



If a conflict arises between a Clinical Payment and Coding Policy (“CPCP”) and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. “Plan documents” include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. BCBSNM may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSNM has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act (“HIPAA”) approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing (“UB”) Editor, American Medical Association (“AMA”), Current Procedural Terminology (“CPT®”), CPT® Assistant, Healthcare Common Procedure Coding System (“HCPCS”), ICD-10 CM and PCS, National Drug Codes (“NDC”), Diagnosis Related Group (“DRG”) guidelines, Centers for Medicare and Medicaid Services (“CMS”) National Correct Coding Initiative (“NCCI”) Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

## **Nerve Fiber Density Testing**

**Policy Number: CPCPLAB064**

**Version 1.0**

**Plan CMO Approval Date: July 27, 2022**

**Plan Effective Date: January 1, 2023**

### **Description**

BCBSNM has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

### **Reimbursement Information:**

1. Skin biopsy with epidermal nerve fiber density measurement for the diagnosis of small-fiber neuropathy **may be reimbursable** when ALL of these conditions are met:
  - a. Individual presents with symptoms of painful sensory neuropathy; AND
  - b. There is no history of a disorder known to predispose to painful neuropathy (e.g., diabetic neuropathy, toxic neuropathy, HIV neuropathy, celiac neuropathy, inherited neuropathy); AND

- c. Physical examination shows no evidence of findings consistent with large-fiber neuropathy, such as reduced or absent muscle-stretch reflexes or reduced proprioception and vibration sensation; AND
  - d. Electromyography and nerve-conduction studies are normal and show no evidence of large-fiber neuropathy.
2. Skin biopsy with epidermal nerve fiber density measurement **is not reimbursable** for all other conditions, including, but not limited to, the monitoring of disease progression or response to treatment.
  3. Measurement of sweat gland nerve fiber density **is not reimbursable**.

## Procedure Codes

Codes
88305, 88314, 88341, 88342, 88344, 88346, 88350, 88356

## References:

- AAN. (2019, 1/26/2019). EVALUATION OF DISTAL SYMMETRIC POLYNEUROPATHY: ROLE OF AUTONOMIC TESTING, NERVE BIOPSY, AND SKIN BIOPSY. *Policy & Guidelines*. Retrieved from <https://www.aan.com/Guidelines/Home/GuidelineDetail/316>
- ADA. (2018). 10. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2018 *Diabetes Care*, 41(Supplement 1), S105. Retrieved from [http://care.diabetesjournals.org/content/41/Supplement\\_1/S105.abstract](http://care.diabetesjournals.org/content/41/Supplement_1/S105.abstract)
- ADA. (2020). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*, 43(Suppl 1), S14-S31. doi:10.2337/dc20-S002
- ADA. (2021). Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers. *Clinical Diabetes*, 39(1), 14-43. doi:10.2337/cd21-as01
- Alam, U., Jeziorska, M., Petropoulos, I. N., Asghar, O., Fadavi, H., Ponirakis, G., . . . Malik, R. A. (2017). Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy. *PLoS One*, 12(7), e0180175. doi:10.1371/journal.pone.0180175
- BakoDx. (2021). Epidermal Nerve Fiber Density (ENFD) Testing. Retrieved from <https://bakodx.com/enfd/>
- Burlina, A. P., Sims, K. B., Politei, J. M., Bennett, G. J., Baron, R., Sommer, C., . . . Hilz, M. J. (2011). Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. *BMC Neurol*, 11, 61. doi:10.1186/1471-2377-11-61
- Callaghan, B. C., Gao, L., Li, Y., Zhou, X., Reynolds, E., Banerjee, M., . . . Ji, L. (2018). Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. *Ann Clin Transl Neurol*, 5(4), 397-405. doi:10.1002/acn3.531

- Callaghan, B. C., Xia, R., Reynolds, E., Banerjee, M., Rothberg, A. E., Burant, C. F., . . . Feldman, E. L. (2016). Association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. *JAMA Neurol*, *73*(12), 1468-1476. doi:10.1001/jamaneurol.2016.3745
- Caro, X. J., & Winter, E. F. (2014). Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. *Arthritis Rheumatol*, *66*(7), 1945-1954. doi:10.1002/art.38662
- Cazzato, D., Castori, M., Lombardi, R., Caravello, F., Bella, E. D., Petrucci, A., . . . Lauria, G. (2016). Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. *Neurology*, *87*(2), 155-159. doi:10.1212/wnl.0000000000002847
- Chao, C. C., Huang, C. M., Chiang, H. H., Luo, K. R., Kan, H. W., Yang, N. C., . . . Hsieh, S. T. (2015). Sudomotor innervation in transthyretin amyloid neuropathy: Pathology and functional correlates. *Ann Neurol*, *78*(2), 272-283. doi:10.1002/ana.24438
- Chien, H. F., Tseng, T. J., Lin, W. M., Yang, C. C., Chang, Y. C., Chen, R. C., & Hsieh, S. T. (2001). Quantitative pathology of cutaneous nerve terminal degeneration in the human skin. *Acta Neuropathol*, *102*(5), 455-461. Retrieved from <http://dx.doi.org/>
- Collongues, N., Samama, B., Schmidt-Mutter, C., Chamard-Witkowski, L., Debouverie, M., Chanson, J. B., . . . Boehm, N. (2018). Quantitative and qualitative normative dataset for intraepidermal nerve fibers using skin biopsy. *PLoS One*, *13*(1), e0191614. doi:10.1371/journal.pone.0191614
- CRL. (2020). SMALL FIBER NEUROPATHY IS PAINFUL. DIAGNOSING IT SHOULDN'T BE. Retrieved from <https://corinthianreferencelab.com/>
- Cruccu, G., Sommer, C., Anand, P., Attal, N., Baron, R., Garcia-Larrea, L., . . . Treede, R. D. (2010). EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol*, *17*(8), 1010-1018. doi:10.1111/j.1468-1331.2010.02969.x
- Dalsgaard, C. J., Rydh, M., & Haegerstrand, A. (1989). Cutaneous innervation in man visualized with protein gene product 9.5 (PGP 9.5) antibodies. *Histochemistry*, *92*(5), 385-390. Retrieved from <http://dx.doi.org/>
- Devigili, G., Rinaldo, S., Lombardi, R., Cazzato, D., Marchi, M., Salvi, E., . . . Lauria, G. (2019). Diagnostic criteria for small fibre neuropathy in clinical practice and research. *Brain*, *142*(12), 3728-3736. doi:10.1093/brain/awz333
- Devigili, G., Tugnoli, V., Penza, P., Camozzi, F., Lombardi, R., Melli, G., . . . Lauria, G. (2008). The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain*, *131*(Pt 7), 1912-1925. doi:10.1093/brain/awn093
- Duchesne, M., Danigo, A., Richard, L., Vallat, J. M., Attarian, S., Gonnaud, P. M., . . . Magy, L. (2018). Skin Biopsy Findings in Patients With CMT1A: Baseline Data From the CLN-PXT3003-01 Study Provide New Insights Into the Pathophysiology of the Disorder. *J Neuropathol Exp Neurol*, *77*(4), 274-281. doi:10.1093/jnen/nly001
- EFNS. (2010). 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. *J Peripher Nerv Syst*, *15*(2), 79-92. doi:10.1111/j.1529-8027.2010.00269.x

England, J. D., Gronseth, G. S., Franklin, G., Carter, G. T., Kinsella, L. J., Cohen, J. A., . . . Sumner, A. J. (2009a). Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (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*, *72*(2), 185-192. doi:10.1212/01.wnl.0000336370.51010.a1

England, J. D., Gronseth, G. S., Franklin, G., Carter, G. T., Kinsella, L. J., Cohen, J. A., . . . Sumner, A. J. (2009b). Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). *Neurology*, *72*(2), 177. doi:10.1212/01.wnl.0000336345.70511.0f

Evdokimov, D., Dinkel, P., Frank, J., Sommer, C., & Üçeyler, N. (2020). Characterization of dermal skin innervation in fibromyalgia syndrome. *PLoS One*, *15*(1), e0227674. doi:10.1371/journal.pone.0227674

Garber, A. J., Abrahamson, M. J., Barzilay, J. I., Blonde, L., Bloomgarden, Z. T., Bush, M. A., . . . Davidson, M. H. (2015). AACE/ACE comprehensive diabetes management algorithm 2015. *Endocr Pract*, *21*(4), 438-447. doi:10.4158/ep15693.cs

Garber, A. J., Handelsman, Y., Grunberger, G., Einhorn, D., Abrahamson, M. J., Barzilay, J. I., . . . Umpierrez, G. E. (2020). Consensus Statement by The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocr Pract*, *26*(1), 107-139. doi:10.4158/cs-2019-0472

Gibbons, C. H., Griffin, J. W., Polydefkis, M., Bonyhay, I., Brown, A., Hauer, P. E., & McArthur, J. C. (2006). The utility of skin biopsy for prediction of progression in suspected small fiber neuropathy. *Neurology*, *66*(2), 256-258. doi:10.1212/01.wnl.0000194314.86486.a2

Gibbons, C. H., Illigens, B. M., Wang, N., & Freeman, R. (2009). Quantification of sweat gland innervation: a clinical-pathologic correlation. *Neurology*, *72*(17), 1479-1486. doi:10.1212/WNL.0b013e3181a2e8b8

Gupta, N., Arora, M., Sharma, R., & Arora, K. S. (2016). Peripheral and Central Nervous System Involvement in Recently Diagnosed Cases of Hypothyroidism: An Electrophysiological Study. *Ann Med Health Sci Res*, *6*(5), 261-266. doi:10.4103/amhsr.amhsr\_39\_16

Haanpaa, M., Attal, N., Backonja, M., Baron, R., Bennett, M., Bouhassira, D., . . . Treede, R. D. (2011). NeuPSIG guidelines on neuropathic pain assessment. *Pain*, *152*(1), 14-27. doi:10.1016/j.pain.2010.07.031

Indelicato, E., Nachbauer, W., Eigentler, A., Rudzki, D., Wanschitz, J., & Boesch, S. (2018). Intraepidermal Nerve Fiber Density in Friedreich's Ataxia. *J Neuropathol Exp Neurol*, *77*(12), 1137-1143. doi:10.1093/jnen/nly100

Ipsum\_Diagnostics. (2020). Nerve Testing. Retrieved from <https://ipsumdiagnostics.com/homepage/nerve-testing/>

Jeziorska, M., Atkinson, A., Kass-Iliyya, L., Javed, S., Kobylecki, C., Gosal, D., . . . Malik, R. A. (2019). Increased Intraepidermal Nerve Fiber Degeneration and Impaired Regeneration Relate

to Symptoms and Deficits in Parkinson's Disease. *Front Neurol*, 10, 111.  
doi:10.3389/fneur.2019.00111

Lauria, G., & Devigili, G. (2007). Skin biopsy as a diagnostic tool in peripheral neuropathy. *Nat Clin Pract Neurol*, 3(10), 546-557. doi:10.1038/ncpneuro0630

Lawson, V. H., Grewal, J., Hackshaw, K. V., Mongiovi, P. C., & Stino, A. M. (2018). Fibromyalgia syndrome and small fiber, early or mild sensory polyneuropathy. *Muscle Nerve*.  
doi:10.1002/mus.26131

Lim, S. H., Ferdousi, M., Kalteniece, A., Mahfoud, Z. R., Petropoulos, I. N., Malik, R. A., . . . Silverdale, M. Corneal Confocal Microscopy Identifies Parkinson's Disease with More Rapid Motor Progression. *Movement Disorders*, n/a(n/a). doi:https://doi.org/10.1002/mds.28602

Loseth, S., Stalberg, E., Jorde, R., & Mellgren, S. I. (2008). Early diabetic neuropathy: thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies. *J Neurol*, 255(8), 1197-1202. doi:10.1007/s00415-008-0872-0

Luo, K. R., Chao, C. C., Chen, Y. T., Huang, C. M., Yang, N. C., Kan, H. W., . . . Hsieh, S. T. (2011). Quantitation of sudomotor innervation in skin biopsies of patients with diabetic neuropathy. *J Neuropathol Exp Neurol*, 70(10), 930-938. doi:10.1097/NEN.0b013e318230b0f4

Magri, F., Buonocore, M., Oliviero, A., Rotondi, M., Gatti, A., Accornero, S., . . . Chiovato, L. (2010). Intraepidermal nerve fiber density reduction as a marker of preclinical asymptomatic small-fiber sensory neuropathy in hypothyroid patients. *Eur J Endocrinol*, 163(2), 279-284. doi:10.1530/eje-10-0285

Mantyh, W. G., Dyck, P. J., Engelstad, J. K., Litchy, W. J., Sandroni, P., & Davis, M. D. (2016). Epidermal Nerve Fiber Quantification in Patients With Erythromelalgia. *JAMA Dermatol*. doi:10.1001/jamadermatol.2016.4404

McArthur, J. C., Stocks, E. A., Hauer, P., Cornblath, D. R., & Griffin, J. W. (1998). Epidermal nerve fiber density: normative reference range and diagnostic efficiency. *Arch Neurol*, 55(12), 1513-1520. Retrieved from <http://dx.doi.org/>

McCarthy, B. G., Hsieh, S. T., Stocks, A., Hauer, P., Macko, C., Cornblath, D. R., . . . McArthur, J. C. (1995). Cutaneous innervation in sensory neuropathies: evaluation by skin biopsy. *Neurology*, 45(10), 1848-1855. Retrieved from <http://dx.doi.org/>

NeuroPath. (2020). We're Your In For Nerve Fiber Density Testing. Retrieved from <https://neuropathdx.com/index.html>

Piscosquito, G., Provitera, V., Mozzillo, S., Caporaso, G., Borreca, I., Stancanelli, A., . . . Nolano, M. (2021). The analysis of epidermal nerve fibre spatial distribution improves the diagnostic yield of skin biopsy. *Neuropathology and Applied Neurobiology*, 47(2), 210-217. doi:https://doi.org/10.1111/nan.12651

Pop-Busui, R., Boulton, A. J., Feldman, E. L., Bril, V., Freeman, R., Malik, R. A., . . . Ziegler, D. (2017). Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care*, 40(1), 136-154. doi:10.2337/dc16-2042

Provitera, V., Gibbons, C. H., Wendelschafer-Crabb, G., Donadio, V., Vitale, D. F., Loavenbruck, A., . . . Nolano, M. (2018). The role of skin biopsy in differentiating small-fiber neuropathy from ganglionopathy. *Eur J Neurol*, *25*(6), 848-853. doi:10.1111/ene.13608

Quattrini, C., Tavakoli, M., Jeziorska, M., Kallinikos, P., Tesfaye, S., Finnigan, J., . . . Malik, R. A. (2007). Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes*, *56*(8), 2148-2154. doi:10.2337/db07-0285

Shun, C. T., Chang, Y. C., Wu, H. P., Hsieh, S. C., Lin, W. M., Lin, Y. H., . . . Hsieh, S. T. (2004). Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. *Brain*, *127*(Pt 7), 1593-1605. doi:10.1093/brain/awh180

Smith, A. G., & Gibson, S. (2020). Skin biopsy for the evaluation of peripheral nerve disease - UpToDate. In A. Eichler (Ed.), *UpToDate*. Retrieved from [https://www.uptodate.com/contents/skin-biopsy-for-the-evaluation-of-peripheral-nerve-disease?source=search\\_result&search=nerve%20fiber%20density%20testing&selectedTitle=3~150](https://www.uptodate.com/contents/skin-biopsy-for-the-evaluation-of-peripheral-nerve-disease?source=search_result&search=nerve%20fiber%20density%20testing&selectedTitle=3~150)

Smith, A. G., Russell, J., Feldman, E. L., Goldstein, J., Peltier, A., Smith, S., . . . Singleton, J. R. (2006). Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care*, *29*(6), 1294-1299. doi:10.2337/dc06-0224

Smith, S. M., Dworkin, R. H., Turk, D. C., Baron, R., Polydefkis, M., Tracey, I., . . . Witter, J. (2017). The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *J Pain*, *18*(7), 757-777. doi:10.1016/j.jpain.2017.02.429

Sorensen, L., Molyneaux, L., & Yue, D. K. (2006). The relationship among pain, sensory loss, and small nerve fibers in diabetes. *Diabetes Care*, *29*(4), 883-887. Retrieved from <http://dx.doi.org/>

Therapath. (2020). Small Fiber Neuropathy Testing. Retrieved from <https://www.therapath.com/services/small-fiber-neuropathy-testing/>

Torvin Moller, A., Winther Bach, F., Feldt-Rasmussen, U., Rasmussen, A., Hasholt, L., Lan, H., . . . Staehelin Jensen, T. (2009). Functional and structural nerve fiber findings in heterozygote patients with Fabry disease. *Pain*, *145*(1-2), 237-245. doi:10.1016/j.pain.2009.06.032

van der Tol, L., Verhamme, C., van Schaik, I. N., van der Kooi, A. J., Hollak, C. E., & Biegstraaten, M. (2016). In Patients with an alpha-Galactosidase A Variant, Small Nerve Fibre Assessment Cannot Confirm a Diagnosis of Fabry Disease. *JIMD Rep*, *28*, 95-103. doi:10.1007/8904\_2015\_503

Vinik, A. I., Camacho, P. M., Davidson, J. A., Handelsman, Y., Lando, H. M., Leddy, A. L., . . . Ziegler, D. (2017). American Association of Clinical Endocrinologists And American College Of Endocrinology Position Statement On Testing For Autonomic And Somatic Nerve Dysfunction. *Endocr Pract*, *23*(12), 1472-1478. doi:10.4158/ep-2017-0053

Vlckova-Moravcova, E., Bednarik, J., Dusek, L., Toyka, K. V., & Sommer, C. (2008). Diagnostic validity of epidermal nerve fiber densities in painful sensory neuropathies. *Muscle Nerve*, *37*(1), 50-60. doi:10.1002/mus.20889

von Cossel, K., Muschol, N., Friedrich, R. E., Glatzel, M., Ammer, L., Lohmöller, B., . . . Godel, T. (2021). Assessment of small fiber neuropathy in patients carrying the non-classical Fabry variant p.D313Y. *Muscle Nerve*, 63(5), 745-750. doi:<https://doi.org/10.1002/mus.27196>

Wang, M., Zhang, C., Zuo, A., Li, L., Chen, L., & Hou, X. (2021). Diagnostic utility of corneal confocal microscopy in type 2 diabetic peripheral neuropathy. *Journal of Diabetes Investigation*, 12(4), 574-582. doi:<https://doi.org/10.1111/jdi.13381>

Wilkinson, K. D., Lee, K. M., Deshpande, S., Duerksen-Hughes, P., Boss, J. M., & Pohl, J. (1989). The neuron-specific protein PGP 9.5 is a ubiquitin carboxyl-terminal hydrolase. *Science*, 246(4930), 670-673. Retrieved from <http://dx.doi.org/>

### Policy Update History:

1/1/2023	New policy
----------	------------