Clinical Policy Bulletin: 
Nerve Fiber Density Measurement

Number: 0774

Policy

Aetna considers measurement of intra-epidermal nerve fiber density (IENFD) by skin biopsy medically necessary for the diagnosis of small-fiber neuropathy when all of the following criteria are met:

- Individual presents with painful sensory neuropathy; and
- 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); and
- 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; and
- Electromyography and nerve conduction velocity studies are normal and show no evidence of large-fiber neuropathy.

Aetna considers measurement of IENFD experimental and investigational for monitoring disease progression or response to treatment, or for the following indications and all other indications because its effectiveness for these indications has not been established (not an all-inclusive list):

- As a marker of pre-clinical asymptomatic small-fiber sensory neuropathy in hypothyroid persons
- Evaluation of individuals with Fabry disease
- Evaluation of individuals with postural tachycardia syndrome

Aetna considers measurement of sweat gland nerve fiber density for the diagnosis of complex regional pain syndrome, small-fiber neuropathy and other indications experimental and investigational because its effectiveness has not been established.

See also CPB 0485 - Autonomic Testing / Sudomotor Tests.
Background

Small-fiber neuropathy (SFN), also known as small-fiber sensory/peripheral neuropathy, is a peripheral nerve disease that selectively afflicts small diameter myelinated and non-myelinated nerve fibers. It most commonly occurs in middle-aged and older people, and is characterized by painful burning feet with reduced pain and temperature perception, and in some cases autonomic dysfunction. Although SFN can be caused by metabolic disorders (e.g., diabetes, metabolic syndrome), viruses and infectious diseases (e.g., human immunodeficiency virus, herpes zoster), genetic abnormalities (e.g., Fabry's disease, hereditary sensory and autonomic neuropathies), drugs and toxins (e.g., metronidazole, alcohol, and arsenic), and autoimmune diseases (e.g., vasculitis, Sjögren's syndrome), the cause often remains a mystery because standard electrophysiological tests for nerve injury do not detect small-fiber function. Despite the magnitude of the symptoms, there are few objective methods to identify and quantify these neuropathies.

Diagnosis of SFN is made on the basis of clinical features, normal nerve conduction velocity studies (NCVS) and abnormal specialized tests of small nerve fibers, which include measurement of intra-epidermal nerve fiber density (IENFD) and quantitative sudomotor axon reflex for autonomic fibers. Unless an underlying disease is identified, treatment is usually symptomatic and directed towards alleviation of neuropathic pain (Hoitsma et al, 2004; Fink and Oaklander, 2006).

Measurement of IENFD is an objective diagnostic test of SFN. For a diagnostic test to be clinically useful, it should correspond well with clinically meaningful physical findings. Walk and co-workers (2007) performed a retrospective analysis of the concordance between foot IENFD and clinical findings in all patients seen at their institution with possible idiopathic SFN who underwent skin biopsy for IENFD determination. They found a high concordance between reduced foot IENFD and loss of pinprick sensitivity in this patient population. These findings indicated that IENFD determination is a clinically relevant objective test in patients undergoing evaluation for possible SFN.

Darby et al (2007) assessed the loss of autonomic nerve fibers in patients with clinical pure sensory SFN. These investigators performed skin punch biopsies in age-matched (n = 17) and sex-matched (n = 15) controls. Biopsies were taken 10 cm above the lateral malleolus, and thin sections were stained with hematoxylin and eosin and the panaxonal marker protein-gene-product (PGP) 9.5. Positively stained fibers, represented as dots, innervating the erector pili muscles, arterioles, and sweat glands (SG) were counted. The ratios between the number of nerve fibers and nuclei of each structure were calculated. The autonomic innervation was significantly reduced in the patients' group compared with controls in all the examined autonomic-innervated structures: SG (0.27 +/- 0.15 versus 0.66 +/- 0.37, p = 0.001), arterioles (0.38 +/- 0.32 versus 0.86 +/- 0.45, p = 0.002), and the erector pili muscle (0.58 +/- 0.27 versus 1.23 +/- 0.87, p = 0.036). These findings suggested that autonomic involvement occurs in patients with sensory SFN and
that punch skin biopsy using thin sections is a simple and convenient method to
detect these dermal autonomic small-fiber abnormalities.

Quattrini and colleagues (2007) quantified small nerve fiber pathological changes
by means of IENFD measurement and corneal confocal microscopy (CCM) in
patients with diabetic neuropathy (DN). A total of 54 subjects stratified for
neuropathy, using neurological evaluation, neurophysiology, and quantitative
sensory testing (QST), and 15 control subjects were studied. They underwent a
punch skin biopsy to measure IENFD and CCM to quantify corneal nerve fibers.
Intra-epidermal nerve fiber density, branch density, and branch length showed a
progressive reduction with increasing severity of neuropathy, which was significant
in patients with mild, moderate, and severe neuropathy. Corneal confocal
microscopy also showed a progressive reduction in corneal nerve fiber density
(CNFD) and branch density, but the latter was significantly reduced even in
diabetic patients without neuropathy. Both IENFD and CNFD correlated
significantly with cold detection and heat as pain thresholds. Intra-epidermal and
corneal nerve fiber lengths were reduced in patients with painful DN compared
with their painless counterparts. Both IENFD and CCM assessment accurately
quantify small nerve fiber damage in diabetic patients. However, CCM quantifies
small fiber damage rapidly and non-invasively and detects earlier stages of nerve
damage compared with IENF pathology. This may make it an ideal technique to
accurately diagnose and assess progression of DN.

Umapathi and associates (2007) identified an early stage of DN by measuring
injury to epidermal nerve fibers. These researchers compared IENFD at the ankle
and thigh of 29 diabetic subjects who had no clinical or electrophysiological
evidence of SFN or large-fiber neuropathy to that of 84 healthy controls. The
mean ankle IENFD of diabetic subjects was 9.1 +/- 5.0 mm and that of controls,
13.0 +/- 4.8 mm (p < 0.001). The thigh IENFD did not differ significantly. The
IENFD ratio (thigh IENFD divided by ankle IENFD) was 2.39 +/- 1.30 in diabetic
subjects and 1.77 +/- 0.58 in controls (p < 0.001), indicating a length-dependent
reduction of IENFD in diabetics. Ankle IENFD remained significantly lower and the
IENFD ratio higher in diabetic subjects after adjusting for age. Two subjects had
parasympathetic dysfunction, 2 had retinopathy, and 2 early nephropathy. Age,
height, weight, duration of diabetes, and average HbA1c did not influence IENFD
among diabetic subjects. These researchers used receiver operating
characteristic (ROC) curves to describe and compare the utility of various
threshold values of ankle IENFD and IENFD ratio for the diagnosis of early DN.
The sensitivity and specificity of diagnosing DN using ankle IENFD of less than 10
mm were 72.4 % and 76.2 %, respectively. Thus, asymptomatic diabetics have a
measurable, length-dependent reduction of distal epidermal nerves. Analogous to
microalbuminuria in DN, reliable identification and quantitation of nascent DN may
have potential therapeutic implications.

In a prospective study, Vickova-Moravcova et al (2008) quantified IENFD and sub-
epidermal nerve plexus densities (SENPD) by immunostaining in skin punch
biopsies from the distal calf in 99 patients with clinical symptoms of painful sensory
neuropathy and from 37 age-matched healthy volunteers. The clinical diagnosis
was based on history and abnormal thermal thresholds on QST. In patients with
neuropathy, IENFD and SENPD were reduced to about 50 % of controls.
Elevated warm detection thresholds on QST correlated with IENFD but not with
SENPD. Using 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. 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.

Sommers (2008) stated that the sensitivity and specificity of skin biopsy in detecting SFN is supported by new data. Skin innervation is affected in neuropathies formerly considered as the large-fiber type, such as porphyria and chronic inflammatory demyelinating neuropathy. New methods have been devised to complement histological evaluation of skin innervation by in-vivo microscopy and by neurophysiological assessment of small nerve fibers. Skin biopsies have been used to learn more about the pathophysiology of neuropathies, such as the discovery of reduced vascular endothelial growth factor expression in DN and the increase in cytokine expression in some painful SFN. Quantification of skin innervation has been used as a measure for treatment success in experimental studies and is presently used for follow-up in clinical trials. Skin biopsy in the diagnosis of neuropathy is moving from a method giving descriptive results to a tool that may be helpful in etiological diagnostics, as a follow-up in clinical trials, and in pathophysiological research.

Devigili et al (2008) stated that SFN is frequently encountered in clinical practice either as prevalent manifestation of more diffuse neuropathy or distinct nosologic entity. Due to their physiological characteristics, small nerve fibers can not be investigated by routine electrophysiological tests, making the diagnosis particularly difficult. Quantitative sensory testing to evaluate the psychophysical thresholds for cold and warm sensations and skin biopsy with quantification of somatic IENF have been used to ascertain the damage to small nerve fibers. These investigators screened 486 patients referred to their institutions and collected 124 patients with sensory neuropathy. Among them, they identified 67 patients with pure SFN using a new diagnostic "gold standard", based on the presence of at least two abnormal results at clinical, QST and skin biopsy examination. The diagnosis of SFN was achieved by abnormal clinical and skin biopsy findings in 43.3 % of patients, abnormal skin biopsy and QST findings in 37.3 % of patients, abnormal clinical and QST findings in 11.9 % of patients, whereas 7.5 % patients had abnormal results at all the examinations. 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. However, these researchers found a significant inverse correlation between IENFD and both cold and warm thresholds at the leg. Clinical examination revealed pinprick and thermal hypoesthesia in about 50 % patients, and signs of peripheral vascular autonomic dysfunction in about 70 % of patients. Spontaneous pain dominated the clinical picture in most SFN patients. Neuropathic pain intensity was more severe in patients with SFN than in patients with large or mixed fiber neuropathy, but there was no significant correlation with IENFD. The etiology of SFN was initially unknown in 41.8 % of patients and at 2-year follow-up a potential cause could be determined in 25 % of them. Over the same period, 13 % of SFN patients showed the involvement of large nerve fibers, whereas in 45.6 % of them the clinical picture did not change. Spontaneous
remission of neuropathic pain occurred in 10.9% of SFN patients, while it worsened in 30.4% of them.

Laaksonen et al (2008) examined the neurological and neurophysiological findings and neurological symptoms in 12 women with Fabry disease and studied the relationship between the subjective symptoms and the findings on the various tests -- neurography, vibratory and thermal QST, skin biopsy for measuring IENFD, heart rate variability and sympathetic skin response (SSR) tests for detecting autonomic dysfunction, pain-, depression- and somatic symptom- questionnaires and clinical examination. Only 2 women had no persistent symptoms or signs of polyneuropathy, 10 had symptoms of SFN. Neurological examination was normal in most patients; 5 patients had decreased IENFD or thermal hypoesthesia in QST. In QST, A-delta-fiber function for innocuous cold was more often impaired than C-fiber function. Conventional NCVS were mostly normal. Carpal tunnel syndrome (CTS) incidence was increased, 25% had symptomatic CTS. The authors concluded that heterozygous women carrying the gene for Fabry disease have symptoms and findings of small-fiber polyneuropathy more often than has previously been considered. The prevalence of CTS is also increased. While the clinical diagnosis of SFN is difficult, the diagnostic yield can be increased using a combination of thermal QST and IENFD measurements.

The American Academy of Neurology’s assessment on QST (Shy et al, 2003) stated that abnormalities on QST must be interpreted in the context of a thorough neurological examination and other appropriate testing, such as electromyography, nerve biopsy, skin biopsy, or appropriate imaging studies.

Teoh and associates (2008) compared simple tests of small nerve fiber function with IENFD in the evaluation of SFN. Patients with idiopathic SFN of the hands were prospectively studied. Evaluation involved clinical examination, NCVS, SSR and skin wrinkling stimulated by water and EMLA (eutectic mixture of local anaesthetics). Of 21 patients, 16 (76%) had low IENFD, 15 (71%) impaired water-induced wrinkling, 14 (67%) impaired EMLA-induced wrinkling, and 9 (43%) abnormal SSR. The authors concluded that stimulated skin wrinkling was nearly as sensitive as IENFD in diagnosing SFN, whereas SSR was of less use. Stimulated skin wrinkling is a useful supportive test when IENFD or other tests of small nerve fiber function are not available.

Scherens and colleagues (2009) noted that dysesthesias of the lower limbs are a common complaint of patients and may be indicative of peripheral neuropathy. These investigators examined the prevalence and type of neuropathy in patients presenting with this complaint and compared the diagnostic performance of different diagnostic modalities. A total of 42 patients were recruited prospectively and underwent a clinical examination, NCVS, QST, and skin biopsy at the dorsum of the foot. All patients had a correlate for their dysesthesias in at least one diagnostic modality. Most patients (over 90%) had signs of small fiber loss or dysfunction. In approximately 50% of all patients large fibers were also affected. Nerve conduction velocity studies were abnormal in 23/42 patients (54.8%). Cold or warm detection thresholds in QST were abnormal in 15/42 (35.7%) patients. Decreased IENFD was found in 37 patients (88.1%), including some patients with normal QST findings. Nearly all patients with pathological QST had a reduced IENFD, indicating a high positive predictive value (93%) of QST in screening for reduced IENFD as correlate for neuropathy. Thus, in all patients with lower limb
dysesthesias of unknown origin, the non-invasive methods of NCVS and QST should be used and potentially complemented by skin biopsy.

Løseth and associates (2008) examined if neuropathy in diabetic patients with normal NCVS could be detected by measurements of thermal thresholds and quantification of IENFD, and assessed differences in parameters between patients with and without neuropathic symptoms. A total of 22 patients with and 37 patients without sensory symptoms suggesting distal neuropathy were included. Measurements of warm and cold perception thresholds and skin biopsy for quantification of IENFD were performed distally on the leg. Reference data were used to normalize test results for age and height or gender of individual patients by calculating the Z-scores. Intra-epidermal nerve fiber density was significantly reduced in both symptomatic and asymptomatic patients compared to controls ($p < 0.001$), and in patients with symptoms compared to those without ($p = 0.01$). Thermal thresholds were significantly elevated (more abnormal) in patients with symptoms compared to controls ($p < 0.01$), but only for cold perception threshold (CPT) ($p < 0.001$) in the asymptomatic group. When comparing symptomatic and asymptomatic patients, there was no statistically significant difference in thermal thresholds. Depletion of IENFs in skin biopsy was the most frequent abnormal finding in the subgroup of patients with neuropathic symptoms (36 %) followed by abnormal CPT (27 %). The authors concluded that patients with diabetes and normal NCVS had significantly lower IENFD and higher CPT than controls, whether they had symptoms of polyneuropathy or not. In patients with neuropathic symptoms, abnormal IENFD predominated and thus, seemed to be the most sensitive tool of detecting small diameter nerve fiber involvement.

The European Federation of Neurological Societies' guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy (Lauria et al, 2005) noted that for diagnostic purposes in peripheral neuropathies, a 3-mm punch skin biopsy at the distal leg and quantifying the linear density of IENF in at least three 50-micrometer thick sections per biopsy, fixed in 2 % periodate-lysine-paraformaldehyde or Zamboni's solution, by bright-field immunohistochemistry or immunofluorescence with anti-PGP 9.5 antibodies is recommended (level A recommendation). Quantification of IENFD closely correlated with warm and heat-pain threshold, and appeared more sensitive than sensory NCVS and sural nerve biopsy in diagnosing sensory SFN. Diagnostic efficiency and predictive values of this technique were very high (level A recommendation). Confocal microscopy may be particularly useful to investigate myelinated nerve fibers, dermal receptors and dermal annex innervation.

The Australia and New Zealand Horizon Scanning Network (Purin et al, 2007) assessment on skin biopsy diagnosis of peripheral neuropathy noted that "[a] lthough the evidence for the use of skin biopsy to diagnose SFN was mainly from small scale studies, the technique appears to perform well".

The American Academy of Neurology practice parameter Evaluation of Distal Symmetric Polyneuropathy (England et al, 2009) recommends that autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction. Such testing should be considered especially for the evaluation of suspected autonomic neuropathy and distal small fiber sensory polyneuropathy. In addition, it states that for
symptomatic patients with suspected polyneuropathy, skin biopsy is a validated technique for determining IENFD and may be considered for the diagnosis of distal symmetric polyneuropathy, especially small fiber sensory polyneuropathy.

Torvin Moller and associates (2009) stated that Fabry disease is an X-linked inherited lysosomal disorder with dysfunction of the lysosomal enzyme alpha-galactosidase A causing accumulation of glycolipids in multiple organs including the nervous system. Pain and somatosensory disturbances are prominent manifestations of this disease. Until recently, disease manifestations in female carriers of Fabry disease have been questioned. To explore the frequency of symptoms and the functional and structural involvement of the nervous system in female patients, these investigators examined the presence of pain, manifestations of peripheral neuropathy and nerve fiber density in skin biopsies in 19 female patients with Fabry disease and 19 sex- and age-matched controls. Diaries, quantitative sensory testing, neurophysiologic tests and skin biopsies were performed. Daily pain was present in 63 % of patients, with a median VAS score of 4.0. Tactile detection threshold and pressure pain threshold were lower and cold detection thresholds increased in patients. Sensory nerve action potential amplitude and maximal sensory conduction velocity were not different, whereas there was a highly significant reduction in IENFD. There were no correlations between pain VAS score, quantitative sensory testing, and IENFD.

Nebuchennykh and co-workers (2010) examined involvement of large and small nerve fibers in patients with hypothyroidism and symptoms and signs of polyneuropathy. A total of 16 patients with established diagnosis of hypothyroidism were extracted from a patient population participating in a "polyneuropathy study". In addition, 7 patients with other additional potential causes of polyneuropathy than hypothyroidism were investigated. The patients underwent neurological examination, routine blood tests, nerve conduction studies (NCS), QST and skin biopsies with assessment of IENFD. A total fo 63 % of the patients with "pure" hypothyroidism had abnormalities on NCS, 25 % had reduced IENFD and 31 % had abnormalities on QST. Four patients (25 %) met criteria for small fiber polyneuropathy, the other (75 %) were classified as having mixed fiber polyneuropathy. There were no differences in the amount of abnormalities on NCS, QST and skin biopsy between patients with hypothyroidism and those with hypothyroidism and other potential causes of polyneuropathy. The authors concluded that the majority of patients with hypothyroidism had involvement of both large and small nerve fibers. However, some patients had isolated small fiber polyneuropathy. Patients with "pure" hypothyroidism had essentially the same degree of peripheral nerve fiber involvement as those with other additional causes of polyneuropathy.

Magri and colleagues (2010) assessed by means of IENFD in 18 untreated patients with hypothyroidism, either overt (OH) or subclinical (SH), who did not complain of neurological symptoms; 15 healthy, age-matched, controls were also studied. A nerve conduction study was performed. Skin biopsy was performed using the skin of upper thigh and distal leg. Nerve fiber density was measured using an immunofluorescence technique. The density of innervation was calculated by counting only fibers crossing the basement membrane. Electroneurographic parameters were similar in patients and controls. When compared with healthy controls, patients with OH or SH showed a significantly
lower IENFD. As assessed by the proximal/distal fiber density ratio, the hypothyroid neuropathy was length-dependent. When individually considered, an abnormally reduced IENFD was observed in 60% of patients with OH at the distal leg and in 20% at the proximal site. In patients with SH, an abnormal IENFD was found at the distal leg in 25% of cases and at the proximal thigh in 12.5% of cases. The authors concluded that the results of this study provided the first direct demonstration of reduced IENFD in patients with OH or SH. In all patients, the IENFD reduction was length-dependent. They stated that these findings suggested that a considerable number of untreated hypothyroid patients may have pre-clinical asymptomatic small-fiber sensory neuropathy. The findings of this small study needs to be validated by well-designed studies.

Sweat glands, innervated by the autonomic nerves, are involved with regulation of body temperature and hydration. Symptoms of autonomic neuropathy may entail abnormal sweating or temperature regulation, among others (e.g., gastroparesis, incomplete bladder emptying, irregular bowel movements, irregular heart rate, postural hypotension, sexual dysfunction, and urinary urgency). Both sweat gland nerve fiber density (SGNFD) and IENFD can be reduced in generalized SFN, but in some autonomic neuropathies (e.g., Ross syndrome), only the SGNFD is reduced (Sommer et al, 2002).

Gibbon et al (2009) evaluated a novel method to quantify the density of nerve fibers innervating sweat glands in healthy control and diabetic subjects, and compared the results to an unbiased stereological technique, and identified the relationship to standardized physical examination and patient-reported symptom scores. A total of 30 diabetic and 64 healthy subjects had skin biopsies performed at the distal leg and distal and proximal thigh. Nerve fibers innervating sweat glands, stained with protein gene product 9.5, were imaged by light microscopy. Sweat gland nerve fiber density was quantified by manual morphometry. As a gold standard, 3 additional subjects had biopsies analyzed by confocal microscopy using unbiased stereological quantification. Severity of neuropathy was measured by standardized instruments including the Neuropathy Impairment Score in the Lower Limb (NIS-LL) while symptoms were measured by the Michigan Neuropathy Screening Instrument. Manual morphometry increased with unbiased stereology (r = 0.93, p < 0.01). Diabetic subjects had reduced SGNFD compared to controls at the distal leg (p < 0.001), distal thigh (p < 0.01), and proximal thigh (p < 0.05). The SGNFD at the distal leg of diabetic subjects decreased as the NIS-LL worsened (r = -0.89, p < 0.001) and was concordant with symptoms of reduced sweat production (p < 0.01). In summary, the authors described a novel method to quantify the density of nerve fibers innervating sweat glands. 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. The validity of this novel technique needs to be confirmed by well-designed studies.

Gibbons et al (2010) stated that peripheral sudomotor dysfunction is present in many peripheral neuropathies, but structural assessments of sudomotor fibers rarely occur. These researchers evaluated 36 diabetic and 72 healthy control subjects who underwent detailed neurologic examinations and punch skin biopsies. Physical examination findings were quantified by neuropathy impairment score in the lower limb. Skin biopsies quantified IENFD and SGNFD by a manual,
automated, and semi-quantitative method. The automated and manual SGNFD correlated with the IENFD at the same site ($r = 0.62$, $p < 0.05$ automated method, $r = 0.67$, $p < 0.05$ manual method). As neuropathy worsened, the SGNFD at the distal leg declined (automated counting $r = -0.81$, $p < 0.001$; manual counting $r = -0.88$, $p < 0.001$). The semi-quantitative method displayed poor inter- and intra-reviewer reliability and correlated poorly with standard neuropathy evaluation scores.

The European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS)'s guideline on the use of skin biopsy in the diagnosis of SFN (2010) stated that the quantification of sudomotor nerve fibers is technically challenging because of the complex 3-dimensional structure of the sweat glands. Different methods have been proposed but none has been standardized (Lauria et al, 2005). A novel method using an unbiased stereologic technique has been recently proposed (Gibbons et al, 2009). The authors examined blindly 30 diabetic neuropathy patients and 64 healthy subjects finding a significant difference between groups. The density of sweat gland nerve fibers at the distal leg of diabetic patients decreased as the Neuropathy Impairment Score in the Lower limbs worsened ($p < 0.001$) and was concordant with symptoms of reduced sweat production ($p < 0.01$). In a further work, the authors reported a significant correlation between the stereologic unbiased method and a new automated technique for quantification of sudomotor nerve fibers, and showed that the descriptive semi-quantitative approach has a poor inter- and intra-observed reliability (Gibbons et al, 2010).

The EFNS/PNS guideline noted that morphometric data on sweat gland innervation density in healthy subjects and in patients with SFN are limited and further studies are warranted. The descriptive semi-quantitative approach should not be used to quantify sweat gland innervation (level B recommendation). The unbiased stereologic technique recently proposed could be a helpful tool (level B recommendation). The guideline also stated that the reliability of already tested or new methods to quantify the density of nerve fibers in the sub-epidermal dermis and autonomic structures (e.g., sweat gland nerve, erector pili muscle, and vessels) should be confirmed by further studies in patients with homogeneous types of peripheral neuropathy, including SFN. Correlative studies between skin biopsy, autonomic tests, and non-conventional neurophysiologic tools are also warranted.

Kharkar et al (2012) stated that accumulating experimental and clinical evidence supports the hypothesis that complex regional pain syndrome type I (CRPS-I) may be a small fiber neuropathy. These researchers evaluated the use of commercially available standard biopsy methods to detect intra-dermal axon pathology in CRPS-I, and examined if these structural changes can explain quantitative sensory testing (QST) findings in CRPS-I. Skin biopsies from 43 patients with CRPS-I were stained with PGP 9.5, and ENFD, sweat gland nerve fiber density, as well as morphological abnormalities were evaluated. A total of 35 patients had QST. Alterations in skin innervation were seen in approximately 20% of CRPS-I patients with commercial processing. There were no patient characteristics, including duration of disease, which predicted a decreased ENFD. There was no consistent relationship between QST changes and ENFD measured by standard commercial skin biopsy evaluation procedures. The authors...
concluded that the negative results indicate that CRPS-I may be associated with changes in the ultramicroscopic small fiber structure that cannot be visualized with commercially available techniques. Alternatively, functional rather than structural alterations of small fibers or pathological changes at a more proximal site such as the spinal cord or brain may be responsible for the syndrome.

Also, an UpToDate review on “Etiology, clinical manifestations, and diagnosis of complex regional pain syndrome in adults” (Abdi, 2013) does not mention measurement of sweat gland nerve fiber density as a diagnostic tool.

Gibbons et al (2013) defined the neuropathology, clinical phenotype, autonomic physiology and differentiating features in individuals with neuropathic and non-neuropathic postural tachycardia syndrome (POTS), a disorder of orthostatic intolerance characterized by excessive tachycardia of unknown etiology. A total of 24 subjects with POTS and 10 healthy control subjects had skin biopsy analysis of IENFD, QST and autonomic testing. Subjects completed quality of life, fatigue and disability questionnaires; they were divided into neuropathic and non-neuropathic POTS, defined by abnormal IENFD and abnormal small fiber and sudomotor function. Overall, 9 of 24 subjects had neuropathic POTS and had significantly lower resting and tilted heart rates; reduced parasympathetic function; and lower phase 4 Valsalva maneuver overshoot compared with those with non-neuropathic POTS (p < 0.05). Neuropathic POTS subjects also had less anxiety and depression and greater overall self-perceived health-related quality of life scores than non-neuropathic POTS subjects. A sub-group of POTS patients (cholinergic POTS) had abnormal proximal sudomotor function and symptoms that suggest gastro-intestinal and genito-urinary parasympathetic nervous system dysfunction. The authors concluded that POTS subtypes may be distinguished using small fiber and autonomic structural and functional criteria. Patients with non-neuropathic POTS have greater anxiety, greater depression and lower health-related quality of life scores compared to those with neuropathic POTS. They stated that these findings suggested different pathophysiological processes underlie the postural tachycardia in neuropathic and non-neuropathic POTS patients. The findings have implications for the therapeutic interventions to treat this disorder.

Haensch et al (2014) evaluated the correlation between C-fiber involvement shown by skin biopsy and adrenergic cardiac MIBG-uptake in POTS patients. Skin biopsies of 84 patients with POTS were examined by Protein Gene Product 9.5 (PGP9.5) immunohistochemistry and were compared to MIBG myocardial scintigraphy imaging data. Mean IENFD was in the lower normal age-adjusted range, 7.2 ± 2.9 /mm (normal greater than or equal to 7/mm), and it was slightly below the normal range in 45 % of POTS patients; MIBG-uptake was reduced in 21 %. Low IENFD correlated with reduced cardiac MIBG uptake (r = 0.39, p = 0.001). The authors concluded that a subset of neuropathic POTS patients might harbor mild SFN with abnormalities of unmyelinated nerve fibers in the skin associated with reduced myocardial post-ganglionic sympathetic innervation. The clinical value of IENFD in the management of patients with POTS needs to be further investigated.

An UpToDate review on “Postural tachycardia syndrome” (Freeman and Kaufmann, 2014) does not mention measurement of epidermal nerve fiber density as a management tool.
Caro and Winter (2014) stated that a subset of patients with fibromyalgia (FM) exhibit a large fiber demyelinating peripheral polyneuropathy akin to that seen in chronic inflammatory demyelinating polyneuropathy (CIDP). It has been suggested that this demyelinating process is likely to be immune mediated. Because it is known that similar large fiber neuropathic lesions may be associated with a cutaneous SFN, these researchers determined the prevalence of SFN, as measured by ENFD, in a series of patients with FM and clinically healthy control subjects. A total of 41 consecutive patients with FM and 47 control subjects underwent a 3-mm punch skin biopsy at the proximal thigh and distal leg near the ankle, for analysis of the ENFD. Patients with FM who had clinical evidence of a disorder known to be associated with SFN were excluded. The patients with FM also underwent pinwheel testing and vibratory testing for hypesthesia and serologic testing for a series of cytokine, circulating immune complex, and complement measurements. All patients with FM had evidence of stocking hypesthesia. The ENFD of patients with FM was lower than that of control subjects at both the calf (mean ± SD 5.8 ± 2.8 versus 7.4 ± 1.9; P = 0.0002) and thigh (9.3 ± 3.2 versus 11.3 ± 2.0; p = 0.0007). There was an inverse correlation between calf ENFD and age at the time of skin biopsy in patients with FM (r = -0.29, p = 0.03) but not in control subjects; however, analysis of covariance showed that this relationship could not be explained by aging alone. Serologic evaluation showed an inverse correlation between calf ENFD in patients with FM and the interleukin-2 receptor (IL-2R) level (r = -0.28, p = 0.04). However, an inverse correlation between thigh ENFD and serum IL-2R levels did not reach significance (p = 0.08). Analysis of thigh-to-calf ENFD ratios suggested that the ENFD decline in FM is affected by both a diffuse and a length-dependent process. The authors concluded that the calf and thigh ENFD in patients with FM is significantly diminished compared with that in control subjects. Advancing age alone cannot explain this finding. Calf ENFD was inversely correlated, although weakly, with serum levels of IL-2R. They stated that these findings suggested that SFN 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.

CPT Codes / HCPCS Codes / ICD-9 Codes

There are no specific codes for Intra-Epidermal Nerve Fiber Density Measurement or sweat gland nerve fiber density measurement:

Other CPT codes related to the CPB:

88305
+ 88314
88342
88343
88356
Nerve Fiber Density Measurement

Other HCPCS codes related to the CPB:

G0461  Immunohistochemistry or immunocytochemistry, per specimen; first single or multiplex antibody stain

G0462  each additional single or multiplex antibody stain (list separately in addition to code for primary procedure)

ICD-9 codes covered if selection criteria are met:

354.8 - 354.9  Mononeuritis of upper limb

355.71 - 355.9  Mononeuritis of lower limb

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

243 - 244.9  Congenital and acquired hypothyroidism [as a marker of pre-clinical asymptomatic small-fiber sensory neuropathy]

250.60 - 250.63  Diabetes with neurological manifestations

272.7  Lipidoses [Fabry's disease]

337.20 - 337.29  Reflex sympathetic dystrophy

356.0  Hereditary peripheral neuropathy

356.2  Hereditary sensory neuropathy

357.2 - 357.3  Polyneuropathy in diabetes or other malignant diseases

357.6 - 357.7  Polyneuropathy due to drugs or other toxic agents

The above policy is based on the following references:


