MAYO CLINIC LABORATORIES

Test Definition: SPBX

Epidermal Nerve Fiber Density Consultation, Varies

Overview

Useful For

Investigating 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 (protein gene product 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.

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.

For more information see Pathology Consultation Ordering Algorithm.

Special Instructions

- Epidermal Nerve Fiber Density Patient Information
- Epidermal Nerve Fiber Density Preparation Instructions

- Pathology Consultation Ordering Algorithm

Highlights
Our consultative practice strives to provide the highest quality diagnostic consultative service, balancing optimal patient care with a cost-conscious approach that supports the rapid turnaround time for diagnostic results.

Method Name
Calculation of Epidermal Nerve Fiber Density

NY State Available
Yes

Specimen

Specimen Type
Varies

Shipping Instructions
Transport specimen per instructions on the Epidermal Nerve Fiber Density Preparation Instructions (T703).

Necessary Information
All requisition and supporting information must be submitted in English.

Each of the following items is required:
1. All requisitions must be labeled with:
-Patient name, date of birth, and medical record number
-Name and phone number of the referring pathologist or ordering provider
-Anatomic site and collection date
2. Epidermal Nerve Fiber Density Patient Information (T702)
3. Additional clinical information:
-Neurology clinical notes
-Electromyography results if performed

Specimen Required
Preferred:
Specimen Type: Skin punch biopsy
Supplies: Epidermal Nerve Fiber Density Kit (T696)
Source: Distal leg, mid-thigh, dorsal foot, or lower abdomen
Container/Tube: Epidermal Nerve Fiber Density Kit (**required**, no substitutions accepted)
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 specimen per instructions on the Epidermal Nerve Fiber Density Preparation Instructions (T703).

Acceptable:
Specimen Type: PGP 9.5-reacted slides
Additional Information:
1. At least one slide reacted with PGP 9.5, using a PGP 9.5 protocol for visualizing epidermal nerve fibers, is required.
2. At least one hematoxylin and eosin-stained slide and one Congo red-stained slide are optional.
Additional Information: Stained slides that were broken and repaired (ie, double mounted) at the client site will not be rejected, as, in most cases, they can still be reviewed under the microscope. However, due to the double mounting, digital scanning cannot be performed.

Specimen Type: PGP 9.5-reacted slides **and** tissue block
Note: Visualization of epidermal nerve fibers cannot be done on paraffin blocks.
Additional Information:
1. At least one slide reacted with PGP 9.5, using a PGP 9.5 protocol for visualizing epidermal nerve fibers, is required.
2. Tissue block may **only** be used to create hematoxylin and eosin-stained slides and Congo red-stained slides.
Additional Information: Stained slides that were broken and repaired (ie, double mounted) at the client site will not be rejected, as, in most cases, they can still be reviewed under the microscope. However, due to the double mounting, digital scanning cannot be performed.

Forms

Epidermal Nerve Fiber Density Patient Information (T702) is required.

Reject Due To

Broken or cracked unstained slides	Reject
Broken or cracked stained slides that cannot be repaired	Reject

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 (protein gene product 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

An interpretive 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. For more information see Epidermal Nerve Fiber Density Preparation Instructions.

Broken or cracked unstained slides are not compatible with the instrumentation used in our performing laboratories and will be rejected. Additional material may be requested.

Attempts will be made to repair broken or cracked stained slides; however, if they are unable to be repaired (ie, shattered in transit), they will be rejected and discarded due to safety concerns.

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;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;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;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;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;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;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;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;39(1):106-115
9. Landowski LM, Dyck PJB, Engelstad J, Taylor BV. Axonopathy in peripheral neuropathies: Mechanisms and therapeutic approaches for regeneration. J Chem Neuroanat. 2016;76(Pt A):19-27. doi:10.1016/j.jchemneu.2016.04.006

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.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
7 to 14 days: Cases requiring additional material or ancillary testing may require additional time.

Specimen Retention Time
Slides and blocks: Indefinitely

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

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 account representative. 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. It 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