BlueCross BlueShield of Louisiana

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Nerve Fiber Density Testing

Policy # 00240
Original Effective Date: 10/14/2009
Current Effective Date: 09/17/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber neuropathy to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber neuropathy may be considered when ALL of the following criteria are met:

- Individual presents with symptoms of painful sensory neuropathy; AND
- There is no history of a disorder known to predispose to painful neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy); AND
- Physical examination shows no evidence of findings consistent with large-fiber neuropathy, such as reduced or absent muscle-stretch reflexes or reduced proprioception and vibration sensation; AND
- Electromyography and nerve-conduction studies are normal and show no evidence of large-fiber neuropathy.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers skin biopsy with epidermal nerve fiber density measurement for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment, to be **investigational.***

The use of skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber neuropathy when patient selection criteria are not met is considered to be **investigational.***

Based on review of available data, the Company considers measurement of sweat gland nerve fiber density to be **investigational.***

Background/Overview

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 being investigated as an objective measure of small fiber neuropathy by identifying a reduction in the density of nerve fibers.

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The majority of patients with peripheral neuropathy exhibit evidence of large fiber involvement, characterized by numbness, tingling, loss of deep tendon reflexes, and abnormal electrophysiologic studies. In contrast, damage to small fibers is not detected by routine nerve conduction studies. Patients with small fiber neuropathy, involving myelinated A delta and unmyelinated C fibers, may complain of severe pain and exhibit diminished thermal and pain perception. The pain, which is frequently reported in the feet, is described as burning, prickling, stabbing, jabbing, or tight band-like pressure. 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, human immunodeficiency virus (HIV) infection, and toxic neuropathy from antiretroviral drugs. For many patients, no specific etiology is identified.

Small fiber neuropathy is diagnosed clinically but has traditionally been a diagnosis of exclusion based on clinical findings and the absence of large fiber involvement, as determined by electrophysiologic studies. The disparity between subjective complaints and objective signs increases the difficulty of diagnosis. In addition, conditions other than nerve fiber damage, including venous insufficiency, spinal stenosis, myelopathy, and psychosomatic disturbances may mimic small fiber neuropathy. There is no treatment to cure small fiber peripheral neuropathy. Medications may be provided for pain management, and for some etiologies, treatment of the underlying condition (e.g., glucose control, intravenous immunoglobulin or plasma exchange) may be given to reduce progression of the disease and its symptoms.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Assessment of IENF and SGNF density with *PGP 9.5* is commercially available from Therapath (New York) with a biopsy kit, although IENF-density measurement (i.e., tissue preparation, immunostaining with *PGP 9.5*, and counting) may also be done by local research pathology labs.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage decision (NCD) specifically regarding IENF density testing. The NCD for services provided for the diagnosis and treatment of diabetic sensory neuropathy with loss of protective sensation (also known as diabetic peripheral neuropathy) (70.2.1) provides the following information:

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Effective for services furnished on or after July 1, 2002, Medicare covers, as a physician service, an evaluation (examination and treatment) of the feet no more often than every six months for individuals with a documented diagnosis of diabetic sensory neuropathy and loss of protective sensation, as long as the beneficiary has not seen a foot care specialist for some other reason in the interim. Loss of protective sensation shall be diagnosed through sensory testing with the 5.07 monofilament using established guidelines, such as those developed by the National Institute of Diabetes and Digestive and Kidney Diseases guidelines. Five sites should be tested on the plantar surface of each foot, according to the National Institute of Diabetes and Digestive and Kidney Diseases guidelines. The areas must be tested randomly since the loss of protective sensation may be patchy in distribution, and the patient may get clues if the test is done rhythmically. Heavily callused areas should be avoided. As suggested by the American Podiatric Medicine Association, an absence of sensation at two or more sites out of 5 tested on either foot when tested with the 5.07 Semmes-Weinstein monofilament must be present and documented to diagnose peripheral neuropathy with loss of protective sensation.

Rationale/Source

Diagnostic Tests

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

Literature searches using the MEDLINE database have been performed through August 23, 2013. In addition to recent studies, the searches identified a systematic review by the European Federation of Neurological Societies (EFNS) from 2005, updated guidelines from EFNS in 2010, and a jointly published evidence review and practice parameter for the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and American Academy of Physical Medicine and Rehabilitation (AAPMR) from 2009.

Intraepidermal Nerve Fiber (IENF) Density

Technical Performance

The EFNS systematic review determined that skin biopsy from the distal leg or foot with immunostaining with anti-protein-gene-product 9.5 (*PGP 9.5*) is a safe, validated, and reliable technique for the determination of IENF density, indicating adequate technical performance of this test. The EFNS also concluded that IENF density is diagnostically efficient at distinguishing polyneuropathy patients (including small fiber neuropathy) from normal controls.

Clinical Validity

Assessment of clinical validity necessitates that studies include a representative patient population with an appropriate spectrum of patients and that the test be compared with an independently assessed gold standard. As discussed in the jointly published 2009 practice parameters of the AAN, AANEM, and AAPMR, the EFNS systematic review did not assess the more clinically relevant question, which is: what is the diagnostic accuracy of skin biopsy in distinguishing symptomatic patients with polyneuropathy from

symptomatic patients without polyneuropathy? For example, in patients with painful feet, would skin biopsy accurately distinguish patients with polyneuropathy from other conditions causing painful feet?

To address these questions, a committee of the AAN, AANEM, and AAPMR performed a literature review to evaluate the diagnostic accuracy of IENF density in the detection of small fiber neuropathy. They adopted a clinical diagnosis of small fiber neuropathy as the independent reference standard for calculation of sensitivity and specificity. Eight studies were reviewed that employed a case-control design with patients with established polyneuropathy and normal controls. Significant differences were found between the 2 groups. For example, McArthur et al. studied 98 normal controls and 20 patients with sensory neuropathies. The density of epidermal nerve fibers in the controls was 13.8 per mm in the calf (5th percentile of controls: 3.8 per mm), with a significant mean reduction in the patient population (value not reported) and a diagnostic efficiency of 88% (compared to healthy controls). An earlier report by this group showed a mean IENF density of 4.9 in 20 patients with sensory neuropathy and a mean IENF density of 16.3 in 20 age-matched controls. However, none of the studies reviewed included an appropriate group of patients, i.e., those with conditions causing lower extremity pain or sensory complaints that might be confused with polyneuropathy. In addition, the sensitivity of IENF density ranged from 45% to 90% compared to healthy controls, indicating that the absence of reduced IENF density would not rule out polyneuropathy.

The American Association of Clinical Endocrinologists (AACE) conducted an evidence review on diabetic neuropathy for their 2011 guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. The evidence review found that there is level 3 evidence (cross-sectional studies) to show that intraepidermal nerve fiber density correlates inversely with both cold and heat detection thresholds and is significantly reduced in symptomatic patients with normal findings from nerve conduction studies and those with metabolic syndrome, impaired glucose tolerance, and impaired fasting glucose, suggesting early damage to small nerve fibers. Level 3 evidence (surveillance studies) indicates that intraepidermal nerve fiber density is reduced in painful neuropathy compared with that observed in painless neuropathy. Level-2 evidence (prospective cohort studies) indicates that diet and exercise intervention in impaired glucose tolerance lead to increased intraepidermal nerve fiber density. The review concludes that these data suggest that intraepidermal nerve fiber loss is an early feature of metabolic syndrome, prediabetes, and established diabetes mellitus and that the loss progresses with increasing neuropathic severity. In addition, there may be nerve regeneration with treatment (diet and exercise).

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

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Additional studies identified in the MEDLINE search for this policy included a 2007 retrospective evaluation by Walk et al. of the concordance between foot IENF density and clinical findings in patients with possible idiopathic small fiber neuropathy who underwent skin biopsy for IENF density determination. Of 178 patients referred for evaluation, 106 met the inclusion criteria of idiopathic symmetric burning, paresthesias, hyperalgesia, or allodynia in a length-dependent distribution, with normal strength, reflexes, and nerve conduction studies. Sensory examination included assessment of pinprick sensitivity and a qualitative determination of vibration perception using a 128 Hz tuning fork at the great toe. An IENF density of 8 per mm was found to have the highest sensitivity (88%) and specificity (81%), using sensory deficit to pinprick as the standard. The mean foot IENF density for patients with normal sensation was 13.9 +/- 7.7 per mm, with a range of 0 to 36 per mm. The mean IENF density in the foot in the patient population was reduced to approximately 3 per mm (standard deviations: 4.9, 8.0, and 5.7 for the 3 patient groups, respectively; range: 0 to 29.5 per mm), depending on the severity of sensory deficit. Thus, there was considerable overlap in the range of IENF density between patients who showed a sensory deficit and those who did not. In a 2009 review, Walk concluded that a reduction in IENF density provides supportive evidence of a loss of cutaneous efferents, but "clinical features remain paramount in the diagnostic process and the possibility of small-fiber dysfunction is not excluded by an IENF density in the normal range."

In 2008, Devigili and colleagues published a retrospective review of 486 patients referred for suspected sensory neuropathy. A total of 150 patients met the entry criteria for the study, which were symptoms suggesting sensory neuropathy and availability of 1) clinical examination, including spontaneous and stimulus-evoked pain, 2) a sensory and motor nerve conduction study, 3) warm and cooling thresholds assessed by quantitative sensory testing (QST), and 4) skin biopsy with distal IENF density. Based on the combined assessments, neuropathy was ruled out in 26 patients; 124 patients were diagnosed with sensory neuropathy, 67 of whom were diagnosed with small fiber neuropathy. Using a cutoff of 7.63 IENF/mm at the distal leg (based on the 5th percentile of controls), 59 patients (88%) were considered to have abnormal nerve density. Only 7.5% of patients had abnormal results for all 3 examinations (clinical, QST, skin biopsy), 43% had both abnormal skin biopsy and clinical findings, and 37% of patients had both abnormal skin biopsy and QST results. The combination of abnormal clinical and QST results was observed in only 12% of patients. These results indicate that most of the patients evaluated showed IENF of less than 7.63 together with either abnormal spontaneous or evoked pain (clinical examination) or abnormal thermal thresholds (QST). The authors of this study recommended a new diagnostic "gold standard" based on the presence of at least 2 of 3 abnormal results (clinical, QST, and IENF density). This study is limited by the lack of an independent reference standard, particularly since the IENF results affected whether patients were included in the study group. Prospective studies are needed to evaluate whether the addition of skin biopsy to clinical diagnoses improves detection of small fiber neuropathy in an appropriately mixed patient population.

Scherens and colleagues conducted a prospective study to assess the percentage of patients with lower limb dysesthesias (painful or painless) who had evidence of small fiber neuropathy. Forty-two patients who presented to clinic with dysesthesias underwent standard neurophysiology, quantitative sensory testing and measurement of IENF density. Thirty-seven of the patients (88%) were found to have abnormal IENF density, defined as a reduction of one standard deviation below the mean of healthy controls (mean IENF density: 12 per mm) from a prior study. Four patients (9.5%) were categorized with pure large fiber neuropathy, 15 (35.7%) with pure small fiber neuropathy, and 22 (52.4%) with mixed large and small fiber

neuropathy. Given that nearly 90% of patients with dysesthesias showed abnormal IENF density, this study raises questions about the value added from skin biopsy in a clinical setting. In another study, Krishnan et al. compared dermal nerve density, quantitative sensory testing (vibration, cold, warmth, and heat pain), and a new functional test of dermal vasodilation, called the laser Doppler imager (LDI) flare in 2 groups of patients with type 2 diabetes (10 with painful neuropathy and 12 with more advanced painless neuropathy), and 15 healthy controls. This study measured dermal (instead of intraepidermal) nerve density as a direct measure of the structural integrity of the innervation of dermal blood vessels as a reference for the noninvasive functional test. These and other authors have noted that deficits in nerve function may precede anatomic changes. Studies are needed to evaluate when in the course of disease (i.e., severity of clinical symptoms) decreases in IENF density become apparent.

In 2009, Bakkers and colleagues reported a multicenter assessment of IENF density in 188 healthy volunteers and 72 patients with sarcoidosis to assess the discriminative ability of IENF density. Of the 72 patients with sarcoidosis, 58 had symptoms of small fiber neuropathy, and 14 were without symptoms. Normative values were stratified for age and sex, showing age-dependent decreases in IENF density and lower densities in men compared with women. Two of the 14 patients (14%) with sarcoidosis without symptoms of small fiber neuropathy had reduced IENF density. Nineteen of the 58 patients (33%) with sarcoidosis and symptoms of small fiber neuropathy had reduced IENF density (less than 5th percentile of age- and sex-stratified normative values). Thus, a reduction in IENF density was able to identify one-third of sarcoidosis patients with symptoms of small fiber neuropathy.

Nebuchennykh et al. assessed the diagnostic characteristics of skin biopsy in 210 patients with 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 with preserved vibration and joint sense. Mixed fiber neuropathy (n=165) was diagnosed if there were more extensive sensory findings with a proximo-distal gradient, muscle weakness, or abnormal nerve conduction studies. Z-scores were calculated from a reference set of 134 healthy individuals, with gender and age associated with a decrease in IENF density. Using a Z-score less than 2 as the threshold, IENF density had a sensitivity of 31% and a specificity of 98%. Using the 5th percentile as a threshold (6.7 fibers/mm), the sensitivity of IENF density was 35% and specificity was 95%. When sensitivity was maximized from receiver operating characteristic (ROC) analysis (78% sensitivity, at a threshold of 10.3 fibers/mm), specificity decreased to 64%.

In 2010, Lauria and colleagues published a multicenter study (8 sites) of normative reference values for IENF density at the distal leg. Groups that previously reported normative IENF density values using bright-field immunohistochemistry provided available data to a coordinating center. Density data from a total of 550 healthy subjects (age of 18 to 84 years) in the U.S., Europe, and Asia were included in the analysis. There was a significant decrease in IENF density in both men and women with age. For women, the 5^{th} percentile ranged from 8.4 fibers per mm at 20-29 years of age to 1.6 fibers per mm at $\geq$80 years. For men, the 5^{th} percentile ranged from 6.1 fibers per mm at 20-29 years of age to 1.7 at $\geq$80 years. IENF density was lower in men than women between 20 and 69 years of age, but not for subjects 70 years or older. This finding may be limited by the smaller sample size in the older age groups. There was no significant influence of height, weight, or body mass index for the IENF density normative scores (5^{th} percentile).

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Clinical Utility

Another issue to consider for this diagnostic test is whether objective confirmation in patients with a clinical diagnosis of small fiber neuropathy will alter treatment decisions and lead to improved health outcomes. A 2013 retrospective analysis by Boruchow and Gibbons found a change in diagnosis or management in 36 of 69 patients (52%) who had a skin biopsy at their institution for evaluation of possible small fiber neuropathy. Determination of low or borderline IENF density led to newly identified diseases in 8 patients, more aggressive management of diabetes mellitus in 8 patients, and further laboratory testing in 4 patients. Of the 35 patients who had normal skin biopsies, 14 had new treatments and/or diagnoses, including musculoskeletal pain, plantar fasciitis, Morton's neuroma, restless legs syndrome, lumbar spinal stenosis, Raynaud's syndrome, peripheral nerve hyperexcitability, autoimmune autonomic ganglionopathy, and depression. The authors reported that examination findings were not effective at distinguishing patients with or without pathologic determination of small fiber neuropathy, and that some physicians at their institution appeared to use skin biopsies as a way to rule out, rather than rule in, a diagnosis of small fiber neuropathy. The authors did not report if the changes in diagnosis or management led to an improvement in health outcomes.

A 2006 review of diagnostic tools for diabetic sensorimotor polyneuropathy by Kles and Bril (Eli Lilly Research Institute, Washington, DC) indicates that although many therapies are in clinical trials, current treatment options only palliate pain symptoms and do not target the underlying disease etiology. Kles and Bril concluded that although biopsy of skin and nerve may be beneficial for identifying the underlying pathology of the damaged nerve and extending our knowledge concerning the pathophysiology of diabetic sensory polyneuropathy when used in carefully controlled clinical trials, "initial testing in the primary care and diabetes clinic settings can be done with simple tests for signs of neuropathy such as tuning fork, monofilament, and pinprick insensitivity." A 2011 review of the diagnosis and treatment of pain in small-fiber neuropathy indicates that the history and physical exam are still considered the gold standard and that further testing may be unnecessary, particularly in the context of an associated disease. However, the authors suggest that IENF-density testing may provide diagnostic confirmation or additional guidance if the diagnosis is less clear.

Sweat Gland Nerve Fiber (SGNF) Density

Technical Performance

In a 2009 report, Gibbons et al. evaluated SGNF density measurements in punch skin biopsies from 30 diabetic subjects and 64 controls that were sectioned and stained with *PGP 9.5* and compared with confocal microscopy with stereology. Measurements of SGNF density were normalized by area due to the large variability in sweat gland size, and specific methods were used to reduce the high inter- and intra-reviewer variability in manual outlining of sweat gland area. The authors noted nonspecific background staining of the sweat glands with *PGP 9.5* that made it difficult to measure individual nerve fibers and sweat gland margins. There was an average of 1.6 sweat glands per biopsy. Blinded evaluation found a correlation of r=0.93 between SGNF density and the stereologic estimate of sweat gland nerve fiber length. The intra-reviewer intraclass correlation coefficient (ICC) was 0.886 and the inter-reviewer ICC was 0.892. A 2010 publication by the same authors found good reliability for either automated or manual quantification of SGNF density, but poor inter- and intra-reviewer reliability when using a semi-quantitative approach (5-point scale).

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Clinical Validity
In their 2009 report, Gibbons et al. found a significant decrease in the mean SGNF density of diabetic subjects compared to controls, although there was considerable overlap in the ranges. There was also a significant association between the SGNF density and neuropathy scores measured by the Neuropathy Impairment Score in the Lower Limb, the Michigan Diabetic Neuropathy Score part 1, and the Toronto Clinical Scoring System, but not the Michigan Neuropathy Screening Instrument. There was a moderate correlation (r=0.66) between SGNF density and IENF density.

Luo et al. evaluated SGNF density in 35 patients with type 2 diabetes and sensory neuropathy (stocking distribution and reduced IENF density). Normative values were established in 107 control subjects, and sudomotor denervation was defined as a SGNF density less that the 5th percentile cutoff value for the sex (1.58% for men and 2.63% for women). There was no effect of age on the SGNF density. Sudomotor denervation was present in 42.86% of patients with diabetic neuropathy. The SGNF was lower in patients with anhidrosis of the feet compared with patients with normal sweating (0.89% vs. 3.10%) and was not associated with autonomic symptoms in the cardiovascular, gastrointestinal, or genitourinary systems.
No studies were identified that evaluated the sensitivity or specificity of SGNF density measurement.

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

Ongoing Clinical Trials
A search of the online site ClinicalTrials.gov in August 2013 identified a number of relevant trials on small fiber neuropathy.

- NCT00956033 will evaluate sensitivity of IENF density measurements for chemotherapy-induced neuropathy. Skin biopsies will be taken from 100 patients with multiple myeloma treated with bortezomib. The estimated study completion date is listed as November 2011. The status of this trial is unknown.
- NCT01288937 is a randomized, double-blind trial of milnacipran for the treatment of idiopathic neuropathy pain. Included in the study will be 52 patients with signs and symptoms of a peripheral neuropathy, with either abnormal nerve conductions or abnormal epidermal nerve fiber density with neuropathic pain. Exclusion criteria include other causes of neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, and inherited neuropathy). The estimated study completion date is October 2013.
- NCT01503892 is a randomized double-blind placebo controlled trial of Metanx for improving and reversing nerve damage in type 2 diabetic patients with peripheral neuropathy. IENF density will be measured at baseline and at the end of 12 months of treatment. The study has an expected enrollment of 100 patients with completion anticipated in October 2013.
- NCT01498211 will establish normative IENF density in 300 subjects without pain or neurologic impairment. The estimated study completion date is June 2013.
- The Department of Veteran Affairs is conducting a study (NCT00780559) to determine if an individually tailored diet and physical enhancement program can improve mobility, physical activity,

and neuropathy in people with early diabetes. The primary outcome measure is the 6-minute walk test. Secondary outcome measures are physical activity and IENF density. There is an estimated enrollment of 142 patients; the estimated study completion date is January 2016.

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

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

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, which were subsequently reviewed. The input was mixed. Some respondents indicated that the gold standard for diagnosis of small fiber neuropathy is the history and clinical examination combined with nerve conduction studies and that the skin biopsy only supports a clinical impression of a small fiber polyneuropathy and cannot exclude the diagnosis. Among those who supported the medical necessity of IENF-density testing, several commented that this is the only test to allow an objective diagnosis and that small fiber neuropathy may be effectively managed with products such as L-methylfolate, methylcobalamin, and/or pyridoxal 5'-phosphate (study discussed above). Another reviewer commented that patients who benefit from this test are those who suffer from the symptoms of small fiber neuropathy but have no predisposing condition (idiopathic). Other reviewers, who were generally in support of the medical necessity of IENF density management for diagnosis, acknowledged that the test has limited utility when disease is clinically advanced and that evidence to demonstrate that the use of skin biopsy with IENF density measurement improves clinical outcomes is only now emerging.

Summary
Techniques to measure IENF density have led to an improved understanding of the relation between the loss of small nerve fibers and symptoms of peripheral neuropathy. The literature also indicates that low IENF density may provide supportive evidence of a lesion in the peripheral somatosensory system. For example, there is a significant decrease in the average IENF in groups of patients diagnosed with small fiber neuropathy in comparison with groups of controls, and an IENF density of 4 to 8 per mm in the calf is near the 5th percentile of normal values, suggesting an increased probability of small fiber neuropathy below these cutoffs.

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However, there is limited evidence to indicate that measurement of IENF density in a patient clinically diagnosed with probable small fiber neuropathy improves health outcomes. Clinical input on the medical necessity of IENF density measurements was mixed but suggests acceptance of the procedure as an objective measure for diagnosis among some providers. One population that may particularly benefit from IENF density measurement is individuals who have no known causes of neuropathy.

Overall, a number of questions remain about whether a quantitative assessment of IENF density results in improved health outcomes. Additional prospective studies are needed to evaluate the effect of this procedure in comparison with clinical diagnosis alone in patients with known causes of neuropathy. IENF density measurement may be considered medically necessary in patients with suspected idiopathic small fiber neuropathy when the individual presents with symptoms of painful sensory neuropathy, and there is no history of a disorder known to predispose to painful neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy), and physical examination shows no evidence of findings consistent with large-fiber neuropathy, such as reduced or absent muscle-stretch reflexes or reduced proprioception and vibration sensation, and electromyography and nerve-conduction studies are normal and show no evidence of large-fiber neuropathy. Assessment of IENF density in all other conditions is considered investigational.

Measurement of SGNF density may lead to an improved understanding of the relation between the loss of sudomotor nerve fibers and symptoms of peripheral neuropathy. However, evidence is insufficient to permit conclusions regarding the impact of measurement of SGNF density on health outcomes. Measurement of SGNF density is considered investigational.

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	88305, 88314, 88342, 88356
HCPCS	No codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 10/14/2009
Current Effective Date: 09/17/2014
10/01/2009 Medical Policy Committee approval
10/14/2009 Medical Policy Implementation Committee approval. New policy.
10/14/2010 Medical Policy Committee review
10/20/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011 Medical Policy Committee review
10/19/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2012 Medical Policy Committee review
09/19/2012 Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible for coverage with criteria.
09/05/2013 Medical Policy Committee review
09/18/2013 Medical Policy Implementation Committee approval. "Based on review of available data, the Company considers measurement of sweat gland nerve fiber density to be investigational" was added. Intraepidermal was dropped from title.
09/04/2014 Medical Policy Committee review
09/17/2014 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 09/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.