Nerve Fiber Density Testing

Policy Number: 2.04.58  Last Review: 12/2016
Origination: 12/2015  Next Review: 12/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Nerve Fiber Density Testing when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber neuropathy may be considered **medically necessary** when all of the following conditions are met:
1. Individual presents with symptoms of painful sensory neuropathy; AND
2. There is no history of a disorder known to predispose to painful neuropathy (eg, diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy); AND
3. 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
4. Electromyography and nerve-conduction studies are normal and show no evidence of large-fiber neuropathy.

When Policy Topic is not covered
Skin biopsy with epidermal nerve fiber density measurement is **investigational** for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment.

Measurement of sweat gland nerve fiber density is **investigational**.

Considerations
There are no specific codes for this analysis. Multiple CPT pathology codes would be used such as:
88305 - Level IV - Surgical pathology, gross and microscopic examination;
88314 - Special stains (List separately in addition to code for primary service); histochemical staining with frozen section(s)
88342 - Immunohistochemistry (including tissue immunoperoxidase), each antibody; and
88356 - Morphometric analysis; nerve.
Skin biopsy is used to assess the density of epidermal (intraepidermal) and sweat gland (sudomotor) nerve fibers using antibodies to a marker found in peripheral nerves. This procedure is being investigated as an objective measure of small fiber neuropathy by identifying a reduction in the density of nerve fibers.

The evidence for intraepidermal nerve fiber (IENF) density testing in patients who have suspected small fiber neuropathy includes reports on technical performance, diagnostic accuracy, and the effect on health outcomes. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Techniques to measure IENF density have led to an improved understanding of the relation between the loss of small nerve fibers and symptoms of peripheral neuropathy. The literature also indicates that low IENF density may provide supportive evidence of a lesion in the peripheral somatosensory system. For example, there is a significant decrease in average IENF density in patients diagnosed with small fiber neuropathy compared with controls, and an IENF density of 4 to 8 per mm in the calf is near the 5th percentile of normal values, suggesting an increased probability of small fiber neuropathy below these cutoffs. Thus, IENF density measurement may be helpful for the diagnosis of idiopathic small fiber neuropathy in those who have no known causes of neuropathy and no evidence of large fiber neuropathy. IENF density testing has not been shown to improve health outcomes when the individual presents with symptoms of painful sensory neuropathy and there is history of a disorder known to predispose to painful neuropathy (eg,
diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy). The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for sweat gland nerve fiber (SGNF) density testing in patients who have suspected small fiber neuropathy includes comparisons with control values. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Measurement of SGNF density may lead to an improved understanding of the relation between the loss of sudomotor nerve fibers and symptoms of peripheral neuropathy. However, no studies were identified that evaluated the diagnostic accuracy of SGNF density measurement. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for IENF density testing in patients who have established small fiber neuropathy is limited. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Although a number of trials are in progress, current treatments for small fiber neuropathy only palliate symptoms and do not target the underlying disease. There is no evidence that monitoring disease progression has clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Skin biopsy is used to assess the density of epidermal (intraepidermal) and sweat gland (sudomotor) nerve fibers using antibodies to a marker found in peripheral nerves. This procedure is being investigated as an objective measure of small fiber neuropathy by identifying a reduction in the density of nerve fibers.

The majority of patients with peripheral neuropathy exhibit evidence of large fiber involvement, characterized by numbness, tingling, loss of deep tendon reflexes, and abnormal electrophysiologic studies. In contrast, damage to small fibers is not detected by routine nerve conduction studies. Patients with small fiber neuropathy, involving myelinated A delta and unmyelinated C fibers, may complain of severe pain and exhibit diminished thermal and pain perception. The pain, which is frequently reported in the feet, is described as burning, prickling, stabbing, jabbing, or tight band-like pressure. If there is involvement of autonomic C fibers, symptoms such as coldness, discoloration, and hyper- or hypohidrosis may be present. Small fiber neuropathy occurs most often in patients with diabetic neuropathy but may also be found in patients with impaired glucose tolerance, severe hypertriglyceridemia, metabolic syndrome, HIV infection, and toxic neuropathy from antiretroviral drugs. For many patients, no specific etiology is identified.

Small fiber neuropathy is diagnosed clinically but has traditionally been a diagnosis of exclusion based on clinical findings and the absence of large fiber involvement, as determined by electrophysiologic studies. The disparity between subjective complaints and objective signs increases the difficulty of diagnosis. In addition, conditions other than nerve fiber damage, including venous insufficiency, spinal stenosis, myelopathy, and psychosomatic disturbances may mimic small fiber
There is no treatment to cure small fiber peripheral neuropathy. Medications may be provided for pain management, and for some etiologies, treatment of the underlying condition (eg, glucose control, intravenous immunoglobulin or plasma exchange) may be given to reduce progression of the disease and its symptoms.

In the last decade, a specific test to assess IENF density and SGNF density using skin biopsy and immunostaining of the tissue have been developed that allow the identification and counting of intraepidermal and sudomotor nerve fibers. Assessment of nerve fiber density typically involves a 3-mm punch biopsy of skin from the calf (and sometimes foot or thigh). After sectioning by microtome, the tissue is immunostained with anti-protein-gene-product 9.5 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods. This technique has improved research and contributed greatly to the understanding of small fiber neuropathy. Skin biopsy with measurement of IENF density has also been investigated as an objective measure for the diagnosis of small fiber neuropathy. SGNF density can be assessed from the same tissue that has been prepared for IENF density testing, provided that the biopsy sample is of sufficient depth. Tissue samples may also be counterstained to better identify the boundaries of the sweat glands.

**Rationale**

This evidence review was created in 2009 and has been updated periodically using the MEDLINE database. The most recent literature update was performed through November 9, 2015. In addition to recent studies, the searches identified a systematic review by the European Federation of Neurological Societies (EFNS) from 2005, updated guidelines from EFNS in 2010, and a jointly published evidence review and practice parameter for the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and American Academy of Physical Medicine and Rehabilitation (AAPM&R) from 2009.(1-3)

Assessment of a diagnostic technology typically focuses on the following 3 categories of evidence: (1) technical performance, (2) clinical validity in an appropriate patient population (diagnostic accuracy including sensitivity, specificity, and positive and negative predictive value), and (3) demonstration that the diagnostic information can be used to improve patient outcomes.

**Intraepidermal Nerve Fiber Density**

**Technical Performance**

The EFNS systematic review determined that skin biopsy from the distal leg or foot with immunostaining with anti-protein-gene-product 9.5 (PGP 9.5) is a safe, validated, and reliable technique for the determination of intraepidermal nerve fiber (IENF) density, indicating adequate technical performance of this test.(1) The EFNS also concluded that IENF density is diagnostically efficient at distinguishing polyneuropathy patients (including small fiber neuropathy) from normal controls.
In 2010, Lauria et al published a multicenter study (8 sites) of normative reference values for IENF density at the distal leg.(4) Groups that previously reported normative IENF density values using bright-field immunohistochemistry provided available data to a coordinating center. Density data from a total of 550 healthy subjects (age range, 18-84 years) in the United States, Europe, and Asia were included in the analysis. There was a significant decrease in IENF density in both men and women with age. For women, the 5th percentile ranged from 8.4 fibers per mm at 20 to 29 years of age to 1.6 fibers per mm at 80 years or older. For men, the 5th percentile ranged from 6.1 fibers per mm at 20 to 29 years of age to 1.7 at 80 years or older. IENF density was lower in men than women between 20 and 69 years of age, but not for subjects 70 years or older. This finding may be limited by the smaller sample size in the older age groups. There was no significant influence of height, weight, or body mass index for the IENF density normative scores (5th percentile).

**Diagnostic Accuracy**
Assessment of diagnostic accuracy necessitates that studies include a representative patient population with an appropriate spectrum of patients and that the test be compared with an independently assessed gold standard. As discussed in the jointly published 2009 practice parameters of the AAN, AANEM, and AAPM&R (reaffirmed in 2013),(3) the EFNS systematic review did not assess the more clinically relevant question, which is: What is the diagnostic accuracy of skin biopsy in distinguishing symptomatic patients with polyneuropathy from symptomatic patients without polyneuropathy? For example, in patients with painful feet, would skin biopsy accurately distinguish patients with polyneuropathy from other conditions causing painful feet?

To address these questions, a committee of the AAN, AANEM, and AAPM&R performed a literature review to evaluate the diagnostic accuracy of IENF density in the detection of small fiber neuropathy. They adopted a clinical diagnosis of small fiber neuropathy as the independent reference standard for calculation of sensitivity and specificity. Eight studies were reviewed that employed a case-control design with patients with established polyneuropathy and normal controls. Significant differences were found between the 2 groups. For example, McArthur et al studied 98 normal controls and 20 patients with sensory neuropathies.(5) The density of epidermal nerve fibers in the controls was 13.8 per mm in the calf (5th percentile of controls, 3.8 per mm), with a significant mean reduction in the patient population (value not reported) and a diagnostic efficiency of 88% (vs healthy controls). An earlier report by this group showed a mean IENF density of 4.9 in 20 patients with sensory neuropathy and a mean IENF density of 16.3 in 20 age-matched controls.(6) However, none of the studies reviewed included an appropriate group of patients, ie, those with conditions causing lower extremity pain or sensory complaints that might be confused with polyneuropathy. In addition, the sensitivity of IENF density ranged from 45% to 90% compared to healthy controls, indicating that the absence of reduced IENF density would not rule out polyneuropathy.
The American Association of Clinical Endocrinologists conducted an evidence review on diabetic neuropathy for their 2011 guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan.(7) The evidence review found that there is level 3 evidence (cross-sectional studies) to show that intraepidermal nerve fiber density correlates inversely with both cold and heat detection thresholds and is significantly reduced in symptomatic patients with normal findings from nerve conduction studies and those with metabolic syndrome, impaired glucose tolerance, and impaired fasting glucose, suggesting early damage to small nerve fibers. Level 3 evidence (surveillance studies) indicates that intraepidermal nerve fiber density is reduced in painful neuropathy compared with that observed in painless neuropathy. Level 2 evidence (prospective cohort studies) indicates that diet and exercise intervention in impaired glucose tolerance lead to increased intraepidermal nerve fiber density. The review concludes that these data suggest that intraepidermal nerve fiber loss is an early feature of metabolic syndrome, prediabetes, and established diabetes mellitus and that the loss progresses with increasing neuropathic severity. In addition, there may be nerve regeneration with treatment (diet and exercise).

The single prospective study that was identified in the 2009 AAN, AANEM, and AAPM&R literature review included a series of 117 patients presenting with bilateral painful feet.(8) In this report, skin biopsy was done only in the subset of 32 patients who had normal nerve conduction studies, and the study did not compare the results of the IENF density to an independent reference standard to confirm the presence of small fiber neuropathy. AAN, AANEM, and AAPM&R concluded that IENF density assessment is “possibly useful” to identify distal symmetric polyneuropathy, including small fiber neuropathy, in symptomatic patients with suspected polyneuropathy (level C recommendation). Future research recommendations included the need for studies to characterize the diagnostic accuracy of skin biopsy in distinguishing patients with suspected polyneuropathy (particularly small fiber neuropathy) from appropriate patients with sensory complaints or pain unrelated to peripheral neuropathy, using a predetermined reference standard.

Diagnostic accuracy of skin biopsy was assessed in a 2009 study with 210 patients who had signs of small fiber neuropathy from various conditions.(9) The diagnosis of pure small fiber neuropathy (n=45) was established if patients had clinical symptoms and sensory deficits but preserved vibration and joint sense. Using a z score less than 2 from a reference set of 134 healthy individuals as the threshold, IENF density had a sensitivity of 31% and a specificity of 98%. Using the 5th percentile as a threshold (6.7 fibers/mm), the sensitivity of IENF density was 35% and specificity was 95%. When sensitivity was maximized from receiver operating characteristic analysis (78% sensitivity, at a threshold of 10.3 fibers/mm), specificity decreased to 64%. Scherens et al assessed the percentage of patients with lower limb dysesthesias (painful or painless) who had evidence of small fiber neuropathy.(10) Thirty-seven of the 42 patients (88%) with dysesthesias were found to have abnormal IENF density, 4 patients (9.5%) were categorized with pure large fiber neuropathy, 15 (35.7%) with pure small fiber neuropathy, and 22 (52.4%) with mixed large and small fiber neuropathy. Given that nearly 90% of
patients with dysesthesias showed abnormal IENF density, this study raises questions about the value added from skin biopsy in a clinical setting.

Additional studies include large retrospective series. Walk et al examined the concordance between foot IENF density and clinical findings in 106 patients with possible idiopathic small fiber neuropathy.(11) An IENF density of 8 per mm was found to have the highest sensitivity (88%) and specificity (81%), using sensory deficit to pinprick as the standard. In a 2009 review, Walk concluded that a reduction in IENF density provides supportive evidence of a loss of cutaneous efferents, but “clinical features remain paramount in the diagnostic process and the possibility of small fiber dysfunction is not excluded by an IENF density in the normal range.”(12) Devigili et al published a retrospective review of 486 patients referred for suspected sensory neuropathy.(13) Based on combined assessments of (1) clinical examination, (2) nerve conduction study, (3) quantitative sensory testing, and (4) skin biopsy, 124 patients were diagnosed with sensory neuropathy, of whom 67 were diagnosed with small fiber neuropathy. Using a cutoff of 7.63 IENF/mm at the distal leg (based on the 5th percentile of controls), 59 patients (88%) were considered to have abnormal nerve density. This study is limited by the lack of an independent reference standard, since the IENF results affected whether patients were included in the study group.

**Effect on Health Outcomes**

Another issue to consider for this diagnostic test is whether objective confirmation in patients with a clinical diagnosis of small fiber neuropathy will alter treatment decisions and lead to improved health outcomes. Oaklander et al conducted a prospective study to evaluate whether small fiber neuropathy may have been the cause of symptoms in patients who had a prior diagnosis of fibromyalgia by an independent physician.(14) Of 27 patients, skin biopsies were consistent with small fiber neuropathy (<5th percentile of the norm) in 41% compared with 3% of matched control subjects, leading to investigation of other potential causes. A 2013 retrospective analysis by Boruchow and Gibbons found a change in diagnosis or management in 36 of 69 patients (52%) who had a skin biopsy at their institution for evaluation of possible small fiber neuropathy.(15) Determination of low or borderline IENF density led to newly identified diseases in 8 patients, more aggressive management of diabetes mellitus in 8 patients, and further laboratory testing in 4 patients. Of the 35 patients who had normal skin biopsies, 14 had new treatments and/or diagnoses, including musculoskeletal pain, plantar fasciitis, Morton neuroma, restless legs syndrome, lumbar spinal stenosis, Raynaud syndrome, peripheral nerve hyperexcitability, autoimmune autonomic ganglionopathy, and depression. The authors reported that examination findings were not effective at distinguishing patients with or without pathologic determination of small fiber neuropathy, and that some physicians at their institution appeared to use skin biopsies as a way to rule out, rather than rule in, a diagnosis of small fiber neuropathy. The authors did not report if the changes in diagnosis or management led to an improvement in health outcomes.

A 2011 review of the diagnosis and treatment of pain in small fiber neuropathy indicates that the history and physical exam are still considered the gold standard
and that further testing may be unnecessary, particularly in the context of an associated disease.(16) However, the authors suggest that IENF-density testing may provide diagnostic confirmation or additional guidance if the diagnosis is less clear.

**Sweat Gland Nerve Fiber Density**

**Technical Performance**

In a 2009 report, Gibbons et al evaluated sweat gland nerve fiber (SGNF) density measurements in punch skin biopsies from 30 diabetic subjects and 64 controls that were sectioned and stained with *PGP 9.5* and compared with confocal microscopy with stereology.(17) Measurements of SGNF density were normalized by area due to the large variability in sweat gland size, and specific methods were used to reduce the high inter- and intrareviewer variability in manual outlining of sweat gland area. The authors noted nonspecific background staining of the sweat glands with *PGP 9.5* that made it difficult to measure individual nerve fibers and sweat gland margins. There was an average of 1.6 sweat glands per biopsy. Blinded evaluation found a correlation of \( r \) equal to 0.93 between SGNF density and the stereologic estimate of sweat gland nerve fiber length. The intrareviewer intraclass correlation coefficient (ICC) was 0.886 and the interreviewer ICC was 0.892. A 2010 publication by the same authors found good reliability for either automated or manual quantification of SGNF density, but poor inter- and intrareviewer reliability when using a semiquantitative approach (5-point scale).(18)

**Diagnostic Accuracy**

In their 2009 report, Gibbons et al found a significant decrease in the mean SGNF density of diabetic subjects compared to controls, although there was considerable overlap in the ranges.(17) There was also a significant association between the SGNF density and neuropathy scores measured by the Neuropathy Impairment Score in the Lower Limb, the Michigan Diabetic Neuropathy Score part 1, and the Toronto Clinical Scoring System, but not the Michigan Neuropathy Screening Instrument. There was a moderate correlation \( (r=0.66) \) between SGNF density and IENF density.

Luo et al evaluated SGNF density in 35 patients with type 2 diabetes and sensory neuropathy (stocking distribution and reduced IENF density).(19) Normative values were established in 107 control subjects, and sudomotor denervation was defined as a SGNF density less that the 5th percentile cutoff value for the sex (1.58% for men, 2.63% for women). There was no effect of age on the SGNF density. Sudomotor denervation was present in 42.86% of patients with diabetic neuropathy. The SGNF was lower in patients with anhidrosis of the feet compared with patients with normal sweating (0.89% vs 3.10%) and was not associated with autonomic symptoms in the cardiovascular, gastrointestinal, or genitourinary systems.

No studies were identified that evaluated the sensitivity or specificity of SGNF density measurement.
Effect on Health Outcomes
Analysis of SGNF density could potentially be considered complementary to IENF density, since they assess autonomic and somatic nerves, respectively.(20) However, no studies were identified to support an improvement in health outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>NCT No.</th>
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<th>Completion Date</th>
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<td>Dec 2015</td>
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<td>Feb 2018</td>
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<td><strong>Unpublished</strong></td>
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<td>NCT01288937a</td>
<td>A Placebo Controlled, Randomized, Double Blind Trial of Milnacipran for the</td>
<td>52</td>
<td>Oct 2014</td>
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<tr>
<td></td>
<td>Treatment of Idiopathic Neuropathy Pain</td>
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NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

Summary of Evidence
The evidence for intraepidermal nerve fiber (IENF) density testing in patients who have suspected small fiber neuropathy includes reports on technical performance, diagnostic accuracy, and the effect on health outcomes. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Techniques to measure IENF density have led to an improved understanding of the relation between the loss of small nerve fibers and symptoms of peripheral neuropathy. The literature also indicates that low IENF density may provide supportive evidence of a lesion in the peripheral somatosensory system. For example, there is a significant decrease in average IENF density in patients diagnosed with small fiber neuropathy compared with controls, and an IENF density of 4 to 8 per mm in the calf is near the 5th percentile of normal values, suggesting an increased probability of small fiber neuropathy below these cutoffs. Thus, IENF density measurement may be helpful for the diagnosis of idiopathic small fiber neuropathy in those who have no known causes of neuropathy and no evidence of large fiber neuropathy. IENF density testing has not been shown to improve health outcomes when the individual presents with symptoms of painful sensory neuropathy and there is history of a disorder known to predispose to painful neuropathy (eg, diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy). The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
The evidence for sweat gland nerve fiber (SGNF) density testing in patients who have suspected small fiber neuropathy includes comparisons with control values. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Measurement of SGNF density may lead to an improved understanding of the relation between the loss of sudomotor nerve fibers and symptoms of peripheral neuropathy. However, no studies were identified that evaluated the diagnostic accuracy of SGNF density measurement. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for IENF density testing in patients who have established small fiber neuropathy is limited. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Although a number of trials are in progress, current treatments for small fiber neuropathy only palliate symptoms and do not target the underlying disease. There is no evidence that monitoring disease progression has clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies and 2 academic medical centers while this policy was under review in 2011. References were provided, which were subsequently reviewed. The input was mixed. Some respondents indicated that the gold standard for diagnosis of small fiber neuropathy is the history and clinical examination combined with nerve conduction studies and that the skin biopsy only supports a clinical impression of a small fiber polyneuropathy and cannot exclude the diagnosis. One reviewer commented that patients who benefit from this test are those who suffer from the symptoms of small fiber neuropathy but have no predisposing condition (idiopathic). Other reviewers, who were generally in support of the medical necessity of IENF density management for diagnosis, acknowledged that the test has limited utility when disease is clinically advanced and that evidence to demonstrate that the use of skin biopsy with IENF density measurement improves clinical outcomes is only now emerging.

Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists
The American Association of Clinical Endocrinologists (AACE) published 2011 guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan.(7) The guidelines state, based on consensus opinion, that diabetic painful neuropathy is diagnosed clinically and must be differentiated from other
painful conditions. AACE references the European Federation of Neurological Societies’ guidelines on the use of IENF quantification to confirm the clinical diagnosis of small fiber neuropathy (consensus). (2)

American Academy of Neurology et al
The 2009 practice parameters from 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) concluded that IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology and provided a level C (possibly useful) recommendation to consider use of skin biopsy to diagnose the presence of a polyneuropathy, particularly small fiber neuropathy. (3) This guideline was reaffirmed by the AAN in 2013.

In 2005, AANEM, in conjunction with AAN and AAPM&R, published an ordered set of case definitions of “distal symmetrical polyneuropathy” for clinical research ranked by the likelihood of disease. (21) The recommendations for case definitions that include symptoms, signs, and nerve conduction studies were for clinical research studies and based on a systematic analysis of peer-reviewed literature supplemented by consensus from an expert panel. IENF density was not included in the case definitions.

European Federation of Neurological Societies
The European Federation of Neurological Societies (EFNS) published a 2005 guideline on the use of skin biopsy in peripheral neuropathy. (1) EFNS concluded that skin biopsy is a safe, validated, and reliable technique for the determination of IENF density. EFNS published updated guidelines on the use of skin biopsy in the diagnosis of small fiber neuropathy in 2010. (2) The guidelines stated that IENF density is a reliable and efficient technique to assess the diagnosis of small fiber neuropathy (recommendation level A). Normative reference values are available for bright-field immunohistochemistry (recommendation level A) but not for confocal immunofluorescence. The guidelines recommended that newly established laboratories should provide their own stratified for age and gender normative values, intra- and interobserver reliability, and interlaboratory agreement. Proposals for new studies included:

- A clinimetric approach to assess the correlation between skin innervation and the clinical symptoms and signs of small fiber neuropathy. Such studies should include patients whose clinical picture mimics that of small fiber neuropathy, to definitely assess specificity and sensitivity of skin biopsy in the diagnosis of this type of neuropathy.
- A consensus definition of small fiber neuropathy is needed to plan new studies that will determine the sensitivity and specificity of skin biopsy and other potential diagnostic strategies.
- Further studies should focus on the ability of skin biopsy to detect early changes of nerve fibers that predict the progression of neuropathy and that assist in assessing nerve degeneration and regeneration rates over time, to
confirm the potential usefulness of the technique as an outcome measure in clinical practice and research.

**U.S. Preventive Services Task Force Recommendations**

Nerve fiber density testing is not a preventive service.

**Medicare National Coverage**

There is no national coverage decision (NCD) specifically regarding IENF density testing. The NCD for services provided for the diagnosis and treatment of diabetic sensory peripheral neuropathy with loss of protective sensation (also known as diabetic peripheral neuropathy) (70.2.1) provides the following information:

Effective for services furnished on or after July 1, 2002, Medicare covers, as a physician service, an evaluation (examination and treatment) of the feet no more often than every six months for individuals with a documented diagnosis of diabetic sensory neuropathy and loss of protective sensation, as long as the beneficiary has not seen a foot care specialist for some other reason in the interim. Loss of protective sensation shall be diagnosed through sensory testing with the 5.07 monofilament using established guidelines, such as those developed by the National Institute of Diabetes and Digestive and Kidney Diseases guidelines. Five sites should be tested on the plantar surface of each foot, according to the National Institute of Diabetes and Digestive and Kidney Diseases guidelines. The areas must be tested randomly since the loss of protective sensation may be patchy in distribution, and the patient may get clues if the test is done rhythmically. Heavily callused areas should be avoided. As suggested by the American Podiatric Medicine Association, an absence of sensation at two or more sites out of 5 tested on either foot when tested with the 5.07 Semmes-Weinstein monofilament must be present and documented to diagnose peripheral neuropathy with loss of protective sensation.

References:


**Billing Coding/Physician Documentation Information**

**88305** Level IV - Surgical pathology, gross and microscopic examination

Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation of surgical margins Breast, reduction mammoplasty Bronchus, biopsy Cell block, any source Cervix, biopsy Colon, biopsy Duodenum, biopsy Endocervix, curettings/biopsy
Endometrium, curettings/biopsy 
Esophagus, biopsy 
Extremity, amputation, traumatic Fallopian tube, biopsy 
Fallopian tube, ectopic pregnancy 
Femoral head, fracture Fingers/toes, amputation, non-traumatic 
Gingiva/oral mucosa, biopsy 
Heart valve Joint, resection 
Kidney, biopsy 
Larynx, biopsy 
Leiomyoma(s), uterine myomectomy - without uterus 
Lip, biopsy/wedge resection 
Lung, transbronchial biopsy 
Lymph node, biopsy 
Muscle, biopsy 
Nasal mucosa, biopsy 
Nasopharynx/oropharynx, biopsy 
Nerve, biopsy 
Odontogenic/dental cyst 
Omentum, biopsy 
Ovary with or without tube, non-neoplastic 
Ovary, biopsy/wedge resection 
Parathyroid gland 
Peritoneum, biopsy 
Pituitary tumor 
Placenta, other than third trimester 
Pleura/pericardium - biopsy/tissue 
Polyp, cervical/endometrial 
Polyp, colorectal 
Polyp, stomach/small intestine 
Prostate, needle biopsy 
Prostate, TUR 
Salivary gland, biopsy 
Sinus, paranasal 
Skin, other than cyst/tag/debridement/plastic repair 
Small intestine, biopsy 
Soft tissue, other than tumor/mass/lipoma/debridement 
Spleen Stomach, biopsy 
Synovium Testis, other than tumor/biopsy/castration 
Thyroglossal duct/brachial cleft cyst 
Tongue, biopsy 
Tonsil, biopsy 
Trachea, biopsy 
Ureter, biopsy 
Urethra, biopsy 
Urinary bladder, biopsy 
Uterus, with or without tubes and ovaries, for prolapse 
Vagina, biopsy 
Vulva/labia, biopsy

88314 Special stain including interpretation and report; histochemical stain on frozen tissue block (List separately in addition to code for primary procedure)

88342 Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

88356 Morphometric analysis; nerve

11100 Biopsy of skin, subcutaneous tissue and/or mucous membrane (including simple closure), unless otherwise listed; single lesion

ICD-10 Codes

G56.90- G56.92 Unspecified mononeuropathy of upper limb, code range

G57.90- G57.92 Unspecified mononeuropathy of lower limb, code range

G58.9 Mononeuropathy, unspecified

G62.9 Polyneuropathy, unspecified

M79.2 Neuralgia and neuritis, unspecified

Additional Policy Key Words

N/A

Policy Implementation/Update Information

12/1/15 New Policy; considered medical necessary in certain circumstances. Considered investigational for measurement of sweat gland nerve fiber density.

12/1/16 No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.