Screening and Management of Peripheral Neuropathy using DPNCheck®

Provider Training

NEUROMetrix® | DPNCheck®

Learning Objectives

- Pathophysiology and epidemiology of peripheral neuropathy
- Gaps in clinical screening methods
- Nerve conduction principles
- DPNCheck device and how to interpret results
- Strategies for working up patients with suspected peripheral neuropathy

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Peripheral Neuropathy Background

- Pathophysiology
- Epidemiology
- Clinical findings

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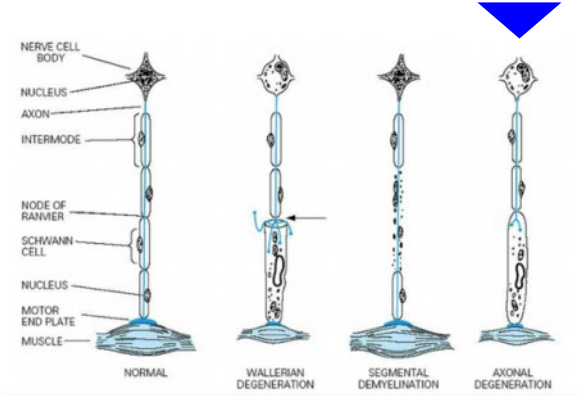
Peripheral neuropathy (polyneuropathy) is a systemic pathological change in peripheral nerves

- Distinct from focal neuropathy
- 90%+ (in primary care) are distal symmetric polyneuropathy (DSPN, DSP)
  - Affect feet / lower legs first
  - Symmetrical symptoms/signs, sensory > motor
  - Chronic, slowly progressing
  - Occasional autonomic involvement
- DSPN pathology
  - Primarily axonal degeneration
  - Both sensory and motor fibers usually affected
  - Maladaptive CNS changes (hyperalgesia, allodynia)
- Complex pathogenesis*
- Many causes including metabolic abnormalities, nutritional deficiencies, inflammation, toxins



*Oxidative stress, microvascular disease, impaired Na+/K+ ATPase activity, advanced glycation end products, mitochondrial dysfunction, axonal transport disruption, Schwann cell injury, inflammation, ion channel dysfunction

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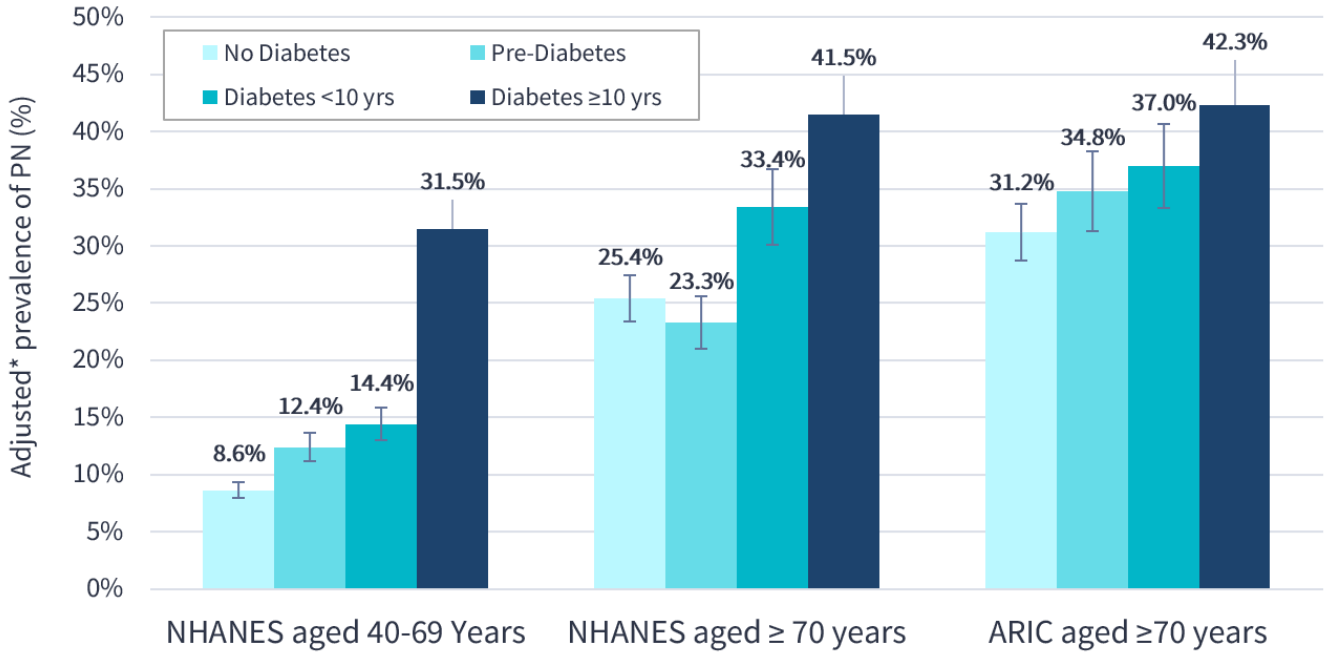
Approximately 30% of elderly patients have peripheral neuropathy

NHANES: 1999–2004 National Health and Nutrition Examination Survey

ARIC: 2016-2017 Atherosclerosis Risk in Communities Study



*Age, sex and race-adjusted prevalence of peripheral neuropathy stratified by diabetes status in US adults aged 40-69 and ≥ 70 Years (NHANES, 1999-2004) and ARIC participants aged ≥ 70 years (Visit 6, 2016-2017).

References: Hicks et al. Sci Rep, 2021.

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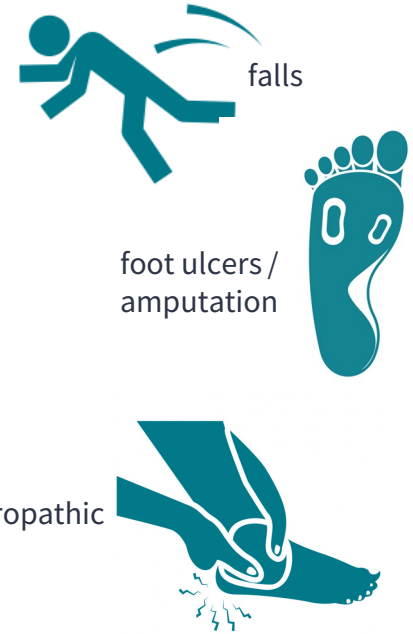
Peripheral neuropathy is associated with reduced quality of life, poor overall health & increased mortality

- Peripheral neuropathy independently associated with all-cause mortality (HR 1.4) and cardiovascular mortality (HR 1.3)
- Poor balance, unsteady gait and increased risk of falls
- Unrecognized skin trauma → ulcers, amputation
- Neuropathic pain
- Mobility limitations
- Muscle cramps
- Lower extremity weakness
- Charcot joints



HR, hazard ratio.

References: Hicks et al. Ann Intern Med, 2021. Richardson and Hurvitz. J. Gerontoloy, 1996. Ward et al. Aging & Disease, 2016. Boulton et al. NEJM, 2004. Richardson and Hurvitz. J Gerontol, 1995. Cheng et al. J Clin Nurs, 2002. Erlandson et al. J Acquir Immune Defic Syndr, 2019. Riskowski et al. Journal of Foot and Ankle Research, 2012.

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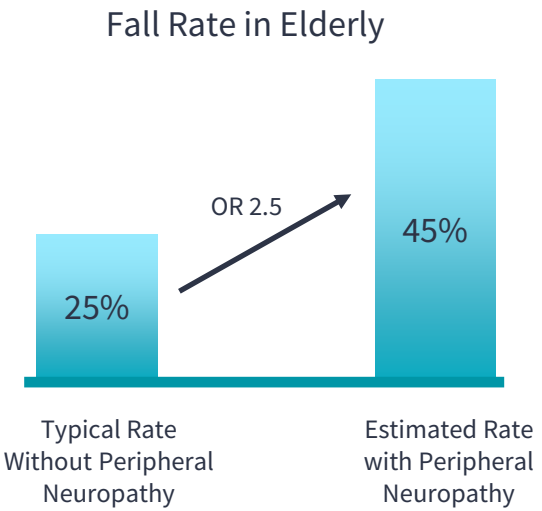
Peripheral neuropathy is an independent risk for falling and fall severity

Peripheral Neuropathy

- Decreased Sensation
- Altered Proprioception (sense of body position and movement)
- Weakness
- Neuropathic Pain

- Impaired postural stability
- Unstable gait

Increased Fall Risk (OR 1.5 – 2.5)
Increased Fall Severity



OR, odds ratio.

References: Richardson and Hurvitz. J Gerontol, 1995. Cheng et al. J Clin Nurs, 2002. Erlandson et al. J Acquir Immune Defic Syndr, 2019. Riskowski et al. Journal of Foot and Ankle Research, 2012.

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Diabetic peripheral neuropathy triggers a pathological cascade leading to foot ulceration and amputation

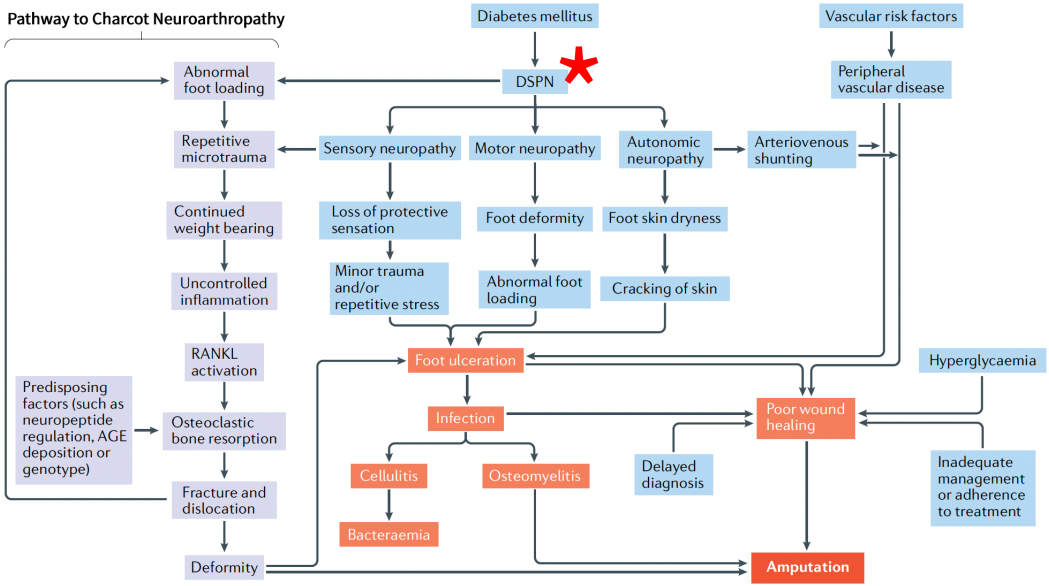

Fig. 1 | **The pathways to foot ulceration and amputation.** Diabetic sensorimotor peripheral neuropathy (DSPN), vascular disease and foot deformity might result in foot ulceration. In Charcot neuroarthropathy, minor trauma of the foot or ankle triggers an inflammatory cascade with a subsequent imbalance of the receptor activator of NF-κB ligand (RANKL)–osteoprotegerin axis, promoting osteoclastic bone resorption[288,289]. A cycle of fracture and dislocation develops, which is further compounded by weight bearing[289]. Blue boxes signify risk factors to foot ulceration and poor wound healing. Orange boxes represent the pathway to amputation of the ulcerated foot. The grey boxes indicate the pathway to Charcot neuropathy. AGE, advanced glycation end-product.

References: Sloan et al. Nature Reviews Endocrinology.

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Screening for peripheral neuropathy

- Limitations of traditional screening approaches
- Importance of nerve conduction testing
- Comparison of clinical screening and nerve conduction
- Implications of delayed detection

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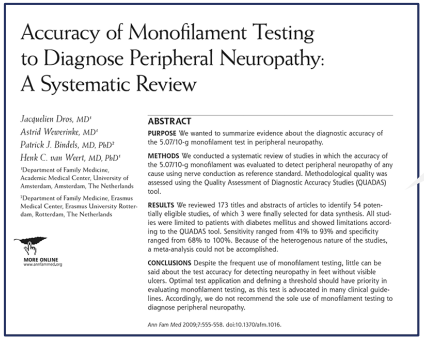
Clinical screening for peripheral neuropathy is subjective and diagnostically limited

- Common clinical approaches
  - 10 g Semmes-Weinstein monofilament
  - 128 Hz tunning-fork
  - Pinprick
  - Ankle reflexes
  - Symptoms

- Issues with clinical screening methods
  - **Do not localize disease to peripheral nerves**
  - **Detect late-stage disease (low sensitivity)**
  - High variability
  - Psychophysical responses
  - Subjective, require patient compliance
  - Non-standardized, many different techniques
  - Not adjusted for patient demographics

Dros et al. Med. 2009.



Accuracy of Monofilament Testing to Diagnose Peripheral Neuropathy: A Systematic Review

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Astrid Wewerinke, MD[2]
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ABSTRACT

PURPOSE We wanted to summarize evidence about the diagnostic accuracy of the 5.07/10-g monofilament test in peripheral neuropathy.

METHODS We conducted a systematic review of studies in which the accuracy of the 5.07/10-g monofilament was evaluated to detect peripheral neuropathy of any cause using nerve conduction as reference standard. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

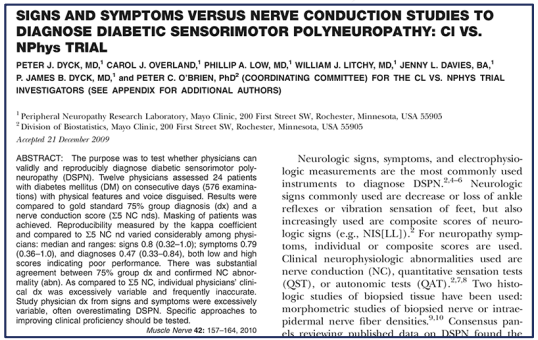
RESULTS We reviewed 173 titles and abstracts of articles to identify 54 potentially eligible studies, of which 3 were finally selected for data synthesis. All studies were limited to patients with diabetes mellitus and showed limitations according to the QUADAS tool. Sensitivity ranged from 41% to 93% and specificity ranged from 68% to 100%. Because of the heterogenous nature of the studies, a meta-analysis could not be accomplished.

CONCLUSIONS Despite the frequent use of monofilament testing, little can be said about the test accuracy for detecting neuropathy in feet without visible ulcers. Optimal test application and defining a threshold should have priority in evaluating monofilament testing, as this test is advocated in many clinical guidelines. Accordingly, we do not recommend the sole use of monofilament testing to diagnose peripheral neuropathy.

Ann Fam Med 2009;7:555-558. doi:10.1370/afm.1016.

"Despite the frequent use of monofilament testing, little can be said about the test accuracy for detecting neuropathy in feet without visible Ulcers … Accordingly, we do not recommend the sole use of monofilament testing to diagnose peripheral neuropathy."

Dyck et al. 2010.



SIGNS AND SYMPTOMS VERSUS NERVE CONDUCTION STUDIES TO DIAGNOSE DIABETIC SENSORIMOTOR POLYNEUROPATHY: CI VS. NPhys TRIAL

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Accepted 21 December 2009

ABSTRACT: The purpose was to test whether physicians can validly and reproducibly diagnose diabetic sensorimotor polyneuropathy (DSPN). Twelve physicians assessed 24 patients with diabetes mellitus (DM) on consecutive days (576 examinations) with physical features and voice disguised. Results were compared to gold standard 75% group diagnosis (dx) and a nerve conduction score (Σ5 NC nds). Masking of patients was achieved. Reproducibility measured by the kappa coefficient and compared to Σ5 NC nd varied considerably among physicians: median and ranges: signs 0.8 (0.32–1.0); symptoms 0.79 (0.36–1.0), and diagnoses 0.47 (0.33–0.84), both low and high scores indicating poor performance. There was substantial agreement between 75% group dx and confirmed NC abnormality (abn). As compared to Σ5 NC, individual physicians' clinical dx was excessively variable and frequently inaccurate. Study physician dx from signs and symptoms were excessively variable, often overestimating DSPN. Specific approaches to improving clinical proficiency should be tested.

Muscle Nerve **42:** 157–164, 2010

Neurologic signs, symptoms, and electrophysiologic measurements are the most commonly used instruments to diagnose DSPN.[2,4–6] Neurologic signs commonly used are decrease or loss of ankle reflexes or vibration sensation of feet, but also increasingly used are composite scores of neurologic signs (e.g., NIS[LL]).[2] For neuropathy symptoms, individual or composite scores are used. Clinical neurophysiologic abnormalities used are nerve conduction (NC), quantitative sensation tests (QST), or autonomic tests (QAT).[2,7,8] Two histologic studies of biopsied tissue have been used: morphometric studies of biopsied nerve or intraepidermal nerve fiber densities.[9,10] Consensus panels, reviewing published data on DSPN found the

"As compared to Σ5 NC [nerve conduction], individual physicians' clinical dx was excessively variable and frequently inaccurate. Study physician dx from signs and symptoms were excessively variable, often overestimating DSPN."

References: Dros et al. Ann Fam Med, 2009. Dyck et al. Muscle Nerve, 2010.

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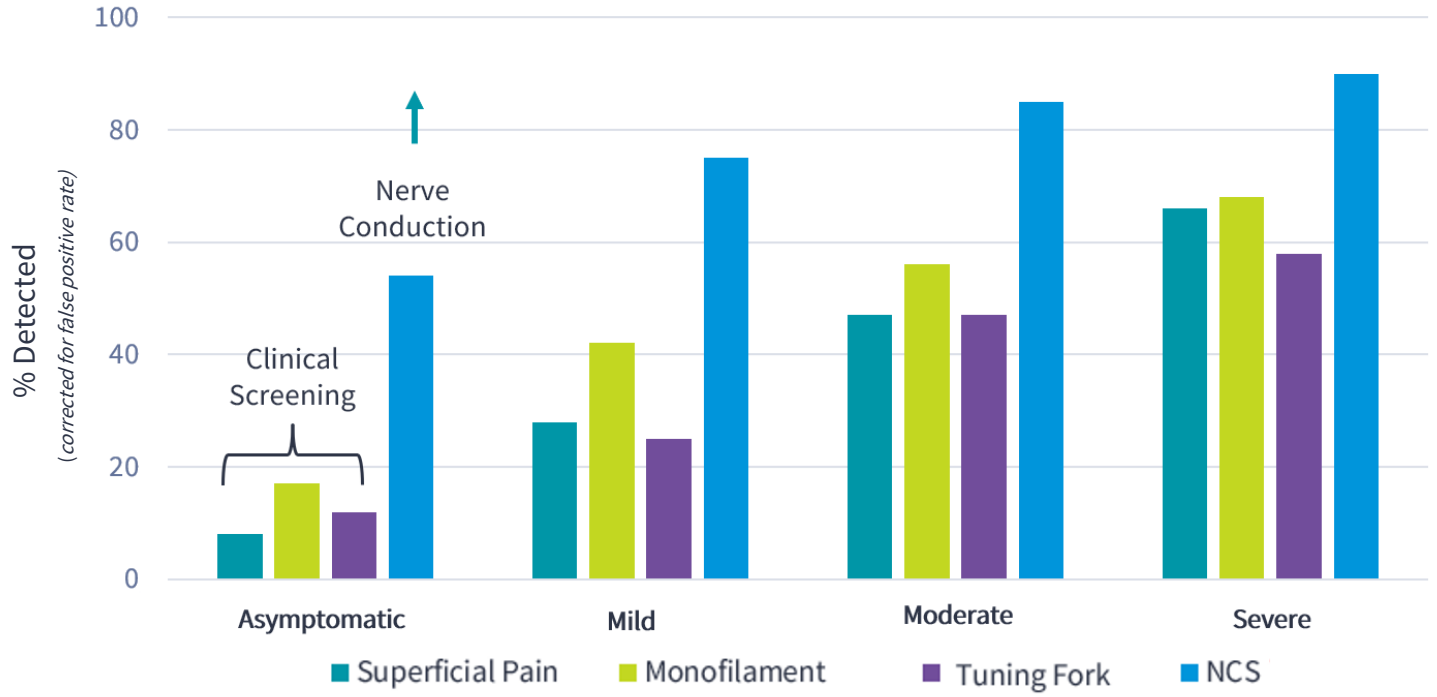
Clinical screening tests have low sensitivity for peripheral neuropathy compared to nerve conduction



References: Perkins et al. Diabetes Care, 2001.

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Monofilament and tuning fork only detect half of peripheral neuropathy cases identified by sural nerve conduction*

Research Article

A Comparison of Screening Tools for the Early Detection of Peripheral Neuropathy in Adults with and without Type 2 Diabetes

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(b) Sensitivity and specificity of screening tests and subcomponents

	Prevalence	Sensitivity	Specificity	PPV*	NPV*
128 Hz tuning fork	52.90%	50.00%	75.00%	69.20%	57.10%
1 g monofilament	26.50%	66.70%	72.00%	46.20%	85.70%
10 g monofilament	55.90%	47.40%	73.30%	69.20%	52.40%
QOL-DN total	29.40%	60.00%	70.80%	46.20%	81.00%
QOL-DN symptoms	32.40%	36.40%	60.90%	30.80%	66.70%
QOL-DN large fiber	35.30%	58.30%	72.70%	53.80%	76.20%
QOL-DN small fiber	97.10%	39.40%	100.00%	100.00%	4.80%
QOL-DN ADLS	76.50%	42.30%	75.00%	84.60%	28.60%
QOL-DN autonomic	61.80%	42.90%	69.20%	69.20%	42.90%

*Normoglycemic, PD, and T2D. PPV = positive predictive value; NPV = negative predictive value; based off R/L SNAP values. Prevalence indicates presence of findings for indications of neuropathy.

QOL-DN, Norfolk Quality of Life Diabetic Neuropathy questionnaire
*Performed with DPNCheck

References: Brown et al. Journal of Diabetes Research, 2017. Wang et al. Muscle Nerve, 2012. Baraz et al. J Diabetes Metab Disord, 2014.

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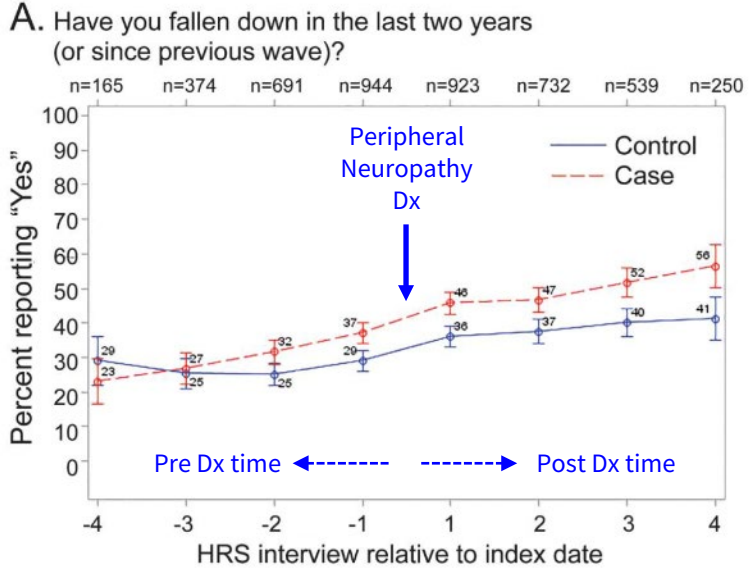
Implication of late detection is that falls, lower quality of life and pain precede diagnosis by several years

Figure 1 **Comparison of the patient-oriented outcome trajectories between patients with neuropathy and propensity-matched controls**



"We found that older adults with neuropathy have more falls and pain and lower self-rated health compared to carefully matched controls without neuropathy. These differences were present 3–5 years prior to a neuropathy diagnosis and persist for several years after diagnosis."

"This finding may be partly explained by a delay in diagnosis in this highly prevalent condition, and also highlights the fact that neuropathy often develops slowly over time. Patients typically report neuropathic symptoms to their physician years after their insidious onset."

References: Callaghan et al. Neurology, 2015.

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Nerve conduction principles

- Stimulation and recording
- Interpretation
- Why test sural nerve

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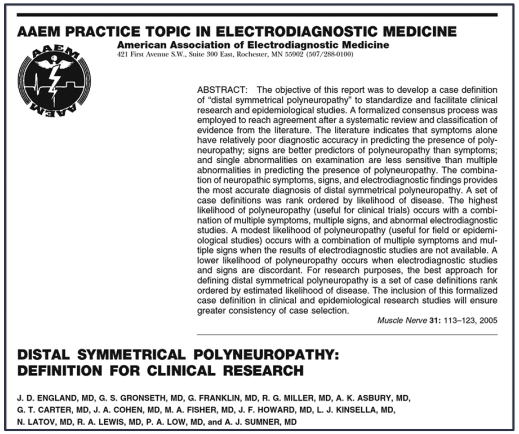
Nerve conduction is the gold standard diagnostic test for peripheral neuropathy

- Position statement of American Academy of Neurology, AANEM, AAPM&R

Likelihood of Peripheral Neuropathy



AAEM PRACTICE TOPIC IN ELECTRODIAGNOSTIC MEDICINE

American Association of Electrodiagnostic Medicine

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ABSTRACT: The objective of this report was to develop a case definition of "distal symmetrical polyneuropathy" to standardize and facilitate clinical research and epidemiological studies. A formalized consensus process was employed to reach agreement after a systematic review and classification of evidence from the literature. The literature indicates that symptoms alone have relatively poor diagnostic accuracy in predicting the presence of polyneuropathy; signs are better predictors of polyneuropathy than symptoms; and single abnormalities on examination are less sensitive than multiple abnormalities in predicting the presence of polyneuropathy. The combination of neuropathic symptoms, signs, and electrodiagnostic findings provides the most accurate diagnosis of distal symmetrical polyneuropathy. A set of case definitions was rank ordered by likelihood of disease. The highest likelihood of polyneuropathy (useful for clinical trials) occurs with a combination of multiple symptoms, multiple signs, and abnormal electrodiagnostic studies. A modest likelihood of polyneuropathy (useful for field or epidemiological studies) occurs with a combination of multiple symptoms and multiple signs when the results of electrodiagnostic studies are not available. A lower likelihood of polyneuropathy occurs when electrodiagnostic studies and signs are discordant. For research purposes, the best approach for defining distal symmetrical polyneuropathy is a set of case definitions rank ordered by estimated likelihood of disease. The inclusion of this formalized case definition in clinical and epidemiological research studies will ensure greater consistency of case selection.

Muscle Nerve **31:** 113–123, 2005

DISTAL SYMMETRICAL POLYNEUROPATHY: DEFINITION FOR CLINICAL RESEARCH

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AANEM, American Association of Neuromuscular & Electrodiagnostic Medicine. AAN, American Academy of Neurology. AAPM&R, American Academy of Physical Medicine and Rehabilitation.

Table 1. Estimated likelihood of distal symmetrical polyneuropathy for case definitions that include symptoms, signs, and nerve conduction studies (recommendations for clinical research studies).

Neuropathic symptoms	Decreased or absent ankle reflexes*	Decreased distal sensation	Distal muscle weakness or atrophy	NCS†	Ordinal likelihood
Present	Present	Present	Present	Abnormal	++++
Absent	Present	Present	Present	Abnormal	++++
Present	Present	Present	Absent	Abnormal	++++
Present	Present	Absent	Absent	Abnormal	++++
Present	Absent	Present	Absent	Abnormal	++++
Absent	Present	Absent	Present	Abnormal	+++
Present	Absent	Absent	Absent	Abnormal	+++
Absent	Absent	Absent	Absent	Abnormal	++
Absent	Present	Absent	Absent	Abnormal	++
Present	Present	Present	Absent	Normal	++
Present‡	Absent	Present‡	Absent	Normal‡	+
Present§	Present§	Present§	Present§	Normal§	–

Neuropathic symptoms: numbness, altered sensation, or pain in the feet. NCS, nerve conduction studies. For clinical research studies enrollment should be limited to cases above the bold horizontal line (i.e., ++++).

**Ankle reflexes may be decreased in normal individuals >65–70 years.*

†Abnormal NCS is defined in text.

‡This phenotype is common in "small-fiber" sensory polyneuropathy. Determination of intraepithelial nerve fiber density in skin biopsy may be useful to confirm the diagnosis (see text).

§This phenotype in the presence of normal NCS is not a distal symmetrical polyneuropathy. This situation is given a negative (–) ordinal likelihood because the condition cannot be classified as a distal symmetrical polyneuropathy. It is included here to emphasize the importance of including NCS as part of the case definition for clinical research studies.

References: England et al. Muscle Nerve, 2005.

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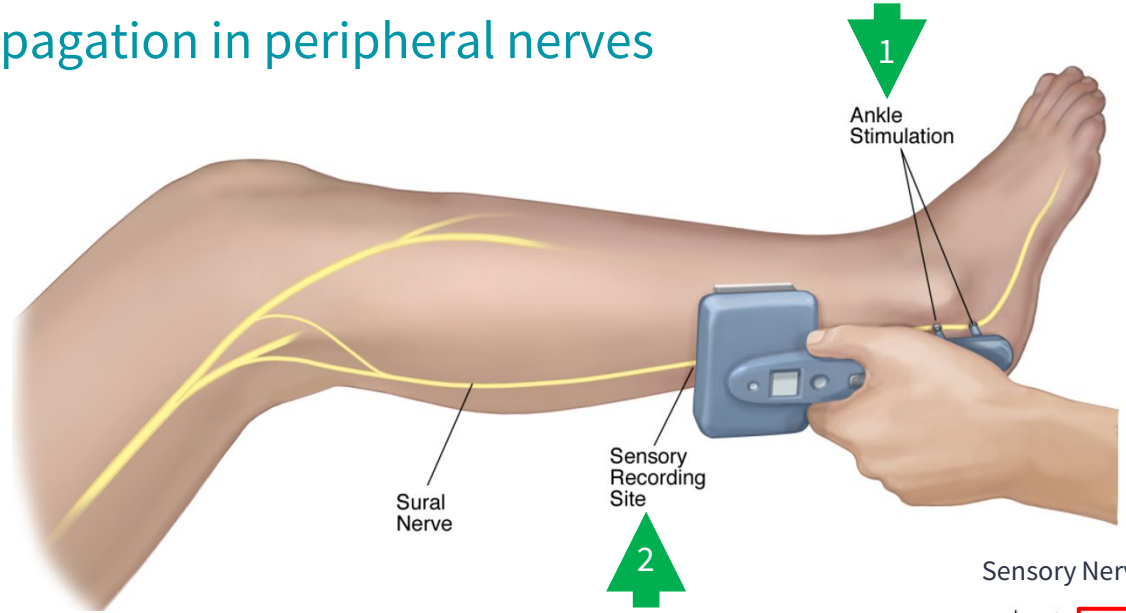
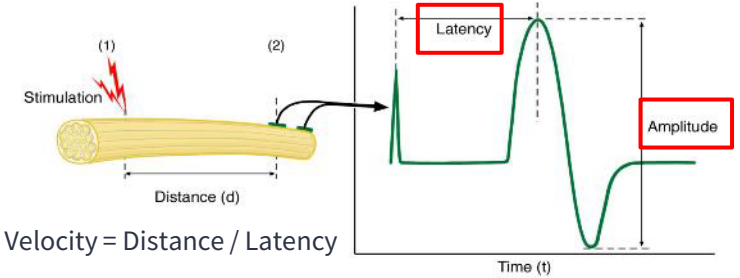
Nerve conduction is the measurement of action potential propagation in peripheral nerves



Nerve conduction measures the large myelinated axons (Aα, Aβ)

Sensory Nerve Action Potential



Conduction Velocity = Distance / Latency

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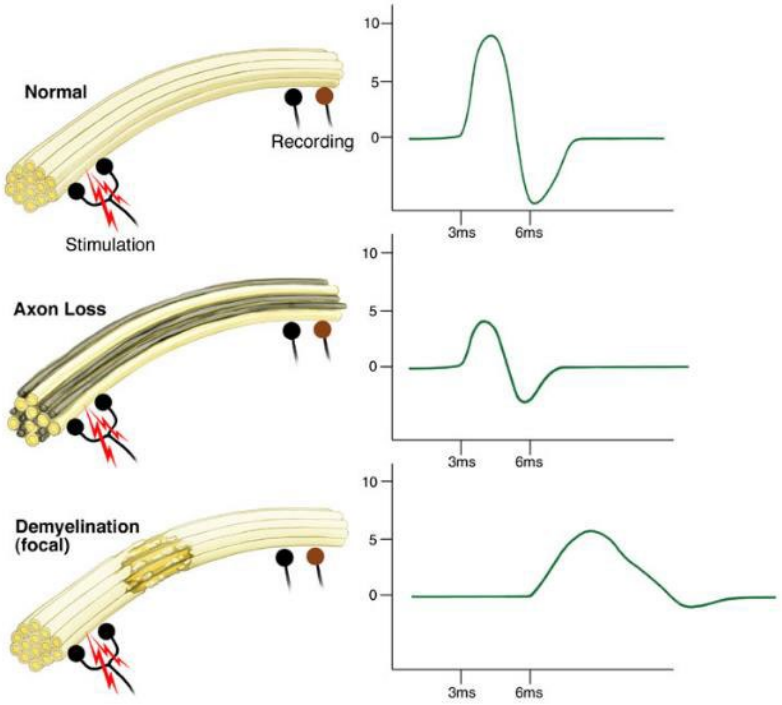
Sensory nerve amplitude correlates with nerve fiber density



"Virtual Nerve Biopsy"

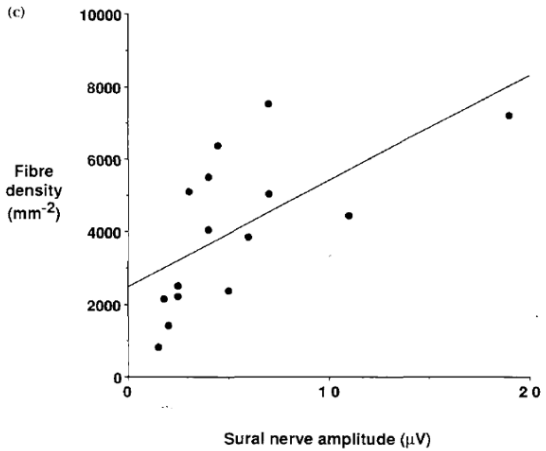
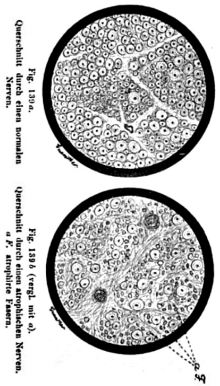


Figure 1. Relation between myelinated fibre density in sural nerve biopsies and electrophysiological measures in patients with mild diabetic neuropathy. Significant correlations were found with peroneal conduction velocity, $r = 0.58$, $p < 0.02$ (a), sural conduction velocity, $r = 0.84$, $p < 0.001$ (b), and sural nerve amplitude, $r = 0.74, p < 0.001$ (c)



Oppenheim. Textbook of nervous disease.. 1894.

References: Veves et al. Diabetic Medicine 1991.

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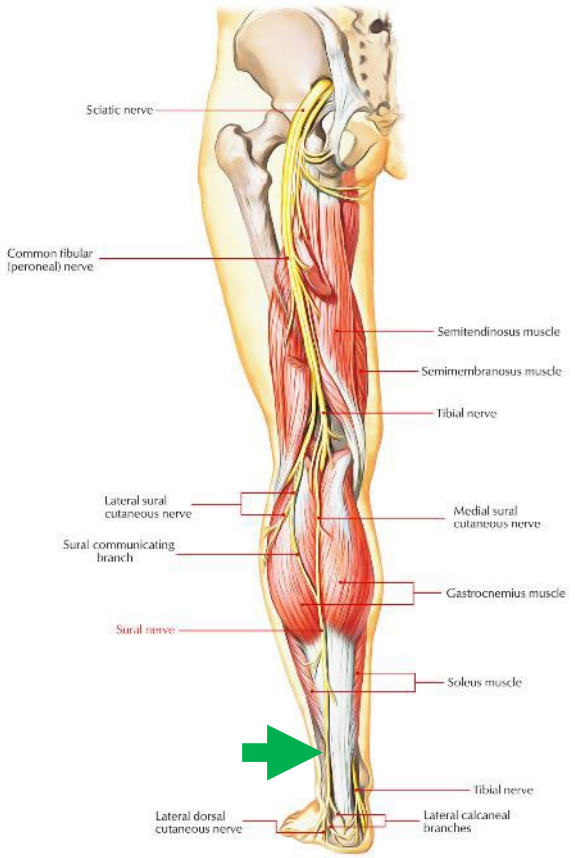
Sural nerve conduction is a sensitive and specific indicator of distal nerve fiber loss

- Neuroanatomy
  - Distal sensory nerve
  - Comprised of branches from the tibial and common fibular nerves
  - Supplies sensation to the skin of the lateral foot and lateral lower ankle
- Sensitive indicator of distal nerve fiber loss
- Abnormalities are specific for peripheral neuropathy
  - Unaffected by lumbosacral disc herniation
  - Focal neuropathy of sural nerve (or proximal fibers) uncommon
  - Sural nerve response is detectable in most non-neuropathic elderly patients



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DPNCheck

- Device overview
- Why test sural nerve
- Clinical validation
- Interpretation of results
- Quality control

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DPNCheck is a standardized and automated sural nerve conduction test

Testing in 4 Easy Steps

1

Position patient, prepare skin

2

Place biosensor, apply gel

3

Position device, start test

4

View results after 10-15 seconds

- Performed in minutes by medical assistant
- Gold standard NCS technology
- Device + single-patient use biosensor
- Reports amplitude and conduction velocity
- Straightforward interpretation
- 2M patients tested over 10 years

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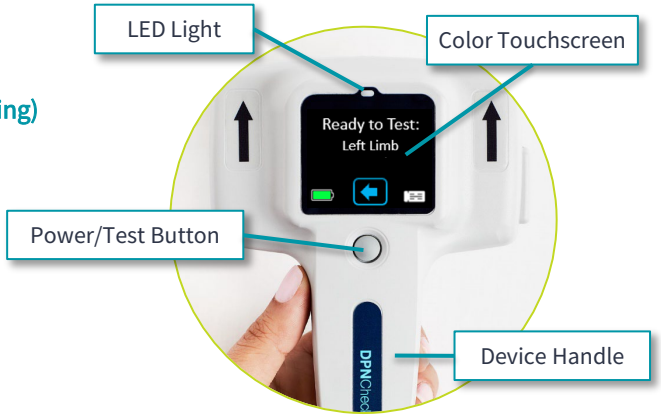
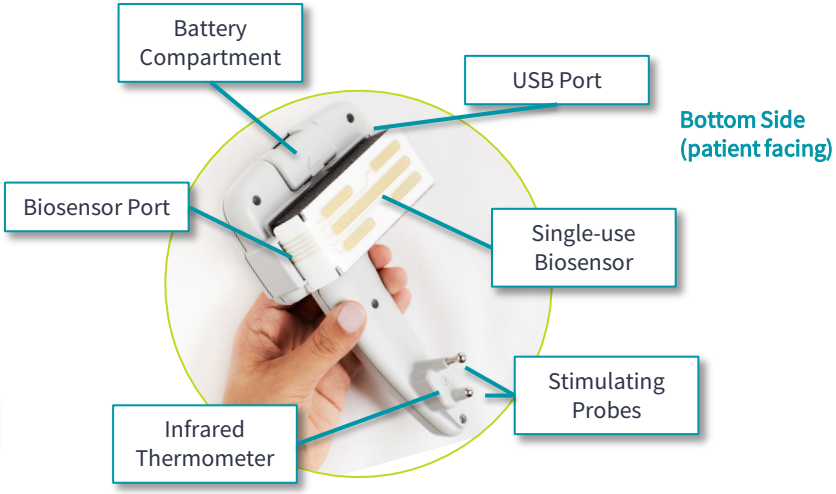
DPNCheck 2.0 device overview

Top Side (tester facing)



Bottom Side (patient facing)



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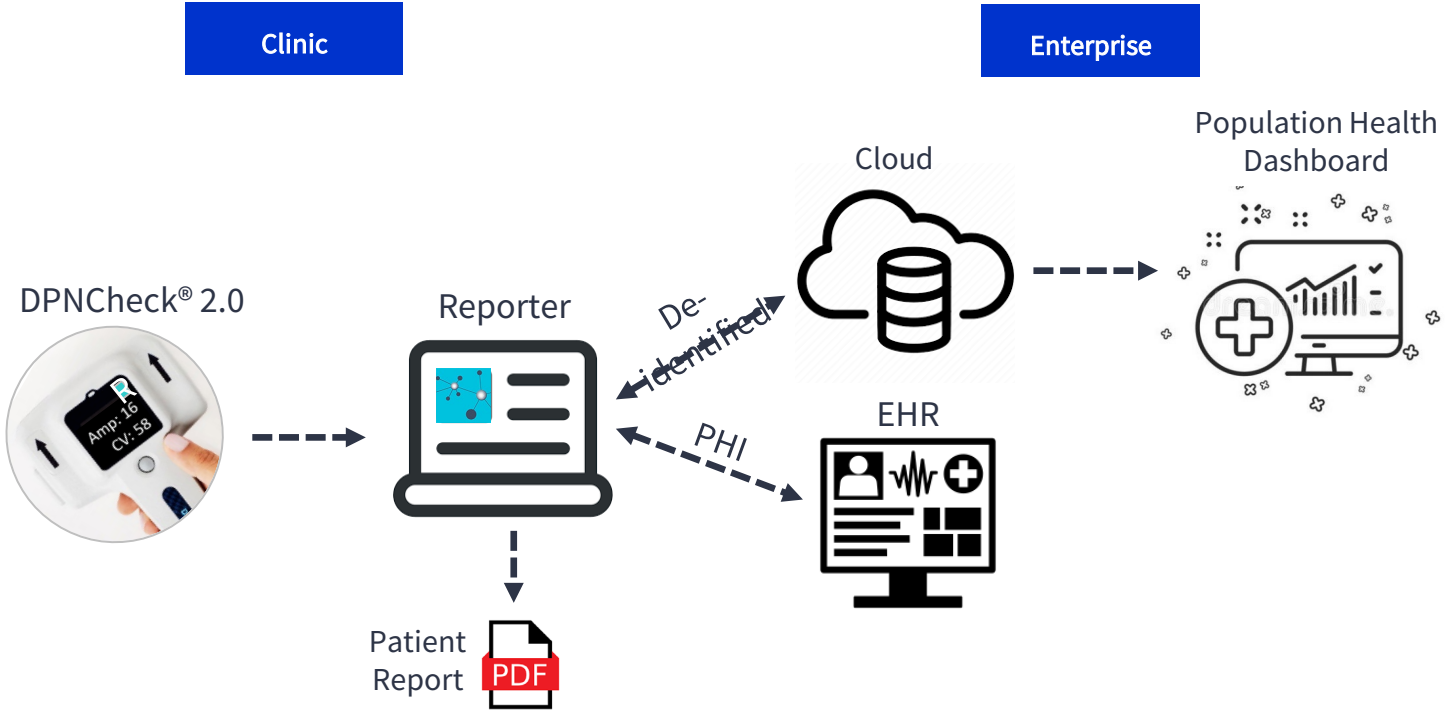
DPNCheck software ecosystem propagates point-of-care results throughout healthcare enterprise



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Seven independent studies on 892 subjects demonstrate that DPNCheck exhibits good diagnostic accuracy

	Diabetes Type				Peripheral Neuropathy		
Study Publication	**Type 2**	**Type 1**	**No Diabetes**	**Total**	**Reference Diagnosis**	**Sensitivity**	**Specificity**
Binns-Hall et al. 2018	231	5	0	236	Clinical	0.84	0.68
Papanas et al. 2019	0	53	0	53	Clinical	0.96	0.93
Chatzikosma et al. 2016	114	0	46	160	Clinical	0.91	0.86
Hirayasu et al. 2018	92	0	0	92	Clinical	0.85	0.86
Lee et al. 2014	28	16	0	44	NCS	0.95	0.71
Kural et al. 2018	168	0	0	168	NCS	0.82	0.85
Scarr et al. 2018	0	68	71	139	NCS	0.86	0.79
Total	**633**	**142**	**117**	**892**		**0.88***	**0.82***

*Summary sensitivity and specificity determined by bivariate meta-analysis.

Youden Index = 0.70
(effective diagnostic test has Youden Index > 0.50, Power et al. 2013)

Youden Index = sensitivity + specificity – 1.

References: Power et al. Principles for high-quality, high-value testing. Evid Based Med, 2013.

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Interpretation of DPNCheck results is straightforward

1. Perform test to obtain results (3 possibilities – all valid)

Amp + CV

Amp only

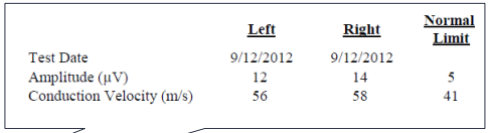
Undetectable

2. Determine abnormalities.
   - Abnormal if value < normal limit or undetectable
   - Normal limit can be fixed or age/height adjusted
3. Interpret*

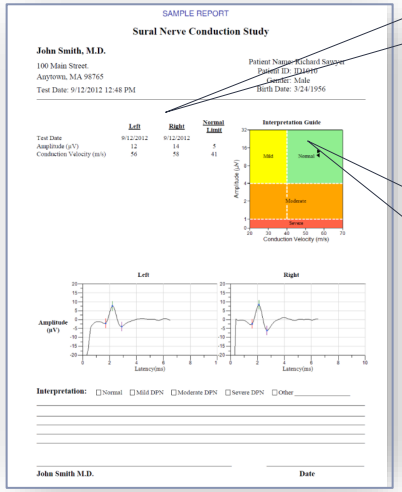
Peripheral Neuropathy	Amplitude	Conduction Velocity
No Neuropathy	Normal	Normal
Mild	Normal	Abnormal
Moderate	Abnormal	Normal / Abnormal
Severe	Undetectable	

*Diagnosis of peripheral neuropathy is based on providers' medical judgement and institutional protocols.

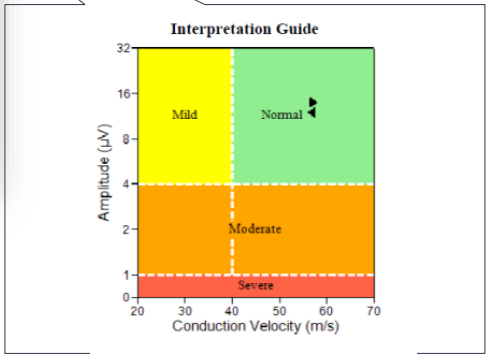
Results, normal limits
Abnormalities indicated with *



	Left	Right	Normal Limit
Test Date	9/12/2012	9/12/2012	
Amplitude (μV)	12	14	5
Conduction Velocity (m/s)	56	58	41



Interpretation guide



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Interpretation examples

Age (Years)	Height (Inches)	Amplitude		Conduction Velocity		Abnormalities	Interpretation*
		Result	Normal Limit	Result	Normal Limit		
65	60	12	5	53	47	None	Normal
65	60	3	5	40	46	Amp, CV	Moderate
85	72	3	3	40	38	None	Normal
85	72	2	3	35	38	Amp, CV	Moderate
85	72	Undetectable**	3	--	38	Undetectable	Severe
85	72	2	3	--	38	Amp	Moderate

*Diagnosis of peripheral neuropathy is based on providers' medical judgement and institutional protocols.
**Undetectable indicates amplitude < 1.5 microvolts

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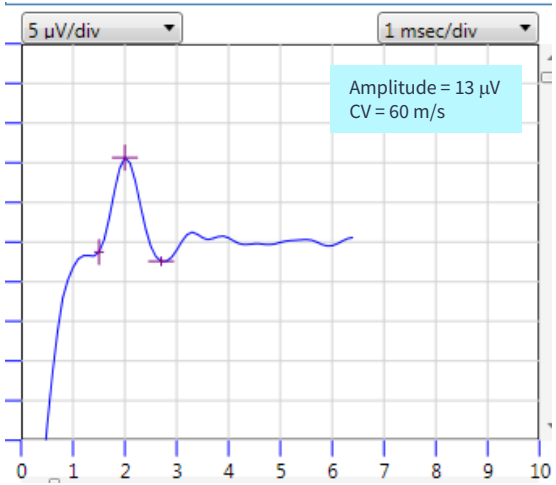
DPNCheck automated quality control helps confirm that reliable and valid nerve responses are acquired

- Patient skin temperature is not too cold
- Stimulators placed on skin without excessive gel
- Biosensor placed directly on skin (e.g., liner removed)
- Adequate stimulation intensity* to overcome edema, adipose tissue and neuropathy
- Average at least 4 nerve responses
- Confirm that nerve response is not contaminated by artifacts (e.g., stimulus, electrical interference, movement)
- Confirm that correct limb was selected



*Up to 70 milliamps.

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Patient Work-up

- Underdiagnosis of peripheral neuropathy
- Assessment framework
- Common etiologies
- Clinical vignettes

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50%+ of peripheral neuropathy in elderly patients may be undetected or undertreated

- Prevalence of peripheral neuropathy by ICD-10 codes ~15%
  - Diabetic PN (~10%) and non-diabetic PN (~5%)
- Most non-diabetic peripheral neuropathy coded as non-specific (ICD-10 G6289, G629)
  - At least 50% may have an identifiable etiology
  - Potential causes often coded in these patients (RA, alcoholism, AIDS/HIV, kidney disease/dialysis)
- Peripheral neuropathy documentation is often incomplete
  - Lack of specificity, status and current treatment
  - Possibly due to use of auto-populated EMR defaults

Coded comorbidities that may cause peripheral neuropathy*	G6289/ G629 (Unspecified Polyneuropathy)	2019 Claims Data
Rheumatoid Arthritis	Yes	0.71%
Substance Dependence	Yes	0.61%
AIDS/ HIV	Yes	0.03%
Cancer	Yes	0.89%
Unspecified Diabetes	Yes	0.71%
Cirrhosis/ End-Stage Liver	Yes	0.13%
Dialysis	Yes	0.76%
Any Comorbids (1+)	**Yes**	**2.81%**
No comorbidity*	**Yes**	**2.58%**
Total Unspecified/ General Neuropathy		**5.39%**

*Additional potential causes include metabolic syndrome, hypoxic conditions, nutritional deficiencies

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Source: Gorman Health Group analysis, 2021 (4 Medicare Advantage plans)

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Evaluation and diagnosis of peripheral neuropathy often does not follow highest levels of evidence

- 10-year study evaluating 1031 patients who received a new ICD-9 diagnosis of peripheral neuropathy (average age 78 years)
- 48% of patients with diabetes diagnosed as having idiopathic peripheral neuropathy
- 80% of patients without diabetes diagnosed as having idiopathic peripheral neuropathy
- Low utilization of recommended tests (Figure 1 on right)
- MRI of brain / spinal cord performed in 23% of patients

ORIGINAL INVESTIGATION

Tests and Expenditures in the Initial Evaluation of Peripheral Neuropathy

Brian Callaghan, MD; Ryan McCammon, AB; Kevin Kerber, MD; Xiao Xu, PhD; Kenneth M. Langa, MD, PhD; Eva Feldman, MD, PhD

"For a condition that affects the peripheral nervous system, this degree of utilization is substantial and suggests that many physicians have significant uncertainty when localizing neuropathy symptoms to the peripheral nervous system."

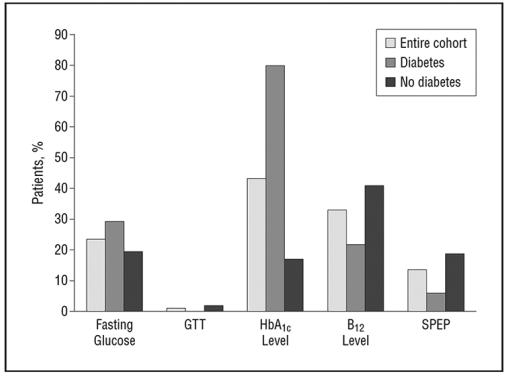

Figure 1. Utilization of diabetic and American Academy of Neurology–recommended tests in 1031 patients with peripheral neuropathy. GTT indicates glucose tolerance test; HbA_{1c}, hemoglobin A_{1c}; and SPEP, serum protein electrophoresis.

References: Callaghan et al. Arch Int Med, 2012.

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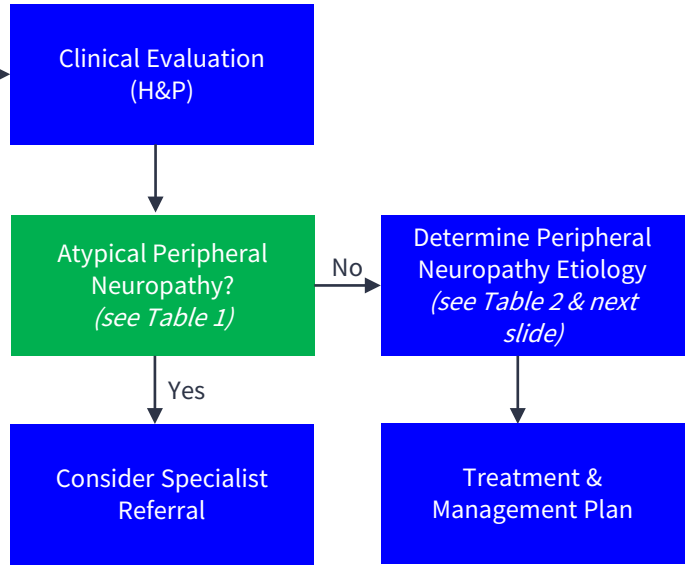
Patient assessment framework

Positive DPNCheck Screening Test



CONCISE REVIEW FOR CLINICIANS

MAYO CLINIC

Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management

James C. Watson, MD, and P. James B. Dyck, MD

TABLE 1. Neuropathies in Which Specialty Consultation Would Be Beneficial

- Acute, subacute in onset
- Rapidly progressive
- Severe, functionally limiting

} Regardless of clinical pattern or affected modality

- Length independent (polyradiculoneuropathy)
- Multifocal
- Motor predominant
- Associated with severe dysautonomia

TABLE 2. Recommended Evaluation of Chronic, Length-Dependent Peripheral Neuropathy

- Complete blood cell count
- Renal function
- Liver function tests
- Erythrocyte sedimentation rate (extractable nuclear antigen if dry eyes/mouth and sensory neuropathy are present)
- Fasting glucose[a] (11%) or hemoglobin A_{1c}[a] (26%)
- Thyroid stimulating hormone
- Monoclonal protein[a] (serum protein immunofixation electrophoresis) (10%)
- Vitamin B_{12} (2%) (with methylmalonic acid 9%)[a]
- Infectious (if risk factors or endemic region): Lyme disease, human immunodeficiency virus
- Family history of peripheral neuropathy, pes cavus, hammertoes[a]

[a]Indicates highest-yield serologic tests with percentage of cases identified.

References: Watson and Dyck. Mayo Clin Proc, 2015.

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History, physical exam and serologic evaluation should identify cause of ~80% of peripheral neuropathy cases

Endocrine / Metabolic*
- Diabetes mellitus
- Prediabetes
- Hypothyroidism / hyperthyroidism
- Chronic renal failure
- Liver disease

Autoimmune
- Connective tissue disease*
- Vasculitis
- Inflammatory bowel disease
- Sarcoidosis
- Celiac disease

Nutritional
- Vitamin B12*
- Vitamin B1 deficiency
- Vitamin B6 deficiency or toxicity
- Vitamin E deficiency
- Copper deficiency
- Post-gastric bypass

Cancer Associated
- Paraprotein-associated
  - MGUS*
  - Multiple myeloma
  - Waldenstrom's macroglobulinemia
  - Lymphoma
- Primary amyloidosis
- Paraneoplastic syndromes

Toxic
- Ethanol*
- Heavy metals
- Organic solvents

Medications (incomplete list)
- Chemotherapy*
  - Platinums
  - Taxanes
  - Vincristine
  - Bortezomib
- Phenytoin
- Fluoroquinolones
- Disulfiram

Infections
- HIV
- HTLV-1
- Leprosy
- COVID-19

Hypoxia
- Obstructive sleep apnea
- Chronic obstructive pulmonary disease

Inherited
- Charcot-Marie-Tooth
- Familial amyloidosis

Peripheral neuropathy pearls

- Over 60% of cases may not be associated with diagnosed diabetes
- Consider metabolic syndrome in patients without clear etiology
- Vitamin B12 deficiency may be found in 2 – 8% of patients
- Approximately 10% of patients have a serum paraprotein
- Consider conditions causing generalized hypoxia (obstructive sleep apnea, COPD)
- Explore family history for potential inherited peripheral neuropathy if long standing and pes cavus
- Consider post-acute sequelae of SARS-CoV-2 infection (PASC, Long COVID) if recent condition

*Most common causes of peripheral neuropathy.

References: Doughty and Seyedsadjadi. The American J. of Medicine, 2018. Oaklander et al. Neurol Neuroimmunol Neuroinflamm, 2022. Hanewinckel et al. Journal of Neurology, Neurosurgery & Psychiatry, 2016. Lehmann et al. Neurological Research and Practice, 2020. Dziewas et al. J Neurol Neurosurg Psychiatry, 2007. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165–85.

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Peripheral neuropathy treatment and management

Patient education	Educational brochure		
Treat underlying disease (etiology)	Intensification of glucose control	B12 therapy	Remove toxin exposure
Treat symptoms	Neuropathic pain	Poor sleep	Anxiety, Depression
Risk mitigation	Fall prevention	Foot care	
Referrals	Neurology (atypical presentation)	Podiatry (at-risk foot)	Hematology (gammopathy)

Protecting Yourself from Peripheral Neuropathy

This pamphlet will help you understand your DPNCheck test and provide you with an overview of peripheral neuropathy.

What is the DPNCheck test?

It is a sophisticated diagnostic test of your nerves. It helps your doctor determine whether your nerves are healthy or if they are impaired, which is called peripheral neuropathy. If you do have peripheral neuropathy, the test will also help your doctor determine the severity.

Peripheral neuropathy may have no signs or symptoms until the nerves have been substantially damaged. Therefore, the DPNCheck test may be the only way to detect the problem at an early stage and initiate treatment that is critical to controlling its impact on your life.

Why were you given this test?

Your doctor determined that you are at risk for peripheral neuropathy.

What does a positive result mean?

A positive test means you probably have peripheral neuropathy.

What is peripheral neuropathy?

Peripheral nerves run from your spine to your arms, hands, legs and feet. There are two types of peripheral nerves; sensory and motor. Sensory nerves convey sensations such as your ability to feel, the temperature of objects you touch, and pain to your brain. Motor nerves carry signals from the brain to your muscles instructing them to contract or relax. For example, if you step on a sharp object, the sensory nerves in your feet send a signal to your brain telling it you're on something sharp. Your brain then processes that information and sends signals through your motor nerves to the muscles in your foot which results in moving your foot off the sharp object. Peripheral neuropathy is a disorder where the peripheral nerves are damaged in some fashion. This damage disrupts their ability to transmit messages to and from the brain. This can result is a reduction in your ability to sense, it may also lead to pain and poor balance, and in severe cases to weakness.

Why do you have peripheral neuropathy?

Peripheral neuropathy affects over 30 million Americans. There are many causes, the most common being diabetes which is referred to as diabetic peripheral neuropathy. People who are pre-diabetic, overweight, have high blood pressure or have elevated cholesterol levels are at increased risk. Other common causes include chemotherapy, autoimmune conditions such as rheumatoid arthritis, excessive alcohol use and low vitamin B12 levels. The risk of peripheral neuropathy goes up with age. Among people 65 or older, over one-quarter have peripheral neuropathy.

What are some common symptoms of peripheral neuropathy?

The symptoms of peripheral neuropathy are usually felt first in the feet, though some people may experience them in the hands if the disease is advanced. You may experience some of the following symptoms with your peripheral neuropathy:

- Pain or burning
- Numbness or tingling
- Sensation of pins and needles
- Increased sensitivity to normal touch
- Trouble feeling hot or cold
- Trouble feeling your feet when you walk

What health risks are associated with peripheral neuropathy?

There are several health risks associated with peripheral neuropathy including:

Pain:
You may experience pain which can be severe. It is often described as burning or stabbing pain.

Falls:
People with peripheral neuropathy, especially the elderly, are at a higher risk of falling that may result in serious injuries.

Foot Ulcers:
If you have diabetes and peripheral neuropathy, you are at increased risk of foot ulcers. Ulcers occur most often on the ball of the foot or on the bottom of the big toe. Remember, even though some ulcers do not hurt, every ulcer should be seen by your doctor right away.

Poor Sleep:
The pain associated with peripheral neuropathy may disrupt your normal sleep patterns. The lack of sleep can then increase your sensitivity to pain and generally harm your health.

Here is the good news – now that we have objectively confirmed that you have peripheral neuropathy, it can be addressed and its progression can be monitored.

Can peripheral neuropathy be cured?

There is no "cure" for peripheral neuropathy. However, there are several things that can be done that will slow down its progression and even partially reverse it. Depending on the reason for your peripheral neuropathy, your doctor will give you a plan of action that you should follow as closely as possible. Just by reading this pamphlet you are taking the important step of educating yourself about peripheral neuropathy.

You also need to manage the risks associated with peripheral neuropathy. The most important step you can take is talk to your doctor about your symptoms.

Manage Pain

- If you are experiencing pain, discuss your pain management options with your doctor.

Make Sure You Sleep Well

- If pain is interfering with your sleep, discuss this with your doctor.

Lower Your Risk for Falls

- Remove all items that may be a tripping hazard around your home.
- Keep items you use often in cabinets you can reach easily without using a step stool.
- Use non-slip mats in the bathtub and on shower floors.
- Improve the lighting in your home and always use nightlights.

If You Have Diabetes, Practice Good Foot Care

- Check your feet for sores and other injuries every day.
- Have your feet examined each time you see your doctor.
- Wear shoes that fit right and do not rub or pinch your feet, or cause blisters.
- Never walk barefoot or while wearing just socks.
- Make sure you see a podiatrist on a regular basis.

To learn more, visit www.DPNCheck.com

References: Doughty and Seyedsadjadi. The American J. of Medicine, 2018. Watson and Dyck. Mayo Clin Proc, 2015.

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American Academy of Neurology
Distal Symmetric Polyneuropathy Quality Measures

Quality Measures	Potential Methods
Appropriate diagnosis	
Documentation of neuropathic symptoms and signs	History & Physical Examination*
Electrodiagnostic studies	DPNCheck
Underuse of effective services	
Diabetes/prediabetes screening	Fasting Blood Sugar, HbA1C, OGTT
Screening for unhealthy alcohol use	History
Quality of life/morbidity	
Querying about pain and pain interference with function	History, Brief Pain Inventory (BPI) questionnaire
Querying about falls (past 12 mo)	History

*Neuropathic symptoms: numbness, altered sensation, or pain in the feet. Neuropathic signs: decreased or absent ankle reflexes, decreased distal sensation, and distal muscle weakness or atrophy.

References: England et al. Neurology, 2014.

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Appendix:
DOCUMENTATION
Gorman Health Group analysis of polyneuropathy coding in Medicare Advantage (2021)

- Analysis of claims data from 4 MA plans (2018-2020 data sets)
- Recommended best practices for polyneuropathy documentation and coding

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Peripheral Neuropathy - HCC & ICD-10

CMS HCC	CMS HCC DESCRIPTION	Coeff
18	Diabetes with Chronic Complications (Diabetic Neuropathies)	.302
75	Myasthenia Gravis/Myoneural Disorders and Guillain-Barre Syndrome/Inflammatory and Toxic Neuropathy	.472

Inflammatory & Toxic Neuropathies	
G611	Serum neuropathy
G6181-G619	Inflammatory Neuropathies
G620	Drug-induced polyneuropathy
G621	Alcoholic polyneuropathy
G622	Polyneuropathy due to other toxic agents
G6281	Critical illness polyneuropathy
G6282	Radiation-induced polyneuropathy
G63	Polyneuropathy in diseases classified elsewhere
G651-G652	Sequelae of other inflammatory; toxic neuropathy
Diabetic Neuropathy	
E1140	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E1142	Type 2 diabetes mellitus with diabetic polyneuropathy
E1143	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
*Assign appropriate diabetes type for first 3 characters (E08 due to underlying condition; E09 Drug or Chemical Induced; E10 Type 1; E13 Other specified type	

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Source: Gorman Health Group analysis, 2021

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Two HCC codes capture peripheral neuropathy risk

CMS_HCC	CMS_HCC Description	2020 CMS-HCC Model (V24) Crosswalk
18 **Diabetic Peripheral Neuropathy (DPN)**	Diabetes with Chronic Complications	E08.21-E08.638, E08.649-E08.8, E09.21-E09.638, E09.649-E09.8, E10.21-E10.638, E10.649-E10.8, **E11.21-E11.638**, E11.649-E11.8, E13.21-E13.638, E13.649-E13.8
75 **Non-diabetic peripheral neuropathy (must be specified)**	Myasthenia Gravis/Myoneural Disorders and Guillain-Barre Syndrome/Inflammatory and Toxic Neuropathy	D86.82, G13.0, G13.1, G61.-, G62.0-G62.82, G63, G65.-, G70.-, G73.1-G73.3, M05.5-, M34.83

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Source: Gorman Health Group analysis, 2021

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Half of peripheral neuropathy is coded as non-specific, but may have an identifiable etiology

HCC075	Coded comorbidities that may be causative for peripheral neuropathy*	G6289/ G629 (Unspecified Polyneuropathy)	2019 Claims Data
No	Rheumatoid Arthritis	Yes	0.71%
No	Substance Dependence	Yes	0.61%
No	AIDS/ HIV	Yes	0.03%
No	Cancer	Yes	0.89%
No	Unspecified Diabetes	Yes	0.71%
No	Cirrhosis/ End-Stage Liver	Yes	0.13%
No	Dialysis	Yes	0.76%
Possible Yes	**At least one comorbidity**	**Yes**	**2.81%**
No	**No comorbidity***	**Yes**	**2.58%**
		Total Unspecified/ General Neuropathy	**5.39%**

*Additional potential causes include metabolic syndrome, hypoxic conditions, nutritional deficiencies

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Source: Gorman Health Group analysis, 2021

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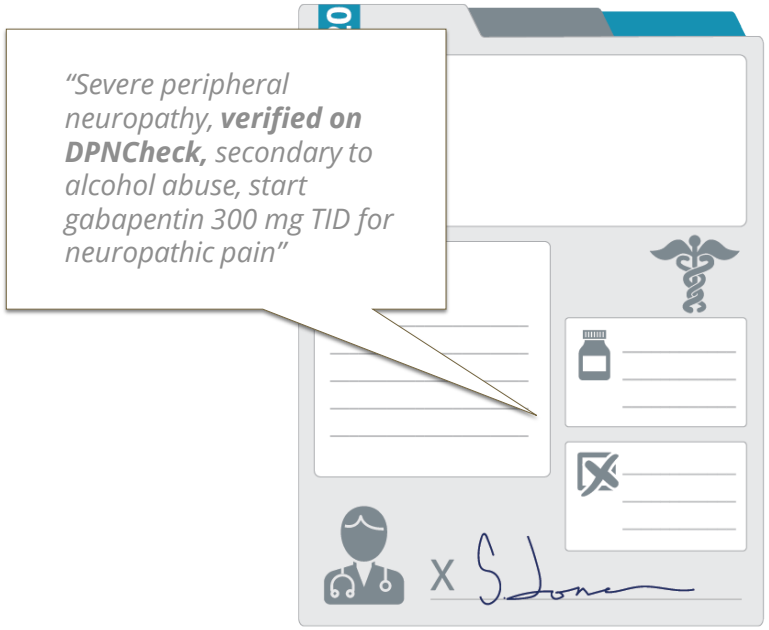
Peripheral neuropathy documentation is often incomplete

- Peripheral Neuropathy should be documented with a minimum of:
  - Specificity (Type: Diabetic, Rheumatoid; Cause: due to Chemotherapy, Due to Alcoholism)
  - Current status (Asymptomatic with medications, worsening)
  - Current treatment (Continue Gabapentin, referral to neurology)
- Ensure all pieces of the encounter notes flow with the final diagnosis, often these are left in the auto-populated state and may conflict with the condition
  - HPI, ROS
  - Physical Exam (diminished sensation)
  - Assessment and Plan
  - DPNCheck® results



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Peripheral neuropathy should be coded with specificity if underlying cause is identified

- **Accurate assignment of ICD10 code is dependent upon the underlying cause for the peripheral neuropathy, which also impacts HCC qualification**
  - Idiopathic (G603) and unspecified neuropathies (G629) are not included in the risk adjustment models
  - Unspecified or idiopathic codes are often reported when a specific cause should be identified via clinical work-up

- **ICD10 guidelines assume a causal relationship between peripheral neuropathy and diabetes only**
  - Causational or linking verbiage is needed for all other specific types of neuropathy

Inflammatory & Toxic Neuropathies	
G611	Serum neuropathy
G6181-G619	Inflammatory Neuropathies
G620	Drug-induced polyneuropathy
G621	Alcoholic polyneuropathy
G622	Polyneuropathy due to other toxic agents
G6281	Critical illness polyneuropathy
G6282	Radiation-induced polyneuropathy
G63	Polyneuropathy in diseases classified elsewhere
G651-G652	Sequelae of other inflammatory; toxic neuropathy
Diabetic Neuropathy	
E1140	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
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E1143	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
*Assign appropriate diabetes type for first 3 characters (E08 due to underlying condition; E09 Drug or Chemical Induced; E10 Type 1; E13 Other specified type	
Rheumatoid Polyneuropathies	
M0550 – M0559	Rheumatoid polyneuropathy with rheumatoid arthritis (site specificity needed, or unspecified site)

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Avoid these common peripheral neuropathy coding pitfalls:

- Omitting a coexisting/underlying peripheral neuropathy diagnosis 1x per year in an otherwise uncomplicated patient when managed with neuropathy medications or other neuropathy interventions
- Failing to assign code combinations of diabetes and another specific neurological manifestation
  - Peripheral neuropathy may have multiple underlying causes
  - Diabetic peripheral neuropathy may be exacerbated by other events or conditions (e.g., chemotherapy, alcoholism)
- Defaulting to unspecified/idiopathic peripheral neuropathy when likely to be associated with a known underlying condition/cause following clinical work-up
- Conflicting documentation within the review of symptoms (ROS) or physical exam
  - Many EHR templates auto-populate as 'normal'
  - It is important to update these fields when assigning diagnosis codes in the Assessment and Plan if clinically indicated
  - Patients with peripheral neuropathy may not report symptoms due to asymptomatic disease or lack of recognition due to slow progression

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There are gaps in capturing risk associated with non-diabetic peripheral neuropathies (HCC 75)

HCC 75 captures peripheral neuropathy from common non-diabetic reasons:

- Metabolic syndrome, nutritional (B12 deficiency)
- Immune (Rheumatoid arthritis), infectious (COVID-19, HIV, Lyme disease)
- Chemotherapy Induced Peripheral Neuropathy, toxic (alcohol)
- Uremia, liver disease, chronic hypoxia (sleep apnea, COPD)

Why such a significant gap in HCC 75 detection?

- Peripheral neuropathies often do not have clear signs and symptoms
- Physicians are not sufficiently focused on signs and symptoms of peripheral neuropathy in non-diabetic patients
- Traditional clinical screening tools (e.g., monofilament) are inadequate
- Peripheral neuropathy work-up may be incomplete

Undocumented PN creates clinical and financial risk

- Skin trauma, foot ulcers
- Increased fall risk
- Increased hospitalization rates
- **Decreased quality of life**

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Accurate RAF assessment requires complete and specific coding

EXAMPLE

Complete and Accurate Coding	
72 year old male	0.394
Hypertension - I10	0
Alcohol dependence, in remission, F1020, HCC 55	0.329
Alcoholic polyneuropathy, G621, HCC 75	0.472
Total RAF	1.195
PMPM	$ 850.00
Year	$ 12,189.00

Some conditions coded, lacking specificity	
72 year old male	0.394
Hypertension - I10	0
Alcohol dependence, in remission, F1020, HCC 55	0.329
Polyneuropathy, unspecified - G62.9	0
Total RAF	0.723
PMPM	$ 850.00
Year	$ 7,374.60

No conditions coded	
72 year old male	0.394
Hypertension - I10	0
Alcohol Abuse, in remission - F1011	0
Numbness and Tingling (Parasthesia of Skin) - R202	0
Total RAF	0.394
PMPM	$ 850.00
Year	$ 4,018.80

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Questions and discussion

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