Prediction of Incident Diabetic Neuropathy Using the Monofilament Examination

A 4-year prospective study

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OBJECTIVE — To determine the specific monofilament examination score that predicts the subsequent 4-year incidence of diabetic neuropathy with the highest degree of diagnostic accuracy.

RESEARCH DESIGN AND METHODS — Longitudinal follow-up of 175 of 197 (89%) participants in the Toronto Diabetic Neuropathy Cohort without baseline neuropathy for incident neuropathy. We examined the baseline monofilament examination score (and other simple sensory screening tests) by receiver operating characteristic (ROC) curve analysis.

RESULTS — Incident diabetic neuropathy developed in 50 (29%) participants over a mean follow-up of 4.1 years (interquartile range 2.6–7.1 years). Although male sex, longer diabetes duration, taller height, and higher blood pressure at baseline were associated with incident neuropathy, the strongest association was with a lower baseline monofilament score (score out of 8 was 3.7 ± 2.5 for incident neuropathy vs. 5.7 ± 2.3 for those who did not develop neuropathy; $P < 0.001$). The optimal threshold score for risk of incident neuropathy was ≤5 sensate stimuli out of 8, with 72% sensitivity, 64% specificity, positive and negative likelihood ratios of 2.5 and 0.35, and positive and negative predictive values of 87 and 46%, respectively ($\chi^2 = 20.7$, $P < 0.001$). Area under the ROC curve was significantly greater for the monofilament examination compared with that for other simple sensory tests.

CONCLUSIONS — A simple threshold of ≤5 sensate stimuli out of 8 discriminates 4-year risk of diabetic neuropathy with acceptable operating characteristics. Although there are limitations in its specificity for prediction of future neuropathy onset, the monofilament examination is appropriate as a simple diabetic neuropathy screening instrument generalizable to the clinical setting.

Diabetes Care 33:1549–1554, 2010

The diffuse injury to peripheral nerves, defined as diabetic sensorimotor polyneuropathy but commonly referred to as "diabetic neuropathy," has exceptionally high incidence (1) and is observed in up to 50% of people with diabetes when evaluated using objective tests such as nerve conduction studies (2). It represents a progressive, diffuse, and length-dependent process of nerve injury, involving factors other than simple exposure to hyperglycemia (1). It begins with a long subclinical latency period whose identification and management is challenging; notwithstanding, it is important to identify neuropathy in its earliest stages because it may progress to produce extreme morbidity and health care costs (3,4). Valid identification at early stages will probably provide the best opportunity for effective intervention.

At present, underdiagnosis of diabetic neuropathy is a fundamental issue: it impedes the benefits of early identification, impedes the emphasis on early management necessary to improve glycemic control, and impedes the prevention of neuropathy-related sequelae (5). That practice recommendations for screening, such as examination with the monofilament or vibration tuning fork, are not being systematically carried out contributes to the issue of underdiagnosis and may be related to challenges with applicability of a screening test in clinical practice (6). Whereas measurement of microalbuminuria and funduscopic examinations serve as objective tests for incipient nephropathy and retinopathy in type 1 diabetes, evidence for the validity of a comparably objective test is lacking for neuropathy.

The Semmes-Weinstein 10-g monofilament examination is a simple, practical, and accurate tool for diabetic neuropathy screening. It involves a hand-held calibrated nylon thread that buckles once it has delivered a force of 10 g; in this way, when applied to the skin surface, it provides a standardized measure of a patient's ability to sense a point of pressure. Although first studied as a specific prognostic indicator for skin infection, ulceration, and amputation (7,8), it has been studied for identification of diabetic neuropathy (9–12). In the study with the highest level of evidence for identifying the presence of diabetic neuropathy, a score of 7 or 8 correct responses out of 8 was associated with 78% sensitivity, whereas a score of ≤3 correct responses was associated with 96% specificity (10,12). The monofilament examination became part of clinical practice guidelines on the basis of this concurrent validity (13).

The most relevant question is whether the monofilament score can represent incipient nerve injury before the development of clinically recognized diabetic neuropathy; that is, does the monofilament examination have sufficient predictive validity? Guided by this consideration, we monitored for a mean of 4 years patients with diabetes but without

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Received 2 October 2009 and accepted 20 March 2010. Published ahead of print at http://care.diabetesjournals.org on 31 March 2010. DOI: 10.2337/dc09-1835.
B.A.P., A.O., and V.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

neuropathy for the future onset of diabetic neuropathy through the Toronto Diabetic Neuropathy Cohort (10,12). To our knowledge, it represents the only prospective observational study designed to assess the predictive validity (the validity in identifying future risk of neuropathy onset) of a simple screening test for diabetic neuropathy.

RESEARCH DESIGN AND METHODS

— Subjects without diabetic neuropathy in the first cross-sectional examination of the Toronto Diabetic Neuropathy Cohort were eligible for the current study (10,12). The protocol and consent procedures were approved by the Multidisciplinary Research Ethics Board of the Toronto General Hospital Research Institute.

From 1999 and 2001, 478 subjects were examined as part of the Toronto Diabetic Neuropathy Cohort, a cross-sectional study investigating the concurrent validity of screening tests (10,12). A clinical stratification method based on the Toronto Clinical Neuropathy Score was used in the accrual of this cohort to ensure that it would consist of subjects with a broad spectrum of nerve injury (10,14). Four severity strata, including no neuropathy, mild neuropathy, moderate neuropathy, and severe neuropathy, were graded according to the score quartiles, and accrual of subjects into the study was terminated only when the smallest stratum contained 50 subjects. A comprehensive evaluation was also conducted to exclude risk of neuropathy from other etiologies such as familial, alcoholic, nutritional, and uremic polyneuropathy. The 51 nondiabetic reference subjects in the total cohort of 478 were excluded from the current analysis. Of the remaining 427 subjects with diabetes (65 type 1 and 362 type 2 diabetes), 197 did not meet the diagnostic criteria for diabetic neuropathy and were thus eligible for study. We were able to reevaluate 175 of the 197 subjects (89%) from 2004 until 2007 using the same clinical and electrophysiological examination to identify incident cases of diabetic neuropathy.

Determination of the monofilament score and other sensory screening test scores

The monofilament examination was performed bilaterally using a 10-g (size 5.07) monofilament according to previous study (10,12). In brief, first a reference stimulus was applied to the forehead or the sternum. With the patient's eyes closed, the monofilament was applied to a noncallused site on the dorsum of the great toe just proximal to the nail bed using a smooth motion: the skin was touched and the monofilament was bent for a full second and then lifted from the skin. This maneuver was repeated 4 times per foot in a random arrhythmic manner. The responses were tallied to produce a score ranging from 0 to 8 (normal [1 point assigned], decreased [0.5 point assigned], or absent [0 points assigned]) A score of 0 represented a complete lack of perception, whereas a score of 8 represented full perception of all stimuli. Inter- and intrarater reproducibility was very good to excellent for the performance of the monofilament examination according to this protocol (10). Superficial pain sensation was measured using a sterile Neurotip (Owen Mumford, Oxford, U.K.) applied four times to the same sites, and the score (from 0 to 8) was defined as the total number of times the application of the pain sensation was perceived. Vibration testing by the on-off method was conducted using a 128-Hz tuning fork applied to the bony prominence at the dorsum of the first toe just proximal to the nail bed. The patient reported perception of both the start of the vibration sensation and the cessation on dampening, conducted twice on each toe, and the score (between 0 and 8) was defined as the total number of times application and dampening were felt. Vibration testing by the timed method was measured by the patient reporting 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 added from both sides to provide a single score. Vibration perception threshold (VPT) testing was measured quantitatively by the method of limits using the Medoc device (Medoc Advanced Medical Systems, Durham, NC). Each test was performed by an examiner blinded to results of all other examinations.

Determination of incident diabetic neuropathy: the reference standard

Incident diabetic neuropathy was defined by clinical and electrophysiological criteria according to the consensus of the American Association of Neurology, the American Academy of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation (15). Based on this consensus, incident case definition generally required the presence of electrophysiological polyneuropathy as defined by abnormality of three or more parameters in two or more nerves in combination with the presence of more than one neuropathic symptom or sign of peripheral neuropathy. This same criterion was used to both exclude the presence of diabetic neuropathy at baseline and to define incident neuropathy during follow-up.

For the electrophysiological component of incident case definition, evaluation of the unilateral median, ulnar, peroneal, tibial, and sural nerves was performed at baseline and subsequent examinations were performed using standardized nerve conduction studies (16). These were performed using the Counterpoint instrument (Natus Medical, San Carlos, CA) according to the standards of the American Association for Neuromuscular and Electrodiagnostic Medicine and the Canadian Society of Clinical Neurophysiology. Low interobserver and intraobserver variabilities have been observed for these measurements using the techniques described (17). Individual nerve conduction parameters were scored as normal or abnormal according to laboratory reference values.

Statistical analysis

Analyses were performed in SAS (version 9.1 for Windows). Using the methods for power calculation in the ROC analysis of Hanley and McNeil (18), given a type 1 error (α level) of 0.05, we anticipated 94.5% power to discriminate an area under the curve from the null hypothesis in which the diagnostic accuracy is no different from chance alone (area under the curve [AUC] = 0.5) under the assumption that incident diabetic neuropathy would occur in approximately one-third of diabetic individuals. Differences in baseline characteristics between individuals with incident cases of diabetic neuropathy and control subjects were assessed using χ^2 tests for categorical variables. For these differences in baseline characteristics, continuous variables were compared using the two-sided Mann-Whitney *U* test (Wilcoxon rank-sum test) because some variables (height, in meters) were not normally distributed. Significance was based on an α level of 0.05. We also pursued a multivariate logistic regression model to determine clin-

Table 1—*Baseline characteristics of the 175 subjects according to the 4-year incident diabetic neuropathy*

Characteristic	Incident diabetic neuropathy: Absent	Incident diabetic neuropathy: Present	*P* value*
n	125	50	
Age at baseline (years)	56 ± 8	57 ± 8	0.08
Male sex (%)	78 (62)	40 (80)	0.03
Type 2 diabetes (%)	106 (85)	41 (82)	0.65
Diabetes duration (years)	11 ± 9	15 ± 9	0.02
Current/past smoking (%)	68 (54)	28 (56)	0.65
Alcohol consumption ≥3 equivalents/day	17 (14)	7 (14)	0.96
Diabetes therapy			
Insulin use	50 (40)	24 (48)	0.38
Oral hypoglycemic agent use	63 (55)	26 (52)	0.38
ACE inhibitor agents†	28 (22)	18 (36)	0.14
Retinopathy history‡	18 (14)	11 (22)	0.19
Nephropathy history‡	8 (16)	9 (18)	0.89
Foot ulcer history‡	6 (5)	3 (6)	0.88
Height (m)	1.69 ± 0.09	1.73 ± 0.07	0.10
Weight (kg)	82.8 ± 14.6	86.5 ± 16.5	0.73
BMI (kg/m^2)	29.0 ± 4.7	29.0 ± 5.1	0.57
Systolic blood pressure (mmHg)	132 ± 15	139 ± 14	0.04
Diastolic blood pressure (mmHg)	82 ± 8	86 ± 8	0.05
A1C (%)	8.2 ± 1.5	8.6 ± 1.3	0.22
Monofilament score			<0.001
Mean ± SD	5.7 ± 2.3	3.7 ± 2.5	
Interquartile range	4.0–8.0	1.5–5.5	
Other screening test scores			
Vibration by the on-off method (score 0–8)	6.5 ± 2.4	5.5 ± 3.0	0.03
Vibration by the timed method (in seconds)	28 ± 13	34 ± 14	0.02
Superficial pain score (score 0–8)	6.5 ± 2.2	5.5 ± 3.0	0.04
VPT (μm)	21.9 ± 14.8	30.5 ± 15.3	<0.001

Data are means ± SD or *n* (%) unless otherwise indicated. *Categorical variables report *P* values for χ^2 test statistics. Although continuous variables were generally normally distributed except for height, we report *P* values for the two-sided Mann-Whitney *U* Test (Wilcoxon rank-sum test). †ACE inhibitor agents. The most commonly used agents were ramipril, enalapril, and lisinopril, respectively. ‡By subject self-report.

ical variables that were independently associated with future diabetic symmetrical polyneuropathy (DSP) onset. In this model, the dependent variable was DSP case-control status, and the independent variables were age, sex, diabetes duration, BMI, diastolic blood pressure, A1C, and the monofilament score. This logistic regression model was associated with seven events per independent variable and a χ^2 value in a log-likelihood test of 27.1 (P = 0.007). To obtain the AUC and optimal decision threshold level for incident neuropathy, a receiver operating characteristic (ROC) curve was generated (19). The positive monofilament score result was defined by the threshold equal to or below the threshold determined from ROC curve analysis by visual inspection. Comparisons of the AUC for the monofilament score and the other screening tests were based on the method of Pencina et al. (20). In the absence of a validation set, a bootstrap analysis consisting of 1,000 datasets produced by the random selection of 175 subjects with replacement was performed and analyzed for mean AUC of each sensory test.

RESULTS — The 175 subjects were examined for a second evaluation a mean of 4.1 years after baseline examination. This distribution was skewed to the right with an interquartile range of 2.6 to 7.1 years. Among those with incident DSP, the median follow-up was 3.9 years (interquartile range 2.5–7.1 years), whereas for those without incident DSP it was 4.3 (interquartile range 2.5–7.1 years), with a Wilcoxon rank-sum two-sided test *P* value of 0.35. The clinical characteristics of the 22 eligible subjects who we were unable to reexamine did not differ from those of subjects who were examined. Incident diabetic neuropathy developed in 50 (29%) of the 175 subjects. In none of the subjects was polyneuropathy owing to nondiabetic causes recognized.

The characteristics of the 175 study subjects at the time of baseline evaluation are summarized in Table 1, according to the absence or presence of incident diabetic neuropathy at the final examination. Incident diabetic neuropathy occurred more frequently in male subjects. Although no age differences were seen, case subjects had significantly longer diabetes duration. No differences in diabetes type, smoking, or alcohol consumption were observed at baseline between subjects with incident cases and their control subjects. Height, weight, and BMI were similar between case and control subjects, yet both systolic and diastolic blood pressure values were significantly higher in subjects with incident cases of diabetic neuropathy. Differences between subjects with incident cases and control subjects without onset of neuropathy were observed for the baseline monofilament score and the VPT values. To further explore these observations, we pursued a multivariate model that included all of the variables listed in the table, including those likely to be collinear (the simple screening tests and VPT testing scores). A lower baseline monofilament score was the only variable independently associated with neuropathy incidence (χ^2 10.5; $P = 0.0012$). By using the median value of the score to determine odds ratios for risk, the adjusted odds ratio for incident diabetic neuropathy associated with a monofilament score >5 compared with ≤5 was 5.5 (95% CI 1.9–15.9). Although demonstrating a trend toward higher values among subjects with incident cases of diabetic neuropathy, the baseline A1C values were not significantly different either in the univariate or adjusted comparisons. The duration of time between baseline and follow-up examinations did not differ between case and control subjects.

In view of the strong odds ratio observed for the monofilament score, we pursued ROC curve analysis to determine the optimal threshold score for prediction of 4-year incident diabetic neuropathy.

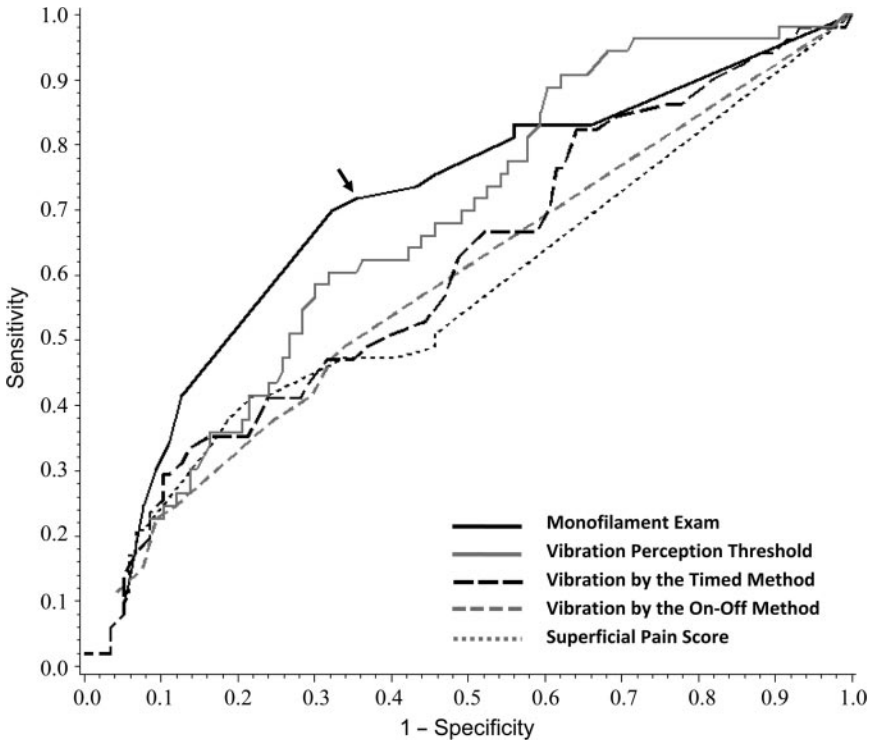

Figure 1—*ROC curve for 4-year incident diabetic neuropathy in the 175 subjects with diabetes. The ROC curve for the monofilament examination is indicated by the solid black line. The point on this curve that indicates a combination of maximal sensitivity and the lowest false-positive rate (false-positive rate is mathematically equivalent to 1 − specificity) is indicated by the arrow and defines the threshold value for positivity at ≤5 correct responses out of 8. Such a score is associated with 72% sensitivity and 64% specificity. The area under the curve was 0.71 (95% CI 0.66–0.72). See Table 2 for estimates of AUC for each test.*

The result of the ROC analysis for the monofilament score is represented by the solid black line in Fig. 1. The combination of an optimal sensitivity of 72% and optimal specificity of 64% was observed at a cutoff level for positivity of ≤5 sensate stimuli out of 8. This threshold was associated with 38 true positives out of 50 incident cases of diabetic neuropathy and 81 true negatives of 125 control subjects. Thus, the calculated positive predictive value at this cutoff level was only 46%, whereas the negative predictive value was 87%. Positive and negative likelihood ratios were 2.5 and 0.35, respectively. The AUC was 0.71 (95% CI 0.66–0.72) for the monofilament score, which exceeded that of the other simple sensory tests and VPT testing shown in Fig. 1. As detailed in Table 2, the AUC for the monofilament score was significantly greater than the AUC for the other tests. In the absence of a validation set, bootstrap analysis was performed, which paralleled the results of the derivation set.

CONCLUSIONS— In a cohort of 175 diabetic subjects with the absence of diabetic neuropathy, the 4-year risk of incident diabetic neuropathy was high (50 cases, 29%). Among all the measured clinical and biochemical variables, the strongest independent association was observed with a lower baseline monofilament examination score. In ROC analysis, the AUC, as a measure of overall diagnostic accuracy, surpassed those of other simple screening tests and quantitative VPT testing. The optimal threshold monofilament score for the prediction of neuropathy incidence was a score of ≤5 correct responses out of 8. This threshold was associated with very good sensitivity (72%) and negative predictive value (87%), implying that the finding of a negative test result, a monofilament score >5 correct responses out of 8, implies the lowest 4-year risk for the onset of neuropathy. This sensitivity highlights the major advantage of the monofilament examination in clinical practice, which is to rule out subsequent risk of disease in those without neuropathy. However, this advantage is limited by a lower specificity and positive predictive value (65 and 46%, respectively), indicating that the monofilament score cannot confidently rule in risk of disease. Rather, the monofilament score can be used to rule out such risk, which ultimately is the necessary characteristic of a routine screening test.

Of critical importance in the clinical care of patients with diabetes is the process of risk stratification for diabetes complications at a preclinical stage when injury is absent or incipient and when clinical interventions are most likely to be effective for prevention of progression to advanced injury. For example, urinary albumin excretion is a quantitative variable for which a specific range of values, termed microalbuminuria, has become firmly entrenched in clinical practice as it is seen as a marker of incipient renal injury in diabetes (21). Identification of microalbuminuria permits interventions that are designed to prevent progression to advanced kidney disease, years before its development. Conversely, identifica-

Table 2—***Comparison of area under the ROC curve between the monofilament score and the other screening test scores***

Test	Area under the ROC curve	*P* value*	Bootstrap analysis (1,000 datasets): Mean AUC (95% distribution)	Bootstrap analysis (1,000 datasets): *P* value†
Monofilament	0.71	—	0.71 (0.62, 0.80)	—
Other simple tests				
Vibration by the on-off method	0.59	0.007	0.59 (0.50, 0.67)	<0.0001
Vibration by the timed method	0.61	0.008	0.61 (0.52, 0.70)	<0.0001
Superficial pain score	0.57	<0.0001	0.57 (0.48, 0.66)	<0.0001
Quantitative tests				
VPT	0.67	0.094	0.67 (0.59, 0.76)	<0.0001

*P value for comparison with the AUC for the monofilament score, according to the method of Pencina et al. (>20). †Student t test P value for comparison with the AUC for the monofilament score.

tion of normal levels, termed normoalbuminuria, serves to identify those individuals with the lowest subsequent risk of diabetic nephropathy. However, the longitudinal clinical studies that are necessary for identifying a comparable marker of incipient nerve injury are insufficient. The current evidence for neuropathy is only supported by cross-sectional studies (10–13,22,23).

With the aim of finding the comparable marker of incipient nerve injury, we chose to evaluate the quantitative monofilament score. Previous work had demonstrated in cross-sectional analysis that a monofilament score of ≥7 correct responses out of 8 had high sensitivity (77%), whereas a score of ≤3 correct responses out of 8 had very high specificity (96%) for the concurrent presence of diabetic neuropathy (10). The question remained whether a single score or range of scores in between these two thresholds could represent incipient nerve injury. The current analysis was designed to answer this specific question by identifying a large group of subjects without diabetic neuropathy and to determine the operating characteristics of the monofilament score for the 4-year incidence of neuropathy. Because a score of ≤3 correct responses out of 8, associated with presence of neuropathy in the cross-sectional study, was uncommon in the current study (18% of participants), we can interpret the results of both the cross-sectional and longitudinal study together: When the monofilament examination is applied as a screening test, a score of ≤3 correct responses out of 8 indicates a very high likelihood of current diabetic neuropathy. A score of 4–5 correct responses out of 8 indicates incipient neuropathy. Subjects with these scores are unlikely to have neuropathy at the time of examination but, rather, have a high 4-year risk of its incidence. In clinical practice, knowledge of this risk might help motivate attainment of glycemic targets as glycemic control is the only known disease-modifying intervention for DSP. For research into disease-modifying therapies, subjects with such scores could be accrued as high-risk subjects for inclusion in clinical trials. The remaining scores of 6–8 correct responses out of 8 indicate both a lack of neuropathy and the lowest 4-year risk of its incidence.

The theoretical comparisons between the monofilament examination and assessment of urinary albumin excretion extend to the performance characteristics of these two tests. The low positive predictive value of the monofilament score threshold of ≤5 correct responses out of 8 (the upper threshold for incipient nerve injury) is in fact very consistent with the low positive predictive value for microalbuminuria (24). Despite this limitation, assessment of microalbuminuria remains a standard of diabetes care, owing to the benefit of its sensitivity. Similarly, we view the benefit of the monofilament examination as a screening test for diabetic neuropathy to be attributable to its sensitivity.

Although unique as a longitudinal study of predictive validity in diabetic neuropathy, there are potential limitations to the interpretation of the results of this study. First, the study group included a mixed cohort of type 1 and type 2 diabetic subjects, which makes an assumption that diabetic neuropathy and its clinical assessment are consistent between diabetes types. Second, the interval of time between baseline and final evaluation of the participants in this study was variable, but we were not able to detect an influence of follow-up time on the likelihood of incident diabetic neuropathy. Third, we explored our hypothesis in a derivation set without access to a validation set. To address this issue of certainty, we performed a bootstrap analysis. Finally, the reference standard definition of diabetic sensorimotor polyneuropathy remains challenging as it combines clinical and electrophysiological criteria that are not consistently aligned in individual subjects. To overcome this feature of the definition as much as possible, we used the most up-to-date definition of neuropathy (15).

Knowledge of the monofilament score permits general risk stratification of patients for future incident neuropathy. Our findings demonstrate that the monofilament examination, a valid and clinically feasible biomarker for diabetic neuropathy in cross-sectional study, also has sufficiently valid operating characteristics as a marker of incipient nerve injury in longitudinal study. Thus, the quantitative monofilament score can be used to identify those at the lowest and highest 4-year risk of diabetic neuropathy incidence. In this capacity it is aligned with other clinical tests for diabetes complications and is limited by suboptimal specificity. To further refine risk prediction of diabetic neuropathy in clinical practice, evaluation of future novel biomarkers of diabetic neuropathy must aim to report the results of longitudinal evaluation for predictive validity and compare these to the operating characteristics reported here for the monofilament examination.

Acknowledgments— This research was supported by Canadian Diabetes Association grant AR-2-06-2056-BP. B.A.P. is a Canadian Diabetes Association Scholar and was supported by the Banting and Best Diabetes Center.

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in poster form at the 69th annual meeting of the American Diabetes Association, New Orleans, Louisiana, 5–9 June 2009.

We acknowledge the assistance of Alessandro Doria and Monika Niewczas with the statistical tests comparing receiver operating characteristic area under the curve and of Tim Shin for aspects of manuscript preparation. We are also indebted to the dedicated work of Rachel Kaufman for assistance with data management and manuscript preparation.

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