DPNCheck®

Provider Training Module

Screening and Management of Peripheral Neuropathy Using DPNCheck

Alera/TES

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PN2206097 Rev A

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

- Pathophysiology
- Epidemiology
- Clinical findings
- Implications of delayed detection

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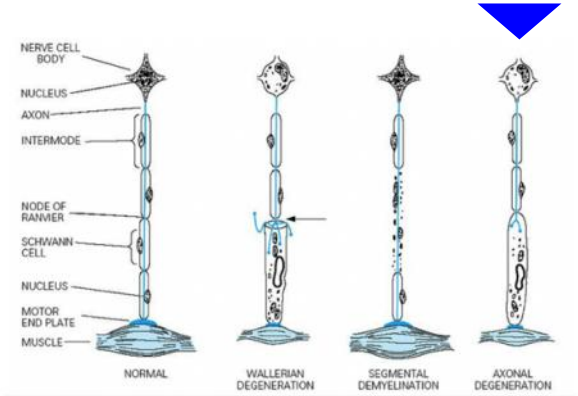
Peripheral neuropathy (polyneuropathy) is a systemic pathological change in peripheral nerves

- 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

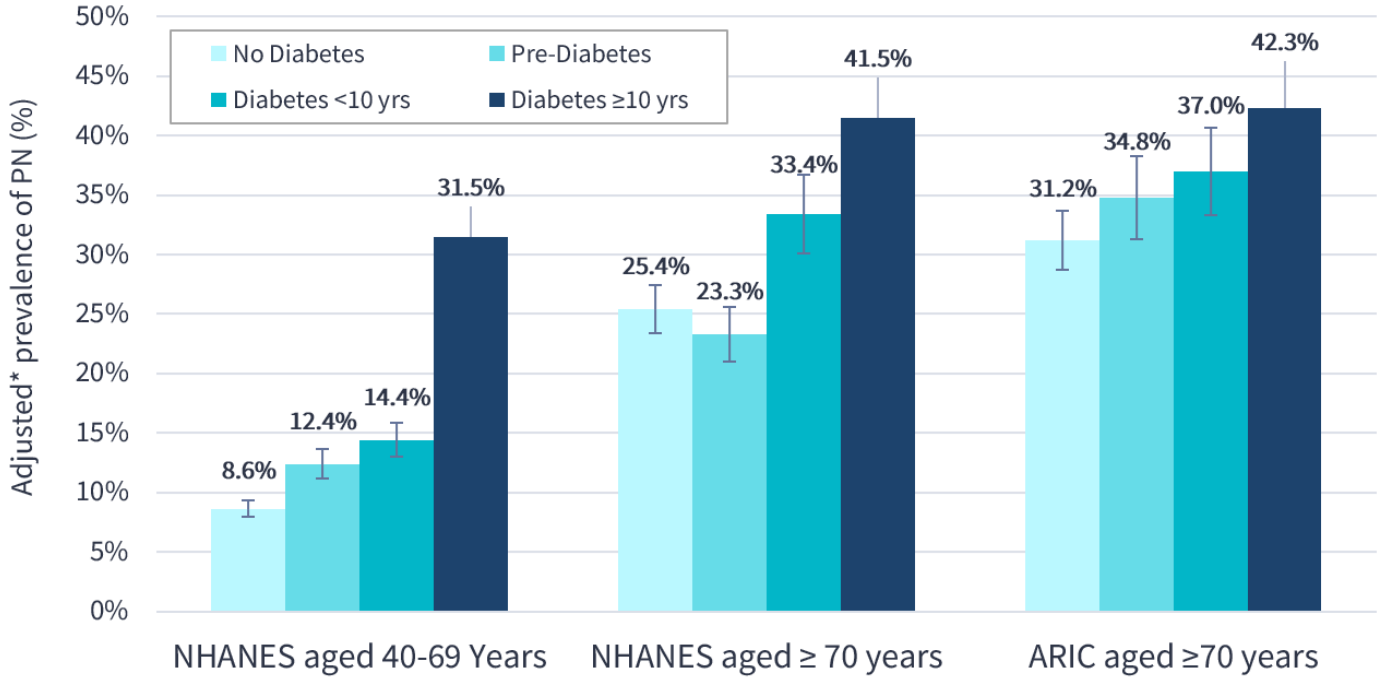


*Oxidative stress, microvascular disease, impaired Na+/K+ ATPase activity, advanced glycation end products, mitochondrial dysfunction, axonal transport disruption, Schwann cell injury, inflammation, ion channel dysfunction

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

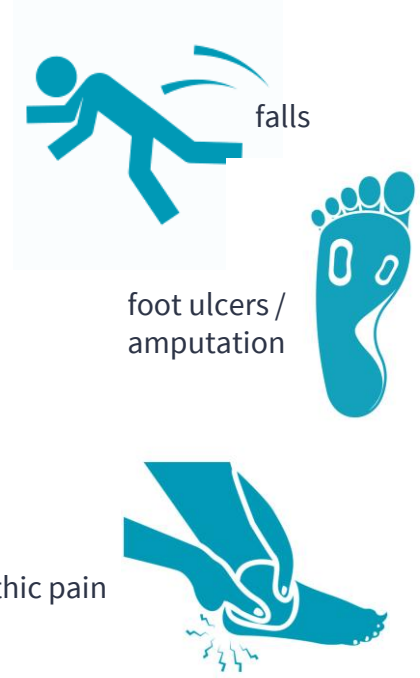


*Age, sex and race-adjusted prevalence of peripheral neuropathy stratified by diabetes status in US adults aged 40-69 and ≥ 70 Years (NHANES, 1999-2004) and ARIC participants aged ≥ 70 years (Visit 6, 2016-2017).

References: Hicks et al. Sci Rep, 2021.

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.

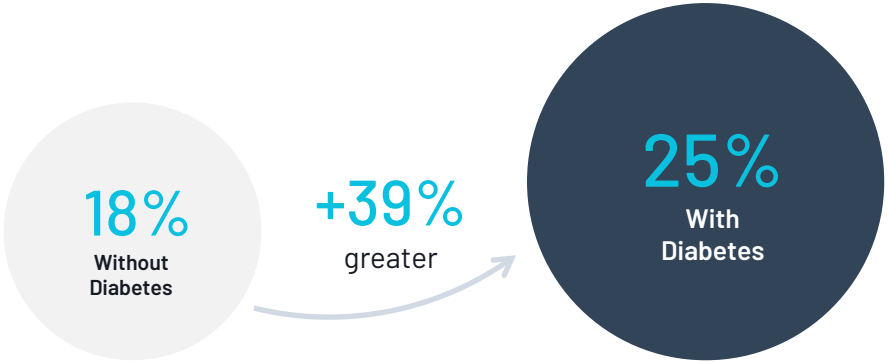
References: Hicks et al. Ann Intern Med, 2021. Richardson and Hurvitz. J. Gerontoloy, 1996. Ward et al. Aging & Disease, 2016. Boulton et al. NEJM, 2004. Richardson and Hurvitz. J Gerontol, 1995. Cheng et al. J Clin Nurs, 2002. Erlandson et al. J Acquir Immune Defic Syndr, 2019. Riskowski et al. Journal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

Peripheral neuropathy and increased risk of falls and fractures

"Diabetic Peripheral Neuropathy is associated with a **risk of major fractures due to falls"**

- Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes

Fall & fracture risk among adults 65 or older



Callaghan B, et al. *Neurology* 2015

Longitudinal Patient-oriented Outcomes in Neuropathy - Importance of early detection and falls:

*"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. Interventions to improve early peripheral neuropathy detection are needed."*

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

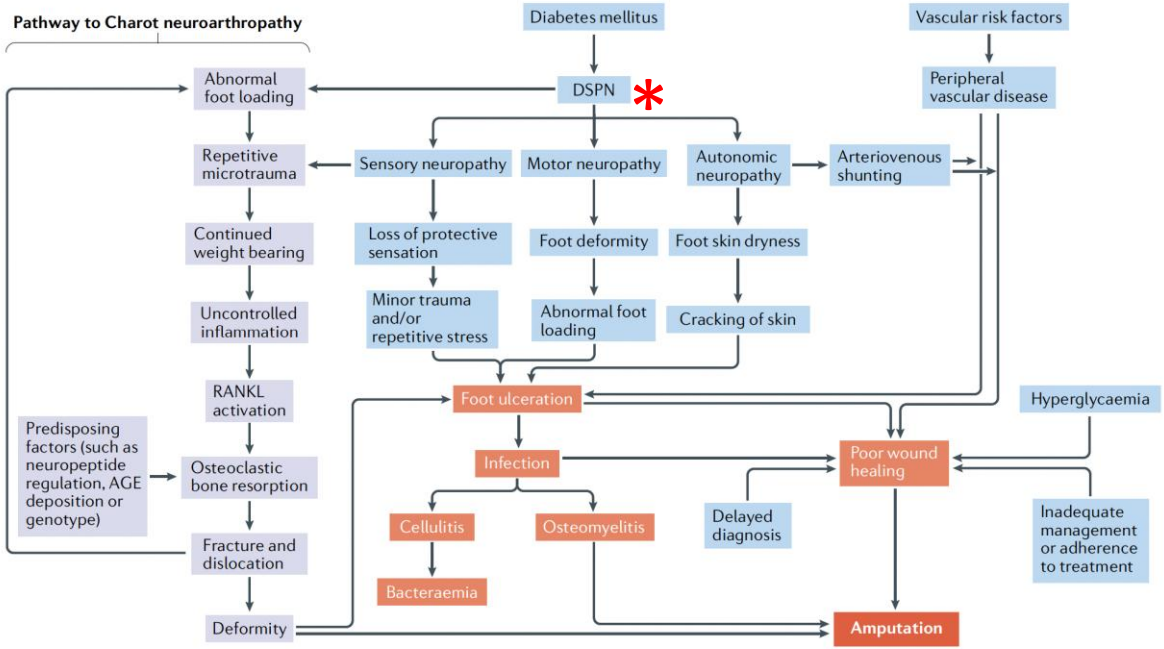


Fig. 1 | **The pathways to foot ulceration and amputation.** Diabetic sensorimotor peripheral neuropathy (DSPN), vascular disease and foot deformity might result in foot ulceration. In Charcot neuroarthropathy, minor trauma of the foot or ankle triggers an inflammatory cascade with a subsequent imbalance 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.

Peripheral Neuropathy as Predictive Indicator of Microvascular Complications

Suggests early asymptomatic detection is critical to patient outcomes

Ke, J et al. Diabetes, Metabolic Syndrome and Obesity 2023

A Nomogram for Predicting Vision-Threatening Diabetic Retinopathy (VTDR) Among Mild Diabetic Retinopathy (DR) Patients: A Case–Control and Prospective Study of Type 2 Diabetes:

"In the current study, we combined Amp and CV and graded severity of SNCI [sural nerve conduction impairment] detected by DPN Check®, and the new finding indicated **SNCI could be a strong predictor of VTDR.** The roles of nerve damage in the pathophysiology of DR are worthy of further study."

Fukuda, T et al. Journal of Clinical Medicine 2023

Association between Diabetic Peripheral Neuropathy as Measured Using a Point-of-Care Sural Nerve Conduction Device and Urinary Albumin Excretion in Patients with Type 2 Diabetes

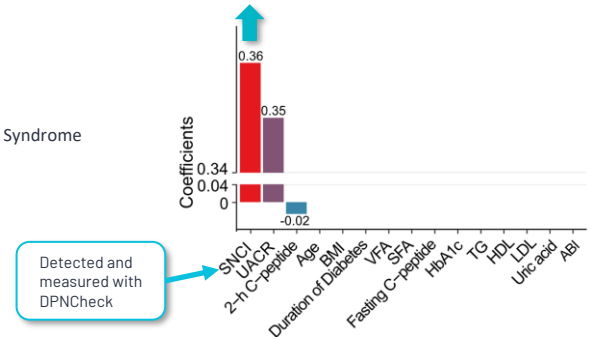
"Patients with DPNCheck-determined diabetic peripheral neuropathy had significantly higher urinary albumin excretion than those without…This finding suggests that DPNCheck could serve as a useful tool for identifying diabetic patients at risk for kidney damage, and may help to guide early interventions for both diabetic peripheral neuropathy and kidney complications."

Predicting Vision-Threatening Diabetic Retinopathy:

A case–control and prospective study of type 2 diabetes

- It is difficult to predict who will progress from mild diabetic retinopathy (i.e., NPDR) to vision-threatening diabetic retinopathy (VTDR)
- Study to identify predictors of progression (median of 42 months) from NPDR to VTDR
  - Predictors included Sural Nerve Conduction Impairment (**SNCI**) **using DPNCheck**, renal function (UACR), C-peptide, age, BMI, HbA1c, ABI and other laboratory measures.
  - The only independent predictors were DPNCheck, renal function and C-peptide.

Ke, J et al. Diabetes, Metabolic Syndrome and Obesity 2023
doi:10.2147/DMSO.S394607



Conclusion and Results:

- ***SNCI (peripheral neuropathy) detected by DPNCheck is an independent predictor of VTDR***
- ***50%*** of patients who had moderate or severe peripheral neuropathy (PN) progressed from NPDR to VTDR
- ***21%*** with mild PN progressed to VTDR
- ***Only 6%*** of those without PN progressed

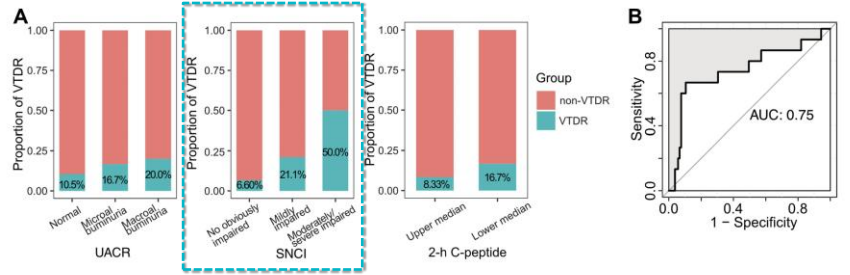


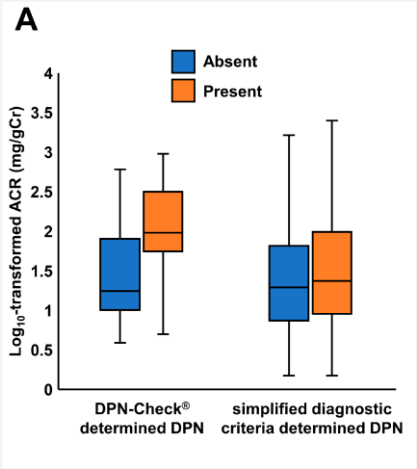
Figure 4 Proportion of VTDR and predicting AUC in the prospective cohort. As the grade of UACR and SNCI increased, the proportion of VTDR increased. Besides, more VTDR occurred in the lower-median 2-h C-peptide group than that in the upper median 2-h C-peptide group (**A**). AUC of prediction was excellent (**B**).

DPNCheck Test Results Predict Risk of Diabetic Nephropathy

"Accurately identifying and characterizing DPN may not only help to manage this debilitating condition more effectively, but also may be beneficial in identifying patients at risk for future declines in kidney function."

- Fukuda T, et al. Journal of Clinical Medicine 2023 - doi: 10.3390/jcm12124089

- Study evaluated the association of DPN with urinary albumin excretion (UAE) in patients with type 2 diabetes. UAE is an early diagnostic marker for kidney damage, another prevalent complication in diabetes.
- *Patients with DPNCheck®-determined diabetic peripheral neuropathy* ***had significantly higher early diagnostic markers*** *(UAE) for kidney damage than those without.*
- ***Other simplified diagnostic criteria*** *revealed* ***no difference*** *in those same markers between patients with and without diabetic peripheral neuropathy.*



Conclusion and Results:

- Diabetic peripheral neuropathy (DPN) diagnosed **using DPNCheck®** is **significantly associated** with diabetic nephropathy.
- **DPN diagnosed with tuning fork or other simplified diagnostic criteria did not confer any predictive advantage**
- *Study identifies the significance of* ***detecting CV abnormalities early using DPNCheck®*** *in patients at increased risk for kidney damage in diabetes.*

Peripheral Neuropathy as Predictive Indicator of All-Cause Mortality

Suggests early asymptomatic detection is critical to overall patient outcomes

Goonoo, M S et al. Diabetes 2023

489-P: Abnormal Combined Point-of-Care-Device DPNCheck and SUDOSCAN Results Predict All-Cause Mortality in People with Diabetes. doi:10.2337/db23-489-P

"The prevalence of screen-detected DPN was **12.6%** for 10g-MFT [monofilament test], **27.7%** for TCNS [Toronto Clinical Neuropathy Score], and **33.4%** for combined POCDs [point of care devices]. After adjusting for age, HbA1c and Total Cholesterol, **only abnormal POCDs was significantly associated with all-cause mortality.**

This is the first prospective study showing abnormal combined DPNCheck and SUDOSCAN results predict all-cause mortality after adjusting for other risk factors. However, 10g-MFT and TCNS that diagnose DPN late did not predict all-cause mortality."

Screening for peripheral neuropathy

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

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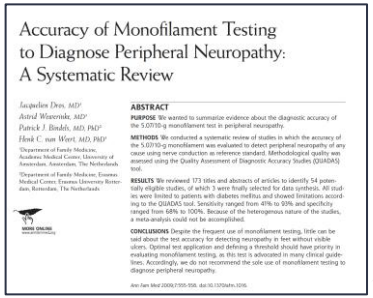
Clinical screening for peripheral neuropathy is subjective and diagnostically limited

- Traditional clinical approaches
  - 10 g Semmes-Weinstein monofilament
  - 128 Hz tuning-fork
  - Pinprick
  - Ankle reflexes
  - Symptoms

- Issues with traditional testing 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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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.

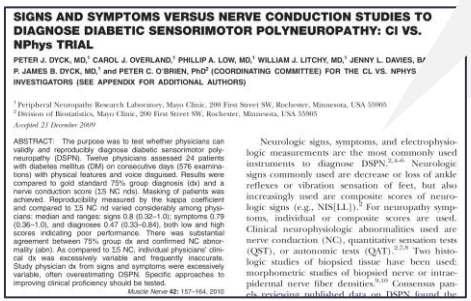
RESULTS We reviewed 173 titles and abstracts of articles to identify 54 potentially eligible studies, of which 3 were finally selected for data synthesis. All studies were limited to patients with diabetes mellitus and showed limitations according to the QUADAS tool. Sensitivity ranged from 4% to 93% 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 (≥5 NC nds). Masking of patients was achieved. Reproducibility measured by the kappa coefficient and compared to ≥5 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 ≥5 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.[1,2,4] 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]).[5] 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 ≥5 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.

New Study Demonstrates Poor Diagnostic Accuracy of Monofilament Test for Diabetic Polyneuropathy (DPN)

> ***"The monofilament test should not be used to diagnose DPN, nor be used as an inclusion tool in diabetes research."***
>
> - Dunker, O et al. BMJ Open Diabetes Research & Care 2023 - doi: 10.1136/bmjdrc-2023-003545

BMJ Journals
BMJ Open Diabetes Research & Care

- Rigorous multi-center study conducted over 5 years to assess the diagnostic accuracy of the 5.07/10 g monofilament test (SWME) in 506 patients referred for polyneuropathy assessment
- Nerve conduction study (NCS), considered gold standard, was used in reference standard
- Now that modern point-of-care devices such as DPNCheck have become more cost-effective, investigators recommend reconsidering testing standards

Results and Conclusions:

*"This multicenter study demonstrates **poor diagnostic performance** for the 5.07/10g SWME in patients with diabetes referred to polyneuropathy assessments"*

*"The diagnostic accuracy of the SWME was not influenced by NCS-based disease severity, demonstrating that **it does not perform better in patients with later stages of DPN."***

*"Due to low sensitivity, **almost half of patients with DPN are overlooked**, diminishing the clinical value of a negative result."*

"In addition, receiving a true DPN diagnosis empowers the patient to take an active part in the disease management"

Traditional screening tests have low sensitivity for peripheral neuropathy compared to nerve conduction study (NCS)

Traditional methods may miss most mild and asymptomatic cases

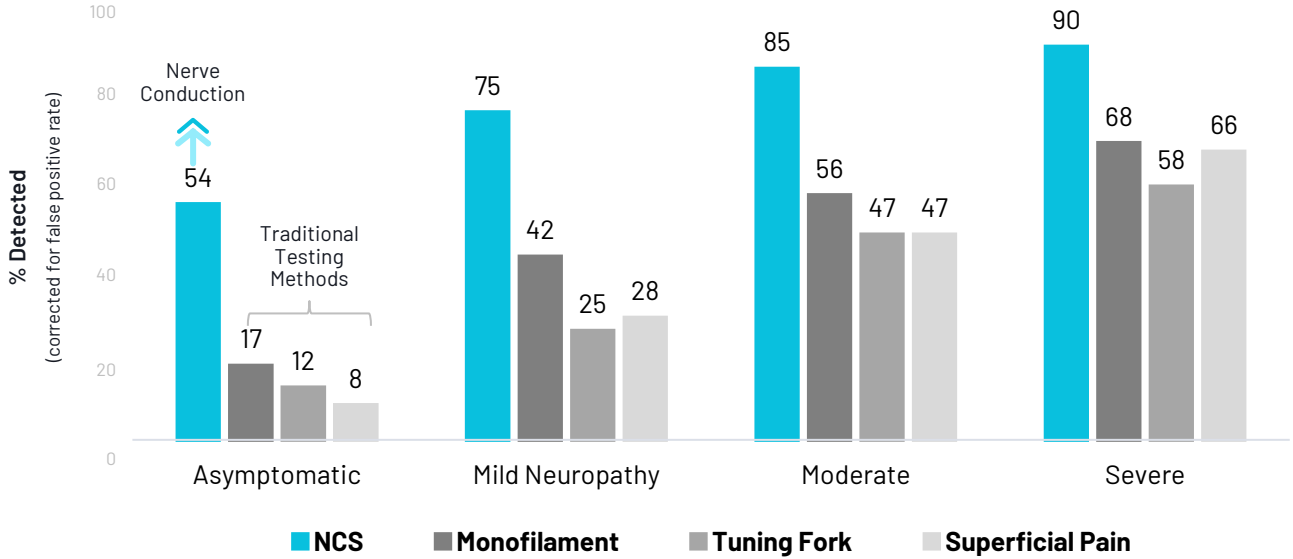
3x

cases can be detected by NCS than by traditional methods if someone is asymptomatic.

54% NCS

vs

17% Traditional methods



Source : Perkins, et.al., Diabetes Care 2001 doi:10.2337/diacare.24.2.250
adjusted for false positives

New Study Demonstrates Accuracy of DPNCheck's Point-of-Care NCS vs. traditional NCS in the Diagnosis of Diabetic Polyneuropathy (DPN)

> ***Simplified electrophysiological approach combining a point-of-care nerve conduction device and an electrocardiogram produces an accurate diagnosis of diabetic polyneuropathy***
> - Hayashi et al. *Journal of Diabetes Investigation* 2024

JDI Journal of Diabetes Investigation
Official Journal of the Asian Association for the Study of Diabetes

- Study goal was to establish if two simple point-of-care tests could reproduce results derived from more resource-intensive nerve conduction studies (NCS), considered gold standard.
- 167 subjects with type 1 and type 2 diabetes were tested with the DPNCheck and an EKG (reporting CVR-R*). A combination of two tests was intended to capture signs of sensorimotor (DPNCheck) and autonomic (CVR-R) neuropathy.
- The results from the two point-of-care tests exhibited good diagnostic accuracy: The area under the curve in a receiver operating characteristic (ROC) analysis was 0.88.

**CVR-R: a coefficient of variation of R-R intervals, a standard value reported by EKG's*

Results and Conclusions:

Investigators successfully verified that the diagnosis obtained from DPNCheck and CVR-R at the point of care could reproduce the diagnosis based on traditional NCS. In addition, similar performance was reported when using just DPNCheck to diagnose DPN.

*"By combining these tests, we have developed an estimation formula with **excellent diagnostic performance**. The use of DPNCheck and electrocardiogram would **simplify the diagnosis** of diabetic polyneuropathy, making it **more accessible**, **reproducible** and **reliable**."*

https://doi.org/10.1111/jdi.14174

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Nerve conduction principles

- Nerve conduction studies as gold standard
- Components of NCS results
- Why test sural nerve

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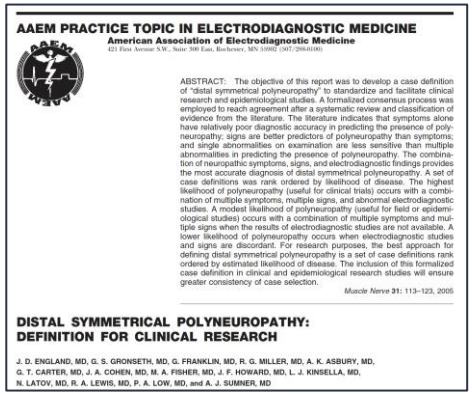
Nerve conduction is the gold standard diagnostic test for peripheral neuropathy

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



AAEM PRACTICE TOPIC IN ELECTRODIAGNOSTIC MEDICINE

American Association of Electrodiagnostic Medicine

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.

Likelihood of Peripheral Neuropathy

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.*

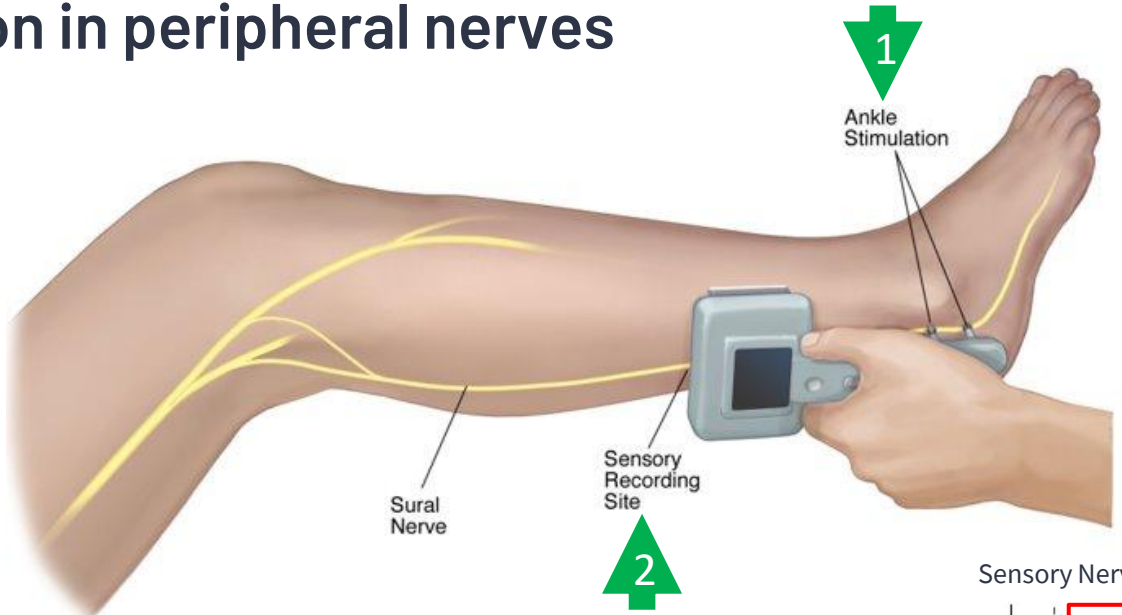
†Abnormal NCS is defined in text.

‡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).

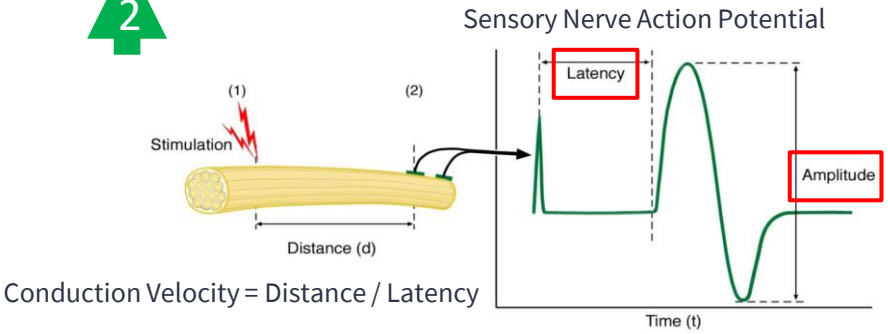
§This phenotype in the presence of normal NCS is not a distal symmetrical polyneuropathy. This situation is given a negative (–) ordinal likelihood because the condition cannot be classified as a distal symmetrical polyneuropathy. It is included here to emphasize the importance of including NCS as part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

References: England et al. Muscle Nerve, 2005.

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

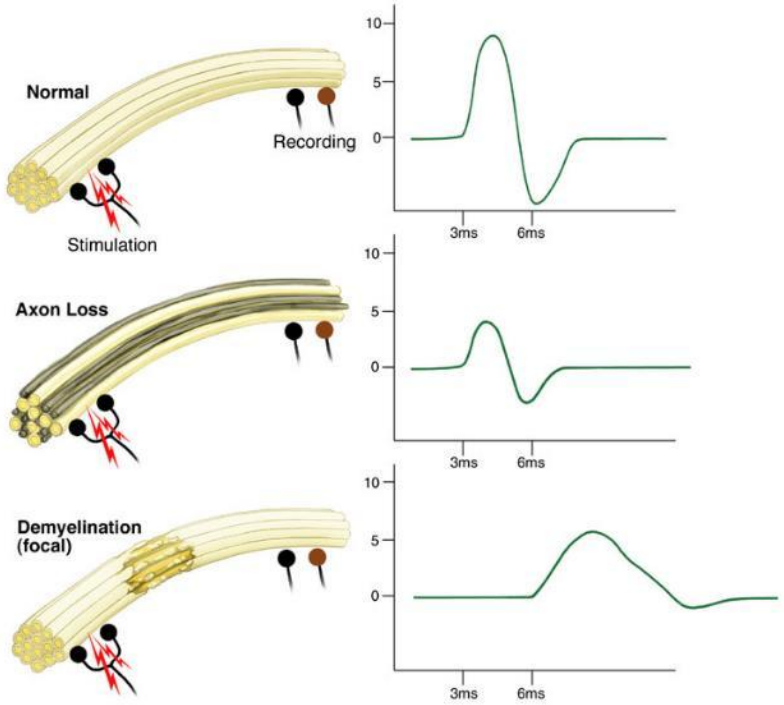


Nerve conduction measures the large myelinated axons (Aα, Aβ)



Conduction Velocity = Distance / Latency

Sensory nerve amplitude correlates with nerve fiber density



"Virtual Nerve Biopsy"

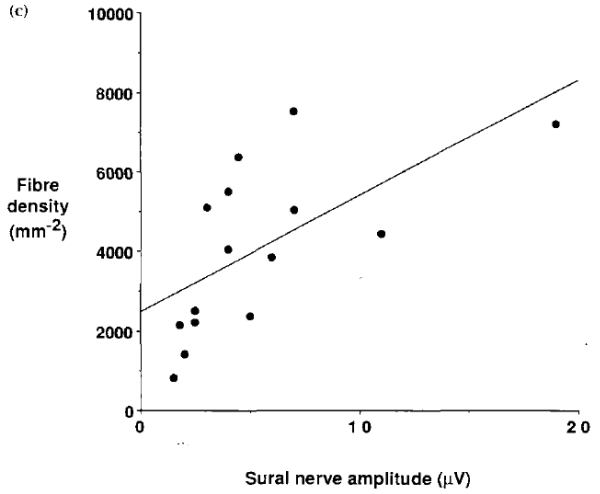
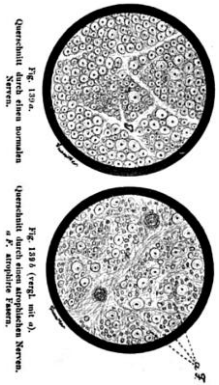


Figure 1. Relation between myelinated fibre density in sural nerve biopsies and electrophysiological measures in patients with mild diabetic neuropathy. Significant correlations were found with peroneal conduction velocity, $r = 0.58$, $p < 0.02$ (a), sural conduction velocity, $r = 0.84$, $p < 0.001$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

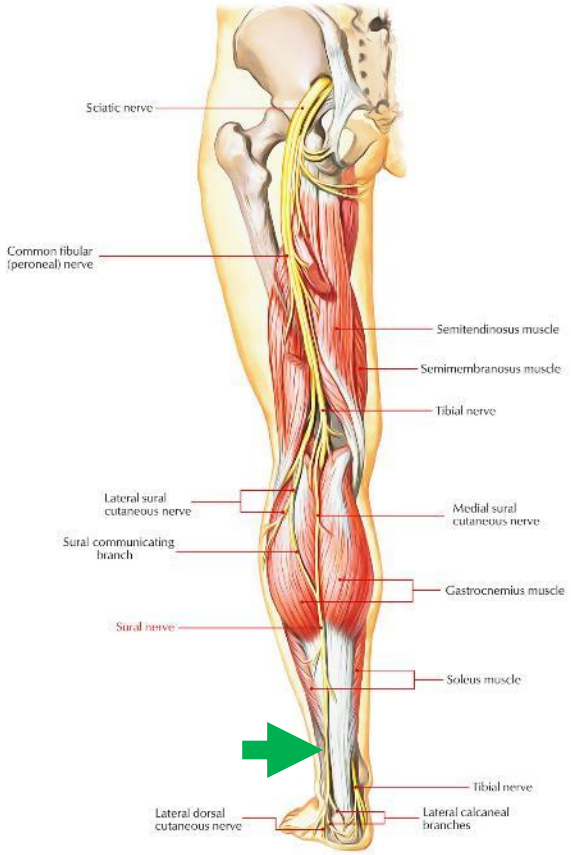


Oppenheim. Textbook of nervous disease.. 1894.

References: Veves et al. Diabetic Medicine 1991.

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



DPNCheck

- Device overview
- Interpretation of results
- Quality control

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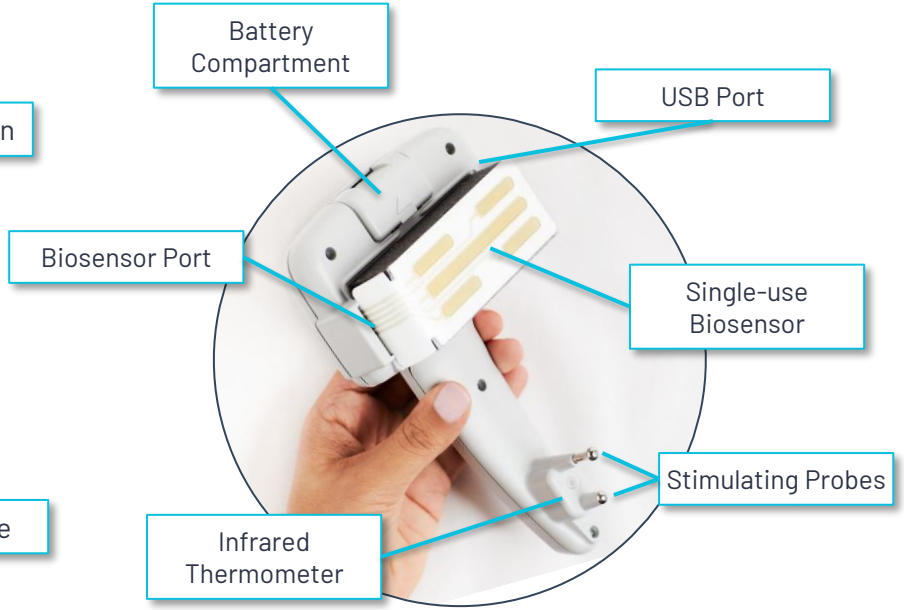
DPNCheck is a standardized and automated sural nerve conduction test

Testing in 4 Easy Steps:

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

DPNCheck 2.0 Device Overview

Top Side
(tester facing)



Bottom Side
(patient facing)

Interpretation of DPNCheck results is straightforward

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

Amp + CV

Amp only

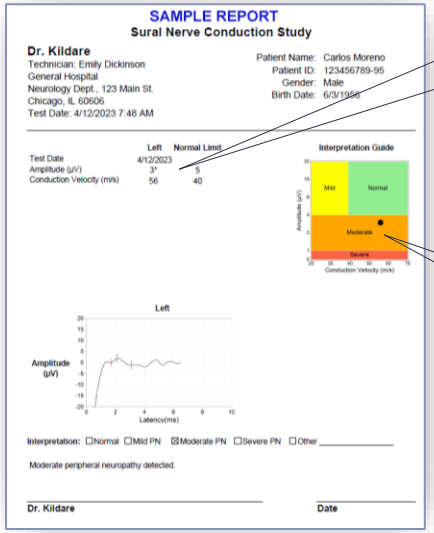
Undetectable

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 *


SAMPLE REPORT
Sural Nerve Conduction Study

Dr. Kildare
Technician: Emily Dickinson
General Hospital
Neurology Dept., 123 Main St.
Chicago, IL 60606
Test Date: 4/12/2023 7:48 AM

Patient Name: Carlos Moreno
Patient ID: 123456789-95
Gender: Male
Birth Date: 6/3/1956

	Left	Normal Limit
Test Date	4/12/2023	
Amplitude (µV)	3*	5
Conduction Velocity (m/s)	56	40

Interpretation Guide

Left

Amplitude (µV)

Latency(ms)

Interpretation: ☐Normal ☐Mild PN ☒Moderate PN ☐Severe PN ☐Other _____

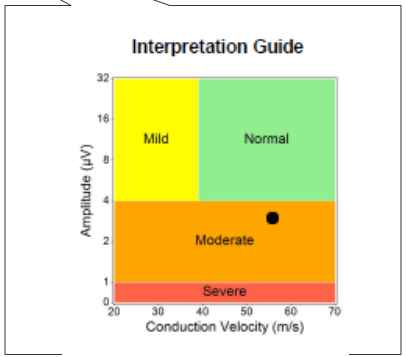
Moderate peripheral neuropathy detected.

Dr. Kildare

Date

	Left	Normal Limit
Test Date	4/12/2023	
Amplitude (µV)	3*	5
Conduction Velocity (m/s)	56	40

Interpretation guide



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.

Patient Work-up

- Assessment framework
- Treatment and management plan
- Patient management and engagement pathways
- Quality measures and coding considerations

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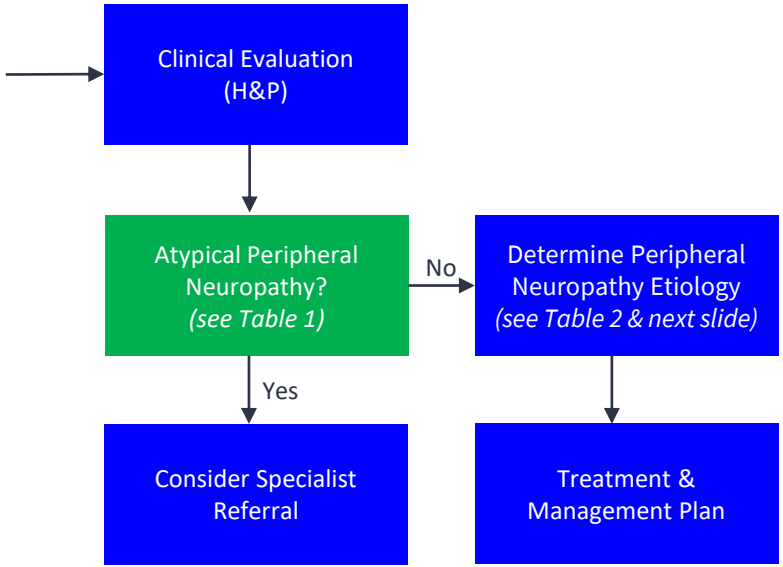
Patient Assessment Framework

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.

Peripheral neuropathy treatment and management

Patient education	Awareness of condition and implications	Educational brochure (see example)	
Treat underlying disease (etiology)	Intensification of glucose control	Increase exercise/ reduce BMI	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)

Sample patient education materials

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

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Patient Engagement and Management Pathways

Patient Engagement and Education:

- Inform patient of their need to understand and manage the risks associated with peripheral neuropathy.
- Provide materials such as the DPNCheck patient educational brochure

Patient Management:

- **Encourage focus on managing underlying disease** - regulate glucose levels and encourage physical activity when feasible, with an aim to reducing BMI.
- **Foot care** - instruct and encourage frequent foot self-checks, encourage use of supportive and well-fitting shoes, discourage going barefoot or socks-only
- **Pain management** - discuss and explore pain management options that work best for patient.
- **Effective management of symptoms** the American Academy of Neurology maintains a practice guideline that provides recommendations for managing neuropathic pain, including typical doses for medications practical use in clinic.
- **Ensure adequate sleep** - if pain is interfering with sleep, discuss options.
- **Fall risk awareness and mitigation** - advise patient to remove items that may be a tripping hazard around their home, suggest adding non-slip surfaces, improve lighting in home, and avoid going barefoot.
- **Enhanced monitoring for microvascular complications –** recent research associates peripheral neuropathy with vision-threatening diabetic retinopathy (VTDR) and diabetic nephropathy. Consider closer monitoring of patients for these conditions.
- **Other approaches:**
  - Consider Alpha Lipoic Acid supplementation, setting reasonable expectations for results with patient
  - Address possible non-diabetic causes; B12 repletion therapy, alcohol cessation, etc.

Possible Referrals:

- Neurology if atypical presentation occurs, podiatry, hematology (paraproteinemia)

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.

DPNCheck is a recognized nerve conduction test with an associated CPT code 95905

- DPNCheck is a sensory nerve conduction test that uses a preconfigured electrode array to measure sural response amplitude and conduction velocity and produces a patient-specific report for clinician interpretation.

- The service performed by the DPNCheck is described by **CPT 95905**:
  - *Motor and/or sensory nerve conduction, using preconfigured electrode array(s), amplitude and latency/velocity study, each limb, includes F-wave study when performed, with interpretation and report.*

- Screenings with DPNCheck are not typically covered. DPNCheck as a diagnostic test may be covered, but coverage will vary by insurance provider.

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NEUROMetrix® | DPNCheck®

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customerservice@neurometrix.com

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APPENDIX:

Additional Details, Studies, and Supplementary Information

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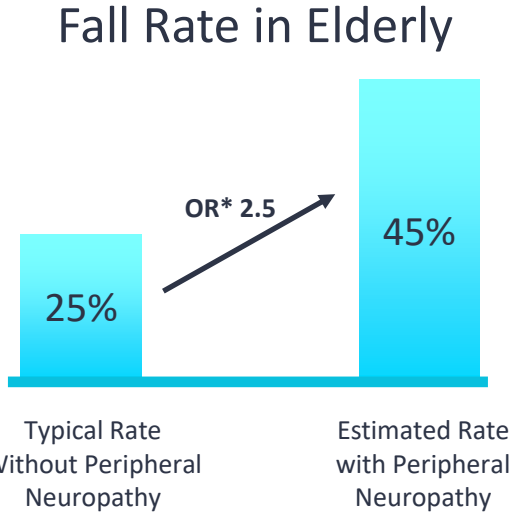
Peripheral neuropathy is an independent risk for falling and fall severity

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.

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

Jennifer J. Brown,[1,2] Shana L. Pribesh,[2] Kimberly G. Baskette,[2] Aaron I. Vinik,[3] and Sheri R. Colberg[2]

[1]*Elizabeth City State University, Elizabeth City, NC, USA*
[2]*Old Dominion University, Norfolk, VA, USA*
[3]*Eastern Virginia Medical School, Norfolk, VA, USA*

(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.

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)

*Note: specificity when referenced against healthy controls is **95%***

Youden Index = sensitivity + specificity – 1.

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

Two independent studies on 101 subjects demonstrate that DPNCheck exhibits good to excellent intra-rater and good inter-rater reliability

Reference	Population	Age	Sample Size	Intra-Rater (ICC)		Inter-Rater (ICC)	
				Amplitude	CV	Amplitude	CV
Lee et al. 2014	Diabetes	56 ± 18	44	0.97	0.94	0.83	0.79
Shibata et al. 2019	Diabetes	58 ± 14	57	0.84	0.88	0.81	0.78

Reliability scale (ICC)
Koo and Li 2017

Figure from Shibata et al. 2019.

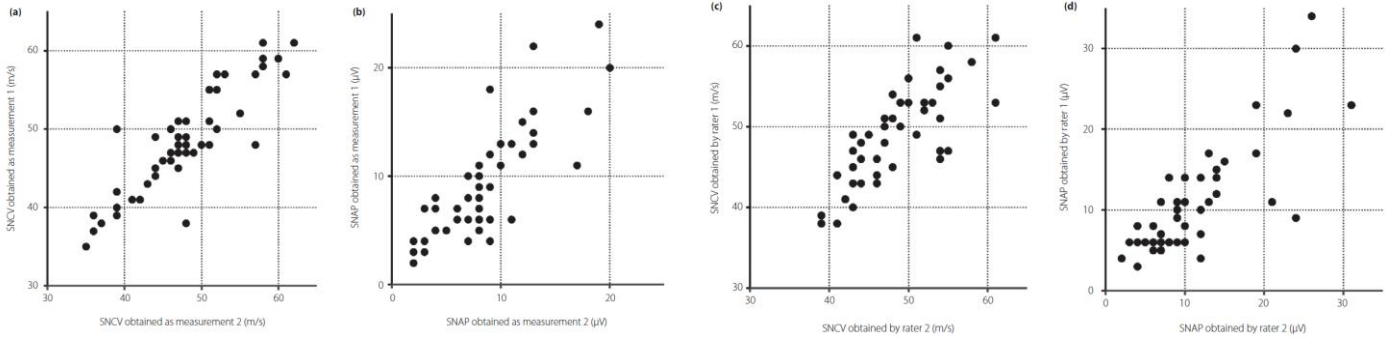


Figure 2 | Interclass reliability analyses of nerve conduction studies by the point-of-care device in the sural nerve. (a,b) Intrarater reproducibility analyses with scatterplots of (a) sensory nerve conduction velocities (SNCVs) and (b) amplitudes of sensory nerve action potential (SNAP) between two measurements carried out by one rater. (c,d) Interrater reliability analyses with scatterplots of (c) SNCVs and (d) amplitudes of SNAP between two raters.

ICC, intraclass correlation coefficient.

References: Koo and Li. A Guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med, 2017. Lee et al. Reliability and validity of a point-of-care sural nerve conduction device for identification of diabetic neuropathy. PLoS One, 2014. Shibata et al. Validity and reliability of a point-of-care nerve conduction device in diabetes patients. J Diabetes Investig., 2019.