BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Nerve Fiber Density Measurement

Policy #: 392
Latest Review Date: December 2024
Category: Medicine

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the individual's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the individual's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the individual's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small fiber neuropathy** as a **covered** benefit 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 (e.g., 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.

Blue Advantage will treat **skin biopsy with epidermal nerve fiber density measurement as a non-covered benefit** and as **investigational** for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment**.**

Blue Advantage will treat **measurement of sweat gland nerve fiber density** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

Peripheral Neuropathy

Most individuals with peripheral neuropathy exhibit evidence of large fiber involvement, characterized by numbness, tingling, loss of deep tendon reflexes, and abnormal electrophysiological studies. In contrast, damage to small fibers is not detected by routine nerve conduction studies. Individuals 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 individuals with diabetic neuropathy but may also be found in individuals with impaired glucose tolerance, severe hypertriglyceridemia, metabolic syndrome, human immunodeficiency virus (HIV) infection, and toxic neuropathy from antiretroviral drugs. For many individuals, 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 electrophysiological studies. The disparity between subjective complaints and objective signs increases the difficulty of diagnosis. In addition, conditions other than nerve fiber damage, including venous insufficiency, spinal stenosis, myelopathy, and psychosomatic disturbances may mimic small fiber neuropathy.

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 (SGNF) 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. SGNF density can be assessed from the same tissue that has been prepared for IENF density testing, provided that the biopsy sample is of sufficient depth. Tissue samples may also be counterstained to better identify the boundaries of the sweat glands.

Treatment
There is no treatment to cure 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.

KEY POINTS:
Literature searches using the PubMed database have been performed through November 25, 2024.

Summary of Evidence
For individuals with suspected idiopathic small fiber neuropathy who receive intraepidermal nerve fiber (IENF) density testing, the evidence includes reports on technical reliability, diagnostic accuracy, and the effect on health outcomes. 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 also indicates 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 individuals 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 (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 be helpful for the diagnosis of 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 established small fiber neuropathy who receive repeated IENF density testing, 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 that assess the efficacy of activity and medications on small fiber neuropathy. If successful, there might be a potential role for repeated IENF density measurements to result in a change in management such as 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 individuals 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 sweat gland nerve fiber (SGNF) density testing, 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.

Practice Guidelines and Position Statements
American Association of Clinical Endocrinologists
The American Association of Clinical Endocrinologists (AACE) published 2015 guidelines for clinical practice for developing a diabetes mellitus comprehensive 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 AACE references the (2010) European Federation of Neurological Societies’ guidelines on the use of IENF quantification to confirm the clinical diagnosis of small fiber neuropathy (consensus).

In 2022, the AACE published updated clinical practice guidelines on developing a diabetes mellitus comprehensive care plan. The guidelines state that "skin biopsy and/or standardized

quantitative sensory testing are sensitive tests for small-fiber neuropathy and should be considered if the clinical features are atypical and a different etiology is suspected."

American Academy of Neurology et al
The 2009 practice parameters from the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPMR) concluded that IENF density assessment using PGP 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. This guideline was reaffirmed by the AAN in 2013.

In 2009, AANEM, in conjunction with AAN and AAPMR, 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 include 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.

U.S. Preventive Services Task Force Recommendations
Nerve fiber density testing is not a preventive service.

KEY WORDS:
Epidermal nerve fiber density, intraepidermal nerve fiber density, IENF, painful small fiber neuropathy, small fiber neuropathy, TheraPath, Nerve Fiber Density, Sweat Gland, sudomotor nerve fibers, sweat gland nerve fiber, SGNF, sweat gland nerve fiber density

APPROVED BY GOVERNING BODIES:
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). These tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA 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 local research pathology labs may also do IENF density measurement (i.e., tissue preparation, immunostaining with anti-protein-gene-product 9.5, and counting). Some laboratories that offer IENF density testing include Therapath Neuropathology, Advanced Laboratory Services, Mayo Medical Laboratories, Corinthian Reference Lab, and Bako Integrated Physician Solutions.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:
There is not a specific code for this analysis. Claims should be billed with the following code:

CPT Codes:

88399	Unlisted surgical pathology procedure

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POLICY HISTORY:

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Medical Policy Group, September 2010
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Medical Policy Group, December 2013
Medical Policy Group, October 2014
Medical Policy Group, December 2015
Medical Policy Group, December 2016
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Medical Policy Group, January 2019
Medical Policy Group, January 2020
Medical Policy Group, January 2021
Medical Policy Group, December 2021
Medical Policy Group, December 2022
Medical Policy Group, December 2023
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, December 2024
UM Committee January 2025: Annual review of policy approved by UM Committee for use for Blue Advantage business.
