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Nerve Fiber Density Testing

Policy Number: AHS – M2112 – Nerve Fiber Density Testing	Original Effective Date: 05/15/2022 Current Effective Date: 05/01/2026

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I. Policy Description

Nerve fiber density testing involves analysis of skin biopsy stained with an antibody to antiprotein gene product 9.5[1] which avidly stains all axons.[2] The number and morphology of axons within the epidermis are evaluated to determine epidermal nerve fiber density[3] and assess for the presence and degree of neuropathy.[4]

II. Related Policies

Policy Number	Policy Title
N/A	Not applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For the diagnosis of small-fiber neuropathy, epidermal nerve fiber density measurement from a skin biopsy **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
   a) An individual presents with symptoms of painful sensory neuropathy;
   b) There is no history of a disorder known to predispose to painful neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy);
   c) Physical examination shows no evidence of findings consistent with large-fiber neuropathy, such as reduced or absent muscle-stretch reflexes or reduced proprioception and vibration sensation;
   d) Electromyography and nerve-conduction studies are normal and show no evidence of large-fiber neuropathy.

2) For all other situations not described above, epidermal nerve fiber density measurement from a skin biopsy **DOES NOT MEET COVERAGE CRITERIA**.

3) Measurement of sweat gland nerve fiber density **DOES NOT MEET COVERAGE CRITERIA**.

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IV. Table of Terminology

Term	Definition
AACE	American Association of Clinical Endocrinologists
AAN	American Academy of Neurology
AANEM	American Association of Neuromuscular and Electrodiagnostic Medicine
AAPM&R	American Academy of Physical Medicine and Rehabilitation
ACE	American College of Endocrinology
ADA	American Diabetes Association
BAEPs	Brainstem auditory evoked potentials
CCM	Corneal confocal microscopy
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMS	Centers for Medicare and Medicaid Services
CMT1A	*Charcot-Marie-Tooth Disease Type 1A*
CNBD	Corneal nerve branch density
CNFD	Corneal nerve fiber density
CNFL	Corneal nerve fiber length
CTBD	Corneal total branch density
DNFL	Dermal nerve fiber length
DSP	Distal symmetric polyneuropathy
DSPN	Diabetes and neuropathy
EDS	Ehlers-Danlos Syndrome
EFNS	European Federation of Neurological Societies
ENFD	Epidermal nerve fiber density
FAP	Familial amyloid polyneuropathy
FD	Fabry disease
FM	Fibromyalgia
FMS	Fibromyalgia syndrome
FRDA	Friedreich's ataxia
H&E	Haematoxylin and eosin
HIV	Human immunodeficiency virus
IASP	International Association for the Study of Pain
IENF	Intraepidermal nerve fiber
IENFD	Intraepidermal nerve fiber density
IETNFL	Intraepidermal total nerve fiber length
IGT	Impaired glucose tolerance
IHC	Immunohistochemistry
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MAL	Mean axonal length
MP	Medial plantar

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NCS	Nerve conduction studies
NeuPSIG	Neuropathic Pain Special Interest Group
NIS-LL	Neuropathy Impairment Score in the Lower Limb
OH	Overt hypothyroidism
PASC-SFN	Post-Acute Sequelae Small Fiber Neuropathy
PCC	Post-COVID Condition
PD	Parkinson's Disease
PGP	Protein gene product
PNS	Peripheral Nerve Society
Product 9.5	Protein gene product 9.5
QST	Quantitative sensory testing
ROC	Receiver-operating characteristic
SENPD	Subepidermal nerve plexus densities
SFN	Small fiber neuropathy
SFSG	Small-fiber sensory ganglionopathy
SFSN	Small fiber sensory neuropathy
SFSPN	Small fiber sensory polyneuropathy
SGII	Sweat gland innervation index
SGNF	Sweat gland nerve fiber
SH	Subclinical hypothyroidism
T1DM	Type 1 diabetes without neuropathy
VAS	Visual analog scale
VEPs	Visual evoked potentials
VIP	Vasoactive intestinal peptide

V. Scientific Background

Neuropathy can be defined as dysfunction of the peripheral nerves, leading to weakness or a numbness feeling in the hands, feet, arms, or legs. This disorder can be caused by several ailments including infections, traumatic injuries, and metabolic problems such as diabetes. As the pathology of neuropathy is usually first evident in nerve terminals; both sensory and autonomic nerves have terminals in the epidermis of the skin,[5] evaluation of nerve fibers in skin biopsy is a reasonable approach to the diagnosis of neuropathy. Skin biopsy is a commonly used technique for assessment of peripheral nerve disease. The biopsy is a benign procedure with few and reasonably tolerated side effects. Multiple biopsies can be performed without issue. The skin tissue is obtained with a 3 mm "punch," which is then cut into thick sections. These segments are stained with antiprotein gene product 9.5 antibody (PGP 9.5), which stains all axons. The status of these axons is then evaluated to determine epidermal nerve density. The biopsy site depends on the specific indication; for example, a length-dependent peripheral neuropathy typically uses biopsies at the distal leg and a proximal site such as the lateral thigh. Nerve fiber biopsy has numerous applications, such as differentiating between neurogenic and myopathic conditions, characterizing muscular disease, and evaluation of peripheral neuropathies. However, the most common use for skin biopsy is evaluation of small fiber sensory neuropathy.[4]

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Many chronic disorders lead to small fiber peripheral neuropathy, including diabetes, thyroid dysfunction, sarcoidosis, vitamin B12 deficiency, human immunodeficiency virus (HIV), celiac disease, and paraneoplastic syndromes. Small fiber neuropathy is often a challenging clinical problem as patients commonly have severe complaints, but standard electrophysiologic testing is often normal; moreover, sural nerve biopsy may be normal or only minimally abnormal. The range of applications of skin biopsy has been expanded to include autonomic neuropathies and immune-mediated and inherited demyelinating neuropathies.[6] However, skin biopsy is not useful in assessment of the etiology of neuropathy. Skin biopsy cannot replace nerve biopsy when neuropathological examination of mixed or large-fiber neuropathy is needed or when a vasculitis pathogenesis is suspected.[6]

Proprietary Testing

The assessment of epidermal nerve fiber (ENFD) and sweat gland nerve fiber (SGNF) density with PGP 9.5, for the evaluation of small fiber neuropathy, is commercially available from Therapath with a biopsy kit[7] and from BakoDx with a biopsy kit that also provides an assessment of SFN's degree of severity. BakoDx's specificity of ENFD is 95%-97%; and the sensitivity is approximately 90%.[8] Intraepidermal nerve fiber (IENF)-density measurement may also be performed with proprietary tests done by local research pathology labs. Ipsum Diagnostics developed a ENFD test that uses H&E as the background stain opposed to the IHC background stain that is regularly implemented by other labs.[9] Additional labs, such as Corinthian Reference Lab, also offer commercial ENFD tests kits to physicians to aid in a diagnosis of small fiber neuropathy.[10]

Clinical Utility and Validity

A committee consisting of the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) and the American Academy of Physical Medicine and Rehabilitation (AAPM&R) performed a literature review to evaluate the diagnostic accuracy of intraepidermal nerve fiber (IENF) density in the detection of small fiber neuropathy. A total of 106 articles were reviewed.[11]

The committee noted that all the case control studies showed a significant reduction in IENF density in polyneuropathy patients compared to controls. The sensitivity of decreased IENF density for the diagnosis of polyneuropathy ranged from 45% to 90%. The specificity of normal IENF density for the absence of polyneuropathy ranged from 95% to 97%. The committee suggested that the absence of reduced IENF density (using the clinical impression as the diagnostic reference standard) would not "rule out" polyneuropathy, but reduced IENF density would raise the likelihood of polyneuropathy.[11]

The authors also assessed the sensitivity of IENF density assessment at the ankle. Four studies were identified. In these studies, the specificity of the test ranged from 95% to 97.5%, and the sensitivities ranged from 24% to 100%. This study found that "among patients with symptoms of SFSN [small fiber sensory neuropathy] and an abnormal pinprick examination in the feet, but normal ankle reflexes, normal vibration sensibility, and normal NCS [nerve conduction studies], 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."[11] The committee concluded that "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

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[distal symmetric polyneuropathy] which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III)."[11]

Collongues, et al. (2018) created a normative dataset for intraepidermal nerve fibers from the distal leg. Three hundred healthy controls contributed samples. The authors measured nerve density with protein gene product-9.5 immunocytochemistry and brightfield microscopy. The fifth percentile of intraepidermal nerve fiber density was calculated to be "7.6156-0.0769 x age (years) + 1.5506 x gender (woman = 1; man = 0)."[12]

Piscosquito, et al. (2021) studied how understanding nerve fiber spatial distribution could help improve the diagnostic yield of skin biopsy. The study included 31 patients with SFN symptoms, normal nerve conduction study, abnormal quantitative sensory testing, and normal IENF density, 31 healthy controls, and 31 SFN patients with reduced IENF density. The distance between consecutive IENFs in the three groups was measured. It was found that the mean interfiber distances did not differ between patients with normal counts and healthy controls. An inter-fiber distance of 350 um was identified "as the measure that better differentiated patients from controls (AUC = 0.85, sensitivity: 74%, specificity: 94%)." The authors conclude that "the presence of a stretch of denervated epidermis longer than 350 µm is a parameter able to increase the diagnostic efficiency of skin biopsy."[13]

Corrà, et al. (2021) have developed an automated method of IENFD determination aiming to improve diagnostic accuracy and applicability in clinical practice. IENFD generally requires manual analysis by one to three operators, but the automated method requires reduced operator count. The authors studied 60 skin biopsy specimens stained with PGP 9.5. IENFD was first determined manually by three operators, then automatically. The automated method resulted in less variability and similarly high reliability compared to the manual method. The automated method took 15 seconds; the manual method took 10 minutes. The authors conclude that "this automated method rapidly and reliably detects small nerve fibers in skin biopsies with clear advantages over the classical manual technique."[14]

Sensory Neuropathy

McArthur, et al. (1998) established the normative reference range and diagnostic efficiency of nerve fiber density testing for sensory neuropathies in 98 normal controls and 20 patients with sensory neuropathies. The density of intraepidermal fibers in normal controls was found to be 21.4 ± 10.4 per mm in the thigh with the fifth percentile to be 5.2/mm. Density of normal controls in the leg was found to be 13.8±6.7 per mm with the fifth percentile to be 3.8/mm. Using the fifth percentile for the leg as a cutoff, the technique had a "positive predictive value of 75%, a negative predictive value of 90%, and a diagnostic efficiency of 88%."[15]

Chien, et al. (2001) evaluated skin biopsy specimens from the distal leg and distal forearm of 55 healthy controls and 35 patients with sensory neuropathy. In the healthy controls, conventional IENF densities in the distal forearm and in the distal leg were correlated (r=0.55) with significantly higher values in the distal forearm than in the distal leg (17.07±6.51 verses 12.92±5.33 fibers/mm). Compared to IENF densities of healthy controls, these values of neuropathic patients were significantly reduced in the distal forearm (5.82±6.50 fibers/mm) and in the distal leg (2.40±2.30). The specificity of the test was found to be 95%.[5]

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Devigili, et al. (2008) screened 486 patients and collected samples from 124 patients with sensory neuropathy. Among them, they identified 67 patients with pure small fiber neuropathy (SFN) using a new diagnostic "gold standard" based on the presence of at least two abnormal results after clinical examination, quantitative sensory testing (QST), and skin biopsy examination. They found that "Skin biopsy showed a diagnostic efficiency of 88.4%, clinical examination of 54.6% and QST of 46.9%. Receiver operating characteristic curve analysis confirmed the significantly higher performance of skin biopsy comparing with QST."[16]

Devigili, et al. (2019) also screened 150 patients previously diagnosed with sensory neuropathy and 352 new patients with suspected sensory neuropathy to establish diagnostic criteria for small fiber neuropathy. The diagnostic criteria were based on both QST and intraepidermal nerve fiber density (IENFD) measurements. Of the 352 new patients, small fiber neuropathy was diagnosed in 149 "based on the combination between two clinical signs and abnormal QST and IENFD (69.1%), abnormal QST alone (5.4%), or abnormal IENFD alone (20.1%)."[17] The authors noted that "The combination of clinical signs and abnormal QST and/or IENFD findings can more reliably lead to the diagnosis of small fibre neuropathy than the combination of abnormal QST and IENFD findings in the absence of clinical signs."[17] Further, sensory symptoms alone were not a reliable screening method for sensory neuropathy in this study.

Vlckova-Moravcova, et al. (2008) measured IENF densities and subepidermal nerve plexus densities (SENPD) quantified by immunostaining in skin punch biopsies. Samples were taken from the distal calf in 99 patients with clinical symptoms of painful sensory neuropathy; samples were also taken from 37 age-matched healthy volunteers. They found that "In patients with neuropathy, IENFD and SENPD were reduced to about 50% of controls. Using receiver-operating characteristic (ROC) curve analysis of IENFD values, the diagnostic sensitivity for detecting neuropathy was 0.80 and the specificity 0.82. For SENPD, sensitivity was 0.81 and specificity 0.88. With ROC analysis of both IENFD and SENPD together, the diagnostic sensitivity was further improved to 0.92."[18] The authors concluded that "the combined examination of IENFD and SENPD is a highly sensitive and specific diagnostic tool in patients suspected to suffer from painful sensory neuropathies but with normal values on clinical neurophysiological studies."[18]

Gibbons, et al. (2006) studied 28 patients with "sensory complaints of unknown etiology." Each patient had repeated skin biopsies. Patients with large nerve fiber swellings on initial biopsy showed a decline in epidermal nerve fiber density on repeated biopsies whereas patients without nerve fiber swellings did not have changes in nerve fiber density between biopsies. Patients with large nerve fiber swellings were most likely to present clinically with paresthesia.[19]

Autonomic Neuropathy

Gibbons, et al. (2009) developed a new technique to quantify the sweat gland nerve fiber density (SGNFD) using tissue prepared for the standard analysis of IENFD. The technique "differentiates groups of patients with mild diabetic neuropathy from healthy control subjects and correlates with both physical examination scores and symptoms relevant to sudomotor dysfunction"; further, this technique is proposed to provide a "reliable structural measure of sweat gland innervation that complements the investigation of small fiber neuropathies."[20] The authors validated the technique in 30 diabetic and 64 healthy subjects. Diabetic subjects had reduced SGNFD compared to controls at the distal leg, distal thigh, and proximal thigh. The SGNFD at the distal leg of diabetic subjects decreased as the Neuropathy

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Impairment Score in the lower limb (NIS-LL) worsened (r = -0.89) and was concordant with symptoms of reduced sweat production.

Luo, et al. (2011) developed an alternative staining system using PGP 9.5 and counterstaining with Congo red which reduced the variations in measurements of sweat gland areas compared to the commonly used method by ~5.6-fold (2.47% ± 2.54% vs 13.97% ± 14.24%). The authors examined 35 diabetic patients and compared these results to controls. Diabetic patients had lower sweat gland innervation index (SGII) values than age- and sex-matched controls (2.60% ± 1.96% vs 4.84% ± 1.51%). The SGII values were lower in patients with anhidrosis of the feet versus those with normal sweating of the feet (0.89% ± 0.71% vs 3.10% ± 1.94%). The authors concluded that "skin biopsy offers combined assessment of sudomotor innervation."[21]

Diabetic Neuropathy

Those with both diabetes and metabolic syndrome have double the risk of peripheral neuropathy,[22] and the prevalence of polyneuropathy is high in obese individuals, even those with normoglycemia.[23] Diabetes and obesity are common metabolic drivers of peripheral neuropathy.[24]

Alam, et al. (2017) compared the diagnostic capability of corneal confocal microscopy (CCM) against a range of established measures of nerve damage in patients with diabetic neuropathy. Thirty patients with Type 1 diabetes without neuropathy (T1DM), 31 patients with Type 1 diabetes and neuropathy (DSPN), and 27 healthy controls underwent CCM, as well as QST, electrophysiology, and skin biopsy. Intra-epidermal nerve fiber density was found to have a diagnostic sensitivity of 0.61, specificity of 0.80, and area under the ROC curve of 0.73.[25]

Wang, et al. (2021) studied the diagnostic utility of corneal confocal microscopy in type 2 diabetes peripheral neuropathy. 172 patients with Type 2 DM and 48 healthy patients were enrolled in the study and assessed for neurological symptoms and corneal nerve fiber density was measured. "Corneal nerve fiber density, corneal nerve fiber length and corneal nerve branch density were significantly reduced in patients with type 2 diabetes mellitus compared with normal healthy control subjects."[26] Cut-off values for corneal nerve fiber density (24.68), corneal nerve branch density (39), and corneal nerve fiber length (15.315) were determined. The authors state that corneal confocal microscopy can be applied to diagnose type 2 diabetes peripheral neuropathy; however, the cost of the equipment is expensive which hinders its large-scale clinical application.[26]

Familial Amyloid Polyneuropathy (FAP)

Chao, et al. (2015) investigated the "the pathology and clinical significance of sudomotor denervation." Skin biopsies of 28 familial amyloid polyneuropathy (FAP) patients were stained with two markers: protein gene product 9.5 (PGP 9.5) and vasoactive intestinal peptide (VIP) followed by quantitation according to SGII for PGP 9.5 (SGIIPGP 9.5) and VIP (SGIIVIP). The researchers found that "The SGIIPGP 9.5 and SGIIVIP of FAP patients were significantly lower than those of age- and gender-matched controls. The reduction of SGIIVIP was more severe than that of SGIIPGP 9.5 (p=0.002). Patients with orthostatic hypotension or absent sympathetic skin response at palms were associated with lower SGIIPGP 9.5 (p = 0.019 and 0.002, respectively). SGIIPGP 9.5 was negatively correlated with the disability grade at the time of skin biopsy (p=0.004) and was positively correlated with the interval from the time of skin biopsy to the time of wheelchair usage (p=0.029)."[27] The authors documented "the pathological evidence of

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sudomotor denervation in FAP. SGIIPGP 9.5 was functionally correlated with autonomic symptoms, autonomic tests, ambulation status, and progression of disability."[27]

Erythromelalgia

Mantyh, et al. (2016) investigated the clinical utility of nerve fiber density testing for erythromelalgia in a retrospective study of 52 consecutive patients with erythromelalgia. Most patients were found to have "abnormalities on functional nerve testing," but less than 10% of patients had decreased epidermal nerve fiber density. The authors concluded that "Skin biopsy for evaluation of epidermal nerve fiber density is not useful in the diagnosis of erythromelalgia; instead, physicians may wish to focus on functional nerve testing, which more reliably identifies this disease."[28]

Fibromyalgia (FM)

Caro and Winter (2014) studied 41 consecutive patients with fibromyalgia (FM) and 47 controls to establish the prevalence of small fiber neuropathy (SFN) in FM. The authors found that the epidermal nerve fiber density (ENFD) of patients with FM was more than controls at the calf and thigh (calf: mean ± SD 5.8 ± 2.8 versus 7.4 ± 1.9; thigh 9.3 ± 3.2 versus 11.3 ± 2.0). Advanced age was insufficient to explain this finding. The authors suggested that "small fiber neuropathy is likely to contribute to the pain symptoms of FM; that pain in this disorder arises, in part, from a peripheral immune-mediated process; and that measurement of ENFD may be a useful clinical tool in FM."[29]

Lawson, et al. (2018) sought to characterize and distinguish the subset of patients with both fibromyalgia and small fiber polyneuropathy in 155 FM patients. These FM patients completed a Short Form McGill Questionnaire and visual analog scale in addition to having skin biopsies, nerve conduction studies (NCS), and serologic testing. The authors found that "Sural and medial plantar (MP) response amplitudes correlated with epidermal nerve fiber density, with markers of metabolic syndrome being more prevalent in this subset of patients. Pain intensity and quality did not distinguish patients."[30] The authors concluded that "the FM-SFSPN subset of patients may be identified through sural and MP sensory NCS and/or skin biopsy but cannot be identified by pain features and intensity."[30]

Evdokimov, et al. (2020) characterized dermal skin innervation in patients with fibromyalgia syndrome (FMS). 86 patients with FMS and 35 healthy patients were enrolled in the study and the skin was immunoreacted with antibodies against protein gene product 9.5, calcitonine gene-related peptide, substance P, CD31, and neurofilament 200 for small fiber subtypes. Skin sections were assessed on each patient and dermal nerve fiber length (DNFL) was assessed. In FMS patients, DNFL of fibers with vessel contact was found to be reduced compared to healthy individuals. Overall, the authors conclude that there were less dermal nerve fibers in contact with blood vessels in FMS patients than in controls, which suggests "the possibility of a relationship with impaired thermal tolerance commonly reported by FMS patients."[31]

Ganglionopathy

Provitera, et al. (2018) researched the role of skin biopsy in differentiating SFN from small-fiber sensory ganglionopathy (SFSG). Both thigh and leg IENF were studied from 314 participants with small-fiber pathology and 288 healthy controls. The researchers found that "The leg:thigh IENF density ratio was significantly ($P < 0.01$) lower in patients with length-dependent SFN (0.44 ± 0.23) compared with patients

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with SFSG (0.68 ± 0.28)."[32] Overall, measurement of the thigh and leg IENF ratio has shown clinical utility in differentiating diagnoses between SFSG and length-dependent SFN.

Hypothyroidism

Magri, et al. (2010) evaluated 18 neurologically asymptomatic patients newly diagnosed with overt (OH) or subclinical hypothyroidism (SH) and 15 healthy controls. The density of innervation was measured. The authors found that "an abnormal IENF density consistent with SFN was found in 60% of patients with OH at the distal leg and in 20% at the proximal site with OH and in 25% of cases at the distal leg and in 12.5% of cases at the proximal thigh in patients with SH."[33] The authors suggested that a "considerable number of untreated hypothyroid patients may have preclinical asymptomatic small-fiber sensory neuropathy."[33]

Gupta, et al. (2016) investigated the "electrophysiological alterations of some selected variables of nerve conduction, brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs) in hypothyroid patients." Sixty patients with hypothyroidism and 60 controls had nerve conduction studies (including parameters as latencies, conduction velocities, and amplitude of motor and sensory nerves) performed. BAEPs and VEPs were also assessed. The authors found that on comparative evaluation, there was a significant increase in latency of median, ulnar, tibial, and sural nerves; the authors also found a decrease in conduction velocities of all the tested nerves and a decrease in amplitude of median, tibial, and sural nerves was observed in hypothyroid patients. The authors suggested that "peripheral and central neuropathy develops in patients of hypothyroidism at an early stage of disease and the electrophysiological investigations of such patients can help in timely detection and treatment of neurological disorders that occur due to thyroid hormone deficiency."[34]

Fabry Disease (FD)

About 80% of patients with Fabry disease (FD) suffer from painful neuropathy; neuropathic pain in FD is associated with SFN. Torvin Moller, et al. (2009) explored the frequency of symptoms and the functional and structural involvement of the nervous system in female patients by examining the presence of pain, manifestations of peripheral neuropathy, and nerve density in skin biopsies in 19 female patients with FD and 19 sex- and age-matched controls. They found that sensory nerve action potential amplitude and maximal sensory conduction velocity were not different, whereas there was a highly significant reduction in intraepidermal nerve fiber density; however, there was no correlation between pain and visual analog scale (VAS) score, QST, and intraepidermal nerve fiber density.[35]

Further, van der Tol, et al. (2016) assessed the diagnostic value of QST and IENFD testing in patients with an indeterminate FD diagnosis. Twenty-six patients were tested, 18 with nonclassical FD, 5 without FD, and 3 uncertain. The investigators found that "of the patients classified as nonclassical FD, 28% had ≥1 abnormal QST modalities, and 83% had an abnormal IENFD. From the patients without FD, 20% had ≥1 abnormal QST modality, and IENFD was abnormal in 25%."[36] Overall, the sensitivity was 28% and specificity was 80%.

von Cossel, et al. (2021) studied the significance of the Fabry-related, non-classical variant p.D313Y in female patients. Nine females carrying the p.D313Y variant underwent intraepidermal nerve fiber density testing and results were compared to reference values. Compared to sex-matched reference values per decade, intraepidermal nerve fiber density was decreased in seven out of nine patients.

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Patients experienced acral paresthesia, neuropathic pain, and acute pain crises. The diagnosis of small fiber neuropathy was made in seven out of nine females carrying the non-classical variant p.D313Y. The authors conclude that neuropathic pain and other symptoms related to autonomic nervous system dysfunction may be of clinical significance and warrant therapeutic intervention.[37]

Parkinson Disease (PD)

Jeziorska, et al. (2019) explored the relationship between nerve degeneration/regeneration and the clinical signs of Parkinson disease (PD). Twenty-three PD patients and 10 controls underwent IENF and clinical assessment. IENFD, total length (IETNFL), mean axonal length (MAL), and IETNFL/Area were all found to be reduced in PD patients. IENFD also correlated with disease duration and clinical measures of PD such as the Unified Parkinson's Disease Rating Scale, Part III. The authors concluded that "increased IENF degeneration and impaired regeneration correlates with somatic and autonomic symptoms and deficits in patients with PD."[38]

Lim, et al. (2021) studied the use of corneal confocal microscopy (CCM) to identify Parkinson's Disease (PD) patients with rapid motor progression. 64 patients with PD were assessed at baseline and at 12 month follow up for assessment on corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL), corneal total branch density (CTBD), and corneal nerve fiber area. All four parameters were significantly lower in participants with PD compared with healthy control subjects. The mean difference between PD patients at baseline and control subjects were measured for CNFD (4.55 no./mm^2), CNBD (8.18 no./mm^2), CNFL (2.53 mm/mm^2), and CTBD (11.19 no./mm^2). The authors suggests that "CCM may be a useful marker of neurodegeneration to identify patients with PD with a more progressive and severe disease phenotype, termed "fast progressors."[39]

Charcot-Marie-Tooth Disease Type 1A (CMT1A)

Duchesne, et al. (2018) investigated whether unmyelinated fibers are lost in Charcot-Marie-Tooth disease type 1A (CMT1A). Eighty CMT1A patients and 94 healthy controls provided skin biopsies from the distal leg, and the IENFD was calculated. The mean IENFD was found to be less in CMT1A patients compared to healthy controls (5.8 vs 9.57), and 48% of CMT1A patients had a reduction of IENFD below the "normal lower limit" of the fifth percentile of 4.8/mm. IENFD was also noted to decrease with age and to be higher in females than males. The authors suggested that small sensory nerve fibers were affected in CMT1A.[40]

Ehlers-Danlos Syndrome (EDS)

Cazzato, et al. (2016) investigated neuropathy in 20 adults with joint hypermobility syndrome/hypermobility Ehlers-Danlos syndrome (EDS), three patients with vascular EDS, and one patient with classic EDS. They found that all except one patient had neuropathic pain, but sural nerve conduction was normal in all patients. All patients showed decreased intraepidermal nerve fiber density consistent with small fiber neuropathy regardless of EDS type. The authors concluded that "small fiber neuropathy is a common feature of Ehlers-Danlos syndromes, and that skin biopsy could be considered an additional diagnostic tool to investigate pain manifestations in EDS."[41]

Friedreich's Ataxia (FRDA)

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Indelicato, et al. (2018) explored the association between Friedreich's ataxia (FRDA) and IENF. Seventeen patients with FRDA were enrolled. The mean IENF density was found to be lower in FRDA patients compared to healthy controls (5.77 ± 4.68 vs 9.33 ± 1.41 / mm). IENF was also found to be lower in early-onset FRDA patients compared to late-onset patients (early-onset median value: 1.7, late-onset median value: 8.8). From there, a correlation between IENF density and shorter GAA repeat in FRDA patients was determined ($r^2 = 0.573$).[42]

COVID-19

Bandinelli, et al. (2025) conducted a systematic review to highlight the clinical and diagnostic features of post-acute sequelae small fiber neuropathy (PASC-SFN), a rare complication caused by viral infections, like SARS-CoV-2. Evidence suggests that COVID-19 increases symptoms of pre-existent SFN and might trigger de novo onset of SFN. Their literature supports the notion that persistent inflammation and immune activation are plausible factors responsible for PASC-SFN.[43]

Abrams, et al. (2022) retrospectively examined the clinical features and outcomes of patients who were referred to them between May 2020 and May 2021 for painful paresthesia and numbness that developed during or after SARS-CoV-2 infection. In this study, 13 patients were identified ranging from ages 38 to 67 years. Approximately two months following the initial infection, all patients developed new-onset paresthesia, with an acute onset in seven. This indicates that symptoms of SFN may develop during or after COVID-19 and paresthesia may be associated with long-haul post-COVID-19 symptoms.[44]

Azcue, et al. (2025) evaluated a sample of 90 participants, including 30 individuals with post-COVID condition (PCC), 30 with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and 30 healthy controls. PCC and ME/CFS patients exhibited sensory SFN, characterized by impaired heat detection and abnormal small fiber morphology in corneal nerve fibers. This underscores the importance of a multimodal approach in the detection of SFN and provide insight to the neuropathic symptomology associated with these conditions.[45]

Sarcoidosis

Gavrilova, et al. (2021) studied the correlation of small fiber neuropathy and sarcoidosis. The study included 50 patients with pulmonary sarcoidosis and 25 healthy controls. A punch biopsy of the skin and staining with PGP 9.5 was performed. “A negative, statistically significant correlation between the intraepidermal nerve fiber density (IEND) and SFN-SL score was revealed.” In Sarcoidosis patients, the median IEND in 1mm was 7.68. The authors conclude that small fiber neuropathy and sarcoidosis are correlated and “small fiber neuropathy might develop as a result of systemic immune-mediated inflammation.”[46]

VI. Guidelines and Recommendations

American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) and the American Academy of Physical Medicine and Rehabilitation (AAPM&R)

A committee of the AAN, AANEM and AAPM&R published guidance on IENF density’s use:[47]

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- "Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction (Level B)."
- "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)."
- "Skin biopsy is a validated technique for determining intraepidermal nerve fiber 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."

The American Academy of Neurology reaffirmed these guidelines on February 8, 2025.[48]

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)

The 2015 AACE and ACE review of the literature, by Garber, et al. (2015), in development of a comprehensive diabetes management algorithm found that skin punch biopsy, a minimally invasive procedure, allows morphometric quantification of intraepidermal nerve fibers. The European Federation of the Neurological Societies and the Peripheral Nerve Society endorse intraepidermal nerve fiber quantification to confirm the clinical diagnosis of SFN with a strong recommendation.[50] Intraepidermal nerve fiber density inversely correlates with both cold and heat detection thresholds.[51] Intraepidermal nerve fiber density is significantly reduced in symptomatic patients with normal findings from nerve conduction studies and those with metabolic syndrome, IGT, and IFG, suggesting early damage to small nerve fibers.[52,53] Intraepidermal nerve fiber density is also reduced in painful neuropathy compared with that observed in painless neuropathy.[54] Diet and exercise intervention in IGT lead to increased intraepidermal nerve fiber density.[55] These data suggest that intraepidermal nerve fiber loss is an early feature of the metabolic syndrome, prediabetes, and established DM, and the loss progresses with increasing neuropathic severity. There may be nerve regeneration with treatment.

A consensus statement by the AACE and ACE on the Type 2 diabetes management algorithm was published in 2020. This statement was released in the form of an executive summary and does not mention skin punch biopsies or the quantification of intraepidermal nerve fibers.[56]

In 2017, AACE[57] published a position statement on nerve dysfunction that recommends:

- The presence of silent or overt autonomic neuropathy has dire consequences for the patient with diabetes, particularly if accompanied by peripheral neuropathy.
- All patients with type 2 diabetes should be assessed for both peripheral neuropathy at diagnosis and after 5 years, in type 1 diabetes at diagnosis and thereafter annually.
- Somatic neuropathy can be diagnosed by bedside testing with a 10-gram monofilament and a 128-Hz tuning fork for vibration perception and touch and prickling pain perception and ankle reflexes. This can be complemented by rapid and easily quantified sensory and sudomotor perception.

They found that: "It is a noninvasive objective test, takes a mere 2 minutes, has a sensitivity for diagnosis of neuropathy >75% and a specificity of 95%. These statistics have now been supported in studies by several authors amongst others and provide sensitive and specific diagnostic criteria for somatic

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neuropathy, which when combined with indices of HRV, provide better predictive value for CVD and mortality than traditional risk factors such as the tried and tested Framingham predictive index."[57]

European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS)

The EFNS/PNS published guidelines on the use of skin biopsy in the diagnosis of small fiber neuropathy which recommended that "Distal leg skin biopsy with quantification of the linear density of intraepidermal nerve fibers (IENF), using generally agreed upon counting rules, is a reliable and efficient technique to assess the diagnosis of SFN." EFNS added that "sweat gland innervation can be examined using an unbiased stereologic technique recently proposed. A reduced IENF density is associated with the risk of developing neuropathic pain, but it does not correlate with its intensity. Serial skin biopsies might be useful for detecting early changes of IENF density, which predict the progression of neuropathy, and to assess degeneration and regeneration of IENF. However, further studies are warranted to confirm the potential usefulness of skin biopsy with measurement of IENF density as an outcome measure in clinical practice and research. Skin biopsy has not so far been useful for identifying the etiology of SFN. Finally, we emphasize that 3-mm skin biopsy at the ankle is a safe procedure based on the experience of 10 laboratories reporting absence of serious side effects in approximately 35,000 biopsies and a mere 0.19% incidence of non-serious side effects in about 15 years of practice."[50]

The EFNS also published guidance on assessment of neuropathic pain. In it, they recommend:

- "Skin biopsy should be performed in patients with painful/burning feet of unknown origin and clinical impression of small fibre dysfunction (grade B)."
- "In postherpetic neuralgia, skin innervation is reduced (grade B) and higher numbers of preserved fibres are associated with allodynia (grade B)."
- "IENFD shows only a weak negative correlation with the severity of pain and cannot be used to measure pain in individual patients (grade C)."[58]

American Diabetes Association (ADA)

In 2017 the ADA released a position statement on the early recognition and appropriate treatment of diabetic neuropathies which only mentions intraepidermal nerve fiber density as a measure of small fiber damage and repair in the context of clinical trials.[59]

In the Standards of Medical Care in Diabetes, the ADA recommends that "All patients should be assessed for [diabetic peripheral neuropathy] starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter." (Grade B). Concerning the mode of assessment, they recommend, "Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation" (Grade B).[60-65] They note the importance of diagnosis since "numerous treatment options exist for symptomatic diabetic neuropathy."[66]

International Expert Panel on Neuropathy in Fabry Disease

An international expert panel focused on early diagnosis of peripheral nervous system involvement in Fabry disease recommended: "Given the availability of an accurate diagnostic laboratory test, nerve or

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skin biopsies are not required for diagnosing Fabry disease, although skin biopsy can detect small fiber disease in yet asymptomatic patients and may be used to quantify loss of skin innervation."[67]

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)

IMMPACT released guidelines on sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials. Their guidance on skin biopsy is as follows:

- "Skin biopsy may be a useful tool to diagnose small fiber neuropathy (SFN) and may allow for earlier diagnosis of neuropathy and neuropathic pain conditions."
- "Although IENFD has promise as a diagnostic tool, it is important to recognize that in many of the data presented, IENFD was used to diagnose peripheral neuropathies that may or may not involve pain, rather than specifically to diagnose pain conditions themselves. In order to utilize IENFD as a diagnostic biomarker, additional research is needed that focuses specifically on the identification of pain conditions. Further research should also seek to validate the use of IENFD as a diagnostic tool for FM."[68]

Assessment Committee of the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP)

NeuPSIG released guidelines on neuropathic pain, with two recommendations relevant to skin biopsy. These are as follows:

- "Skin biopsy with appropriate histological processing and image analysis of the specimen should be performed in patients with clinical signs of small fiber dysfunction to determine intraepidermal nerve fiber density (level B)."
- "Measurement of intraepidermal nerve fiber density may be used in the follow up and to detect a treatment response in diabetic patients with small fiber neuropathy (level C)."[69]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
88313	Special stain including interpretation and report; Group II, all other (eg, iron, trichrome), except stain for microorganisms, stains for enzyme constituents, or immunocytochemistry and immunohistochemistry
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
88344	Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88356	Morphometric analysis; nerve

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

1. Wilkinson KD, Lee KM, Deshpande S, Duerksen-Hughes P, Boss JM, Pohl J. The neuron-specific protein PGP 9.5 is a ubiquitin carboxyl-terminal hydrolase. *Science (New York, NY)*. Nov 03 1989;246(4930):670-3. doi:10.1126/science.2530630
2. Dalsgaard CJ, Rydh M, Haegerstrand A. Cutaneous innervation in man visualized with protein gene product 9.5 (PGP 9.5) antibodies. *Histochemistry*. 1989;92(5):385-90. doi:10.1007/BF00492495
3. McCarthy BG, Hsieh ST, Stocks A, et al. Cutaneous innervation in sensory neuropathies: evaluation by skin biopsy. *Neurology*. Oct 1995;45(10):1848-55. doi:10.1212/wnl.45.10.1848
4. Smith AG, Gibson S. Skin biopsy for the evaluation of peripheral nerve disease. Updated January 30, 2025. https://www.uptodate.com/contents/skin-biopsy-for-the-evaluation-of-peripheral-nerve-disease
5. Chien HF, Tseng TJ, Lin WM, et al. Quantitative pathology of cutaneous nerve terminal degeneration in the human skin. *Acta neuropathologica*. Nov 2001;102(5):455-61. doi:10.1007/s004010100397
6. Lauria G, Devigili G. Skin biopsy as a diagnostic tool in peripheral neuropathy. *Nature clinical practice Neurology*. Oct 2007;3(10):546-57. doi:10.1038/ncpneuro0630
7. Therapath. Small Fiber Neuropathy Testing. https://www.therapath.com/services/small-fiber-neuropathy-testing/
8. BakoDx. Epidermal Nerve Fiber Density (ENFD) Testing. https://bakodx.com/enfd/
9. Ipsum Diagnostics. Nerve Testing. 2022;
10. CRL. Small Fiber Neuropathy is Painful. Diagnosing it Shouldn't Be. https://corinthianreferencelab.com/
11. England JD, Gronseth GS, Franklin G, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). *Neurology*. 2009;72(2):177. doi:10.1212/01.wnl.0000336345.70511.0f

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12. Collongues N, Samama B, Schmidt-Mutter C, et al. Quantitative and qualitative normative dataset for intraepidermal nerve fibers using skin biopsy. *PloS one*. 2018;13(1):e0191614. doi:10.1371/journal.pone.0191614
13. Piscosquito G, Provitera V, Mozzillo S, et al. The analysis of epidermal nerve fibre spatial distribution improves the diagnostic yield of skin biopsy. *Neuropathology and Applied Neurobiology*. 2021;47(2):210-217. doi:10.1111/nan.12651
14. Corrà MF, Sousa M, Reis I, et al. Advantages of an Automated Method Compared With Manual Methods for the Quantification of Intraepidermal Nerve Fiber in Skin Biopsy. *J Neuropathol Exp Neurol*. Aug 11 2021;80(7):685-694. doi:10.1093/jnen/nlab045
15. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density: normative reference range and diagnostic efficiency. *Archives of neurology*. Dec 1998;55(12):1513-20. doi:10.1001/archneur.55.12.1513
16. Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain : a journal of neurology*. Jul 2008;131(Pt 7):1912-25. doi:10.1093/brain/awn093
17. Devigili G, Rinaldo S, Lombardi R, et al. Diagnostic criteria for small fibre neuropathy in clinical practice and research. *Brain : a journal of neurology*. Dec 1 2019;142(12):3728-3736. doi:10.1093/brain/awz333
18. Vlckova-Moravcova E, Bednarik J, Dusek L, Toyka KV, Sommer C. Diagnostic validity of epidermal nerve fiber densities in painful sensory neuropathies. *Muscle & nerve*. Jan 2008;37(1):50-60. doi:10.1002/mus.20889
19. Gibbons CH, Griffin JW, Polydefkis M, et al. The utility of skin biopsy for prediction of progression in suspected small fiber neuropathy. *Neurology*. Jan 24 2006;66(2):256-8. doi:10.1212/01.wnl.0000194314.86486.a2
20. Gibbons CH, Illigens BM, Wang N, Freeman R. Quantification of sweat gland innervation: a clinical-pathologic correlation. *Neurology*. Apr 28 2009;72(17):1479-86. doi:10.1212/WNL.0b013e3181a2e8b8
21. Luo KR, Chao CC, Chen YT, et al. Quantitation of sudomotor innervation in skin biopsies of patients with diabetic neuropathy. *J Neuropathol Exp Neurol*. Oct 2011;70(10):930-8. doi:10.1097/NEN.0b013e318230b0f4
22. Hovaguimian A, Gibbons CH. Clinical Approach to the Treatment of Painful Diabetic Neuropathy. *Ther Adv Endocrinol Metab*. Feb 2011;2(1):27-38. doi:10.1177/2042018810391900
23. Callaghan BC, Xia R, Reynolds E, et al. Association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. *JAMA neurology*. Dec 1 2016;73(12):1468-1476. doi:10.1001/jamaneurol.2016.3745
24. Callaghan BC, Gao L, Li Y, et al. Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. *Annals of clinical and translational neurology*. Apr 2018;5(4):397-405. doi:10.1002/acn3.531
25. Alam U, Jeziorska M, Petropoulos IN, et al. Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy. *PloS one*. 2017;12(7):e0180175. doi:10.1371/journal.pone.0180175
26. Wang M, Zhang C, Zuo A, Li L, Chen L, Hou X. Diagnostic utility of corneal confocal microscopy in type 2 diabetic peripheral neuropathy. *Journal of Diabetes Investigation*. 2021;12(4):574-582. doi:10.1111/jdi.13381

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27. Chao CC, Huang CM, Chiang HH, et al. Sudomotor innervation in transthyretin amyloid neuropathy: Pathology and functional correlates. *Annals of neurology*. Aug 2015;78(2):272-83. doi:10.1002/ana.24438
28. Mantyh WG, Dyck PJ, Engelstad JK, Litchy WJ, Sandroni P, Davis MD. Epidermal Nerve Fiber Quantification in Patients With Erythromelalgia. *JAMA dermatology*. Dec 7 2016;doi:10.1001/jamadermatol.2016.4404
29. Caro XJ, Winter EF. Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. *Arthritis & rheumatology (Hoboken, NJ)*. Jul 2014;66(7):1945-54. doi:10.1002/art.38662
30. Lawson VH, Grewal J, Hackshaw KV, Mongiovi PC, Stino AM. Fibromyalgia syndrome and small fiber, early or mild sensory polyneuropathy. *Muscle & nerve*. Mar 23 2018;doi:10.1002/mus.26131
31. Evdokimov D, Dinkel P, Frank J, Sommer C, Üçeyler N. Characterization of dermal skin innervation in fibromyalgia syndrome. *PloS one*. 2020;15(1):e0227674. doi:10.1371/journal.pone.0227674
32. Provitera V, Gibbons CH, Wendelschafer-Crabb G, et al. The role of skin biopsy in differentiating small-fiber neuropathy from ganglionopathy. *Eur J Neurol*. Jun 2018;25(6):848-853. doi:10.1111/ene.13608
33. Magri F, Buonocore M, Oliviero A, et al. Intraepidermal nerve fiber density reduction as a marker of preclinical asymptomatic small-fiber sensory neuropathy in hypothyroid patients. *European journal of endocrinology*. Aug 2010;163(2):279-84. doi:10.1530/eje-10-0285
34. Gupta N, Arora M, Sharma R, Arora KS. Peripheral and Central Nervous System Involvement in Recently Diagnosed Cases of Hypothyroidism: An Electrophysiological Study. *Annals of medical and health sciences research*. Sep-Oct 2016;6(5):261-266. doi:doi.org/10.4103/amhsr.amhsr_39_16
35. Torvin Moller A, Winther Bach F, Feldt-Rasmussen U, et al. Functional and structural nerve fiber findings in heterozygote patients with Fabry disease. *Pain*. Sep 2009;145(1-2):237-45. doi:10.1016/j.pain.2009.06.032
36. van der Tol L, Verhamme C, van Schaik IN, van der Kooi AJ, Hollak CE, Biegstraaten M. In Patients with an alpha-Galactosidase A Variant, Small Nerve Fibre Assessment Cannot Confirm a Diagnosis of Fabry Disease. *JIMD reports*. 2016;28:95-103. doi:10.1007/8904_2015_503
37. von Cossel K, Muschol N, Friedrich RE, et al. Assessment of small fiber neuropathy in patients carrying the non-classical Fabry variant p.D313Y. *Muscle & nerve*. 2021;63(5):745-750. doi:10.1002/mus.27196
38. Jeziorska M, Atkinson A, Kass-Iliyya L, et al. Increased Intraepidermal Nerve Fiber Degeneration and Impaired Regeneration Relate to Symptoms and Deficits in Parkinson's Disease. *Frontiers in neurology*. 2019;10:111. doi:10.3389/fneur.2019.00111
39. Lim SH, Ferdousi M, Kalteniece A, et al. Corneal Confocal Microscopy Identifies Parkinson's Disease with More Rapid Motor Progression. *Movement Disorders*. 2021;n/a(n/a)doi:10.1002/mds.28602
40. Duchesne M, Danigo A, Richard L, et al. Skin Biopsy Findings in Patients With CMT1A: Baseline Data From the CLN-PXT3003-01 Study Provide New Insights Into the Pathophysiology of the Disorder. *J Neuropathol Exp Neurol*. Apr 1 2018;77(4):274-281. doi:10.1093/jnen/nly001
41. Cazzato D, Castori M, Lombardi R, et al. Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. *Neurology*. Jul 12 2016;87(2):155-9. doi:10.1212/wnl.0000000000002847
42. Indelicato E, Nachbauer W, Eigentler A, Rudzki D, Wanschitz J, Boesch S. Intraepidermal Nerve Fiber Density in Friedreich's Ataxia. *J Neuropathol Exp Neurol*. Dec 1 2018;77(12):1137-1143. doi:10.1093/jnen/nly100

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43. Bandinelli F, Carlo MD, Colantuono VA, et al. Post-COVID-19 Small Fiber Neuropathy as a New Emerging Quality of Life-Threatening Disease: A Systematic Review. *Microorganisms*. 2025;(2025;13(2):328)doi:10.3390/microorganisms13020328
44. Abrams RMC, Simpson DM, Navis A, Jette N, MD LZ, Shin SC. Small fiber neuropathy associated with SARS-CoV-2 infection. *Muscle & nerve*. 2022;doi:10.1002/mus.27458
45. Azcue N, Teijeira-Portas S, Tijero-Merino B, et al. Small fiber neuropathy in the post-COVID condition and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical significance and diagnostic challenges. *Eur J Neurol*. 2025;32(2)doi:10.1111/ene.70016
46. Gavrilova N, Starshinova A, Zinchenko Y, et al. Small Fiber Neuropathy in Sarcoidosis. *Pathophysiology*. Dec 20 2021;28(4):544-550. doi:10.3390/pathophysiology28040035
47. England JD, Gronseth GS, Franklin G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. Jan 13 2009;72(2):185-92. doi:10.1212/01.wnl.0000336370.51010.a1
48. AAN. Evaluation of Distal Symmetric Polyneuropathy: Role of Autonimc Testing, Nerve Biopsy, and Skin Biopsy American Academy of Neurology. Updated February 8, 2025. https://www.aan.com/Guidelines/home/GuidelineDetail/315
49. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive diabetes management algorithm 2015. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. Apr 2015;21(4):438-47. doi:10.4158/ep15693.cs
50. EFNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Journal of the peripheral nervous system : JPNS*. Jun 2010;15(2):79-92. doi:10.1111/j.1529-8027.2010.00269.x
51. Shun CT, Chang YC, Wu HP, et al. Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. *Brain : a journal of neurology*. Jul 2004;127(Pt 7):1593-605. doi:10.1093/brain/awh180
52. Loseth S, Stalberg E, Jorde R, Mellgren SI. Early diabetic neuropathy: thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies. *Journal of neurology*. Aug 2008;255(8):1197-202. doi:10.1007/s00415-008-0872-0
53. Quattrini C, Tavakoli M, Jeziorska M, et al. Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes*. Aug 2007;56(8):2148-54. doi:10.2337/db07-0285
54. Sorensen L, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. *Diabetes care*. Apr 2006;29(4):883-7. doi:10.2337/diacare.29.04.06.dc05-2180
55. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes care*. Jun 2006;29(6):1294-9. doi:10.2337/dc06-0224
56. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. Jan 2020;26(1):107-139. doi:10.4158/CS-2019-0472
57. Vinik AI, Camacho PM, Davidson JA, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on Testing for Autonomic and Somatic Nerve Dysfunction *Endocrine practice : official journal of the American College of Endocrinology and the*

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American Association of Clinical Endocrinologists. Dec 2017;23(12):1472-1478. doi:10.4158/ep-2017-0053
58. Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol*. Aug 2010;17(8):1010-8. doi:10.1111/j.1468-1331.2010.02969.x
59. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes care*. Jan 2017;40(1):136-154. doi:10.2337/dc16-2042
60. ADA. 10. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2018. 10.2337/dc18-S010. *Diabetes care*. 2018;41(Supplement 1):S105.
61. ADA. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes care*. Jan 2020;43(Suppl 1):S14-s31. doi:10.2337/dc20-S002
62. ADA. Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers. *Clinical Diabetes*. 2021;39(1):14-43. doi:10.2337/cd21-as01
63. ADA. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. *Clinical Diabetes*. 2022;40(1):10-38. doi:10.2337/cd22-as01
64. ADA. Standards of Care in Diabetes-2023 Abridged for Primary Care Providers. *Clin Diabetes*. Winter 2023;41(1):4-31. doi:10.2337/cd23-as01
65. ADA. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2025. *Diabetes care*. 2025;48(Supplement_1):S252-S265. doi:doi.org/10.2337/dc25-S012
66. ADA. Standards of Medical Care in Diabetes—2019 Abridged for Primary Care Providers. *Clinical Diabetes*. 2019;37(1):11-34. doi:10.2337/cd18-0105
67. Burlina AP, Sims KB, Politei JM, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. *BMC Neurol*. 2011;11:61. doi:10.1186/1471-2377-11-61
68. Smith SM, Dworkin RH, Turk DC, et al. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *J Pain*. Jul 2017;18(7):757-77. doi:10.1016/j.jpain.2017.02.429
69. Haanpaa M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain*. Jan 2011;152(1):14-27. doi:10.1016/j.pain.2010.07.031

X. Review/Revision History

Effective Date	Summary
05/01/2026	Clinical Advisory Board Meeting, policy review and approval: 12/03/2025 Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
05/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Reordered wording in CC1 and CC2 to make it clear that the policy is covering the nerve fiber density testing, not the skin biopsy. Previously read "skin biopsy with epidermal nerve fiber density measurement", now reads "epidermal nerve fiber density measurement from a skin biopsy".

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	CC2 further edited for clarity. Removed CPT 88305, 88314 Coding Enhancement: Added CPT 88313
03/10/2023	Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. CC1 and CC2 were edited for clarity and consistency.
05/15/2022	Initial Policy Implementation

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