
Medical Policy



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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Nerve Fiber Density Measurement

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.

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. 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.

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

Treatment

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.

Skin Biopsy

A specific test to assess epidermal (ENF)/intraepidermal nerve fiber (IENF) and sweat gland nerve fiber (SGNF) density using skin biopsy and immunostaining of the tissue has been developed that allows the identification and counting of intraepidermal 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.

Regulatory Status

Assessment of intraepidermal nerve fiber (IENF) and sweat gland nerve fiber density with *PGP 9.5* is commercially available from 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. Some laboratories who offer IENF density testing include Therapath, Advanced Laboratory Services, Mayo Medical Laboratories, Corinthian Reference Lab, and Bako Integrated Physician Solutions.

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

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/ 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 is considered experimental/investigational.

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:

11102	11103	11104	11105	11106	11107
88305	88314	88342	88356		

Other codes (investigational, not medically necessary, etc.):

88399*

*When used to indicate sweat gland nerve fiber density testing.

Rationale

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

Intraepidermal Nerve Fiber Density Measurement (IENF)

Clinical Context and Test Purpose

The purpose of IENF density measurement is to provide a diagnostic option that is an alternative to or an improvement on existing testing in individuals with suspected idiopathic small fiber neuropathy.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with suspected idiopathic small fiber neuropathy.

Interventions

The test being considered is IENF density measurement.

Comparators

Comparators of interest include standard clinical workup.

Outcomes

The general outcomes of interest are test accuracy, change in disease status, symptoms, and QOL. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Though not completely standardized, follow-up for suspected idiopathic small fiber neuropathy symptoms would typically occur in the weeks to months after starting treatment.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

1. The study population represents the population of interest. Eligibility and selection are described.
2. The test is compared with a credible reference standard.
3. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
4. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC [receiver operating characteristic], AUROC [area under receiver operating characteristic, statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation (2009) performed a literature review to evaluate the diagnostic accuracy of IENF density in the detection of small fiber neuropathy.¹ 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.² 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.³ 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.⁴ 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).

Prospective Diagnostic Accuracy Studies

The single prospective study (1999) that was identified in the 2009 AAN, AANEM and AAPMR literature review included a cohort of 117 patients presenting with bilateral painful feet.⁵ 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.

Retrospective Diagnostic Accuracy Studies

Diagnostic accuracy of skin biopsy was assessed in a 2020 single-center retrospective study of 245 patients with symptoms compatible with small fiber neuropathy.⁶ The diagnosis of small fiber neuropathy was established based on clinical features and if abnormal results were present in at least 2 of 6 tests (IENF density evaluation by skin biopsy, quantitative sensory testing, quantitative sweat measurement system, laser evoked potentials, autonomic cardiovascular testing, and electrochemical skin conductance measurement). Using a density lower than the 5th percentile as a threshold for diagnosis, the sensitivity of IENF density was 58% and specificity was 91%. Nerve fiber density was 4.61 versus 7.83 fibers per mm in patients with definite versus no small fiber neuropathy, respectively.

Another 2009 study assessed diagnostic accuracy in of 210 patients who had signs of small fiber neuropathy from various conditions.⁷ 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 mm), the sensitivity of IENF density was 35%, and specificity was 95%.

Observational Studies

Additional studies include large retrospective series. Devigili et al retrospectively reviewed 486 patients referred for suspected sensory neuropathy.⁸ This study lacked an independent reference standard, because the IENF results determined whether patients were included in the study group. Walk et al examined the concordance between foot IENF density and clinical findings in 106 patients with possible idiopathic small fiber neuropathy.⁹ 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.”¹⁰

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about 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. 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.¹¹ 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.¹² 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's neuroma, restless legs syndrome, lumbar spinal stenosis, Raynaud's 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 indicate 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.¹³ However, the authors suggest that IENF-density testing 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 potentially change management.

Section Summary: Intraepidermal Nerve Fiber Density Measurement

Intraepidermal nerve fiber 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 fifth percentile of healthy controls may support a diagnosis of small fiber neuropathy, but IENF density above the fifth percentile cannot be used to rule it out. There would be little benefit to health outcomes in patients who can be diagnosed clinically or who have a condition (e.g., 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 (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 diagnose idiopathic small fiber neuropathy, potentially changing management.

Repeated IENF Density Measurement

Clinical Context and Test Purpose

The purpose of repeated IENF density measurement is to provide a diagnostic option that is an alternative to or an improvement on existing testing in individuals with an established diagnosis of small fiber neuropathy.

The following **PICOs** were used to select literature to inform this review.

Population

The relevant population of interest are individuals with an established diagnosis of small fiber neuropathy.

Interventions

The test being considered is repeated IENF density measurement.

Individuals with an established diagnosis of small fiber neuropathy are actively managed by neurologists and primary care providers in an outpatient clinical setting.

Comparators

Comparators of interest include continued clinical monitoring.

Outcomes

The general outcomes of interest are test accuracy, change in disease status, symptoms, and QOL. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Though not completely standardized, follow-up for an established diagnosis of small fiber neuropathy would typically occur in the weeks to months after starting treatment.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

1. The study population represents the population of interest. Eligibility and selection are described.
2. The test is compared with a credible reference standard.
3. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
4. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Further studies are needed to establish the sensitivity, specificity, and predictive values of repeated IENF density testing in patients with small fiber neuropathy.

Review of Evidence

No studies have been identified that evaluate repeated IENF density measurement in patients with small fiber neuropathy. Further studies are needed to establish the sensitivity, specificity, and predictive values of repeated IENF density measurement testing in patients with an established diagnosis of small fiber neuropathy.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No such studies have been identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Repeated Intraepidermal Nerve Fiber Density Measurement

There are no RCTs that have directly evaluated the use of repeat testing of nerve fiber density to improve health outcomes for patients with small fiber neuropathy. The available evidence does not demonstrate that the addition of repeat nerve fiber density testing to standard clinical assessment would influence treatment or define a treatment pathway.

SWEAT GLAND NERVE FIBER DENSITY MEASUREMENT

Clinical Context and Test Purpose

The purpose of SGNF density measurement is to provide a diagnostic option that is an alternative to or an improvement on existing testing in individuals with suspected small fiber neuropathy.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with suspected small fiber neuropathy.

Interventions

The test being considered is SGNF density measurement.

Individuals with suspected small fiber neuropathy are actively managed by neurologists and primary care providers in an outpatient clinical setting.

Comparators

Comparators of interest include standard clinical workup.

Outcomes

The general outcomes of interest are test accuracy, change in disease status, symptoms, and QOL. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Though not completely standardized, follow-up for suspected small fiber neuropathy would typically occur in the weeks to months after starting treatment.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

1. The study population represents the population of interest. Eligibility and selection are described.
2. The test is compared with a credible reference standard.
3. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
4. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Prospective Open Label Quantification Studies

In their report, Gibbons et al (2009) found a significant decrease in the mean SGNF density of diabetic subjects compared to controls, although there was considerable overlap in the ranges.¹⁴ 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).¹⁵ Normative values were established in 107 control subjects, and sudomotor denervation was defined as a SGNF density less than the 5th percentile cutoff value for the sex (1.58% for men and 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Analysis of SGNF density could potentially be considered complementary to IENF density, since they assess autonomic and somatic nerves, respectively.¹⁸ However, no studies were identified to support an improvement in health outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: SGNF Density Measurement

There is considerable overlap in the ranges of SGNF density in patients with diabetic neuropathy and controls. No studies were identified that evaluated the diagnostic accuracy 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 intraepidermal nerve fiber (IENF) density measurement, the evidence 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 (e.g., 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.

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 that 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 such as 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 (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.

Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05546138	Characterization and Prediction of Early Onset Diabetic Peripheral Neuropathy (NeuroPredict)	200	Dec 2029
Unpublished			
NCT04071535	Skin biopsy in the diagnosis of small fiber neuropathy in Chinese patients with Diabetes	100	Jul 2021
NCT02341261	Activity for diabetic polyneuropathy: the ADAPT study	140	Apr 2022
NCT01503892 ^a	Metanx effects on nerve fiber density in neuropathic diabetics	100	Oct 2013 (unknown)
NCT00780559	Improving neuropathy and mobility in subjects with early Diabetes	72	Feb 2018

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

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.

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 2015 on developing a comprehensive diabetes care plan.⁴ The guidelines state, “Painful neuropathies may have no physical signs, and diagnosis may require skin biopsy or other surrogate measures of small-fiber neuropathy (SFN) (Grade D, not evidence-based; BEL 4, no evidence).” 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).¹⁷

In 2022, the AACE published updated clinical practice guidelines on developing a diabetes mellitus comprehensive care plan. The guidelines state that “skin biopsy and/or standardized quantitative sensory testing are sensitive tests for small-fiber neuropathy and should be considered if the clinical features are atypical and a different etiology is suspected.”¹⁸

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 (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 This guideline was reaffirmed by the AAN in 2013, but were retired by AAN in 2019.¹⁹

In 2009, 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.

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.²⁰

Local:

No LCD on this topic.

(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

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, 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
5/1/14	2/24/14	3/3/14	<ul style="list-style-type: none"> Title changed from “Epidermal/Intraepidermal Nerve Fiber Density Testing (ENFD or IENFD) and Sweat Gland Nerve Fiber Density Testing (SGNFD)” to Nerve Fiber Density Testing” to mirror BCBSA. Updated rationale and references.
11/1/15	8/24/15	9/14/15	<ul style="list-style-type: none"> Routine update of rationale and references. No change in policy status
11/1/16	8/16/16	8/16/16	<ul style="list-style-type: none"> Routine policy maintenance, no change in policy status
11/1/17	8/15/17	8/15/17	<ul style="list-style-type: none"> Title change from “testing” to “measurement”. No change in policy status
11/1/18	8/21/18	8/21/18	Routine policy maintenance, no change in status.
5/1/19	2/19/19		Routine policy maintenance, added codes 11102-11107 effective 1/1/19. Deleted code 11100, effective 1/1/19.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.
5/1/23	2/21/23		Routine policy maintenance, no change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: Avalon (ds)

5/1/25	2/18/25		Routine policy maintenance, no change in policy status. Vendor managed: Avalon (ds)
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Next Review Date: 1st Qtr. 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: NERVE FIBER DENSITY MEASUREMENT

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. Sweat gland nerve fiber density testing is experimental/investigational.
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- 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.