Anthem

Clinical UM Guideline

Subject: Skin Nerve Fiber Density Testing
Guideline #: CG-LAB-13
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Description

This document addresses the pathological analysis from skin biopsy specimens of intra-epidermal nerve fiber (IENF) density for the diagnosis of small-fiber neuropathy (SFN). This document also addresses the pathological analysis of sweat gland nerve fiber density for the diagnosis of SFN. The assessment of nerve fibers is a component of evaluating peripheral nerve disease. Most nerve disease targets the small nerve fibers, (as opposed to large nerve fibers).

Clinical Indications

Medically Necessary:

Pathological analysis of intra-epidermal nerve fiber density for the diagnosis of small-fiber neuropathy is considered **medically necessary** when **both** of the following conditions are met:

A. Individual presents with painful sensory neuropathy; **and**
B. No evidence of large-fiber neuropathy is present on the following:
    1. Physical examination (for example, reduced or absent muscle-stretch reflexes or reduced proprioception and vibration sensation); **and**
    2. Electromyography and nerve-conduction studies.

Not Medically Necessary:

Pathological analysis of intra-epidermal nerve fiber density for the diagnosis of small-fiber neuropathy is considered **not medically necessary** in all other cases.

Pathological analysis of sweat gland nerve fiber density testing for the diagnosis of small-fiber neuropathy is considered **not medically necessary** for all indications.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
88356	Morphometric analysis; nerve [when specified as analysis of intra-epidermal nerve fiber density]
88399	Unlisted surgical pathology procedure [when specified as analysis of intra-epidermal nerve fiber density]

ICD-10 Diagnosis	
E08.40-E08.49	Diabetes mellitus due to underlying condition with neurological complications
E09.40-E09.49	Drug or chemical induced diabetes mellitus with neurological complications
E10.40-E10.49	Type 1 diabetes mellitus with neurological complications
E11.40-E11.49	Type 2 diabetes mellitus with neurological complications
E13.40-E13.49	Other specified diabetes mellitus with neurological complications
G56.90-G56.93	Unspecified mononeuropathy of upper limbs
G57.90-G57.93	Unspecified mononeuropathy of lower limbs
G58.9	Mononeuropathy, unspecified
G60.0-G60.9	Hereditary and idiopathic neuropathy [no specific diagnosis code for small fiber neuropathy]
G62.0-G62.9	Other and unspecified polyneuropathies
G63	Polyneuropathy in diseases classified elsewhere
G64	Other disorders of peripheral nervous system
G90.01-G90.09	Idiopathic peripheral autonomic neuropathy
G90.50-G90.59	Complex regional pain syndrome I (reflex sympathetic dystrophy)
G90.8	Other disorders of autonomic nervous system
G90.9	Disorder of the autonomic nervous system, unspecified
M79.2	Neuralgia and neuritis, unspecified

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, or when the code describes a procedure, such as analysis of sweat gland nerve fiber density, designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

Neuropathy is an abnormal and usually degenerative state of the nervous system or nerves. Typically, it affects the lower extremities. It can affect one nerve or many nerves. The form of neuropathy can be broken down by the size of the fiber involvement (that is, small-fiber or large-fiber neuropathy). Small nerve fibers are those near the surface of the skin and the symptoms deal with sensation. The small nerve fibers within the epidermis generally assist with perception of hot and cold sensation, as well as pain. In addition, small autonomic fibers assist with control of sweating and blood vessel tone. SFN is among the least understood of all neuropathies,

primarily because standard diagnostic tests for neuropathy, such as electromyography (EMG) and nerve conduction studies (NCS) are usually normal in this group of individuals. The test involves a 3 mm punch biopsy of skin from the leg performed under local anesthesia. The tissue is stained with PGP 9.5 antibodies and examined. The staining allows the IENF to be identified and counted. A deeper biopsy (6-8 mm) may be required for the sweat glands. SFN is identified when there is a reduction of the IENF density.

SFN generally presents as a painful neuropathy that may rarely become disabling. Symptoms suggestive of this condition may include pain (burning, tingling, shooting, or prickling in character), paresthesia, sheet intolerance, or restless legs syndrome. Symptoms of autonomic dysfunction may include altered sweating, diarrhea or constipation, urinary incontinence or retention, gastroparesis, sicca syndrome, blurry vision, facial flushes, orthostatic hypotension, or sexual dysfunction. Leading causes of SFN include diabetes, alcohol abuse, human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), certain neurotoxins, various genetic diseases, as well as an idiopathic form.

If SFN is secondary to another condition, then treatment appropriate for that condition should be administered. In addition, treatment of SFN itself is usually based on symptoms, and may include tricyclic antidepressants, anticonvulsants, opioid medications, or local anesthetics applied to the painful areas. Nonpharmacologic treatment may include cool soaks, heat, massage, skin moisturizers, elevation or lowering of the limbs, exercise, spinal cord stimulation, intrathecal morphine, or transcutaneous electrical nerve stimulation.

There are challenges involved in quantifying sweat gland nerve fibers, including the complex 3-D structure of individual sweat glands, the variable number and size of sweat glands in different tissue segments and the lack of a “Gold standard” technique.

Comprehensive information about the natural history of SFN is scarce. Some individuals may evolve to a large-fiber sensory neuropathy, while spontaneous remission also may occur. One review suggested that about one-third of individuals experienced continuous symptoms, another one-third had intermittent symptoms, and the remaining one-third had a monophasic course with symptom resolution after months or years (Hoitsma, 2004).

In a 2005 study of 30 individuals with neuropathy including SFN and diabetic neuropathy and 22 healthy controls, the number of small nerve fibers per epidermal area and per epidermal length was significantly reduced in individuals with SFN or diabetic neuropathy versus individuals in the control group (Koskinen, 2005). There was good correlation between area and length measurements, and between two different pathologists who counted the specimens. Overall, this study showed a sensitivity of 90% and specificity of 95% for the diagnosis of SFN or diabetic neuropathy. In a population with a similar distribution of individuals with and without neuropathy, the positive predictive value was therefore estimated to be 95% and the negative predictive value 91%. In addition, diagnosis in this study would obviate the need for the more traditional sural nerve biopsy, which is often painful and can produce permanent residual paresthesias (Koskinen, 2005). In another study of individuals with and without diabetic neuropathy, IENF density was not reduced until after the first 5 years following the diagnosis of diabetes (Pittenger, 2004). These and other researchers raised some doubt as to the ability of the stain, protein-gene-product (PGP) 9.5, to completely stain all epidermal nerve fibers, especially under conditions of neuropathy.

In 2013, Boruchow and colleagues reported on a retrospective chart review in which they looked at the role of skin biopsy in the evaluation and management of individuals with suspected SFN. A total of 69 individuals underwent skin biopsy. Twenty-five of those individuals had pathological evidence of an SFN and 9 individuals had evidence of borderline SFN. A change in treatment plan or diagnosis occurred in 14 out of 25 individuals with SFN. Of the 9 individuals with borderline SFN, 6 had a change in treatment plan or diagnosis.

There is a paucity of evidence in the peer-reviewed literature that diagnosis of SFN by skin biopsy significantly alters treatment outcomes. Treatment of SFN is generally symptomatic, and the long-term course of this disease, with or without treatment, is still poorly understood (Mendell, 2003).

The consensus opinion from neurologists and pain specialists suggests that many individuals with chronic pain syndromes often travel from specialist to specialist in search of both relief and answers. The pain management literature is replete with examples of the importance of establishing a diagnosis whenever possible. Individuals with chronic pain often seek out and utilize multiple healthcare services and therapies, while remaining frustrated and concerned as their chronic pain persists. In one study of 62 adults under chronic pain management, regression analysis revealed that the strongest unique predictors of treatment satisfaction involved the individual feeling that his or her evaluation was complete, that he or she had received an explanation for clinic procedures, and that treatment helped improve his or her daily activity (McCracken, 2002). In another study, assessment of individuals attending a pain clinic revealed that the explanation of the etiology of their pain problem is as important as the cure or relief of their pain (Petrie, 2005).

Consequently, in view of the under-recognized prevalence of SFN, it is plausible to consider that attaching a specific diagnosis to individuals with this condition may promote both increased satisfaction, as well as greater adherence to continuity of care with a specific provider and pain control protocol. This, in turn, may lead to enhanced clinical outcomes. Until additional, larger, well-designed studies are available, pathological analysis of IENF is limited to the diagnosis of SFN for selected individuals when medically necessary criteria are met.

In 2010, the European Federation of Neurological Societies updated their guidelines for neuropathic pain assessment. Their recommendations are that skin biopsy should be performed in those individuals with painful or burning feet of unknown origin and a clinical impression of small fiber dysfunction.

Gibbons and colleagues (2009) reported on a new test to quantify the sweat gland nerve fiber density using the same tissue which was prepared for IENF density testing. A total of 94 subjects (30 diabetic and 64 healthy controls) had punch skin biopsies in the distal leg, distal thigh and proximal thigh. Participants were assessed using three systems; the Neuropathy Impairment Score in the Lower Limb system, the Michigan Diabetic Neuropathy Score and the Toronto Clinical Scoring System. For the diabetic participants, the sweat gland nerve fiber density at the distal leg was 20.8, 28.2 at the distal thigh and 42.5 at the proximal thigh. In the control group, distal leg showed 40.8, distal thigh was 28.2 and proximal thigh was 51.3. Density of the sweat gland nerve fibers at the distal leg of diabetic participants decreased as the Neuropathy Impairment Score in the Lower Limbs worsened. While the results showed that sweat gland nerve density fibers can be quantified by skin punch biopsies, there is currently no standardized methodology, and further studies are required with larger participant groups and outcomes data.

Definitions

Small-fiber neuropathy (SFN): A disease characterized by diminished nerve fiber density in the epidermis (outer layer) of the skin, resulting in painful symptoms, usually in the extremities, which may rarely become disabling. It may occur either independently or as the result of another disease, such as diabetes or alcohol abuse.

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Websites for Additional Information

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References and Websites for Additional Information sections.
Revised	11/10/2022	MPTAC review. The MN criteria for analysis of intra-epidermal nerve fiber density have been reformatted with no changes. References were updated.
Reviewed	11/11/2021	MPTAC review. References were updated.
Reviewed	11/05/2020	MPTAC review. References were updated. Reformatted Coding section.
Reviewed	11/07/2019	MPTAC review. References were updated.

Reviewed	01/24/2019	MPTAC review. References were updated.
New	03/22/2018	MPTAC review. Moved content of LAB.00020 Skin Nerve Fiber Density Testing to new clinical utilization management guideline document with the same title. The References section was updated.
