FEP Medical Policy Manual

FEP 2.04.58 Nerve Fiber Density Measurement

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2023

Related Policies:

2.01.39 - Quantitative Sensory Testing

Nerve Fiber Density Measurement

Description

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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. This procedure is proposed as an objective measure of small fiber neuropathy by identifying a reduction in the density of nerve fibers.

OBJECTIVE

The objective of this evidence review is to evaluate whether the use of intraepidermal nerve fiber density and sweat gland density measurements in the diagnosis and monitoring of small fiber neuropathy in individuals with suspected idiopathic small fiber neuropathy, an established diagnosis of small fiber neuropathy, or suspected small fiber neuropathy improves the net health outcome.

POLICY STATEMENT

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:

1. Individual presents with symptoms of painful sensory neuropathy; AND
2. There is no history of a disorder known to predispose to painful neuropathy (eg, diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy); AND
3. 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
4. Electromyography and nerve conduction studies are normal and show no evidence of large-fiber neuropathy.

Skin biopsy with epidermal nerve fiber density measurement is **investigational** for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment.

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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 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 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

Summary of Evidence

For individuals with suspected idiopathic small fiber neuropathy who receive intraepidermal nerve fiber (IENF) density measurement, the evidence includes reports assessing whether IENF density measurement is technically reliable, clinically valid, and clinically useful. Relevant outcomes are test accuracy, change in disease status, symptoms, and quality of life. Techniques to measure IENF density have led to an improved understanding of the relation between the loss of small nerve fibers and symptoms of peripheral neuropathy. The literature has also indicated that low IENF density may provide supportive evidence of a lesion in the peripheral somatosensory system. For example, there is a significant decrease in average IENF density in patients diagnosed with small fiber neuropathy compared with controls, and an IENF density of 4 to 8 per mm in the calf is near the 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 an 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 (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 that the technology results in an improvement in the net health outcome.

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association of Clinical Endocrinologists

In 2015, the American Association of Clinical Endocrinologists published guidelines on developing a comprehensive diabetes care plan.[4,] 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).[17,]

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.[1,]These guidelines were reaffirmed by AAN in 2013, but were retired by AAN in 2019.[18,]

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.[19,] 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 European Federation of Neurological Societies (EFNS) jointly updated its guidelines with Peripheral Nerve Society on the use of skin biopsy in the diagnosis of small fiber neuropathy in 2010.[17,] The guidelines stated that IENF density is a reliable and efficient technique to assess the diagnosis of small fiber neuropathy (recommendation level A). Normative reference values are available for bright-field immunohistochemistry (recommendation level A) but not for confocal immunofluorescence. The guidelines recommended that newly established laboratories should provide their own 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 or sweat gland nerve fiber density measurement testing. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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[20,]

"...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."

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through September 19, 2022; no references added. Policy statements unchanged. FEP Benefit changes, new policy.