

Reimbursement Policy

Nerve Fiber Density Testing

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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 (Wilkinson et al., 1989) which avidly stains all axons (Dalsgaard et al., 1989). The number and morphology of axons within the epidermis are evaluated to determine epidermal nerve fiber density (McCarthy et al., 1995) and assess for the presence and degree of neuropathy (Smith & Gibson, 2022).

II. 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 **MEETS COVERAGE CRITERIA** when all 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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III. 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
<i>CMT1A</i>	<i>Charcot-Marie-Tooth Disease Type 1A</i>
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 polyneuropath
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	Hematoxylin 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

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IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MAL	Mean axonal length
MP	Medial plantar
NCS	Nerve conduction studies
NeuPSIG	Neuropathic Pain Special Interest Group
NIS-LL	Neuropathy Impairment Score in the Lower Limb
OH	Overt hypothyroidism
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

IV. 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 (Chien et al., 2001), 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.

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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 (Smith & Gibson, 2022).

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 (Lauria & Devigili, 2007). 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 (Lauria & Devigili, 2007).

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 (Therapath, 2022) 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%-to-97%; and the sensitivity is approximately 90% (BakoDx, 2022). 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 (Ipsum Diagnostics, 2022). Additional labs, such as Corinthian Reference Lab, also offer commercial ENFD tests kits to physicians to aid in a diagnosis of small fiber neuropathy (CRL, 2022; NeuroPath, 2022).

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 (England et al., 2009b).

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 (England et al., 2009b).

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

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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” (England et al., 2009b). 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 [distal symmetric polyneuropathy] which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III)” (England et al., 2009b).

Collongues et al., (2021) 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 “ $7.6156 - 0.0769 \times \text{age (years)} + 1.5506 \times \text{gender (woman = 1; man = 0)}$ ” (Collongues et al., 2018).

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 μm 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” (Piscosquito et al., 2021).

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” (Corrà et al., 2021)

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%” (McArthur et al., 1998).

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

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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 versus 12.92 ± 5.33 fibers/mm). Compared to IENFD 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% (Chien et al., 2001).

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” (Devigili et al., 2008).

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%)” (Devigili et al., 2019). 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” (Devigili et al., 2019). Further, sensory symptoms alone were not a reliable screening method for sensory neuropathy in this study.

Vlckova-Moravcova et al., (2008) measured IENFD 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” (Vlckova-Moravcova et al., 2008). 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” (Vlckova-Moravcova et al., 2008).

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 (Gibbons et al., 2006).

Autonomic Neuropathy

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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” (Gibbons et al., 2009). 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 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 ($2.47\% \pm 2.54\%$ vs $13.97\% \pm 14.24\%$). 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 ($2.60\% \pm 1.96\%$ vs $4.84\% \pm 1.51\%$). The SGII values were lower in patients with anhidrosis of the feet versus those with normal sweating of the feet ($0.89\% \pm 0.71\%$ vs $3.10\% \pm 1.94\%$). The authors concluded that “skin biopsy offers combined assessment of sudomotor innervation” (Luo et al., 2011).

Diabetic Neuropathy

Those with both diabetes and metabolic syndrome have double the risk of peripheral neuropathy (Hovaguimian & Gibbons, 2011), and the prevalence of polyneuropathy is high in obese individuals, even those with normoglycemia (Callaghan et al., 2016). Diabetes and obesity are common metabolic drivers of peripheral neuropathy (Callaghan et al., 2018).

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 (Alam et al., 2017).

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” (Wang et al., 2021). 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 (Wang et al., 2021).

Familial Amyloid Polyneuropathy (FAP)

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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 ($p=0.029$)” (Chao et al., 2015). The authors documented “the pathological evidence of sudomotor denervation in FAP. SGIIPGP 9.5 was functionally correlated with autonomic symptoms, autonomic tests, ambulation status, and progression of disability” (Chao et al., 2015).

Erythromelagia

Mantyh et al., (2016)

Investigated the clinical utility of nerve fiber density testing for erythromelagia in a retrospective study of 52 consecutive patients with erythromelagia. 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 erythromelagia; instead, physicians may wish to focus on functional nerve testing, which more reliably identifies this disease” (Mantyh et al., 2016).

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 \pm 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” (Caro & Winter, 2014).

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” (Lawson et al., 2018). 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” (Lawson et al., 2018).

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

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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" (Evdokimov et al., 2020).

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 with SFSG (0.68 ± 0.28)" (Provitera et al., 2018). 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" (Magri et al., 2010). The authors suggested that a "considerable number of untreated hypothyroid patients may have preclinical asymptomatic small-fiber sensory neuropathy" (Magri et al., 2010).

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" (Gupta et al., 2016).

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

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in intraepidermal nerve fiber density; however, there was no correlation between pain and visual analog scale (VAS) score, QST, and intraepidermal nerve fiber density (Torvin Moller et al., 2009).

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%” (van der Tol et al., 2016). 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. 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 (von Cossel et al., 2021).

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” (Jeziorska et al., 2019).

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./mm²), CNBD (8.18 no./mm²), CNFL (2.53 mm/mm²), and CTBD (11.19 no./mm²). 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” (Lim et al., 2021). *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

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be higher in females than males. The authors suggested that small sensory nerve fibers were affected in CMT1A (Duchesne et al., 2018).

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” (Cazzato et al., 2016).

Friedreich's Ataxia (FRDA)

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 ($r^2 = 0.573$) (Indelicato et al., 2018).

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” (Gavrilova et al., 2021)

V. 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 (England et al., 2009a):

- “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

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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 January 2, 2022 (AAN, 2022).

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 (EFNS, 2010). Intraepidermal nerve fiber density inversely correlates with both cold and heat detection thresholds (Shun et al., 2004). 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 (Loseth et al., 2008; Quattrini et al., 2007). Intraepidermal nerve fiber density is also reduced in painful neuropathy compared with that observed in painless neuropathy (Sorensen et al., 2006). Diet and exercise intervention in IGT lead to increased intraepidermal nerve fiber density (Smith et al., 2006). 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 (Garber et al., 2020).

In 2017, AACE (Vinik et al., 2017) 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 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” (Vinik et al., 2017).

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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” (EFNS, 2010).

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)” (Cruccu et al., 2010).

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 (Pop-Busui et al., 2017).

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 (ADA, 2018, 2020, 2021, 2022, 2023)” (Grade B). They note the importance of diagnosis since “numerous treatment options exist for symptomatic diabetic neuropathy” (ADA, 2019).

International Expert Panel on Neuropathy in Fabry Disease

An international expert panel (Burlina et al., 2011) focused on early diagnosis of peripheral nervous system involvement in Fabry disease recommended: “Given the availability of an accurate diagnostic laboratory test, nerve or skin biopsies are not required for diagnosing Fabry disease, although skin biopsy

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can detect small fiber disease in yet asymptomatic patients and may be used to quantify loss of skin innervation” (Burlina et al., 2011).

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” (Smith et al., 2017).

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)” (Haanpaa et al., 2011).

VI. 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)

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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.

VII. Applicable CPT/HCPCS Procedure Codes

88313	Special stain including interpretation and report; Group II, all other (e.g., 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.

VIII. Evidence-based Scientific References

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