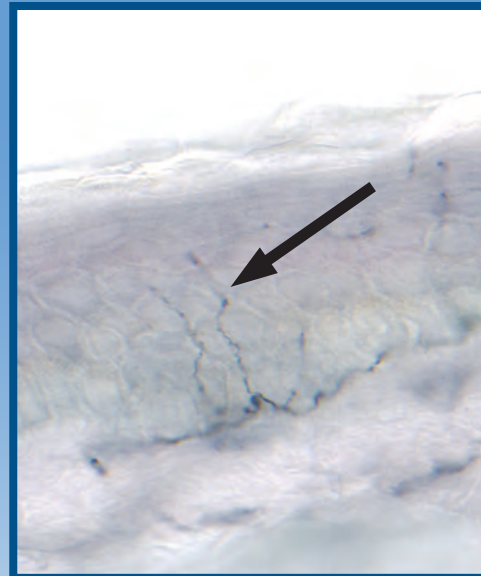


Let us help *YOU* make the diagnosis of small fiber peripheral neuropathy

Epidermal Nerve Fiber Density

Bako Integrated Physician Solutions is a pioneer in the development and use of *epidermal nerve fiber density analysis*, a state-of-the-art test for the diagnosis of small fiber neuropathy.



 BAKO PATHOLOGY SERVICES <small>6240 Shook Road, Alpharetta, GA 30005 Phone: 877-376-7284 Fax: 770-475-0533 www.bako.com</small>		Accession #: NF13-099990
Patient: DOE, JOHN Z <small>Phone: 704-377-2646 DOB (Age) / Sex: 03/19/58 (M) / M Collected Date: 5/17/2013</small>	Ref Physician: JANE DOE, DPM <small>111 FOUR ADDRESS HERE, ST ATLANTA, GA 30309 877-376-7284 / 770-475-0533</small>	Copy To:
EPIDERMAL NERVE FIBER DENSITY ANALYSIS		
DIAGNOSIS:		
A. SKIN, RIGHT CALF, PUNCH BIOPSY:		
<ul style="list-style-type: none"> - INTRA-EPIDERMAL NERVE DENSITY MILDLY DECREASED (5.86 FIBERS/MM) - MILD MORPHOLOGIC DEGENERATIVE CHANGES ARE SEEN AMONG INTRA-EPIDERMAL NERVE FIBERS - SEE COMMENT. 		
B. SKIN, LEFT CALF, PUNCH BIOPSY:		
<ul style="list-style-type: none"> - INTRA-EPIDERMAL NERVE DENSITY MILDLY DECREASED (6.73 FIBERS/MM) - MILD MORPHOLOGIC DEGENERATIVE CHANGES ARE SEEN AMONG INTRA-EPIDERMAL NERVE FIBERS - SEE COMMENT. 		
COMMENT, AB: The nerve fiber density reductions and degenerative changes identified in 50 µm sections on which an anti-PGP 9.5 immunostain was performed, are consistent with a <i>mild (early-evolving) neuropathic</i> process affecting small fibers.		
<small>The published normative range for epidermal nerve fiber density at 10 cm proximal to the lateral malleolus is 13.8 ± 4.7 fibers per millimeter. Values under 7.1 fibers/mm are below the normative range in this location. Reference: Diagnostic neuropathy. Arch Neurol 2001; 58:1510-1516, 1998.</small>		
<small>Based on the epidermal nerve fiber density analysis in this case, one potential clinical course for this patient could include a dietary supplement containing Alpha-Lipoic Acid (3000mg daily) and Benfotiamine (600mg daily). When clinically indicated, such products may be helpful to both diminish the symptoms of neuropathy, and to improve overall epidermal nerve health. Additionally, investigators have shown benefit to using combination therapy that includes L-methylfolate, methylcobalamin (B12) and pyridoxal 5'-phosphate (B6). Reference: Siegel D. Effect of 4-year antioxidant treatment with alpha-lipoic acid in diabetic polyneuropathy: the NATHAN-1 trial. Diabetes 2007; 56(Suppl 1):A2. Luong KV, et al. The impact of thiamine treatment in diabetes mellitus. J Clin Med Res 2012; 4(3): 153-160. Walker M, et al. Improvement of cutaneous sensitivity in diabetic peripheral neuropathy. Rev Neurol (Paris) 2010; 76(1):132-136.</small>		
CLINICAL INFORMATION: A. Rule out neuropathy, right calf B. Rule out neuropathy, left calf		
<small>Bradley W. Bakotic, DPM, DO Joseph "Jody" Hackel, MD Wayne L. Bakotic, DO Medical Director</small>		<small>Page 1 of 2</small>

Instructive reports with the most rapid turn-around time in the industry



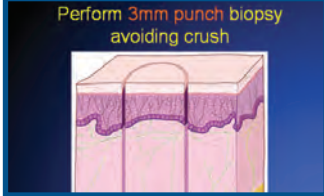



ENFD REFERENCE GUIDE

Peripheral neuropathy affects roughly 15-20 million persons over the age of 40 in the United States

<p>What is small fiber peripheral neuropathy (SFPN)?</p>		<ul style="list-style-type: none"> • Small fiber peripheral neuropathy is a disease which primarily affects the terminal end-branches of peripheral nerves • The net result is disintegration of the nerve fiber cytoskeleton, and eventually complete nerve loss • Often manifests as pain, tingling, or numbness in a stocking and/or glove distribution • Usually not identified by large nerve fiber tests such as nerve conduction studies
<p>Conditions which may cause small fiber peripheral neuropathy (SFPN)</p>		<ul style="list-style-type: none"> • Metabolic causes such as diabetes mellitus, metabolic syndrome, hyperlipidemia • Inherited causes such as Fabry's disease, Tangier's disease, familial amyloid polyneuropathy • Toxic causes such as chemotherapy, alcoholism, solvent exposure. • Autoimmune causes such as Sjogren's syndrome, vasculitis/polyarteritis nodosa • Amyloidosis (non-inherited forms of amyloidosis, e.g. lymphoma or plasma cell dyscrasias) • Infection (HIV, Hepatitis C, Lyme disease) • Idiopathic (For a relatively large percentage of cases, there is no identifiable cause of SFPN)
<p>What is Epidermal Nerve Fiber Density analysis (ENFD)?</p>		<ul style="list-style-type: none"> • Epidermal Nerve Fiber Density analysis is a test which allows direct visualization of small nerve fibers. • Small nerve fibers are assessed for structural integrity, and counted • Changes indicative of degeneration are predictive of future disease • A diminished number of small nerve fibers are indicative of established disease; the lower the count, the more severe the disease state
<p>How is ENFD analysis performed?</p> <p>Note: The diagnosis and treatment of small fiber peripheral neuropathy is within the scope of podiatric medicine.</p>		<ul style="list-style-type: none"> • Request an ENFD kit from Bako (The kit will include a mailing container and label, a punch biopsy instrument, Zamboni's fixative and rinse solutions) • Anesthesia is applied around (but not directly at) the biopsy site located 10cm proximal to the lateral malleolus (normal ranges established at this site) • A 3mm punch biopsy is performed taking care not to crush the surface epithelium • The biopsy is either placed in Zamboni's fixative overnight, rinsed, and mailed; or placed in Zamboni's fixative and mailed immediately
<p>Is ENFD analysis reimbursed by 3rd party payors?</p>	<p>Yes!</p>	<ul style="list-style-type: none"> • The vast numbers of insurers pay for Epidermal Nerve Fiber Density analysis. • Bako maintains an in-network status with all national 3rd party payors • Bako offers a number of programs to assist persons in financial need, assuring the best possible care regardless of fiscal limitations. • Possible ICD-10 codes may include: G60.9 or G60.8 • CPT 11100, 11101 (for each subsequent punch performed)

Questions? Don't hesitate to call us: **855-4BAKO-CTS**

ENFD PROCEDURE REVIEW

<p>1 Call BAKO to order your ENFD kit(s)</p>		<ul style="list-style-type: none"> • It is best to order your ENFD kit 1-2 weeks prior to the procedure date. • Receive kit / PLACE COOL-PACK IN FREEZER TO BE READY FOR RETURN SHIPPING.
<p>2 Mark (with a sharpie), prep and anesthetize the biopsy site</p>		<ul style="list-style-type: none"> • The ideal location is 10 cm proximal to the lateral malleolus • Prep the biopsy site with alcohol or an alternate topical antiseptic • Infiltrate lidocaine with epinephrine around the biopsy site in a "V" pattern (apex proximal) <p><i>Note:</i> anesthesia administered within the biopsy site may negatively affect the test quality</p>
<p>3 Perform the punch biopsy, keeping the instrument perpendicular with the skin surface</p>		<p>Softly push the punch instrument down while rotating back and forth, allowing the blade "to do the work". The punch should enter the skin to the level of the subcutis.</p>
<p>4 Remove the punch instrument and lift out the biopsy specimen</p>		<p>When removing the sample, use atraumatic forceps, being careful to grasp the biopsy deep to the surface epithelium. Lift the punch out, and cut the fat attachment with scalpel or scissor.</p> <p>BE CAREFUL TO AVOID CRUSHING THE SURFACE EPITHELIUM</p>
<p>5 Place biopsy immediately into Zamboni's fixative and refrigerate (yellow fluid, labeled #1)</p>		<p>Your specimen MUST be placed in Zamboni's for at least 8 hours (better if fixed overnight)</p>
<p>6 Ship your specimen to BAKO for analysis</p>		<p>Because Zamboni's fixative is a weak acid, samples may not remain submerged for more than 24 hours.</p> <p>Two shipping options:</p> <ul style="list-style-type: none"> • Place biopsy in Zamboni's and FedEx to Bako on THAT DAY • Place biopsy in Zamboni's overnight, rinse the following day, and call FedEx for pick-up • Place cool-pack from freezer into styrofoam cooler. <p>NOTE: Taking the time to perform the rinse step will eliminate any chance of test compromise due to delays in shipping.</p>

Questions? Don't hesitate to call us: **855-4BAKO-CTS**

Simple, easy specimen fixation/rinse process:

<h3>Immediately After Biopsy</h3>	<ol style="list-style-type: none"> Place the 3mm punch biopsy in yellow fixative (Zamboni's, labeled #1) for no less than 8 hours, but no more than 24 hours (it's best to fix overnight). Refrigerate; DO NOT FREEZE! 	
<h3>The Following Morning</h3>	<ol style="list-style-type: none"> Pour off the Zamboni's fixative, leaving the skin biopsy in its vial (pour into dish rather than a sink to prevent losing the biopsy). Refill specimen vial with buffer rinse (labeled #2), to neutralize the Zamboni's. 	 
	<ol style="list-style-type: none"> Pour off buffer rinse (into dish), again leaving skin biopsy in its original vial. Repeat steps 3 and 4 using the remaining buffer rinse (labeled #2). 	 
	<ol style="list-style-type: none"> Fill vial containing the biopsy with cryoprotectant (labeled #3), again making sure that the specimen is fully submerged. Screw the blue vial cap on TIGHTLY. COMPLETE VIAL LABEL AND AFFIX TO THE VIAL. Place vial containing biopsy and the frozen cool-pack into the styrofoam cooler. 	 <div data-bbox="1823 1009 2039 1118" style="border: 1px solid black; padding: 5px;"> <p>Sample A Site</p>  <p>Name: _____</p> <p>ET1001</p> </div>
<h3>Shipping Information</h3>	<ol style="list-style-type: none"> Ship to BAKO in ENFD box using FedEx Priority Overnight (prepaid shipping labels provided within transport kit). Call 1-800-463-3339 (GoFedEx) to schedule pickup at least 2 hours before closing. To avoid charges, ask for an agent, read them the tracking number on the airbill and mention this is prepaid by Bako Pathology Services. Call us at 855-4BAKO-CTS (855-422-5628) to advise us the specimen has been shipped. 	 

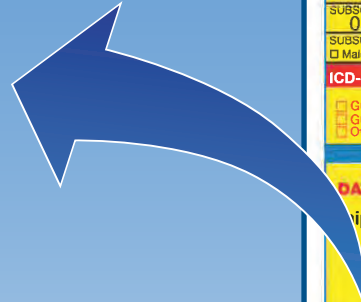
Questions? Don't hesitate to call us: **855-4BAKO-CTS**


ENFD Requisition Form - Example

To avoid delayed diagnosis, please make sure to provide complete information on the ENFD requisition form AND affix completed label to the specimen vial.


AFFIXED LABEL

Indicate Test Site	
Sample A Site	
Name:	E11001
Sample B Site	
Name:	E11001
Sample C Site	
Name:	E11001
Sample D Site	
Name:	E11001



E00001 

EPIDERMAL NERVE FIBER DENSITY REQUISITION FORM



Bako Pathology Services
6240 SHILOH ROAD
ALPHARETTA, GA 30005
PH: 877-376-7284 • FAX: 770-475-0533

Integrated Physician Solutions

PHYSICIAN/CLINIC INFORMATION

BILL: INSURANCE PATIENT

PATIENT INFORMATION

LAST NAME: Smith FIRST NAME: Patricia M.I.: M

STREET ADDRESS: _____ APT. #: _____

CITY: Warren STATE: MI ZIP CODE: 48088

PHONE NUMBER: 810-123-4567

DATE OF BIRTH: 06/23/1948 AGE: 65 SEX: F PATIENT ID: _____

BILLING/INSURANCE INFORMATION (ATTACH A COPY OF INSURANCE CARD - BOTH SIDES)

SUBSCRIBER PRIMARY INSURANCE
SUBSCRIBER NAME/RELATIONSHIP TO SUBSCRIBER: Self Spouse Dependent
Smith, Patricia

SUBSCRIBER SECONDARY INSURANCE
SUBSCRIBER NAME/RELATIONSHIP TO SUBSCRIBER: Self Spouse Dependent
Smith, Patricia

INSURANCE NAME: Smith, Patricia INSURANCE NAME: United Health Care- Choice Plus

ADDRESS: _____ ADDRESS: PO Box 740800

CITY: _____ STATE: _____ ZIP CODE: _____ CITY: Atlanta STATE: GA ZIP CODE: _____

SUBSCRIBER DOB: 06/23/1948 GROUP/CONTRACT #: _____ MEMBER ID #: _____ SUBSCRIBER DOB: 06/23/1948 GROUP/CONTRACT #: 6G1234 MEMBER ID #: 3777721

SUBSCRIBER SEX: Male Female MEDICARE ID #: 123-45-6789A MEDICAID ID #: _____ SUBSCRIBER SEX: Male Female MEDICARE ID #: _____ MEDICAID ID #: _____

ICD-10 CODE **CLINICAL INFORMATION**

G60.9 (Hereditary and idiopathic neuropathy, unspecified)
 G60.8 (Other hereditary idiopathic neuropathies)
 Other

DATE COLLECTED: 05/23/2014 **TIME COLLECTED:** 11:30 a.m. **REPEAT BIOPSY:**

Shipped in: Zamboni's/#1 (24-hr maximum exposure) Cryoprotectant/#3 (after >8 hours Zamboni's fixation and rinse)**

**For specimen fixation and rinsing techniques video instruction is available at www.bakocts.com

Indicate Test Selected: Epidermal Nerve Fiber Density (ENFD)
 ENFD and Amyloid Stain* *In Cases of Lymphoma, Myeloma, Familial Amyloidosis, Etc.

Indicate Test Site	Circle Laterality	Circle Laterality	Circle Laterality
Sample A Site P. Smith Name: L	<input checked="" type="checkbox"/> Calf L or R	<input type="checkbox"/> Thigh L or R	<input type="checkbox"/> Other _____ L or R
Sample B Site P. Smith Name: R	<input checked="" type="checkbox"/> Calf L or R	<input type="checkbox"/> Thigh L or R	<input type="checkbox"/> Other _____ L or R
Sample C Site Name: _____	<input type="checkbox"/> Calf L or R	<input type="checkbox"/> Thigh L or R	<input type="checkbox"/> Other _____ L or R
Sample D Site Name: _____	<input type="checkbox"/> Calf L or R	<input type="checkbox"/> Thigh L or R	<input type="checkbox"/> Other _____ L or R

SPECIMEN CONTAINER MUST INCLUDE PATIENT NAME, SITE AND BARCODED LABEL

PHYSICIAN SIGNATURE

Signature: D. Robinson

PATIENT SIGNATURE

I authorize Bako Pathology Services to bill my insurance.

Signature: P. Smith Date: 5 / 23 / 14

It is OK to attach copy of face sheet and insurance cards!

Questions?

Don't hesitate to call us: **855-4BAKO-CTS**

Patient: DOE, JOHN Z	Ref Physician:	JANE DOE, DPM
Phone: 704-377-2648		111 YOUR ADDRESS HERE ST
DOB (Age) / Sex: 5/9/1955 (58) / M		ATLANTA, GA 30309
Collect Date:		877-376-7284/ 770-475-0533
Received Date: 5/17/2013	Copy To:	

EPIDERMAL NERVE FIBER DENSITY ANALYSIS

DIAGNOSIS:

A. SKIN, RIGHT CALF, PUNCH BIOPSY:

- INTRA-EPIDERMAL NERVE DENSITY MILDLY DECREASED (5.86 FIBERS/MM).
- MILD MORPHOLOGIC DEGENERATIVE CHANGES ARE SEEN AMONG INTRA-EPIDERMAL NERVE FIBERS.
- SEE COMMENT.

B. SKIN, LEFT CALF, PUNCH BIOPSY:

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- SEE COMMENT.

COMMENT, A/B: The nerve fiber density reductions and degenerative changes identified in 50 µm sections on which an anti-PGP 9.5 immunostain was performed, are consistent with a **mild (early-evolving) neuropathic process affecting small fibers.**

The published normative range for epidermal nerve fiber density at 10 cm proximal to the ankles is 5.0-10.0 fibers/mm, +/- 6.7 fibers per millimeter. Values under 7.1 fibers/mm are below the normative range for this location. **Reference:** McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal Nerve Fiber Density. Normative reference range and diagnostic efficiency. Arch Neurol 55:1513-15120, 1998.

Based on the epidermal nerve fiber density analysis in this case, one potential clinical course for this patient could include a dietary supplement containing **Alpha-Lipoic Acid (≥600mg daily)** and **Benfotiamine (600mg daily)**. When clinically indicated, such products may be helpful to both diminish the symptoms of neuropathy, and to improve overall epidermal nerve health. Additionally, investigators have shown benefit to using combination therapy that includes L-methylfolate, methylcobalamin (B12) and pyridoxal 5'-phosphate (B6). **References:** Ziegler D. Effect of 4-year antioxidant treatment with alpha-lipoic acid in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes 2007; 56(Suppl.1):A2. Luong KV, et al.. The impact of thiamine treatment in diabetes mellitus. J Clin Med Res 2012; 4(3):153-160. Walker M, et al.. Improvement of cutaneous sensitivity in diabetic peripheral neuropathy. Rev Neurol Dis 2010; 7(4):132-139.



CLINICAL INFORMATION:

- A. Rule out neuropathy; right calf.
- B. Rule out neuropathy; left calf.

ENFD reporting can provide **YOU** with a definitive diagnosis of small fiber peripheral neuropathy and an assessment of its degree of severity.

“Based on the epidermal nerve fiber density analysis in this case, one potential clinical course for this patient could include a dietary supplement containing **Alpha-Lipoic Acid (≥600mg daily)** and **Benfotiamine (600mg daily)**. When clinically indicated, such products may be helpful to both diminish the symptoms of neuropathy, and to improve overall epidermal nerve health. Additionally, investigators have shown benefit to using combination therapy that includes L-methylfolate, **methylcobalamin (B12)** and **pyridoxal 5'-phosphate (B6)**. (References: Ziegler D. Diabetes 2007; 56(Suppl.1):A2. Luong KV, et al. J Clin Med Res 2012; 4(3):153-160. Walker M, et al.. Rev Neurol Dis 2010; 7(4):132-139).”

NeuRx-TF™

TABLETS

Total Formulation For Peripheral Nerve Health



- Combination of powerful antioxidants which help protect nerves from oxidative damage
- Curbs oxidative stress related to aging and environmental stress
- Improves microvascular blood flow which can help nourish nerve endings
- May increase insulin efficiency and improve glucose metabolism

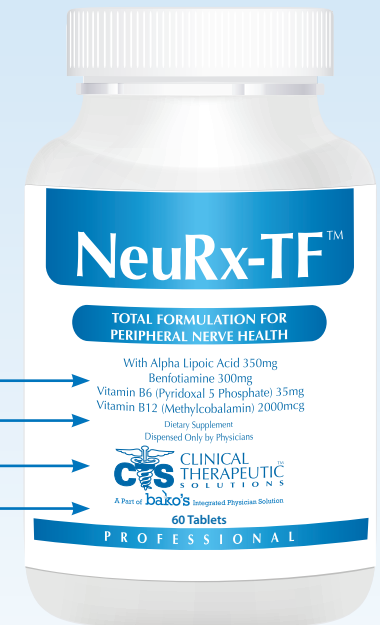
NeuRx-TF™ Tablets are ideal for nerve function support, as they combine powerful antioxidants that help protect nerve cells from oxidative damage related to aging and environmental stress.

Alpha Lipoic Acid 350 mg

Benfotiamine 300 mg

Vitamin B6 (Pyridoxal 5 Phosphate) 35 mg

Vitamin B12 (Methylcobalamin) 2 mg



*These statements have not been evaluated by the Food and Drug Administration. The product is not intended to diagnose, treat, cure, or prevent any disease.

A blue-tinted background image of a microscope, showing the eyepiece, objective lenses, and the stage.

bako

Integrated Physician Solutions

Questions? Call 855-4BAKO-CTS or visit www.BakoCTS.com