IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Quantitative sensory testing (QST) systems are used for the noninvasive assessment and quantification of sensory nerve function in patients with symptoms of, or the potential for, neurologic damage or disease. Pain conditions evaluated may include diabetic neuropathy and uremic and toxic neuropathies, complex regional pain syndrome, carpal tunnel syndrome, and other nerve entrapment/compression disorders or damage.

QST systems measure and quantify the amount of physical stimuli required for sensory perception to occur in the patient. As sensory deficits increase, the perception threshold of QST will increase, which may be informative in documenting progression of neurologic damage or disease. QST has not been established for use as a sole tool for diagnosis and management, but has been used in conjunction with standard evaluation and management procedures (e.g., physical and neurologic examination, monofilament testing, pinprick, grip and pinch strength, Tinel, Phalen and Roos sign) to enhance the diagnosis and treatment planning process, and confirm physical findings with quantifiable data. Stimuli used in QST include touch, pain, pressure, vibratory, and thermal (warm and cold) stimuli. All of the systems discussed here have received US Food and Drug Administration 510(k) marketing clearance.

The gold standard for evaluation of myelinated large fibers is the electromyographic nerve conduction study (EMG-NCS). However, the function of smaller myelinated and unmyelinated sensory nerves, which may show pathologic changes before the involvement of the motor nerves, cannot be detected by
NCS. Small fiber neuropathy has traditionally been a diagnosis of exclusion in patients who have symptoms of distal neuropathy and a negative nerve conduction study. Depending on the type of stimuli used, QST can assess both small and large fiber dysfunction. For example, touch and vibration devices such as the (Vibration Perception Threshold) VPT Meter (Xilas Medical), and the CASE IV Computer Aided Sensory Evaluator (WR Medical Electronics), measure the function of large myelinated A-alpha and A-beta sensory fibers. Thermal stimuli devices are used to evaluate pathology of small myelinated and unmyelinated nerve fibers.

Current perception threshold (CPT) testing involves the quantification of the sensory threshold to transcutaneous electrical stimulation. In CPT testing, typically 3 different frequencies are tested: 5 Hz, designed to assess C fibers; 250 Hz, designed to assess A-delta fibers; and 2,000 Hz, designed to assess A-beta fibers. Results are compared with those of a reference population. The Neurometer® Current Perception Threshold (CPT®; Neurotron, Inc) and the Medi-Dx 7000® (NeuroDiagnostic Associates) are 2 of these devices.

Pressure-specified sensory devices assess large myelinated sensory nerve function by quantifying the thresholds of pressure detected with light, static, and moving touch. The Nk Pressure-Specified Sensory Device™ (Nk Biotechnical Engineering) consists of 1 or 2 blunt probes and sensitive transducers to measure and record the perception thresholds of pressure on the surface of the body in grams per square millimeter. The device has been used to aid in the diagnosis and assessment of nerve function, including diabetic peripheral neuropathy, carpal tunnel syndrome, and other nerve entrapment or compression syndromes, and postoperative assessment of sensory outcomes after liposuction, breast reduction mammoplasty, etc.

Because QST combines the objective physical sensory stimuli with the subjective patient response, it is psychophysical in nature and requires patients who are alert, able to follow directions, and cooperative. Psychophysical tests have greater inherent variability, making their results more difficult to standardize and reproduce.

**MEDICAL POLICY CRITERIA**

All types of quantitative sensory testing (QST) are considered **investigational**, including but not limited to the following:

A. Current perception threshold testing  
B. Pressure-specified sensory device testing  
C. Vibration perception threshold testing  
D. Thermal threshold testing

**SCIENTIFIC EVIDENCE**

Quantitative sensory testing (QST) can either be used in initial diagnostic testing or in the monitoring of patients to assess ongoing sensory deficits. The type of data required to validate QST in these 2 different
settings is different. For example, as an initial diagnostic test, one would like to see standard measures of diagnostic performance, such as sensitivity; specificity; positive and negative predictive values, as compared to conventional tests, such as monofilament testing, pinprick, etc. Where QST has been proposed as an alternative to NCS, the diagnostic performances of these 2 tests should be compared. Additionally, where QST is used as a monitoring technique, test/retest reliability is an important outcome, and one which must be associated with defining a clinically significant change in sensory perception. In any proposed application, it is important to evaluate whether results from QST enhance patient management and improve health outcomes, either in terms of instituting more prompt or effective therapy, or in the avoidance of more invasive tests, such as NCS. Therefore, the focus of this review is on trials demonstrating clinical utility of QST.

**Current Perception Threshold Testing (CPT)**

CPT testing has been investigated for a broad range of clinical applications, including evaluation of peripheral neuropathies, detection of carpal tunnel syndrome, spinal radiculopathy, evaluation of the effectiveness of peripheral nerve blocks, quantification of hypoesthetic and hyperesthetic conditions, and differentiation of psychogenic from neurologic disorders.

In 1999, the American Association of Electrodiagnostic Medicine (AAEM) published a technology review of the Neurometer® device.[1] This evaluation suggested the following criteria for evaluation of the device:

- A prospective study,
- Independent ascertainment of the clinical condition evaluated,
- A detailed description of the methodology,
- Attention to testing conditions that could potentially affect the results,
- A suitable reference population from the same laboratory, and
- Criteria for abnormality obtained from the reference population and defined in statistical terms

The AAEM assessment concluded there was inadequate scientific literature meeting the above criteria to validate the clinical role of CPT testing. Much of the literature compared the results of Neurometer testing to NCS in patients with known disease. In many instances, the results of the Neurometer testing demonstrated more numerous or pronounced abnormalities compared to NCS, a finding that was consistent with the hypothesis that abnormalities of small nerve fibers precede those of large nerve fibers tested in NCS. However, this observation could also have been related to the fact that the Neurometer involved testing at multiple sites with 3 different frequencies, and that any identified abnormality was considered significant.

Testing the perception threshold at different frequencies was designed to evaluate the function of different subclasses of nerve fibers. However, this hypothesis had not been adequately evaluated, in part due to a lack of a diagnostic gold standard for comparison purposes. In this situation, validation of a diagnostic technology required studying how the technique was used in the management of the patient and whether subsequent changes were associated with improved health outcomes. Finally, results of the Neurometer testing were compared to a normal reference population. The review by the AAEM found that the source of the normal values was not apparent from the published literature. The AAEM assessment concluded with the following recommendations regarding research to validate the clinical utility of the Neurometer:

- Reference values need to be established for well-characterized and representative populations.
• Reproducibility and interoperator variability of the Neurometer CPT normal values need to be established and expressed statistically in control subjects and patients with specific diseases.
• The sensitivity and specificity need to be established and compared to an appropriate standard.

To date no studies of clinical utility of CPT testing have been identified. The following studies are representative of the breadth and depth of available literature (most of which consists of small short-term or cross-sectional studies which include healthy volunteers):

• Park and colleagues attempted to validate CPT testing against the gold standard references for thermal sensory testing and von Frey tactile hair stimulation in a randomized, double-blind, placebo-controlled trial on 19 healthy volunteers.[2] The authors reported finding that all CPT measurements showed a higher degree of variability than thermal sensory testing and von Frey measurements. However, they concluded there was some evidence that similar fiber tracts may be measured, especially C-fiber tract activity at 5 Hz, using CPT, thermal sensory, and von Frey testing methods. None of these studies sufficiently addressed the AAEM recommendations for research to validate the clinical utility of CPT testing.

• A 2009 study used the Neurometer device in individuals with hand-arm vibration exposure.[3] However, the primary purpose of the study was to evaluate the utility of a staging scale (the Stockholm sensorineural scale), not to determine the accuracy of QST. Therefore, it did not provide additional evidence on the clinical utility of current perception testing as part of the initial evaluation of individuals with possible hand-arm vibration syndrome.

• Two comparative studies reported on attempts to establish the diagnostic utility of CPT testing.[2,4] In 2002, Yamashita and colleagues evaluated CPT using the Neurometer by comparing findings in 48 patients with lumbar radiculopathy and 11 healthy controls.[4] The authors reported finding significantly higher CPT values in the affected legs of patients with lumbar radiculopathy at 2000, 250, and 5 Hz frequencies than in the unaffected legs. CPT values in the affected legs were also significantly higher in control subjects at 2000 and 250 Hz frequencies, but not significantly different at 5 Hz. The authors concluded that CPT testing may be useful in quantifying sensory nerve dysfunction in patients with radiculopathy. However, there was no discussion of how this quantification could be used in the management of the patient.

• In 2012, Ziccardi and colleagues evaluated 40 patients presenting with trigeminal nerve injuries involving the lingual branch.[5] Patients underwent current perception threshold testing, as well as standard clinical sensory testing. Statistically significant correlations were found between findings of electrical stimulation testing at 250 Hz and the reaction to pinprick testing (p=0.02), reaction to heat stimulation (p=0.01) and reaction to cold stimulation (p=0.004). In addition, significant correlations were found between electrical stimulation at 5 Hz and the reaction to heat stimulation (p=0.017), reaction to cold stimulation (p=0.004), but not the reaction to pinprick testing (p=0.096).

**Pressure-Specified Sensory Device (PSSD) Testing**

Evidence supporting the use of PSSD testing must demonstrate that PSSD testing provides additional information beyond that ordinarily determined during standard evaluation and management of patients with potential nerve compression, disease, or damage. Standard evaluation and management consist of physical examination techniques and may include Semmes-Weinstein monofilament testing and, in some more complex cases, nerve conduction velocity testing.
While PSSD may be a useful adjunct in neurosensory testing, no clinical trials were identified that demonstrated that use of the PSSD resulted in earlier and/or more accurate diagnoses of nerve damage and improved patient outcomes. The literature discussed below is representative of the available evidence on PSSD (mostly focused on the technical feasibility of the testing technique, and limited by use of healthy controls):

- In 2012, Suokas and colleagues published a systematic review of studies evaluating QST in painful osteoarthritis; the majority of studies used pressure testing. The authors did not report finding any studies that evaluated the impact of QST on health outcomes.

- Nath and colleagues evaluated 30 patients with winged scapula and upper trunk injury and 10 healthy controls. They used the FDA-cleared PSSD by Sensory Management Services to measure the minimum perceived threshold in both arms for detecting 1-point static (1PS) and 2-point static (2PS) stimuli. The authors used a published standard reference threshold value for the dorsal hand first web (DHFW) skin, and calculated threshold values for both the DHFW and the deltoid using the upper limit of the 99% normal confidence interval. No published threshold values were available for the deltoid location. PSSD testing was done on both arms of all participants, and EMG testing was performed only on the affected arms of symptomatic patients. Using calculated threshold values, patients with normal EMG results had positive PSSD results on 50% (8/16) of 1PS deltoid, 71% (10/14) of 2PS deltoid, 65% (11/17) of 1PS DHFW, and 87% (13/15) of 2PS DHFW tests. The authors stated that the findings suggested that PSSD was more sensitive than needle EMG in detecting brachial plexus upper trunk injury. These findings should be confirmed in additional studies. In addition, the thresholds used to categorize a PSSD finding as positive for the deltoid should be validated in future reports.

- A 2000 study by Weber and colleagues evaluated the sensitivity and specificity of PSSD and nerve conduction velocity testing in a total of 79 patients including 26 healthy controls. The NCV test had a sensitivity of 80% and a specificity of 77%. The pressure-specified sensory device had a sensitivity of 91% and a specificity of 82%; the difference between the two tests was not significantly different.

**Vibration Perception Threshold (VPT) Testing**

No trials of clinical utility were identified for VPT testing. The 2 non-randomized comparative studies cited below are representative of the type of literature (addressing technical feasibility or diagnostic accuracy) available for VPT testing.

- A multicenter study funded by a pharmaceutical company compared VPT testing (CASE IV, biothesiometer, C64 graduated tuning fork) with standard NCS in 195 (86% follow-up) subjects with diabetes mellitus. The tests were performed independently by trained technicians; all NCS evaluations were sent to a central reading center. Intra-class correlation coefficients for the tests ranged from 0.81 to 0.95, indicating excellent to highly reproducible results. Correlation coefficients for the various vibration QST instruments were moderate at -0.55 (CASE IV vs. tuning fork) to 0.61 (CASE IV vs. biothesiometer). In contrast, the correlation coefficient between CASE IV and a composite score for nerve conduction was low (r: 0.24). These results indicated that VPT testing could not replace NCS testing but might provide a complementary outcome measure.

- A 2010 study from India evaluated 100 patients with type 2 diabetes using a vibration perception threshold device, the Sensitometer (Dhansai Lab), which is produced in Mumbai and is not FDA-
approved.\[^{10}\]\ The authors reported sensitivities and specificities using standard NCS. For VPT testing, a positive finding (i.e., presence of neuropathy) was defined as patient reporting of no vibration sensation at a voltage of more than 15V. According to the NCS findings, 70 of 100 patients had evidence of neuropathy; sensitivity was 86% and the specificity was 76%. Semmes-Weinstein monofilament testing, which was also done, had a higher sensitivity than VPT testing (98.5%), and a lower specificity (55%). Finally, a diabetic neuropathy symptom score, determined by responses to a patient questionnaire, had a sensitivity of 83% and a specificity of 79%. The authors commented that the simple neurologic examination score appeared to be as accurate as VPT testing. The Sensitometer is not available in the United States and it is not known how similar this device is to FDA-cleared VPT testing devices.

### Thermal Threshold Testing

An example from the research literature on the diagnostic accuracy of QST with thermal stimuli is detailed below. Current literature on thermal threshold testing consists of observational, small or retrospective comparative studies on the detection of small fiber neuropathy in a variety of clinical conditions (including knee osteoarthritis and diabetic neuropathy). There is no literature addressing the clinical utility of this type of testing.

A 2012 systematic review by Moloney and colleagues examined the literature on the reliability of thermal QST.\[^{11}\] A total of 21 studies met the review’s inclusion criteria, which included using an experimental design, assessing reliability, comparing thermal QST with other methods of assessment and testing at least twice. The investigators used a quality appraisal checklist to evaluate the reliability of the studies that were identified. Only 5 of the 21 studies were considered to be high quality. The review authors found considerable variation in the reliability of thermal QST; this included the 5 studies considered to be of high-quality. The authors also noted several methodologic issues that could be improved in future studies, including better descriptions of raters and their training, blinding and randomization, and better standardization of test protocols.

In 2008, Devigili et al. published a retrospective review of 486 patients referred for suspected sensory neuropathy.\[^{12}\] A total of 150 patients met the entry criteria for the study, which included symptoms suggesting sensory neuropathy and availability of:

- Clinical examination (including spontaneous and stimulus-evoked pain),
- Sensory and motor NCS,
- Warm and cooling thresholds assessed by QST, and
- Skin biopsy with distal intraepidermal nerve fiber (IENF) density.

Based on the combined assessments, neuropathy was ruled out in 26 patients; 124 patients were diagnosed with sensory neuropathy; of these, 67 patients were diagnosed with small nerve fiber neuropathy. Using a cutoff of 7.63 IENF/mm at the distal leg (based on the 5th percentile of controls), 59 patients (88%) were considered to have abnormal IENF (small nerve fiber) density. Only 7.5% of patients had abnormal results for all 3 examinations (clinical, QST, skin biopsy), 43% of patients had both abnormal skin biopsy and clinical findings, and 37% of patients had both abnormal skin biopsy and QST results. The combination of abnormal, clinical, and QST results was observed in only 12% of patients. These results indicate that most of the patients evaluated showed IENF density of less than 7.63 together with either abnormal spontaneous or evoked pain (clinical examination) or abnormal thermal thresholds (QST). The authors of this study recommended a new diagnostic “gold standard” based on the presence of at least 2 of 3 abnormal results (clinical, QST, and IENF density). Additional
prospective studies are needed to evaluate whether the addition of thermal QST results in improved outcomes over clinical diagnosis alone.

Results from several small non-comparative studies have raised questions about the reliability of QST. For example, one study noted “significant” variability in thermal perception thresholds during a 1-hour time in 24 female volunteers.\(^{[13]}\) In another small study, mean QST thresholds for vibration, cold, warmth, and heat pain were no different in 10 patients (with type 2 diabetes and painful neuropathy) than in 15 healthy control subjects.\(^{[14]}\) In the same study, QST thresholds were also evaluated in 12 patients with type 2 diabetes and advanced painless neuropathy; these were found to be significantly higher than the control thresholds for all stimuli, suggesting that QST was not able to detect early stages of neuropathy. The study found that the laser Doppler imager flare, a new functional test of dermal vasodilation, showed significant changes in both the painful (mild) and painless (severe) neuropathy patients.

Other examples of non-randomized comparative studies have focused on the use of thermal QST to identify early clinical markers and predictors of neurotoxicity with chemotherapy drugs and are detailed below. There are no studies of clinical utility of this type of testing; neither have the devices used in these studies received clearance by the FDA for use in the United States.

- Attal and colleagues conducted a study to identify early clinical markers and predictors of neurotoxicity with the chemotherapy drug oxaliplatin.\(^{[15]}\) Of 67 consecutive patients with mainly colorectal cancer, 48 (72%) were able to be evaluated prospectively before, during, and after 9 cycles of oxaliplatin (n=28) or cisplatin (n=20) treatment. Eighteen of the oxaliplatin patients were reassessed at 12 months. Evaluation with QST included detection/pain thresholds for mechanical, vibration, and cold and heat stimuli. Thermal testing (cold or heat) 2 weeks after the third cycle identified sustained neurotoxicity during oxaliplatin treatment, while cold-evoked symptoms lasting 4 days or more after the third cycle predicted chronic neuropathy (odds ratio of 22; 95% confidence interval [CI]: 1.5-314.7) and severe neuropathy (odds ratio of 39; 95% CI 1.8-817.8). These results were limited by the small number of patients and large confidence intervals. Additional studies are needed to evaluate the predictive value of abnormal thermal QST and their clinical implications.

- In 2011, Scott and colleagues in the U.K. evaluated 23 patients with cancer-induced bone pain before and after treatment with radiotherapy.\(^{[16]}\) Patients were evaluated using monofilament tests, pin prick stimulus, and thermal perception testing (Rolltemp device). Pain was tested at the area reported as painful by the patient and a control area. Patients were also assessed with the short-form Brief Pain Inventory, a validated measure of cancer pain. To maximize reproducibility, one researcher conducted all QST measurements. For QST measurements, responses were recorded as increased, reduced, or equivalent sensation as the normal control (rather than measuring actual thresholds). Compared to the pre-radiotherapy values, there was no change in response to warm stimulation in 16 of 23 (70%) of patients. Six patients (26%) had reduced sensation and 1 had increased sensation. There was no change in response to cool stimulation in 15 of 23 (65%) of patients; 6 (26%) had reduced sensation and 2 had increased sensation. Among patients who responded to radiotherapy according to other measures, 5 of the 7 patients (71%) who had abnormal response to warm sensation at baseline had reduced sensation (normal) at follow-up. Four of 6 (67%) patients who had an abnormal response to cool sensation at baseline experienced reduced sensation (normal) at follow-up. The numbers of patients who experienced a change in thermal sensation after radiotherapy are too small to draw conclusions about the accuracy of thermal threshold testing with the Somedic device for predicting response to radiotherapy.
Clinical Practice Guidelines and Position Statements

Several evidence-based guidelines have been published which evaluate QST as a diagnostic tool; however, none have recommended the use of QST in the diagnosis or management of any indication.

- A 2003 evidence-based report from the American Academy of Neurology (AAN; reaffirmed in 2005 and 2008) concluded that QST is probably an effective tool in documenting sensory abnormalities and changes in sensory thresholds in longitudinal evaluation of patients with diabetic neuropathy. (This is a level B recommendation: Probably useful/predictive or not useful/predictive for the given condition in the specified population)[17] Evidence was weak or insufficient to support the use of QST in patients with other conditions (small fiber sensory neuropathy, pain syndromes, toxic neuropathies, uremic neuropathy, acquired and inherited demyelinating neuropathies, or malingering). The report also stated that QST should not be used as a sole method for diagnosing pathology. QST poses technical challenges in the methodology of testing, reproducibility, and psychophysical factors that limit the objectivity of testing results.

- In 2005, the American Association of Electrodiagnostic Medicine (AAEM), in conjunction with the AAN and American Academy of Physical Medicine and Rehabilitation developed a formal case definition of distal symmetrical polyneuropathy based on an evidence-based analysis of peer-reviewed literature supplemented by consensus from an expert panel.[18] QST was not included as part of the final case definition, given that the reproducibility of QST ranged from poor to excellent, and the sensitivities and specificities of QST were found to vary widely among studies.

- The 2010 American Academy of Orthopaedic Surgeons (AAOS) evidence-based clinical guideline on diagnosis of carpal tunnel syndrome specifically recommends against the use of pressure specified sensorimotor devices, stating, “The physician should not routinely evaluate patients suspected of having carpal tunnel syndrome with new technology, such as magnetic resonance imaging (MRI), computerized axial tomography (CAT), and pressure specified sensorimotor devices (PSSD) in the wrist and hand.” This recommendation is based upon the lowest level of evidence (Level V; expert opinion).

Several consensus-based statements on the use of QST have also been published:

- In 2004, the American Association of Electrodiagnostic Medicine (AAEM) published a consensus-based technology literature review on QST (light touch, vibration, thermal, and pain), which concluded that QST is a reliable psychophysical test of large- and small-fiber sensory modalities.[19]

- In their 2010 consensus and evidence-based clinical practice guideline on the diagnosis and treatment of heel pain, the American College of Foot and Ankle surgeons stated that pressure-specified sensory device (PSSD) tests may be used in the diagnosis of neurologic heel pain.[20]

However, the evidence used to make these statements was not clearly cited or critically appraised. In general, the lack of a direct link between scientific evidence and consensus-based statements limits the ability to interpret these statements.

Summary

Current evidence is uncertain concerning whether quantitative sensory testing systems for the diagnosis,
monitoring, and quantification of sensory nerve function in patients with neurologic damage or disease results in enhanced patient management and improved health outcomes. Therefore, the use of current perception threshold testing, pressure-specified sensory device testing, vibration perception threshold testing, or thermal threshold testing, for any indication, is considered investigational. There is inadequate scientific literature to validate the reliability and clinical utility of quantitative sensory testing systems, and further study is needed.

REFERENCES


CROSS REFERENCES

Automated Point-of-Care Nerve Conduction Studies, Medicine, Policy No. 128

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