Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Quantitative Sensory Testing

Description/Background

NERVE DAMAGE AND DISEASE

Nerve damage and nerve diseases can reduce functional capacity and lead to neuropathic pain. There are also racial and ethnic disparities due to biological factors as well as social and environmental contributors in diseases that can lead to neuropathic pain.[1] For example, incidence of neuropathy due to diabetic microvascular complications is higher in minority populations compared to non-Hispanic Whites.[2]

Treatment

There is a need for tests that can objectively measure sensory thresholds. Moreover, quantitative sensory testing (QST) could aid in the early diagnosis of disease. Also, although the criterion standard for evaluation of myelinated, large fibers is the electromyography nerve conduction study, there are no criterion standard reference tests to diagnose small fiber dysfunction.

QUANTITATIVE SENSORY TESTING

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

Quantitative sensory testing systems measure and quantify the amount 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. Currently, 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 (eg, 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), or vibratory stimuli.

The criterion standard for evaluation of myelinated, large fibers is the electromyography nerve conduction study. 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 nerve conduction studies. 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. Touch and vibration measure the function of large myelinated A alpha and A beta sensory fibers. Thermal stimulation devices are used to evaluate pathology of small myelinated and unmyelinated nerve fibers; they can be used to assess heat and cold sensation, as well as thermal pain thresholds. Pressure-specified sensory devices assess large myelinated sensory nerve function by quantifying the thresholds of pressure detected with light, static, and moving touch. Finally, current perception threshold testing involves the quantification of the sensory threshold to transcutaneous electrical stimulation. In current perception threshold testing, typically 3 frequencies are tested: 5 Hz, designed to assess C fibers; 250 Hz, designed to assess A delta fibers; and 2000 Hz, designed to assess A beta fibers. Results are compared with those of a reference population.

Because QST combines the objective physical, sensory stimuli with the subject patient response, it is psychophysical and requires patients who are alert, able to follow directions, and cooperative. Also, to get reliable results, examinations need to include standardized instructions to the patients, and stimuli must be applied consistently by trained staff. Psychophysical tests have greater inherent variability, making their results more difficult to reproduce.

Primarily, QST has been applied in patients with conditions associated with nerve damage and neuropathic pain. A retrospective analysis of a prospective database maintained by the German Research Network on Neuropathic Pain by Forstenpointner et al (2021) compared QST profiles between patients with painful neuropathic conditions (n=332), patients with neuropathic conditions who did not report pain (n=111), and healthy controls (n=112). After extensive QST testing, including thermal, mechanical/vibration, and pain sensitivity, the researchers found similar QST profiles between patients who reported pain and patients who did not report pain, which raises concern about the role of QST in general in decision-making for neuropathic conditions.[3] There have also been preliminary investigations to identify sensory deficits associated with conditions such as autism spectrum disorder, Tourette syndrome, restless legs syndrome, musculoskeletal pain, and response to opioid treatment.

Regulatory Status

A number of quantitative sensory testing (QST) devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Examples are listed in Table 1.

Table 1. FDA-Approved Quantitative Sensory Testing Devices

Device	Manufacturer	Date Cleared	510(k)	Indications
FDA product code: LLN				
Neurometer®	Neurotron	Jun 1986	K853608	Current perception threshold testing
NK Pressure-Specified Sensory Device, Model PSSD	NK Biotechnical Engineering	Aug 1994	K934368	Pressure-specified sensory testing
AP-4000, Air Pulse Sensory Stimulator	Pentax Precision Instrument	Sep 1997	K964815	Pressure-specified sensory testing
Neural-Scan	Neuro-Diagnostic Assoc.	Dec 1997	K964622	Current perception threshold testing
Vibration Perception Threshold (VPT) METER	Xilas Medical	Dec 2003	K030829	Vibration perception testing
Pain Vision, Model PS-2100	Osachi Co., LTD	Jan 2009	K072882	Current perception threshold testing
FDA product code: NTU				
Contact Heat-Evoked Potential Stimulator (Cheps)	Medoc, Advanced Medical Systems	Feb 2005	K041908	Thermal sensory testing
Modified Contact-Heat Evoked Potential Stimulator (Cheps)	Medoc, Advanced Medical Systems	Jun 2005	K051448	Thermal sensory testing
Pathway - Ats/Cheps	Medoc, Advanced Medical Systems	Jan 2006	K052357	Thermal sensory testing

FDA: Food and Drug Administration

Medical Policy Statement

Quantitative sensory testing is considered experimental/investigational. There is insufficient scientific data available in the peer reviewed medical literature to support the effectiveness of this testing.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0106T	0107T	0108T	0109T	0110T	G0255

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Literature searches focus on types of quantitative sensory testing (QST) approved or cleared by the U.S. Food and Drug Administration (FDA). This includes current perception threshold testing, pressure-specified sensory testing, vibration perception threshold (VPT) testing, and thermal threshold testing.

CURRENT PERCEPTION THRESHOLD TESTING

Clinical Context and Test Purpose

The purpose of current perception threshold 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 (eg, diabetic neuropathy, carpal tunnel syndrome).

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 (eg, diabetic neuropathy, carpal tunnel syndrome).

Interventions
The test being considered is current perception threshold testing.

Quantitative sensory testing 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 patient 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.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, receiver operating characteristic [ROC], area under receiver operating characteristic [AUROC]), c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

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).

Review of Evidence
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. For example, Ziccardi et al (2012) evaluated 40 patients presenting with trigeminal nerve injuries involving the lingual branch.[4] 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).

In addition, Park et al (2001) 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.[5] 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.

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 testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients 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 were identified.

Chain of Evidence
Indirect evidence of 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.

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

Clinical Context and Test Purpose
The purpose of pressure-specified sensory testing is to provide a diagnostic option 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 (eg, diabetic neuropathy, carpal tunnel syndrome).

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 (eg, diabetic neuropathy, carpal tunnel syndrome).

Interventions
The test being considered is pressure-specified sensory testing.

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.

Study Selection Criteria
See the information under the first indication.

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).

Review of Evidence
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. For example, a study by Weber et al (2000) evaluated the sensitivity and specificity of pressure-specified sensory testing and nerve conduction velocity testing in 79 patients, including 26 healthy controls.[6] 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 2 tests was not statistically significant.

A study by Nath et al (2010) evaluated 30 patients with winged scapula and upper trunk injury and 10 healthy controls.[7] 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 (CI). 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.

A systematic review by Hubscher et al (2013) evaluated the relation between QST and self-reported pain and disability in patients with spinal pain.[8] 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% CI, -0.18 to -0.11) and -0.16 (95% CI, -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.

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 patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

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. Suokas et al (2012) published a systematic review of studies evaluating QST for painful osteoarthritis; most studies used pressure testing.[9] Reviewers did not report finding any studies evaluating the impact of QST on health outcomes.

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 pressure-specified sensory testing, no inferences can be made about clinical utility.

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.

VIBRATION PERCEPTION TESTING

Clinical Context and Test Purpose
The purpose of vibration perception testing is to provide a diagnostic option 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 (eg, diabetic neuropathy, carpal tunnel syndrome).

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 (eg, diabetic neuropathy, carpal tunnel syndrome).

Interventions
The test being considered is vibration perception testing.

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.

Study Selection Criteria
See the information under the first indication.

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).

Review of Evidence
A study from India, Mythili et al (2010) evaluated 100 patients with type 2 diabetes using a vibration perception testing device (Sensitometer; Dhansai Lab).[10] 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 NCS, 70 of 100 patients had evidence of neuropathy. The vibration perception testing device 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.

Abraham et al (2015) retrospectively reviewed the charts of 70 patients with chronic inflammatory demyelinating polyneuropathy who were evaluated with a vibration perception testing device (Neurothesiometer).[11] 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 patients with CIDP 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.

Goel et al (2017) published a cross-sectional study comparing the diagnostic performance of several testing methods to detect early symptoms of diabetic peripheral neuropathy (DPN).[12] 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.

Azzopardi et al (2018) published a prospective multicenter cross-sectional study comparing 3 types of vibration screening used to diagnose DPN.[13] 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.

Papanas et al (2019) 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.[14] 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 at least ≥ 3 and at least ≥ 6 were used to establish the diagnosis of DSPN. Compared to the Neuropathy Disability Score threshold of at least 3, VibraTip demonstrated a sensitivity, negative predictive value, specificity, and positive predictive value of 91.3%, 92%, 85.2%, and 84% with protocol A, respectively; with protocol B, the sensitivity, negative predictive value, specificity, and positive predictive value were 95.6%, 96.1%, 90.7%, and 89.8%, respectively; 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%, respectively. 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.

A prospective nonrandomized cohort study by Ferdousi et al (2020) compared several strategies for evaluating DPN severity.[15] 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.

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 testing.

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

No direct evidence from clinical trials was identified demonstrating that use of vibration testing resulted in changes in patient management or improved patient outcomes.

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 does not demonstrate the test performance of VPT, no inferences can be made about clinical utility.

Section Summary: Vibration Perception Testing
A few studies have evaluated the diagnostic performance of vibration perception testing using devices that are not FDA cleared. In 1 study, a neurologic examination score had similar accuracy to vibration testing and Semmes-Weinstein monofilament testing had a higher sensitivity than VPT but a lower specificity. A second 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 chronic inflammatory demyelinating polyneuropathy compared with patients with normal VPT results. A third study compared VPT with electrochemical skin conductance and determined that electrochemical skin conductance was superior for early identification of diabetic peripheral neuropathy, a fourth study concluded that multiple methods of assessment were necessary to diagnose diabetic peripheral neuropathy, and a fifth study found that VPT findings increased with increasing diabetic peripheral neuropathy severity. Lastly, a sixth study concluded that VPT may be useful for ruling out a diagnosis of distal symmetrical polyneuropathy. 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.

THERMAL SENSORY TESTING

Clinical Context and Test Purpose
The purpose of thermal sensory testing is to provide a diagnostic option 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 (eg, diabetic neuropathy, carpal tunnel syndrome).

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 (eg, diabetic neuropathy, carpal tunnel syndrome).

Interventions
The test being considered is thermal sensory testing.

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.

Study Selection Criteria
See the information under the first indication.

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).

Review of Evidence
Devigili et al (2008) assessed 150 patients referred for suspected sensory neuropathy and tested with a Medoc thermal perception testing device.[16] 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).

Lefaucheur et al (2015) compared 5 tests for diagnosing small fiber neuropathy, including QST using a Medoc thermal perception testing device.[17] 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. The sensitivity and specificity of each test in the series of 87 patients are shown in Table 2.

Table 2. Sensitivity and Specificity (N=87)

Test	Sensitivity, %	Specificity, %
Warm detection threshold	44.8	91.4
Cold detection threshold	26.4	97.1
Laser-evoked potential	64.4	87.4
Sympathetic skin response	33.3	77.6
Electrochemical skin conductance	49.4	92.5

Adapted from Lefaucheur et al (2015).[17]

Laser-evoked potential was the most sensitive test.[17] However, not all patients were correctly categorized with laser-evoked potential. Fifteen patients with at least one 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.

Anand et al (2017) assessed 30 patients with nonfreezing cold injury, or trench foot, described as a peripheral vaso-neuropathy.[18] The authors evaluated use of skin biopsies immunohistochemistry, clinical examination of the feet, including pinprick, as well as QST assessments, and NCS 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; NCS assessment 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.

A retrospective study by Fabry et al (2020) 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.[19] Thermal sensory testing findings were not statistically different between patients who ultimately received a diagnosis of no small fiber neuropathy and those who received a diagnosis of definite small fiber neuropathy. 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%).

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 testing.

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

No direct evidence from clinical trials was identified demonstrating that use of thermal testing resulted in changes in patient management or improved patient outcomes.

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 of limited evidence about test performance for thermal threshold testing, no inferences can be made about clinical utility.

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.

SUMMARY OF EVIDENCE
For individuals who have conditions linked to nerve damage or disease (eg, 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 (eg, 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 accuracy of pressure-specified sensory testing for diagnosing any condition linked with 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 pressure-specified 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.

For individuals who have conditions linked to nerve damage or disease (eg, diabetic neuropathy, carpal tunnel syndrome) who receive vibration perception testing (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 U.S. Food and Drug Administration FDA. Also, there is a lack of direct evidence on the clinical utility of vibration perception testing 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 (eg, 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 quantitative sensory testing (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 the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, the Blue Cross Blue Shield Association received input from 1 specialty society and 1 academic medical center regarding use of quantitative sensory testing while their policy was under review in 2008. Input from both sources agreed with the policy statement that quantitative sensory testing is considered investigational.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

The American Academy of Neurology (2003; reaffirmed 2022) concluded that 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.[20,21] 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).

American Association of Neuromuscular & Electrodiagnostic Medicine

In 2004, the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) published a technology literature review on QST (light touch, vibration, thermal, pain).[22] The review concluded that QST is a reliable psychophysical test of large- and small-fiber sensory modalities but is highly dependent on the full patient cooperation. Abnormalities do not localize dysfunction to the central or peripheral nervous system, and no algorithm can reliably distinguish between psychogenic and organic abnormalities. The AAEM review also indicated that QST has been shown to be reasonably reproducible over a period of days or weeks in normal subjects, but for individual patients, more studies are needed to determine the maximum allowable difference between 2 quantitative sensory tests that can be attributed to experimental error.

In 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.[23] Quantitative sensory testing 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.

American Diabetes Association

The American Diabetes Association annually updates its standard for retinopathy, neuropathy, and foot care.[24] 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

U.S. Preventive Services Task Force Recommendations

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04393363	Early Detection of Neuropathy and Cognitive Impairment Following Treatment for Haematological Malignancies (NOVIT1)	20	Dec 2030
NCT05546138	Characterization and Prediction of Early Onset Diabetic Peripheral Neuropathy (NeuroPredict)	200	Dec 2029
NCT05959954	Quantitative Sensory Testing to Predict Progression to Nociplastic Pain in Carpal Tunnel Syndrome: A Prospective Cohort Study	120	Nov 2024
Unpublished			
NCT03909464	Exploration Of The Sensitivity And Specificity Of The Pressure-Specified Sensory Device™ (PSSD) For Chemotherapy-Induced Peripheral Neuropathy	26	Nov 2019

NCT: national clinical trial

Government Regulations
National/Local:

National Coverage Determination (NCD) for Sensory Nerve Conduction Threshold Tests (sNCTs) (160.23)
Effective date 4/1/2004

Item/Service Description
A. General
The sNCT is a psychophysical assessment of both central and peripheral nerve functions. It measures the detection threshold of accurately calibrated sensory stimuli. This procedure is intended to evaluate and quantify function in both large and small caliber fibers for the purpose of detecting neurologic disease. Sensory perception and threshold detection are dependent on

the integrity of both the peripheral sensory apparatus and peripheral-central sensory pathways. In theory, an abnormality detected by this procedure may signal dysfunction anywhere in the sensory pathway from the receptors, the sensory tracts, the primary sensory cortex, to the association cortex.

This procedure is different and distinct from assessment of nerve conduction velocity, amplitude and latency. It is also different from short-latency somatosensory evoked potentials.

Effective October 1, 2002, CMS initially concluded that there was insufficient scientific or clinical evidence to consider the sNCT test and the device used in performing this test reasonable and necessary within the meaning of section 1862(a)(1)(A) of the law. Therefore, sNCT was noncovered.

Effective April 1, 2004, based on a reconsideration of current Medicare policy for sNCT, CMS concludes that the use of any type of sNCT device (e.g., “current output” type device used to perform current perception threshold (CPT), pain perception threshold (PPT), or pain tolerance threshold (PTT) testing or “voltage input” type device used for voltage-nerve conduction threshold (v-NCT) testing) to diagnose sensory neuropathies or radiculopathies in Medicare beneficiaries is not reasonable and necessary.

Indications and Limitations of Coverage
B. Nationally Covered Indications
Not applicable.

C. Nationally Noncovered Indications
All uses of sNCT to diagnose sensory neuropathies or radiculopathies are noncovered.
(This NCD last reviewed June 2004.)

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Nerve Fiber Density Measurement

References

1. Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. Curr Diab Rep. Dec 2013; 13(6): 814-23. PMID 24037313
2. Taylor YJ, Davis ME, Mahabaleshwarkar R et al. Racial/ethnic disparities in diabetes care and outcomes: A mixed methods study. Journal of Health Disparities Research and

Practice. 2018; 11(2). https://digitalscholarship.unlv.edu/jhdrp/vol11/iss2/9 Accessed 6/13/24.
3. Forstenpointner J, Ruscheweyh R, Attal N, et al. No pain, still gain (of function): the relation between sensory profiles and the presence or absence of self-reported pain in a large multicenter cohort of patients with neuropathy. Pain. Mar 01 2021; 162(3): 718-727. PMID 32868752
4. Ziccardi VB, Dragoo J, Eliav E et al. Comparison of current perception threshold electrical testing to clinical sensory testing for lingual nerve injuries. J Oral Maxillofac Surg. Feb 2012; 70(2):289-94. PMID 22079068
5. Park R, Wallace MS, Schulteis G. Relative sensitivity to alfentanil and reliability of current perception threshold vs von Frey tactile stimulation and thermal sensory testing. J Peripher Nerv Syst. Dec 2001; 6(4):232-40. PMID 11800047
6. Weber RA, Schuchmann JA, Albers JH et al. A prospective blinded evaluation of nerve conduction velocity versus Pressure-Specified Sensory Testing in carpal tunnel syndrome. Ann Plast Surg. Sep 2000; 45(3):252-7. PMID 10987525
7. Nath RK, Bowen ME, Eichhorn MG. Pressure-specified sensory device versus electrodiagnostic testing in brachial plexus upper trunk injury. J Reconstr Microsurg. May 2010; 26(4):235-42. PMID 20143301
8. Hubscher M, Moloney N, Leaver A et al. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-A systematic review and meta-analysis. Pain. Sep 2013; 154(9):1497-504. PMID 23711482
9. Suokas AK, Walsh DA, McWilliams DF et al. Quantitative sensory testing in painful osteoarthritis: A systematic review and meta-analysis. Osteoarthritis Cartilage. Oct 2012; 20(10):1075-85. PMID 22796624
10. Mythili A, Kumar KD, Subrahmanyam KA et al. A Comparative study of examination scores and quantitative sensory testing in diagnosis of diabetic polyneuropathy. Int J Diabetes Dev Ctries. Jan 2010; 30(1):43-8. PMID 20431806
11. Abraham A, Albulaihe H, Alabdali M, et al. Elevated vibration perception thresholds in CIDP patients indicate more severe neuropathy and lower treatment response rates. PLoS One. 2015;10(11):e0139689. PMID 26545096
12. Goel A, Shivaprasad C, Kolly A, et al. Comparison of electrochemical skin conductance and vibration perception threshold measurement in the detection of early diabetic neuropathy. PLoS One. Sep 2017;12(9):e0183973. PMID 28880907
13. Azzopardi K, Gatt A, Chockalingam N, et al. Hidden dangers revealed by misdiagnosed diabetic neuropathy: A comparison of simple clinical tests for the screening of vibration perception threshold at primary care level. Prim Care Diabetes. Apr 2018;12(2):111-115. PMID 29029862
14. Papanas N, Pafili K, Demetriou M, et al. The Diagnostic Utility of VibraTip for Distal Symmetrical Polyneuropathy in Type 2 Diabetes Mellitus. Diabetes Ther. Jan 2020; 11(1): 341-346. PMID 31782049
15. Ferdousi M, Kalteniece A, Azmi S, et al. Corneal confocal microscopy compared with quantitative sensory testing and nerve conduction for diagnosing and stratifying the severity of diabetic peripheral neuropathy. BMJ Open Diabetes Res Care. Dec 2020; 8(2). PMID 33355206
16. Devigili G, Tugnoli V, Penza P et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain. Jul 2008; 131(Pt 7):1912-25. PMID 18524793

17. Lefaucheur JP, Wahab A, Plante-Bordeneuve V, et al. Diagnosis of small fiber neuropathy: A comparative study of five neurophysiological tests. Neurophysiol Clin. Dec 2015;45(6): 445-455. PMID 26596193
18. Anand P, Privitera R, Yiangou Y, et al. Trench foot or non-freezing cold injury as a painful vaso-neuropathy: clinical and skin biopsy assessments. Front Neurol. Sep 2017;8:514. PMID 28993756
19. Fabry V, Gerdelat A, Acket B, et al. Which method for diagnosing small fiber neuropathy? Front Neurol. 2020; 11: 342. PMID 32431663
20. Shy ME, Frohman EM, So YT, et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. Mar 25 2003;60(6):898-904. PMID 12654951
21. American Academy of Neurology. Quantitative Sensory Testing (reaffirmed 2022). 2003; Quantitative Sensory Testing (aan.com) Accessed 7/13/23.
22. Chong PS, Cros DP. Technology literature review: quantitative sensory testing. Muscle Nerve. May 2004;29(5):734-747. PMID 15116380
23. England JD, Gronseth GS, Franklin G et al. Distal symmetrical polyneuropathy: definition for clinical research. Muscle Nerve. Jan 2005; 31(1):113-23. PMID 15536624
24. ElSayed NA, Aleppo G, Aroda VR, et al. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes-2023. Diabetes Care. Jan 01 2023; 46(Suppl 1): S203-S215. PMID 36507636
25. Centers for Medicare Medicaid Services (CMS). National Coverage Determination (NCD) for Sensory Nerve Conduction Threshold Tests (sNCTs) (160.23). 2004; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=270&ncdver=2&bc=AgAAgAAAAAAAAA%3d%3d& Accessed 6/13/24.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 6/13/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/07	10/2/07	10/20/07	Joint policy established
5/1/09	2/10/09	2/10/09	Routine maintenance
5/1/12	2/21/12	2/21/12	Routine maintenance
5/1/14	2/24/14	3/3/14	Routine maintenance
5/1/16	2/16/16	2/16/16	Routine maintenance
5/1/17	2/21/17	2/21/17	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		Routine maintenance
1/1/22	10/19/21		Routine maintenance. Ref 1,13,17,22 added
1/1/23	10/18/22		Routine maintenance (ls) Ref 1, 2 added
11/1/23	8/15/23		Routine maintenance (jf) Vendor Managed: NA Ref 24 replaced
11/1/24	8/20/24		Routine maintenance (jf) Vendor Managed: NA -Quantitative Sensory Testing added to the background of the policy.

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: QUANTITATIVE SENSORY TESTING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.