Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania & Keystone First	Submission Date: 7/1/2025
Policy Number: CCP.1263	Effective Date: 1/1/2017 Revision Date: 6/2025
Policy Name: Epidermal nerve fiber density testing	

Type of Submission:

☐ New Policy	☒ Prior Authorization Policy
☒ Revised Policy*	☐ Base Policy
☐ Annual Review- no revisions	☐ Experimental/Investigational Policy
	☐ Statewide PDL
	☐ Other:

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual:

Keystone First
Family of Health Plans

Epidermal nerve fiber density testing

Clinical Policy ID: CCP.1263

Recent review date: 6/2025

Next review date: 10/2026

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

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, on a case by case basis, 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

Epidermal nerve fiber density testing by skin biopsy is clinically proven and, therefore, may be 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 investigational/not clinically proven and, therefore, not medically necessary.

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 (Cascio, 2022). 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, 2012). 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 (Raicher, 2022; Genetics Home Reference, 2012; Görlach, 2020). In up to 50% of cases, the etiology is idiopathic and often presents as burning feet. With repeated skin biopsies over 12-18 months, an intraepidermal decrease in nerve fiber density is seen in the legs, which demonstrates the progressive degeneration of this condition (Raicher, 2022).

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 (Cascio, 2022).

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 (Cascio, 2022; Raicher, 2022). 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).

Normative values vary depending on sampling site, quantification technique, 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 to assess morphological changes of intra-epidermal nerve fibers and dermal nerve fibers (Lauria, 2010).

Findings

Guidelines

A joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society concluded that intraepidermal nerve fiber density is safe, validated, and reliable for distinguishing patients with polyneuropathy from asymptomatic normal controls. Further studies were needed to determine the diagnostic accuracy of axonal swellings as a predictor of progression of polyneuropathy (Lauria, 2010).

A joint guideline by the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation further examined the ability of intraepidermal nerve fiber density to distinguish symptomatic patients with polyneuropathy from symptomatic patients without polyneuropathy. In this setting, the sensitivity for the diagnosis of polyneuropathy

ranged from 0.45 to 0.90, but the specificity was consistently higher, ranging from 0.95 to 0.97, raising the likelihood of polyneuropathy in the presence of reduced intraepidermal nerve fiber density. Therefore, skin biopsy may be considered in symptomatic patients with suspected polyneuropathy to diagnose the presence of a polyneuropathy, particularly small fiber sensory polyneuropathy (England, 2009, reaffirmed 2025).

Evidence review

We identified six individual studies (Caro, 2014; Grone, 2014; Kim, 2014; Kosmidis, 2014; Shikuma, 2015; Timar, 2016) 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 and for which normative data exist to characterize findings as normal or abnormal. Epidermal nerve fiber density testing has a high diagnostic yield[1] (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.

One systematic review examining the diagnostic criteria for idiopathic small fiber neuropathy highlighted the need to develop standardized, evidence-based guidelines (Haroutounian, 2021).

Løseth (2024) analyzed the extent to which epidermal nerve fiber density testing and quantitative sensory testing were abnormal in an unselected cohort (n = 203) of participants with symptoms suggestive of small fiber neuropathy and normal nerve conduction studies. The most prevalent underlying conditions were diabetes mellitus, cancer/cytostatics, sarcoidosis, fibromyalgia, hypothyreosis, and Sjögren syndrome, but 113 (55.7%) participants had no established cause. Less than half (45.3 %) had reduced epidermal nerve fiber density, and 50% had abnormal quantitative sensory testing. There were no gender differences in epidermal nerve fiber density testing results.

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 updated the references with no policy changes warranted.

[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.

In 2022, we identified no new relevant information to add to the policy. No policy changes are warranted.

In 2024, we updated the references and made no policy changes.

In 2025, we updated the references and identified no new relevant information to add to the policy. No policy changes are warranted.

References

On April 1, 2025, 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, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

42 U.S.C. 263a. Certification of laboratories.

Caro XJ, Winter EF. Evidence of abnormal epidermal nerve fiber density in fibromyalgia: Clinical and immunologic implications. *Arthritis Rheumatol.* 2014;66(7):1945-1954. Doi: 10.1002/art.38662.

England JD, Gronseth GS, Franklin G, et al. Practice parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology.* 2009;72(2):177-184. Doi: 10.1212/01.wnl.0000336345.70511.0f. https://www.aan.com/Guidelines/home/GuidelineDetail/315. Reaffirmed February 8, 2025.

Genetics Home Reference. Small fiber neuropathy. National Institutes of Health National Library of Medicine website. https://ghr.nlm.nih.gov/condition/small-fiber-neuropathy. Last updated November 1, 2012.

Görlach J, Amsel D, Kölbel H, et al. Diagnostic utility of small fiber analysis in skin biopsies from children with chronic pain. *Muscle Nerve.* 2020;61(2):173-181. Doi: 10.1002/mus.26766.

Grone E, Uceyler N, Abahji T, et al. Reduced intraepidermal nerve fiber density in patients with chronic ischemic pain in peripheral arterial disease. *Pain.* 2014;155(9):1784-1792. Doi: 10.1016/j.pain.2014.06.003.

Haroutounian S, Todorovic MS, Leinders M, et al. Diagnostic criteria for idiopathic small fiber neuropathy: A systematic review. *Muscle Nerve.* 2021;63(2):170-177. Doi: 10.1002/mus.27070.

Kim TW, Shim WH, Kim JM, et al. Clinical characteristics of pruritus in patients with scalp psoriasis and their relation with intraepidermal nerve fiber density. *Ann Dermatol.* 2014;26(6):727-732. Doi: 10.5021/ad.2014.26.6.727.

Kosmidis ML, Koutsogeorgopoulou L, Alexopoulos H, et al. Reduction of intraepidermal nerve fiber density (iENFD) in the skin biopsies of patients with fibromyalgia: A controlled study. *J Neurol Sci.* 2014;347(1-2):143-147. Doi: 10.1016/j.jns.2014.09.035.

Lauria G, Hsieh ST, Johansson O, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol.* 2010;17(7):903-912, e944-909. Doi: 10.1111/j.1468-1331.2010.03023.x.

Løseth S, Nebuchennykh M, Brokstad RT, Lindal S, Mellgren SI. Cutaneous nerve biopsy in patients with symptoms of small fiber neuropathy: A retrospective study. *Scand J Pain*. 2024;24(1). Doi: 10.1515/sjpain-2023-0071.

Raicher I, Casartelli-Ravagnani LH, Correa SG, et al. Investigation of nerve fibers in the skin by biopsy: technical aspects, indications, and contribution to diagnosis of small-fiber neuropathy. *Einstein (Sao Paulo)*. 2022;20:eMD8044. Doi: 10.31744/einstein_journal/2022MD8044.

Shikuma CM, Bennett K, Ananworanich J, et al. Distal leg epidermal nerve fiber density as a surrogate marker of human immunodeficiency-associated sensory neuropathy risk: Risk factors and change following initial antiretroviral therapy. *J Neurovirol.* 2015;21(5):525-534. Doi: 10.1002/mus.23834.

Timar B, Popescu S, Timar R, et al. The usefulness of quantifying intraepidermal nerve fibers density in the diagnostic of diabetic peripheral neuropathy: A cross-sectional study. *Diabetol Metab Syndr.* 2016;8;31. Doi: 10.1186/s13098-016-0146-4.

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.

12/2022: Policy references updated.

6/2024: Policy references updated.

6/2025: Policy references updated.