AANEM PRACTICE PARAMETER

ABSTRACT: Distal symmetric polyneuropathy (DSP) is the most common variety of neuropathy. Since the evaluation of this disorder is not standardized, the available literature was reviewed to provide evidence-based guidelines regarding the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy. A literature review using MEDLINE, EMBASE, Science Citation Index, and Current Contents was performed to identify the best evidence regarding the evaluation of polyneuropathy published between 1980 and March 2007. Articles were classified according to a four-tiered level of evidence scheme and recommendations were based on the level of evidence. (1) Autonomic testing may be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction (Level B). Such testing should be considered especially for the evaluation of suspected autonomic neuropathy (Level B) and distal small fiber sensory polyneuropathy (SFSN) (Level C). A battery of validated tests is recommended to achieve the highest diagnostic accuracy (Level B). (2) Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, mononeuropathy multiplex due to vasculitis, or with atypical forms of chronic inflammatory demyelinating polyneuropathy (CIDP). However, the literature is insufficient to provide a recommendation regarding when a nerve biopsy may be useful in the evaluation of DSP (Level U). (3) Skin biopsy is a validated technique for determining intraepidermal nerve fiber (IENF) density and may be considered for the diagnosis of DSP, particularly SFSN (Level C). There is a need for additional prospective studies to define more exact guidelines for the evaluation of polyneuropathy.

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EVALUATION OF DISTAL SYMMETRIC POLYNEUROPATHY: THE ROLE OF AUTONOMIC TESTING, NERVE BIOPSY, AND SKIN BIOPSY (AN EVIDENCE-BASED REVIEW)

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INTRODUCTION

Justification. Polyneuropathy is a relatively common neurological disorder.[10] The overall prevalence is ≈2,400 (2.4%) per 100,000 population, but in individuals older than 55 years the prevalence rises to ≈8,000 (8%) per 100,000.[9,32] Since there are many etiologies of polyneuropathy, a logical clinical approach is needed for evaluation and management.

This practice parameter provides recommendations for the evaluation of distal symmetric polyneuropathy (DSP) based on a prescribed review and analysis of the peer-reviewed literature. The parameter was developed to provide physicians with evidence-based guidelines regarding the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy. The diagnosis of DSP should be based on a combination of clinical symptoms, signs, and electrodiagnostic criteria as outlined in the previous case definition.[10] (See Mission Statement, below, for details.)

Formation of Expert Panel. The Polyneuropathy Task Force included 19 physicians with representatives from the American Academy of Neurology (AAN), the American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPM&R). All of the task force members had extensive experience and expertise in the area of polyneuropathy. Additionally, four members had expertise in evidence-based methodology and practice parameter development. Three are current members (J.D.E., G.S.G., G.F.), and one is a former member (R.G.M.) of the Quality Standards Subcommittee (QSS) of the AAN. The task force developed a set of clinical questions relevant to the evaluation of DSP, and subcommittees were formed to address each of these questions.

DESCRIPTION OF THE ANALYTIC PROCESS

The literature search included OVID MEDLINE (1966 to March 2007), OVID Excerpta Medica (EMBASE; 1980 to March 2007), and OVID Current Contents (2000 to March 2007). The search included articles on humans only and in all languages. The search terms selected were peripheral neuropathy, polyneuropathy, and distal symmetric polyneuropathy. These terms were cross-referenced with the terms diagnosis, electrophysiology, autonomic testing, nerve biopsy, and skin biopsy.

Panel experts were asked to identify additional articles missed by the initial search strategy. Further, the bibliographies of the selected articles were reviewed for potentially relevant articles.

Subgroups of committee members reviewed the titles and abstracts of citations identified from the original searches and selected those that were potentially relevant to the evaluation of polyneuropathy. Articles deemed potentially relevant by any panel member were also obtained.

Each potentially relevant article was subsequently reviewed in entirety by at least three panel members. Each reviewer graded the risk of bias in each article by using the diagnostic test classification-of-evidence scheme (Appendix 2). In this scheme, articles attaining a grade of Class I are judged to have the lowest risk of bias, and articles attaining a grade of Class IV are judged to have the highest risk of bias. Disagreements among reviewers regarding an article's grade were resolved through discussion. Final approval was determined by the entire panel.

The Quality Standards Subcommittee (AAN), the Practice Issues Review Panel (AANEM), and the Practice Guidelines Committee (AAPM&R) (Appendix 1A–C) reviewed and approved a draft of the article. The draft was next sent to members of the AAN, AANEM, and AAPM&R for further review and then to *Neurology* for peer review. Boards of the AAN, AANEM, and AAPM&R reviewed and approved the final version of the article. At each step of the review process, external reviewers' suggestions were explicitly considered. When appropriate, the expert panel made changes to the document.

ANALYSIS OF THE EVIDENCE

The search yielded 1,045 references with abstracts. After reviewing titles and abstracts, 106 articles were reviewed and classified.

Role of Clinical Autonomic Testing in the Evaluation of Polyneuropathy. Autonomic nervous system dysfunction occurs in several phenotypes. It may occur as one component of a generalized polyneuropathy such as DSP of diabetes. Such polyneuropathies are usually diagnosed by a combination of neuropathic symptoms, decreased or absent ankle reflexes, decreased distal sensation, distal muscle weakness or atrophy, and abnormal nerve conduction studies (NCSs).[10] The majority of these features constitute evidence of "large fiber" sensory and motor involvement. However, signs of autonomic nervous system involvement may also constitute findings indicative of DSP. In DSP with autonomic involvement, the most common clinical findings are abnormalities of sweating and circulatory instability in the feet.[9,10]

A second phenotype is that of an autonomic neuropathy such as in amyloidosis and autoimmune autonomic neuropathy, where autonomic nerves are affected disproportionately relative to somatic nerves.[29] In these neuropathies, autonomic fibers can be affected in isolation and their involvement may precede somatic fiber involvement.[47]

A third relatively common phenotype is distal small fiber sensory polyneuropathy (SFSN), which can manifest as burning pain affecting the feet, often with allodynia and sometimes with erythromelalgia (red hot and painful skin). Involvement of autonomic and somatic C fibers usually occurs concurrently in small fiber polyneuropathy.[47]

What Is the Usefulness of Clinical Autonomic Testing in the Evaluation of Polyneuropathy, and Which Tests Have the Highest Sensitivity and Specificity? Currently available autonomic tests can provide indices of cardiovagal, adrenergic, and postganglionic sudomotor function. As such they provide indices for both parasympathetic and sympathetic autonomic function. Heart rate variability testing is a simple and reliable test of cardiovagal function. It detects the presence of diabetic polyneuropathy with nearly the same sensitivity as NCSs (Class II).[7] Specificity is high (97.5%) for identifying parasympathetic deficits if the recommended age-controlled values are used (Class II).[26] Intrinsic cardiac disease can affect the results of this test, and this possibility must be considered in the interpretation.

Cardiovagal function can be evaluated using different indices in the time and frequency domains.[56] There is no compelling evidence that one method is better than another or that the use of multiple indices confers any advantage. Heart rate variability to deep breathing is the most widely used test of car-

diovagal function and has a specificity of ≈80% (Class II).[24]

The vagal component of the baroreflex can be evaluated by quantitating the heart period response to induced changes in blood pressure (BP). A well-studied test is the modified Oxford method.[8] The test consists of an evaluation of heart period responses to induced increases and decreases in arterial BP. The increase is evoked by intravenous phenylephrine and decrease by nitroprusside in incremental doses. Baroreflex sensitivity is defined by the slope of the heart period to BP relationship. Linearity is required ($R > 0.85$). The advantage of this test is that it evaluates vagal baroreflex sensitivity; however, the disadvantage is that the test is invasive and not widely performed. Approximation of this method is possible by relating heart period alterations to changes in BP induced by the Valsalva maneuver.[52] The sensitivity and specificity of invasive and noninvasive tests of baroreflex function are high, but these tests are not generally used in the study of neuropathy since their value is considered only additive to current tests of cardiovagal function (Class II).[24,29,44,54]

Thermoregulatory sweat testing (TST) is a sensitive test of sudomotor function that utilizes an indicator substance whose color changes upon exposure to sweat.[12,30] The test results can be semiquantitated by estimating the percentage of skin surface that is anhidrotic. Since the test is tedious, messy, and time-consuming, it is not routinely done. Additionally, TST is not able to distinguish between postganglionic, preganglionic, and central lesions.[12,30] The most quantitative test of sudomotor function is the quantitative sudomotor axon reflex test (QSART).[25] QSART is mediated by impulses traveling antidromically then orthodromically along the postganglionic sympathetic sudomotor axon. QSART can detect distal sudomotor loss with a sensitivity of 75%–90% (Class III).[26,35,50,51] Several studies have demonstrated that QSART can determine sudomotor abnormalities with relatively high sensitivity and specificity in many types of polyneuropathies (Class II and III).[7,25,26,28,29,31,35,47,50] In three Class III studies, QSART was shown capable of detecting distal small fiber polyneuropathy with a sensitivity of >75%.[35,50,51]

Skin vasomotor reflexes assessed by monitoring skin blood flow using laser Doppler flowmeter has not been well studied. Limited data from one Class III study using this technique demonstrated an unacceptably large coefficient of variation.[27]

Analysis of the available Class II and III studies on autonomic testing indicate that a combination of autonomic reflex screening tests provides distinct

advantages over single modality methods. The composite autonomic scoring scale (CASS), which includes QSART, orthostatic blood pressure, heart rate response to tilt, heart rate response to deep breathing, the Valsalva ratio, and beat-to-beat BP measurements during Phases II and IV of the Valsalva maneuver, tilt, and deep breathing provides a useful 10-point scale of autonomic function (Class II).[24,29] In a study of 78 patients with graded autonomic failure obtained by selecting approximately equal numbers of patients with multiple system atrophy, Parkinson's disease, autonomic neuropathies, and idiopathic peripheral neuropathies, this combination of tests provided a noninvasive, sensitive, specific, and reproducible methodology for grading the degree of autonomic dysfunction (Class II).[24]

Conclusions. Autonomic testing is probably useful in documenting autonomic nervous system involvement in polyneuropathy (Class II and III). The sensitivity and specificity vary with the particular test. The utilization of the combination of autonomic reflex screening tests in the CASS provides the highest sensitivity and specificity for documenting autonomic dysfunction (Class II).

Recommendations. Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system involvement (Level B). Autonomic testing should be considered in the evaluation of patients with suspected autonomic neuropathies (Level B) and may be considered in the evaluation of patients with suspected distal SFSN (Level C). The combination of autonomic screening tests in the CASS should be considered to achieve the highest diagnostic accuracy (Level B). If the full battery of tests in the CASS is not available, a combination of tests of cardiovagal function (e.g., heart rate response to deep breathing) and some test of adrenergic function may be considered as an alternative (Level C).[24]

Role of Nerve Biopsy in the Evaluation of Polyneuropathy.
Nerve biopsy is generally accepted as useful in the diagnosis of inflammatory diseases of nerves such as vasculitis, sarcoidosis, CIDP, infectious diseases such as leprosy, or infiltrative disorders such as tumor or amyloidosis.[9] Nerve biopsy is most valuable in mononeuropathy multiplex or suspected vasculitic neuropathy. There are no studies regarding the role of nerve biopsy in the evaluation of DSP, although on occasion the above-noted diseases may present in that fashion.

What Is the Usefulness of Nerve Biopsy in Determining the Etiology of Distal Symmetric Polyneuropathy?

Out of 50 articles judged to be relevant, no article attained a grade greater than Class IV. Most of the articles discussed the nerve biopsy findings in specific diseases, the clinical suspicion of which had prompted the biopsy.[1–3,5,6,13,14,34,39,40–42] No article provided guidance regarding when to perform a nerve biopsy in the evaluation of DSP.

Conclusions. There is no evidence to support or refute a conclusion regarding the role of nerve biopsy in the evaluation of DSP (Class IV).

Recommendations. No recommendations can be made regarding the role of nerve biopsy in determining the etiology of DSP (Level U).

Role of Skin Biopsy in the Evaluation of Polyneuropathy.
Skin biopsy is being increasingly used to evaluate patients with polyneuropathy. The most common technique involves a 3-mm punch biopsy of skin from the leg. After sectioning by microtome, the tissue is immunostained with anti-protein-gene-product 9.5 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods. This staining allows for the identification and counting of intraepidermal nerve fibers (IENF). PGP 9.5 immunohistochemistry has been validated as a reliable method for IENF density determination with good intra- and interobserver reliability in normal controls and patients with DSP.[15,20,33,48]

In March 2005 the European Federation of Neurological Societies (EFNS) published a guideline on the use of skin biopsy in peripheral neuropathy.[20] This comprehensive review focused on the technical aspects of skin biopsy as well as normative data and correlations with other clinical, physiologic, and pathologic tools. The EFNS concluded that skin biopsy is a safe, validated, and reliable technique for the determination of IENF density. The major conclusion was that skin biopsy (IENF density) was diagnostically efficient at distinguishing polyneuropathy patients (including small fiber neuropathy) from normal controls. The EFNS guideline also reviewed the literature on IENF morphologic changes such as axonal swellings as a measure of distal symmetric polyneuropathy.[16,20,21] The EFNS concluded that axonal swellings may be predictive of progression of polyneuropathy but further studies were needed to determine their diagnostic accuracy.[20]

What Is the Usefulness and Diagnostic Accuracy of Skin Biopsy in the Evaluation of Polyneuropathy?
Beyond distinguishing asymptomatic normals from polyneuropathy patients, one clinical question not addressed by the EFNS guideline was the diagnostic accuracy of skin biopsy in distinguishing symptomatic patients

Table 1. Evidence table for autonomic testing.

Reference	Year	Target disorder	Predictor	Reference standard	Cases	Controls	Design	Spectrum	Masked	Class	Sens	Spec
50	1992	Distal small fiber neuropathy	QSART, QST, HRV	Neurologic exam and EDx	40	129	Retrospective Review	N	N	III	80%	72%
7	1992	Diabetic PN	QAE	EDx	380	357*	Concurrent comparative	B	Unmasked/ Independent	II	QAE:97%	>90%
26	1997	PN, Parkinson's, multisystem atrophy	QSART	Older scale	18	557	Concurrent comparison	B	Unmasked/ Independent	II	>90%	>90%
51	1999	Peripheral (small fiber) neuropathy	QSART, QST, Clinical Symptoms	EDx	138	357* (per Dr. Low)	Concurrent comparative	B	Unmasked/ Independent	III	QSART:80%; QST:67%	93%
35	2001	Painful neuropathy	QSART, ART, CASS	Clinical evaluation	126	357* (per Dr. Low)	Non-comparative	N	N	III	ART:93%; QSART: 73%	94%
24	1993	Diabetic PN	CASS	EDx and standard clinical exam	78	350	Concurrent comparative	N	Unmasked/ Independent	II	>90%	>90%
44	2007	Adrenergic autonomic failure	BRSI	MSNA	84	29	Concurrent comparative	B	Unmasked/ Independent	II	86%	>90%
54	2005	Multi system atrophy, peripheral neuropathy	PRT, CASS	Clinical exam	162	32	Concurrent comparative	B	Unmasked/ Independent	II	>90%	>90%
47	2004	DSFN, PN, DN, IAN	CASS	Neurological exam	11	38	Concurrent comparative	N	Unmasked/ Independent	III	95%	90%

Acronyms Distal small fiber neuropathy: DSFN; Diabetic peripheral neuropathy: DPN; Peripheral neuropathy: PN; Quantitative sudomotor axon reflex testing: QSART; Composite autonomic severity score: CASS; Quantitative autonomic examination: QAE; Idiopathic autonomic neuropathy: IAN; Quantitative sensory testing: QST; Autonomic reflex testing: ART; Electrodiagnosis: Edx; Heart rate variability: HRV; Quantitative sweat testing; Baroreflex sensitivity index: BRSI; Muscle sympathetic nerve activity: MSNA; Blood pressure recovery time: PRT.

with polyneuropathy from symptomatic patients without polyneuropathy. For example, in patients with painful feet, would skin biopsy accurately distinguish patients with polyneuropathy from patients with other conditions causing painful feet?

To address this separate question, a subgroup of the Polyneuropathy Task Force (J.D.E., R.A.L., D.H., G.L., M.P., and G.S.G.) independently reviewed the literature regarding the diagnostic accuracy of skin biopsy in DSP and in the SFSN form of DSP. To be considered for review, studies needed to determine IENF density in patients with and without polyneuropathy. Furthermore, the data from studies had to be presented in such a way as to allow calculation of the sensitivity and specificity of skin biopsy for polyneuropathy.

Nine studies met inclusion criteria.[4,16–18,21–22,33,36–37] One was a prospective cohort survey of patients presenting with bilateral painful feet and normal strength, but skin biopsy was done only in those with normal NCS.[36] Patients with reduced IENF density and normal NCS were assumed to have painful small fiber neuropathies. However, the study did not compare the results of the IENF density to an independent reference standard to confirm the presence of small fiber neuropathy. Thus, for the purposes of determining the diagnostic accuracy of skin biopsy for polyneuropathy, this study was graded Class IV.

The remaining studies employed a case-control design.[16,18,21,22,33] In these studies the investigators performed skin biopsies on patients with established polyneuropathy and normal controls. No study included patients with conditions causing lower extremity pain or sensory complaints that might be confused with polyneuropathy. Thus, all studies had potential spectrum bias. Following the evidence classification scheme for studies of diagnostic accuracy, all of these studies were graded Class III.

All of the case-control studies showed a significant reduction in IENF density in polyneuropathy patients as compared to controls.[16,18,21,22,33] The sensitivity of decreased IENF density for the diagnosis of polyneuropathy was moderate to good (range 45%–90%). The specificity of normal IENF density for the absence of polyneuropathy was very good (range 95%–97%). Thus, the absence of reduced IENF density (using the clinical impression as the diagnostic reference standard) would not "rule out" polyneuropathy, but the presence of reduced IEFN density would importantly raise the likelihood of polyneuropathy.

The form of DSP for which IENF assessment is particularly diagnostically attractive is SFSN for the following reasons: (1) IENF are the nerve terminals of somatic unmyelinated C fibers, which are hypothesized to be predominantly affected in SFSN; (2) There has been a lack of a direct objective measure of small fiber sensory nerves since objective measures of large fiber function (e.g., NCS) are by most definitions normal in SFSN[19]; 3) Patients in whom SFSN is clinically suspected manifest with symptoms of small fiber sensory dysfunction (e.g., tingling, numbness, and neuropathic pain) but few objective signs, making it difficult to diagnose and to distinguish SFSN from nonneurological causes of sensory complaints.[19]

Since no validated objective gold standard exists for the diagnosis of SFSN, the authors considered whether demonstration of a pathologic lesion (small sensory fiber pathology on skin biopsy) should be the de facto diagnostic standard or whether a clinical impression of SFSN should be the independent reference standard. For the purposes of this parameter, a clinical impression of SFSN was adopted as the independent reference standard for calculation of sensitivity and specificity of IENF density in the detection of SFSN.

In order to assess the diagnostic accuracy of IENF density assessment for SFSN, the literature was surveyed for studies assessing IENF density in subjects with clinically suspected SFSN (symptoms or symptoms and signs of DSP but with normal NCS) and controls where the diagnostic accuracy of IENF density for clinically defined SFSN could be determined. Four Class III studies met these criteria.[18,23,46,55] The sensitivity of IENF density assessment at the ankle for DSP with normal NCS was 58% (20% for subjects with symptoms but no signs of SFSN; 100% for subjects with symptoms and signs of SFSN),[46] 90%,[18] and 24%.[23] In these studies, the specificity of the test ranged from 95%–97.5%.[18,23,46] The other case-control study found that among patients with symptoms of SFSN and an abnormal pinprick examination in the feet, but normal ankle reflexes, normal vibration sensibility, and normal NCS that an IENF density of <8 fibers/mm at the dorsal foot provided a sensitivity of 88%, a specificity of 91%, a positive predictive value of 0.9, and a negative predictive value of 0.83 for the diagnosis of SFSN.[55]

Conclusions. IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology. Skin biopsy with IENF density assessment is possibly useful to identify DSP that includes SFSN in symptomatic patients with suspected polyneuropathy. (Class III).

Recommendations. For symptomatic patients with suspected polyneuropathy, skin biopsy may be

considered to diagnose the presence of a polyneuropathy, particularly SFSN (Level C).

RECOMMENDATIONS FOR FUTURE RESEARCH

This comprehensive review reveals several weaknesses in the current approach to the evaluation of polyneuropathy and highlights opportunities for research.

- *Autonomic testing.* Autonomic testing can, with a high degree of accuracy, document autonomic system dysfunction in polyneuropathy. This is particularly relevant to small fiber polyneuropathy and the autonomic neuropathies. Research is necessary to determine whether the documentation of autonomic abnormalities is important in modifying the evaluation and treatment of polyneuropathy. Specific tests such as QSART can document small fiber (i.e., sudomotor axon) loss with a high degree of sensitivity, making the test useful to confirm the diagnosis of small fiber polyneuropathy. Since skin biopsy with determination of IENF density can also document small fiber loss, there is a need for studies that compare and correlate the two techniques.
- *Nerve biopsy.* There are no studies of nerve biopsy in the evaluation of DSP. Although it would be useful to know the outcome of well-designed prospective studies in this area, it is unlikely that such studies will be done.
- *Skin biopsy.* Skin biopsy with determination of IENF density is a technique that has come of age for the objective documentation of small fiber loss. This technique provides a unique opportunity for research in different varieties of neuropathy. Further studies are needed to characterize the diagnostic accuracy of skin biopsy in distinguishing patients with suspected polyneuropathy, particularly SFSN, from patients with sensory complaints or pain unrelated to peripheral neuropathy. Prospective studies with appropriate "other disease" controls should be done to assess the sensitivity, specificity, and predictive values of IENF density measurement to identify SFSN in patients with lower extremity pain or sensory complaints. A predetermined independent reference standard for the diagnosis of SFSN should be specifically stated in such studies.
- A case definition of SFSN should be developed. Investigators need to determine whether this case definition should be based on clinical criteria, pathological criteria (e.g., skin biopsy), or a combination of clinical, paraclinical, and pathologic criteria.
- The diagnostic accuracy of morphologic changes (e.g., axonal swellings) in the diagnosis of SFSN versus healthy controls and disease controls needs to be better defined.
- Studies exploring other uses for skin biopsy beyond identification and quantification of DSP and SFSN have been reported and should be further explored. Biopsies of glabrous skin and dermal skin include myelinated nerve fibers, and have been shown to have potential utility in the diagnosis of immune-mediated neuropathies, Charcot–Marie–Tooth (CMT), and related diseases.[22] Other studies have employed skin biopsy for detection or monitoring of leprosy, hereditary amyloidosis, vasculitic neuropathy, and Fabry's disease.[49,53] Additional studies are required to determine the usefulness of skin biopsy in the diagnosis and monitoring of these and other varieties of neuropathy.
- Serial IENF density measurements and IENF regenerative capacity are being studied and used as outcome measures in therapeutic trials.[38,43] Further studies are needed to validate and determine the value of skin biopsy for this purpose.

Mission Statement. The AAN, the AANEM, and the AAPM&R determined that there was a need for an evidence-based and clinically relevant practice parameter for the evaluation of polyneuropathy. As a prelude to this project, the three organizations developed a formal case definition of distal symmetric polyneuropathy DSP.[10] As outlined in this previous publication, the most accurate diagnosis of distal symmetric polyneuropathy is provided by a combination of neuropathic symptoms, signs, and electrodiagnostic (EDX) studies. Since EDX studies are sensitive, specific, and validated measures of the presence of polyneuropathy and can distinguish between demyelinating and axonal types of neuropathy, they should be included as an integral part of the diagnosis.[10] This practice parameter assumes that a clinical diagnosis of polyneuropathy has been determined based on such criteria.

Disclaimer. The diagnosis and evaluation of polyneuropathy is complex. The practice parameter is not intended to replace the clinical judgment of experienced physicians in the evaluation of polyneuropathy. The particular kinds of tests utilized by a physician in the evaluation of polyneuropathy de-

pend on the specific clinical situation and the informed medical judgment of the treating physician.

This statement is provided as an educational service of the AAN, AANEM, and the AAPM&R. 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 test or procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN, AANEM, and AAPM&R recognize that specific care decisions are the prerogative of the patient and physician caring for the patient, based on all of the circumstances involved.

Conflict of Interest. The AAN, AANEM, and AAPM&R are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN, AANEM, and AAPM&R keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN, AANEM, and AAPM&R limit the participation of authors with substantial conflicts of interest. The AAN, AANEM, AAPM&R forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, AANEM and AAPM&R committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

APPENDIX 1A

Quality Standards Subcommittee (AAN). Jacqueline French, MD, FAAN (co-chair); Gary S. Gronseth, MD (co-chair); Charles E. Argoff, MD; Eric Ashman, MD; Stephen Ashwal, MD, FAAN (ex-officio); Christopher Bever Jr., MD, MBA, FAAN; John D. England, MD, FAAN (QSS facilitator); Gary M. Franklin, MD, MPH, FAAN (ex-officio); Deborah Hirtz, MD (ex-officio); Robert G. Holloway, MD, MPH, FAAN; Donald J. Iverson, MD, FAAN; Steven R. Messé, MD; Leslie A. Morrison, MD; Pushpa Narayanaswami, MD, MBBS; James C. Stevens, MD, FAAN (Ex-Officio) David J. Thurman, MD, MPH (ex-officio); Samuel Wiebe, MD; Dean M. Wingerchuk, MD, MSc, FRCP(C); and Theresa A. Zesiewicz, MD, FAAN.

APPENDIX 1B

Practice Issues Review Panel (AANEM). Yuen T. So, MD, PhD (chair); Michael T. Andary, MD; Atul Patel, MD; Carmel Armon, MD; David del Toro, MD; Earl J. Craig, MD; James F. Howard, MD; Joseph V. Campellone Jr., MD; Kenneth James Gaines, MD; Robert Werner, MD; Richard Dubinsky, MD.

APPENDIX 1C

Practice Guidelines Committee (AAPM&R). Dexanne B. Clohan, MD (chair); William L. Bockenek, MD; Lynn Gerber, MD; Edwin Hanada, MD; Ariz R. Mehta, MD; Frank J. Salvi, MD, MS; and Richard D. Zorowitz, MD.

APPENDIX 2

Classification of Evidence for Studies of Diagnostic Accuracy. *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 a 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 to a broad spectrum of controls, where a 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 when either persons with the established condition or controls are of a narrow spectrum, and where a test is applied in a blinded evaluation.

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

APPENDIX 3

Classification of Recommendations. *A* = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires as least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

(Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

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[Note. Strength of evidence is indicated for references used to formulate conclusions and recommendations.]

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