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.

Instructive reports with the most rapid turn-around time in the industry
Peripheral neuropathy affects roughly 15-20 million persons over the age of 40 in the United States.

| What is small fiber peripheral neuropathy (SFPN)? | • 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 |
| Conditions which may cause small fiber peripheral neuropathy (SFPN) | • 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) |
| What is Epidermal Nerve Fiber Density analysis (ENFD)? | • 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 |
| How is ENFD analysis performed? | • 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 |
| Is ENFD analysis reimbursed by 3rd party payors? | Yes! |

Is ENFD analysis reimbursed by 3rd party payors?  
• 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
1. **Call BAKO to order your ENFD kit(s)**

   - 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.**

2. **Mark (with a sharpie), prep and anesthetize the biopsy site**

   - 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)
   - **Note:** anesthesia administered within the biopsy site may negatively affect the test quality

3. **Perform the punch biopsy, keeping the instrument perpendicular with the skin surface**

   - 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.

4. **Remove the punch instrument and lift out the biopsy specimen**

   - 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 scissors.
   - **BE CAREFUL TO AVOID CRUSHING THE SURFACE EPITHELIUM**

5. **Place biopsy immediately into Zamboni’s fixative and refrigerate (yellow fluid, labeled #1)**

   - Your specimen MUST be placed in Zamboni’s for at least 8 hours (better if fixed overnight)

6. **Ship your specimen to BAKO for analysis**

   - Because Zamboni’s fixative is a weak acid, samples may not remain submerged for more than 24 hours.
   - **Two shipping options:**
     - 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.
   - **NOTE:** Taking the time to perform the rinse step will eliminate any chance of test compromise due to delays in shipping.

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Questions? Don’t hesitate to call us: **855-4BAKO-CTS**
## Simple, easy specimen fixation/rinse process:

### Immediately After Biopsy

1. 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!**

### The Following Morning

2. 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).
3. Refill specimen vial with buffer rinse (labeled #2), to neutralize the Zamboni’s.
4. Pour off buffer rinse (into dish), again leaving skin biopsy in its original vial.
5. Repeat steps 3 and 4 using the remaining buffer rinse (labeled #2).
6. Fill vial containing the biopsy with cryoprotectant (labeled #3), again making sure that the specimen is fully submerged.
7. Screw the blue vial cap on **TIGHTLY.**
   **COMPLETE VIAL LABEL AND AFFIX TO THE VIAL.**
8. Place vial containing biopsy and the frozen cool-pack into the styrofoam cooler.

### Shipping Information

9. Ship to BAKO in ENFD box using FedEx Priority Overnight (prepaid shipping labels provided within transport kit).
10. 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.
11. Call us at 855-4BAKO-CTS (855-422-5628) to advise us the specimen has been shipped.

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**Questions? Don’t hesitate to call us: 855-4BAKO-CTS**
To avoid delayed diagnosis, please make sure to provide complete information on the ENFD requisition form AND affix completed label to the specimen vial.

Questions? Don’t hesitate to call us: 855-4BAKO-CTS
ENFD reporting can provide YOU with a definitive diagnosis of small fiber peripheral neuropathy and an assessment of its degree of severity.

<table>
<thead>
<tr>
<th>Patient:</th>
<th>DOE, JOHN Z</th>
</tr>
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<tbody>
<tr>
<td>Phone:</td>
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<tr>
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**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:

- INTRA-EPIDERMAL NERVE DENSITY MILDLY DECREASED (6.73 FIBERS/MM).
- MILD MORPHOLOGIC DEGENERATIVE CHANGES ARE SEEN AMONG INTRA-EPIDERMAL NERVE FIBERS.
- SEE COMMENT.

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


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.)

**CLINICAL INFORMATION:**

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

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

- 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.