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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Idiopathic distal sensory polyneuropathy: ACTTION diagnostic criteria

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Abstract

Objective: To present standardized diagnostic criteria for idiopathic distal sensory polyneuropathy (iDSP) and its subtypes: idiopathic mixed fiber sensory neuropathy (iMFN), idiopathic small fiber sensory neuropathy (iSFN), and idiopathic large fiber sensory neuropathy (iLFN) for use in research.

Methods: The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) public-private partnership with the Food and Drug Administration convened a meeting to develop consensus diagnostic criteria for iMFN, iSFN, and iLFN. After background presentations, a collaborative, iterative approach was used to develop expert consensus for new criteria.

Results: An iDSP diagnosis requires at least one small fiber (SF) or large fiber (LF) symptom, at least one SF or LF sign, abnormalities in sensory nerve conduction studies (NCS) or distal intra-epidermal nerve fiber density (IENFD), and exclusion of known etiologies. An iMFN diagnosis requires that at least one of the above clinical features is SF and one clinical feature is LF. Diagnostic criteria for iSFN require at least one SF symptom and at least one SF sign with abnormal IENFD, normal sensory NCS, and the absence of LF symptoms and signs. Diagnostic criteria for iLFN require at least one LF symptom and at least one LF sign with normal IENFD, abnormal NCS, and absence of SF symptoms and signs.

Conclusions: Adoption of these standardized diagnostic criteria will advance research and clinical trials and spur development of novel therapies for iDSPs..

1. Introduction

Peripheral neuropathies, most of which are chronic distal sensory polyneuropathies (DSPs), are among the most prevalent of neurological disorders. In 20% to 50% of DSP cases, laboratory investigations fail to find a cause, leading to a diagnosis of idiopathic DSP (iDSP, also known as cryptogenic polyneuropathy).[1, 2] No drugs are approved for the treatment of iDSP and its subtypes, idiopathic mixed fiber sensory neuropathy (iMFN), idiopathic small fiber sensory neuropathy (iSFN), and idiopathic large fiber sensory neuropathy (iLFN)). Thus, clinical trials of iDSPs are urgently needed to develop evidence-based therapies.

One potential barrier to developing therapies for iDSP is that eligibility criteria for iDSP research studies do not exist or have considerable variability, depending on the subtype.[3-7] While some diagnostic criteria are available for DSPs of specific etiology,[8, 9] and more recently for SFN,[3, 10, 11] no generally accepted criteria are available for iMFN, iSFN and iLFN. The goal of this article is to present comprehensive and contrasting standardized diagnostic criteria for iMFN, iSFN, and iLFN for clinical research and clinical trials. Clinical trials for novel treatments for iDSP could be designed to examine efficacy and safety in all patients who meet diagnostic criteria for iDSP, e.g., any one of the three subtypes, or only in one or two of the subtypes, depending on the mechanism of action of the treatment.

2. Methods

The Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials (CONCEPPT) of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) public-private partnership with the FDA convened in April of 2018 to develop consensus diagnostic criteria for iDSP and its subtypes. An international group of neurologists, clinical trialists, and regulatory experts from academia,

government, and the pharmaceutical industry attended. Participants were selected based on their research, clinical, or regulatory expertise relevant to peripheral neuropathy and clinical trial design to broadly represent the relevant disciplines and perspectives while limiting the meeting size in order to promote productive and efficient discussion. To facilitate discussion, participants presented a set of background lectures, including the results of a systematic review of current diagnostic criteria and research study entry criteria used for iSFN. Lectures and the meeting transcript are available at on the ACTTION-CONCEPPT webpage.[12] Dr. Freeman served as the facilitator to obtain an initial consensus at the meeting. Based on this initial consensus, an initial draft of the manuscript was developed by Drs. Freeman and Gewandter (i.e., lead authors). The manuscript was sent to all authors for feedback. Subsequently, the lead authors synthesized the input and redistributed the manuscript for futher feedback. This process occurred 4 times, until no new major themes emerged and all authors approved the final manuscript.

3. Background

The sensory neuropathy nomenclature (MFN, SFN, LFN) is derived from the population of nerve fibers affected in these conditions. These fibers are classified as Aβ, Aδ, and C fibers based on their cell body size, axon diameter, amount of myelination, and conduction velocity. The Aβ fibers have large cell bodies, are heavily myelinated, and have conduction velocities that range from 16-100 m/s; the Aδ fibers have medium sized cell bodies, are lightly myelinated and have conduction velocities between 5 and 30 m/s; and the C fibers have small cell bodies, are unmyelinated with conduction velocities less than 5 m/s. Aβ fibers are considered large fibers whereas the Aδ and C fibers are considered small fibers.[13-15] Because of their anatomic and consequent neurophysiological characteristics, Aδ and C fibers, which are predominantly or exclusively injured in SFN, cannot be assessed using standard clinical neurophysiological techniques. The clinical phenomenology associated with these neuropathies is a function of the sensory modalities subserved by the damaged nerve fibers.

Small fiber sensory modalities include pain, temperature, and poorly localized light touch; consequently, symptoms associated with SFN include spontaneous and evoked pain, numbness, pruritic sensation, and paresthesias.[13-20] Large fiber sensory modalities encompass touch, proprioception, pressure, and vibration perception. The deep tendon reflexes are also mediated by the large fibers. Thus, symptoms associated with LFN include numbness, balance impairment, paresthesias, and sensory distortion.[13-20] Hence, the symptoms of numbness and paresthesias and impaired light touch perception may be present in both large and small fiber polyneuropathies.[13-20]

In this article we provide diagnostic criteria for iMFN (i.e., a polyneuropathy with both small and large fiber features), pure (or isolated) iSFN and pure (or isolated) iLFN. In doing so we recognize that pure SFN and LFN may have subclinical large and small fiber pathology or pathophysiology, respectively, e.g., detectable with sural nerve biopsy or microneurographic techniques, and that pure SFN and pure LFN may, in some patients, evolve over time into a MFN. The diagnostic criteria for iDSP are fulfilled when the specific diagnostic criteria for any one of the three iDSP subtypes are met <u>or</u> in those patients who meet all criteria for SFN and have abnormal nerve conduction studies (termed clinical SFN with abnormal large fiber neurophysiology) <u>or</u> in those patients who meet all criteria for LFN and have abonormal IENFD (termed clinical LFN with abnormal nerve fiber density).

4. Diagnostic Criteria for idiopathic distal sensory polyneuropathy (iDSP)

4.1 Symptoms

Polyneuropathy symptoms should be present in a symmetrical, length-dependent distribution for clinical trial inclusion. In some patients, iDSP presents in an asymmetric or non-length dependent manner. We did not define criteria for that disorder in this manuscript.

To maximize sensitivity and ensure that patients are not excluded based on unique sensory symptom descriptions, a specific list of painful and non-painful sensory symptom

descriptors was deliberately excluded and only one sensory symptom was required (Tables 1).

This potentially non-rigorous symptom definition is unlikely to adversely affect diagnosis since

the requirements related to signs (see Section 4.2) and neurophysiological and

neuropathological tests (see Section 4.6) would be expected to increase the specificity of the

criteria. However, to further increase the specificity for entry into clinical trials, investigators may

consider requiring at least one symptom from at least two of the symptom bullets listed in Table

1.

4.2 Signs

The diagnosis of iDSP requires abnormality in at least one of the clinical signs assessed

by sensory neurological examination (Table 1). The following four signs: abnormal pinprick

perception, abnormal light touch perception, abnormal vibratory perception, and abnormal

proprioception were selected because they constitute the core elements of the neurologic

clinical exam. Additionally, in a recent systematic review, they were found to be the most

common signs of sensory dysfunction evaluated in clinician-rated outcome measures for

peripheral neuropathy related to chemotherapy, diabetes, HIV, and hATTR.[21] Hyperalgesia and

allodynia were also included because they are positive signs that indicate a pathological

increase in nerve excitability and are commonly evaluated in patients with neuropathic pain.[22]

Deep tendon reflexes have been excluded from the diagnostic criteria because of age-related

changes in the healthy elderly.[23, 24] To further increase the specificity for entry into clinical trials,

investigators may consider requiring at least one sign from at least two of the sign bullets listed

in Table 1.

Standardized assessment procedures and normative values should be used to identify

abnormality in clinical signs (e.g., Rydel-Seiffer tuning fork for vibration[25]). However, many

clinical examination components do not have evidence-based cut-offs and require judgement by

a neurologist or a clinician trained in neurological examination (see Gewandter et al.[21] for a

description of the available standardized examination assessments and normative values). For

clinical trials, the method used to assess each of the clinical signs should be standardized

across sites and investigators should be trained to maximize consistency as much as possible.

In addition, publication of the standardization methods used in clinical trials would help future

investigators and standardize the manner in which these signs are evaluated across studies.

4.3 Motor involvement

Muscle weakness (i.e., the main indicator of a motor neuropathy) should be excluded by

a neurologist or a clinician trained in neurological examination. However, depending on the

research question, the study goals, or a drug's mechanism of action, it may not be necessary to

eliminate motor involvement in all studies. Such an exception should be noted in the entry

criteria.

4.4 Etiology

Evaluating the cause of all DSPs is important for guiding treatment and entry into clinical

trials. Although associations do not guarantee causality, DSP is more prevalent in individuals

with certain conditions, exposures to drugs or toxins, and genetic variants, than those in the

general population. Thus, these potential causes are likely to contribute to the development of

all DSP subtypes and must be excluded as potential etiologies (Table 1) when making a

diagnosis of iDSP subtypes. The etiologies were selected based on consensus among the

authors and from research studies demonstrating associations between these potential

etiologies and DSPs.[2, 24, 26-34] These possible etiologies should be considered first-line

exclusions and further exclusions[35] might be considered under certain circumstances, for

example, in phase 2 or 3 clinical trials or in patients with specific medical histories or

abnormalities on examination or routine testing. Because some of these excluded disorders

(e.g., prediabetes and monoclonal gammopathy) have a high prevalence, and may not

necessarily be causative in particular patients, depending on the nature of the therapeutic

agent, clinical trial or study, one might include patients with these features. If doing so, it should

be explicitly stated in the entry criteria.

Furthermore, some, but not all, recent studies[36, 37] have identified low-frequency gain-of-function mutations in genes encoding sodium channels $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ (*SCN9A*, *SCN10A*, and *SCN11A*, respectively) in some SFN patients.[30-34] Some studies have observed similar findings in patients with diabetic peripheral neuropathy.[33, 37, 38] These observations have underscored the need for SFN research and a broadly accepted approach for classifying pure or isolated iSFN. Investigators may wish to include patients with specific genetic variants in clinical research studies of DSP subtypes. If so, this should be explicitly stated in the entry criteria.

The role of genetic screening in observational and interventional studies in peripheral neuropathy is evolving as genetic sequencing costs decrease. Depending on the mechanism of action of a putative disease modifying agent, sequencing may be helpful, but it is not required in all iSFN trials. However, when possible, blood should be drawn and banked for later analysis. Excluding patients with one or more first-degree relatives with a DSP may help exclude patients with a hereditary peripheral neuropathy, but given the high population prevalence of DSP, not all studies may require this exclusion.

4.5 Duration

Sensory polyneuropathy symptoms should be present and stable for at least 3 months to increase the likelihood that the condition is not acute and reversible. The 3-month minimum is consistent with the requirement of pain chronicity defined by the International Association for the Study of Pain (IASP)[39] and the ACTTION-American Pain Society Pain Taxonomy (AAPT).[40] Certain forms of peripheral neuropathy can spontaneously improve; thus, for clinical trials, a longer minimum duration of 6 months could be considered. These criteria only apply to patients with chronic iDSPs and not acute or subacute DSPs.

4.6. Neurophysiological and neuropathological tests

A confirmed or definite iDSP diagnosis requires either abnormal sensory nerve conduction studies, e.g., sural sensory nerve action potential amplitudes (SNAPs) and/or nerve conduction velocity (NCV), or decreased intraepidermal nerve fiber density (IENFD). Sensory

nerve conduction and IENFD were chosen as the two diagnostic tests for confirming DSP

because they detect abnormalities in large and small sensory neurons, respectively, and they

have the most available age-based normative values for identifying abnormal cases.[41, 42]

However, multiple technical details should be considered when performing these tests. Nerve

conduction study values can be affected by electrode setup, accuracy of distance

measurements, limb temperature, and testing parameters.[43] It is important to standardize nerve

conduction analyses and employ similar techniques as those used to generate the normative

reference values for identifying abnormal cases. The Normative Data Task Force of the

American Association of Neuromuscular & Electrodiagnostic Medicine identified high-quality

studies reporting nerve conduction normative values with sufficiently detailed technical methods

to reproduce the technique in a test sample.[43]

For IENFD, two large, multi-center and multi-national studies have established age- and

sex-based normative data for identifying abnormal cases.[41, 42] Importantly, skin biopsy with

IENFD analysis is technically challenging and susceptible to false positives of low IENFDs

resulting from sub-optimal handling including, e.g., tissue crush or stretch, or thermal damage

from inadequate cryoprotection. Strict adherence to handling and processing guidelines is

therefore essential (e.g., 50 micron thick sections on frozen tissue and not paraffin embedded

thin sections).[44] To maximize reliability, it is highly recommended to send skin biopsies for

processing and evaluation to experienced laboratories with documented expertise in quantifying

IENFD.

Performing nerve conduction studies and assessing IENFDs may be challenging in a

multi-center clinical trial. In cases where these tests are not feasible, and in other specific

research situations, a diagnosis of clinically-defined iDSP based solely on symptoms, signs, and

exclusion of known potential etiologies may be appropriate (see Section 4.6); however, this

should be explicitly noted in the inclusion criteria. Under this circumstance, to increase

specificity for entry into clinical trials, investigators could consider requiring two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 1.

Quantitative sensory testing (QST) is an extension of the clinical sensory examination using standardized sensory stimuli and response paradigms. The utility of QST for diagnosing iDSP is still exploratory. The Mayo Clinic Peripheral Nerve group[45] and German Research Network on Neuropathic Pain (DFNS) [46] used different equipment and test paradigms to standardized the testing of multiple QST modalities for diagnosing iMFN, iSFN or iLFN. In order to improve the feasibility of QST in the clinical setting and for large, multi-site clinical trials, bedside QST testing methods are currently being developed by several groups.[47, 48 49] Limitations of QST are that it is a psychophysical test with inherent subjective variability, a lack of equipment availability in many centers, variability in equipment and test paradigms, limited normative data for non-painful neuropathies, and that it has no localizing value. The diagnostic criteria for all sensory neuropathies could be supplemented by including QST if performed in centers with technical experience, as in a recent study.[10]

Corneal confocal microscopy (CCM) has also been used to diagnose DSP. The evidence-base supporting this technique is growing, and it may become a promising tool in the future. Using CCM to distinguish patients with and without diabetic peripheral neuropathy (diagnosed *via* the Toronto Criteria[8]) has acceptable sensitivity and specificity.[50, 51] Normative values from a multinational study of healthy volunteers are published.[52] However, CCM is currently available at few centers, studies have only been published by a small number of investigators, and its specificity for different nerve fiber populations is not established. More definitive conclusions on its use as a diagnostic tool await larger studies.

The quantitative sudomotor axon reflex test (QSART) quantifies post-ganglionic C-fiber mediated sudomotor function (i.e., sweating) *via* an axon reflex, which is triggered by iontophoresis of a cholinergic agonist. Studies suggest this is a sensitive diagnostic test for

iSFN.[53] QSART abnormalities may also add diagnostic value for identifying a subpopulation of iSFN patients with clinical or subclinical autonomic involvement. QSART results are not highly correlated with QST or IENFD;[54] thus, adding QSART to the diagnostic panel for iSFN increases sensitivity without reducing specificity.[55] Normative QSART values are available from a sample of 357 healthy volunteers.[56]

Laboratory-based QST, CCM, and QSART require specialized equipment and standardized protocols for multi-site studies. They are not recommended as core diagnostic criteria or confirmatory tests for multi-site iDSP trials at present due to their limited availability, need for trained personnel, and an insufficient evidence-base of normative values.

5. Specific diagnostic criteria for iDSP subtypes

5.1. Diagnostic criteria for idiopathic mixed fiber sensory neuropathy (iMFN)

IMFN has both small and large fiber features without specific fiber selectivity. An iMFN diagnosis requires that at least one clinical feature is SF and one clinical feature is LF. (Table 1). To increase specificity for entry into clinical trials, investigators could consider requiring two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 1.

To confirm a diagnosis of definite iMFN, abnormal nerve conduction or abnormal IENFD are required (Table 1). In research situations, where nerve conduction or IENFD analyses are not feasible, or are deemed unnecessary based on the specific research question, a diagnosis of clinically-defined iMFN could be made based on symptoms and signs alone. Under this circumstance, more rigorous clinical criteria are proposed, such as two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 1.

5.2. Diagnostic criteria for idiopathic small fiber neuropathy (iSFN)

Pure SFN is more frequently diagnosed in the clinical setting because of the development, validation and widespread availability of IENFD assessment from skin punch

biopsy.[3, 10] An iSFN diagnosis requires the presence of one characteristic painful or non-painful small fiber symptom (e.g., spontaneous or intermittent pain, paresthesias) present in a symmetrical, length-dependent distribution (Table 2) and at least one small fiber sign. To increase specificity for entry into clinical trials, investigators could consider requiring two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 2. A pure iSFN diagnosis requires demonstrating normal distal vibration perception and proprioception.[3, 10] Patients with pure iSFN should have preserved deep tendon reflexes; however, this requirement has been excluded from the diagnostic criteria based on considerations outlined in Section 4.2.[23, 24]

Some patients, otherwise fulfilling all iSFN criteria may report non-painful sensory symptoms only (e.g., paresthesias). Such patients can be classified as having painless iSFN. Autonomic features may be a clinical accompaniment of iSFN. iSFN patients may be classified as iSFN with or without autonomic involvement.[54]

To confirm a diagnosis of pure iSFN, normal nerve conduction studies and abnormal IENFDs are required. In some research situations, where nerve conduction or IENFD analyses are not feasible, confirmation of normal vibration perception and proprioception could be used to a make a diagnosis of clinically-defined iSFN. Under this circumstance, more rigorous clinical criteria are proposed, such at two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 2.

5.3. Diagnostic criteria for idiopathic large fiber neuropathy (iLFN)

LFN is well-recognized because of the wide-spread availability of nerve conduction studies, the diagnostic gold standard for large nerve fiber dysfunction. A diagnosis of pure iLFN requires the presence of at least one non-painful sensory symptom (e.g., paresthesias) and one large-fiber associated sign, e.g., abnormal vibration perception or abnormal proprioception). Pinprick perception must be normal and allodynia and hyperalgesia must be absent. To increase specificity for entry into clinical trials beyond the core criteria, investigators could

consider requiring at least two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 3.

To confirm an iLFN diagnosis, abnormal nerve conduction with normal IENFD are required. In some research situations, where nerve conduction or IENFD analyses are not feasible, confirmation of abnormal proprioception and vibration perception with normal pinprick perception and absence of allodynia and hyperalgesia could be used to make a diagnosis of clinically-defined iLFN. Under this circumstance, more rigorous clinical criteria are proposed, such at two (or more) symptoms and two (or more) signs from the symptom and sign bullets listed in Table 3.

6. Limitations

These diagnostic criteria are based, in part, on systematic literature reviews (one completed prior to the meeting[21] and a second presented at the meeting). Subsequently, the criteria were developed using a collaborative, iterative expert consensus approach during and after the face-to-face meeting. Others have drawn attention to the methodological limitations of the existing literature that analyzes the sensitivity and specificity of the symptoms, signs, and investigations used to make a diagnosis of DSP, and the challenges inherent to using this literature to develop neuropathy diagnostic criteria.[57, 58] In particular, the role played by bias in potentially inflating the sensitivity and specificity of signs, symptoms and investigations in these studies.[57, 58] These challenges lend support to an expert consensus approach to diagnostic criteria that could provide the basis for future methodologically sound studies to determine the sensitivity and specificity of the peripheral neuropathy signs and symptoms.

In these diagnostic criteria, we have attempted to balance sensitivity, specificity and accuracy, while simultaneously providing sufficient flexibility so that the specific criteria could be tailored to the particular needs of the trial by adding or omitting diagnostic features. This flexible approach will allow these criteria to be used, for example, in community-based epidemiological

studies and clinical trials conducted at centers lacking some diagnostic technology. We have not

provided specific guidelines on interviewing patients to best identify symptoms or to perform

physical exams or neurophysiological tests. Optimizing and standardizing diagnostic methods

and analyses should be a research priority. Finally, while these criteria were developed for

clinical research, they may, with modifications for individual practice capabilities, guide clinical

practice and facilitate research translation into the clinic.

7. Conclusions

iDSPs are common and often debilitating, and currently have no proven efficacious

disease-modifying therapies. Due to advances in understanding the pathophysiological and

mechanistic basis of SFN, targeted therapies may be on the horizon. No broadly accepted,

comprehensive standardized diagnostic criteria are currently available that segregate iMFN,

iSFN, and iLFN. Widespread use of the criteria presented in this article could accelerate

progress in developing therapies for these prevalent and often refractory conditions.

Appendix 1: Authors

Name	Location	Contribution
Roy Freeman	Boston, MA, USA	Co-organized, moderated consensus meeting, contributed to writing first draft and incorporating author feedback.
Jennifer S. Gewandter	Rochester, NY, USA	Co-organized consensus meeting, prepared first draft, and contributed to incorporating author feedback.
Catharina G. Faber	Maastricht, the Netherlands	Attended the consensus meeting and provided input on iterative manuscript drafts.
Christopher Gibbons	Boston, MA, USA	Attended the consensus meeting and provided input on iterative manuscript drafts.
Simon, Haroutounian	St. Louis, MO, USA	Attended the consensus meeting and provided input on iterative manuscript drafts.
Giuseppe Lauria	Milan, Italy	Attended the consensus meeting and provided input on iterative manuscript drafts.
Todd Levine	Phoenix, Arizona	Attended the consensus meeting and

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Josh Bell	Cambridge, MA, USA	Attended the consensus meeting and provided input on iterative manuscript drafts.
Robert H. Dworkin	Rochester, NY, USA	Obtained funding for and attended the consenus meeting and provided input on iterative manuscript drafts.
Eva Feldman	Ann Arbor, MI, USA	Attended the consensus meeting and provided input on iterative manuscript drafts.
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9. Acknowledgements

Table 1. Diagnostic criteria for idiopathic mixed fiber sensory neuropathy (iMFN)
At least 1 of the following sensory symptoms is present in a symmetrical, length-dependent distribution (i.e., neuroanatomically plausible distribution): • Spontaneous constant or intermittent pain (e.g., burning pain, sharp or shooting pain)† • Patient-reported evoked pain to a normally non-painful stimulus† • A non-painful sensory symptom [e.g., paresthesias (tingling, pins and needles),†* numbness,†* sensory distortion*]
At least 1 of the following distal signs assessed on the basis of a physical examination: • Abnormal pinprick perception† • Allodynia (i.e., pain evoked by a normally non-painful stimulus like light touch, pressure, warm)† • Hyperalgesia (i.e., increased pain evoked by a normally painful stimulus)† • Abnormal light touch perception†* • Abnormal vibratory perception* • Abnormal proprioception*
Absence of muscle weakness
Absence of the following: • Abnormal glucose metabolism (e.g., diabetes, impaired fasting glucose, impaired glucose tolerance) • Paraproteinemia • HIV infection • Vitamin B12 deficiency • Sjogren's syndrome and other systemic connective tissue disorders • Vasculitic neuropathies • Sensory chronic inflammatory demyelinating polyneuropathy (CIDP) and atypical CIDP • Sensory neuronopathies • Neurotoxin exposure (e.g., neurotoxic chemotherapeutic or HIV treatment, excessive alcohol ingestion) • Inherited neuropathy (e.g., familial amyloid polyneuropathy due to hATTR amyloidosis or other pathologic mutations)
3 months minimum duration to ensure disease stability (e.g., to exclude acute or subacute immune mediated neuropathy)
Abnormalities in at least 1 of the following: • Distal lower extremity intraepidermal nerve fiber density (IENFD)† • Sensory nerve conduction studies*
An iMFN diagnosis requires that at least one of the above symtpoms or signs is SF and one is LF with confirmation by abnormalities in sensory nerve conduction studies (NCS) or distal intra-epidermal nerve fiber density (IENFD).

If an individual meets the above criteria for iMFN, the critieria for iDSP are also fulfilled. In addition, those patients who meet all criteria for SFN and have abnormal nerve conduction studies (termed clinical SFN with abnormal large fiber neurophysiology) or in those patients who meet all criteria for LFN and have abonormal IENFD fulfill criteria for iDSP (termed clinical LFN with abnormal nerve fiber density).

† Indicates a symptom, sign or neurophysiological test that is associated with SFN.

* Indicates a symptom, sign or neurophysiological test that is associated with LFN.

To increase specificity for entry into clinical trials, investigators could consider requiring two (or more) symptoms and two (or more) signs from the symptom and sign bullets.

Table 2. Diagnostic criteria for idiopathic small fiber sensory neuropathy (iSFN)
At least 1 of the following sensory symptoms must be present in a symmetrical, length-dependent distribution (i.e., neuroanatomically plausible distribution): • Spontaneous constant or intermittent pain (e.g., burning pain, sharp or shooting pain) • Patient-reported evoked pain to a normally non-painful stimulus • A non-painful sensory symptom [e.g., paresthesias (tingling, pins and needles)]
At least 1 of the following distal signs assessed on the basis of a physical examination: • Allodynia (i.e., pain evoked by a normally non-painful stimulus like light touch, pressure, warm) • Hyperalgesia (i.e., increased pain evoked by a normally painful stimulus) • Abnormal pinprick perception
Requires both of the following distal signs assessed on the basis of a physical examination: • Normal vibratory perception • Normal proprioception
Absence of muscle weakness
Absence of the following: • Abnormal glucose metabolism (e.g., diabetes, impaired fasting glucose, impaired glucose tolerance) • Paraproteinemia • HIV infection • Vitamin B12 deficiency • Sjogren's syndrome and other systemic connective tissue disorders • Vasculitic neuropathies • Sensory chronic inflammatory demyelinating polyneuropathy (CIDP) and atypical CIDP • Sensory neuronopathies • Neurotoxin exposure (e.g., neurotoxic chemotherapeutic or HIV treatment, excessive alcohol ingestion) • Inherited neuropathy (e.g., familial amyloid polyneuropathy due to hATTR amyloidosis or other pathologic mutations)
3 months minimum duration to ensure disease stability (e.g., to exclude acute or subacute immune mediated neuropathy)
Abnormal reduced distal lower extremity intraepidermal nerve fiber density (IENFD)
Normal sensory nerve conduction studies

If an individual meets the above criteria for iSFN, the critieria for iDSP are also fulfilled.

To increase specificity for entry into clinical trials, investigators could consider requiring two (or more) symptoms and two (or more) signs from the symptom and sign bullets.

Numbness is a symptom that is common to both small and large fiber neuropathies and is not listed as an inclusion criterion however, the presence of numbness is not an exclusion criterion for SFN

Table 3. Diagnostic criteria for idiopathic large fiber sensory neuropathy (iLFN)
At least 1 of the following sensory symptoms must be present in a symmetrical, length-dependent distribution (i.e., neuroanatomically plausible distribution): • A non-painful sensory symptom [e.g., paresthesias (tingling, pins and needles), sensory distortion]
At least 1 of the following distal signs assessed on the basis of a physical examination: • Abnormal vibratory perception • Abnormal proprioception
Requires all of the following distal signs assessed on the basis of a physical examination: • Normal pinprick perception • Absence of allodynia (i.e., pain evoked by a normally non-painful stimulus) • Absence of hyperalgesia (i.e., increased pain evoked by a normally painful stimulus)
Absence of muscle weakness
Absence of the following: • Abnormal glucose metabolism (e.g., diabetes, impaired fasting glucose, impaired glucose tolerance) • Paraproteinemia • HIV infection • Vitamin B12 deficiency • Sjogren's syndrome and other systemic connective tissue disorders • Vasculitic neuropathies • Sensory chronic inflammatory demyelinating polyneuropathy (CIDP) and atypical CIDP • Sensory neuronopathies • Neurotoxin exposure (e.g., neurotoxic chemotherapeutic or HIV treatment, excessive alcohol ingestion) • Inherited neuropathy (e.g., familial amyloid polyneuropathy due to hATTR amyloidosis or other pathologic mutations)
3 months minimum duration to ensure disease stability (e.g., to exclude acute or subacute immune mediated neuropathy)
Abnormal sensory nerve conduction studies
Normal distal lower extremity intraepidermal nerve fiber density (IENFD)

If an individual meets the above criteria for iLFN, the critieria for iDSP are also fulfilled.

To increase specificity for entry into clinical trials, investigators could consider requiring two (or more) symptoms and two (or more) signs from the symptom and sign bullets.
Numbness is a symptom that is common to both small and large fiber neuropathies and is not listed as an inclusion criterion however, the presence of numbness is not an exclusion criterion for LFN.