Clinical Policy Title: Epidermal nerve fiber density testing

Clinical Policy Number: 09.01.12

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

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

Related policies:
- CP# 09.01.01 Autonomic nervous system monitoring for neuropathy
- CP# 09.01.04 Electrodiagnostic studies — electromyography and nerve conduction studies
- CP# 09.01.10 Somatosensory evoked potentials (SEPs or SSEPs) test

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’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 Keystone First 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. Keystone First’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. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the use of epidermal nerve fiber density (ENFD) testing by skin biopsy to be clinically proven and, therefore, medically necessary for the detection of small fiber neuropathy (SFN) when all of the following criteria are met:

- 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 ENFD testing are not medically necessary because their clinical utility has not been established, including:
  o Monitoring disease progression or response to treatment.
  o Distinguishing causes of peripheral neuropathy.
  o Evaluating preclinical neuropathy in persons with known disease and mixed neuropathy status.
  o Evaluation of disease severity.

**Alternative covered services:**

• Neurologic consultation.
• Screening for other treatable causes of SFN.
• Functional tests e.g., quantitative sensory testing (QST).
• Autonomic testing.
• Nerve conduction testing.
• SEPs.
• Nerve biopsy.

**Background**

SFN, 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 SFN vary widely in pattern and severity, ranging from a normal or near-normal physical and neurologic examination to paresthesias, dysesthesias and insensitivity to pain. Symptoms of SFN typically begin in the feet or hands and spread to other regions with disease progression. In other patients, the presentation is more sporadic and may affect many nerves. SFN may result in autonomic and enteric dysfunction (Hovaguimian 2011).

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

Presently, there is no clinically established reference standard for diagnosing SFN and no reference standard for verification. SFN 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. Conditions that mimic SFN and the disparity in subjective complaints and objective signs increase the difficulty of diagnosis. There is no treatment to cure SFN. 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 (Hovaguimian 2011).

When the diagnosis is less clear, ancillary testing and specialty consultation may provide additional guidance. Testing includes screening for other treatable causes of SFN, 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 SFN.

**ENFD testing:**

ENFD testing, also called intra-epidermal nerve fiber density (IENFD) testing assesses the structural integrity of small nerve fibers using skin biopsy and immunostaining (Meyers 2013, Hovaguimian 2011). Two methods are available to sample the epidermis. Assessment of ENFD typically involves a 3-mm punch biopsy of skin from the distal end of the leg (or area of interest). After sectioning the punch biopsy by microtome, the tissue is immunostained with anti-protein-gene-product 9.5 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods. 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 IENFs, which limits its use in clinical practice (Lauria 2007). ENFD testing is regulated under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a).

ENFD testing quantifies the IENFs crossing the epidermis, and results are expressed as the number of IENFs per millimeter. Normative values vary depending on sampling site, quantification technique, and patient age and gender. For distal leg samples using bright-field immunohistochemistry, normative values (mean ± SD) range from 13.8 ± 6.7 IENFs per millimeter to 9.8 ± 3.6 IENFs per millimeter (Lauria 2010). Laboratories may use established normative values or develop their own methods for determining reference ranges and cutoff values (Lauria 2007).

ENFD below a normal reference range suggests peripheral neuropathy, raising the suspicion of disorders known to cause SFN such as diabetes, IGT and certain autoimmune diseases. ENFD within the normal range suggests the need to test for etiologies other than those known to produce peripheral neuropathy. In addition, ENFD testing may be used assess morphological changes of IENFs and dermal nerve fibers (Meyers 2013, Hovaguimian 2011, Lauria 2007).

**Searches**

Keystone First searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
We conducted searches on August 17, 2016. Search terms were: "Nerve Fibers/classification"(MeSH), "Nerve Fibers/diagnosis"(MeSH), "Nerve Fibers/innervation"(MeSH), and "Epidermis"(MeSH).

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 one comprehensive systematic review (Hayes 2010, last updated in 2015), two evidence-based guidelines (Lauria 2010, England 2009), six individual studies published since the systematic review (Caro 2014, Grone 2014, Kim 2014, Kosmidis 2014, Shikuma 2015, Timar 2016), and no economic studies for this policy. The best available evidence for ENFD 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 ENFD testing to detect preclinical neuropathy in persons with known disease and mixed neuropathy status, disease severity, and response to treatment. No studies have assessed the ability of ENFD testing to distinguish disease etiology, change clinical management (particularly in the presence of known causes of neuropathy such as diabetes), or improve patient outcomes.

ENFD 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. ENFD testing has a high diagnostic yield (in this case, equivalent to sensitivity) for identifying pathologic changes in unmyelinated SNFs. Presently, the true value of ENFD for diagnosing sensory neuropathy depends on its ability to distinguish patients with SFN from patients whose symptoms are unrelated to neuropathy. Therefore, there is sufficient evidence to support using ENFD testing to rule out non-neuropathic involvement in patients with symptoms that suggest SFN who have no evidence of large fiber neuropathy and no disorder known to predispose to painful neuropathy.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Hayes (2010, last updated 2014)</td>
<td><strong>Key points:</strong></td>
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<td>--------------------------------</td>
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<tr>
<td>Diagnostic performance of ENFD testing</td>
<td>- Systematic review of 13 cross-sectional or case-control studies.</td>
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<td>- Overall quality: Low-to-moderate. Healthy controls only. No study included patients with conditions causing lower extremity pain or sensory complaints that might be confused with polyneuropathy (potential spectrum bias).</td>
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<td>- ENFD has modest to high diagnostic yield for ruling out non-neuropathic disease in patients with clinical sensory neuropathy referred to neurology specialty clinics (eight studies with 20 to 210 patients each). Greater pre-test probability of small or large fiber pathology improves diagnostic yield.</td>
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<td>- ENFD can identify preclinical SFN in the presence of a disease known to cause sensory neuropathy (five studies with 29 to 101 patients each). Diagnoses included diabetes, HIV infection or sarcoidosis.</td>
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<td>- ENFD is more likely than QST to detect SNF pathology.</td>
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|                                      | - Inconclusive evidence for:  
  - Identification of etiology, changes in clinical management, or improvement in neuropathic symptoms.  
  - Morphological changes as prognosis of future ENFD loss.  
- Low complication rate associated with skin biopsy, generally suturing not required. |
|                                      | - Update included six controlled comparative studies, three case series, one pilot study, one prospective pilot study, and one retrospective review. New clinical applications identified: diagnosing complex regional pain syndrome, epidermal nerve fiber length density estimation using global spatial sampling, patients with prurigo nodularis. No changes to earlier findings. |

<table>
<thead>
<tr>
<th>Lauria (2010) for the European Federation of Neurological Societies and the Peripheral Nerve Society Guideline</th>
<th><strong>Key points:</strong></th>
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<td></td>
<td>- Distal leg skin biopsy with quantification of ENFs, using generally agreed upon counting rules, is a reliable and efficient technique to assess SFN (Recommendation Level A).</td>
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<td>- Normative reference values are available for bright-field immunohistochemistry (Recommendation Level A) but not for confocal immunofluorescence or blister technique.</td>
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<td>- The morphometric analysis of ENFD should always refer to age-matched normative values (Recommendation Level A).</td>
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|                                                            | - 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 ENFD is associated with the risk of developing neuropathic pain (Recommendation Level B), but not pain intensity. |
|                                                            | - Skin biopsy cannot identify the etiology of SFN. |
|                                                            | - Skin punch biopsy at the ankle is safe. |

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<thead>
<tr>
<th>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</th>
<th><strong>Key points:</strong></th>
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<tr>
<td></td>
<td>- Skin biopsy is a validated technique for determining ENFD.</td>
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<td>- For symptomatic patients with suspected polyneuropathy, consider skin biopsy to diagnose the presence of a polyneuropathy, particularly SFN. (Level C).</td>
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</tbody>
</table>
|                                                                | - 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 SFN vs. healthy controls and disease controls.  
  - Serial ENFD 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). |
**Glossary**

**Autonomic nervous system** — A division of the peripheral nervous system that influences the function of internal organs.

**Diagnostic yield** — The probability that ENFD 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.

**Dysesthesia** — Unpleasant sensation, either spontaneous or evoked.

**Paresthesia** — Abnormal sensation often described as numbness, burning, cold, prickling, pins and needles along with other symptoms.

**Peripheral neuropathy** — Damage to the peripheral nerves, characterized by pain or numbness, usually in the feet or hands.

**Polyneuropathy** — Generalized disorder of peripheral nerves.

**Quantitative sensory testing (QST)** — An extension of the physical examination that can provide a threshold for detection of thermal sensation, thermal pain, and vibratory sensation. QST has been used in a number of longitudinal studies and clinical trials of neuropathy and is widely available.

**Small fiber neuropathy (SFN)** — A type of peripheral neuropathy that occurs from damage to the small unmyelinated peripheral nerve fibers present in skin, peripheral nerves, and organs. Characterized by severe pain attacks that typically begin in the feet or hands.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**

August 17, 2016.


**Clinical trials:**

Searched clinicaltrials.gov on August 22, 2016 using terms: epidermal nerve fiber | small nerve fiber | Open Studies | United States. Seventeen studies found, one relevant.


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**

No LCDs 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>
<tr>
<th>CPT Codes</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>
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<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>
<td></td>
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<tr>
<td>88356</td>
<td>Morphometric analysis; nerve</td>
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<tr>
<th>ICD-10 Codes</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>G60.0</td>
<td>Motor and sensory neuropathy</td>
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<tr>
<td>G60.8</td>
<td>Sensory neuropathy</td>
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<tr>
<td>G62.9</td>
<td>Peripheral neuropathy</td>
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<tr>
<th>HCPCS Level II Codes</th>
<th>Description</th>
<th>Comments</th>
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<tr>
<td>N/A</td>
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