



Advantages & Limitations of Diabetic Peripheral Neuropathy Evaluation Methods

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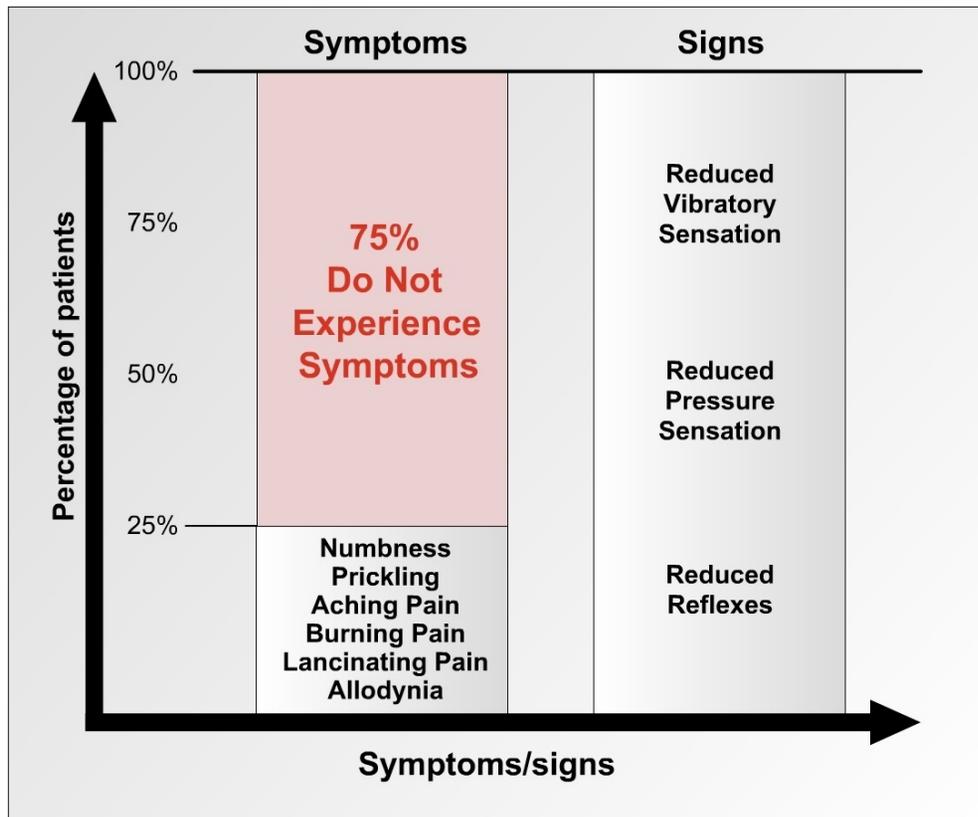
Agenda

- Diabetic Peripheral Neuropathy (DPN)
- DPN Evaluation Methods
- Electrodiagnostics & Sural Nerve Conduction Principles
- NC-stat DPNCheck Overview
- Summary

Diabetic Peripheral Neuropathy (DPN) is Common

- 60%-70% of patient with diabetes may have DPN¹
 - Similar rates for type 1 & 2 diabetics
 - Increased risk with longer duration and poorer glycemic control
- Key factor (along with PAD) leading to LE amputation¹

DPN is Easily Overlooked



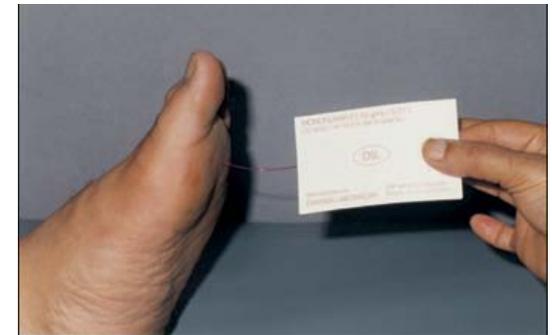
- 75% of DPN patients experience none of these symptoms at any given point in time²
- Most DPN patients display one or more of these signs
- Periodic evaluation is essential for all patients since many are not aware of DPN

Standard of Care for DPN Screening

- To identify LOPS, not early neuropathy
 - 10-g monofilament
 - Vibratory sensation (128Hz tuning fork)
 - Pinprick sensation
 - Ankle reflexes
 - Vibratory perception threshold (biothesiometer)

DPN Screening

- Inexpensive
- Easy to do
- Detects late stage DPN only
- Recommended in practice guidelines
- Shown to be predictive of amputation
- Subjective
- Not standardized
- Poor reproducibility (intra and interprovider variability)³



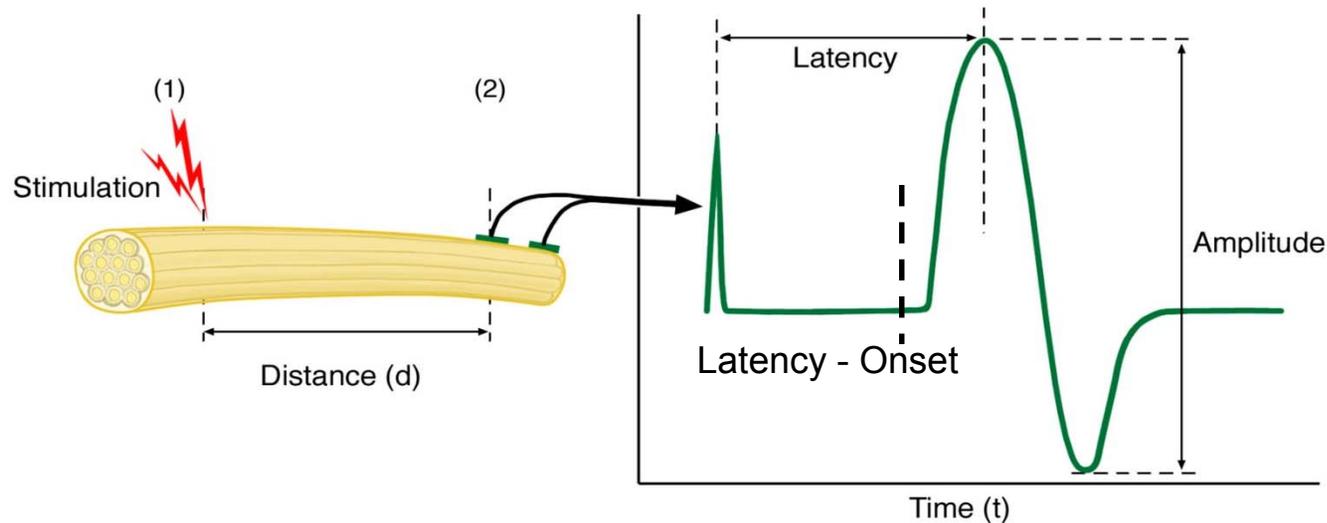
Issues with Standards

- Monofilament
 - Where to test
 - How many times to test
 - How many misses are acceptable
- Tuning fork
 - Toe vs. examiner finger
 - Toe vs. patient's finger
 - On/off
 - Extinction duration

Nerve Conduction Studies are Helpful in Diabetes

- Electrophysiological assessment of peripheral nerve
 - evaluates response of nerves to electrical stimulation
- Diagnostic for DPN
 - high sensitivity and specificity
 - identify early, preclinical disease
 - quantitative
 - can monitor change over time
- Can differentiate PDN from other neuropathies (i.e. lumbar radiculopathy, spinal stenosis)
- Requires referral to specialist
- Expensive

Clinical Neurophysiology: A Sensory Nerve Conduction Study



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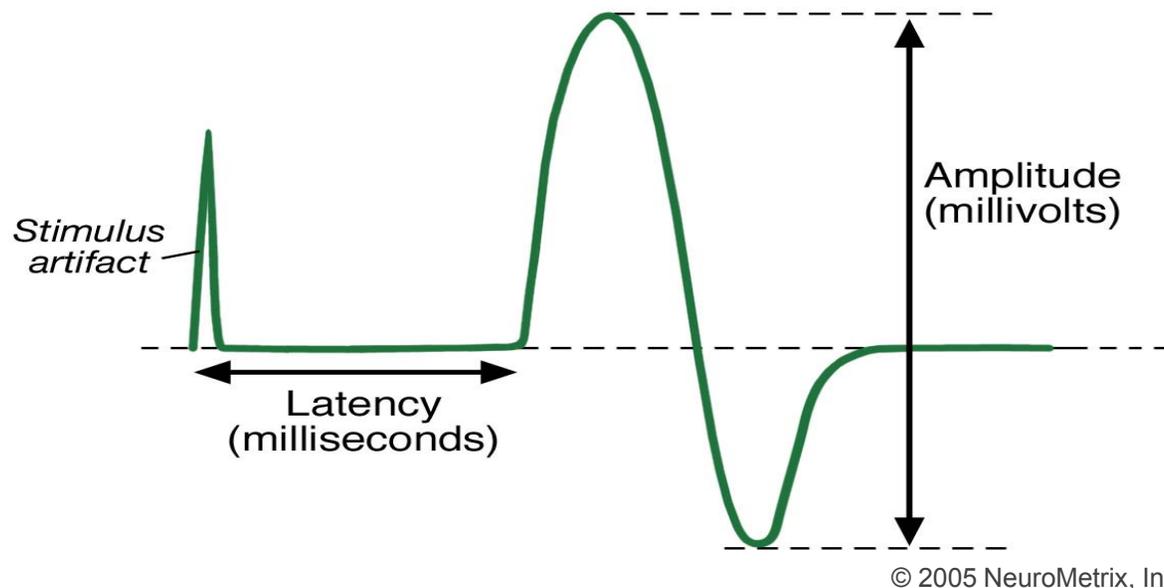
The nerve is stimulated at one site (1) and the response recorded at a second site (2) after propagating a distance (d)

Latency – time it takes the impulse to travel distance (d) between the stimulator (1) and the detector (2); measured in milliseconds

Conduction Velocity – speed with which impulse propagates, calculated as d/t ; measured in meters per second

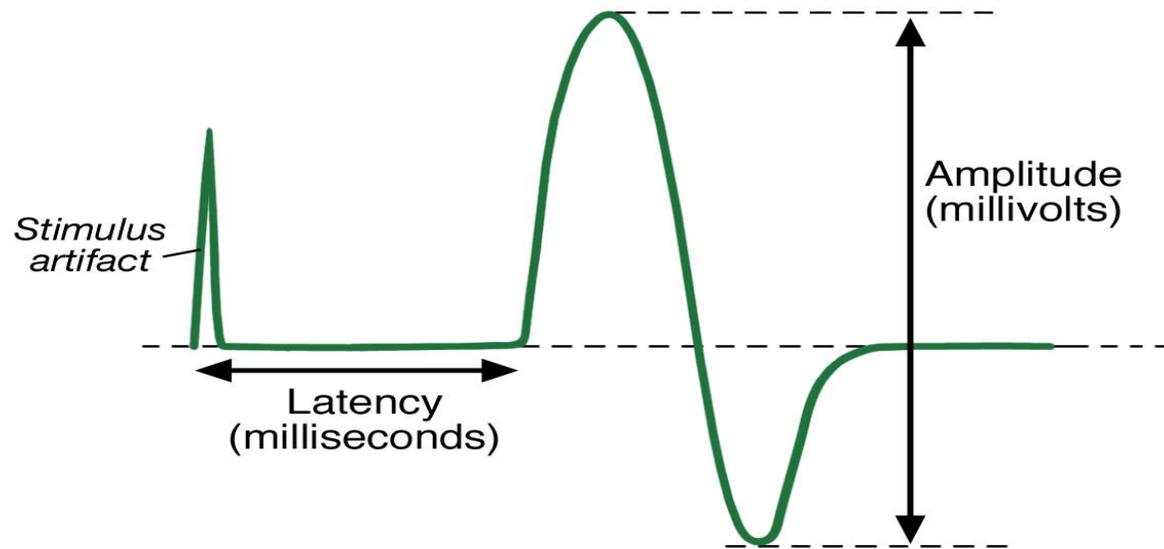
Amplitude – height of the response, can be measured from the baseline to the peak or from peak to peak; measured in microvolts for sensory responses

Sensory Response: The “Sensory Nerve Action Potential” (SNAP)



- NCS activate both large and small fibers
 - Large fibers mediate touch, vibration and position
 - Small fibers mediate temperature and pain
- The SNAP is the sum of the large fiber action potentials
- The small fibers are not detected

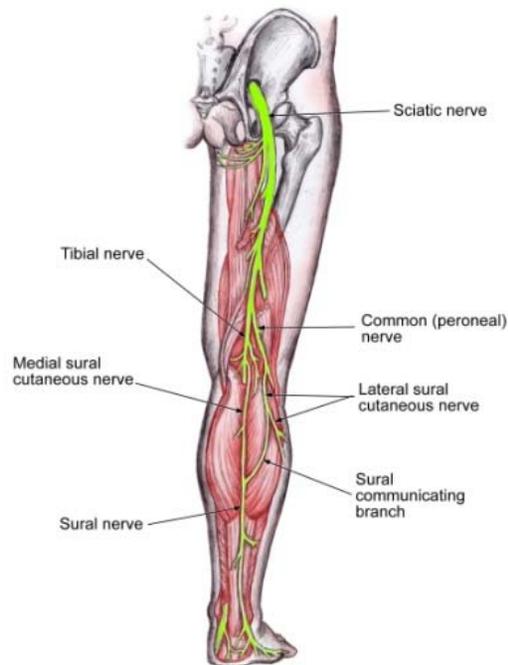
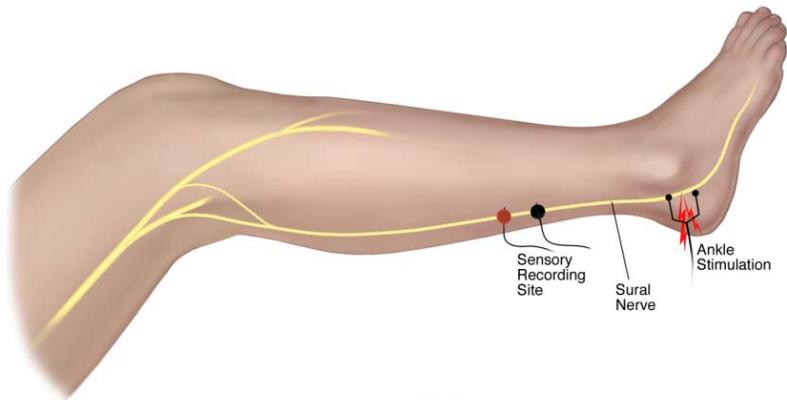
Sensory Response: The “Sensory Nerve Action Potential” (SNAP)



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- Loss of large fiber number will decrease amplitude
- Damage to myelin will decrease conduction velocity
- DPN affects both large and small fibers
- DPN affects both large fiber number and myelin

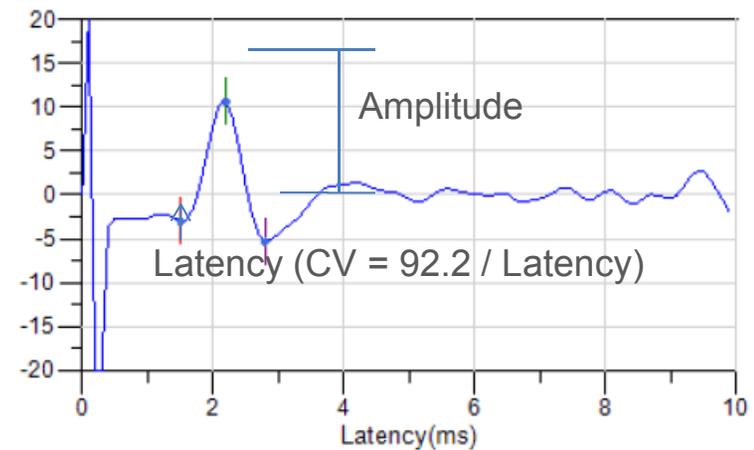
Sural Nerve Conduction



Sural Nerve

- Distal sensory nerve
- It innervates at lateral and posterior third of leg and lateral aspect of foot and heel and lateral portion of the ankle
- Sensitive to DPN; recognized biomarker of DPN

Sural SNAP

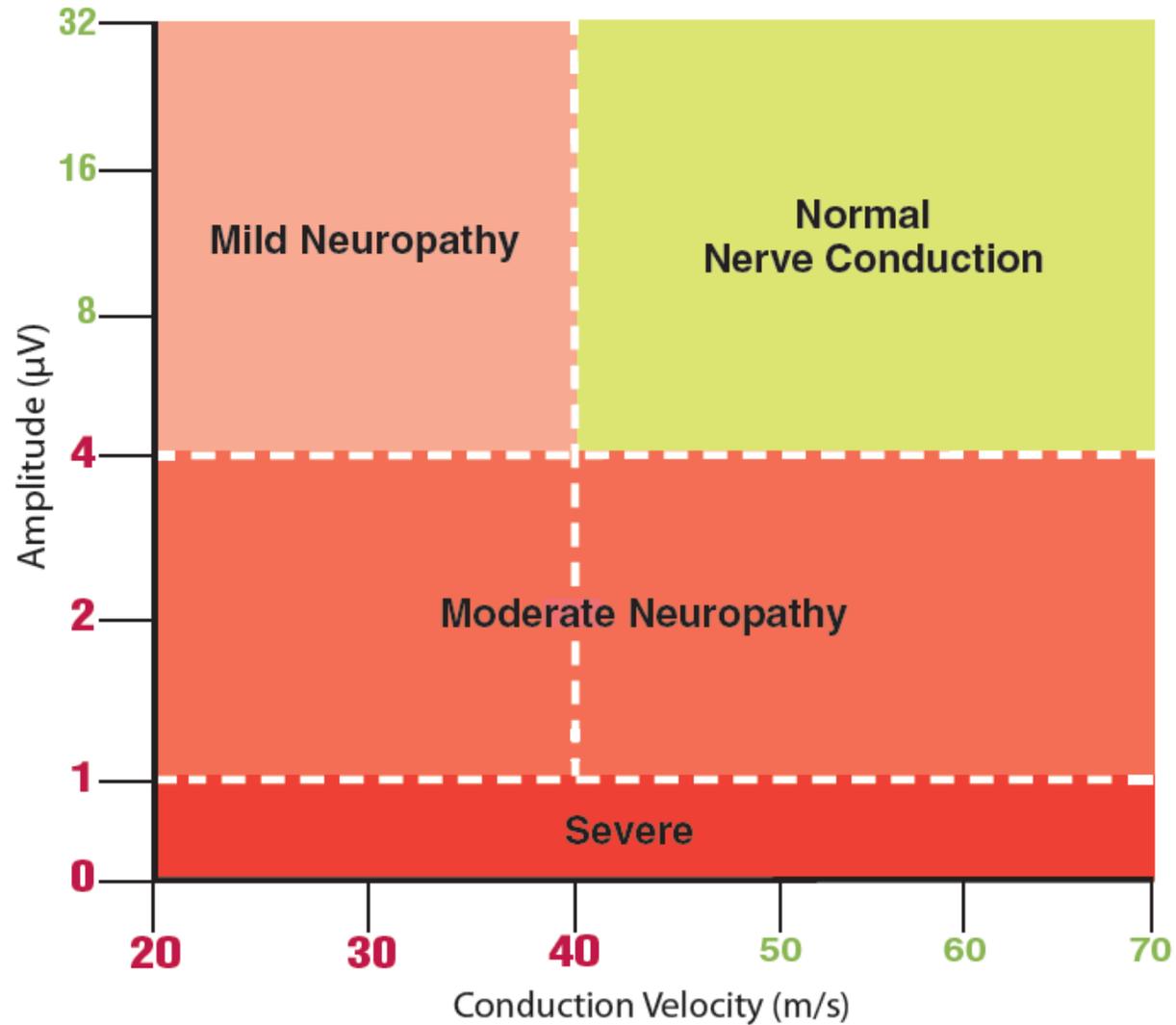


Fast, Accurate, Quantitative

- Point-of-care sural nerve conduction test
 - Standard biomarker for DPN
 - Sensitive and specific for DPN
 - Identifies pre-clinical (“early”) DPN
 - Can confirm suspected diagnosis
 - Can be used to monitor progression
- Easy operation
 - 30-60 seconds per test
 - Does not disrupt patient flow
 - Immediate results
 - Straightforward clinical evaluation
- FDA cleared NC-stat®
 - Over a decade on the market
 - Extensive record of scientific papers and studies



Sural Nerve Conduction Guide



DPN Evaluation Overview: Abnormal Results

- Abnormal Sural Nerve Conduction Results When Physical Exam is Normal
 - NC-stat DPNCheck detects early stage neuropathy, even in the absence of signs and symptoms
 - If a patient has a normal monofilament test, the NC-stat DPNCheck test could identify
 - Mild or moderate nerve conduction abnormalities even in the absence of symptoms

DPN Evaluation Overview:

Normal Results

- Normal Sural Nerve Conduction Results When Physical Exam is Abnormal
 - **False positive monofilament test** - patient has a callous over the area being tested or if the patient was inattentive.
 - **Diagnosis other than DPN**
 - **Lumbosacral Radiculopathy** - cell bodies giving rise to the axons making up the sural nerve are located in dorsal root ganglia located outside the spinal cord. Radicular compression of nerve roots, such as due to spinal stenosis or disc herniation, does not disrupt the distal axons and sural nerve conduction is generally unaffected.

DPN Evaluation Overview: Results Variation

- Like other physiological measurements, sural nerve conduction velocity and amplitude will vary from test to test.
 - Reasons: underlying variation in the measurements, small differences in test setup (e.g. exact placement of device on leg), and random electrical interference (e.g. nearby computer and medical equipment)
- Variation should be less than 5% for conduction velocity and 25% for amplitude.⁴
- If a result that is on the border between normal and abnormal, the test can be repeated to confirm the finding. Amplitude results that are above 4 microvolts (normal) may have greater variability but are nonetheless generally considered normal.

Sensitivity and Specificity of Monofilament vs. NCS

- Study of 195 patients with Type 1 Diabetes⁵
 - Mean age 43, duration 35 yrs
 - Normal monofilament $\geq 8/10$
 - Abnormal monofilament as missing $\geq 3/10$
- Sensitivity/specificity of monofilament = 0.15/1.0 compared to NCS of sural nerve
- 100% of patients with an abnormal monofilament test also had abnormal sural nerve conduction (PPV)
- 60% of patients with a negative monofilament test actually had neuropathy as defined by abnormal sural nerve conduction (NPV=40%)

Sensitivity and Specificity of Monofilament vs. NCS

- Study of 478 patients with Type 1 or 2 Diabetes⁶
 - Mean age 56, duration 13 yrs
 - Normal monofilament $\geq 7/8$
 - Abnormal monofilament as missing $\geq 2/8$
- Sensitivity/specificity of monofilament = 0.77/0.67 compared to NCS
 - Less stringent diagnostic criteria lead to higher sensitivity and lower specificity
- 1 out of 4 patients with neuropathy were missed by monofilament screening
- 1 out of 3 patients without neuropathy had an abnormal screening with a monofilament

NC-stat DPNCheck Clinical Data Review

- Based on validated NC-stat Technology⁵⁻¹⁰
 - Testing on over 1.5 million patients, 5 million nerves*
- Sural nerve conduction is a standard, quantitative biomarker of DPN¹¹
- Detects DPN with high diagnostic sensitivity^{12,13}
- Reveals abnormalities indicative of subclinical DPN¹⁴
- Correlated to morphological severity (myelinated fiber loss¹⁵) of DPN^{16,17}
- Detectable sural response suggestive of low foot ulcer risk¹⁸
- Predictive of concurrent microvascular complications¹⁹

Summary

- DPN is common
- Screening tests for neuropathy have limited sensitivity/specificity, are not standardized and lack quantification
- NCS are the gold standard of nerve testing
- NC-stat DPNCheck is a simple way to perform POC NCS. It is highly sensitive/specific and provides a quantitative result

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