Quantitative Sensory Testing

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DESCRIPTION

Note: This document addresses in the outpatient setting only. It does not address intraoperative neurophysiologic testing.

Quantitative sensory testing (QST) systems measure and quantify the number of physical stimuli required for sensory perception to occur. As sensory deficits increase, the perception threshold of QST will increase, which may be informative in documenting the 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 with standard evaluative and management procedures (e.g., physical and neurologic examination, monofilament testing, pinprick, grip and pinch strength, Tinel sign, and Phalen and Roos test) to enhance the diagnosis and treatment-planning process, and to confirm physical findings with quantifiable data.

Stimuli used in QST include touch, pressure, pain, thermal (warm and cold), vibratory, or electric current stimuli. Depending on the type of stimuli used, QST can assess small or

large fiber dysfunction. QST with touch and vibration can evaluate large, myelinated A alpha and A beta sensory fibers. Thermal stimuli can assess small, myelinated fibers and unmyelinated sensory nerve function. Low strength alternating electrical currents of selected frequencies are also reported to selectively stimulate different axons. Information on sensory deficits identified using QST has been used in research settings to understand neuropathic pain better and has been investigated for a broad range of other clinical applications, including detection of carpal tunnel syndrome, spinal radiculopathy, evaluating the effectiveness of peripheral nerve blocks, quantification of hypoesthetic and hyperesthetic conditions and differentiation of psychogenic from neurologic disorders. It is theorized could be used to for the noninvasive assessment and quantification to diagnose conditions linked to nerve damage and disease, thus improving patient outcomes by impacting management strategies.

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 motor nerves, cannot be detected by nerve conduction studies. Small fiber neuropathy has traditionally been a diagnosis of exclusion in patients who have symptoms of distal neuropathy and a negative conduction study.

Because QST combines the objective physical sensory stimuli with the individual's response, it is psychophysical in nature and requires individuals who are alert, able to follow directions, and cooperative. Due to the subjective component of testing, psychological factors must be taken into consideration during testing and in evaluating test results, making the results more difficult to standardize and reproduce, thus reducing the degree of objectivity QST can provide.

Clinical Context and Test Purpose

The purpose of current perception threshold, vibration perception testing, pressure-specified sensory testing, and thermal sensory testing is to provide a diagnostic option and a treatment that is an alternative to or an improvement on existing tests, such as standard clinical evaluation and other sensory assessment tests, in individuals with conditions linked to nerve damage or disease (e.g., diabetic neuropathy, carpal tunnel syndrome).

The question addressed in this evidence review is: Does QST improve the net health outcome in patients with conditions linked to nerve damage or disease?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with conditions linked to nerve damage or disease (e.g., diabetic neuropathy, carpal tunnel syndrome).

Interventions
The test being considered is current perception threshold, vibration perception testing, pressure-specified sensory and thermal sensory testing in the outpatient setting.

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. Types of sensory testing include current perception threshold testing. Information on sensory deficits identified using QST has been used in research settings to understand neuropathic pain better. It could be used to diagnose conditions linked to nerve damage and disease, and to improve individual outcomes by impacting management strategies.

Comparators
Comparators of interest include standard clinical evaluation and other sensory assessment tests.

Outcomes
The general outcomes of interest are test accuracy, test validity, symptoms, and functional outcomes.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No direct evidence from comparative studies evaluating the impact of current perception testing on patient management decisions or health outcomes was identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the evidence is insufficient to demonstrate test performance for current perception threshold testing, no inferences can be made about clinical utility.

Review of Evidence

Current Perception Threshold (CPT) Testing
Limited published evidence is available on diagnostic performance. Several studies have compared current perception threshold testing with other testing methods, but sensitivity and specificity have not been reported.

(2012) Ziccardi et al. for example, evaluated 40 patients presenting with trigeminal nerve injuries involving the lingual branch. Patients underwent current perception threshold testing and 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=.02), reaction to heat stimulation (p=.01), and reaction to cold stimulation (p=.004). Also, significant correlations were found between electrical stimulation at 5 Hz and the reaction to heat stimulation (p=.017), to cold stimulation (p=.004), but not to pinprick testing (p=.096).

(2001) Park et al. compared current perception threshold testing with standard references for thermal sensory testing and von Frey tactile hair stimulation in a randomized, double-blind, placebo-controlled trial with 19 healthy volunteers. All current perception threshold measurements showed a higher degree of variability than thermal sensory testing and von Frey measurements but there was some evidence that similar fiber tracts can be measured, especially C-fiber tract activity at 5 Hz, with current perception threshold, thermal sensory, and von Frey testing methods. This study only included healthy volunteers.

Section Summary: Current Perception Threshold Testing
There is insufficient evidence on the accuracy of current perception threshold testing for diagnosing any condition linked to nerve damage or disease using current perception threshold testing. Several studies have compared current perception threshold testing with other testing methods, but sensitivity and specificity were not reported. No direct evidence was identified for the clinical utility of current perception testing and, since there is insufficient evidence on test performance, a chain of evidence for clinical utility cannot be constructed.

Pressure-Specified Sensory Testing

Standard evaluation and management of patients with potential nerve compression, disease, or damage consists of physical examination techniques and may include Semmes-Weinstein monofilament testing and, in more complex cases, nerve conduction velocity testing. Several studies have compared the performance of pressure-specified sensory testing devices.

(2013) Hubscher et al. completed a systematic review evaluated the relationship between QST and self-reported pain and disability in patients with spinal pain.6, Twenty-eight of 40 studies identified used pressure-specified sensory testing devices. The overall analysis found low or no correlations between pain thresholds, as assessed by QST and self-reported pain intensity or disability. For example, the pooled estimate of the correlation between pain threshold and pain was -0.15 (95% confidence interval, -0.18 to -0.11) and -0.16 (95% confidence interval, -0.22 to -0.10) between pain threshold and disability. The findings suggested that QST provides low accuracy for diagnosing patients' level of spinal pain and disability.

(2012) Suokas et al. published a systematic review of studies evaluating QST for painful osteoarthritis; most studies used pressure testing. Reviewers did not report finding any studies evaluating the impact of QST on health outcomes.

(2010) Nath et al. evaluated 30 patients with winged scapula and upper trunk injury and 10 healthy controls. They used the pressure-specified sensory testing device by Sensory Management Services cleared by the FDA to measure the minimum perceived threshold in both arms for detecting 1-point static and 2-point static stimuli. The authors used a published standard reference threshold value for the dorsal hand first web skin and calculated threshold values for both the dorsal hand first web and the deltoid using the upper limit of the 99% normal confidence interval. No published threshold values were available for the deltoid location. Pressure-specified sensory testing was done on both arms of all participants, and electromyography testing only on the affected arms of symptomatic patients. Using calculated threshold values, patients with normal electromyography results had positive pressure-specified sensory testing results on 50% (8/16) of 1-point static deltoid, 71% (10/14) of 2-point static deltoid, 65% (11/17) of 1-point static dorsal hand first web, and 87% (13/15) of 2-point static dorsal hand first web tests. Study findings suggested that pressure-specified sensory testing is more sensitive than needle electromyography in detecting brachial plexus upper trunk injury.

(2000) Weber et al. evaluated the sensitivity and specificity of pressure-specified sensory testing and nerve conduction velocity testing in 79 patients, including 26 healthy controls. The nerve conduction velocity test had a sensitivity of 80% and a specificity of 77%; the pressure-specified sensory testing had a sensitivity of 91% and a specificity of 82%. The difference between the two tests was not statistically significant.

Section Summary: Pressure-Specified Sensory Testing
The available evidence on the diagnostic accuracy of pressure-specified sensory testing for conditions linked with nerve damage or disease is limited, but available studies have reported relatively low diagnostic accuracy. There is insufficient direct evidence on the clinical utility of pressure-specified sensory testing and, because there is insufficient evidence on test performance, an indirect chain of evidence for clinical utility cannot be constructed.
No direct evidence from clinical trials identified has demonstrated that use of the pressure-specified sensory testing resulted in changes in patient management or improved patient outcomes

Thermal Sensory Testing
(2020) Fabry et al. a retrospective study in 245 patients with small fiber neuropathy symptoms compared several methods of evaluating small fibers: skin biopsy to determine intra-epidermal nerve fiber density, thermal sensory testing using QST (Thermotest device), quantitative sweat measurement, laser-evoked potentials, electrochemical skin conductance measurement, and autonomic cardiovascular tests. Thermal sensory testing findings were not statistically different between patients who ultimately received a diagnosis of no SFN and those who received a diagnosis of definite SFN. The sensitivity, specificity, positive predictive value, and negative predictive value of thermal sensory testing were 72%, 39%, 57%, and 55%, respectively. All other testing methods had higher specificity (69% to 96%) but lower sensitivity (15% to 66%) compared to thermal sensory testing. The authors concluded that the best diagnostic strategy was a combination of skin biopsy, thermal sensory testing, laser-evoked potentials, and electrochemical skin conductance measurement (sensitivity, 92%; specificity, 88%; positive predictive value, 90%; negative predictive value, 91%).

(2017) Anand et al. assessed 30 patients with nonfreezing cold injury, or trench foot, described as a peripheral vaso-neuropathy. The authors evaluated use of skin biopsies immunohistochemistry, clinical examination of the feet, including pinprick, as well as QST assessments, and NCSs as diagnostic tools. Abnormal pinprick sensation was reported in 67% of patients. Monofilament perception threshold was abnormal in 63% of patients, 40% for VPT thresholds, and between 67% and 83% for the various thermal thresholds; NCSs showed 23% of subjects had axonal neuropathy. It was noted that performing QST could be difficult for patients with cutaneous hypersensitivity and severe limb pain. No study limitations were reported.

(2015) Lefaucheur et al. compared 5 tests for diagnosing small fiber neuropathy, including QST using a Medoc thermal perception testing device. The QST device was used to assess the warm detection threshold and cold detection threshold. Other tests were laser-evoked potential, sympathetic skin response, and electrochemical skin conductance. The study enrolled 87 consecutive patients being evaluated for definite (n=33) or possible

(n=54) painful small fiber neuropathy. All 5 tests were conducted in a single session. Findings were compared with those for 174 healthy subjects, matched for age and sex. Results of each test were categorized as normal or abnormal, using findings in healthy subjects as the reference range for normal values. All patients with definite small fiber neuropathy and 70% of those with possible small fiber neuropathy had at least 1 abnormal test. Laser-evoked potential was the most sensitive test. However, not all patients were correctly categorized with laser-evoked potential. Fifteen patients with at least 1 abnormal test had normal laser-evoked potential tests, but abnormal warm detection threshold or electrochemical skin conductance tests. Findings of the other 2 tests (cold detection threshold, sympathetic skin response) were redundant. As noted by the authors, their study lacked a definitive criterion standard for small fiber neuropathy with which to compare test findings.

(2008) Devigili et al. assessed 150 patients referred for suspected sensory neuropathy and tested with a Medoc thermal perception testing device. Patients underwent (1) clinical examination, (2) a sensory and motor NCS, (3) warm and cooling thresholds assessed by QST, and (4) skin biopsy with distal intraepidermal nerve fiber density. Based on the combined assessments, neuropathy was ruled out in 26 patients; 124 patients were diagnosed with sensory neuropathy, and of these, 67 patients were diagnosed with small nerve fiber neuropathy. Using a cutoff of 7.63 intraepidermal nerve fiber per millimeter at the distal leg (based on the 5th percentile of controls), 59 (88%) patients were considered to have abnormal intraepidermal nerve fiber (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 indicated that most patients evaluated showed an intraepidermal nerve fiber density of less than 7.63 together with either abnormal spontaneous or evoked pain (clinical examination) or abnormal thermal thresholds (QST). Study authors recommended a new diagnostic criterion standard based on the presence of at least 2 of 3 abnormal results (clinical, QST, intraepidermal nerve fiber density).

Section Summary: Thermal Sensory Testing

Two studies have evaluated the diagnostic accuracy of thermal QST using the same FDA cleared device. Neither found a high diagnostic accuracy of thermal QST but both found the test had potential when used in combination with other tests. An additional study using a different device also supports the potential of thermal QST in combination with other tests. The optimal combination of tests is not well-defined. No studies reporting on the clinical utility for thermal sensory testing were identified, and, because there is insufficient evidence on test performance, an indirect chain of evidence on clinical utility cannot be constructed.

Vibration Perception Testing

(2020) Ferdousi et al. a prospective nonrandomized cohort study by compared several strategies for evaluating DPN severity. A total of 143 patients with diabetes and 30 controls underwent QST with VPT and thermal perception testing, nerve conduction studies, and a measure of corneal nerve loss (corneal confocal microscopy). Compared to controls, VPT was significantly higher in patients with no neuropathy (p=.02), mild neuropathy (p<.0001), and moderate-severe neuropathy (p<.0001), with a sensitivity of 55% and specificity of 90%. VPT findings worsened with worsening neuropathy severity. Thermal testing, nerve conduction testing, and corneal confocal microscopy were also significantly different between patients with DPN and controls (all p<.05). All other testing methods had lower specificity than VPT, but all had higher sensitivity than VPT with the exception of warm perception threshold. The study may have been limited by using Neuropathy Disability Scores to quantify DPN severity, which may explain the abnormal findings among patients categorized as having no neuropathy.

(2019) Papanas et al. assessed the performance of VibraTip against 2 thresholds of the Neuropathy Disability Score for diagnosing distal symmetrical polyneuropathy (DSPN) in 100 consecutive patients with type 2 diabetes. The mean age was 62.3 years, and the mean duration of illness was 12.6 years; 54 subjects were men. Two protocols were used to assess vibration perception: A) 1 foot site at the pulp of the hallux and B) 3-foot sites at the pulp of the hallux and first and third metatarsal head. Neuropathy Disability Score thresholds of ≥ 3 and ≥ 6 were used to establish the diagnosis of DSPN. Compared to the Neuropathy Disability Score ≥ 3 threshold, VibraTip demonstrated a sensitivity, negative predictive value, specificity, and positive predictive value of 91.3%, 92%, 85.2%, and 84% with protocol A; with protocol B, the sensitivity, negative predictive value, specificity, and positive predictive value were 95.6%, 96.1%, 90.7%, and 89.8%. Compared to the Neuropathy Disability Score ≥ 6 threshold, VibraTip demonstrated a sensitivity, negative predictive value, specificity, and positive predictive value of 100%, 100%, 95.2%, and 92.7% with protocol A; with protocol B, the sensitivity, negative predictive value, specificity, and positive predictive value were 100%, 100%, 96.8%, and 95%. The authors conclude that there appears to be no need to explore sites beyond the hallux, and that the device may be especially useful for the exclusion of DSPN. The study is limited by the lack of healthy controls and the use of an outdated version of the Neuropathy Disability Score.

(2018) Azzopardi et al. published a prospective multicenter cross-sectional study comparing 3 types of vibration screening used to diagnose DPN. The study collected data from 100 patients (age range, 40-80 years) who had type 2 diabetes for at least 10 years. Each participant was assessed with a VibraTip (not registered with the FDA), neurothesiometer, and 128-Hz tuning fork in both feet. Vibrations were not perceived by 28.5% of patients when using VibraTip, 21% using a neurothesiometer, and 12% using a tuning fork; a small-to-moderately strong association (Cramer's V, 0.167) was found

between the instruments. The study lacked a criterion standard for assessing neuropathy. The authors concluded that multiple methods of assessment would be necessary to avoid a false-negative diagnosis.

(2017) Goel et al. published a cross-sectional study comparing the diagnostic performance of several testing methods to detect early symptoms of diabetic peripheral neuropathy (DPN).10, Five hundred twenty-three patients with type 2 diabetes between the ages of 18 and 65 years (mean, 49.4 years) were first assessed with the modified Neuropathy Disability Score as the reference standard; then both feet were tested with electrochemical skin conductance, VPT, and Diabetic Neuropathy Symptom Score. For feet electrochemical skin conductance less than 60 μS, VPT, and Diabetic Neuropathy Symptom Score, the sensitivity was 85%, 72%, and 52%, respectively; specificity was 85%, 90%, and 60%, respectively. There was a significant inverse linear relation between VPT and feet electrochemical skin conductance ($r = -0.45$, $p<.001$); feet electrochemical skin conductance was determined to be superior to VPT for identifying early signs of DPN. The study lacked follow-up data.

(2015) Abraham et al. retrospectively reviewed the charts of 70 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who were evaluated with a VPT device (Neurothesiometer). The stimulus was applied to the first finger and toe on each side; the voltage was gradually increased, and patients were asked to state when they first perceived vibration. The threshold for a normal test result was 5 volts or less in the fingers and 15 volts or less in the toes. Data on the results of neurologic examinations were also reviewed, including testing using semiqualitative vibration testing with a 128-Hz tuning fork. Fifty-five (79%) patients had elevated VPT values. Abnormal neurologic findings were more common in CIDP patients with elevated VPT scores (92.7%) at the toes than those without elevated VPT scores (46.7%; $p<.001$). Compared with patients with normal VPT values, patients with elevated VPT values were more likely to meet European Federation of Neurological Societies and Peripheral Nerve Society electrophysiologic criteria for CIDP (51% vs 13%, $p=.01$) and had significantly lower treatment response rates (54% vs 93%, $p=.03$). The authors did not report the sensitivity or specificity of the device compared with standard diagnostic tests. The Neurothesiometer is not FDA approved or cleared.

(2010) Mythili et al. completed a study from India, evaluated 100 patients with type 2 diabetes using a VPT device (Sensitometer; Dhansai Lab). The device is not FDA approved or cleared. The authors reported on sensitivities and specificities for the device and standard nerve conduction study (NCS). For vibration testing, a positive finding (ie, the presence of neuropathy) was defined as patients reporting no vibration sensation at more than 15 volts. According to NCSs, 70 of 100 patients had evidence of neuropathy. VPT had a sensitivity of 86% and a specificity of 76%. Semmes-Weinstein monofilament testing, which was also done, had a higher sensitivity than vibration testing (98.5%) but

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 noted that the simple neurologic examination score appeared to be as accurate as vibration testing. It is not known how similar the Sensitometer device is to FDA-approved vibration threshold testing devices.

Section Summary: Vibration Perception Testing
A few studies have evaluated the diagnostic performance of VPT using devices that are not FDA cleared. In one study, a neurologic examination score had similar diagnostic accuracy to vibration testing, and Semmes-Weinstein monofilament testing had a higher sensitivity than VPT but a lower specificity. The other study did not report sensitivity or specificity for VPT but reported that patients with elevated VPT findings were significantly more likely to meet society criteria for CIDP compared with patients with normal VPT results. Another study compared VPT with electrochemical skin conductance and determined that electrochemical skin conductance was superior for early identification of DPN, a fourth study concluded that multiple methods of assessment were necessary to diagnose DPN , and another study found that VPT findings increased with increasing DPN severity. Another study concluded that VPT may be useful for ruling out a diagnosis of DSPN. No direct evidence for the clinical utility of VPT was identified and because there is insufficient evidence about test performance, an indirect chain of evidence on clinical utility cannot be constructed.

Quantitative Sensory Testing: Miscellaneous
(2019) Georgopoulos et al. systematically reviewed the evidence for ability of quantitative sensory testing (QST) to predict pain, disability and negative affect. Of the 37 eligible studies included in the review (n=3860 participants), 32 were prospective cohort studies and 5 randomized controlled trials. Pain was an outcome in 30 studies, disability in 11 and negative affect in 3. Metaanalysis revealed that baseline QST predicted musculoskeletal pain and disability. Baseline modalities quantifying central mechanisms such as temporal summation (TS) and conditioned pain modulation (CPM) were associated with follow-up pain, whereas baseline mechanical threshold modalities were predictive of follow-up disability. According to the authors, QST indices of pain hypersensitivity might help develop targeted interventions aiming to improve outcomes across a range of musculoskeletal conditions. However, this needs to be validated in additional studies. Assessment of pain processing by quantitative sensory testing (QST) prior to surgery has been proposed as a method to identify patients at risk for postoperative pain, although results have been conflicting.

(2017) O'Leary et al completed a systematic review which investigated whether nervous system sensitization in peripheral musculoskeletal (MSK) conditions predicts poorer clinical outcomes in response to a surgical or conservative intervention. Four electronic databases were searched to identify the relevant studies. Eligible studies had a

prospective design, with a follow-up assessing the outcome in terms of pain or disability. Studies that used baseline indices of nervous system sensitization were included, such as quantitative sensory testing (QST) or questionnaires that measured centrally mediated symptoms. Thirteen studies met the inclusion criteria, of which six were at a high risk of bias. The peripheral MSK conditions investigated were knee and hip osteoarthritis, shoulder pain, and elbow tendinopathy. QST parameters indicative of sensitization (lower electrical pain thresholds, cold hyperalgesia, enhanced temporal summation, lower punctate sharpness thresholds) were associated with negative outcome (more pain or disability) in 5 small exploratory studies. Larger studies that accounted for multiple confounders in design and analysis did not support a predictive relationship between QST parameters and outcome. Two Neurophysiologic Testing and Monitoring Page 14 of 23 UnitedHealthcare Commercial Medical Policy Effective 12/01/2021 Proprietary Information of UnitedHealthcare. Copyright 2021 United HealthCare Services, Inc. studies used self-report measures to capture comorbid centrally mediated symptoms and found higher questionnaire scores were independently predictive of more persistent pain following a total joint arthroplasty. The authors concluded that this systematic review found insufficient evidence to support an independent predictive relationship between QST measures of nervous system sensitization and treatment outcome. Self-report measures demonstrated better predictive ability. According to the authors, further high-quality prognostic research is needed.

(2017) Sangesland et al. conducted a systematic review to evaluate whether assessment of experimental pain processing including measures of central pain mechanisms prior to surgery was associated with pain intensity after surgery. The authors performed systematic database searches for studies that assessed the association between QST and pain after surgery. Studies were included if (1) QST was performed prior to surgery, (2) pain was assessed after surgery, and (3) the association between QST and pain after surgery was investigated. Forty-four unique studies were identified, with 30 studies on 2738 subjects meeting inclusion criteria. Most studies showed moderate to high risk of bias. The majority of the preoperative QST variables showed no consistent association with pain intensity after surgery. Thermal heat pain above the pain threshold and temporal summation of pressure pain were the QST variables which showed the most consistent association with acute or chronic pain after surgery. The authors concluded that QST before surgery does not consistently predict pain after surgery. According to the authors, high quality studies investigating the presence of different QST variables in combination or along with other pain-related psychosocial factors are warranted to confirm the clinical relevance of QST prior to surgery.

(2017) Wang et al. systematically evaluated the diagnostic accuracy of monofilament tests for detecting diabetic peripheral neuropathy. The authors searched EMBASE (OvidSP), MEDLINE (OvidSP), the Cochrane Library, and Web of Science to identify diagnostic accuracy trials of monofilament tests for detecting diabetic peripheral

neuropathy. A total of 19 comparative trials met the inclusion criteria and were part of the qualitative synthesis. Eight trials using nerve conduction studies as the reference standard were selected for the meta-analysis. The pooled sensitivity and specificity of monofilament tests for detecting diabetic peripheral neuropathy were 0.53 and 0.88, respectively. The pooled positive likelihood ratio and negative likelihood ratio were 4.56 and 0.53, respectively. The authors concluded that the review indicated that monofilament tests had limited sensitivity for screening diabetic peripheral neuropathy. According to the authors, the clinical use of the monofilament test in the evaluation of diabetic peripheral neuropathy cannot be encouraged based on currently available evidence.

(2016) Marcuzzi et al. conducted a systematic review to summarize the emerging body of evidence investigating the prognostic value of QST measures in people with low back pain (LBP). An electronic search of six databases was conducted from inception to October 2015. Experts in the field were contacted to retrieve additional unpublished data. Studies were included if they were prospective longitudinal in design, assessed at least one QST measure in people with LBP, assessed LBP status at follow-up, and reported the association of QST data with LBP status at follow-up. Statistical pooling of results was not possible due to heterogeneity between studies. Of 6,408 references screened after duplicates removed, three studies were finally included. None of them reported a significant association between the QST measures assessed and the LBP outcome. Three areas at high risk of bias were identified which potentially compromise the validity of these results. The authors indicated that due to the paucity of available studies and the methodological shortcomings identified, it remains unknown whether QST measures are predictive of outcome in LBP.

(2015) Katz et al. conducted a systematic review of clinical studies to evaluate the use of quantitative sensory testing methods to detect hyperalgesia in chronic pain patients on long-term opioids. Fourteen articles were included in the review; there was one randomized controlled trial, one prospective controlled study, three prospective uncontrolled studies, and nine cross-sectional observation studies. Hyperalgesia measurement paradigms used included cold pain, heat pain, pressure pain, electrical pain, ischemic pain, and injection pain. Although none of the stimuli were capable of detecting patients' hyperalgesia, heat pain sensitivity showed some promising results. The authors concluded that none of the quantitative sensory testing methods reviewed met the criteria of a definitive standard for the measurement of hyperalgesia. According to the authors, additional studies that use improved study design should be conducted.

(2015) Yildirim and Gunduz investigated the ability of Semmes-Weinstein Monofilament testing to detect carpal tunnel syndrome, as well as moderate-to-severe carpal tunnel syndrome using varying thresholds and methods. Clinical and electrophysiological data of 62 patients (124 hands) with a mean age of 49.09±10.5 years were evaluated in this

study. The criteria of 2.83-conventional method yielded a sensitivity of 98% and a specificity of 17% in the diagnosis of carpal tunnel syndrome. The threshold value of 3.22 using a conventional method was found to detect moderate-to-severe carpal tunnel syndrome with high sensitivity (80%) and excellent specificity (93%). A statistically significant difference was observed in the mean strength values of the monofilaments in moderate-to-severe carpal tunnel syndrome hands and hands without carpal tunnel syndrome. The authors concluded that Semmes-Weinstein monofilament testing might be a valuable quantitative method for detecting moderate-to-severe carpal tunnel syndrome. According to the authors, future studies with a larger sample size, as well as further analyses of different threshold abnormalities of moderate-to-severe CTS hands, are needed. According to a National Institute for Health and Care Excellence (NICE) Guidance for VibraTip for testing vibration perception to detect diabetic peripheral neuropathy, the current evidence does not support the case for routine adoption of this device (NICE 2014, Updated March 2015).

(2003) Freeman et al. conducted a case series to determine the differentiation between QST results for small and large fiber sensory loss between individuals with peripheral neuropathy (PN), normal controls and a group of normal subjects who were asked to attempt simulating sensory loss during the testing. The subjects were tested for cold and vibration perception levels with the CASE IV sensory testing system. There were no differences between performance characteristics in the two simulation trials. Responses to null stimuli did not differentiate between groups. Freeman and colleagues concluded, "Test performance characteristics do not permit discrimination among subjects simulating sensory loss, subjects with normal responses, and subjects with peripheral neuropathy."

Summary of Evidence

For individuals who have conditions linked to nerve damage or disease (e.g., diabetic neuropathy, carpal tunnel syndrome) who receive current perception threshold testing, the evidence includes several studies on technical performance and diagnostic accuracy. Relevant outcomes are test accuracy and validity, symptoms, and functional outcomes. The existing evidence does not support the accuracy of current perception threshold testing for diagnosing any condition linked to nerve damage or disease. Studies comparing current perception threshold testing with other testing methods have not reported on sensitivity or specificity. Also, there is a lack of direct evidence on the clinical utility of current perception testing and, because there is insufficient evidence on test performance, an indirect chain of evidence on clinical utility cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have conditions linked to nerve damage or disease (e.g., diabetic neuropathy, carpal tunnel syndrome) who receive pressure-specified sensory testing, the

evidence includes several studies on diagnostic accuracy. Relevant outcomes are test accuracy and validity, symptoms, and functional outcomes. Current evidence does not support the diagnostic accuracy of pressure-specified sensory testing for diagnosing any condition linked to nerve damage or disease. A systematic review found that pressure-specified sensory testing had low accuracy for diagnosing spinal conditions. Also, there is a lack of direct evidence on the clinical utility of current perception testing and because there is insufficient evidence on test performance, an indirect chain of evidence on clinical utility cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have conditions linked to nerve damage or disease (e.g., diabetic neuropathy, carpal tunnel syndrome) who receive VPT, the evidence includes several studies on diagnostic accuracy. Relevant outcomes are test accuracy and validity, symptoms, and functional outcomes. A few studies have assessed the diagnostic performance of vibration testing using devices not cleared by the FDA. Also, there is a lack of direct evidence on the clinical utility of VPT and, in the absence of sufficient evidence on test performance, an indirect chain of evidence on clinical utility cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have conditions linked to nerve damage or disease (e.g., diabetic neuropathy, carpal tunnel syndrome) who receive thermal sensory testing, the evidence includes diagnostic accuracy studies. Relevant outcomes are test accuracy and validity, symptoms, and functional outcomes. Two studies identified evaluated the diagnostic accuracy of thermal QST using the same FDA -cleared device. Neither found a high diagnostic accuracy for thermal QST but both studies found the test had potential when used with other tests. An additional study using a different device also supports the potential of thermal QST in combination with other tests. The optimal combination of tests is currently unclear. Also, there is a lack of direct evidence on the clinical utility of thermal sensory testing and because there is insufficient evidence on test performance, an indirect chain of evidence on clinical utility cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome**.**

In summary, there is insufficient evidence that the use of quantitative sensory testing for the noninvasive assessment and quantification of sensory nerve function is as accurate as conventional tests. Questions remain about reference values in normal populations and the reproducibility of test results. In addition, there is a lack of evidence that use of quantitative sensory testing impacts patient management or improves the net health outcomes.

Practice Guidelines and Position Statements

American Academy of Neurology (AAN)

(2003; reaffirmed 01/2022) The American Academy of Neurology concluded quantitative sensory testing (QST) is probably (level B recommendation) an effective tool for documenting of sensory abnormalities and changes in sensory thresholds in longitudinal evaluation of patients with diabetic neuropathy.

- 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).
- Based on Class II evidence, QST measuring vibration and thermal perception thresholds is probably an effective tool in the documentation of sensory abnormalities in patients with diabetic neuropathy (Level B recommendation).
- Based on several Class II studies, QST is probably useful in documenting changes in sensory thresholds in longitudinal evaluation of patients with diabetic neuropathy (Level B recommendation).
- Although there is data to suggest that QST abnormalities may be detectable in the absence of clinical evidence of neuropathy in diabetic patients, there is no credible prospective evidence that patients with these abnormalities will ultimately go on to develop clinical neuropathy. Thus, whether QST is useful in preclinical neuropathy detection is unproven (Level U recommendation).
- Although there is limited Class II evidence to suggest that QST may be useful in demonstrating altered thresholds for pain perception in patients with various pain syndromes, the sensitivity and specificity of QST in the diagnosis of such disorders are unclear (Level U recommendation).
- Based on limited Class II evidence, QST is possibly useful in demonstrating sensory abnormalities that result from chemotherapy-induced neuropathy (Level C recommendation).
- There is insufficient evidence to support the use of QST in monitoring the development of neuropathy secondary to workplace exposures (Level U recommendation).
- There is insufficient evidence to support the use of QST in the diagnosis of psychogenic sensory loss or malingering (Level U recommendation)
- Based on limited Class II and Class III evidence, QST is possibly useful in demonstrating thermal threshold abnormalities in patients with small fiber neuropathy (Level C recommendation). The clinical utility of demonstrating such abnormalities has yet to be fully defined.
- QST is a potentially useful tool for measuring sensory impairment for clinical and research studies. However, QST results should not be the sole criteria used to diagnose pathology. Because malingering and other nonorganic factors can influence the test results, QST is not currently useful for the purpose of resolving medicolegal matters. Well-designed studies comparing different QST devices and

methodologies are needed and should include patients with abnormalities detected solely by QST.

- Clinical recommendations.
  - QST has contributed and has the potential to further contribute to research of sensory dysfunction. However, its role is only established when it is used as one of several tools in the evaluation of neurologic disorders. In addition to the recommendations made earlier for specific neurologic disorders, the following general recommendations are warranted.
  - QST results should not be the sole criteria utilized to diagnose structural pathology, of either a peripheral or CNS origin.
  - Abnormalities on QST must be interpreted in the context of a thorough neurologic examination and other appropriate testing such as the EMG, nerve biopsy, skin biopsy, or appropriate imaging studies.
  - Laboratories engaged in QST should demonstrate reproducible results on both controls and patients, and only allow adequately trained personnel to perform such testing. Testing should be preceded by standardized instructions to subjects, and be performed in a designated, quiet room with no distractions.

- Research recommendations.
  - Longitudinal investigations demonstrating the significance of abnormalities detected by QST are lacking. Analysis of normal values and reproducibility of testing suggests a danger of interpreting studies not rigidly controlled in methodology, examiner performance, and testing format. With these concerns in mind, the following recommendations are made for the use of QST in research studies.
  - All centers participating in multicenter clinical trials should utilize the same device since normal values from one device cannot be extrapolated to another. Prior to the use of QST testing in multicenter trials, examiners should be trained so that testing is performed in a uniform manner.
  - Future studies should be undertaken to compare different QST devices and testing algorithms.
  - Studies should be undertaken to compare the results obtained by QST with those of nerve conduction studies, neurologic examinations, nerve biopsy, and skin biopsy.
  - Longitudinal investigations are needed to better understand the significance of abnormalities detected solely by QST.

  (*Accessed March 2022*)

American Association of Electrodiagnostic Medicine (AAEM)
(2005) Completed a practice topic on distal symmetrical polyneutopathy: A definition for clinical research:

- The sensitivities and specificities of quantitative sensory testing (QST) varied widely among studies. These psychophysical tests have greater inherent variability, making their results more difficult to standardize and reproduce. Reproducibility of QST varied from poor to excellent. For these reasons, QST was not included as part of the final case definition.
    - There is too much inconsistency among the studies describing the accuracy of QST for its incorporation into the case definition (Level U).
    - The process just described is an attempt to develop formal criteria for a case definition of distal symmetrical polyneuropathy. The principal purpose of the case definition is the identification of cases for clinical research and epidemiological studies. The criteria were formulated using a nominal group process in addition to the best available scientific evidence. Validation and refinement of these criteria in future studies is encouraged. Specifically, additional studies are needed before conclusions can be made regarding the role of QST and skin biopsy in the diagnosis of distal symmetrical polyneuropathy. As quantitative autonomic testing becomes more routinely available, these tests could easily be incorporated into the case definition. Future studies should also compare the criteria delineated in this study with evolving, new criteria. A major aim of the AAN, AAEM, and AAPM&R is that the case definition be modified and refined as new evidence accumulates.

  (*Accessed March 2022*)

American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)
(2005) The AANEM with American Academy of Neurology and American Academy of Physical Medicine & Rehabilitation developed a formal case definition of distal symmetrical polyneuropathy based on a systematic analysis of peer-reviewed literature supplemented by consensus from an expert panel.

- 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 varied widely among studies. (Accessed March 2022)

American Diabetes Association (ADA)
(2021) The American Diabetes Association published an updated standard for microvascular complications and foot care.

- Although temperature and vibration testing are recommended as part of the evaluation of small fiber and large fiber function, respectively, the specific screening tests for diabetic peripheral neuropathy that are described in the standard are manual/clinical rather than quantitative. Therefore, QST does not appear to have a role in the routine evaluation or diagnosis of diabetic peripheral neuropathy. (*Accessed March 2022*)

Regulatory Status
A number of Quantitative Sensory Testing (QST) devices have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. The table b*elow is a list of some noted QST devices, the list is not intended to be all-inclusive.*

Device	Year Cleared	510(k)	Indications
AP-4000 – Air Pulse Sensory Stimulatory	1997	K964815	Pressure-specified sensory testing
Case IV Computer Aided Sensory Evaluator	1992	K910624	Vibration thermal and pressure threshold testing
Cheps			Thermal sensory testing
Contact Heat-Evoked Potential Stimulator (Cheps)	2005	K041908	Thermal sensory testing
Medi-Dx 7000™	1997	K980866	Current perception threshold testing
Neural-Scan	1997	K964622	Current perception threshold testing
Neurometer®	1986	K853608	Current perception threshold testing
NK Pressure-Specified Sensory Device	1994	K934368	Pressure-specified sensory testing
Vibration Perception Threshold (VPT) METER	2003	K030829	Vibration perception testing

PRIOR APPROVAL

Not applicable.

POLICY

Quantitative sensory testing (QST) including, but not limited to current perception threshold (CPT) testing, pressure-specified sensory device testing, vibration perception threshold testing, and thermal threshold testing, is considered **investigational** for all indications as the evidence is insufficient in determining an impact on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0106T Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation
- 0107T Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation
- 0108T Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia
- 0109T Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia
- 0110T Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation
- G0255 Current perception threshold or sensory nerve conduction test, (SNCT) per limb, any nerve

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POLICY HISTORY

Date	Reason	Action
March 2022	Annual Review	Policy Revision
March 2021	Annual Review	Policy Renewed
March 2020	Annual Review	Policy Revised
March 2019	Annual Review	Policy Renewed
March 2018	Annual Review	Policy Renewed
March 2017	Annual Review	Policy Renewed
March 2016	Annual Review	Policy Renewed
April 2015	Annual Review	Policy Renewed
April 2014	Annual Review	Policy Renewed
June 2013	Annual Review	Policy Renewed
August 2012	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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