MEDICAL POLICY

POLICY TITLE	NERVE FIBER DENSITY MEASUREMENT
POLICY NUMBER	MP-2.238

Original Issue Date (Created):	**5/3/2010**
Most Recent Review Date (Revised):	**6/8/2018**
Effective Date:	**8/1/2018**

I. POLICY

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; 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.

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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Measurement of sweat gland nerve fiber density is **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-references:
MP-2.063 Electromyography and Nerve Conduction Studies
MP-2.098 Quantitative Sensory Testing
MP-2.096 Electromyography (EMG) (Needle and Non-Needle) of the Anal or Urethral Sphincter
MP-2.097 Paraspinal Surface Electromyography to Evaluate and Monitor Back Pain

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MP-2.099 Automated Point of Care Nerve Conduction Tests

II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO- Refer to FEP Medical Policy Manual MP-2.04.58 l, Nerve Fiber Density Testing. The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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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.

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.

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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.

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.

IV. RATIONALE

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For individuals with suspected idiopathic small fiber neuropathy who receive 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 SGNF density measurement, the evidence includes comparisons with control values. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Measurement of SGNF density may lead to an improved understanding of the relation between the loss of sudomotor nerve fibers and symptoms of peripheral neuropathy. However, no studies were identified that evaluated the diagnostic accuracy of SGNF density measurement. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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A-DELTA NERVE FIBERS are small myelinated fibers located in the peripheral sensory nerves that transmit information to the brain related to pain and temperature.

C NERVE FIBERS are small unmyelinated fibers located in the peripheral sensory nerves that transmit information to the brain related to pain, temperature and itch.

EPIDERMAL REFERS to the epidermis, the outermost layer of the skin.

METABOLIC SYNDROME refers to a constellation of conditions that place people at high risk for coronary artery disease. These conditions include type 2 diabetes, obesity, high blood pressure, and a poor lipid profile.

MYELIN IS a layered tissue that sheathes the axons (nerve fibers). This sheath allows efficient conduction of action potentials down the axon.

NEUROPATHY refers to any and all disease or malfunction of the nerves.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®								
11100	11101	88305	88314	88341	88342	88344	88346	88350

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CPT Codes®								
88356								

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ICD-10-CM Diagnosis Codes	Description
G60.9	Hereditary and idiopathic neuropathy, unspecified
G62.9	Polyneuropathy, unspecified

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.238	**CAC 3/30/10** New policy
	CAC 4/26/11 Consensus
	CAC 4/24/12 Adopt BCBSA. Policy statement revised from investigational to medically necessary. Skin biopsy with epidermal nerve fiber density measurement is now considered medically necessary for specific neuropathy-related indications. FEP variation added.
	CAC 6/4/2013 Minor revision. Title changed to Nerve Fiber Density Testing. Measurement of sweat gland nerve fiber density added as investigational. References updated. Administrative code review completed
	CAC 5/20/14 Consensus review. References updated. Rationale added. No changes to the policy statement Codes reviewed.
	1/2015-New 2015 codes added to the policy.
	CAC 7/21/15 Consensus review. No change to policy statements. References and rationale updated**.** Coding reviewed.
	CAC 7/26/16 Consensus review. No change to policy statements. References and rationale updated**.** Codes reviewed.
	Admin Update 11/9/16 Variation Reformatting
	CAC 9/26/17 Consensus review. No changes to the policy statements. Title changed to Nerve Fiber Density Measurement. References reviewed and rationale updated**.** Coding reviewed.
	6/8/18 Consensus review. No changes to the policy statements. Background and rationale revised. References reviewed**.**

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