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Corporate Medical Policy

Nerve Fiber Density Testing AHS – M2112

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Description of Procedure or Service

Nerve fiber density testing involves analysis of skin biopsy stained with an antibody to antiprotein gene product 9.5 (Wilkinson et al., 1989) which avidly stains all axons (Dalsgaard, Rydh, & Haegerstrand, 1989). The number and morphology of axons within the epidermis are evaluated to determine epidermal nerve fiber density (McCarthy et al., 1995) and assess for the presence and degree of neuropathy (A. G. Smith & Gibson, 2018).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for nerve fiber density testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When nerve fiber density testing is covered

Reimbursement for skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber neuropathy is allowed when ALL of these conditions 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 nerve fiber density testing is not covered

Reimbursement is not allowed for skin biopsy with epidermal nerve fiber density for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment.

Reimbursement is not allowed for the measurement of sweat gland nerve fiber density.

Policy Guidelines

As the pathology of neuropathy is usually first evident in nerve terminals, and both sensory and autonomic nerves have terminals in the epidermis of the skin (Chien et al., 2001), evaluation of nerve fibers in skin biopsy is a reasonable approach to the diagnosis of neuropathy. It could potentially be used for the diagnosis of any distal symmetric polyneuropathy (A. G. Smith & Gibson, 2018), however is rarely necessary for the diagnosis of large myelinated fiber neuropathy as less invasive electrophysiologic studies are sensitive for diagnosis. Demonstration of a reduction in the epidermal nerve fiber density in skin biopsy is a highly sensitive and specific test for Small Fiber Neuropathy.

Many chronic disorders lead to small fiber peripheral neuropathy, including diabetes, thyroid dysfunction, sarcoidosis, vitamin B12 deficiency, HIV, celiac disease, and paraneoplastic syndromes. Those with both diabetes and metabolic syndrome have double the risk of having peripheral neuropathy (Hovaguimian, & Gibbons, 2011), and the prevalence of polyneuropathy is high in obese individuals, even those with normoglycemia (Callaghan et al., 2016). Making diabetes and obesity common metabolic drivers of peripheral neuropathy (Callaghan et al., 2018).

Small fiber neuropathy is often a challenging clinical problem as patients commonly have severe complaints but standard electrophysiologic testing is often normal, and sural nerve biopsy may be normal or only minimally abnormal. The range of applications of skin biopsy has been expanded to include autonomic neuropathies and immune-mediated and inherited demyelinating neuropathies (Lauria & Devigili, 2007) however, skin biopsy is not useful in assessment of the etiology of neuropathy. Skin biopsy cannot replace nerve biopsy when neuropathological examination of mixed or large-fiber neuropathy is needed and when a vasculitic pathogenesis is suspected (Lauria & Devigili, 2007).

Clinical Validity
Sensory neuropathy
McArthur et al (1998) established he normative reference range and diagnostic efficiency of nerve fiber density testing for sensory neuropathies in 98 normal controls and 20 patients with sensory neuropathies. They found "the technique had a positive predictive value of 75%, a negative predictive value of 90%, and a diagnostic efficiency of 88%."

Chien et al (Chien et al., 2001) evaluated skin biopsy specimens from the distal leg and distal forearm of 55 healthy controls and 35 patients with sensory neuropathy. They found that "in the healthy controls, conventional intraepidermal nerve fiber densities (IENF densities) as measured using the image analysis system in the distal forearm and in the distal leg were correlated ($r=0.55$, $P<0.0001$), with significantly higher values in the distal forearm than in the distal leg (17.07+/-6.51 vs 12.92+/-5.33 fibers/mm, $P<0.001$). Compared to IENF densities of healthy controls, these values of neuropathic patients were significantly reduced in the distal forearm (5.82+/-6.50 fibers/mm, $P<0.01$) and in the distal leg (2.40+/-2.30, $P<0.001$)." The specificity of the test was found to be 95%.

Several smaller studies have reported similar values(Lauria & Devigili, 2007).

Devigili et al (2008) screened 486 patients and collected 124 patients with sensory neuropathy. Among them, they identified 67 patients with pure SFN using a new diagnostic 'gold standard', based on the presence of at least two abnormal results at clinical, QST and skin biopsy examination. They found "Skin biopsy showed a diagnostic efficiency of 88.4%, clinical examination of 54.6% and QST of 46.9%. Receiver operating characteristic curve analysis confirmed the significantly higher performance of skin biopsy comparing with QST."

Vlcková-Moravcová et al (2008) examined intraepidermal nerve fiber densities (IENFD) and subepidermal nerve plexus densities (SENPD) quantified by immunostaining in skin punch biopsies from the distal calf in 99 patients with clinical symptoms of painful sensory neuropathy and from 37 age-matched healthy volunteers. They found that "In patients with neuropathy, IENFD and SENPD

were reduced to about 50% of controls. Elevated warm detection thresholds on QST correlated with IENFD but not with SENPD. Using receiver-operating characteristic (ROC) curve analysis of IENFD values, the diagnostic sensitivity for detecting neuropathy was 0.80 and the specificity 0.82. For SENPD, sensitivity was 0.81 and specificity 0.88. With ROC analysis of both IENFD and SENPD together, the diagnostic sensitivity was further improved to 0.92. The combined examination of IENFD and SENPD is a highly sensitive and specific diagnostic tool in patients suspected to suffer from painful sensory neuropathies but with normal values on clinical neurophysiological studies."

Hoeijmakers et al (2016) recently published two case reports of nerve fiber density testing identifying small fiber neuropathy in children.

Autonomic neuropathy
Gibbons et al (2009) developed a new technique to quantify the sweat gland nerve fiber density (SGNFD) using tissue prepared for the standard analysis of IENFD. The technique differentiates groups of patients with mild diabetic neuropathy from healthy control subjects and correlates with both physical examination scores and symptoms relevant to sudomotor dysfunction. This method provides a reliable structural measure of sweat gland innervation that complements the investigation of small fiber neuropathies. They validated the technique in 30 diabetic and 64 healthy subjects. Diabetic subjects had reduced SGNFD compared to controls at the distal leg ($p < 0.001$), distal thigh ($p < 0.01$), and proximal thigh ($p < 0.05$). The SGNFD at the distal leg of diabetic subjects decreased as the NIS-LL worsened ($r = -0.89$, $p < 0.001$) and was concordant with symptoms of reduced sweat production ($p < 0.01$).

Luo et al (2011) developed an alternative staining system using anti-protein gene product 9.5 (PGP9.5) and counterstaining with Congo red which reduced the variations in measurements of sweat gland areas compared to the commonly used method by ~5.6-fold (2.47% ± 2.54% vs 13.97% ± 14.24%, $p < 0.001$). They examined 35 diabetic patients and controls. Diabetic patients had lower SGII values than age- and sex-matched controls (2.60% ± 1.96% vs 4.84% ± 1.51%, $p < 0.0001$). The SGII values were lower in patients with anhidrosis of the feet versus those with normal sweating of the feet (0.89% ± 0.71% vs 3.10% ± 1.94%, $p < 0.01$). Thus, skin biopsy offers combined assessment of sudomotor innervation.

Clinical Utility
Gibbons et al (2006) studied "Twenty-eight patients with sensory complaints of unknown etiology had repeated skin biopsies. Patients with large nerve fiber swellings on initial biopsy showed a decline in epidermal nerve fiber density on repeated biopsies ($p < 0.05$ within group; $p < 0.05$ vs those without swellings). Patients without nerve fiber swellings did not have changes in nerve fiber density between biopsies. Patients with large nerve fiber swellings were most likely to present clinically with paresthesias ($p < 0.05$)."

Hlubocky et al (2010) conducted a review of the clinical utility of skin biopsy for diagnosis of small fiber neuropathy which concluded "Detection of reduced IENFD using skin biopsy may be sensitive and specific for clinically-defined syndromes consistent with small fiber neuropathy. Skin biopsy appears to have greater diagnostic utility than the neurologic examination and quantitative sensory testing, both of which rely heavily on subjective patient perception. Prospective studies that evaluate quantitative methodology (rather than modalities that rely on patient report) and do not include the diagnostic tests in the reference standard are needed. Consensus is needed regarding a reference standard definition for small fiber neuropathy."

In 2012 IMMPACT convened a meeting to discuss the potential of 3 types of assessments (i.e., sensory testing, skin punch biopsy, and functional and neurochemical brain imaging) for use as biomarkers in clinical trials of analgesic medications and other pain treatments. They found that "Skin biopsy may be a useful tool to diagnose small fiber neuropathy (SFN), and may allow for earlier diagnosis of neuropathy and neuropathic pain conditions." Furthermore, "Case reports have also demonstrated the utility of skin biopsy to detect clinical changes." "However, the available research does not provide firm evidence supporting the use of skin biopsy to predict treatment benefit or to distinguish between individuals with neuropathy who will or will not experience pain" (S. M. Smith et al., 2017).

Pereira et al (2016) reviewed the utility of measurement of the intraepidermal nerve fiber (IENF) density in the diagnostics of chronic pruritus, as small fiber neuropathy can manifest clinically with pruritus. They found that "Upon suspicion of a small-fiber neuropathy as a cause for chronic pruritus, targeted diagnostic procedures are essential for the early detection of the neuroanatomical changes… Diagnosing a small-fiber neuropathy underlying chronic pruritus has therapeutic relevance. If possible, the underlying cause of the neuropathy should be treated. Alternatively, symptomatic therapy options include topical (capsaicin) and systemic (anticonvulsants and/or antidepressants) agents. Chronification processes may lead to refractory pruritus, and thus treatment should be initiated as soon as possible."

Diabetic Neuropathy
UpToDate found that "Despite growing acceptance as a useful marker of small fiber neuropathy, the clinical role of skin intraepidermal nerve fiber assessment for the quantitation of diabetic autonomic neuropathy (DAN) remains unclear (Gibbons, 2018)"

Erythromelagia
Mantyh et al (2016) investigated the clinical utility of nerve fiber density testing for erythromelagia in a retrospective study of 52 consecutive patients with erythromelalgia and found that "Unlike other diseases of the small nerve fibers that cause acral pain syndromes, erythromelalgia is not characterized by loss of ENFD. However, most patients have impaired function of these small fibers. Physicians would benefit from performing functional rather than structural small fiber studies when evaluating erythromelalgia."

Fabry disease
As about 80% of Fabry patients suffer from painful neuropathy, and neuropathic pain in FD is associated with small fiber neuropathy. Torvin Moller et al explored the frequency of symptoms and the functional and structural involvement of the nervous system in female patients by examining the presence of pain, manifestations of peripheral neuropathy and nerve density in skin biopsies in 19 female patients with Fabry disease and 19 sex- and age-matched controls. They found that sensory nerve action potential amplitude and maximal sensory conduction velocity were not different, whereas there was a highly significant reduction in intraepidermal nerve fiber density, however there was no correlation between pain VAS score, quantitative sensory testing and intraepidermal nerve fiber density.

An international expert panel (Burlina et al., 2011) focused on early diagnosis of peripheral nervous system involvement in Fabry disease recommended: "Given the availability of an accurate diagnostic laboratory test, nerve or skin biopsies are not required for diagnosing Fabry disease, although skin biopsy can detect small fiber disease in yet asymptomatic patients and may be used to quantify loss of skin innervation".

Van der Tol et al (2016) found that quantitative sensory testing and nerve fiber density testing could not be used to confirm Fabry disease in patients with a GLA variant, but without characteristic FD features. The sensitivity was 28% and specificity was 80%.

Familial amyloid polyneuropathy
Chao et al (2015) found studies skin biopsies of 28 Fap patients were stained with 2 markers: protein gene product 9.5 (PGP 9.5), a general neuronal marker, and vasoactive intestinal peptide (VIP), a sudomotor nerve functional marker, followed by quantitation according to sweat gland innervation index (SGII) for PGP 9.5 (SGIIPGP 9.5) and VIP (SGIIVIP) to investigate the pathology and clinical significance of sudomotor denervation. They found that "The SGIIPGP 9.5 and SGIIVIP of FAP patients were significantly lower than those of age- and gender-matched controls. The reduction of SGIIVIP was more severe than that of SGIIPGP 9.5 ($p = 0.002$). Patients with orthostatic hypotension or absent sympathetic skin response at palms were associated with lower SGIIPGP 9.5 ($p = 0.019$ and 0.002, respectively). SGIIPGP 9.5 was negatively correlated with the disability grade at the time of skin biopsy ($p = 0.004$) and was positively correlated with the interval from the time of skin biopsy to the time of wheelchair usage ($p = 0.029$).

Fibromyalgia

Caro et al (2014) studied 41 consecutive patients with fibromyalgia (FM) and 47 controls to establish the prevalence of SFM in FM. They found that "The calf and thigh ENFD in patients with FM is significantly diminished compared with that in control subjects. Advancing age alone cannot explain this finding. Calf ENFD was inversely correlated, although weakly, with serum levels of IL-2R. These findings suggest that small fiber neuropathy is likely to contribute to the pain symptoms of FM; that pain in this disorder arises, in part, from a peripheral immune-mediated process; and that measurement of ENFD may be a useful clinical tool in FM."

Lawson et al (2018) sought to characterize and distinguish the subset of patients with both fibromyalgia and small fiber polyneuropathy in 155 FM patients. They found that "The FM-SFSPN subset of patients may be identified through sural and MP sensory NCS and/or skin biopsy but cannot be identified by pain features and intensity."

UpToDate references these findings, stating that "research studies have also found that a subset of patients with FM have abnormalities on skin biopsies suggestive of small fiber neuropathic changes; the meaning of these findings is uncertain" (Goldenberg, 2018a) and that "these studies have not carefully controlled for levels of physical fitness and activity, and some of the observed abnormalities could be a consequence of pain and deconditioning" (Goldenberg, 2018b).

Ehlers-Danlos Syndrome
Cazzato et al (2016) investigated neuropathy in 20 adults with joint hypermobility syndrome/hypermobility EDS, 3 patients with vascular EDS, and 1 patient with classic EDS. They found that all except one patient had neuropathic pain and sural nerve conduction was normal in all patients. All patients showed decreased intraepidermal nerve fiber density consistent with small fibber neuropathy regardless of EHD type. They concluded that Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes, and that Skin biopsy could be considered an additional diagnostic tool to investigate pain manifestations in EDS.

Hypothyroidism
Magri et al (2010) evaluated 18 neurologically asymptomatic patients newly diagnosed with overt or subclinical hypothyroidism and 15 healthy controls. They found that patients with OH or SH showed a significantly lower IENF density. An abnormal IENF density consistent with SFN was found in 60% of patients with OH at the distal leg and in 20% at the proximal site with OH and in 25% of cases at the distal leg and in 12.5% of cases at the proximal thigh in patients with SH. These findings suggest that a considerable number of untreated hypothyroid patients may have preclinical asymptomatic small-fiber sensory neuropathy.

Gupta et al (2016) found that noninvasive nerve conduction studies can also be used to detect electrophysiological changes early in the disorder. On comparative evaluation of 60 newly diagnosed hypothyroid patients and 60 controls statistically significant increase in latency of median, ulnar, tibial, and sural nerves; decrease in conduction velocities of all the tested nerves and decrease in amplitude of median, tibial, and sural nerves was observed in hypothyroid patients.

UpToDate (Rubin, 2018) reviewed these findings summarizing: "The presence of distal sensory loss and reduced or absent deep tendon reflexes suggests a sensory polyneuropathy in a patient with known hypothyroidism. Electrophysiologic tests help to confirm as well as characterize the polyneuropathy. There are no specific clinical or electrophysiologic features that distinguish hypothyroid polyneuropathy from neuropathy due to other causes. In one report, skin biopsy demonstrated a reduction in the intraepidermal nerve fiber density in neurologically asymptomatic patients with overt or subclinical hypothyroidism; the clinical utility of this evaluation is not established".

State and Federal Regulations, as applicable
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 may also be done by local research pathology labs.

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) and the American Academy of Physical Medicine and Rehabilitation (AAPM&R)
A committee of the AAN, AANEM and AAPM&R performed a literature review (England et al., 2009) to evaluate the diagnostic accuracy of IENF density in the detection of small fiber neuropathy. The committee found that: "All of the case control studies showed a significant reduction in IENF density in polyneuropathy patients as compared to controls. The sensitivity of decreased IENF density for the diagnosis of polyneuropathy was moderate to good (range 45 to 90%). The specificity of normal IENF density for the absence of polyneuropathy was very good (range 95 to 97%). Thus, the absence of reduced IENF density (using the clinical impression as the diagnostic reference standard) would not "rule out" polyneuropathy, but the presence of reduced IENF density would importantly raise the likelihood of polyneuropathy." The authors also found that "The sensitivity of IENF density assessment at the ankle for DSP with normal NCS was 58% (20% for subjects with symptoms but no signs of SFSN; 100% for subjects with symptoms and signs of SFSN), 90%, and 24%. In these studies, the specificity of the test ranged from 95% to 97.5%. The other case control study found that among patients with symptoms of SFSN and an abnormal pinprick examination in the feet, but normal ankle reflexes, normal vibration sensibility, and normal NCS, an IENF density of <8 fibers/mm at the dorsal foot provided a sensitivity of 88%, a specificity of 91%, a positive predictive value of 0.9, and a negative predictive value of 0.83 for the diagnosis of SFSN.". The committee concluded that "IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology. Skin biopsy with IENF density assessment is possibly useful to identify DSP which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III)."

Recommendations (England et al., 2009):

- "Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction (Level B)."
- "Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, mononeuropathy multiplex due to vasculitis, or with atypical forms of chronic inflammatory demyelinating polyneuropathy (CIDP). However, the literature is insufficient to provide a recommendation regarding when a nerve biopsy may be useful in the evaluation of DSP (Level U)."
- "Skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of DSP, particularly SFSN (Level C). There is a need for additional prospective studies to define more exact guidelines for the evaluation of polyneuropathy."

The American Academy of Neurology reaffirmed these current guidelines on April 19, 2016 (AAN, 2016).

American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE)

The AACE/ACE (Garber et al., 2015) review of the literature in development of a comprehensive diabetes management algorithm found that skin punch biopsy, a minimally invasive procedure, allows morphometric quantification of intraepidermal nerve fibers. The European Federation of the Neurological Societies and the Peripheral Nerve Society endorse intraepidermal nerve fiber quantification to confirm the clinical diagnosis of SFN with a strong recommendation (EFNS, 2010). Intraepidermal nerve fiber density inversely correlates with both cold and heat detection thresholds (Shun et al., 2004). Intraepidermal nerve fiber density is significantly reduced in symptomatic patients with normal findings from nerve conduction studies and those with metabolic syndrome, IGT, and IFG, suggesting early damage to small nerve fibers(Loseth, Stalberg, Jorde, & Mellgren, 2008; Quattrini et al., 2007). Intraepidermal nerve fiber density is also reduced in painful neuropathy compared with that observed in painless neuropathy(Sorensen, Molyneaux, & Yue, 2006). Diet and exercise intervention in IGT leads to increased intraepidermal nerve fiber density (A. G. Smith et al., 2006). These data suggest that intraepidermal nerve fiber loss is an early feature of the metabolic syndrome, prediabetes, and established DM, and the loss progresses with increasing neuropathic severity. There may be nerve regeneration with treatment.

In 2017 AACE (Vinik et al., 2017) published a position statement on nerve Dysfunction that recommends:

- The presence of silent or overt autonomic neuropathy has dire consequences for the patient with diabetes, particularly if accompanied by peripheral neuropathy.
- All patients with type 2 diabetes should be assessed for both peripheral neuropathy at diagnosis and after 5 years, in type 1 diabetes at diagnosis and thereafter annually.
- Somatic neuropathy can be diagnosed by bedside testing with a 10-gram monofilament and a 128-Hz tuning fork for vibration perception and touch and prickling pain perception and ankle reflexes. This can be complemented by rapid and easily quantified sensory and sudomotor perception.

They found that: “It is a noninvasive objective test, takes a mere 2 minutes, has a sensitivity for diagnosis of neuropathy >75% and a specificity of 95%. These statistics have now been supported in studies by several authors amongst others and provide sensitive and specific diagnostic criteria for somatic neuropathy, which when combined with indices of HRV, provide better predictive value for CVD and mortality than traditional risk factors such as the tried and tested Framingham predictive index.”

European Federation of Neurological Societies/Peripheral Nerve Society

The European Federation of Neurological Societies/Peripheral Nerve Society published guidelines (EFNS, 2010) on the use of skin biopsy in the diagnosis of small fiber neuropathy which recommended that “Distal leg skin biopsy with quantification of the linear density of intraepidermal nerve fibers (IENF), using generally agreed upon counting rules, is a reliable and efficient technique to assess the diagnosis of SFN.” EFNS added that “sweat gland innervation can be examined using an unbiased stereologic technique recently proposed. A reduced IENF density is associated with the risk of developing neuropathic pain, but it does not correlate with its intensity. Serial skin biopsies might be useful for detecting early changes of IENF density, which predict the progression of neuropathy, and to assess degeneration and regeneration of IENF. However, further studies are warranted to confirm the potential usefulness of skin biopsy with measurement of IENF density as an outcome measure in clinical practice and research. Skin biopsy has not so far been useful for identifying the etiology of SFN. Finally, we emphasize that 3-mm skin biopsy at the ankle is a safe procedure based on the experience of 10 laboratories reporting absence of serious side effects in approximately 35,000 biopsies and a mere 0.19% incidence of non-serious side effects in about 15 years of practice.”

American Diabetes Association

In 2017 the American Diabetes Association released a position statement on the early recognition and appropriate treatment of diabetic neuropathies which only mentions intraepidermal nerve fiber density as a measure of small fiber damage and repair in the context of clinical trials(Pop-Busui et al., 2017)

In the 2018 Standards of Medical Care in Diabetes, the ADA recommends that "All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter." (Grade B) Concerning the mode of assessment, they recommend, "Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation (ADA, 2018)." (Grade B). They note the importance of diagnosis since "numerous treatment options exist for symptomatic diabetic neuropathy."

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 88305, 88314, 88341, 88342, 88344, 88346, 88350, 88356

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

1/1/19	New policy developed. BCBSNC will provide coverage for nerve fiber density testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)
10/29/19	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
11/26/19	Specialty Matched Consultant Advisory Panel review 10/16/2019. Coding table removed from Billing/Coding section. (sk)
12/10/19	Reviewed by Avalon 3rd Quarter CAB. No changes to policy. (sk)