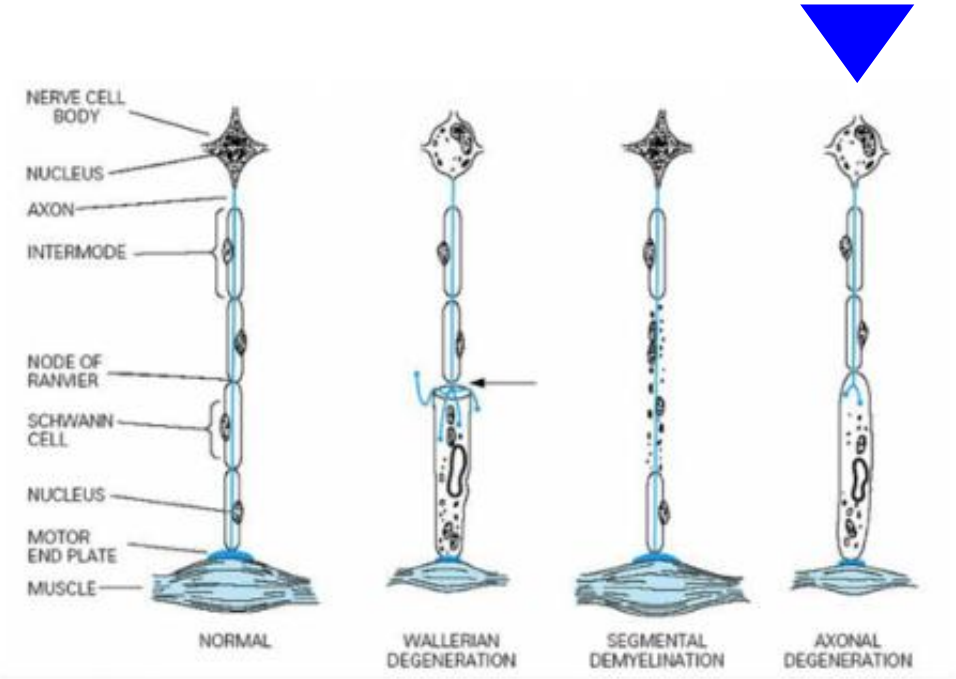
NEUROMetrix® | DPNCheck®

# DPNCheck Product Deep Dive

# What is Peripheral Neuropathy?

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

- **Many causes** including metabolic abnormalities, nutritional deficiencies, inflammation, toxins
- Affect feet / lower legs first
- Symmetrical symptoms/signs
- Chronic, slowly progressing
- Occasional autonomic involvement
- **Primarily axonal degeneration**
- Both sensory and motor fibers usually affected
- Increased sensitivity to pain (hyperalgesia), pain from normal stimuli (allodynia)



## Peripheral Neuropathy:

# Highly-Prevalent

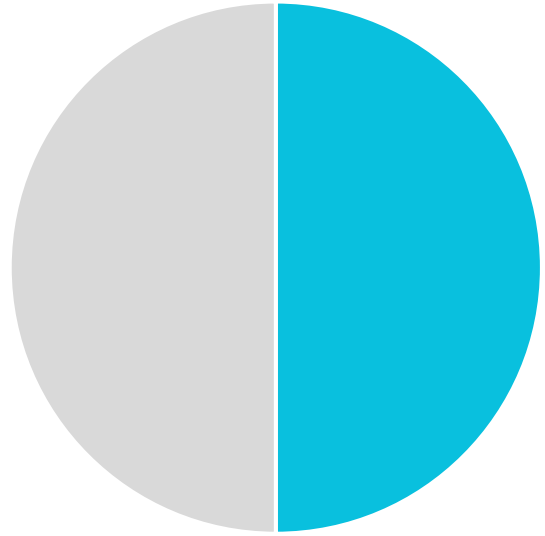
# Debilitating

# Detrimental

# Irreversible Condition

**~30%**

of the 65+ population is affected by Peripheral Neuropathy



**~50%**

of people living with diabetes develop Peripheral Neuropathy

**Up to 50%** of all diabetic peripheral neuropathy patients are **asymptomatic** until the advanced stages of the disease



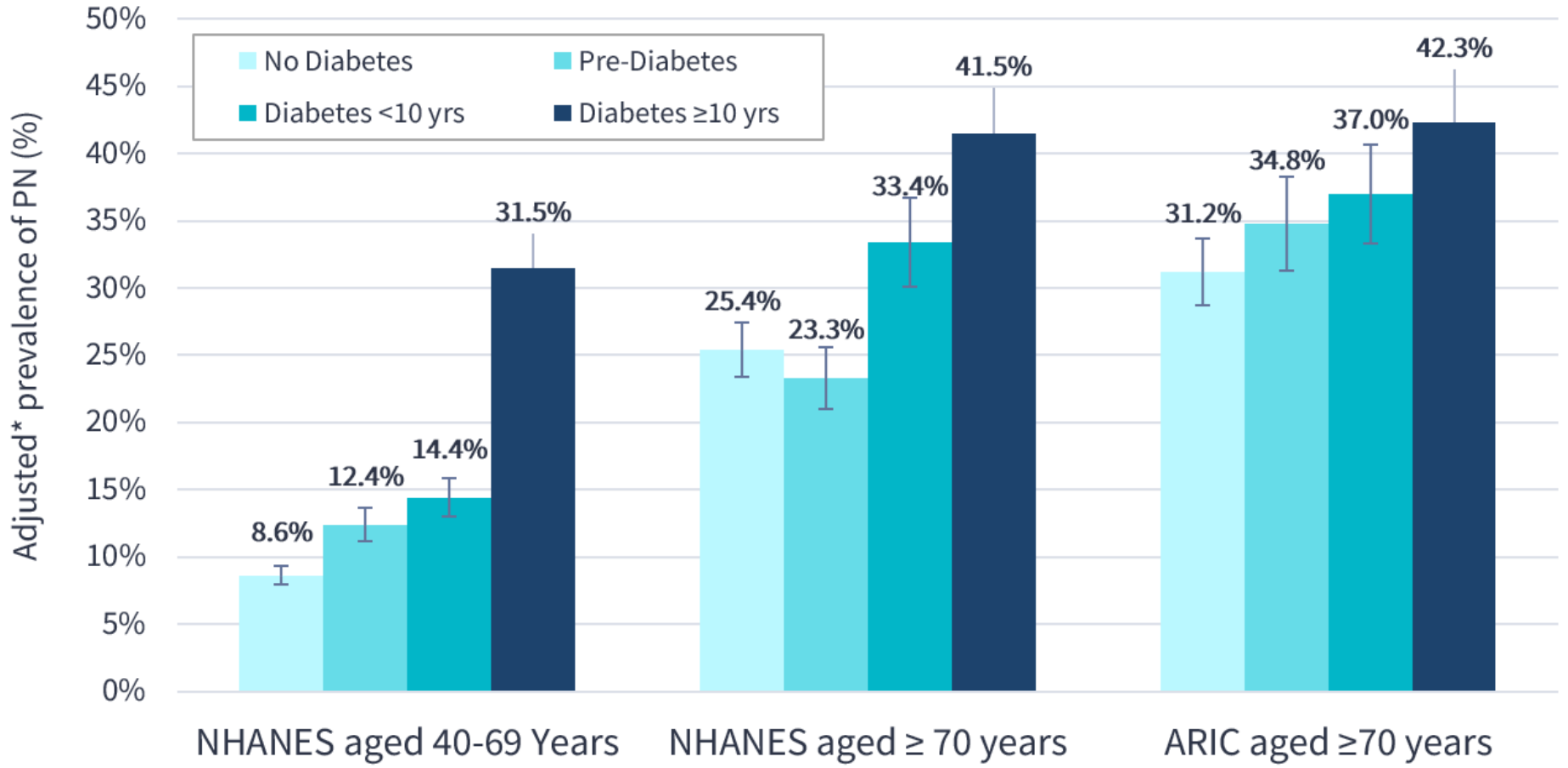
 

Source: Hicks et. al. Sci Rep. doi.org/10.1038/s41598-021-98565-w
ElSayed et.al. Standards of Care in Diabetes 2023 doi.org/10.2337/dc23-S012

# 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.

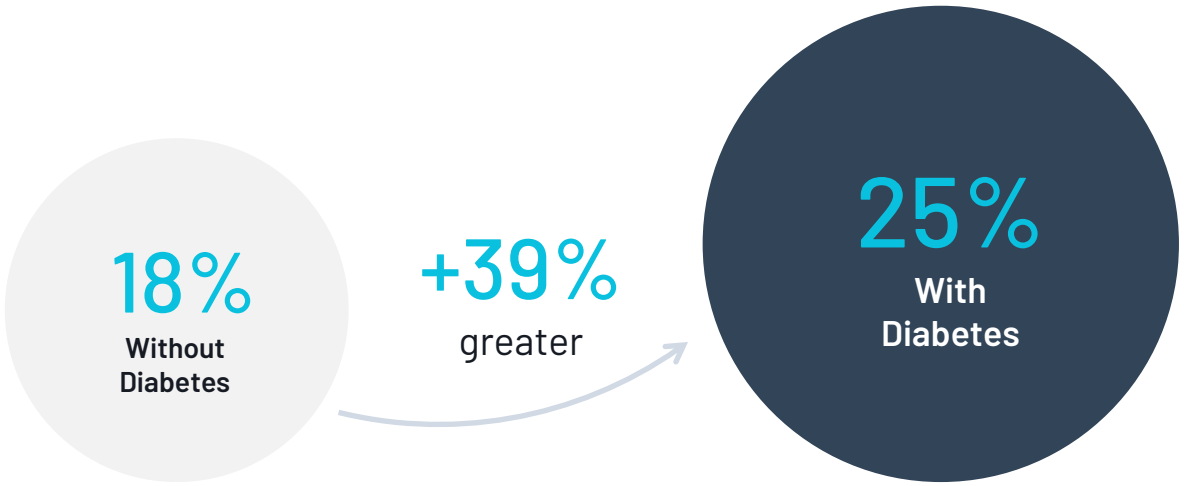
# Peripheral Neuropathy Severely Impacts Quality of Life and Morbidity

# 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."*



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

- Peripheral neuropathy independently associated with all-cause mortality and cardiovascular mortality
- 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

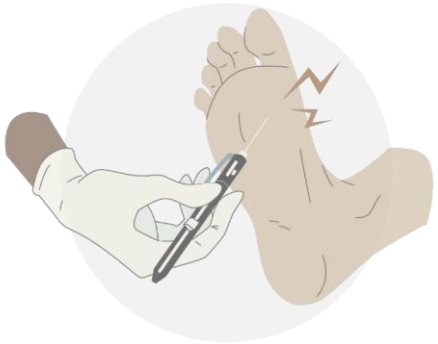
falls

foot ulcers / amputation

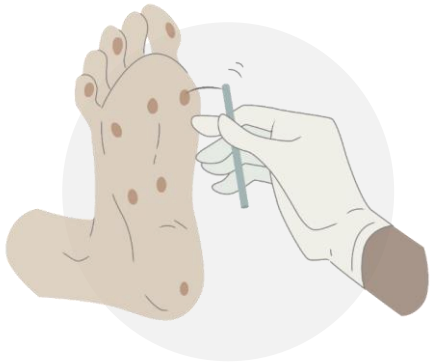
neuropathic pain

# Screening For Peripheral Neuropathy

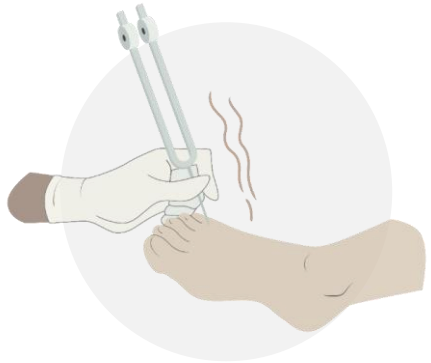
# Clinical screening for peripheral neuropathy is subjective and diagnostically limited



Superficial Pain



Monofilament



Tuning Fork

- Traditional testing methods:
  - **Do not localize disease to peripheral nerves**
  - **Detect late-stage disease (low sensitivity)**
  - High variability
  - Psychophysical responses
  - Subjective, require patient perception and feedback
  - Non-standardized, many different techniques
  - Not adjusted for patient demographics

***Bottom Line: Traditional approaches are unreliable and identify problems too late***

# Traditional Clinical Screening Methods

## Can Miss Most Mild and Asymptomatic Cases

Nerve Conduction Study Results compared to traditional screening methods in patients with diabetic peripheral neuropathy (DPN)

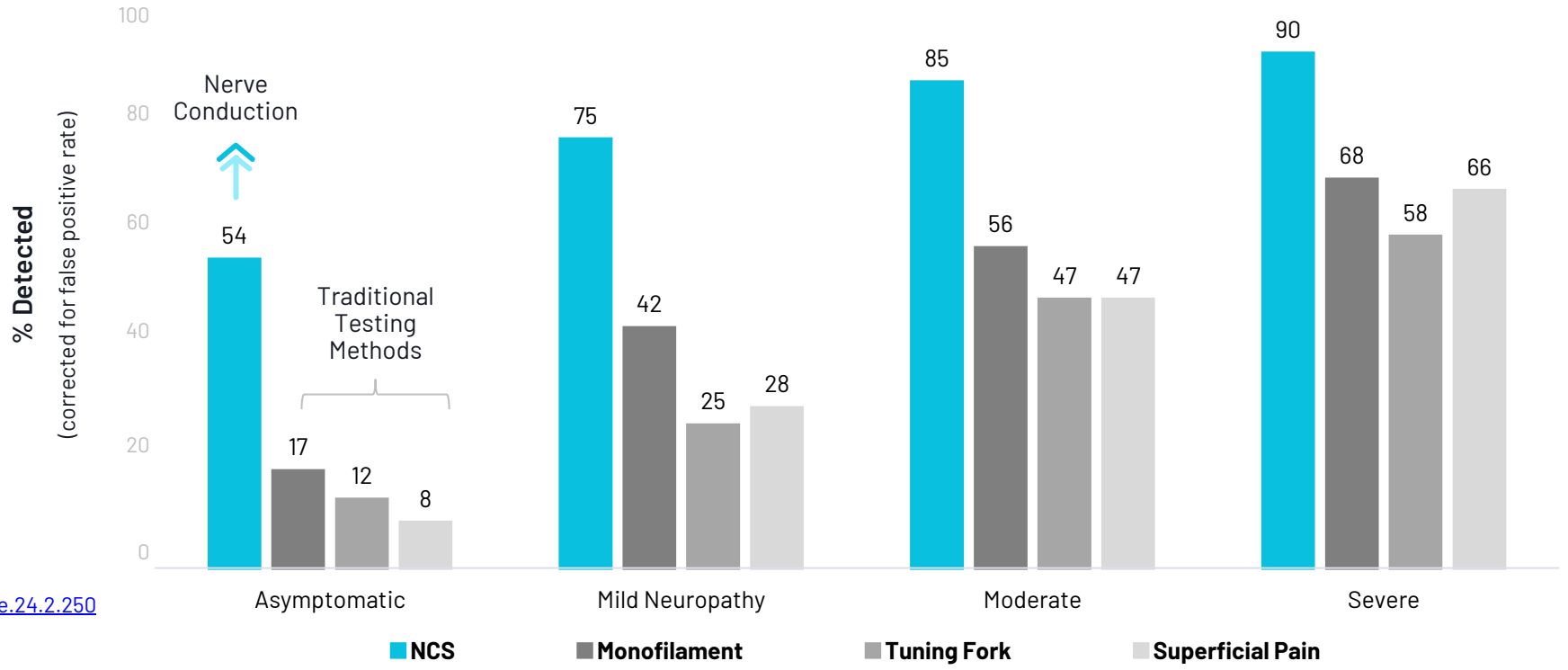
**3x**

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

**54%** NCS

vs

**17%** Traditional methods



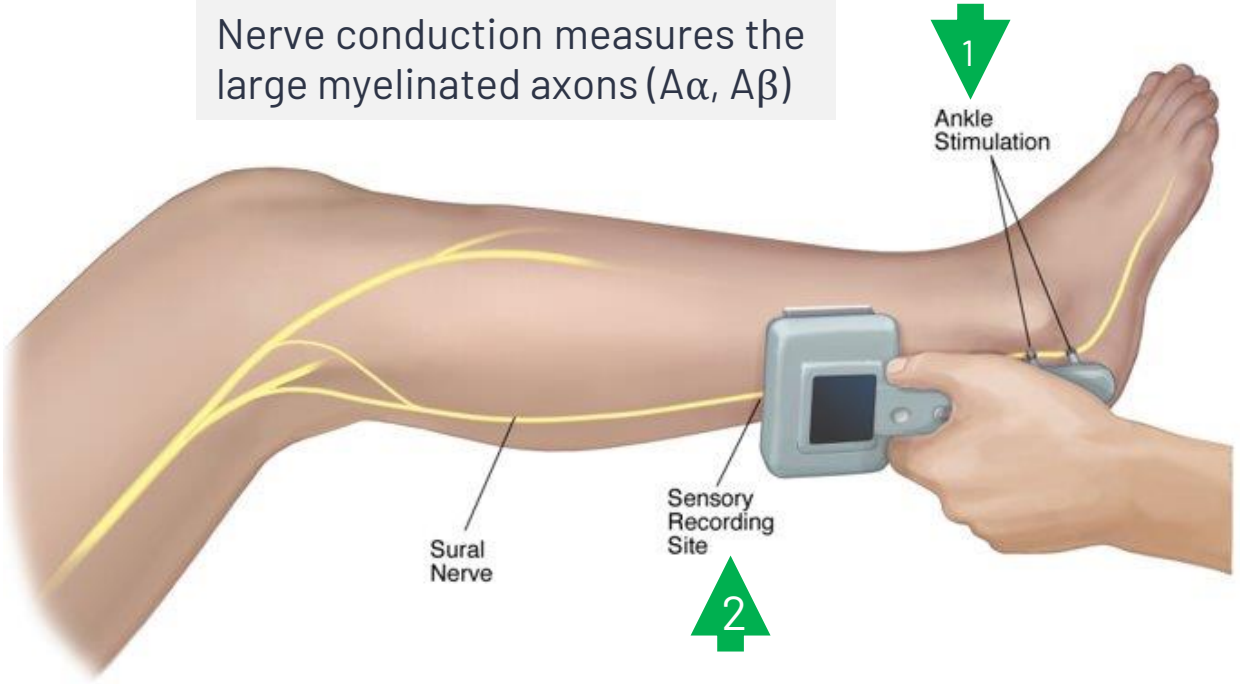

Source : Perkins, et.al., Diabetes Care 2001 doi:10.2337/diacare.24.2.250
adjusted for false positives



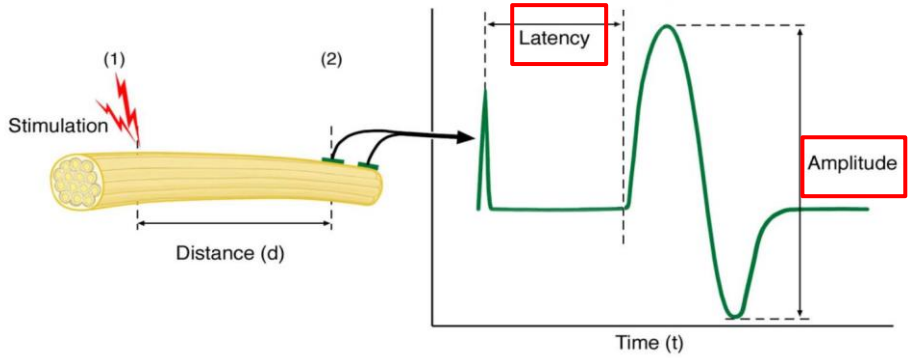
 

# Nerve conduction is the measured action potential propagation in peripheral nerves, gold standard diagnostic test for peripheral neuropathy

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



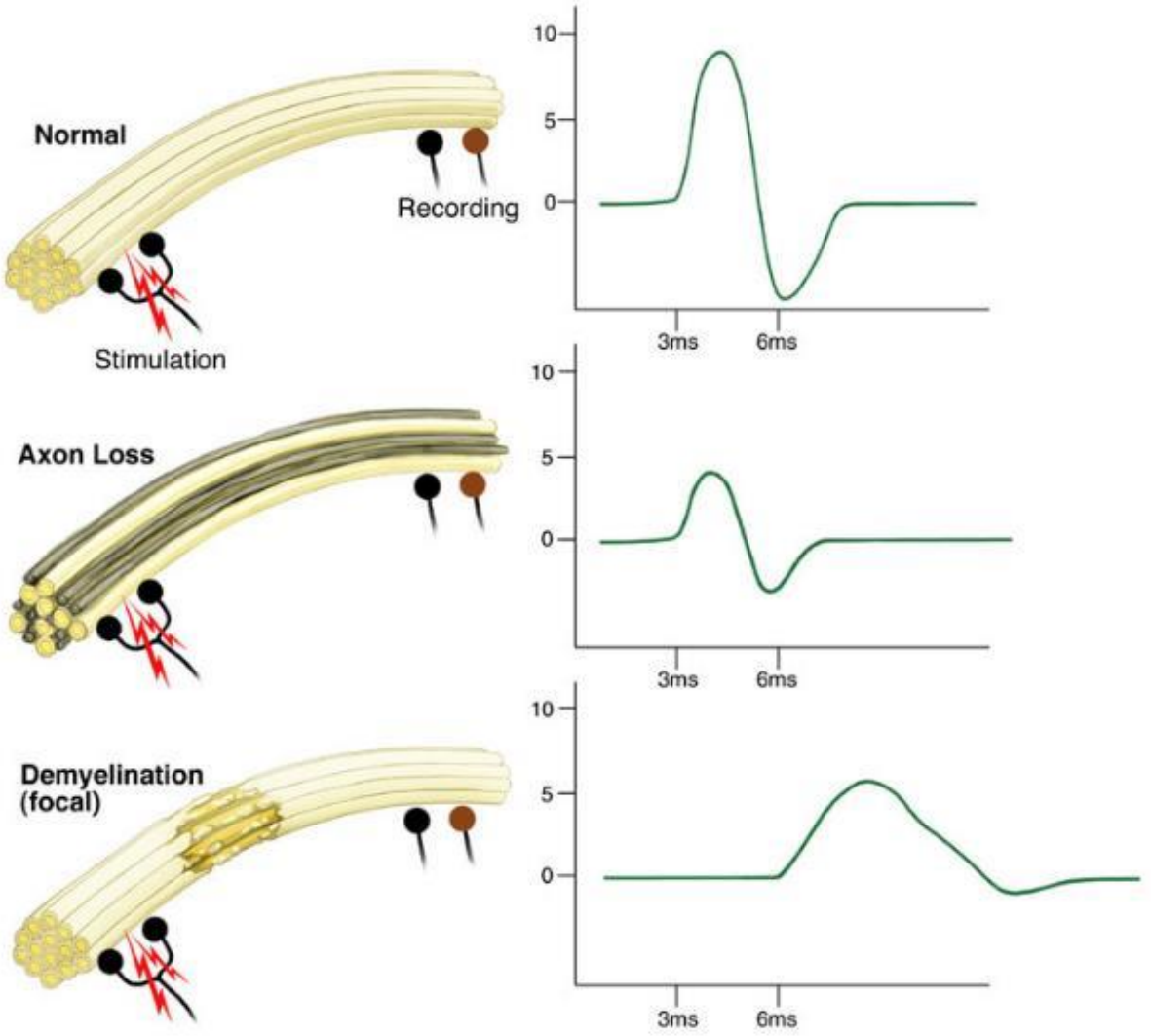

Sensory Nerve Action Potential (SNAP)




Conduction Velocity = Distance / Latency

- Sural nerve conduction is a **sensitive and specific indicator** of distal nerve fiber loss
- **Abnormalities are specific** for peripheral neuropathy
- Measurements are **quantitative and objective**
- Device **does not require subjective response from patients** for results
- Device **quantifies peripheral neuropathy stage and progression** over time

# Sensory nerve amplitude correlates with nerve fiber density




"Virtual Nerve Biopsy"

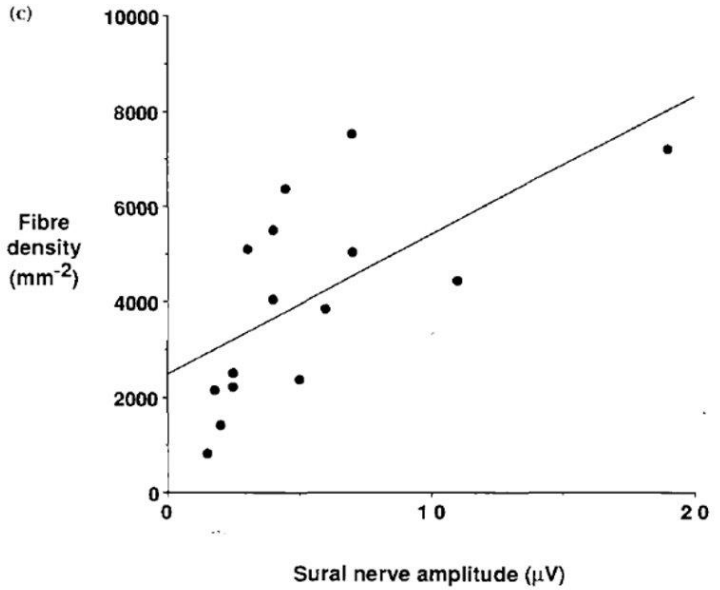
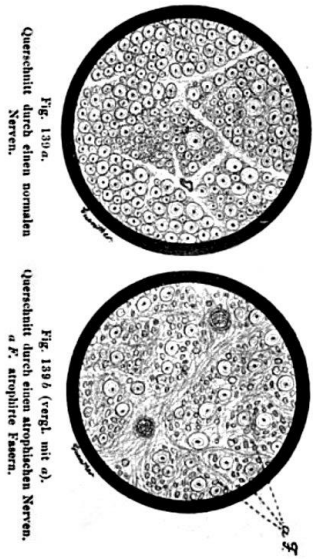



Figure 1. Relation between myelinated fibre density in sural nerve biopsies and electrophysiological measures in patients with mild diabetic neuropathy. Significant correlations were found with peroneal conduction velocity, $r = 0.58$, $p < 0.02$ (a), sural conduction velocity, $r = 0.84$, $p < 0.001$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

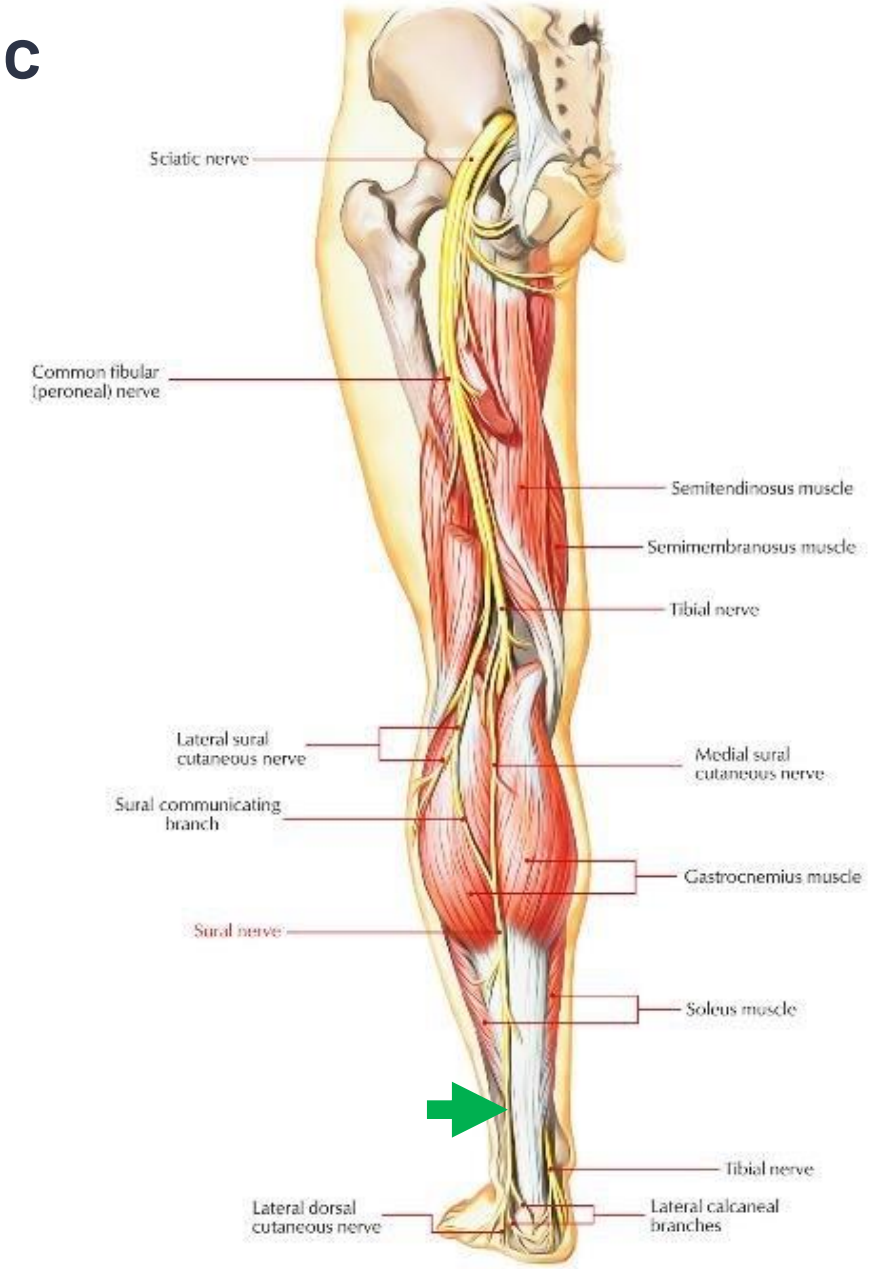


Oppenheim. Textbook of nervous disease.. 1894.

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



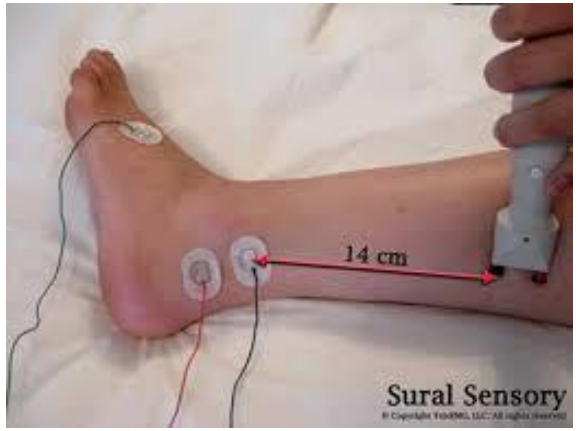
# Why DPNCheck?

# DPNCheck is a standardized and automated sural nerve conduction test

## Testing in 4 Easy Steps:

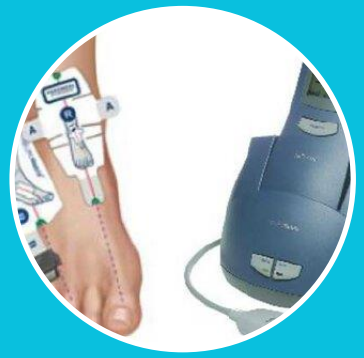

- **Unique>** The **only** point-of-care device leveraging Gold-Standard Nerve Conduction Study (NCS) technology
- **Easy >** Performed in minutes by licensed or non-licensed staff, straight forward interpretation
- **Quantitative & Objective>** Reports amplitude and Conduction Velocity data of Sural Nerve for detection and staging of peripheral neuropathy
- **Low Capital Equipment Need**> Device + single-patient-use biosensor
- **Proven>** 2M+ patients tested over 10 years

# DPNCheck makes nerve conduction possible at point-of-care




Traditional NCS equipment is large, expensive, and requires specialized training

# DPNCheck is built on 20+ years of technology bringing nerve conduction to Point-of-Care



## NC-stat

- NeuroMetrix original Point-of-Care Neurodiagnostic
- Used pre-configured electrodes for testing multiple nerves including sural
- Launched 1999

## Advance

- Sophisticated user interface that could be used by primary care or specialist
- All core NCS testing maintained
- Capability expanded to EMG
- Launched 2008

## DPNCheck

- Tests the sural nerve only
- Streamlined and simplified device and test to focus on cost effective sural NCS testing
- Complementary report generating software
- Launched 2011


## DPNCheck 2.0

- Enhanced Ease of Use
- Core test & technology maintained
- Launched 2022

**NeuroMetrix has a long history in nerve conduction technology**

# DPNCheck is a Validated and Peer-reviewed Solution

FDA cleared

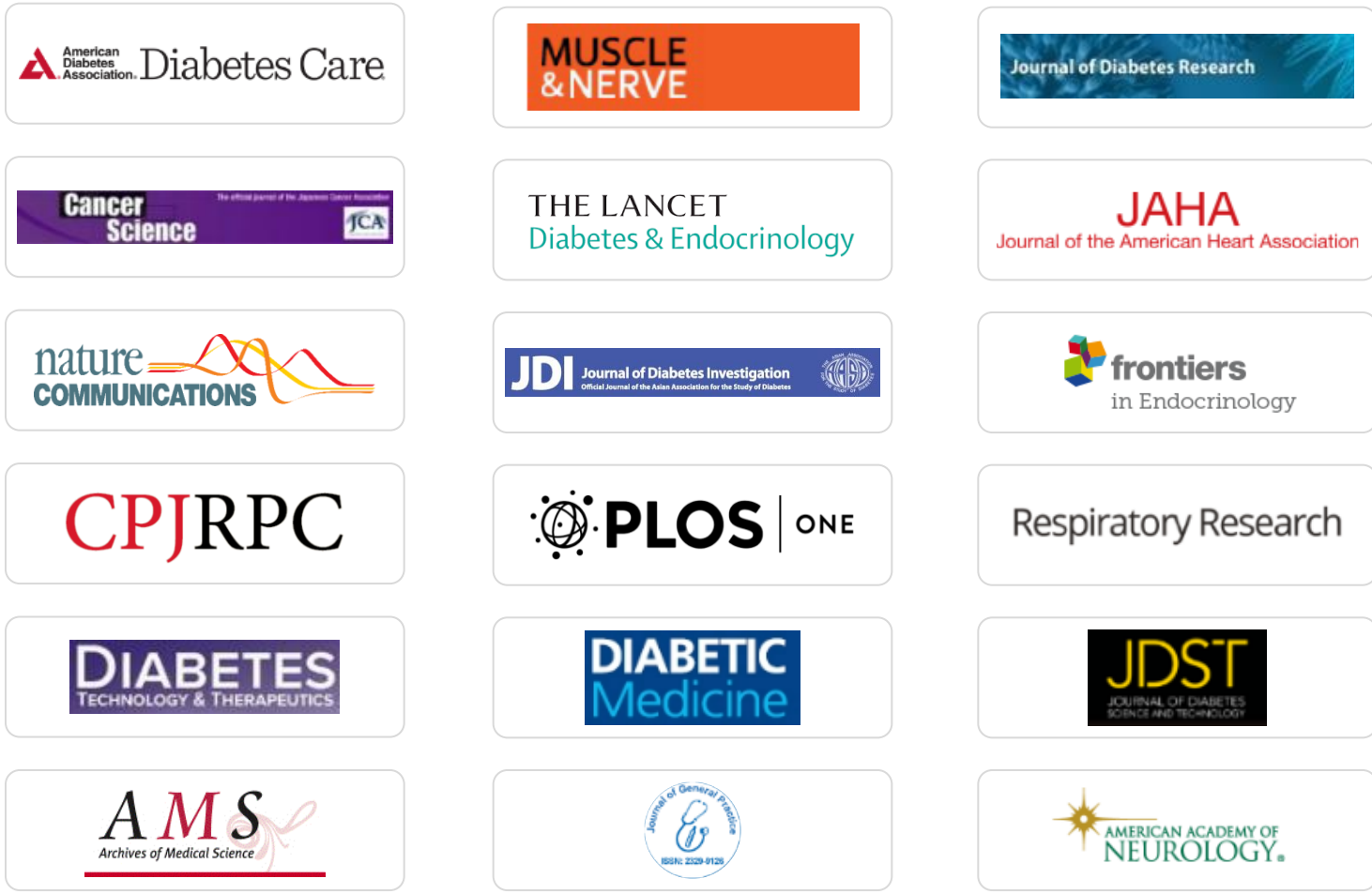
High diagnostic accuracy

**2M+**

Patients tested

**30+**

Validated peer-reviewed studies

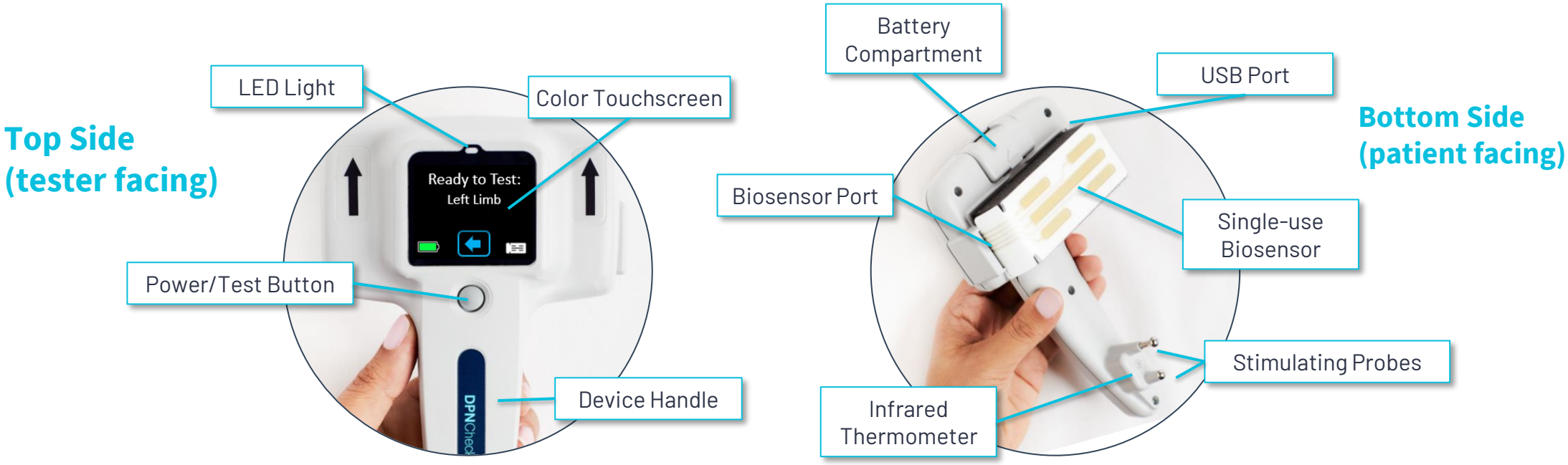




# Device Overview

# DPNCheck device overview

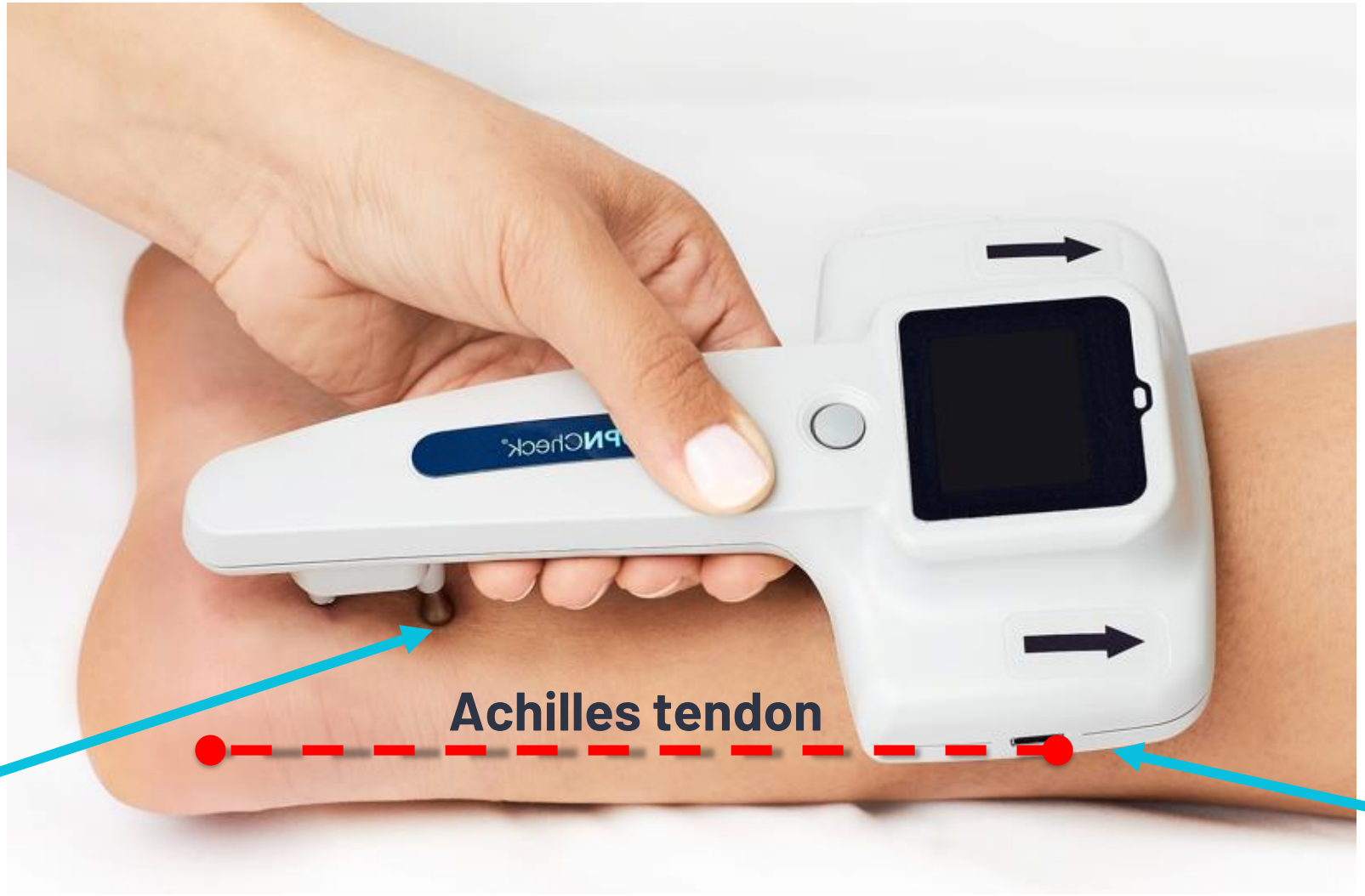



- **Simple interface>** Touchscreen display for easy control and feedback
- **Quality Checks>** Embedded quality control to ensure integrity of results
- **Good Battery Life>** Replaceable battery, typically >100 tests/battery
- **Report Generation>** Upload via USB to the Reporter software for report generation

# DPNCheck offers flexibility for patient positioning

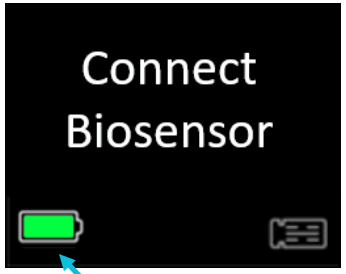
- Key Positioning requirements:
  - Outer ankle bone and Achilles tendon are visible
  - Patient can relax leg muscles
  - Tester can maintain a stable grip on the device

# Easy Alignment to Anatomical Landmarks, device can contour to varying anatomy



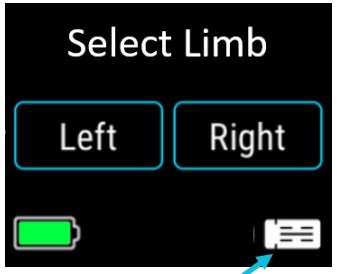
# Touchscreen navigation makes testing easy and intuitive

**1. Connect Biosensor**




Indication of battery level

**2. Select Limb**




Confirmation biosensor is connected

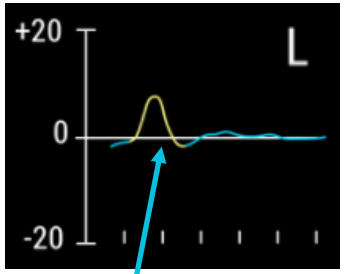
**3. Confirm Selection**


User can correct limb selection

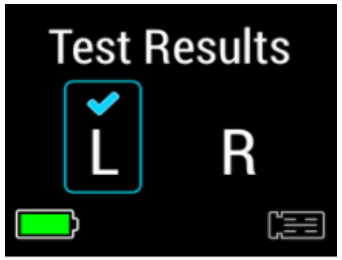
**4. Start Test with button**


*(LED blinking)*

**5. View Results**


Can view of waveform, SNAP in yellow



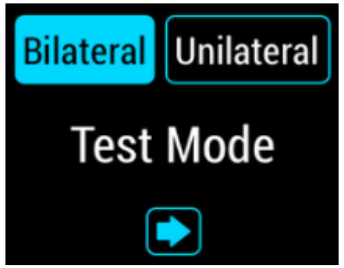

Result are saved on the device and can be reviewed later

# How does the test feel?

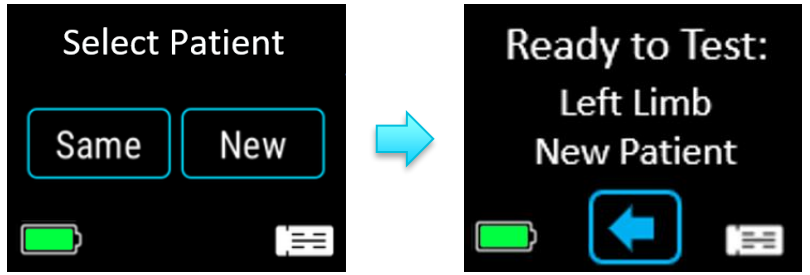
- Stimulations delivered once per second, increasing from low level to the supramaximal level
- Stimulation is felt at the ankle under the stimulating probes
- Sensation may be described as a vibration, a sharp pulse, or a pinching feeling
- It may feel strong to some patients, very light to others
- Current delivered is very low and cannot cause damage ankle or skin

# Settings Option: Bilateral Test Mode

- A **Bilateral test mode** may be selected if both limbs are usually tested. Unilateral is the default.



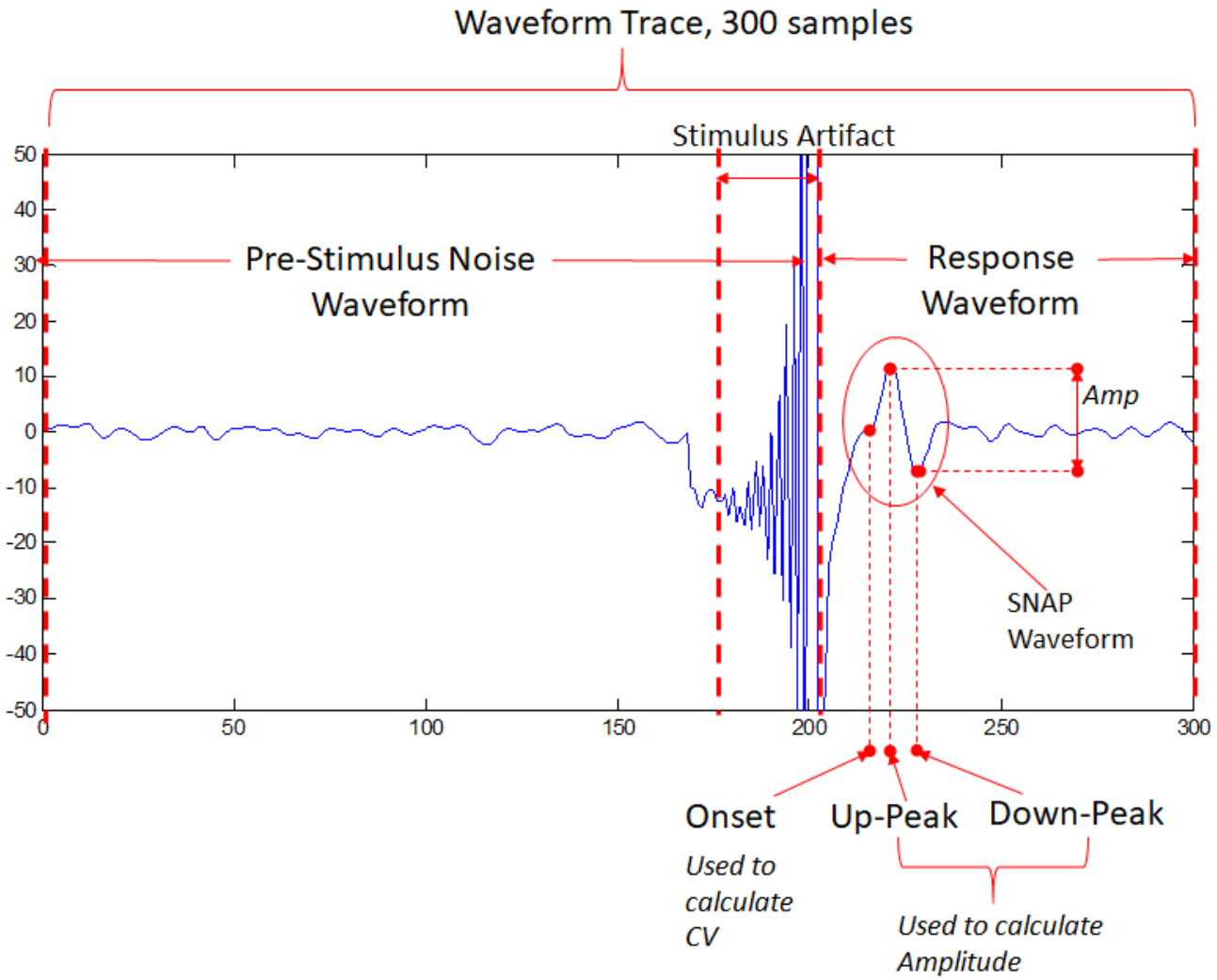

- In this mode, user is also prompted to select whether **Same or New patient**.




- Highlighted limb on results screen indicates that a **result is saved on the other limb**.

# Quality Measures and Controls

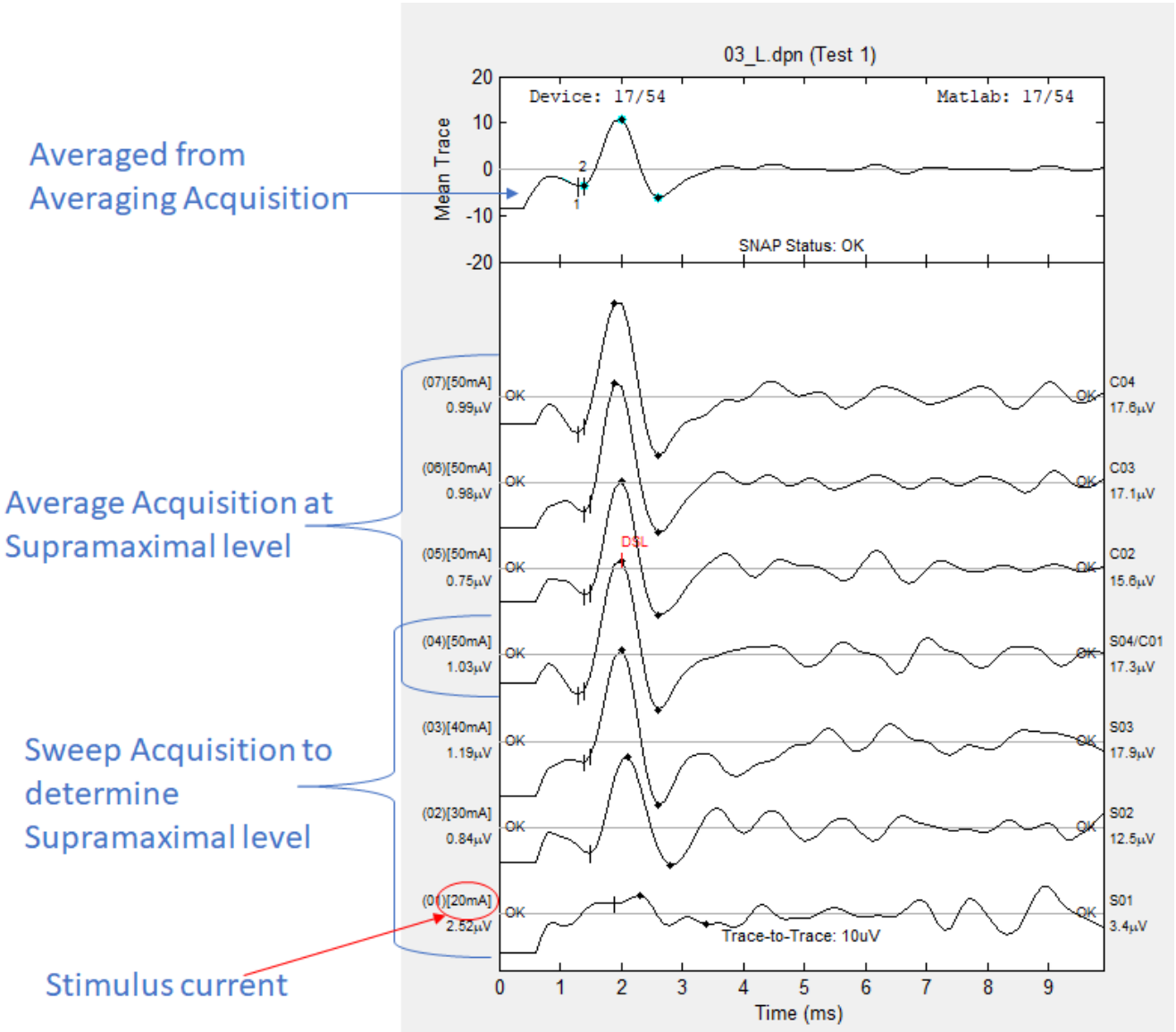
# Sophisticated measurement and signal processing allow DPNCheck to record the nerve response with precision




- Minimal internal noise of the electronics allow reliable measurement of low amplitude signals, critical for tracking disease progression.
- Each recorded wave is filtered to enhance signal quality for analysis.

# Automation determines the needed stimulation level and locates features for calculating results

- Stimulus starts a low level and increases until the amplitude is stable, indicating all nerve fibers are firing. This is known as **supramaximal stimulation**.
- Multiple stimulations are performed at the supramaximal level to create an **averaged SNAP**, removing effects of noise and outliers.
- The averaged SNAP waveform is used for assigning onset and peaks for presenting results. **Averages 8-12 nerve responses.**

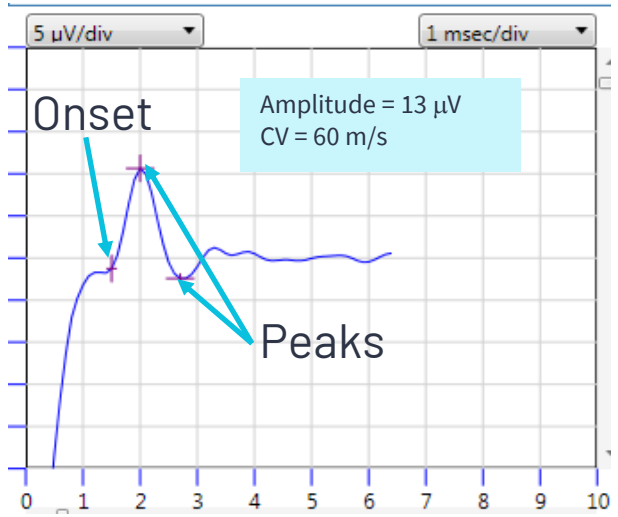


# Quality control checks ensure results will only be reported for signals of adequate quality and reliability

- Patient skin temperature not too cold
- Probes placed on skin without excess gel
- Biosensor on skin with adequate contact (pressure)
- Adequate stimulation level (70 milliamps) to overcome edema, adipose tissue and neuropathy
- Signals contaminated by artifact (stimulus/noise interference/movement) are rejected
- Outliers are removed
- Limb confirmation
- Error messaging to troubleshoot if the test was not successful


# DPNCheck displays traditional NCS results for interpretation

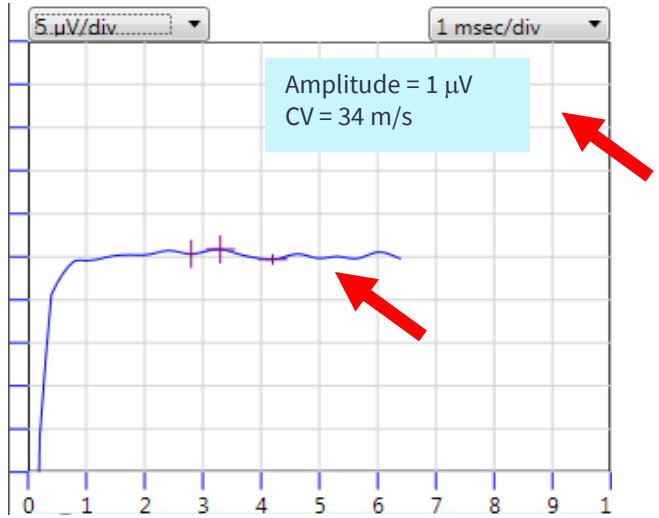
- Conduction velocity is based on SNAP onset, reported in meters/second.
- Amplitude is based on difference between SNAP peaks, reported in microvolts (µV).




- If CV cannot be reliably reported, device may only report the amplitude. Axonal loss results in amplitude reduction.
- A zero (0) will be reported if the amplitude is <1.5µV, indicating severe nerve degradation.



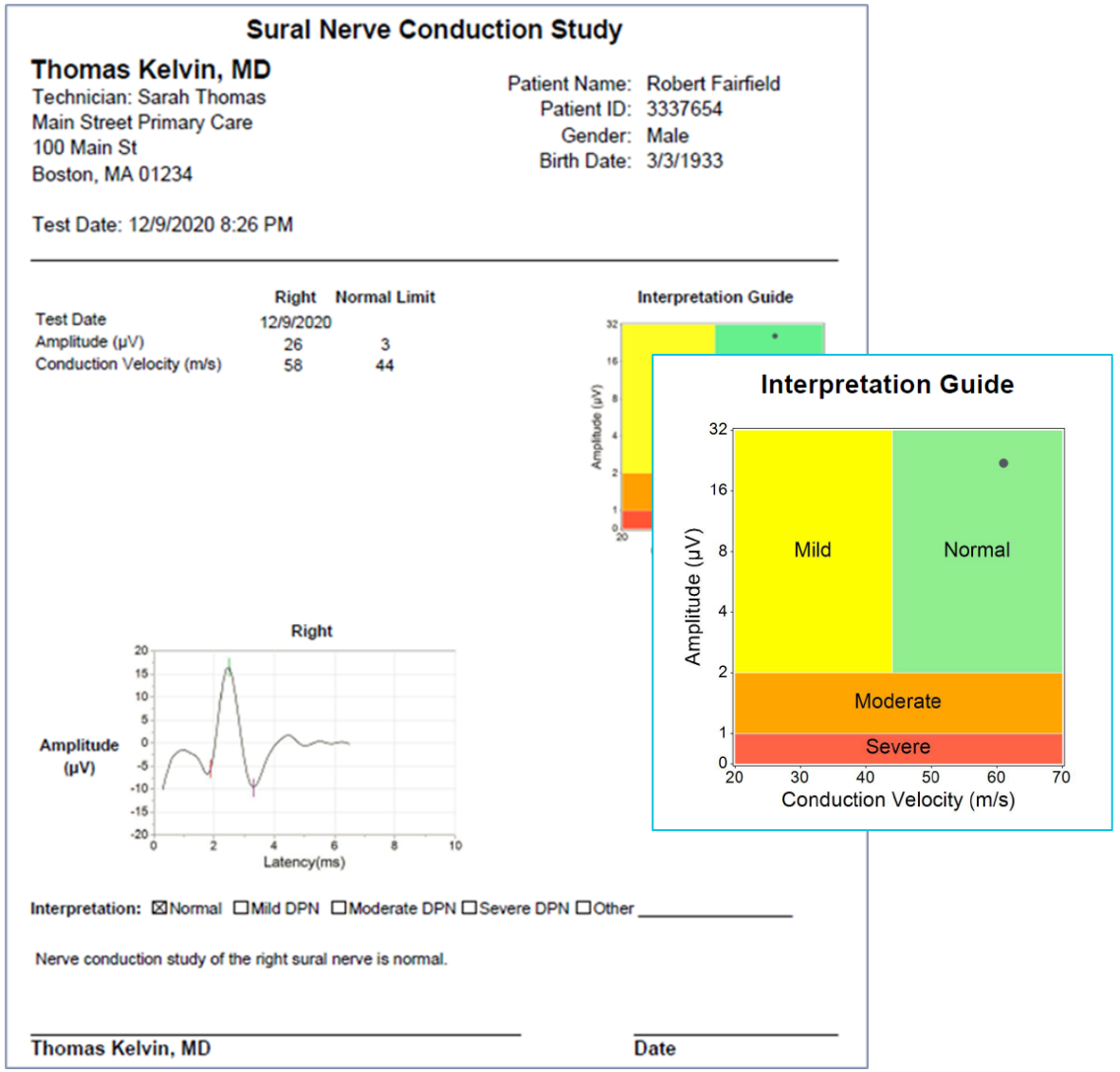
Undetectable Result



# Reporter Software & Cloud Overview

# PC Reporter Software enables report generation and comparison to Normal Limits

- Add height and birthdate, compare to Normal Limits
- Interpretation Guide shows result severity to interpret in conjunction with symptoms
- NCS waveforms and values provide detailed documentation of neuropathy status
- Formats:
  - PDF Report
  - HL7 File, includes PDF Report
  - Relaymed (EMR Integration)
- Optional cloud reporting of de-identified aggregated results



# Appendix

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

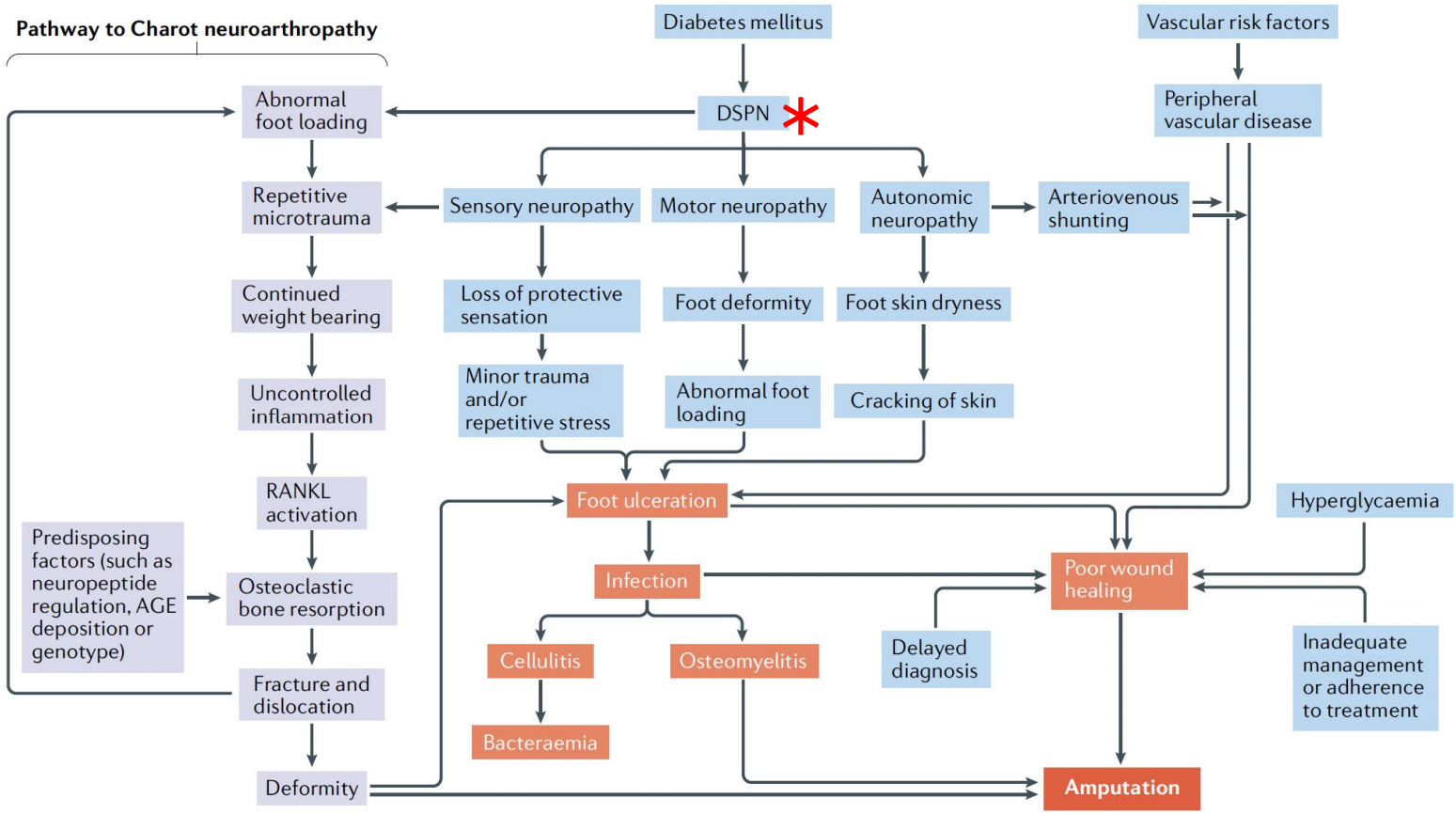



Fig. 1 | **The pathways to foot ulceration and amputation.** Diabetic sensorimotor peripheral neuropathy (DSPN), vascular disease and foot deformity might result in foot ulceration. In Charcot neuroarthropathy, minor trauma of the foot or ankle triggers an inflammatory cascade with a subsequent imbalance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

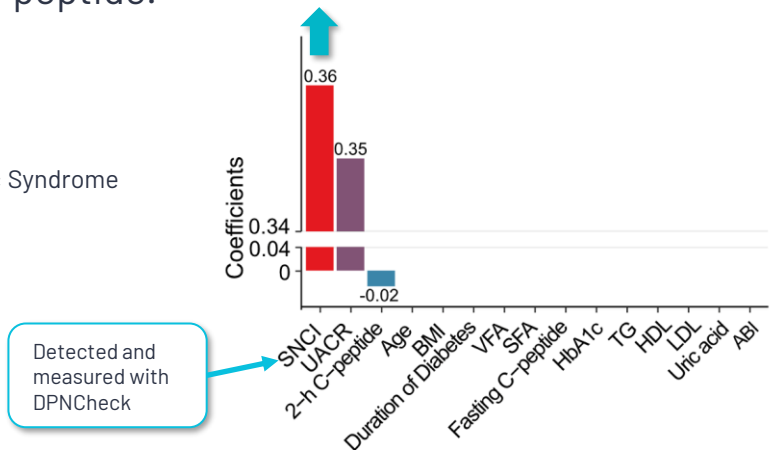

 

# Predicting Vision-Threatening Diabetic Retinopathy:

## 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

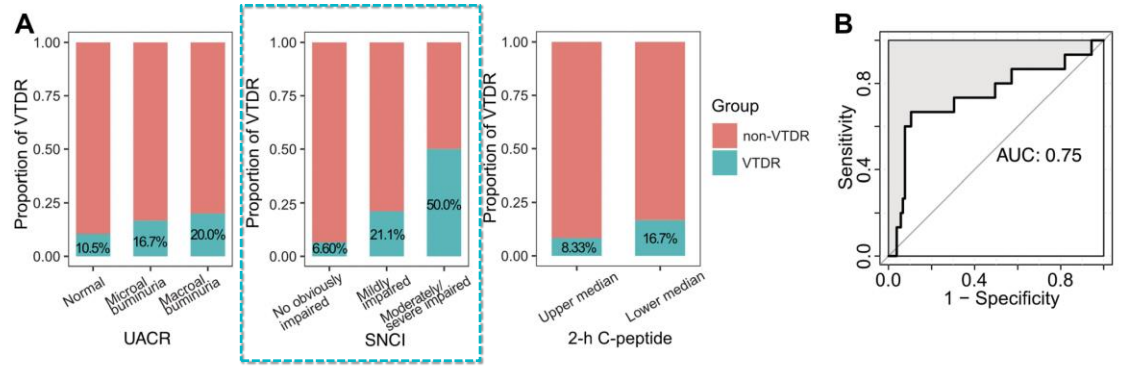



**Figure 4** Proportion of VTDR and predicting AUC in the prospective cohort. As the grade of UACR and SNCI increased, the proportion of VTDR increased. Besides, more VTDR occurred in the lower-median 2-h C-peptide group than that in the upper median 2-h C-peptide group (**A**). AUC of prediction was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

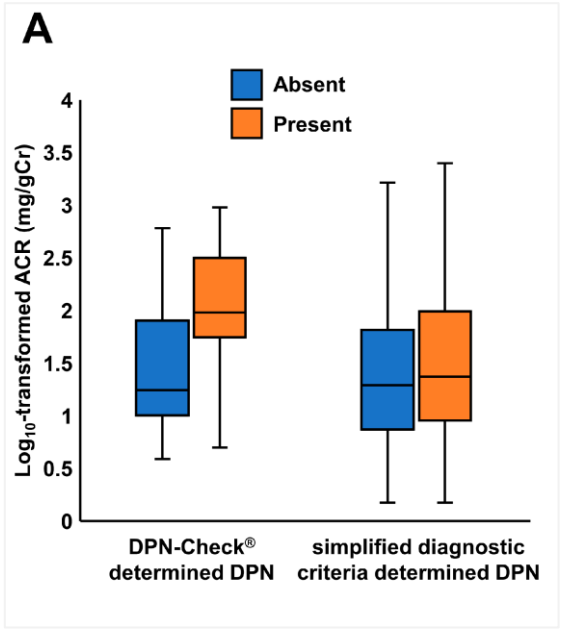

 

# DPNCheck Test Results Predict Risk of Diabetic Nephropathy

*"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."

# DPNCheck®

## Developing a targeted peripheral neuropathy screening program

# Key points in developing a targeted peripheral neuropathy screening program

- Given the ~30% prevalence of peripheral neuropathy in the elderly, any MA screening criteria will generate a high rate of positive tests
- Published peripheral neuropathy prevalence estimates are generally underestimated because nerve conduction was not used
  - DPNCheck utilizes nerve conduction so the positive test rate should meet or exceed prevalence estimates
- Targeting criteria can be based on
  - Demographic, anthropometric and SDoH factors
  - History and symptoms
  - Comorbid medical conditions

# Demographic, anthropometric and SDoH factors associated with a high prevalence of peripheral neuropathy in elderly patients

Demographics

- Age
  - 75-79 years (30%) ← Estimated peripheral neuropathy prevalence
  - ≥ 80 years (42%)
- Male sex (48%)
- Black race (39%)

Anthropometrics

- BMI ≥ 30 (41%)
- Height in 4th quartile (45%)
  - Men > 5’11” Women > 5’6”

SODH

- Less than high school education (43%)

Source: Hicks et al. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. Scientific Reports, 2021 (Estimates based on ARIC cohort in study).

# History and symptoms associated with a high prevalence of peripheral neuropathy in elderly

- Fall in past several years (>40%)
- Diabetic foot ulcer (>80%)
- Neuropathic pain (>80%)
- Chemotherapy (30 – 68%)

Source: 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. Sloan et al. Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathyNature Reviews Endocrinology, 2021. Seretny et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain, 2014.

# Health conditions associated with a high prevalence of peripheral neuropathy in elderly

- Diabetes
  - <10 years (37%)
  - ≥10 years (43%)
  - Prediabetes
- Chronic kidney disease (38%)
- Peripheral arterial disease (44%)
- Cancer (38%)
- Chronic alcoholism (25 – 66%)
- Thyroid disease (>40%)
- Rheumatoid arthritis (up to 85%)

- Additional conditions: metabolic syndrome, B12 deficiency, HIV infection, COPD, OSA, paraproteinemia

Sources: Hicks et al. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. Scientific Reports, 2021 (Estimates based on ARIC cohort in study). 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. Beghi et al. Hypothyroidism and polyneuropathy. J. Neurology, Neurosurgery, and Psychiatry, 1989. Duyff et al. Neuromuscular findings in thyroid dysfunction: a prospective clinical and electrodiagnostic study. J Neurology, Neurosurgery, and Psychiatry, 2000. Chopra and Tiwari. Alcoholic neuropathy: possible mechanisms and future treatment possibilities. British Journal of Clinical Pharmacology, 2011. Agarwal et al. A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. Clin Rheumatol, 2008.