2.04.58	Nerve Fiber Density Measurement		
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Section:	2.0 Medicine	**Page:**	Page 1 of 17

Policy Statement

I. Skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small fiber neuropathy may be considered **medically necessary** when **all** of the following conditions are met:
   A. Individual presents with 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

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

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

There are no specific codes for this analysis. Multiple CPT pathology codes would be used such as:

- **88305** - Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation of surgical margins Breast, reduction mammoplasty Bronchus, biopsy Cell block, any source Cervix, biopsy Colon, biopsy Duodenum, biopsy Endocervix, curettings/biopsy Endometrium, curettings/biopsy Esophagus, biopsy Extremity, amputation, traumatic Fallopian tube, biopsy Fallopian tube, ectopic pregnancy Femoral head, fracture Fingers/toes, amputation, non-traumatic Gingiva/oral mucosa, biopsy Heart valve Joint, resection Kidney, biopsy Larynx, biopsy Leiomyoma(s), uterine myomectomy - without uterus Lip, biopsy/wedge resection Lung, transbronchial biopsy Lymph node, biopsy Muscle, biopsy Nasal mucosa, biopsy Nasopharynx/oropharynx, biopsy Nerve, biopsy Odontogenic/dental cyst Omentum, biopsy Ovary with or without tube, non-neoplastic Ovary, biopsy/wedge resection Parathyroid gland Peritoneum, biopsy Pituitary tumor Placenta, other than third trimester Pleura/pericardium - biopsy/tissue Polyp, cervical/endometrial Polyp, colorectal Polyp, stomach/small intestine Prostate, needle biopsy Prostate, TUR Salivary gland, biopsy Sinus, paranasal biopsy Skin, other than cyst/tag/debridement/plastic repair Small intestine, biopsy Soft tissue, other than tumor/mass/lipoma/debridement Spleen Stomach, biopsy Synovium Testis, other than tumor/biopsy/castration Thyroglossal duct/brachial cleft cyst Tongue, biopsy Tonsil, biopsy Trachea, biopsy Ureter, biopsy Urethra, biopsy Urinary bladder, biopsy Uterus, with or without tubes and ovaries, for prolapse Vagina, biopsy Vulva/labia, biopsy
- **88314** - Special stain including interpretation and report; histochemical stain on frozen tissue block (List separately in addition to code for primary procedure)

- **88342** - Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
- **88356** - Morphometric analysis; nerve

The following codes are defined by method (tangential, punch or incisional), and represent biopsies on primary and additional lesions based on sample thickness:

- **11102**: Tangential biopsy of skin (e.g., shave, scoop, saucerize, curette); single lesion
- **11103**: Tangential biopsy of skin (e.g., shave, scoop, saucerize, curette); each separate/additional lesion (List separately in addition to code for primary procedure)
- **11104**: Punch biopsy of skin (including simple closure, when performed); single lesion

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.

Related Policies

- Quantitative Sensory Testing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 anti-protein-gene-product 9.5 is commercially available using a biopsy kit, although IENF density measurement (i.e., tissue preparation, immunostaining with anti-protein-gene-product 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.

Rationale

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.

Skin Biopsy

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 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.

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 (e.g., glucose control, intravenous immunoglobulin, or plasma exchange) may be given to reduce the progression of the disease and its symptoms.

Literature Review

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. Evidence

reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Nerve Fiber Density Measurement
Intraepidermal Nerve Fiber Density Measurement

Clinical Context and Test Purpose
The purpose of intraepidermal nerve fiber (IENF) density measurement in individuals with suspected idiopathic small fiber neuropathy is to provide a diagnostic option that is an alternative to or an improvement on existing testing.

The following PICO was 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
The following practice is currently being used to make decisions about suspected idiopathic small fiber neuropathy: standard clinical workup.

Outcomes
The general outcomes of interest are test accuracy, change in disease status, symptoms, and quality of life (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
For the evaluation of clinical validity of IENF density measurement, studies that meet the following eligibility criteria were considered:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- 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., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the 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 the 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.[2,] The density of epidermal nerve fibers in the controls was 13.8 per mm in the calf (fifth percentile of controls, 3.8 per mm), with a significant mean reduction in the study population (p-value not reported) and diagnostic efficiency of 88% (vs healthy controls). An earlier report (1997) by this group showed a mean IENF density of 4.9 per mm in 20 patients with sensory neuropathy and a mean IENF density of 16.3 per mm 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 with healthy controls, indicating that the absence of reduced IENF density would not rule out polyneuropathy.

The American Association of Clinical Endocrinologists (2011) conducted an evidence review on diabetic neuropathy for its guidelines used to develop a comprehensive diabetes care plan.[4,] 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).

Prospective Diagnostic Accuracy Studies

The single prospective study (1999) identified in the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine and American Academy of Physical Medicine and Rehabilitation (2009) literature review included a series of 117 patients presenting with painful bilateral feet.[5,] 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.

Another 2009 study assessed diagnostic accuracy in 210 patients who had signs of small fiber neuropathy from various conditions.[6,] 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 fifth percentile as a threshold (6.7 fibers per mm), the sensitivity of IENF density was 35%, and specificity was 95%.

Retrospective Diagnostic Accuracy Studies

The diagnostic accuracy of skin biopsy was assessed in a 2020 single-center retrospective study of 245 patients with symptoms compatible with small fiber neuropathy.[7,] 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 fifth 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.

Observational Studies

Additional studies include large retrospective series. Devigili et al (2008) 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 (2007) 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 fibers per mm was found to have the highest sensitivity (88%) and specificity (81%), using the sensory deficit to a pinprick as the standard. In a review, Walk (2009) 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, more effective therapy, or avoid unnecessary therapy or 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.

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.[11,] Of 27 patients, skin biopsies were consistent with small fiber neuropathy (< fifth percentile of the norm) in 41% compared with 3% of matched control subjects, leading to an investigation of other potential causes. A retrospective analysis by Boruchow and Gibbons (2013) 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.[12,] 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 to 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 associated disease.[13,] However, the 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 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 Intraepidermal Nerve Fiber Density Measurement

Clinical Context and Test Purpose

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

The following PICO was used to select literature to inform this review.

Populations

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.

Comparators

The following practice is currently being used to make decisions about an established diagnosis of small fiber neuropathy: 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
For the evaluation of clinical validity of repeated IENF density measurement, studies that meet the following eligibility criteria were considered:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test, it should also be compared with that test.
- 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., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the 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
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 net 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 sweat gland nerve fiber (SGNF) density measurement in individuals with suspected small fiber neuropathy is to provide a diagnostic option that is an alternative to or an improvement on existing testing.

The following PICO was 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.

Comparators

The following practice is currently being used to make decisions about suspected small fiber neuropathy: 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

For the evaluation of clinical validity of SGNF density measurement testing, studies that meet the following eligibility criteria were considered:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- 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., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the 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 with controls, although there was considerable overlap in the ranges.[14,] 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).[15,] Normative values were established in 107 control subjects, and sudomotor denervation was defined as an SGNF density less than the fifth 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

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 be considered complementary to IENF density because they assess autonomic and somatic nerves, respectively.[16,] However, no studies were identified to support improvement in net 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: Sweat Gland Nerve Fiber Density Measurement

There is considerable overlap in the ranges of SGNF density in patients with diabetic neuropathy and control patients. No studies were identified that evaluated the clinical validity of SGNF density measurement. No studies were identified that showed improvements in net health outcomes with SGNF density measurements.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 (IENF) density management for diagnosis, acknowledged that the test has limited utility when disease is clinically advanced and that evidence to demonstrate that the use of skin biopsy with IENF density measurement improves clinical outcomes is only now emerging.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association of Clinical Endocrinologists

In 2015, the American Association of Clinical Endocrinologists (AACE) published guidelines 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 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

In 2009, the 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.[1,]These guidelines were reaffirmed by AAN in 2013, but were retired by AAN in 2019.[19,]

In 2009, the 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage decision specifically on IENF density or sweat gland nerve fiber density measurement testing. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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[21,]

"...Medicare covers, as a physician service, an evaluation (examination and treatment) of the feet no more often than every 6 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 2 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 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			
NCT00780559	Improving Neuropathy and Mobility in People With Early Diabetes (INMED)	72	Feb 2018 (completed)
NCT04071535	Skin Biopsy in the Diagnosis of Small Fiber Neuropathy in Chinese Patients With Diabetes	100	Jul 2021 (Status: Unknown)
NCT02341261	Activity for Diabetic Polyneuropathy: the ADAPT Study	140	Apr 2022 (Status: Unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results

  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
	11102	Tangential biopsy of skin (e.g., shave, scoop, saucerize, curette); single lesion
	11103	Tangential biopsy of skin (e.g., shave, scoop, saucerize, curette); each separate/additional lesion (List separately in addition to code for primary procedure)
	11104	Punch biopsy of skin (including simple closure, when performed); single lesion
	11105	Punch biopsy of skin (including simple closure, when performed); each separate/additional lesion (List separately in addition to code for primary procedure)
	11106	Incisional biopsy of skin (e.g., wedge) (including simple closure, when performed); single lesion
	11107	Incisional biopsy of skin (e.g., wedge) (including simple closure, when performed); each separate/additional lesion (List separately in addition to code for primary procedure)
	88305	Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation of surgical margins Breast, reduction mammoplasty Bronchus, biopsy Cell block, any source Cervix, biopsy Colon, biopsy Duodenum, biopsy Endocervix, curettings/biopsy Endometrium, curettings/biopsy Esophagus, biopsy Extremity, amputation, traumatic Fallopian tube, biopsy Fallopian tube, ectopic pregnancy Femoral head, fracture Fingers/toes, amputation, non-traumatic Gingiva/oral mucosa, biopsy Heart valve Joint, resection Kidney, biopsy Larynx, biopsy Leiomyoma(s), uterine myomectomy - without uterus Lip, biopsy/wedge resection Lung, transbronchial biopsy Lymph node, biopsy Muscle, biopsy Nasal mucosa, biopsy

Type	Code	Description
		Nasopharynx/oropharynx, biopsy Nerve, biopsy Odontogenic/dental cyst Omentum, biopsy Ovary with or without tube, non-neoplastic Ovary, biopsy/wedge resection Parathyroid gland Peritoneum, biopsy Pituitary tumor Placenta, other than third trimester Pleura/pericardium - biopsy/tissue Polyp, cervical/endometrial Polyp, colorectal Polyp, stomach/small intestine Prostate, needle biopsy Prostate, TUR Salivary gland, biopsy Sinus, paranasal biopsy Skin, other than cyst/tag/debridement/plastic repair Small intestine, biopsy Soft tissue, other than tumor/mass/lipoma/debridement Spleen Stomach, biopsy Synovium Testis, other than tumor/biopsy/castration Thyroglossal duct/brachial cleft cyst Tongue, biopsy Tonsil, biopsy Trachea, biopsy Ureter, biopsy Urethra, biopsy Urinary bladder, biopsy Uterus, with or without tubes and ovaries, for prolapse Vagina, biopsy Vulva/labia, biopsy
	88314	Special stain including interpretation and report; histochemical stain on frozen tissue block (List separately in addition to code for primary procedure)
	88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
	88356	Morphometric analysis; nerve
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/01/2016	BCBSA Medical Policy adoption
02/01/2017	Policy title change from Nerve Fiber Density Testing Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change Coding update
02/01/2020	Annual review. No change to policy statement. Literature review updated.
02/01/2024	Policy reactivated. Previously archived from 09/01/2020 to 01/31/2024.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
Reactivated Policy **Policy Statement:** N/A	**Nerve Fiber Density Measurement 2.04.58** **Policy Statement:** I. Skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small fiber neuropathy may be considered **medically necessary** when **all** of the following conditions are met: A. Individual presents with 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 II. Skin biopsy with epidermal nerve fiber density measurement is considered **investigational** for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment. III. Measurement of sweat gland nerve fiber density is considered **investigational.**