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 laboratory and genetic tests for the assessment of DSP. 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) Screening laboratory tests may be considered for all patients with polyneuropathy (Level C). Those tests that provide the highest yield of abnormality are blood glucose, serum B_{12} with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C). If there is no definite evidence of diabetes mellitus by routine testing of blood glucose, testing for impaired glucose tolerance may be considered in distal symmetric sensory polyneuropathy (Level C). (2) Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies (Level A). Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C). Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic (EDX) features and should focus on the most common abnormalities, which are CMT1A duplication/HNPP deletion, *Cx32 (GJB1)*, and *MFN2* mutation screening. There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (Level U).

Muscle Nerve **39:** 116–125, 2009

EVALUATION OF DISTAL SYMMETRIC POLYNEUROPATHY: THE ROLE OF LABORATORY AND GENETIC TESTING (AN EVIDENCE-BASED REVIEW)

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Abbreviations: AAN, American Academy of Neurology; AANEM, American Academy of Neuromuscular and Electrodiagnostic Medicine; AAPM&R, American Academy of Physical Medicine and Rehabilitation; CMT, Charcot–Marie–Tooth; CPG, clinical practice guideline; CSF, cerebrospinal fluid; DSP, distal symmetric polyneuropathy; EDX, electrodiagnostic; GTT, glucose tolerance testing; immunofixation electrophoresis; QSS, Quality Standards Subcommittee; SPEP, serum protein electrophoresis

Key words: prospective studies; evaluation; distal symmetric polyneuropathy

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Published online 15 December 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mus.21226

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Accepted 9 October 2008

INTRODUCTION

Justification. Polyneuropathy is a relatively common neurological disorder.[8] 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.[7,22] Since there are many etiologies of polyneuropathy; a logical clinical approach is needed for evaluation and management.

This practice parameter provides recommendations for the role of laboratory and genetic tests in 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 laboratory and genetic tests 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.[8] [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 laboratory test, diagnosis, electrophysiology, and genetic testing.

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 4,500 references with abstracts. After reviewing titles and abstracts, 450 articles were reviewed and classified.

Role of Laboratory Testing in the Evaluation of Polyneuropathy. With the exception of electrodiagnostic (EDX) studies, laboratory tests are not utilized to diagnose polyneuropathy; however, laboratory tests are routinely utilized in patients with a diagnosis of polyneuropathy as a screening test for specific etiologies. Several questions regarding the use of laboratory testing as a screening tool in the evaluation of polyneuropathy were assessed.

What Is the Yield of Screening Laboratory Tests in the Evaluation of DSP, and Which Tests Should Be Performed? The cause of most polyneuropathies is evident when the information obtained from the medical history, neurological examination, and EDX studies are combined with simple screening laboratory tests. Such a comprehensive investigation yields an etiological diagnosis in 74%–82% of patients with polyneuropathy.[1,6,9,12,14,21,23,28,29,40] Laboratory test results must be interpreted in the context of other clinical information since the etiologic yield of laboratory testing alone is limited by the low specificity of many of the tests. For example, one study of idiopathic polyneuropathy found that laboratory tests alone had only a 37% diagnostic yield (Class III).[21] In another study, laboratory abnormalities were documented in 58% of 91 patients with chronic cryptogenic polyneuropathy, but only 9% were etiologically diagnostic (Class III).[9] The majority of studies indicated that screening laboratory tests comprised of a complete blood count, erythrocyte sedimentation rate, comprehensive metabolic panel (blood glucose, renal function, liver function), thyroid function tests, serum B_{12}, and serum protein immunofixation electrophoresis are indicated for most patients with polyneuropathy.[1,6,9,12,14,21,23,28,29,40] Five Class III studies indicated that the highest yield of abnormality was seen with screening for blood glucose, serum B_{12}, and serum protein immunofixation electrophoresis (Class III).[1,9,14,21,32] The test with the highest yield was the blood glucose, consistent with the well-known fact that diabetes mellitus is the commonest cause of DSP. In patients with DSP blood glucose was elevated in ≈11%, serum protein electrophoresis or immunofixation was abnormal in 9%, and serum B_{12} was low in ≈3.6%. Two Class III studies showed that routine cerebrospinal fluid (CSF) analysis had a low diagnostic yield except in demyelinating polyneuropathies, which usually showed an increased CSF protein level.[12,28]

Vitamin B_{12} deficiency was relatively frequent in patients with polyneuropathy, and the yield was greater when the metabolites of cobalamin (methylmalonic acid and homocysteine) were tested (Class II and III).[1,19,20,32,33] Serum methylmalonic acid and homocysteine were elevated in 5%–10% of patients whose serum B_{12} levels were in the low normal range of 200–500 pg/dL.[20,33] In large series of patients with polyneuropathy, between 2.2%–8% of patients had evidence of B_{12} deficiency as indicated by elevations of these metabolites.[1,32] In one Class III study involving 27 patients with polyneuropathy and B_{12} deficiency, 12 (44%) had B_{12} deficiency based on the finding of abnormal metabolites alone.[32] Thus, serum B_{12} assays with metabolites (methylmalonic acid and homocysteine) are useful in documenting B_{12} deficiency.

Although both methylmalonic acid and homocysteine are sensitive for B_{12} deficiency, methylmalonic acid is more specific. In a large Class III study involving 434 patients with vitamin B_{12} deficiency, serum methylmalonic acid was elevated in 98.4% and serum homocysteine was elevated in 95.9%.[33] In the same study serum methylmalonic acid was elevated in 12.2%, but serum homocysteine was elevated in 91% of 123 patients with isolated folate deficiency.[33] Homocysteine may also be elevated in pyridoxine deficiency and heterozygous homocysteinemia. Both homocysteine and methylmalonic acid may be elevated in hypothyroidism, renal insufficiency, and hypovolemia.

Several studies highlight the relatively high prevalence of pre-diabetes (impaired glucose tolerance) in patients with DSP who do not fulfill the criteria for definite diabetes mellitus (Class III).[30,35,37] In these studies glucose tolerance testing (GTT) was performed in patients with idiopathic DSP. Impaired glucose tolerance was documented in 25%–36% of patients compared to ≈15% of controls. Additionally, patients with painful sensory polyneuropathies were more likely to have impaired glucose tolerance than those with painless sensory polyneuropathies. Only one major study has not found an increased prevalence of impaired glucose tolerance in chronic idiopathic axonal polyneuropathy (Class III).[11]

Monoclonal gammopathies are more common in patients with polyneuropathy than in the normal population. IgM monoclonal gammopathies may be associated with autoantibody activity, type I or II cryoglobulinemia, macroglobulinemia, or chronic lymphocytic leukemia. IgG or IgA monoclonal gam-

Table 1. Basic laboratory investigation of polyneuropathy.

Hematology: complete blood count, erythrocyte sedimentation rate or C-reactive protein, vitamin B12,* folate. Methylmalonic acid with or without homocysteine for low normal vitamin B12 levels.*
Biochemical and endocrine: comprehensive metabolic panel (fasting blood glucose,* renal function, liver function), thyroid function tests. Serum protein immunofixation electrophoresis.* Glucose tolerance test if indicated to look for impaired glucose tolerance.*
Urine: urinalysis, urine protein electrophoresis with immunofixation.
Drugs and toxins: inquire about drugs and toxins.

**Tests with the highest yield (Class III).*
This list is not intended to include all possible tests or methods that may be useful in the evaluation of polyneuropathy. Neither is it intended to exclude any reasonable alternative tests or methodologies.

mopathies may be associated with myeloma, POEMS syndrome, primary amyloidosis, or chronic inflammatory conditions. In one Class III study of 279 consecutive patients with polyneuropathy of otherwise unknown etiology seen at a referral center, 10% had monoclonal gammopathy, a significant increase over that reported in community studies.[16] Serum protein immunofixation electrophoresis (IFE) is more sensitive than serum protein electrophoresis (SPEP), especially for detecting small or nonmalignant monoclonal gammopathies. Ten of 58 (17%) monoclonal gammopathies, including 10 of 36 (30%) with IgM <5 g/L, were identified by IFE but not by SPEP.[15]

Conclusions. Screening laboratory tests are probably useful in determining the cause of DSP, but the yield varies depending on the particular test (Class III). The tests with the highest yield of abnormality are blood glucose, serum B_{12} with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Class III). Patients with distal symmetric sensory polyneuropathy have a relatively high prevalence of diabetes or pre-diabetes (impaired glucose tolerance), which can be documented by blood glucose, or GTT (Class III).

Recommendations. Screening laboratory tests may be considered for all patients with DSP (Level C). Although routine screening with a panel of basic tests is often performed (Table 1), those tests with the highest yield of abnormality are blood glucose, serum B_{12} with metabolites (methymalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C). When routine blood glucose testing is not clearly abnormal, other tests for pre-diabetes (impaired glucose tolerance) such as a GTT may be considered in patients with distal symmetric sensory polyneuropathy, especially if it is accompanied by pain (Level C).

Although there are no control studies (Level U) regarding when to recommend the use of other specific laboratory tests, clinical judgment correlated with the clinical picture will determine which additional laboratory investigations (Table 2) are necessary.

Role of Genetic Testing in the Evaluation of Polyneuropathy. Hereditary neuropathies are an important subtype of polyneuropathy, with a prevalence of ≈1:

Table 2. Specialized laboratory investigation of acute and chronic polyneuropathy.*

Connective tissue diseases and vasculitis (Sjogren's disease, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, polyarteritis nodosa, Churg–Strauss disease, Wegener's granulomatosis, ANCA syndrome): antinuclear antigen profile, rheumatoid factor, anti-Ro/SSA, anti-La/SSB, antineutrophil cytoplasmic antigen antibody (ANCA) profile, cryoglobulins.
Infectious agents: *Campylobacter jejuni*, cytomegalovirus (CMV), hepatitis panel (B and C), HIV tests, Lyme disease tests, herpes viruses tests, West Nile virus tests, cerebrospinal fluid analysis.
Diseases of gut: antibodies for celiac disease (gliadin, transglutaminase, endomysial), vitamin E level, B vitamin levels; most require endoscopic confirmation with biopsy.
Sarcoidosis: serum angiotensin converting enzyme (ACE), cerebrospinal fluid analysis including ACE.
Heavy metal toxicity: blood, urine, hair and nail analysis for heavy metals (arsenic, lead, mercury, thallium).
Porphyria: blood, urine, and stool for porphyrins.
Dysimmune: antiganglioside antibody profile (GM1, GD1a, GD1b, GD3, GQ1b, GT1b) , anti-myelin associated glycoprotein (MAG) antibodies, paraneoplastic antibody profile (anti -Hu, anti-CV2), cerebrospinal fluid analysis including immunoglobulin oligoclonal bands.
Hereditary:† molecular genetic tests tailored to the clinical profile and available for an increasing number of hereditary neuropathies such as Charcot–Marie–Tooth disease, hereditary neuropathy with liability to pressure palsies, and hereditary amyloidosis.
Malignancies (carcinoma, myeloma, lymphoma): skeletal radiographic survey; mammography; computed tomography or magnetic resonance imaging of chest, abdomen, and pelvis; ultrasound of abdomen and pelvis; positron emission tomography, cerebrospinal fluid analysis including cytology, serum paraneoplastic antibody profile (anti-Hu, anti-CV2).

**No controlled trials exist for most of these specialized laboratory tests (Level U) except for molecular genetic tests in hereditary neuropathies† (Level A and B). Clinical judgment will determine which tests are necessary (Level U).*
This list is not intended to include all possible tests or methods that may be useful in the evaluation of polyneuropathy. Neither is it intended to exclude any reasonable alternative tests or methodologies.

2,500 people. DSP is the predominant phenotype, but phenotypic heterogeneity may be present even within the same family; therefore, when genetic testing is contemplated all neuropathy phenotypes need to be considered. In the evaluation of polyneuropathy a comprehensive family history should always be elicited. A high index of suspicion for a hereditary neuropathy phenotype is essential. Since molecular diagnostic techniques are available, guidelines for their usefulness in the evaluation of polyneuropathy are needed.

The majority of genetically determined polyneuropathies are variants of Charcot–Marie–Tooth (CMT) disease, and genetic testing is available for an increasing number of these neuropathies. The clinical phenotype of CMT is extremely variable, ranging from a severe polyneuropathy with respiratory failure through the classic picture with pes cavus and "stork legs" to minimal neurological findings.[2,3] Since a substantial proportion of CMT patients have de novo mutations, a family history of neuropathy may be lacking.[2,3,10] Additionally, different genetic mutations can cause a similar phenotype (genetic heterogeneity) and different phenotypes can result from the same genotype (phenotypic heterogeneity).

How Accurate Is Genetic Testing for Identifying Patients with Genetically Determined Neuropathies? The CMT phenotype has been linked to 36 loci and mutations have been identified in 28 different genes, several of which can be identified by commercially available genetic testing. Previous segregation studies followed by several prospective cohort studies have documented that the results of currently available genetic testing are unequivocal for diagnosis of established pathogenic mutations, providing a specificity of 100% (i.e., no false-positives) and high sensitivity (Class I and II).[4,5,13,17,24–27,34,39] The interpretation of novel mutations may require further characterization available in specialized centers. Data from six Class I, six Class II, and one Class III study indicate that genetic testing is useful for the accurate classification of hereditary polyneuropathies.[2,4,5,10,13,17,24–27,34,38,39]

Which Patients with Polyneuropathy Should Be Screened for Hereditary Neuropathies? Genetic studies of hereditary neuropathies have tested the prevalence of various mutations in selected patients with the classic CMT phenotype with and without a family history of polyneuropathy.[5,17,24–27,39] (Class III evidence for screening.) For these patients the yield of genetic tests has been relatively high.

Data from seven studies indicate that the demyelinating form of Charcot–Marie–Tooth (CMT1) is the most prevalent, and about 70% of these patients have a duplication of *PMP22* gene (CMT1A).[5,17,24–27,39] CMT1A is also the most common variety of sporadic CMT1, accounting for 76%–90% of cases.[10,26] Six studies showed that when the test for CMT1A duplication is restricted to patients with clinically probable CMT1 (i.e., autosomal dominant, primary demyelinating polyneuropathy), the yield is 54%–80% as compared to testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathy where the yield is only 25%–59% (average of 43%).[5,13,24,26,34,39]

Axonal forms of Charcot–Marie–Tooth (CMT2) are most commonly caused by *MFN2* mutations, which account for ≈33% of the cases.[38] MFN2 mutations have not occurred in the CMT1 group.

Data from eight studies indicate that *Cx32(GJB1)* mutations cause an X-linked neuropathy (CMTX), which may present with either a predominantly demyelinating or axonal phenotype and account for ≈12% of all cases of CMT.[4,5,13,24,25,27,34,39] If the pedigree is uninformative as to whether the inheritance is autosomal dominant or X-linked (lack of father to son transmission), *Cx32(GJB1)* mutation is in the differential diagnosis for both predominantly demyelinating and axonal neuropathies.

Data from seven studies has established average mutation frequencies of 2.5% for *PMP22* point mutations, and 5% for *MPZ* mutations in the CMT population.[4,5,13,24,25,39] CMT caused by other genes is much less frequent (see Fig. 1).

Given the relationships between pattern of inheritance, EDX results, and specific mutations, the efficiency of genetic testing can be improved by following a stepwise evaluation of patients with possible hereditary neuropathy. First, a clinical classification that includes EDX studies should be performed to determine whether the neuropathy is primarily demyelinating or primarily axonal in type. Since EDX studies are sometimes problematic in children, some physicians may opt to proceed directly to genetic testing of symptomatic children suspected of having CMT. Second, the inheritance pattern (autosomal dominant, autosomal recessive, or X-linked) should be ascertained. Based on this information, the most appropriate genetic profile testing can then be performed.

Figure 1 indicates an evidence-based, tiered approach for the evaluation of suspected hereditary neuropathies, and Table 3 shows the relative frequency of the most common genetic abnormalities accounting for the CMT phenotype from population studies.

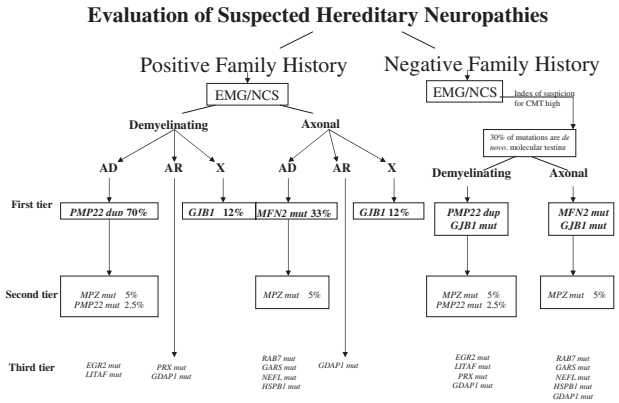

FIGURE 1. Evaluation of suspected hereditary neuropathies. Decision algorithm for use in the diagnosis of suspected hereditary polyneuropathies using family history and NCSs. **PMP22* denotes peripheral myelin protein 22; *MPZ* myelin protein zero; *PRX* periaxin; *GDAP1* ganglioside-induced differentiation-associated protein 1; *GJB1* gap-junction beta-1 protein (connexin 32); *MFN2* mitofusin 2; *EGR2* early growth response 2; *LITAF* lipopolysaccharide-induced tumor necrosis factor α; *RAB7* small guanosine triphosphatase late endosomal protein; *GARS* glycyltransfer RNA synthetase; *NEFL* neurofilament light chain; *HSPB1* heat shock protein beta-1.

The previous discussion applies to patients with polyneuropathy and a classical hereditary neuropathy phenotype with or without a family history. The authors were not able to find studies of the yield of genetic screening in polyneuropathy patients without a classical hereditary neuropathy phenotype. Some patients with CMT genetic mutations have minimal neurological findings and do not have the classical CMT phenotype.[2,3] Thus, some patients with cryptogenic polyneuropathies without the classical CMT phenotype may also have hereditary neuropathies. The prevalence of mutations in this population is unknown.

Conclusions. Genetic testing is established as useful for the accurate diagnosis and classification of hereditary polyneuropathies (Class I). For patients with a cryptogenic polyneuropathy who exhibit a classical hereditary neuropathy phenotype, routine genetic screening may be useful for CMT1A duplication/deletion and *Cx32* mutations in the appropriate phenotype (Class III). Further genetic testing may be considered guided by the clinical question. There is insufficient evidence to determine the usefulness of routine genetic screening in cryptogenic polyneuropathy patients without a classical hereditary neuropathy phenotype.

Recommendations. Genetic testing may be considered in patients with a cryptogenic polyneuropathy and classical hereditary neuropathy phenotype (Level C). To achieve the highest yield, the genetic testing profile should be guided by the clinical phenotype, inheritance pattern (if available), and EDX features (demyelinating versus axonal). (See Fig. 1 for guidance.)

There is insufficient evidence to support or refute the usefulness of routine genetic testing in cryptogenic polyneuropathy patients without a classical hereditary phenotype (Level U).

RECOMMENDATIONS FOR FUTURE RESEARCH

This comprehensive review reveals several weaknesses in the current approach to the evaluation of

Table 3. Mutation frequencies for Charcot-Marie-Tooth (CMT) and related neuropathies in various populations. The mutation frequencies are given in the total CMT cohort and in the clinical phenotypes (CMT1 and HNPP) when available.

Population	Cohort (# of pt) Total/CMT1/*HNPP*	CMT1A Duplication Total/CMT1	HNPP Deletion Total/*HNPP*	*PMP22* mutation Total/CMT1	*Cx32* mutation Total/CMT1	*MPZ* mutation Total/CMT1
American[39]	75/63	56/68	ND	3.9	7.2	3.3
Spanish[4]	52	Excluded	Excluded	3.8 0.8*	19.2 7.7*	9.6 3.8*
Belgian[13]	443	24.6	10.6	2.7	5.4	0.7
Finnish[34]	157	40.7	26.1	ND	7.6	ND
Slovene[17]	71	81	ND	ND	ND	ND
European[26]	975/819/*156*	59.4/70.7	13.4/*84*	ND	ND	ND
Australian[27]	224	61	ND	1.3	12	3.1
Russian[24]	174/108/*3*	33.9/53.7	*100*	1.1/1.9	6.8/7.4	3.4 5.6
Italian[25]	172	57.6	ND	1.2	6.9	2.3
Korean[5]	57	26/54	ND	1.7	5.3	5.3
Average		43%/70%	11%/92%	2.5%	12%	5%

Bold: CMT1 subpopulation.
Italicized: HNPP subpopulation.
**Extrapolated total number and mutation frequencies recalculated for the total number. For the estimation of the total number the authors calculated with the average frequencies for CMT1A duplication and HNPP deletion derived from the other studies.*

Table 4. Evidence table for genetic testing

Reference	Data collection	Setting*	Sampling	Completeness Gene dependent	Masking	Class
[10]	Prospective	Referral center	NA	*PMP22* dup	Waived	II
[39]	Prospective	Referral center	Consecutive	*PMP22* dup	Waived	II
[4]	Prospective	Referral center	Consecutive	*PMP22* mut, *Cx32, MPZ*	Waived	I
[13]	Prospective	Referral center	Consecutive	*PMP22* dup, del, mut, *Cx32, MPZ*	Waived	I
[34]	Prospective	Referral center	Consecutive	*PMP22* dup, del, *Cx32*	Waived	II
[17]	Prospective	NA	NA	*PMP22* dup	Waived	III
[26]	Prospective	Referral center	Consecutive	*PMP22* dup, del	Waived	I
[27]	Prospective	Referral center	Consecutive	*PMP22* dup, mut, *Cx32, MPZ*	Waived	II
[24]	Prospective	Referral center	Consecutive	*PMP22* dup, del, mut, *Cx32, MPZ*	Waived	II
[25]	Prospective	Referral center	Consecutive	*PMP22* dup, mut, *Cx32, MPZ*	Waived	I
[2]	Prospective	Referral center	Consecutive	*PMP22* dup, mut, *Cx32, MPZ*	Waived	I
[5]	Prospective	Referral center	Consecutive	*PMP22* dup, mut, *Cx32, MPZ*	Waived	I
[38]	Prospective	Referral center	Selected	*MFN2*	Waived	II

**Referral center for test, not for patient; patients come from general neurology clinics*

polyneuropathy and highlights opportunities for research.

Laboratory Testing. The finding of a laboratory abnormality does not necessarily mean that the abnormality is etiologically significant. For instance, there is a relatively high prevalence of impaired glucose tolerance in patients with distal symmetric polyneuropathy; however, whether this is etiologically diagnostic is not known. This and other such examples point to the need for more research into the basic pathobiology of the peripheral nervous system. As an extension of this area of research, there is a need to determine whether aggressive treatment or reversal of specific laboratory abnormalities improves or alters the course of polyneuropathy.

Genetic Testing. The genetic revolution has provided great insights into the mechanisms of hereditary neuropathies. Genetically determined neuropathies are more common and clinically diverse than previously appreciated. Further research to identify genotype–phenotype correlation is needed to improve the evaluation process for patients with suspected hereditary neuropathies. The issue of cost/benefit ratio of genetic testing is important since an ever-increasing number of genetic tests are commercially available. More clearly defined guidelines for genetic testing are needed to maximize yield and to curtail the costs of such evaluations. Continued exploration into the genetic basis of neuropathies has tremendous potential for the understanding of basic pathophysiology and treatment of neuropathies.

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 DSP.[8] As outlined in this previous publication, the most accurate diagnosis of distal symmetric polyneuropathy is provided by a combination of neuropathic symptoms, signs, and 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.[8] 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 depend 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, and 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 Members. 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

Clinical Quality Improvement 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 givencondition 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.

Approved by the AANEM Board of Directors on May 1, 2008. With regard to conflicts of interest, the authors disclose the following: (1) Holds financial interests in Pfizer. (2) Holds financial interests in Pfizer and GlaxoSmithKline and Boeheringer Ingelheim for speaker honoraria and Ortho-McNeil for serving on the IDMC Committee. (3) Nothing to disclose. (4) Nothing to disclose. (5) Received royalties from the American Medical Resources, Enduring Medical Materials (CD/DVD), has received honorarium from Medical Education Resources, CME LLC, Expert Witness testimony and record review, Peters Marketing Research, Delve Marketing Research, Cross Country Education and American Medical

Seminars. Dr. Kinsella holds corporate appointments with Cross Country Education and Forest Park Hospital. (6) Nothing to disclose. (7) Receives residual royalties from Elsevier for editorial work done prior to 2005. He receives honoraria from the Dana Foundation, NY, and the International Society for Neuroimmunology. His wife is a consultant for the Dana Foundation. (8) Nothing to disclose. (9) Financial interests in Athena Diagnostics and has received research funding from NIH/NEI, NIH/NIDCR, Charcot-Marie-Tooth Association, and the March of Dimes. (10) Serves as a Scientific Advisor for Quest Diagnostics and is a member of a Steering Committee, Talecris Biotherapeutics. Dr. Latov receives royalties from Demos publications and has received research support from the NIH and Talecris Biotherapeutics. He holds stock options in Therapath LLC and is the beneficiary of license fee payments from Athena Diagnostics to Columbia University. He has given expert testimony in legal proceedings related to neuropathy and has prepared an affidavit with regarding to the legal proceeding related to neuropathy. (11) Financial interests in Talecris and has received research funding from MDA and CMTA. He estimates that approximately 33% of his clinical effort is spent on electromyography. He has received payment for expert testimony regarding the use of IVIg in CIDP; neuropathic pain after breast reduction. (12) Served as a consultant for WR Medical, Viatris, Eli Lilly and Company, Chelsea Therapeutics, and Quigley Corporation. (13) Financial interests in Astrazeneca, Photothera, Wyeth, Jalmarjone Sahron, Inarx, Boehringer-Ingelheim, Dullehi-Arubio, Axaron, U-Servicer, and PAION. (14) Estimates that approximately 15%–20% of his clinical effort is spent on skin biopsies. (15) Serves on a myasthenia gravis medical scientific board, has served as an Associate Editor, *Journal of Clinical Neuromuscular Disease* (1998–2006), receives honoraria from Duke University Medical Center, and Medical Educational Resources. He is the director of MEG laboratories and estimates that 75% of his time is spent there. He also holds stock options in GE, Pfizer, and Johnson & Johnson. In addition, he has provided an affidavit on two cases regarding myasthenia gravis. (16) Financial interests in GlaxoSmithKline and Formenti-Grunenthal. In addition he has received research funding from Pfitzer, Formenti-Grunenthal, Foramenti-Grunenthal, Italian Ministry of Health, and Regione Lombardia. (17) Financial interests in Celgene and Pathologica. (18) Financial interests in DSMB, Pfizer, Johnson & Johnson, Mitsubishi Pharma, Merck, Xenoport, and GSK. He has received research funding from JDRF, NIH, Astellas Pharma, Mitsubishi Pharma, and Sanofi-Aventis. He estimates that 10% of his clinical effort is devoted to EMG, 5% to skin biopsy, and <1% on lumbar puncture. (19) Received payment for expert testimony in the possible neurotoxic injury of the peripheral nerve.

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