
Medical Policy



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***Current Policy Effective Date: 9/1/12**

(See policy history boxes for previous effective dates)

Title: Epidermal/Intraepidermal Nerve Fiber Density Testing (ENFD or IENFD) and Sweat Gland Nerve Fiber Density Testing (SGNFD)

Description/Background

Skin biopsy is used to assess the density of epidermal (intraepidermal) 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.

Background

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. Small fiber neuropathy occurs most often in patients with diabetic neuropathy but may also be found in patients with impaired glucose tolerance, severe hypertriglyceridemia, the metabolic syndrome, human immunodeficiency virus (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 neuropathy. 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 (e.g., 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 epidermal (ENF)/intraepidermal nerve fiber (IENF) density using skin biopsy and immunostaining of the tissue has been developed that allows the identification and counting of intraepidermal nerve fibers. Assessment of IENF 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.

Analysis of sweat gland nerve fiber density has been used as a complementary test to epidermal/intraepidermal nerve fiber density testing in small fiber nerve evaluation, as they assess autonomic and somatic nerves, respectively. 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.

Regulatory Status:

Assessment of epidermal/intraepidermal nerve fiber density with PGP 9.5 is commercially available from Therapath (New York) with a biopsy kit, although IENF-density measurement (i.e., tissue preparation, immunostaining with PGP 9.5, and counting) may also be done by local research pathology labs.

Medical Policy Statement

The safety and effectiveness of epidermal/intraepidermal nerve fiber density testing (ENFD) have been established. It may be considered a useful diagnostic tool for patients meeting patient selection guidelines.

The measurement of sweat gland nerve fiber density for the diagnosis of small-fiber neuropathy and other indications is experimental and investigational. The clinical utility of this test has not been demonstrated. The peer reviewed medical literature has not yet shown that sweat gland nerve fiber density testing has sufficient diagnostic accuracy to provide clinically relevant information.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Skin biopsy with **epidermal/intraepidermal nerve fiber density** measurement for the diagnosis of small-fiber neuropathy may be considered established when all of the following conditions are met:

Inclusions (must meet all):

1. Individual presents with symptoms of painful sensory neuropathy; AND
2. 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
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.

Exclusions:

- Skin biopsy with epidermal/intraepidermal nerve fiber density measurement is considered experimental and investigational for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment.
- The measurement of **sweat gland nerve fiber density** for the diagnosis of small-fiber neuropathy and other indications

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

11100	88305	88314	88342	88356	88399
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Rationale

Diagnostic Tests

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

Literature Review

Epidermal/Intraepidermal Nerve Fiber Density- (ENFD)/(IENFD)

Searches of the MEDLINE database 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 (AAPMR) from 2009. (1-3)

Technical Performance

The EFNS systematic review determined that skin biopsy from the distal leg or foot with immunostaining with PGP 9.5 is a safe, validated and reliable technique for the determination of epidermal/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.

Clinical Validity

Assessment of clinical validity 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 AAPMR, (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 AAPMR 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. (4) The density of epidermal/intraepidermal 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% (compared to 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. (4) However, none of the studies reviewed included an appropriate group of patients, i.e., 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 (AACE) conducted an evidence review on diabetic neuropathy for their 2011 guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. (5) The evidence review found that there is level 3 evidence (cross-sectional studies) to show that epidermal/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 epidermal/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 AAPMR literature review included a cohort of 117 patients presenting with bilateral painful feet. (6) 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. The AAN, AANEM, and AAPMR 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.

Additional studies identified in the MEDLINE search for this policy included a 2007 retrospective evaluation by Walk et al. of the concordance between foot IENF density and clinical findings in patients with possible idiopathic small fiber neuropathy who underwent skin biopsy for IENF density determination. (7) Of 178 patients referred for evaluation, 106 met the inclusion criteria of idiopathic symmetric burning, paresthesias, hyperalgesia or allodynia in a length-dependent distribution, with normal strength, reflexes and nerve conduction studies. Sensory examination included assessment of pinprick sensitivity and a qualitative determination of vibration perception using a 128 Hz tuning fork at the great toe. 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. The mean foot IENF density for patients with normal sensation was 13.9 +/- 7.7 per mm, with a range of 0 to 36 per mm. The mean IENF density in the foot in the patient population was reduced to approximately 3 per mm (standard deviations: 4.9, 8.0, and 5.7 for the 3 patient groups, respectively; range: 0 to 29.5 per mm), depending on the severity of sensory deficit. Thus, there was considerable overlap in the range of IENF density between patients who showed a sensory deficit and those who did not. 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.” (8)

In 2008, Devigili and colleagues published a retrospective review of 486 patients referred for suspected sensory neuropathy. (9) A total of 150 patients met the entry criteria for the study, which were symptoms suggesting sensory neuropathy and availability of 1) clinical examination, including spontaneous and stimulus-evoked pain, 2) a sensory and motor nerve conduction study, 3) warm and cooling thresholds assessed by quantitative sensory testing (QST), and 4) skin biopsy with distal IENF density. Based on the combined assessments, neuropathy was ruled out in 26 patients; 124 patients were diagnosed with sensory neuropathy, and of these 67 patients 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. Only 7.5% of patients had abnormal results for all 3 examinations (clinical, QST, skin biopsy), 43% had both abnormal skin biopsy and clinical findings, and 37% of patients had both abnormal skin biopsy and QST results. The combination of abnormal clinical and QST results was observed in only 12% of patients. These results indicate that most of the patients evaluated showed IENF of less than 7.63 together with either abnormal spontaneous or evoked pain (clinical examination) or abnormal thermal thresholds (QST). The authors of this study recommended a new diagnostic “gold standard” based on the presence of at least 2 of 3 abnormal results (clinical, QST, and IENF density). This study is limited by the lack of an independent reference standard, particularly since the IENF results affected whether patients were included in the study group. Prospective studies

are needed to evaluate whether the addition of skin biopsy to clinical diagnoses improves detection of small fiber neuropathy in an appropriately mixed patient population.

Scherens and colleagues conducted a prospective study to assess the percentage of patients with lower limb dysesthesias (painful or painless) who had evidence of small fiber neuropathy. (10) Forty-two patients who presented to clinic with dysesthesias underwent standard neurophysiology, quantitative sensory testing and measurement of IENF density. Thirty-seven of the patients (88%) were found to have abnormal IENF density, defined as a reduction of one standard deviation below the mean of healthy controls (mean IENF density: 12 per mm) from a prior study. Four 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. In another study, Krishnan et al. compared dermal nerve density, quantitative sensory testing (vibration, cold, warmth, and heat pain), and a new functional test of dermal vasodilation, called the laser Doppler imager (LDI) flare in 2 groups of patients with type 2 diabetes (10 with painful neuropathy and 12 with more advanced painless neuropathy), and 15 healthy controls. (11) This study measured dermal (instead of intraepidermal) nerve density as a direct measure of the structural integrity of the innervation of dermal blood vessels as a reference for the non-invasive functional test. These and other authors have noted that deficits in nerve function may precede anatomic changes. Studies are needed to evaluate when in the course of disease (i.e., severity of clinical symptoms) decreases in IENF density become apparent.

Clinical Utility

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. Although no studies were identified that directly addressed this question, some indirect evidence is available. A 2006 review of diagnostic tools for diabetic sensorimotor polyneuropathy by Kles and Brill (Eli Lilly Research Institute, Washington, DC) indicates that although many therapies are in clinical trials, current treatment options only palliate pain symptoms and do not target the underlying disease etiology. (15) Kles and Brill concluded that although biopsy of skin and nerve may be beneficial for identifying the underlying pathology of the damaged nerve and extending our knowledge concerning the pathophysiology of diabetic sensory polyneuropathy when used in carefully controlled clinical trials, "initial testing in the primary care and diabetes clinic settings can be done with simple tests for signs of neuropathy such as tuning fork, monofilament, and pinprick insensitivity." 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.

Ongoing Clinical Trials

A search of the online site ClinicalTrials.gov in September 2011 identified several relevant trials on small fiber neuropathy.

- NCT00956033 will evaluate sensitivity of IENF density measurements for chemotherapy-induced neuropathy. Skin biopsies will be taken from 100 patients with multiple myeloma treated with bortezomib. The estimated study completion date is November 2011.
- NCT01288937 is a randomized, double-blind trial of milnacipran for the treatment of idiopathic neuropathy pain. Included in the study will be 52 patients with signs and

symptoms of a peripheral neuropathy, with either abnormal nerve conductions or abnormal epidermal/intraepidermal nerve fiber density with neuropathic pain. Exclusion criteria include other causes of neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy). The estimated study completion date is May 2012.

- The Department of Veteran Affairs is conducting a study (NCT00780559) to determine if an individually tailored diet and physical enhancement program can improve mobility, physical activity, and neuropathy in people with early diabetes. The primary outcome measure is the 6-minute walk test. Secondary outcome measures are physical activity and IENF density. There is an estimated enrollment of 142 patients; the estimated study completion date is January 2015.

Identified through clinical input was a 2011 pilot study of 11 patients with confirmed type 2 diabetes mellitus and symptoms consistent with small fiber neuropathy of the feet who were treated with a combination of the B vitamins L-methylfolate, methylcobalamin, and pyridoxal 5'-phosphate. (17) After 6 months of treatment, there was an increase in IENF density from 1.56 fibers/mm to 3.07 fibers/mm. Eight of the 11 patients (73%) had an increase in IENF density; 82% of study patients reported reduced frequency and intensity of paresthesias and dysesthesias. Limitations of this study included its small size, method of participant selection, possible volunteer bias, lack of a placebo-treated group for comparison, lack of blinding, and the subjective nature of the visual analog scale. Randomized double-blinded controlled trials are needed to evaluate this potentially disease-modifying treatment.

Clinical Input Received through 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.

BCBSA requested and received input 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. Among those who supported the medical necessity of IENF density testing, several commented that this is the only test to allow an objective diagnosis and that small fiber neuropathy may be effectively managed with products such as L-methylfolate, methylcobalamin and/or pyridoxal 5'-phosphate (study discussed above). Another 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.

Summary

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 the average IENF in groups of patients diagnosed with small fiber neuropathy in comparison with groups of 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. However, no evidence was identified to indicate that measurement of IENF density in a patient clinically diagnosed with probable small fiber neuropathy improves health outcomes.

Specifically,

- An IENF density above the 5th percentile of controls cannot be used to rule out small fiber neuropathy. (18)
- No literature was identified to evaluate the diagnostic accuracy of IENF density in an appropriate patient population. (3)
- Established treatment options only palliate pain symptoms and do not target the underlying disease etiology. (15,19)
- No evidence was identified to indicate that assessment of nerve fiber density is more effective than clinical diagnosis for early detection and treatment in the context of associated disease. (16)

Clinical input on the medical necessity of IENF density measurements was mixed but suggests acceptance of the procedure as an objective measure for diagnosis among some providers. One population that may particularly benefit from IENF density measurement is individuals who have no known causes of neuropathy.

Overall, a number of questions remain about whether a quantitative assessment of IENF density results in improved health outcomes. Additional prospective studies are needed to evaluate the effect of this procedure in comparison with clinical diagnosis alone in patients with known causes of neuropathy. IENF density measurement may be considered medically necessary in patients with suspected idiopathic small fiber neuropathy when the individual presents with symptoms of 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 studies are normal and show no evidence of large-fiber neuropathy. Assessment of IENF density in all other conditions is considered investigational.

Practice Guidelines and Position Statements

The American Association of Clinical Endocrinologists (AACE) published 2011 guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. (5) The guidelines state, based on consensus opinion, that diabetic painful neuropathy is diagnosed clinically and must be differentiated from other painful conditions. The 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)

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 (AAPMR) 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)

In 2005, AANEM, in conjunction with AAN and AAPMR, 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 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.

The European Federation of Neurological Societies (EFNS) published a 2005 guideline on the use of skin biopsy in peripheral neuropathy. (1) The EFNS concluded that skin biopsy is a safe, validated and reliable technique for the determination of IENF density. The 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 clinometric 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 definitively 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.

Sweat Gland Nerve Fiber Density Testing (SGNFD)

In 2009, Gibbon et al (22) evaluated a novel method to quantify the density of nerve fibers innervating sweat glands in healthy control and diabetic subjects, 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 PGP 9.5, were imaged by light microscopy and sweat gland nerve fiber density (SGNFD) was quantified by manual morphometry. As a gold standard, three additional subjects had biopsies analyzed by confocal microscopy using unbiased stereologic 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. The authors state that this 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. However, validity of this novel technique needs to be confirmed by well-designed studies.

In 2010, Gibbons et al (23) stated that peripheral sudomotor dysfunction is present in many peripheral neuropathies, but structural assessments of sudomotor fibers rarely occur. They 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 authors stated that they had successfully quantified the density of nerve fibers innervating sweat glands using a novel technique. However, future studies are required to correlate these structural changes with sudomotor function, to examine diabetic subjects with more severe diabetic neuropathy, and to provide standard data with physical variables such as height, weight and body surface area.

Sweat glands, which are 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) (24).

Data on sweat gland innervation density in healthy subjects and in patients with peripheral neuropathy as well as data on correlation between sweat gland nerve fibre density and autonomic assessment are limited (class III evidence) (1). Although part of the neuropathological examination of skin biopsy, assessment of sweat gland innervation still lacks extensive validation.

Government Regulations

National:

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 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.

Local:

No LCD on this topic.

Michigan Department of Community Health:

No Medicaid policy on this topic. Codes are payable.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Quantitative Sensory Testing

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February 3, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/12	6/12/12	6/15/12	Joint policy established

Next Review Date: 2nd Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: EPIDERMAL/INTRAEPIDERMAL NERVE FIBER DENSITY TESTING (ENFD OR IENFD) AND SWEAT GLAND NERVE FIBER DENSITY TESTING (SGNFD)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Covered; criteria apply
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Covered; criteria apply

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.