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 being investigated as an objective measure of small fiber neuropathy by identifying a reduction in the density of nerve fibers.

Background

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. 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.

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 has been developed that allows 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.

Regulatory Status

Assessment of intraepidermal nerve fiber and sweat gland nerve fiber density with PGP 9.5 is commercially available with a biopsy kit, although IENF density measurement (i.e., tissue preparation, immunostaining with PGP 9.5, and counting) may also be done by local pathology labs. Some laboratories who offer IENF density testing include Therapath Neuropathology, Advanced Laboratory Services, Mayo Medical Laboratories, Corinthian Reference Lab, and Bako Integrated Physician Solutions.
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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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Intraepidermal Nerve Fiber Density when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Intraepidermal Nerve Fiber Density is covered

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 (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.

When Intraepidermal Nerve Fiber Density is not covered

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

Measurement of sweat gland nerve fiber density is considered investigational.

Policy Guidelines

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
Nerve Fiber Density Testing

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 that 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 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 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 sweat gland nerve fiber (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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: There is no specific code for this service. Multiple CPT pathology codes would be used to submit this analysis. They are 88305, 88314, 88341, 88342, 88344, and 88356. CPT 11104 would be submitted by the provider obtaining the pathology specimen for service provided 1/1/2019 and after. CPT 11100 was deleted 12/31/2018.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Intraepidermal Nerve Fiber Density

Senior Medical Director - 11/2009
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Specialty Matched Consultant Advisory Panel – 10/2018

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>2/2/10</td>
<td>New policy implemented. Reviewed with Senior Medical Director 11/9/09. &quot;Skin biopsy with epidermal nerve fiber density measurement is considered investigational. BCBSNC does not provide coverage for investigational services.&quot; Notice given 2/2/2010. Policy effective date 5/11/2010. (btw)</td>
</tr>
<tr>
<td>6/22/10</td>
<td>Policy Number(s) removed (amw)</td>
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<tr>
<td>12/20/11</td>
<td>Specialty Matched Consultant Advisory Panel review 11/30/2011. “Description” section revised. Policy statement changed from investigational to “BCBSNC will provide coverage for Intraepidermal Nerve Fiber Density when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.” The “When Covered” section updated to indicate; “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.</td>
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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.” The “When Not Covered” section updated to indicate; “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.” References added. (btw)

11/13/12 Minor revisions in the Description section. The When Not Covered statement revised from “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.” to “Skin biopsy with epidermal nerve fiber density measurement is considered investigational for all other clinical situations not specified above, including, but not limited to, the monitoring of disease progression or response to treatment.” for clarification. No change to policy intent. Policy Guidelines updated. Specialty Matched Consultant Advisory Panel review 10/17/12. (btw)


12/31/13 Specialty Matched Consultant Advisory Panel review 10/16/13. No change to policy intent. Added new 2014 CPT code, 88343 to Billing/Coding section. Reference added. (btw)


1/26/16 Reference added. Policy Guidelines updated. (sk)

11/22/16 Specialty Matched Consultant Advisory Panel review 10/26/16. (sk)

1/27/17 Reference added. Policy Guidelines updated. (sk)


1/1/19 Specialty Matched Consultant Advisory Panel review 10/24/2018. Code 11104 added and code 11100 deleted from Billing/Coding section. (sk)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment
Nerve Fiber Density Testing

and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.