

## Overview

### Useful For

Investigation of polyneuropathies

### Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
SS2PC	SpecStain, Grp II, other	No, (Bill Only)	No
COSPC	Consult, Outside Slide	No, (Bill Only)	No
CUPPC	Consult, w/USS Prof	No, (Bill Only)	No
CRHPC	Consult, w/Comp Rvw of His	No, (Bill Only)	No
MANPC	Morph Analysis, Nerve	No, (Bill Only)	No
LV4RP	Level 4 Gross and Microscopic, RB	No, (Bill Only)	No
CSPPC	Consult, w/Slide Prep	No, (Bill Only)	No
EM	Electron Microscopy	Yes	No
IHPCI	IHC Initial	No, (Bill Only)	No

### Testing Algorithm

A battery of enzyme histochemical stains or immunostains are performed; other tests can be performed as indicated at an additional charge.

**Wet tissue for consultation:** When adequately prepared tissue is provided, routine testing will include: PGP 9.5 immunostain, morphometric analysis, Congo red stain, and hematoxylin and eosin stain. PGP 9.5 reactions cannot be done on previously embedded tissue eg, paraffin blocks, epoxy blocks etc.

Slides and blocks sent for consultation must include PGP 9.5-reacted sections:

Special stains and studies performed on the case should be sent with the case for review. In order to determine an accurate diagnosis, some of these stains or studies may be deemed to warrant repeat testing at an additional charge at the discretion of the reviewing Mayo Clinic neuromuscular pathologist. In addition, testing requested by the referring physician (immunostains, molecular studies, etc) may not be performed if deemed unnecessary by the reviewing Mayo Clinic neuromuscular pathologist. For all consultations, ancillary testing necessary to determine a diagnosis is ordered at the discretion of the Mayo Clinic neuromuscular pathologist. An interpretation, which includes an evaluation of the specimen and determination of a diagnosis, will be provided within a formal pathology report.

See [Pathology Consultation Ordering Algorithm](#) in Special Instructions.

### Special Instructions

- [Epidermal Nerve Fiber Density Patient Information](#)

- 
- [Epidermal Nerve Fiber Density Instructions](#)
  - [Pathology Consultation Ordering Algorithm](#)

**Method Name**

Calculation of Epidermal Nerve Fiber Density

**NY State Available**

Yes

**Specimen****Specimen Type**

Varies

**Necessary Information**

**Neurology Clinical Notes information is required** on [Epidermal Nerve Fiber Density Patient Information](#) (T702) in Special Instructions.

**Specimen Required**

**Supplies: A Skin Punch Biopsy Kit containing fixatives, buffer, and cryoprotectant is required** (no substitutions accepted). For ordering information, call 507-284-8065.

Preferred:

**Specimen Type:** Skin punch biopsy tissue**Preferred source:** Distal leg, mid-thigh, dorsal foot, and lower abdomen

Collection Instructions:

1. The standard biopsy for evaluating distal small fiber sensory neuropathy includes two 3-mm skin punch biopsies from the **same side of the body**.
2. Prepare and transport specimen per instructions on the [Epidermal Nerve Fiber Density Instructions](#) (T703) in Special Instructions.

**Specimen Stability:** Refrigerated (preferred)/Ambient

Acceptable:

**Specimen Type:** Slides

Additional Information:

1. **Slides reacted with PGP 9.5, using a PGP 9.5 protocol for visualizing epidermal nerve fibers, are required.**
2. Hematoxylin and eosin-stained slides and Congo red-stained slides are optional.

**Specimen Stability:** Ambient (preferred)/Refrigerated**Specimen Type:** Tissue block and PGP9.5-reacted slides

Additional Information:

1. **Slides reacted with PGP 9.5, using a PGP 9.5 protocol for visualizing epidermal nerve fibers, are required.**
2. Tissue block may be used to create hematoxylin and eosin-stained slides and Congo red-stained slides.

**Note: Visualization of epidermal nerve fibers cannot be done on paraffin blocks.**

**Specimen Stability:** Ambient (preferred)/Refrigerated

**Forms**

[Epidermal Nerve Fiber Density Patient Information \(T702\)](#) is required.

**Reject Due To**

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Refrigerated (preferred)		
	Ambient		

**Clinical & Interpretive**

**Clinical Information**

Small fiber peripheral neuropathy is a common neurological complaint and a frequent source of morbidity in many patient populations. Direct investigation of small fiber involvement has been limited as most classical techniques (eg, electromyography, nerve conduction studies, and nerve biopsy) focus on large diameter nerve fibers and may be normal in patients with small fiber neuropathies.

The advent of epidermal skin biopsies and PGP 9.5 immunohistochemistry allows the direct visualization and morphologic assessment of small sensory fibers innervating the skin.(1) Assessment of intraepidermal nerve fiber density has been used to reliably demonstrate pathologic abnormalities in small fiber neuropathy of various etiologies including diabetes, HIV, systemic lupus erythematosus, and neurosarcoidosis. Further, the technique has been validated, shown to have acceptable sensitivity and specificity, and is minimally invasive. The publication of normative data for commonly tested sites such as the distal and proximal legs and arms permits direct comparison of patients to age- and sex-matched controls facilitating localization and diagnosis.(2-4)

Based on class 1 evidence and American Medical Association CPT code review process acceptance, intraepidermal nerve fiber density (IENFD) measurements are now an accepted investigational method in the workup of polyneuropathy, including the characterization and diagnosis of varieties of length-dependent small fiber polyneuropathies. IEFND measurements have been incorporated in recent practice guidelines published by the American Academy of Neurology and the European Federation of Neurological Science.(5,6)

**Reference Values**

A consultative report will be provided.

**Interpretation**

The number of intraepidermally originating nerve fibers that cross the basement membrane between the dermis and epidermis are counted in several sections.(2,5) The total linear length of the epidermis is measured using standard morphometric techniques and a density of epidermal nerve fibers (number of fibers/mm) is reported. This value is compared to previously published normative data.

---

**Cautions**

Poor fixation, orientation, and improper handling of the tissue may hinder the neuromuscular pathologist's interpretation of the biopsy. See [Epidermal Nerve Fiber Density Instructions](#) in Special Instructions.

**Supportive Data**

Investigators at Mayo Clinic (Bolton, Winkelmann, Dyck) did previous work on cutaneous receptors preceding the recent work on intraepidermal nerve fiber densities. With recent findings, PJ Dyck and colleagues have developed the technique to national standards.(7)

**Clinical Reference**

1. Lauria G, Lombardi R, Camozzi F, Devigili G: Skin biopsy for the diagnosis of peripheral neuropathy. *Histopathology*. 2009 Feb;54(3):273-285
2. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW: Epidermal nerve fiber density: normative reference range and diagnostic efficiency. *Arch Neurol*. 1998 Dec;55(12):1513-1520
3. Goransson LG, Mellgren SI, Lindal S, Omdal R: The effect of age and gender on epidermal nerve fiber density. *Neurology*. 2004 Mar 9;62(5):774-777
4. Umapathi T, Tan WL, Tan NCK, Chan YH: Determinants of epidermal nerve fiber density in normal individuals. *Muscle Nerve*. 2006 Jun;33(6):742-746
5. Lauria G, Cornblath DR, Johansson O, et al: EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. *Eur J Neurol*. 2005 Oct;12(10):747-758
6. 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 Jan 13;72(2):177-184
7. Engelstad JK, Taylor SW, Witt LV, et al: Epidermal nerve fibers: confidence intervals and continuous measures with nerve conduction. *Neurology*. 2012 Nov 27;79(22):2187-2193
8. England JD, Gronseth GS, Franklin G, et al: Evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). *Muscle Nerve*. 2009 Jan;39(1):106-115

**Performance****Method Description**

Immunohistochemical preparations are prepared using standard immunohistochemical techniques for PGP 9.5.(5) Using light microscopy, epidermal nerve fiber density is counted from PGP 9.5-reactive sections. Hematoxylin- and-eosin and Congo red stains are also reviewed.(McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW: Epidermal nerve fiber density: normative reference range and diagnostic efficiency. *Arch Neurol*. 1998 Dec;55[12]:1513-1520; Landowski LM, Dyck PJ, Engelstad J, Taylor BV. Axonopathy in peripheral neuropathies: Mechanisms and therapeutic approaches for regeneration. *J Chem Neuroanat*. 2016 Oct;76(Pt A):19-27. doi: 10.1016/j.jchemneu.2016.04.006)

**PDF Report**

No

### Day(s) Performed

Monday through Friday

### Report Available

12 to 20 days

### Specimen Retention Time

Slides and blocks: Indefinitely

### Performing Laboratory Location

Rochester

## Fees & Codes

### Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

### Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

### CPT Code Information

88305 (if appropriate)

88313 (if appropriate)

88321 (if appropriate)

88323 (if appropriate)

88323-26 (if appropriate)

88325 (if appropriate)

88348 (if appropriate)

88356 (if appropriate)

88342 (if appropriate)

### LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
SPBX	Epidermal Nerve Fiber Density	In Process

Result ID	Test Result Name	Result LOINC® Value
601780	Interpretation	59465-5
601791	Participated in the Interpretation	No LOINC Needed
601792	Report electronically signed by	19139-5

601793	Addendum	35265-8
601794	Gross Description	22634-0
601795	Material Received	81178-6
601824	Case Number	80398-1
601913	Disclaimer	62364-5