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# Epidermal nerve fiber density testing

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Policy contains: Epidermal nerve fiber density testing; skin punch biopsy; small fiber neuropathy.

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## Coverage policy

Epidermal nerve fiber density testing by skin biopsy is clinically proven and, therefore, medically necessary for the detection of small fiber neuropathy when **all** of the following criteria are met (England, 2009; Lauria, 2010):

- 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. Treatment is generally palliative, and not curative.

Small fiber neuropathy occurs most commonly in middle-aged and older persons (Genetics Home Reference, 2020). 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, 2020; Görlach, 2020; Hovaguimian, 2011). In up to 50% 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. 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 (Hovaguimian, 2011; Meyers, 2013). 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.

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. 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 (Hovaguimian, 2011; Meyers, 2013).

## Findings

We identified two evidence-based guidelines (England, 2009; Lauria, 2010), six individual studies (Caro, 2014; Grone, 2014; Kim, 2014; Kosmidis, 2014; Shikuma, 2015; Timar, 2016), 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<sup>1</sup> (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.

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. The policy ID was changed from CP# 09.01.12 to CCP.1263.

In 2019, we identified no new relevant information to add to the policy. No policy changes are warranted.

In 2020, we identified no new relevant information to add to the policy. No policy changes are warranted.

In 2021, we added one systematic review examining the diagnostic criteria for idiopathic small fiber neuropathy, which highlighted the need to develop standardized, evidence-based guidelines (Haroutounian, 2021). No policy changes are warranted.

## References

On September 16, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Nerve Fibers (MeSH)," "Epidermis (MeSH)," "small fiber neuropathy (MeSH)," and the free text term "epidermal nerve fiber density." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses,

<sup>1</sup> 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.

and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

42 U.S.C. 263a.

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## Policy updates

9/2016: initial review date and clinical policy effective date: 1/2017

10/2017: Policy references updated.

10/2018: Policy references updated. Policy ID changed.

10/2019: Policy references updated.

12/2020: Policy references updated.

12/2021: Policy references updated.