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Quantitative sensory testing

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Abstract—*Objective:* This assessment evaluates the clinical utility, efficacy, and safety of quantitative sensory testing (QST). *Methods:* By searching MEDLINE, Current Contents, and their personal files, the authors identified 350 articles. Selected articles utilized computer operated threshold systems, manually operated threshold systems, and electrical threshold devices. The authors evaluated the use of normal values and the degree of reproducibility between the same and different systems. Articles were rated using a standard classification of evidence scheme. *Results:* Because of differences between systems, normal values from one system cannot be transposed to others. Reproducibility of results was also an important concern, and there is no consensus on how it should be defined. The authors identified no adequately powered class I studies demonstrating the effectiveness of QST in evaluating any particular disorder. A number of class II and III studies demonstrated that QST is probably or possibly useful in identifying small or large fiber sensory abnormalities in patients with diabetic neuropathy, small fiber neuropathies, uremic neuropathies, and demyelinating neuropathy. *Conclusions:* 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.

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Quantitative sensory testing (QST) systems have been developed to assess and quantify sensory function in patients with neurologic symptoms or in those at risk of developing neurologic disease. QST measures the detection threshold of accurately calibrated sensory stimuli. Vibratory, thermal, or painful stimuli are often chosen because they relate to distinct neuroanatomic pathways with discrete fiber populations.[1-3] It should be appreciated, however, that natural stimuli rarely activate single types of receptors but rather activate different combinations of receptors.[1]

Quantitative sensory tests are psychophysical in nature, requiring cooperation from the patient. While the sensory stimulus is an objective physical event, the response represents the subjective report from a patient or control subject. If abnormal, the result may signal dysfunction anywhere along the sensory pathway between the receptor apparatus, the primary sensory cortex, and the association cortex. Furthermore, psychological factors figure prominently in sensory function perception. Thus, QST differs from nerve conduction and evoked potential testing in which the stimulus generates an evoked response that is generally independent of cooperation from the subject.[4]

QST devices. QST systems are separable into devices that generate specific physical vibratory or thermal stimuli and those that deliver electrical im-

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pulses at specific frequencies. Vibration is defined as the sensation in response to high-frequency sinusoidal mechanical stimulation. To generate vibration, QST devices typically utilize stimulators with a designed frequency and adjustable amplitude. Frequencies around 200–300 Hz are optimal because Pacinian corpuscles are most sensitive to vibration in this range. Stimulation at 128 Hz is also acceptable for clinical use but is likely to stimulate both Meissner's as well as Pacinian corpuscles.[1] Devices that generate thermal stimuli utilize the Peltier principle, in which the intensity and direction of current flow controls the surface temperature of a test electrode (thermode).[5] The thermode contacts the skin and a subject is asked to report sensation of temperature change or heat pain. An alternative stimulation modality utilizes electrical stimuli of variable frequency and intensity to determine sensory thresholds.

QST methodology. A technical challenge for QST is to determine accurate and reproducible sensory thresholds in a reasonable amount of time. Tests for pain sensation have the additional challenge of minimizing the number of stimuli that are unpleasant to the patient. Algorithms for testing have been developed to facilitate sensory threshold determination. Two general schemes have emerged: the method of limits and the method of levels. In the method of limits, a subject is required to indicate as soon as an increasingly strong stimulus is detected (ascending ramp) or when a decreasing stimulus is no longer detected (descending ramp). In the method of levels, stimuli of defined intensity levels are tested with the subject signaling whether a specific level is detected. In the method of levels, the subject is forced to choose whether or not a stimulus is felt; hence, it is also referred to as a "forced choice" algorithm. An illustration summarizing the methods of limits and levels is shown in the accompanying figure.

In the method of limits, sensory thresholds are dependent on the rate of change of the stimuli (slope of the ramp) and tend to be higher and more variable than for the method of levels.[6-9] This is due in part to a subject's reaction time. A subject needs to consciously perceive the stimulus, process the information, and generate an action to indicate a response. During this period of information processing before the subject indicates a response, the stimulus continues to increase or decrease, leading to a small error in threshold measurement. The method of limits is therefore a "reaction time inclusive" technique. In the method of levels, the response is independent of the speed of response.[10] However, it usually takes longer to complete and is susceptible to errors from decreased attention by the subject.

Normal values. Factors such as electrode size, site of stimulation, and frequency and rate of change of the stimuli all have a direct impact on sensory threshold measurements. Normative values using

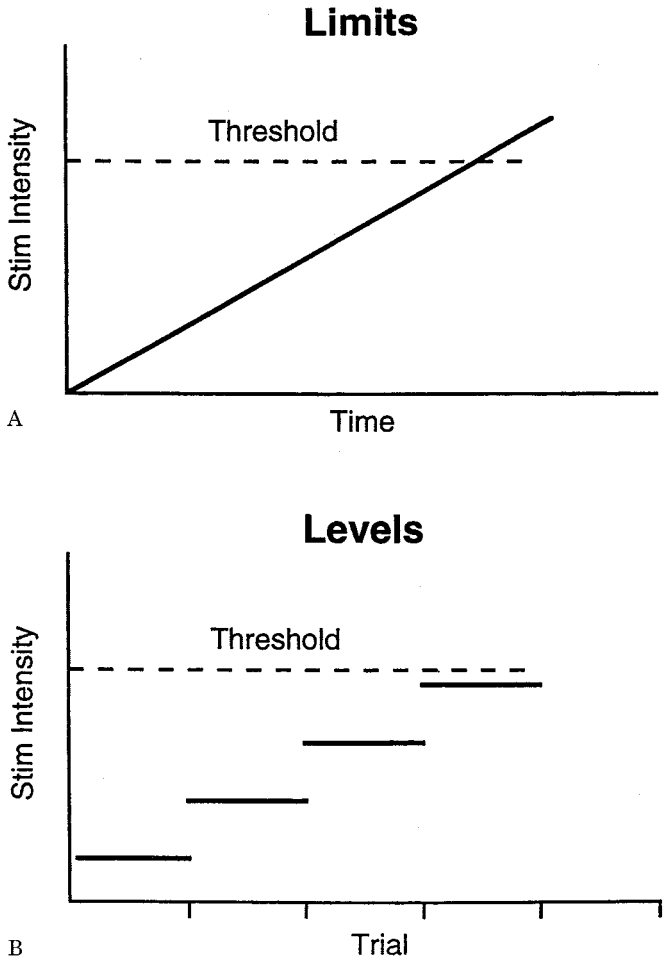

Figure. Summary of the methods of (A) "limits" and (B) "levels."

one system cannot be transposed readily to others. Moreover, the environment of the test laboratory, instructions to the subjects, subjects' motivation, as well as the subjects' age, sex, and ethnicity may also influence the test results. Consequently, each laboratory should in theory generate its own normal values. However, accumulating or comparing normal values is a time-consuming and expensive procedure because more than 500 randomly selected persons may have to participate to obtain a cohort of 300 persons without confounding neurologic disease. Patients of all age strata and sex have to be included. To obtain such a cohort, an initial neurologic evaluation, subsequent testing, and proper statistical analysis must all be performed.[11] Thus, it is not always feasible for individual practitioners or small groups to obtain their own normal values, and they must rely on the published values for their respective apparatus.

Reproducibility. Reproducibility is also an important concern. There is no consensus on how it should be defined. One approach is to use correlation techniques to compare results between separate sessions[12,13] (Class II). Another approach is to calculate

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the repeatability factor "*r*," for which there is a 95% CI that two determinations made on the same subject would differ by less than "*r*." Only intersession differences larger than *r* would be considered "different."[9,14,15]

A reproducible result cannot be obtained without a standardized approach to testing. Users must be adequately instructed by the manufacturer in how to operate the device. The room should be quiet with no distractions. Instructions should be read to the subject by the examiner. The test should always be done in exactly the same manner, and the same examiner should do follow-up testing. There is little published data available to compare the reproducibility of different systems.

Description of the analytical process. In order to evaluate the safety, efficacy, and clinical utility of QST, a panel was assembled based on their expertise in sensory testing. Data for this review were identified by searches of MEDLINE, Current Contents, and references from relevant articles published between 1975 and 2001; numerous articles were also identified through searches of the extensive files of the panel members. Search items "quantitative sensory testing," "QST," and "sensory testing" were used. Abstracts and reports from meetings were included only when they related directly to previously published work. Only English language papers were reviewed. Over 350 articles were reviewed and rated based on the quality of study design. The document was submitted to review internally by the Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology (AAN), AAN member reviewers, AAN Sections, externally by the American Association of Electrodiagnostic Medicine, and through the peer review process of the journal *Neurology*.

Analysis of the evidence. *Diabetic neuropathy.* A consensus conference on diabetic neuropathy recommended that QST be included in diabetic polyneuropathy evaluation.[16] Class III studies in the 1970s suggested that QST for thermal thresholds may detect preclinical diabetic neuropathy.[17] Several Class II and III studies in the diabetic literature measured vibration thresholds with the noncomputer controlled Biothesiometer (Bio Medical Instruments, Newbury, OH), without a clinical examination, to diagnose diabetic neuropathy.[18-20] Other investigators reported abnormalities of thermal QST thresholds in 70% of long-term Type 1 diabetic patients[21] (Class II) and up to 27.5% of newly diagnosed Type 1 diabetic patients[22] (Class II).

In patients with established neuropathy, 280 diabetics and 75 controls were evaluated by neurologic examination, nerve conduction studies, and QST[23] (Class II). Abnormalities in "warm-cold differences" were found in up to 78% and heat pain abnormalities in up to 39% of the diabetics tested. Among the 46 patients with normal clinical examinations, 26 had abnormalities on thermal testing, while only 15 had abnormalities on nerve conduction studies. In another study[24] (Class II), thermal and vibration sensations were assessed with the noncomputerized Marstock device (Somedic AB, Stockholm, Sweden) and Biothesiometer in 47 patients with diabetic neuropathy. Thermal sensation was abnormal in all 22 patients with neuropathy foot ulcers or Charcot joints, 10 of 15 patients with neuropathic pain, and 9 of 10 patients with autonomic neuropathy. Vibration sensation was less often abnormal. In 8 patients, thermal testing was abnormal, while vibration threshold was normal.

In a series of 90 diabetics and 31 healthy controls, the electrical current perception device Neurometer (Neurotron, Incorporated, Baltimore, MD) detected differences between neuropathic and nonneuropathic groups at all test frequencies (5 Hz, 250 Hz, and 2 kHz)[25] (Class II). The current perception threshold (CPT) to 2kHz stimulation correlated best with vibratory thresholds, and CPT to 5Hz stimulation correlated with thermal (warm) discrimination. In a separate study, investigators compared clinical examination, vibratory perception (Vibrameter), and CPT (Neurometer) in 33 healthy controls, 23 patients with diabetes and no clinical neuropathy, 22 patients with diabetes and overt neuropathy, and 38 patients with a diabetic duration of more than 20 years[26] (Class II). Correlation between clinical neuropathy scores and both vibratory perception thresholds (VPT) (method of limits) and CPT (method of limits and levels) were only moderate. Correlation between VPT and CPT were maximal at 2,000 Hz for CPT ($r = 0.61$). Correlation between CPT at 250 Hz or 5 Hz with clinical evaluation of neuropathy were less than for 2,000 Hz.

In all of these studies, the central concern has been the sensitivity of QST in diagnosing diabetic neuropathy. Because of the subjective nature of QST, there are concerns about whether QST by itself can be used to diagnose diabetic neuropathy. The Rochester Diabetic Neuropathy Study addressed this issue utilizing QST with the computerized CASE IV device (WR Medical Electronics, Stillwater, MN)[27] (Class II). In this study, 195 diabetic patients representative of the community population were followed longitudinally for up to 12 years. Based on the study results, the investigators concluded that QST should not be used as the sole criteria for diagnosing diabetic neuropathy, but should be accompanied by at least one other defined abnormality before the diagnosis of diabetic neuropathy can be made.

QST in diabetic neuropathy may be valuable in providing quantitative data in longitudinal natural history or clinical trial studies, in which thresholds can be measured over time. Studies have demonstrated improved thermal[13] and vibratory[28] thresholds with tight control of blood glucose levels (Class II). In the Rochester Diabetic Neuropathy Study, where patients were followed for a 12-year period, QST for vibration was a good measure of the longitu-

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dinal worsening, but a more useful measure was a composite score that included vibration perception threshold, clinical examination, nerve conduction values, and heart rate response to deep breathing[27] (Class II).

- 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).

Small fiber sensory neuropathy. In an evaluation of 20 patients with idiopathic painful small fiber neuropathy utilizing the CASE IV device, investigators found abnormal QST thresholds to cold in 82% and to vibration in 60%. By comparison, QST thresholds were abnormal in 17% of healthy controls[29] (Class II). There was no significant correlation between QST threshold percentiles and either the mean intraepidermal nerve fiber density (IENF) on skin biopsy specimens, or with clinical grade. In a subsequent series in which a reduction in IENF density was a requirement for entry into the study, 57% of 23 patients tested with CASE IV had abnormal QST threshold to cold and 30% had abnormal QST threshold to vibration[30] (Class III).

In a retrospective investigation, QST was performed on 15 of 39 with idiopathic small fiber neuropathy[31] (Class III). Five patients had an abnormality on cold thermal testing and five had abnormalities on vibratory testing. In a comparison of different modalities for detection of suspected small fiber neuropathy, 10 of 15 patients (67%) had abnormal QST thermal testing, while 12 of the 15 (80%) had an abnormal clinical examination consistent with a small fiber neuropathy, 12 of 15 had abnormal quantitative sudomotor axon reflex testing (QSART), and 9 of 12 (75%) had abnormal heart rates with deep breathing[32] (Class III). Ninety-three percent of patients were found to have abnormalities on at least one test, a higher percentage than was detectable using any one individual test. Taken together, these studies suggest that QST is most effective when used in concert with other modalities of neuropathy evaluation.

- 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.

Pain syndromes. In a study of 35 patients with postherpetic neuralgia, investigators utilized a Somedic Thermotest (Somedic AB) to evaluate both pain and thermal thresholds. They found that the lower the threshold at which a person experienced heat as pain, the more likely that the warm or cold thresholds were likely to be normal or only mildly abnormal. Similar results were found with cold pain testing, though not to the same degree as with heat pain[33] (Class II). The authors postulated that these data demonstrated that activity in nociceptors still connected to both peripheral and central targets contributed to the pain. The same group used the computerized TSA-2001 QST device (Medoc Ltd, Ramat Yishai, Israel), along with epidermal nerve fiber counts, to identify a subgroup of postherpetic neuralgia patients who have less peripheral nerve damage. In this series, 11 of 17 patients developed increased pain following capsaicin application, and they had relatively preserved thermal sensory function compared with those who did not respond to capsaicin.[34]

Fifty-five percent of 31 patients with the clinical diagnosis of reflex sympathetic dystrophy had heat-induced hyperalgesia[35] (Class II). In another study, the TSA-2001 was used to demonstrate paradoxical heat sensation to cold stimuli in 42% of 46 patients with end stage renal disease[36] (Class II). Finally, thermal hyperalgesia is part of the diagnostic criteria for disorders such as the Angry Backfiring C nociceptors (ABC) syndrome[37] and the triple cold syndrome (Cold hyperalgesia, Cold hypoesthesia, and Cold skin).[38]

Most of the reports mentioned above concern themselves with the diagnosis of pain and are lacking in longitudinal follow up. Moreover, the specificity of thermal pain threshold determination was not adequately addressed. Given the complex psychosocial and psychological components related to individual pain thresholds, the diagnosis of pain syndromes cannot be made solely based on QST. There is insufficient evidence to support the use of QST in monitoring heat pain thresholds in response to therapeutic agents.

- 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).

Toxic neuropathies. Several studies have used QST testing to screen populations for evidence of neurotoxicity in the work place and to investigate neurotoxicity from medications. One group utilized

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the Vibratron II, clinical examinations, and nerve conduction velocities in a Class II study to determine the incidence of large fiber sensory neuropathy in 21 cancer patients treated with a combination of taxol and cisplatin.[39] Twenty of 21 patients developed at least one abnormal finding on clinical examination. Loss of ankle reflexes occurred in 90%, and 76% developed paresthesias or numbness in the feet within 7 days of the onset of treatment. Following treatment, QST vibratory thresholds rose above baseline values in 17 patients (81%) at the great toe and in 11 patients (52%) at the index finger. QST changes correlated with the cumulative taxol dose at both the great toe (r = 0.68) and index finger (r = 0.62) (Class II).

There are several Class IV studies evaluating the application of QST in the workplace.[40-42] There is a paucity of literature on how often workers with abnormal QST thresholds go on to develop clinically evident neuropathy or other neurologic abnormalities, based on clinical examination or other forms of testing. Thus, the significance of the QST findings detected in these studies is unknown.

- 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).

Uremic neuropathy. Uremic neuropathy presents as a predominantly sensory neuropathy, but unlike diabetic neuropathies, it predominantly affects large, myelinated fibers. Abnormalities in vibratory function were detected in 45% of 97 patients with chronic renal failure, but not in a control group of 85 subjects[43] (Class II). However, QST was less sensitive in detecting abnormality than nerve conduction study. In another series of uremic patients, vibration perception threshold was compared with clinical signs of neuropathy and nerve conduction studies in patients with chronic renal failure[44,45] (Class III). Vibration perception threshold was abnormal in 36% of 64 patients and was again less sensitive than nerve conduction study.

- QST is possibly useful in identifying large sensory fiber dysfunction in uremic patients based on limited Class II and Class III evidence (Level C recommendation).

Acquired and inherited demyelinating neuropathies. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) affects primarily large diameter nerves. Vibratory thresholds were abnormal in 53 of 75 patients using a CASE III device (precursor of the CASE IV), whereas cold thresholds were abnormal in only 11 of 34 patients[46] (Class III). In a Class III study of 37 patients with Charcot Marie Tooth disease type 1A evaluated with CASE IV, patients with more severe clinical sensory loss tended to have higher QST thresholds. Correlation of the QST threshold for vibration with the clinical examination for position sense was particularly significant in the feet (r = 0.8). Correlation was also detected (r = 0.5) between clinical loss of pain and temperature sensation and QST thresholds for cold in the feet.[47] No longitudinal study is available.

- The usefulness of QST in the diagnosis or prognosis of patients with acquired or inherited demyelinating neuropathy is unproven due to the limited Class III evidence available (Level U recommendation).

Malingering. As is the case with other psychophysical tests, such as audiometry and visual acuity, detecting malingerers or other nonorganic abnormalities is a challenge for QST devices. In studies measuring the variance of successive temperature transients, a larger variance was detected for "feigners," who were asked to pretend to be hypoesthetic, than was obtained for those with true disease or controls.[9,48] The use of "null stimuli" in testing algorithms is sometimes effective, though not infallible in the detection of malingerers.[48,49] There is no Class III or better study to validate the use of QST in the diagnosis of malingering in patients who feign sensory loss.

- There is insufficient evidence to support the use of QST in the diagnosis of psychogenic sensory loss or malingering (Level U recommendation).

Legal proceedings. Malingering and other nonorganic factors can influence the testing results, and there is currently no reliable means to account for these factors. At this time, QST is not sufficiently established to justify utilization of this technique for the purpose of resolving medicolegal matters (Level U recommendation). Therefore, it should not be used in legal proceedings.

Summary and recommendations. *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

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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.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all circumstances involved.

Appendix: Definitions for classification of evidence

Class I. Evidence provided by a prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class II. Evidence provided by a prospective study of a narrow spectrum of persons with the suspected condition, or a well designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared with a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class III. Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

Class IV. Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Definitions for strength of recommendations

Rating of Recommendation	Translation of evidence to recommendations
A: Established as useful/predictive or not useful/predictive for the given condition in the specified population	Level A rating requires at least one convincing Class I study or at least two consistent, convincing Class II studies
B: Probably useful/predictive or not useful/predictive for the given condition in the specified population	Level B rating requires at least one convincing Class II study or at least three consistent Class III studies
C: Possibly useful/predictive or not useful/predictive for the given condition in the specified population	Level C rating requires at least two convincing and consistent Class III studies
U: Data inadequate or conflicting. Given current knowledge, test/predictor is unproven	

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