Nerve Fiber Density Testing

Policy # 00240
Original Effective Date: 10/14/2009
Current Effective Date: 10/11/2021

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 Are 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.

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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

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.

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Skin Biopsy
Skin biopsy is used to assess the density of epidermal (intraepidermal) and sweat gland (sudomotor) nerve fibers using antibodies to a marker found in peripheral nerves. A specific test to assess intraepidermal nerve fiber (IENF) density and sweat gland nerve fiber density using skin biopsy and immunostaining of the tissue have been developed that allow the identification and counting of intraepidermal and sudomotor nerve fibers. Assessment of nerve fiber density typically involves a 3-mm punch biopsy of skin from the calf (and sometimes foot or thigh). After sectioning by microtome, the tissue is immunostained with anti-protein-gene-product 9.5 antibodies and examined with immunohistochemical or immunofluorescent methods. This technique has improved research and contributed greatly to the understanding of small fiber neuropathy. Skin biopsy with measurement of IENF density has also been investigated as an objective measure for the diagnosis of small fiber neuropathy. Sweat gland nerve fiber density can be assessed from the same tissue prepared for IENF density testing provided that the biopsy sample is of sufficient depth. Tissue samples may also be counterstained to identify the boundaries of the sweat glands better.

Treatment
There is no curative treatment for small fiber peripheral neuropathy. Medications may be provided for pain management, and for some etiologies, treatment of the underlying condition (eg, glucose control, intravenous immunoglobulin, or plasma exchange) may be given to reduce the progression of the disease and its symptoms.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. FDA has chosen not to require any regulatory review of this test.

Assessment of IENF and sweat gland nerve fiber density with anti-protein-gene-product 9.5 is commercially available using a biopsy kit, although IENF density measurement (ie, tissue preparation, immunostaining with anti-protein-gene-product 9.5, and counting) may also be done by

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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/Source

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.

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. The 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 fifth 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 (eg, 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. The 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

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management (eg, 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 the 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. The 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, 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 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 intraepidermal nerve fiber density measurement improves clinical outcomes is only now emerging.

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Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists
In 2015, the American Association of Clinical Endocrinologists published guidelines on developing a comprehensive diabetes care plan. The guidelines state, "Painful neuropathies may have no physical signs, and diagnosis may require skin biopsy or other surrogate measures of small-fiber neuropathy (SFN) (Grade D, not evidence-based; BEL 4, no evidence)." The Association referenced the 2010 European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society guidelines on the use of IENF quantification to confirm the clinical diagnosis of small fiber neuropathy (consensus).

American Academy of Neurology et al
In 2009, the practice parameters from the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation concluded that IENF density assessment using protein gene product 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology, and provided a level C (possibly useful) recommendation to consider use of skin biopsy to diagnose the presence of a polyneuropathy, particularly small fiber neuropathy. These guidelines were reaffirmed by AAN in 2013, but were retired by AAN in 2019.

In 2009, the American Association of Neuromuscular Electrodiagnostic Medicine, in conjunction with AAN and American Academy of Physical Medicine and Rehabilitation, published an ordered set of case definitions of "distal symmetrical polyneuropathy" for clinical research ranked by the likelihood of disease. 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 and Peripheral Nerve Society
The EFNS jointly updated its guidelines with Peripheral Nerve Society on the use of skin biopsy in the diagnosis of small fiber neuropathy in 2010. 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

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established laboratories should provide their own values 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 information.

"...Medicare covers, as a physician service, an evaluation (examination and treatment) of the feet no more often than every 6 months for individuals with a documented diagnosis of diabetic sensory neuropathy and loss of protective sensation, as long as the beneficiary has not seen a foot care specialist for some other reason in the interim. Loss of protective sensation shall be diagnosed through sensory testing with the 5.07 monofilament using established guidelines, such as those developed by the National Institute of Diabetes and Digestive and Kidney Diseases guidelines. Five sites should be tested on the plantar surface of each foot, according to the National Institute of Diabetes and Digestive and Kidney Diseases guidelines. The areas must be tested randomly since the loss of protective sensation may be patchy in distribution, and the patient may get clues if the test is done rhythmically. Heavily callused areas should be avoided. As suggested by the American Podiatric Medicine Association, an absence of sensation at 2 or more sites out of 5 tested on either foot when tested with the 5.07 Semmes-Weinstein monofilament must be present and documented to diagnose peripheral neuropathy with loss of protective sensation."

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date

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Ongoing			
NCT04071535	Skin Biopsy in the Diagnosis of Small Fiber Neuropathy in Chinese Patients With Diabetes	100	Jul 2021
NCT02341261	Activity for Diabetic Polyneuropathy: the ADAPT Study	140	Apr 2022
Unpublished			
NCT00780559	Improving Neuropathy and Mobility in Subjects With Early Diabetes	72	Feb 2018
NCT01503892[a]	Metanx Effects on Nerve Fiber Density in Neuropathic Diabetics	100	Oct 2013 (unknown)
NCT01079325[a]	A Phase 2b Repeat Dosing Clinical Trial of SB-509 in Subjects With Moderately Severe Diabetic Neuropathy	170	Apr 2016 (completed)

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

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Policy History

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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.

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01/01/2015	Coding Update
02/02/2015	Coding Update
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. No change to coverage. Title changed.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. No change to coverage.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Title changed to Nerve Fiber Density Testing.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2022

Coding

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

Code Type	Code
CPT	64795, 88314, 88341, 88342, 88344, 88356
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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. Food and Drug Administration (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

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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:

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.

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