

Simple Screening Tests for Peripheral Neuropathy in the Diabetes Clinic

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OBJECTIVE — The utility of rapid and reliable sensory tests appropriate for the diagnosis of neuropathy in the diabetes clinic, rather than as prognostic tools for the prediction of foot complications, has been unclear because of limitations inherent in previous studies. Although clinical practice guidelines recommend annual screening for neuropathy, they are unable to support specific recommendations for screening maneuvers because of a lack of evidence for the validity of screening tests in the medical literature. The objective of this study was to assess the operating characteristics of four simple sensory screening maneuvers as compared with standardized electrophysiological tests in the diagnosis of distal symmetrical polyneuropathy.

RESEARCH DESIGN AND METHODS — We assessed four simple tests (the 10-g Semmes-Weinstein monofilament examination [SWME], superficial pain sensation, vibration testing by the on-off method, and vibration testing by the timed method) in 478 subjects with independent blinded evaluations compared against the criterion standard of nerve conduction studies. We present receiver-operating characteristic (ROC) curves, positive and negative likelihood ratios, and sensitivity and specificity values for each test.

RESULTS — The four simple screening maneuvers reveal similar operating characteristics. Cutoff points by ROC curve analyses reveal that a positive or abnormal test is represented by five incorrect responses of eight stimuli applied. A negative or normal test is represented by one or fewer incorrect responses of eight stimuli applied. By these criteria, the point estimates of the positive likelihood ratios for vibration testing by the on-off method, vibration testing by the timed method, the SWME, and superficial pain sensation test are 26.6, 18.5, 10.2, and 9.2, respectively. The point estimates of the negative likelihood ratios are 0.33, 0.51, 0.34, and 0.50, respectively. The screening tests showed comparable sensitivity and specificity results. The 10-g SWME, superficial pain test, and vibration testing by the on-off method are rapid, each requiring ~60 s to administer. The timed vibration test takes longer, and the interpretation is more complicated. The combination of two simple tests (e.g., the 10-g SWME and vibration testing by the on-off method) does not add value to each individual screening test.

CONCLUSIONS — Annual screening for diabetic neuropathy should be conducted using superficial pain sensation testing, SWME, or vibration testing by the on-off method. The reported operating characteristics for each sensory modality can be applied to positive findings on the physical examination of individual patients to predict the likelihood of neuropathy.

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Abbreviations: AUC, area under the curve; DPN, diabetic polyneuropathy; NCS, nerve conduction study; ROC, receiver-operating characteristic; SWME, Semmes-Weinstein monofilament examination; UHN, University Health Network.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The chronic peripheral neuropathy associated with diabetes represents an insidious and progressive process, the pathological severity of which is poorly linked with the development of symptoms (1,2). It is the component cause that initiates the pathophysiological pathway to leg ulceration and amputation, and by itself it is sufficient cause for painful paresthesia, sensory ataxia, and Charcot deformity (3). Screening and the early identification of the neuropathic process offer a crucial opportunity for the patient with diabetes to actively alter the course of suboptimal glycemic control and to implement improved foot care before the onset of significant morbidity. The Diabetes Control and Complications Trial (4) demonstrated that intensive insulin therapy in type 1 diabetes reduced the risk of developing clinical and electrophysiological deficits of diabetic neuropathy by 61%; similarly, the U.K. Prospective Diabetes Study reported a relative risk of 0.60 (95% CI 0.39–0.94, $P = 0.0052$) for neuropathy as measured by a biothesiometer for a mean of 15 years of follow-up in the intensive policy group (5). Furthermore, independent electrophysiological studies have demonstrated the relationship between glycated hemoglobin and the presence and severity of neuropathy (6). In addition, potential new therapies, such as aldose reductase inhibitors and protein kinase C inhibitors, stress the importance of early intervention facilitated through a valid screening mechanism in the diabetes clinic (7–11).

Clinical trial evidence for the efficacy of screening strategies demonstrated reduced outcomes of amputation and ulceration (7,8,12–16), and, consequently, screening for neuropathy is recommended in clinical practice guidelines (17,18). The current level of evidence for the optimal screening method, however, is limited by study cohorts with a restricted spectrum of disease, the lack of independently blinded examiners for individual screening tests, and the inconsistent use of an objective criterion standard. In addition, inconsistent reporting of the required statistical operating characteristics limit the clinical applicability of the results. Nerve conduction studies (NCSs) are strongly correlated with underlying structural changes and are the

Table 1—Baseline demographics of 478 subjects according to stage of neuropathy

Variable	Stratum 1 (reference subjects)	Stratum 2 (without nephropathy)	Stratum 3 (mild nephropathy)	Stratum 4 (moderate nephropathy)	Stratum 5 (severe nephropathy)
n (%)	52 (11)	81 (17)	94 (20)	109 (23)	142 (30)
Sex (% male)	46	68	65	75	65
Age (years)	37.6 ± 10.4	51.0 ± 10.8	56.8 ± 8.5	57.7 ± 10.1	57.0 ± 9.5
Type 1 diabetes	0	19	13	13	20
Diabetes duration (years)	0	9.4 ± 9.9	11.2 ± 11.0	13.3 ± 10.7	15.8 ± 11.7
HbA _{1c} (%)	5.5 ± 0.04	8.3 ± 1.7	8.1 ± 1.9	8.0 ± 1.7	8.7 ± 1.6
Neuropathy duration (years)	0	0	2.9 ± 4.1	4.2 ± 4.3	5.1 ± 5.0
Foot ulcer history	0	0	9	27	64
Retinopathy	0	11	10	20	36
Nephropathy	0	18	14	25	43
Erectile dysfunction (% men)	1.9	27	43	56	49
Postural drop in blood pressure (%)	0	9	16	27	28

Data are means ± SD or %. Strata are defined on the basis of the clinical scoring system.

least subjective and most reliable single criterion standard (19–24).

This study evaluates four standard simple screening maneuvers appropriate for the diabetes clinic (i.e., 10-g Semmes-Weinstein monofilament examination [SWME], superficial pain, vibration testing by the on-off method, and vibration testing by the timed method) for the detection of neuropathy using NCSs as the criterion standard in a large mixed population of nondiabetic reference subjects and diabetic patients with a spectrum of neuropathy.

RESEARCH DESIGN AND METHODS

The study was conducted at the Toronto General Hospital/University Health Network (UHN) in the Diabetic Neuropathy Research Clinic from June 1998 to August 1999. Approval from the UHN Research Ethics Board was obtained before commencing the study. Informed consent for the study was obtained from each subject by an unblinded observer.

Selection of patients

The inception cohort was ascertained from four different sources: unselected patients attending a diabetes clinic with unknown neuropathy status, patients referred to the Diabetic Neuropathy Research Clinic for suspected neuropathy, people with unknown neuropathy status who were recruited through advertisements in the community for patients with diabetes, and reference subjects.

Study protocol

All subjects underwent the following procedures: 1) a comprehensive medical and neu-

rological evaluation to exclude neuropathy of other etiologies (e.g., familial, alcoholic, nutritional, and uremic) performed by the unblinded observer who had obtained the informed consent; 2) standardized bilateral NCSs—including motor (peroneal, tibial, median, and ulnar) and sensory (sural, median, and ulnar) nerves—performed by technicians who were blinded to the status of the subject; 3) a 10-g SWME performed by an independent observer who was blinded to all other results, including history and physical examination; and 4) a vibration sense (by the on-off and timed methods) and superficial pain sensation test performed by three different independent observers per patient blinded to all other results, including history and physical examination.

Each subject was assessed by at least seven different examiners during a 4- to 5-h stay in the clinic. Triplicate screening tests were performed in a subset of subjects using nine different examiners. All data were entered on standardized forms identifying subjects only by number, date of birth, and initials. Data entry was performed by a clerk without knowledge of the category of the subject. Prior to commencing the trial, training and practice sessions were held for all examiners to standardize the testing methods for each screening test.

Clinical stratification method

A clinical stratification method was used to ensure a broad spectrum of patients in the study. The decision was made to close recruitment when the smallest stratum contained 50 subjects. Subjects were graded according to neuropathy severity

using 6 symptom scores (the presence or absence of foot pain, numbness, tingling, weakness, imbalance, and upper limb symptoms), 8 reflex scores (bilateral knee and ankle reflexes, each graded as absent, reduced, or normal), and 5 physical examination scores (the presence or absence of pinprick, temperature, light touch, vibration, and position sense) for a total of 19 possible points. Grading was stratified such that ≤5 indicated no neuropathy, 6–8 indicated mild neuropathy, 9–11 indicated moderate neuropathy, and ≥12 indicated severe neuropathy.

Sensory testing methods

For each testing modality, the patient was given a reference sensation by application of the stimulus to the sternum and then asked the nature of the sensation perceived. When the nature of the sensation was per-

Table 2—Cochran-Mantel-Haenszel χ^2 P values for microvascular complications in different strata

Complication	χ^2 Statistic	P
History of foot ulcers	23.60	0.001
Retinopathy	31.44	0.001
Nephropathy	11.52	0.001
Erectile dysfunction	44.78	0.001

Data are %. The χ^2 statistic, which is used to describe associations between categorical variables, represents here the presence of a complication in subjects with clinical DPN compared with diabetic subjects without neuropathy. The P values indicate a significant association between the complication and presence of DPN. The prevalence of individual complications are seen in Table 1.

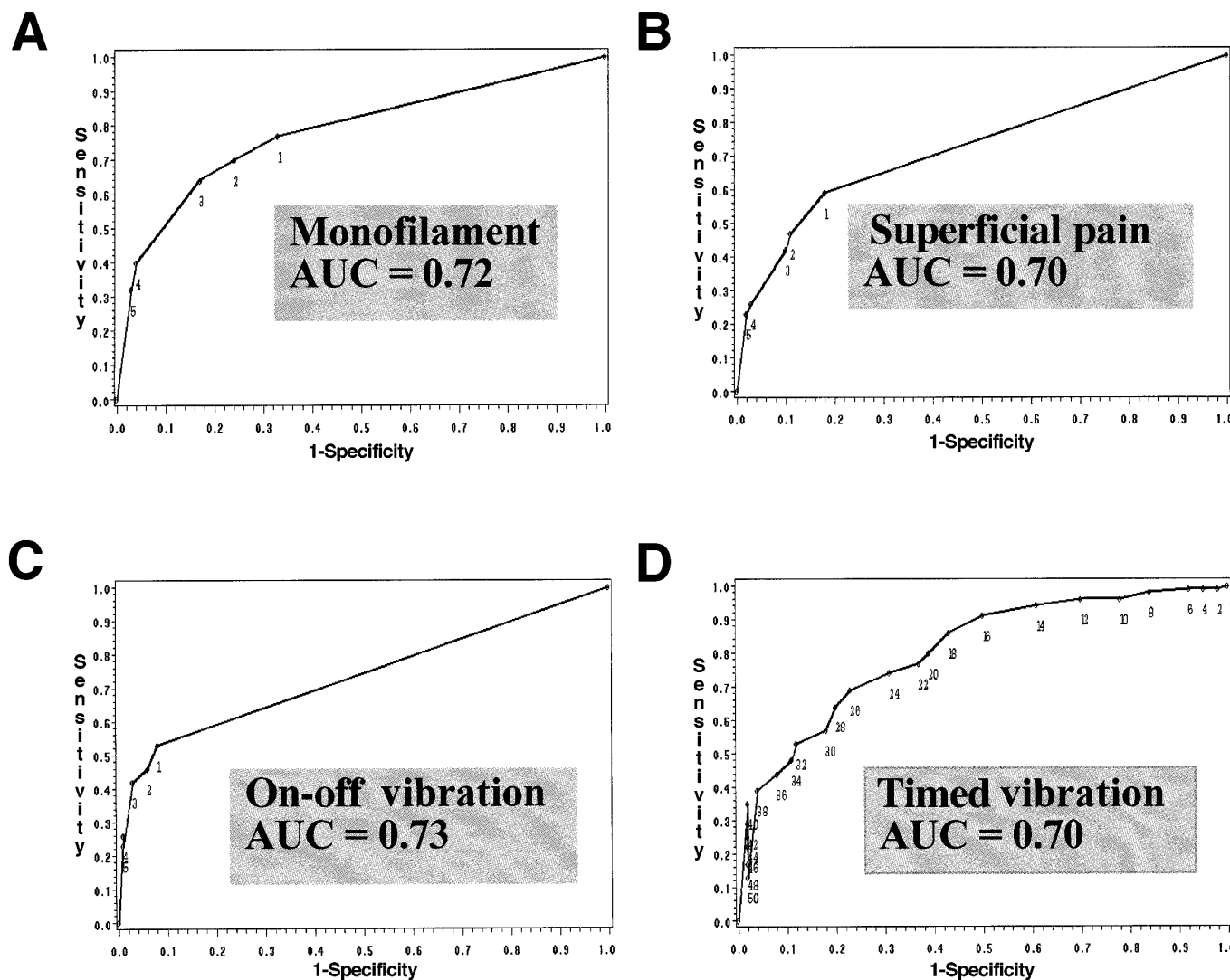


Figure 1—ROC curves for each simple test compared with NCS (gold standard) plotting the sensitivity versus 1-specificity (the false-positive rate) for different test cutoff points. The AUC values are for the cutoff points listed in Table 3 (values derived from multiple linear regression modeling).

ceived accurately on the sternum, the subject was asked, with eyes closed, to describe the sensations experienced sequentially at the sites described below.

The SWME was conducted using a 5.07/10-g monofilament applied to a non-callused site on the dorsum of the first toe just proximal to the nail bed. It was repeated four times on both feet in an arrhythmic manner by an independent examiner, who circled correct responses on the scoring sheet and then added the number of errors. The SWME threshold was defined as the total number of times the application of the 10-g monofilament was not perceived by the subject, and it varied from 0 to 8.

Vibration testing by the on-off method was conducted using a 128-Hz tuning fork applied to the bony prominence bilaterally situated at the dorsum of the first toe just proximal to the nail bed. The patient was asked to report the perception of both the start of the vibration sensation and the cessation of vibration on dampening. The testing was conducted twice on each toe, and correct responses were circled on a standardized sheet. The vibration testing threshold was defined as the total number of times the application of the vibrating tuning fork and the dampening of vibration was not felt, with scores varying between 0 and 8.

Vibration testing by the timed method was conducted using a 128-Hz tuning fork

applied to the same bony prominences bilaterally situated at the dorsum of the first toe. The patient was asked to report the time at which vibration diminished beyond perception. The tuning fork was then applied to the dorsal aspect of the distal phalanx of the examiner's thumb. The time (in seconds) at which vibration sensation diminished beyond the examiner's perception was then recorded on a standardized form. The values from both sides were added to provide a single score for statistical analyses.

Superficial pain sensation was conducted using a sterile Neurotip (Owen Mumford, Oxford, U.K.) applied four times in an arrhythmic manner to the two sites described for the SWME. The superficial

Table 3—Positive and negative likelihood ratios and sensitivity and specificity values for four simple screening tests

Examination maneuver	≥5 out of 8 attempts insensate		≤1 out of 8 attempts insensate	
	Likelihood ratio for an abnormal test	Specificity (%)	Likelihood ratio for a normal test	Sensitivity (%)
Vibration (on-off method)	26.6	99	0.51	53
Monofilament	10.2	96	0.34	77
Superficial pain	9.2	97	0.50	59
Vibration (timed)	18.5	98	0.33	80

Sensitivity is derived from the threshold of the test for normality, whereas specificity is derived from the threshold of the test for abnormality. The timed vibration was designed so that for normal subjects, the persistence of vibration is up to 10 s per toe (as described in the Diabetes Control and Complications Trial), and for abnormal subjects, the persistence of vibration is >20 s per toe. Vibration is tested in two different ways, as described in RESEARCH DESIGN AND METHODS.

pain threshold was defined as the total number of times the application of the pain sensation was not perceived, with scores varying from 0 to 8.

Measurements of each sensory modality and the NCSs were performed by separate observers blinded to the subject's history and physical examination and to the results of the other tests. The physician performing the complete history and physical examination was unaware of the results of the individual sensory parameters tested and the NCSs.

The interobserver variability for each sensory modality was assessed by triplicate independent blinded testing in a subset of at least 10 subjects assessed by three different examiners.

Criterion standard

Standardized techniques for NCSs were applied with temperature control and fixed distances. Measurements of latencies, distances, and amplitudes were assessed in a standard fashion using onset latencies and baseline-to-peak amplitudes. Initial positive peak (if present)–to–negative peak measurements were conducted for sensory responses. *F* waves were generated for all motor nerves, and minimal, reproducible latencies were measured. Conduction velocities were calculated for motor and sensory nerves.

All conduction velocity and distal amplitude values for the NCSs were given a score of 0 for normal and 1 for abnormal. The mean reference values \pm 2 SD were taken as the normal range. The maximum NCS score if all parameters were abnormal was 28 points (16 motor and 12 sensory). The total NCS score was defined as the sum of the number of abnormal values.

Statistical analyses

The χ^2 test was used to detect differences of clinical characteristics across the five strata. $P \leq 0.01$ was considered statistically significant.

Based on the binomial distribution, the sign test justifies the use of eight responses for each sensory modality score (25). On stimulation with a testing modality, the probability of seven of seven random correct responses by chance alone is 0.0078, which is acceptable using the customary cutoff chosen as a criterion for statistical significance.

Receiver-operating characteristic (ROC) curves were generated for each sensory modality, and area under the curve (AUC) and optimal cutoff points were determined.

Comparison of the different screening methods was assessed using Spearman's rank-correlation coefficient and Pearson's correlation coefficient when applicable. Logistic regression modeling was conducted to confirm the AUC measurements for the cutoff points of each sensory modality test as single predictors of NCS scores. The modeling was repeated by controlling for neuropathy strata, which afforded the opportunity to assess 1) whether a sensory modality test was a reliable predictor of NCS scores and 2) whether the observed association was real or spurious. Positive and negative likelihood ratios were evaluated and interpreted in terms of the odds of having an abnormal test result in a neuropathy group (i.e., patients having abnormal NCS scores) compared with a nonneuropathy group (i.e., patients having normal NCS scores). For the subset of subjects who had triplicate screening tests, Wilcoxon's rank-sum test (using the Kruskal-Wallis test) was used for the reproducibility of the screening tests.

RESULTS — The demographic profile of the study population is shown in Table 1. Significant differences were observed between the defined clinical strata as follows: age of patients (with the reference group being younger), duration of diabetes (longer for more severe neuropathy, $P < 0.0001$), and duration of neuropathy (longer for more severe neuropathy, $P < 0.0001$). Contingency table analyses revealed a significantly increasing prevalence of history of foot ulcer, retinopathy, nephropathy, and erectile dysfunction with stage of neuropathy. The χ^2 and P values are shown in Table 2.

The ROC curve for each sensory test is shown in Fig. 1. The AUC is indicated on each curve. No significant differences for AUC were found for any of the simple screening tests.

Logistic regression modeling determined the optimal cutoff points for the sensitivity and specificity values and, thus, the positive and negative likelihood ratios as shown in Table 3. Of the four sensory modalities, vibration testing by the on-off method had the highest positive likelihood ratio and a low negative likelihood ratio. The specificity was 99% for five or more insensate responses. Sensitivity was 56% for two or more insensate responses, and specificity remained high at 92% for this test. Both the 10-g monofilament and superficial pain modalities had comparable likelihood ratios (10.2 and 9.2), but better sensitivity was observed with the 10-g monofilament (40%) and better specificity was observed for superficial pain (97%). Vibration testing by the timed method had comparable results. For this method, the value of 20 was derived from a maximum of 10 s per toe for the lower cutoff for the necessary likelihood ratios, and 40 was derived from a maximum of 20 s per toe for the upper cutoff. Thus, the limits per toe were 10 and 20 s, respectively.

The operating characteristics of a score derived from the combination of vibration testing by the on-off method and SWME testing did not differ significantly from those of each individual modality. For the same cutoff point of ≥ 10 , the specificity was 98% and the positive likelihood ratio was 14.1. For the cutoff point of ≤ 2 for both, the sensitivity was 80% and the negative likelihood ratio was 0.28.

For the subset of patients with repeated testing of each screening modality, Table 4 shows the P values of the Kruskal-Wallis χ^2 test approximation for reproducibility. The lack of a significant difference in P values suggests that each screening test can be

Table 4—P values for Kruskal-Wallis test for reproducibility of screening tests

Test	P
Timed vibration	0.9925
Monofilament	0.7391
Superficial pain	0.9928
On-off vibration	0.6814

reproduced without any significant bias attributable to the different examiners performing the test.

Table 5 shows the prevalence of abnormal test results in each clinical stratum. The percentage of abnormal test results increased with increasing severity of clinical diabetic polyneuropathy (DPN), and the SWME best approached the levels of abnormality observed for NCSs.

SWMEs, superficial pain sensation testing, and vibration testing by the on-off method each required <60 s to perform accurately. Vibration testing by the timed method took longer depending on the degree of normalcy.

CONCLUSIONS — The neuropathies associated with diabetes represent insidious and progressive processes for which the pathological severities are poorly linked with the development of symptoms. DPN is a specific form of axonal neuropathy associated with diabetes and is defined clinically by progressive disease that first includes distal and symmetrical peripheral neuropathy of sensory nerve fibers, with eventual autonomic and motor involvement (3,26).

Polyneuropathy is a diabetes complication that is prevalent, responsible for more than half of all limb amputations, and known to have well-defined economic and quality-of-life costs (27). Moreover, a long asymptomatic latency period is understood as part of the natural history. Allocation of appropriate interventions in high-risk patients with diabetes has been shown to decrease the rate of ulceration by up to 60% and the rate of amputation by 85% (13). The main point of contention regarding screening for DPN is the efficacy of treatment. Currently, no specific pharmacological agent has demonstrated efficacy in reversing neuropathy or preventing disease progression beyond the intervention of optimizing glycemic control (4,28,29). Clearly, autonomic dysfunction and somatic neuropathy symptoms and signs are diminished with intensified glycemic control (4). However, it

is crucial to remember that communicating information regarding the status of a patient's diabetes complications may provide the impetus and empowerment for active participation in the management of the patient's own disease. Screening for neuropathy in the diabetes clinic is therefore justified for diagnosis, patient education, the provision of further impetus for optimization of glycemic control, and the institution of improved foot care for the reduction of lower-extremity complications (4,13).

The optimal method for the detection of neuropathy in patients with diabetes has also been a matter of controversy, and clinical practice guidelines have been based primarily on expert opinion rather than clinical trial evidence (17,18). Clinical practice guidelines either do not recommend a specific screening modality (18) or make recommendations based on grade D evidence (17). The Rochester Neuropathy Score method (30) and the Michigan Neuropathy Screening Instrument (31) are accurate and comprehensive strategies, though time-consuming and costly. These strategies are more suitable for a specialized neurology clinic or research protocol than for general screening in a diabetes or primary care clinic. As a result, these methods are not in routine use by physicians caring for patients with diabetes.

The current level of evidence in the medical literature for the use of simple screening methods for DPN focuses primarily on the use of the Semmes-Weinstein 5.07/10-g monofilament. The SWME allows for a simple calibrated means of assessing protective sensation (32,33) and has been established as a prognostic risk factor for complications of neuropathy. The monofilament is clearly established as a reproducible and practical method (33). A single prospective study investigating the operating characteristics of the monofilament for the prediction of ulcers and amputations reports a positive likelihood

ratio of 15 (12). Several case-control studies report variable sensitivities and specificities up to 95 and 82%, respectively (14,15,34,35). The utility of the SWME as a screening method for the diagnosis of neuropathy—rather than a prognostic tool for the prediction of foot complications—has been unclear before the results of the current study because of limitations inherent in previous trials. The current level of evidence is limited by the restricted spectrum of neuropathy in the study cohorts and the lack of independently blinded examiners for individual screening maneuvers. The lack of a clearly defined and reliable criterion standard (16,36) and inconsistent reporting of the required statistical operating characteristics are features of the current literature. Negative likelihood ratios for the finding of a normal screening test have not been defined previously (14,32,33,36).

The results of this study demonstrate for the first time reliable operating characteristics of simple neurological examination maneuvers using a methodologically sound trial design. The study subjects represented a broad spectrum of neuropathy in terms of extent of disease. The inception cohort consisted of a range of patients offering a diagnostic challenge and did not simply represent groups that were stratified into case and control groups consisting of subjects at either end of the spectrum of disease severity. The testing methods were detailed and reproducible, and the methodology prohibited the screening test results from influencing either the decision to perform NCSs or the interpretation of NCS results.

The 10-g SWME, vibration testing with a 128-Hz tuning fork, and superficial pain sensation testing individually generated positive likelihood ratios with large and conclusive changes from pretest to post-test probability for DPN. Negative likelihood ratios in the presence of normal testing generated small but important changes in prob-

Table 5—Prevalence of abnormal tests in the clinical strata

Test	Stratum 1	Stratum 2	Stratum 3	Stratum 4	Stratum 5
Superficial pain	2	10	30	49	68
Monofilament	16	33	58	72	84
On-off Vibration	2	14	27	49	60
NCS	8	62	83	93	98

Data are % of subjects with abnormal results in each clinical group. For sensory testing (superficial pain, monofilament, and on-off vibration), an abnormal result is defined as two or more of eight abnormal responses. For NCSs, abnormal results are defined as three or more abnormal parameters. Strata are defined in Table 1.

ability. The results of this study are simple to interpret: for the SWME, superficial pain sensation test, and vibration test by the on-off method, if more than one-half of the responses are incorrect (at least five incorrect responses of eight stimuli), then peripheral neuropathy is ruled in. One or fewer incorrect responses rule out peripheral neuropathy by these methods. For vibration testing by the timed method, testing is more time-consuming, and the results are less valid in their interpretation. Vibration tested by the different methods provided different sensitivity and specificity values, probably due to the different testing paradigms. This finding indicates the absolute necessity of following described procedures in the application of any testing method if one is using the results presented in the literature. The combination of two testing modalities does not improve the operating characteristics of screening from the data in this study.

We found that any one of these three simple tests (10-g SWME, superficial pain, and vibration testing by the on-off method) can be confidently used for annual screening of diabetic neuropathy in both diabetes and primary care clinics.

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