Nerve Fiber Density Measurement

Policy Number: MM.02.020
Original Effective Date: 11/01/2013
Line(s) of Business: HMO; PPO; QUEST Integration
Current Effective Date: 05/25/2018
Section: Medicine
Place(s) of Service: Outpatient

I. Description
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 proposed as an objective measure of small fiber neuropathy by identifying a reduction in the density of nerve fibers.

For individuals with suspected idiopathic small fiber neuropathy who receive intraepidermal nerve fiber (IENF) density measurement, the evidence includes reports assessing whether IENF density measurement is technically reliable, clinically valid, and clinically useful. 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 has also indicated 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. For individuals who have symptoms suggestive of neuropathy but no evidence of large nerve neuropathy and no disease associated with neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy), establishing a cause for the symptoms is problematic. Thus, IENF density measurement may help to diagnose idiopathic small fiber neuropathy in those who have no evidence of large fiber neuropathy and no known cause of neuropathy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have an established diagnosis of small fiber neuropathy who receive repeated IENF density measurement, the evidence is limited. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. A number of trials are ongoing or have recently been completed; they assess the efficacy of activity and medications on small fiber neuropathy. If successful, there might be a role for repeated IENF density measurements to result in a change in
management (eg, changing dose or class of medication). However, current treatments for small fiber neuropathy only palliate symptoms and do not modify the underlying changes in nerve fiber density in patients with symptomatic neuropathy. There is no evidence that monitoring progression of neuropathy has clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected small fiber neuropathy who receive sweat gland nerve fiber density measurement, the evidence includes comparisons with control values. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Measurement of sweat gland nerve fiber 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 sweat gland nerve fiber density measurement. The evidence is insufficient to determine the effects of the technology on health outcomes.

BACKGROUND

PERIPHERAL NEUROPATHY
Most 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.

Diagnosis
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. Also, conditions other than nerve fiber damage, including venous insufficiency, spinal stenosis, myelopathy, and psychosomatic disturbances, may mimic small fiber neuropathy.

Treatment
There is no curative treatment for 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.

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. A specific test to assess intraepidermal nerve fiber (IENF) density and sweat gland nerve fiber 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. Sweat gland nerve fiber density can be assessed from the
same tissue prepared for IENF density testing provided that the biopsy sample is of sufficient
depth. Tissue samples may also be counterstained to identify the boundaries of the sweat glands
better.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory
service; laboratory-developed tests must meet the general regulatory standards of the Clinical
Laboratory Improvement Amendments. These tests are available under the auspices of the Clinical
Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be
licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date,
the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
Assessment of IENF and sweat gland nerve fiber density with PGP 9.5 is commercially available
using a biopsy kit, although IENF density measurement (ie, tissue preparation, immunostaining with
PGP 9.5, and counting) may also be done by local research pathology labs. Some laboratories that
offer IENF density testing include Therapath Neuropathology, Advanced Laboratory Services, Mayo
Medical Laboratories, Corinthian Reference Lab, and Bako Integrated Physician Solutions.

II. Criteria/Guidelines
Skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber
neuropathy is covered (subject to Limitations and Administrative Guidelines) when all of the
following conditions are met:

A. The patient has 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.

III. Limitations
A. Skin biopsy with epidermal nerve fiber density measurement is not covered for all other
conditions, including, but not limited to, the monitoring of disease progression or reponse to
treatment, as it is not known to be effective in improving health outcomes.
B. Measurement of sweat gland nerve fiber density is not covered as it is not known to be effective in improving health outcomes.

IV. Administrative Guidelines
Precertification is required. To precertify, complete HMSA’s Precertification Request and mail or fax the form, or use iExchange as indicated along with the following documentation:

A. History and physical examination supporting that the criteria II.A-C are met.
B. Results of electromyography and nerve conduction studies.

V. Scientific Background
This evidence review was created in September 2009 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 16, 2017.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose.

NERVE FIBER DENSITY MEASUREMENT

Clinical Context and Test Purpose
The purpose of intraepidermal small fiber (IENF) density or sweat gland nerve fiber (SGNF) density measurement testing of patients who have a suspected idiopathic small fiber neuropathy or who have an established diagnosis or who are at risk of small fiber neuropathy is to provide objective information which may help to confirm the diagnosis of small fiber neuropathy.

The question addressed in this evidence review is: Does use of IENF or SGNF density measurement testing confirm the diagnosis of small fiber neuropathy leading to a change in management expected to improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with suspected idiopathic small fiber neuropathy or an established diagnosis of small fiber neuropathy or a suspected small fiber neuropathy.

Interventions
The relevant interventions of interest are IENF density measurement or a repeated IENF measurement or an SGNF density measurement.

Comparators
The relevant comparators of interest are standard clinical workup or continued medical monitoring.
Outcomes
The general outcomes of interest are test accuracy, change in disease status, reduction in symptoms such as pain, and quality of life.

Timing
Any associated effect on health outcomes resulting from testing and management changes may occur over a period of weeks to months.

Setting
Patients with small fiber neuropathy would be seen in the outpatient setting by a neurologist.

Intraepidermal Nerve Fiber Density Measurement

Technically Reliable
A 2005 systematic review from the European Federation of Neurological Societies 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 IENF density, indicating adequate technical performance of this test.1 European Federation Neurological Societies 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.2 Groups that previously reported normative IENF density values using bright-field immunohistochemistry provided data to a coordinating center. Density data from 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 millimeter at 20 to 29 years of age to 1.6 fibers per millimeter at 80 years or older. For men, the 5th percentile ranged from 6.1 fibers per millimeter at 20 to 29 years of age to 1.7 at 80 years or older. IENF density was lower in men than in women between 20 and 69 years of age, but not for subjects 70 years or older. This finding might be limited by the smaller sample size in the older age groups. In addition, the analysis did not suggest that height, weight, or body mass index has a significant influence on IENF density normative scores (5th percentile).

Clinically Valid
Assessment of diagnostic accuracy necessitates that studies include a representative patient population with an appropriate spectrum of patients and that the test is compared with an independently assessed criterion standard. The European Federation Neurological Societies 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, the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation performed a literature review (2009) 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 (1998) studied 98 normal controls and 20 patients who have sensory neuropathies. The density of epidermal nerve fibers in the controls was 13.8 per mm in the calf (5th percentile of controls, 3.8 per millimeter), with a significant mean reduction in the study population (p value not reported) and a diagnostic efficiency of 88% (vs healthy controls). An earlier report (1997) by this group showed a mean IENF density of 4.9 per millimeter in 20 patients with sensory neuropathy and a mean IENF density of 16.3 per millimeter in 20 age-matched controls. 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 with 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 its 2011 guidelines used to develop a comprehensive diabetes care plan. The evidence review found level 3 evidence (cross-sectional studies) that IENF density correlated inversely with 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) indicated that IENF density is reduced in painful neuropathy compared with that observed in painless neuropathy. Level 2 evidence (prospective cohort studies) indicated that diet and exercise interventions in impaired glucose tolerance lead to increased IENF density. Reviewers concluded these data suggested that IENF loss is an early feature of metabolic syndrome, prediabetes, and established diabetes and that the loss progresses with increasing neuropathic severity. Also, there may be nerve regeneration with treatment (diet and exercise).

The single prospective study (1999) identified in the 2009 American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine and American Academy of Physical Medicine and Rehabilitation literature review included a series of 117 patients presenting with painful bilateral l feet. In this report, a 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 with an independent reference standard to confirm the presence of small fiber neuropathy. American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation 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.
The diagnostic accuracy of skin biopsy was assessed in a 2009 study of 210 patients who had signs of small fiber neuropathy from various conditions. 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 the 5th percentile as a threshold (6.7 fibers per millimeter), the sensitivity of IENF density was 35%, and specificity was 95%.

Additional studies include large retrospective series. Devigili et al (2008) retrospectively reviewed 486 patients referred for suspected sensory neuropathy. This study lacked an independent reference standard, because the IENF results determined whether patients were included in the study group. Walk et al (2007) examined the concordance between foot IENF density and clinical findings in 106 patients with possible idiopathic small fiber neuropathy. An IENF density of 8 per millimeter was found to have the highest sensitivity (88%) and specificity (81%), using the 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.”

Clinically Useful
An 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 (2013) prospectively evaluated whether small fiber neuropathy may have been the cause of symptoms in patients who had a prior diagnosis of fibromyalgia by an independent physician. 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 an investigation of other potential causes. A 2013 retrospective analysis by Boruchow and Gibbons found a change in diagnosis or management in 36 (52%) of 69 patients who had a skin biopsy at their institution for evaluation of possible small fiber neuropathy. Determination of low or borderline IENF density led to newly identified diseases in 8 patients, more aggressive diabetes management 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 whether the changes in diagnosis or management led to improved health outcomes.

A 2011 review of the diagnosis and treatment of pain in small fiber neuropathy indicated that the history and physical exam are still considered the criterion standard and that further testing may be unnecessary, particularly in the context of an associated disease. However, authors suggested that IENF density measurement may provide diagnostic confirmation or additional guidance if the diagnosis is less clear. Thus, facilitating a diagnosis in patients with idiopathic small fiber neuropathy can lead to an end in the diagnostic odyssey and potentially change management.

Section Summary: Intraepidermal Nerve Fiber Density Measurement
The technical reliability of IENF staining with PGP 9.5 is adequate, reliably showing the density of small nerve fibers in the epidermal layer. IENF density decreases across age and sex in healthy controls and, therefore, density measurements in patients suspected of small fiber neuropathy are compared with age- and sex-adjusted normative values. Few studies have prospectively compared the clinical validity of IENF density measurements in a population of patients suspected of small fiber neuropathy with an established reference standard. The available studies have shown low sensitivity and high specificity, suggesting that an IENF density below the 5th percentile of healthy controls may support a diagnosis of small fiber neuropathy, but IENF density above the 5th percentile cannot be used to rule it out.

There would be little benefit on health outcomes in patients who can be diagnosed clinically or who have a condition (eg, diabetes) associated with neuropathy. However, for individuals who have symptoms suggestive of neuropathy but no evidence of large nerve neuropathy and no disease associated with neuropathy (eg, diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy), establishing a cause for the symptoms is problematic. Thus, IENF density measurement may help diagnose idiopathic small fiber neuropathy, thereby ending the diagnostic odyssey and potentially changing management.

**Repeated IENF Density Measurement**
A number of trials are ongoing or have recently been completed that assess the efficacy of activity and medications on neuropathy (see Table 1). If successful, it might be determined that repeated IENF density measurements results in a change in management (eg, changing dose or class of medication). However, currently, no known treatments can alter the density of small nerve fibers in patients with symptomatic neuropathy. The clinical utility has not been demonstrated for monitoring changes in IENF density over time.

**Sweat Gland Nerve Fiber Density Measurement**

*Technically Reliable*
In a 2009 report, Gibbons et al evaluated SGNF density measurements in punch skin biopsies from 30 diabetic subjects and 64 controls; biopsies were sectioned and stained with PGP 9.5 and compared with confocal microscopy with stereology. 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. The blinded evaluation found a correlation (r) of 0.93 between SGNF density and the stereologic estimate of sweat gland nerve fiber length. The intrareviewer intraclass correlation coefficient was 0.886, and the interreviewer intraclass correlation coefficient was 0.892. A 2010 publication by the same authors found good reliability for automated and manual quantification of SGNF density, but poor inter- and intrareviewer reliability when using a semiquantitative approach (5-point scale).16
Clinically Valid
In their 2009 report, Gibbons et al found a significant decrease in the mean SGNF density of diabetic subjects compared with controls, although there was considerable overlap in the ranges. There was also a significant association between SGNF density and neuropathy scores as 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 by the Michigan Neuropathy Screening Instrument. There was a moderate correlation (r=0.66) between SGNF density and IENF density.

Luo et al (2011) evaluated SGNF density in 35 patients with type 2 diabetes and sensory neuropathy (stocking distribution and reduced IENF density). Normative values were established in 107 control subjects, and sudomotor denervation was defined as an SGNF density less than 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 density was lower in patients with anhidrosis of the feet (0.89%) compared with patients with normal sweating (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.

Clinically Useful
Analysis of SGNF density could be considered complementary to IENF density, because they assess autonomic and somatic nerves, respectively. However, no studies were identified to support an improvement in health outcomes.

Section Summary: Sweat Gland Nerve Fiber Density Measurement
The technical reliability of SGNF measurements appears to be inferior to IENF measurements, and there is considerable overlap in the ranges of SGNF density in patients with diabetic neuropathy and controls. No studies were identified that evaluated the clinical validity of SGNF density measurement. No studies were identified that showed improvements in health outcomes with SGNF density measurements.

SUMMARY OF EVIDENCE
For individuals with suspected idiopathic small fiber neuropathy who receive IENF density measurement, the evidence includes reports assessing whether IENF density measurement is technically reliable, clinically valid, and clinically useful. 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 has also indicated 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. For individuals who have symptoms suggestive of neuropathy but no evidence of large nerve neuropathy and no disease associated with neuropathy (eg, diabetic neuropathy,
toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy), establishing a cause for the symptoms is problematic. Thus, IENF density measurement may help to diagnose idiopathic small fiber neuropathy in those who have no evidence of large fiber neuropathy and no known cause of neuropathy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have an established diagnosis of small fiber neuropathy who receive repeated IENF density measurement, the evidence is limited. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. A number of trials are ongoing or have recently been completed; they assess the efficacy of activity and medications on small fiber neuropathy. If successful, there might be a role for repeated IENF density measurements to result in a change in management (eg, changing dose or class of medication). However, current treatments for small fiber neuropathy only palliate symptoms and do not modify the underlying changes in nerve fiber density in patients with symptomatic neuropathy. There is no evidence that monitoring progression of neuropathy has clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected small fiber neuropathy who receive SGNF density measurement, the evidence 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.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT 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 and reviewed. The input was mixed. Some respondents indicated that the criteria 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 generally supported the medical necessity of intraepidermal nerve fiber 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 intraepidermal nerve fiber 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 guidelines in 2011 on developing a comprehensive diabetes care plan.6 The guidelines stated, based on consensus opinion, that painful diabetic neuropathy is diagnosed clinically and must be differentiated from other painful conditions. The Association referenced the 2010 European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society guidelines on the use of intraepidermal nerve fiber (IENF) quantification to confirm the clinical diagnosis of small fiber neuropathy (consensus).19

American Academy of Neurology et al
The 2009 practice parameters from the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation concluded that IENF density assessment using protein gene product 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 These guidelines were reaffirmed by AAN in 2013.

In 2009, American Association of Neuromuscular Electrodiagnostic Medicine, in conjunction with AAN and American Academy of Physical Medicine and Rehabilitation, published an ordered set of case definitions of “distal symmetrical polyneuropathy” for clinical research ranked by the likelihood of disease.20 The recommendations for case definitions that included 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
EFNS published 2005 guidelines on the use of skin biopsy in peripheral neuropathy.1 EFNS concluded that skin biopsy was a safe, validated, and reliable technique for the determination of IENF density. EFNS jointly updated its guidelines with Peripheral Nerve Society on the use of skin biopsy in the diagnosis of small fiber neuropathy in 2010.19 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 sex normative values, intra- and interobserver reliability, and interlaboratory agreement.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
There is no national coverage decision specifically on IENF density testing. The 2002 national coverage decision for services provided for the diagnosis and treatment of diabetic sensory
neuropathy with loss of protective sensation (also known as diabetic peripheral neuropathy) (70.2.1) provided the following information:

“... 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.”

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 1.

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<th>NCT No.</th>
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<th>Completion Date</th>
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<td>Apr 2016 (completed)</td>
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NCT: national clinical trial.
\(^3\) Denotes industry-sponsored or cosponsored trial.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government
approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA consider the application of this Medical Policy to the case at issue.
VII. References


