, unspecified
I10 - I16.2	Hypertensive disease
I63.00 - I63.9	Cerebral infarction, unspecified
I73.00 - I73.01	Raynaud's syndrome
K21.9	Gastro-esophageal reflux disease without esophagitis
K58.0 - K58.9	Irritable bowel syndrome
R53.82	Chronic fatigue, unspecified
S06.2X0 - S06.310	Diffuse traumatic brain injury
S14.3xxA - S14.3xxS	Injury of brachial plexus

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