Clinical Policy Title: Epidermal nerve fiber density testing

Clinical Policy Number: CCP.1263

Effective Date: January 1, 2017
Initial Review Date: October 19, 2016
Most Recent Review Date: October 2, 2018
Next Review Date: October 2019

Policy contains:
- Epidermal nerve fiber density testing.
- Skin punch biopsy.
- Small fiber neuropathy.

Related policies:

CCP.1005 Autonomic nervous system monitoring for neuropathy
CCP.1081 Electrodiagnostic studies — electromyography and nerve conduction studies
CCP.1033 Somatosensory evoked potentials test

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of epidermal nerve fiber density testing by skin biopsy to be clinically proven and, therefore, medically necessary for the detection of small fiber neuropathy when all of the following criteria are met (Lauria, 2010; England, 2009):

- Member presents with symptoms of painful sensory neuropathy.
- Member has no history of a disorder known to predispose to painful neuropathy (e.g., diabetic neuropathy).
- No evidence of large-fiber neuropathy on both:
  - Physical examination (e.g., reduced or absent muscle-stretch reflexes or reduced proprioception and vibration sensation).
  - Electromyography and nerve-conduction studies.

Limitations:
All other uses of epidermal nerve fiber density testing are not medically necessary, because their clinical utility has not been established, including (Lauria, 2010):

- Monitoring disease progression or response to treatment.
- Distinguishing causes of peripheral neuropathy.
- Evaluating preclinical neuropathy in persons with known disease and mixed neuropathy status.
- Evaluation of disease severity.

**Alternative covered services:**

- Neurologic consultation.
- Screening for other treatable causes of small fiber neuropathy.
- Functional tests e.g., quantitative sensory testing.
- Autonomic testing.
- Nerve conduction testing.
- Somatosensory evoked potentials.
- Nerve biopsy.

**Background**

Small fiber neuropathy, also known as small-fiber sensory/peripheral neuropathy, is a peripheral nerve disease that selectively affects small diameter myelinated and non-myelinated nerve fibers (Hovaguimian, 2011). Sensory symptoms of small fiber neuropathy vary widely in pattern and severity, ranging from a normal or near-normal physical and neurologic examination to paresthesia, dysesthesia, and insensitivity to pain, and autonomic and enteric dysfunction. There is no treatment to cure small fiber neuropathy. Medications may be provided for pain management, and for some etiologies, treatment of the underlying condition may reduce progression of the disease and its symptoms.

Small fiber neuropathy occurs most commonly in middle-aged and older persons, but the actual prevalence is unknown (Genetics Home Reference, 2016). Etiologies associated with small fiber neuropathy include genetic mutations in the SCN9A or SCN10A gene, diabetes, impaired glucose tolerance, several hereditary disorders, certain autoimmune disorders, viral and infectious diseases (e.g., human immunodeficiency virus infection), neurotoxic medications, and alcoholism) (Genetics Home Reference, 2016; Hovaguimian, 2011). In up to 50 percent of individuals with small fiber neuropathy, the etiology is idiopathic.

There is no clinically established reference standard for diagnosing or verifying small fiber neuropathy. It is a diagnosis of exclusion based on clinical findings and the absence of large fiber involvement, particularly in the context of an associated disease, such as diabetes. Ancillary testing and specialty consultation may provide additional guidance. Testing includes screening for other treatable causes of small fiber neuropathy, scoring examinations, and characterizing specific types of pain and genetic
testing. Electromyography and nerve conduction studies assess possible larger myelinated sensory and motor fiber involvement (Hovaguimian, 2011). Nerve biopsy may be indicated when a vasculitic pathogenesis is suspected, and detailed neuropathological examination of mixed or large-fiber neuropathy is needed (Lauria, 2007). However, few objective methods identify and quantify small fiber neuropathy.

**Epidermal nerve fiber density testing:**

Epidermal nerve fiber density testing, also called intra-epidermal nerve fiber density testing, assesses the structural integrity of small nerve fibers using skin biopsy and immunostaining (Meyers, 2013; Hovaguimian, 2011). It quantifies the intra-epidermal nerve fibers crossing the epidermis, and results are expressed as the number of intra-epidermal nerve fibers per millimeter. Epidermal nerve fiber density testing is regulated under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a).

Two methods are available to sample the epidermis—3-mm punch biopsy with immunohistochemistry or immunofluorescence and the blistering method. The blistering method uses a suction capsule that creates a blister to separate the epidermis from the dermis. While less invasive than punch biopsy, it does not provide information on the morphology of intra-epidermal nerve fibers, which limits its clinical use (Lauria, 2007).

Normative values vary depending on sampling site, quantification technique, and patient age and gender. Laboratories may use established normative values or develop their own methods for determining reference ranges and cutoff values (Lauria, 2007).

Epidermal nerve fiber density below a normal reference range suggests peripheral neuropathy, raising the suspicion of disorders known to cause small fiber neuropathy such as diabetes, impaired glucose tolerance and certain autoimmune diseases. Epidermal nerve fiber density within the normal range suggests the need to test for etiologies other than those known to produce peripheral neuropathy. In addition, epidermal nerve fiber density testing may be used assess morphological changes of intra-epidermal nerve fibers and dermal nerve fibers (Meyers, 2013; Hovaguimian, 2011; Lauria, 2007).

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.
We conducted searches on August 15, 2018. Search terms were: “Nerve Fibers/classification (MeSH),” “Nerve Fibers/diagnosis (MeSH),” “Nerve Fibers/innervation (MeSH),” “Epidermis (MeSH),” and the free text term “epidermal nerve fiber density.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We identified two evidence-based guidelines (Lauria, 2010; England, 2009), six individual studies (Timar, 2016; Shikuma, 2015; Caro, 2014; Grone, 2014; Kim, 2014; Kosmidis, 2014), and no economic studies for this policy. The best available evidence for epidermal nerve fiber density testing consists of case-control and cross-sectional studies of patients with clinical sensory neuropathy referred to neurology specialty clinics compared to healthy controls. The remaining studies were of insufficient quality and quantity to assess the ability of epidermal nerve fiber density testing to detect preclinical neuropathy in persons with known disease and mixed neuropathy status, disease severity, or response to treatment. No studies have assessed the ability of epidermal nerve fiber density testing to distinguish disease etiology, change clinical management (particularly in the presence of known causes of neuropathy such as diabetes), or improve patient outcomes.

Epidermal nerve fiber density with skin punch biopsy using bright-field immunohistochemistry is a safe procedure with no major complications, for which normative data exist to characterize findings as normal or abnormal. Epidermal nerve fiber density testing has a high diagnostic yield (in this case, equivalent to sensitivity) for identifying pathologic changes in unmyelinated small nerve fibers. Presently, the true value of epidermal nerve fiber density for diagnosing sensory neuropathy depends on its ability to distinguish patients with small fiber neuropathy from patients whose symptoms are unrelated to neuropathy. Therefore, there is sufficient evidence to support using epidermal nerve fiber density testing to rule out non-neuropathic involvement in patients with symptoms that suggest small fiber neuropathy who have no evidence of large fiber neuropathy and no disorder known to predispose to painful neuropathy.

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1 I.e., the probability that epidermal nerve fiber density will be abnormal in a particular population. A high diagnostic yield would limit the number of patients in whom underlying causes other than peripheral neuropathy need to be investigated. It may or may not provide useful prognostic information beyond that obtained from basic clinical measurements.
**Policy updates:**

In 2017, we identified no new information for the policy, and no policy changes are warranted.

In 2018, we identified no new information to add to the policy, and no policy changes are warranted.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Lauria (2010) for the European Federation of Neurological Societies and the Peripheral Nerve Society Guideline: skin biopsy in the diagnosis of small fiber neuropathy | Key points:  
- Distal leg skin biopsy with quantification of epidermal nerve fibers, using generally agreed upon counting rules, is a reliable and efficient technique to assess small fiber neuropathy (Recommendation Level A).  
- Normative reference values are available for bright-field immunohistochemistry (Recommendation Level A) but not for confocal immunofluorescence or blister technique.  
- The morphometric analysis of epidermal nerve fiber density should always refer to age-matched normative values (Recommendation Level A).  
- Further study needed to confirm the usefulness of (Recommendation Level C):  
  - Quantifying sub-epidermal nerve fibers and autonomic innervated structures.  
  - Serial skin biopsies.  
- A reduced epidermal nerve fiber density is associated with the risk of developing neuropathic pain (Recommendation Level B), but not pain intensity.  
- Skin biopsy cannot identify the etiology of small fiber neuropathy.  
- Skin punch biopsy at the ankle is safe. |
| England (2009) for the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation Evidence review and guideline: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy | Key points:  
- Skin biopsy is a validated technique for determining epidermal nerve fiber density.  
- For symptomatic patients with suspected polyneuropathy, consider skin biopsy to diagnose the presence of a polyneuropathy, particularly small fiber neuropathy. (Level C).  
- Knowledge gaps:  
  - Studies using controls that include other diseases with lower extremity pain or sensory complaints and a predetermined independent reference standard.  
  - Diagnostic accuracy of morphologic changes small fiber neuropathy vs. healthy controls and disease controls.  
  - Serial epidermal nerve fiber density measurement.  
  - Other uses for skin biopsy detection or monitoring (e.g., leprosy, hereditary amyloidosis, vasculitic neuropathy, and Fabry disease, immune-mediated neuropathies, Charcot-Marie-Tooth, and related diseases). |

**References**
Professional society guidelines/other:


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

160.23 Sensory Nerve Conduction Threshold Tests (sNCTs).

70.2.1 Services Provided for the Diagnosis and Treatment of Diabetic Sensory Neuropathy with Loss of Protective Sensation (aka Diabetic Peripheral Neuropathy).

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
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<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
<td>11100</td>
<td>Biopsy of skin, subcutaneous tissue and/or mucous membrane (including simple closure), unless specified, one lesion</td>
<td></td>
</tr>
<tr>
<td>88305</td>
<td>Level IV, surgical pathology, gross and microscopic examination</td>
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<tr>
<td>+88314</td>
<td>Histochemical stain on frozen tissue block</td>
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<tr>
<td>+88341</td>
<td>Each additional single antibody stain procedure</td>
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<tr>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure</td>
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</tr>
<tr>
<td>88356</td>
<td>Morphometric analysis; nerve</td>
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<tr>
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<td>G60.0</td>
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<td>G60.8</td>
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<td>G62.9</td>
<td>Peripheral neuropathy</td>
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