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:

- Individual presents with symptoms of painful sensory neuropathy
- 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)
- 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
- Electromyography and nerve-conduction studies are normal and show no evidence of large-fiber neuropathy

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.

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

### 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 Parathryoid 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
Effective January 1, 2019, the following CPT codes will replace CPT code 11100. The new 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 PGP 9.5 is commercially available using 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 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 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods. This technique has improved research and contributed greatly to the understanding of small fiber neuropathy. Skin biopsy with measurement of IENF density has also been investigated as an objective measure for the diagnosis of small fiber neuropathy. Sweat gland nerve fiber density can be assessed from the same tissue prepared for IENF density testing provided that the biopsy sample is of sufficient depth. Tissue samples may also be counterstained to identify the boundaries of the sweat glands better.

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 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.
Nerve Fiber Density Measurement
Intraepidermal Nerve Fiber Density Measurement

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

The question addressed in this evidence review is: does the evidence on intraepidermal nerve fiber density and sweat gland density measurements effect the diagnosis and monitoring of small fiber neuropathy?

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

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

Interventions
The test being considered is intraepidermal nerve fiber 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 quality of life.

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

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

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, c-statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
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).

The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation performed a literature review (2009) to evaluate the diagnostic accuracy of IENF density in the detection of small fiber neuropathy. They adopted a clinical diagnosis of small fiber neuropathy as the independent reference standard for calculation of sensitivity and specificity. Eight studies were reviewed that employed a case-control design with patients with established polyneuropathy and normal controls. Significant differences were found between the 2 groups. For example, McArthur et al (1998) studied 98 normal controls and 20 patients who have sensory neuropathies. The density of epidermal nerve fibers in the controls was 13.8 per mm in the calf (5th percentile of controls, 3.8 per millimeter), with a significant mean reduction in the study population (p value not reported) and a diagnostic efficiency of 88% (vs healthy controls). An earlier report (1997) by this group showed a mean IENF density of 4.9 per millimeter in 20 patients with sensory neuropathy and a mean IENF density of 16.3 per millimeter in 20 age-matched controls. However, none of the studies reviewed included an appropriate group of patients (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 conducted an evidence review on diabetic neuropathy for its 2011 guidelines used to develop a comprehensive diabetes care plan. The evidence review found level 3 evidence (cross-sectional studies) that IENF density correlated inversely with cold and heat detection thresholds and is significantly reduced in symptomatic patients with normal findings from nerve conduction studies and those with metabolic syndrome, impaired glucose tolerance, and impaired fasting glucose, suggesting early damage to small nerve fibers. Level 3 evidence (surveillance studies) indicated that IENF density is reduced in painful neuropathy compared with that observed in painless neuropathy. Level 2 evidence (prospective cohort studies) indicated that diet and exercise interventions in impaired glucose tolerance lead to increased IENF density. Reviewers concluded these data suggested that IENF loss is an early feature of metabolic syndrome, prediabetes, and established diabetes and that the loss progresses with increasing neuropathic severity. Also, there may be nerve regeneration with treatment (diet and exercise).

The single prospective study (1999) identified in the 2009 American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine and American Academy of Physical Medicine and Rehabilitation literature review included a series of 117 patients presenting with painful bilateral feet. In this report, a skin biopsy was done only in the subset of 32 patients who had normal nerve conduction studies, and the study did not compare the results of the IENF density with an independent reference standard to confirm the presence of small fiber neuropathy. American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation concluded that IENF density assessment is “possibly useful” to identify distal symmetric polyneuropathy, including small fiber neuropathy, in symptomatic patients with suspected polyneuropathy (level C recommendation). Future research recommendations included the need for studies to characterize the diagnostic accuracy of skin biopsy in distinguishing patients with suspected polyneuropathy (particularly small fiber neuropathy) from appropriate patients with sensory complaints or pain unrelated to peripheral neuropathy, using a predetermined reference standard.

The diagnostic accuracy of skin biopsy was assessed in a 2009 study of 210 patients who had signs of small fiber neuropathy from various conditions. The diagnosis of pure small fiber neuropathy (n=45) was established if patients had clinical symptoms and sensory deficits but
preserved vibration and joint sense. Using the 5th percentile as a threshold (6.7 fibers per millimeter), the sensitivity of IENF density was 35%, and specificity was 95%.

Additional studies include large retrospective series. Devigili et al (2008) retrospectively reviewed 486 patients referred for suspected sensory neuropathy. An IENF density of 8 per millimeter was found to have the highest sensitivity (88%) and specificity (81%), using the sensory deficit to pinprick as the standard. In a 2009 review, Walk concluded that a reduction in IENF density provides supportive evidence of a loss of cutaneous efferents, but “clinical features remain paramount in the diagnostic process and the possibility of small fiber dysfunction is not excluded by an IENF density in the normal range.”

Section Summary: Clinical Validity
IENF density decreases across age and sex in healthy controls and, therefore, density measurements in patients suspected of small fiber neuropathy are compared with age- and sex-adjusted normative values. Few studies have prospectively compared the clinical validity of IENF density measurements in a population of patients suspected of small fiber neuropathy with an established reference standard. The available studies have shown low sensitivity and high specificity, suggesting that an IENF density below the 5th percentile of healthy controls may support a diagnosis of small fiber neuropathy, but IENF density above the 5th percentile cannot be used to rule it out.

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.

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. Of 27 patients, skin biopsies were consistent with small fiber neuropathy (<5th percentile of the norm) in 41% compared with 3% of matched control subjects, leading to an investigation of other potential causes. A 2013 retrospective analysis by Bouchow 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. Determination of low or borderline IENF density led to newly identified diseases in 8 patients, more aggressive diabetes management in 8 patients, and further laboratory testing in 4 patients. Of the 35 patients who had normal skin biopsies, 14 had new treatments and/or diagnoses, including musculoskeletal pain, plantar fasciitis, Morton neuroma, restless legs syndrome, lumbar spinal stenosis, Raynaud syndrome, peripheral nerve hyperexcitability, autoimmune autonomic ganglionopathy, and depression. The authors reported that examination findings were not effective at distinguishing patients with or without pathologic determination of small fiber neuropathy, and that some physicians at their institution appeared to use skin biopsies as a way to rule out, rather than rule in, a diagnosis of small fiber neuropathy. The authors did not report whether the changes in diagnosis or management led to improved health outcomes.
A 2011 review of the diagnosis and treatment of pain in small fiber neuropathy indicated that the history and physical exam are still considered the criterion standard and that further testing may be unnecessary, particularly in the context of an associated disease. However, authors suggested that IENF density measurement may provide diagnostic confirmation or additional guidance if the diagnosis is less clear. Thus, facilitating a diagnosis in patients with idiopathic small fiber neuropathy can potentially change management.

**Section Summary: Clinical Utility**

There would be little benefit on 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 intraepidermal nerve fiber density measurement is to provide a diagnostic option that is an alternative to or an improvement on existing testing in patients with an established diagnosis of small fiber neuropathy.

The question addressed in this evidence review is: does the evidence on repeated intraepidermal nerve fiber density effect the diagnosis and monitoring of small fiber neuropathy?

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

**Patients**

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

**Interventions**

The test being considered is repeated intraepidermal nerve fiber density measurement.

**Comparators**

Comparators of interest include continued clinical monitoring.

**Outcomes**

The general outcomes of interest are test accuracy, change in disease status, symptoms, and quality of life.

**Timing**

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.

**Setting**

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

**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, c-statistic, likelihood ratios) may be included but are less informative.

5. Studies should also report reclassification of diagnostic or risk category.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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 intraepidermal nerve fiber density testing in patients with 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 randomized controlled trials. 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: Clinical Utility**
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 sweat gland nerve fiber density measurement is to provide a diagnostic option that is an alternative to or an improvement on existing testing in patients with suspected small fiber neuropathy.

The question addressed in this evidence review is: does the evidence on intraepidermal nerve fiber density and sweat gland density measurements effect the diagnosis and monitoring of small fiber neuropathy?

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

**Patients**
The relevant population of interest are individuals with suspected small fiber neuropathy.
Interventions
The test being considered is sweat gland nerve fiber 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 quality of life.

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

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

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, c-statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
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.15, 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).17, Normative values were established in 107 control subjects, and sudomotor denervation was defined as an SGNF density less than the 5th percentile cutoff value for the sex (1.58% for men, 2.63% for women). There was no effect of age on the SGNF density. Sudomotor denervation was present in 42.86% of patients with diabetic neuropathy. The SGNF density was lower in patients with anhidrosis of the feet (0.89%) compared with patients with normal sweating (3.10%) and was not associated with autonomic symptoms in the cardiovascular, gastrointestinal, or genitourinary systems.

No studies were identified that evaluated the sensitivity or specificity of SGNF density measurement.
Clinically Useful
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.

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

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 controls. No studies were identified that evaluated the clinical validity of SGNF density measurement. No studies were identified that showed improvements in health outcomes with SGNF density measurements.

Summary of Evidence
For individuals with suspected idiopathic small fiber neuropathy who receive intraepidermal nerve fiber (IENF) density measurement, the evidence includes reports assessing whether IENF density measurement is technically reliable, clinically valid, and clinically useful. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Techniques to measure IENF density have led to an improved understanding of the relation between the loss of small nerve fibers and symptoms of peripheral neuropathy. The literature has also indicated that low IENF density may provide supportive evidence of a lesion in the peripheral somatosensory system. For example, there is a significant decrease in average IENF density in patients diagnosed with small fiber neuropathy compared with controls, and an IENF density of 4 to 8 per mm in the calf is near the 5th percentile of normal values, suggesting an increased probability of small fiber neuropathy below these cutoffs. For individuals who have symptoms suggestive of neuropathy, but no evidence of large nerve neuropathy and no disease associated with neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy), establishing a cause for the symptoms is problematic. Thus, IENF density measurement may help to diagnose idiopathic small fiber neuropathy in those who have no evidence of large fiber neuropathy and no known cause of neuropathy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have an established diagnosis of small fiber neuropathy who receive repeated IENF density measurement, the evidence is limited. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. A number of trials are ongoing or have recently been completed; they assess the efficacy of activity and medications on small fiber neuropathy. If successful, there might be a role for repeated IENF density measurements to result in a change in management (e.g., changing dose or class of medication). However, current treatments for small fiber neuropathy only palliate symptoms and do not modify the underlying changes in nerve fiber density in patients with symptomatic neuropathy. There is no evidence that monitoring progression of neuropathy has clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have suspected small fiber neuropathy who receive sweat gland nerve fiber density measurement, the evidence includes comparisons with control values. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Measurement of sweat gland nerve fiber density may lead to an improved understanding of the relation between the loss of sudomotor nerve fibers and symptoms of peripheral neuropathy. However, no studies were identified that evaluated the diagnostic accuracy of sweat gland nerve fiber density measurement. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

In response to requests from Blue Cross Blue Shield Association, 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.6 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).19.

American Academy of Neurology et al
The 2009 practice parameters from the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation concluded that IENF density assessment using protein gene product 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology, and provided a level C (possibly useful) recommendation to consider use of skin biopsy to diagnose the presence of a polyneuropathy, particularly small fiber neuropathy.3. These guidelines were reaffirmed by AAN in 2013.

In 2009, American Association of Neuromuscular Electrodiagnostic Medicine, in conjunction with AAN and American Academy of Physical Medicine and Rehabilitation, published an ordered set of case definitions of “distal symmetrical polyneuropathy” for clinical research ranked by the likelihood of disease.20. The recommendations for case definitions that included symptoms, signs, and nerve conduction studies were for clinical research studies and based on a systematic analysis of peer-reviewed literature supplemented by consensus from an expert panel. IENF density was not included in the case definitions.
European Federation of Neurological Societies
EFNS published 2005 guidelines on the use of skin biopsy in peripheral neuropathy.1 EFNS concluded that skin biopsy was a safe, validated, and reliable technique for the determination of IENF density. EFNS jointly updated its guidelines with Peripheral Nerve Society on the use of skin biopsy in the diagnosis of small fiber neuropathy in 2010.19 The guidelines stated that IENF density is a reliable and efficient technique to assess the diagnosis of small fiber neuropathy (recommendation level A). Normative reference values are available for bright-field immunohistochemistry (recommendation level A) but not for confocal immunofluorescence. The guidelines recommended that newly established laboratories should provide their own stratified for age and sex normative values, intra- and interobserver reliability, and interlaboratory agreement.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage decision specifically on IENF density testing. The 2002 national coverage decision for services provided for the diagnosis and treatment of diabetic sensory neuropathy with loss of protective sensation (also known as diabetic peripheral neuropathy) (70.2.1) provided the following information21:

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

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

Table 1. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<tr>
<td>NCT01503892a</td>
<td>Metanx Effects on Nerve Fiber Density in Neuropathic Diabetics</td>
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<td>NCT01288937a</td>
<td>A Placebo Controlled, Randomized, Double Blind Trial of Milnacipran for the Treatment of Idiopathic Neuropathy Pain</td>
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<td>Oct 2014 (terminated)</td>
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<td>NCT01079325a</td>
<td>A Phase 2b Repeat Dosing Clinical Trial of SB-509 in Subjects With Moderately Severe Diabetic Neuropathy</td>
<td>170</td>
<td>Apr 2016 (completed)</td>
</tr>
</tbody>
</table>

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

19. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- 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**

- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT®</td>
<td>11100</td>
<td>Biopsy of skin, subcutaneous tissue and/or mucous membrane (including simple closure), unless otherwise listed; single lesion (Deleted code effective 1/1/2019)</td>
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<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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<tr>
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<td>11102</td>
<td>Tangential biopsy of skin (e.g., shave, scoop, saucerize, curette); single lesion <em>(Code effective 1/1/2019)</em></td>
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<td>11103</td>
<td>Tangential biopsy of skin (e.g., shave, scoop, saucerize, curette); each separate/additional lesion (List separately in addition to code for primary procedure) <em>(Code effective 1/1/2019)</em></td>
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<td>11104</td>
<td>Punch biopsy of skin (including simple closure, when performed); single lesion <em>(Code effective 1/1/2019)</em></td>
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<td>88305</td>
<td>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</td>
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<tr>
<td></td>
<td>88314</td>
<td>Special stain including interpretation and report; histochemical stain on frozen tissue block (List separately in addition to code for primary procedure)</td>
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<tr>
<td></td>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure</td>
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<tr>
<td></td>
<td>88356</td>
<td>Morphometric analysis; nerve</td>
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**HCPCS**  
None

**ICD-10 Procedure**  
None

**Policy History**

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>04/01/2016</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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<tr>
<td>02/01/2017</td>
<td>Policy title change from Nerve Fiber Density Testing</td>
<td>Medical Policy Committee</td>
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</table>
Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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 (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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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.