Journal of Diabetes Science and Technology
2022, Vol. 16(2) 295–320

DOI: 10.1177/19322968211035375
journals.sagepub.com/home/dst
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Diabetes Distal Peripheral Neuropathy: Subtypes and Diagnostic and Screening Technologies

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Abstract

Diabetes distal symmetrical peripheral neuropathy (DSPN) is the most prevalent form of neuropathy in industrialized countries, substantially increasing risk for morbidity and pre-mature mortality. DSPN may manifest with small-fiber disease, large-fiber disease, or a combination of both. This review summarizes: (1) DSPN subtypes (small- and large-fiber disease) with attention to clinical signs and patient symptoms; and (2) technological diagnosis and screening for large- and small-fiber disease with inclusion of a comprehensive literature review of published studies from 2015-present ($N = 66$). Review findings, informed by the most up-to-date research, advance critical understanding of DSPN large- and small-fiber screening technologies, including those designed for point-of-care use in primary care and endocrinology practices.

Keywords

diabetes, diagnostic technologies, distal symmetrical peripheral neuropathy, large-fiber neuropathy, small-fiber neuropathy

Introduction

Distal symmetric peripheral neuropathy (DSPN) is the most common form of diabetes neuropathy, affecting 50% of adults with diabetes during their lifetime. DSPN afflicts the feet, and less frequently, the hands.[1-4] In addition to severe pain, imbalance, and associated risk for fall, a highly concerning sequela of DSPN is foot ulceration.[5,6] Foot ulceration confers heightened risk for gangrene and lower extremity amputation. Lower extremity amputations increase risk for mortality with a 5-year survival rate of 40%–48% post-amputation.[7] The economic cost of foot ulcerations and amputations is exceptional, with the cost of foot ulcerations due to diabetes alone estimated at $9-$13 billion annually in the United States.[8] Hence, development of reliable, accurate technological methods to detect DSPN, particularly in the early course of its development (even in asymptomatic stages), is critically needed to slow DSPN progression with prompt interventions to prevent or decrease adverse outcomes and contain healthcare costs.[9-16]

The pathogenesis of diabetes DSPN is not fully understood but is believed to involve multiple mechanisms.[4,17,18] There is strong evidence suggesting that diabetes DSPN is caused by hyperglycemia-induced nerve fiber injury and microvascular ischemia with ensuing nerve fiber degeneration and loss. Hyperglycemia causes direct nerve toxicity through several pathways, such as increased oxidative stress, advanced glycation end-product accumulation, and impaired axonal transport, thereby precipitating nerve degeneration.[4,19] At the same time, long-standing hyperglycemia effects the microvasculature, causing nerve ischemia & degeneration.[20] Hypertension, dyslipidemia, elevated body mass index, and smoking may also contribute to DSPN incidence.[21-26]

DSPN is a progressive condition with no cure. Hence, timely diagnosis of DSPN is essential to prevent or mitigate DSPN-related morbidity and mortality. Prompt diagnosis of DSPN is indicated in prediabetes, new-onset T2D, and well-established T2D and T1D. Among those with prediabetes, DSPN may afflict 10%-30% or more, indicating neuropathic

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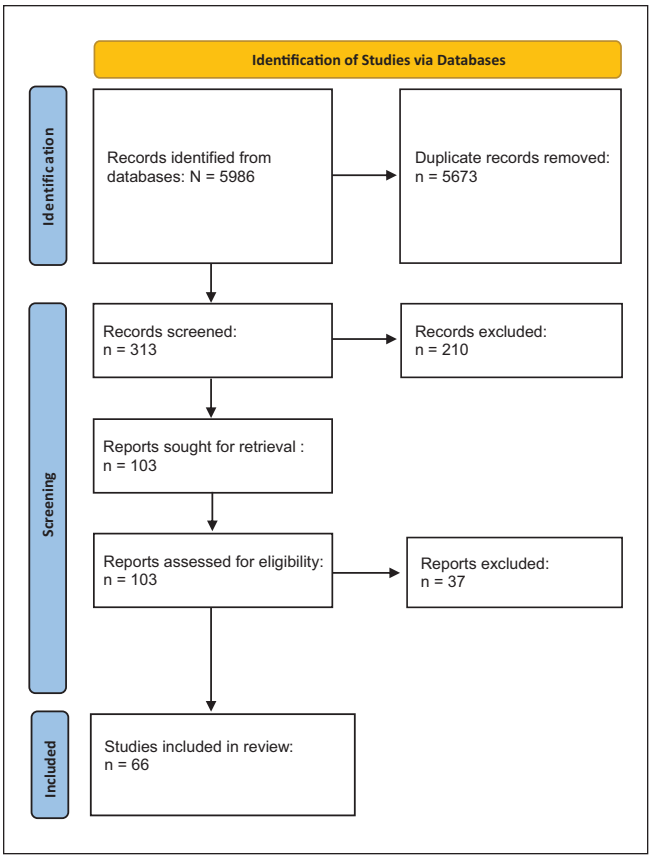

Figure 1. PRISMA Flow Diagram.

damage may occur at glucose levels not meeting the threshold for diagnosis of T2D.[4,27] DSPN prevalence, among patients with newly diagnosed T2D, is estimated at 21%.[28] After 10 years of T2D duration, DSPN rates climb exponentially to 50%.[4] Among patients with T1D, DSPN rates are or exceed 20% after 20 years of disease duration.[15,29] Since DSPN rates increase dramatically with longer diabetes duration, early and ongoing surveillance is warranted. Risk reduction strategies for DSPN and its sequelae are optimization of blood glucose, blood pressure, and lipid levels in addition to healthy lifestyle behaviors (daily foot care, weight loss, increased physical activity, smoking cessation).[4,21-26,30-33]

On the frontline diagnosing and managing prediabetes and diabetes, primary care providers play a critical role in early detection of DSPN. Yet, in primary care, research indicates DSPN may be underdiagnosed or not diagnosed promptly with underutilization of diagnostic tests and sometimes misperceptions about causes or management.[34-36]

Hence, this study examines: (1) DSPN subtypes (small- and large-fiber disease); (2) DSPN screening with attention to guidelines for clinical diagnosis; and (3) well-established diagnostic and more recent, innovative advances in technological screening for DSPN subtypes with attention to performance, reproducibility, and longitudinal outcomes data. Currently, comprehensive, up-to-date reviews on technologies and related advancements for DSPN screening and diagnosis are lacking.

Study inclusion criteria were: (1) examination of technological diagnosis or screening (specifically, nerve conduction study, quantitative sensory testing, contact heat evoked potentials, corneal confocal microscopy, quantitative sudomotor axon reflex testing, and electrochemical skin conductance) approaches for DSPN; (2) related investigation of diagnostic or screening performance, reliability or validity testing, automation procedure, and/or longitudinal outcomes in detecting DSPN; (3) inclusion of adult participants with T1D, T2D, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG); (4) published in English; and (5) published between 2015-April of 2021. Study exclusion criteria were: (1) exclusive use of a descriptive and/or correlational design; (2) investigation of technology in performing the routine foot exam; (3) exclusive examination of DSPN predictors (eg, demographic and clinical factors); (4) intervention studies; (5) conference abstracts; (6) dissertations; and (7) review articles.

We conducted a literature search using the following search engines: PubMed, Scopus, and MEDLINE. The search strategy was conducted by separately entering key search terms (nerve conduction study, quantitative sensory testing, contact heat evoked potentials, corneal confocal microscopy, quantitative sudomotor axon reflex testing, and electrochemical skin conductance) with each term, respectively, accompanied (one at a time) by AND diabetes, AND type 1 diabetes, AND type 2 diabetes, AND prediabetes, AND impaired glucose tolerance, or AND impaired fasting glucose. Then, the key search terms, respectively, were accompanied, individually, by AND peripheral neuropathy AND diabetes; AND peripheral neuropathy AND type 1 diabetes; AND peripheral neuropathy AND type 2 diabetes; AND peripheral neuropathy AND prediabetes; AND peripheral neuropathy AND impaired glucose tolerance; or AND peripheral neuropathy AND impaired fasting glucose. The literature search yielded 66 studies for analysis (see Figure 1).

DSPN Subtypes

The subtypes of DSPN are small- and large-nerve fiber disease. Small- and large-nerve fiber DSPN may present exclusively or together while each subtype may increase risk for foot ulceration due to reduced sensory function, and thereby heightened risk for lower extremity amputations.[4] Small-fiber DSPN typically precedes large-fiber neuropathy. Small-fiber DSPN impairs functional integrity of the small thinly myelinated Aδ and unmyelinated C fibers. These small, peripheral nerve fibers prominently convey pain to the central nervous system. In DSPN, they may stimulate profound pain.[3] Small-fiber DSPN may also adversely affect local autonomic (eg, decreased sweating, dry skin, impaired

Table 1. Symptoms & signs of small & large fiber DSPN.[3]

Type of neuropathy	Subjective symptoms	Objective signs
Small fiber neuropathy	• Hypersensitivity to pressure or touch • Chronic or transient sensations of paresthesias: ○ tingling ○ burning ○ freezing ○ stabbing ○ aching ○ electrical	• *Sensory loss: 0 – + (thermal allodynia-cold metallic device or ice in glove)* • *Pain: 0 – +++* • *Tendon reflex: NL – ↓* • *Motor Deficit: 0* • Reduced sensitivity: ○ 1.0 g Semmes Weinstein Monofilament • Reduced prickling pain perception ○ Waardenberg wheel • Abnormal ANS function (feet and/or hands) ○ decreased sweating ○ dry skin ○ cold feet (impaired vasomotion & blood flow) • Normal NCV findings
Large fiber neuropathy	• Symptoms may be minimal: ○ sensation of walking on cotton ○ floors feeling "strange" ○ inability turn pages of book or button shirt ○ inability to discriminate among coins • In some cases, with severe distal muscle weakness: ○ inability to stand on toes or heels	• Sensory loss: 0 – +++ (touch vibration – 128 Hz tuning fork) • Pain: 0 – +++ • Tendon reflex: 0 – ↓↓↓ • Motor Deficit: 0 – +++ • Impaired light touch &/or joint position perception • Abnormal NCV findings • Sensory ataxia (waddling like a duck) • Wasting of small intrinsic muscles of feet &/or hands ○ hammertoe deformities ○ weakness hands &/or feet • Increased blood flow – hot feet

vasomotion) and thermoreceptor (cold, warm sensations) functions.[3,37,38]

Often, pain and other symptoms and signs (see Table 1) first manifest in the feet and progress proximally to the lower extremities and, in some cases, to the hands with a stocking and glove pattern. However, some with small-fiber DSPN may not experience pain.[39,40] A proportion of patients with small-fiber neuropathy may present with little evidence of the disease, which may delay DSPN diagnosis.[41-42]

Large-fiber disease refers to impairment of Aα and/or Aα/β fibers. These fibers are large myelinated fibers. Aα fibers control motor functions and muscle control while Aα/β fibers are related to sensory functions.[3] In DSPN, damage to Aα fibers may manifest with muscle weakness, painful cramps, among other symptoms.[40] Aα/β fibers are implicated in reduced perception to touch, vibration, balance, and position as well as pain (see Table 1).[3,42] Damaged large Aα/β fibers may increase risk for falls and fractures with reduced or absent sensory input for the control of movement.[3,43]

DSPN Screening and Diagnosis

The American Diabetes Association (ADA) recommends screening for DSPN to promote early interventions (eg, glycemic control and lifestyle modifications), particularly given treatments targeting the underlying nerve damage are lacking. Screening should commence upon the diagnosis of T2D and at least annually thereafter. In the setting of prediabetes, screening may be considered although research suggests 11%-25% of this population may exhibit DSPN and 13%-26% may present with neuropathic pain.[4,44] The ADA suggests, after exclusion of other causes, a diagnosis of DSPN may be based on a supportive patient history plus assessment of either gross temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (large-fiber function). An annual 10-g monofilament test is recommended to assess for risk of foot ulceration and amputation. According to the ADA, the clinical history and physical examination often are sufficient for diagnosis of DSPN. Yet, up to 50% of individuals with DSPN may be asymptomatic.[4] Also, screening methods may not yield valid data to detect early or subclinical stages of DSPN and/or diagnose DSPN in diverse populations.[42,45-48] Therefore, additional DSPN testing may be warranted.

Large-Fiber DSPN Diagnostic Testing and Screening

Nerve Conduction Study (NCS)

NCS is considered the gold standard for diagnosing large-fiber neuropathy. NCS has documented sensitivity and specificity, ranging, for example, from 40%-81% and 91%-95%, respectively, for DSPN.[49-50] NCS measures the rate at which an electrical impulse travels through nerves, such as the sural

sensory, peroneal motor, and tibial nerves. Two electrode patches are placed on the nerve being testing with one electrode stimulating the nerve and the other measuring the electrical impulse. Given NCS findings are complex, data are interpreted by health professionals with requisite advanced training.[3]

Conducted from 2015-present, the literature search on NCS yielded 10 studies that revealed technological advances (see Table 2).[51-60] In particular, a point-of-care device (POCD), DPN-Check (Neurometrix, Waltham, MA, USA), was identified, which rapidly reproduces part of the NCS (sural nerve conduction).61 Overall, studies reveal DPN-Check may be a highly promising automated technology while allowing increased access to DSPN testing and limited clinician technological expertise in its application.[51-60] DPN-Check is a handheld device placed on the lateral aspect of the lower extremity (posterior to the lateral malleolus), following the same measurement principles as standard NCS.[61] Sampling T1D and T2D populations, studies tend to report good to excellent sensitivities (80%-96%) and specificities (80%-97%) for DPN-Check in detecting DSPN and its severity (see Table 2).[51,52,55-59] In comparing NCS to DPN-Check, data reveal intraclass correlation coefficients are excellent overall (intrarater reliability: velocity 0.77, amplitude 0.81; interrater reliability: velocity 0.97, amplitude 0.83).[60]

Among Japanese and possibly other East Asian populations, review findings indicate US normative ranges for DPN-Check parameters, particularly sural nerve action potentional amplitude, may not be valid. Hirayasu et al. propose a promising Japanense regression formula to promote accurate DSPN assessment with DPN-Check.[54]

Small-Fiber DSPN Diagnostic Testing

Intraepidermal Nerve Fiber Density Testing (IENFD)

IENFD testing is the gold standard for diagnosing small-fiber DSPN. IENFD is an invasive procedure wherein a punch biopsy is obtained from the distal leg for quantification of small-fiber densities. Small-fiber DSPN is identified by reduced intraepidermal nerve fiber density or morphological changes.[62,63] IENFD has variable sensitivities and specificities, ranging, for example, from 78%-88% and 64%-90%, respectively.[62] Varied diagnostic accuracy may be partially attributed to IENFD cutoff and reference values used in assessing for small-fiber neuropathy as well as specific location of the biopsy site. Normative values require adjustment for age and gender or results may likely be biased.[62,64-65] A number of studies suggest IENFD values are affected by ethnicity, which may also bias results as revealed in Asian populations.[66-68]

Quantitative Sensory Testing (QST)

QST assesses large- and small-fiber function. With respect to small-fiber function, QST technologies assess the thresholds at which small nerve fibers detect pain and thermal sensations. In suspected DSPN, a thermode is placed on the foot and/or hand areas with pain and/or sensory deficits. Patients are instructed to quickly respond to changes in specified sensations, which yield mean peak values or thresholds for pain and thermal sensations. QST may thus be conceived as a psychophysical test wherein sensation stimuli are controlled and stimuli responses are dependent on the active participation of the patient. QST is thus susceptible to bias related to patient motivation, attention, or cognitive impairment. Interpretation of QST findings requires attention to the clinical context while data is best compared to normative data stratified for age, gender, and body site. QST is not recommended as a stand-alone diagnostic test given variable study results and testing methodologies.[69-70] Compared to IENFD and clincial examination, published reports document the sensitivity of thermal testing ranges from 36%-100% for small-fiber neuropathy although diagnostic criteria for the condition were not uniform across studies.[70]

Since 2015, the literature search identified thirteen studies comparing, for instance, different QST devices and evaluating new methodologies or technological approaches (see Table 3).[71-83] NerveCheck (Phi Med Europe SL, Barcelona, Spain), in particular, reveals technological advancement of traditional QST. NerveCheck is a small, portable device, and yields rapid results. NerveCheck assesses vibration (VPT), cold (CPT) and warm (WPT) perception thresholds, and heat pain threshold. NerveCheck has demonstrated an intraclass agreement for VPT (large-fiber vibration testing), CPT (small-fiber thermal testing) and WPT (small-fiber thermal testing) at 0.79, 0.86, and 0.71, respectively.[82] The diagnostic accuracy of NerveCheck in detecting sensory loss, based on the area under the curve (AUC), is reportedly 0.70 for CPT and 0.69 for WPT with IENFD as the reference.[83]

More well established, the TSA NeuroSensory Analyzer (Medoc, Ramat Yishai, Israel) has advanced over the years with development of a precision enhanced, small portable device for QST; i.e., the TSA-II NeuroSensory Analyzer. Using the TSA-II, Farooqi and colleagues advanced the science of QST by validating cooling detection thresholds (CDT) to detect DSPN in a sample of participants with T2D. While not assessed against IENFD, CDT was found to outperform other measures of DSPN. CDT had acceptable discriminatory ability for detecting clinical DSPN (AUC 0.79) with a sensitivity of 64% and specificity of 83%. Good discriminatory performance for pre-clinical DSPN (AUC 0.80), with a sensitivity of 83% and specificity of 72%, was also observed.[77]

Table 2. Point-of-Care Sural Nerve Conduction.

Author(s) & study aim	Study population & design	Study outcomes & implications (incorrrect font)
Binns-Hall et al.[51] -Evaluate the feasibility of a one-stop microvascular screening service for early diagnosis of diabetic DPN, painful DPN, & the at-risk diabetic foot	*N* = 236 *M* = 63.5 ± 14.1 yrs/age *n* = 231 T2D *n* = 5 T1D *n* = 84 +DPN *n* = 69 −DPN *n* = 83 unclassified Cross-sectional	• Area under ROC curve for DPN-Check (Neurometrix, Waltham, MA, USA) SNAP (threshold ≤ 4.3 μV) & SNCV (threshold ≤ 46.3 m/s) was 0.84 & 0.81; Youden Index was 0.52 & 0.52, respectively • DPN-Check SNAP & SNCV had a sensitivity of 84% & 72% & specificity of 68% & 80%, respectively • DPN-Check may be useful screening device for identifying diabetic DPN with respectable performance values
Chatzikosma et al.[52] -Evaluate the utility of an automated NCS of the sural nerve with a new portable device for the diagnosis of DPN	*N* = 160 *n* = 114 T2D *n* = 46 HCs *M* = 64.6 ± 8.6 yrs/age Cross-sectional	• DPN-Check exhibited 90% sensitivity, 86% specificity, & 79% positive predictive value against NDS with a standard calculated formula • Sural nerve automated NCS with the DPN-Check device exhibited high sensitivity & specificity for diagnosis of DPN in T2D
Hamasaki et al.[53] - Investigate associations between DN & clinical parameters related to the development and progression of DN by using DPN-Check	*N* = 740, Japanese *n* = 18 T1D *n* = 722 T2D *M* = 65.6 ± 2.0 yrs/age Retrospective observational study	• DPN-Check (HDN-1000, Omron, Tokyo, Japan) sensitivity & specificity, with ankle reflex as reference, were 81% & 46%, respectively • DPN-Check had high sensitivity & poor specificity in this study, suggesting the POCD may rule out DN if the test is negative but may not be suitable for a definitive diagnosis of DN in Japanese patients
Hirayasu et al.[54] - Clarify Japanese normal limits of nerve Amp & CV by DPN-Check (Investigation I); examine validity of DPN-Check to identify DSPN (Investigation II)	Investigation I: *N* = 527 USA – data from DPN-Check database *M* = 48.3 ± 18.5 age/yrs *N* = 463, Japanese, −DM, −DPN *M* = 60.8 ± 9.8 age/yrs Investigation II: *N* = 92, Japanese, +DM *M* = 65.7 ± 7.0 age/yrs Cross-sectional	• I. With DPN-Check (HDN-1000, Omron, Tokyo, Japan) assessments, cut-off values for normal limits of Amp & CV for Japanese participants identified by JRF; JRF normal limits higher than those identified for USRF (USRF provided by Neurometrix) • II. Using DPN-Check, prevalence of NCA1 (1or more abnormal value of Amp & CV) was 25.0% (JFR) & 19.6% (USRF) for Japanese sample with +DM • II. Using DPN-Check, prevalence of NCA2 (2 abnormal values of both Amp & CV) was 6.5% (JFR) & 4.4% (USRF) for Japanese sample with +DM • II. DPN-Check detected 'probable DSPN' (NCA1) with sensitivities & specificities of 85% & 86% (JFR) & 71% & 90% (USRF), respectively, for Japanese sample with +DM • II. DPN-Check detected 'probable DSPN' (NCA2) with sensitivities & specificities of 43% & 100% (JFR) & 29% & 100% (USRF), respectively, in Japanese sample with +DM • II. AUC of JRF (0.89) was larger than AUC of USRF to detect 'probable DSPN' (0.82) in Japanese sample with +DM • A significant difference in normal limits of nerve conduction parameters by DPN-Check between Japanese & USA individuals was observed
Kamiya et al.[55] -Validate a novel diagnostic method for DPN using a point-of-care nerve conduction device as an alternative way of diagnosis using a standard EMGS	*N* = 375 T2D, Japanese *n* = 267 +DPN *n* = 108 −DPN *M* = 61.9 ± 14.6 yrs/age Cross-sectional	• A multiple regression model to predict DPN severity was generated from the following data: DPN-Check values, age in yrs, & DPN severity (estimated severity MBC; MBC stage 0 = no DPN, MBC stage 1 = mild DPN, MBC stage 2 = moderate-to-severe DPN • Using ROC curve analysis, an optimal cutoff value of 1.31of eMBC (categorizing stage 2 vs stage 0 or 1 DPN) was identified with excellent discriminative power (AUROC 0.87); sensitivity was 70.1%, specificity was 87.7%, & positive predictive value was 83.0% • Nerve conduction parameters in the sural nerve acquired by DPN-Check successfully predicted severity of DPN • DPN-Check well predicts DPN & may provide comprehensive, sequential management of diabetic complications in the future

(continued)

Table 2. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications (incorrrect font)
Kural et al.[56] -Validate a rapid, accessible method for diagnosing DPN in a large T2D cohort	*N* = 168 T2D *n* = 45 +DPN *Med* = 71.5 yrs/age IQR: 67.2–75.9 *n* = 123 −DPN *Med* = 69.4 yrs/age IQR: 64.9–74.6 Cross-sectional	• DPN-Check performance (against standard NCS sum-scores), using ROC curves, revealed a good sensitivity & specificity for DPN-Check amplitudes with AUCs >0.8, sural nerve CVs showed moderate to good sensitivity & specificity with AUCs between 0.7-0.8 • Against NCS, performance of DPN-Check (abnormal or normal), by mean values of amplitudes & CVs of 1 bilateral measure, showed a sensitivity of 82%, specificity of 85%, & PPV of 67%; with up to 3 bilateral measures, a sensitivity of 78%, specificity of 89%, & PPV of 71% was observed against NCS • DPN-Check values were underestimated compared with NCS • DPN-Check, a POCD, is a suitable screening tool for detection of DPN while patients with abnormal or borderline results should undergo conventional NCS
Papanas et al.[57] -Examine diagnostic performance of the portable DPN-Check for automated measurement of SNC in diagnosis of DPN	*N* = 53, T1D *M* = 36.9 yrs/age Cross-sectional	• DPN-Check revealed 96% sensitivity, 93% specificity, & 92% positive predictive value in detecting DPN with NDS (threshold ≥ 3) as reference • DPN-Check yields high sensitivity, specificity, & positive predictive value for diagnosis of DPN in T1D
Scarr et al.[58] Evaluate validity of a POCD as a proxy for standard NCS in older adults (>50 yrs/age) with T1D	*N* = 139 *n* = 68 T1D *M* = 66 ± 8 yrs/age *n* = 71 Sex- & age- matched controls *M* = 65 ± 8 yrs/age Cross-sectional	• ROC curves generated to obtain threshold values using DPN-Check (POCD) to identify abnormal age-adjusted standard NCS values • SN AMP_{POCD} of ≤6μV had 80% sensitivity & 80% specificity for identifying abnormal SN AMP_{NCS}, while a CV_{POCD} of ≤44 m/s had 81% sensitivity & 82% specificity • Using the derived AMP_{POCD} & CV_{POCD} thresholds, diagnostic POCD performance was evaluated for detection of polyneuropathy based on a modified Toronto consensus. ROC curve analysis showed that abnormality in: (1) either AMP_{POCD} or CV_{POCD}, overall, had good sensitivity (86%) & specificity (79%); & (2) both AMP_{POCD} & CV_{POCD} had a fairly adequate sensitivity (66%) & excellent specificity (97%) for detecting polyneuropathy • POCD has strong agreement with reference standard NCS values & diagnostic accuracy for identification of polyneuropathy in a high-risk group
Sharma et al.[59] -Evaluate a POCD to evaluate the nerve conduction device for detection of DPN & compare with LDIFLARE technique	*N* = 242 *n* = 162 +DM *n* = 60 −DPN *n* = 38 mild DPN *n* = 46 moderate DPN *n* = 18 severe DPN *M* = 47.96 ± 13.98 age/yrs *n* = 80 HCs *M* = 39.67 ± 15.17 age/yrs Cross-sectional	• Highly significant relationship between POCD & LDIFLARE technique in detection of SNCV observed with similar results shown for SNAP • In HCs & +DM group, DPN-Check or PCOD (SNCV & SNAP) significantly related to LDIFLARE technique; significance also found in all categories of DPN • ROC curves for POCD outcomes revealed SNCV AUC 0.90, 0.74, 0.81, 0.91 for -DPN, mild DPN, moderate DPN, & severe DPN, respectively; & SNAP AUC 0.87, 0.70, 0.80, 0.87 for -DPN, mild DPN, moderate DPN, & severe DPN, respectively • Findings indicate that POCD, irrespective of stage of neuropathy, can detect the presence of neuropathy with good to high sensitivity & specificity
Shibata et al.[60] -Examine reliability & validity of nerve conduction parameters acquired by DPN-Check	*N* = 57 *n* = 1 T1D *n* = 56 T2D *n* = 16 +DPN *M* = 63.9 ± 11.0 yrs/age *n* = 26 −DPN *M* = 53.2 ± 13.7 yrs/age	• Bland–Altman plots revealed agreement of values with good correlations between standard EMGS and DPN-Check parameters although DPN-Check produced higher values than EMGS • Using ROC analysis, AUC of amplitudes by DPN-Check (0.70) & standard EMGS (0.72) revealed moderate accuracy • Threshold values with maximized accuracy were ≤6 μV for DPN-Check (sensitivity 86.5%, specificity 43.8%) & ≤3 μV for standard EMGS (sensitivity 96.2%, specificity 40.6%) • Using ROC analysis, the AUC of CV by POCD (0.62) & standard EMGS (0.58) showed low diagnostic accuracy • Threshold value with maximum accuracy was ≤44 m/s (sensitivity 71.2%, specificity 53.6%) for values by EMGS; threshold values for DPN-Check could not be ascertained • Intraclass correlation coefficients were excellent (intrarater: velocity 0.77, amplitude 0.81; interrater: velocity 0.97, amplitude 0.83) • POCD has excellent reproducibility & good agreement with standard EMGS & may be useful to evaluate DPN

Abbreviations: Amp, amplitude; AMP, amplitude potential; AUC, area under the curve; AUROC, area under the receiver operator characteristic; CV, conduction velocity; DM, diabetes mellitus; DN, diabetic neuropathy; DPN, diabetic peripheral neuropathy or diabetic polyneuropathy; DSPN, diabetic symmetric sensorimotor polyneuropathy; eMBC, estimated severity in modified Baba classification; EMGS, electromyography study; HC, healthy control; IQR, interquartile range; JRF, Japanese regression formulas; LDIFLARE, laser doppler image flare; M, mean; Med, median, m/s, meter per second; MBC, modified Baba classification; NCA, nerve conduction abnormality; NCS, nerve conduction study; NDS, neuropathy disability score; POCD, point-of-care-device; ROC, receiver operator characteristic; SN, sural nerve; SNAP, sensory nerve conduction potential; SNC, sural nerve conduction; SNCV, sensory nerve conduction velocity; T1D, type 1 diabetes; T2D, type 2 diabetes; USRF, regression formulas of individuals from USA; μV, microvolts; yrs, years

Table 3. Quantitative Sensory Testing (QST).

Author(s) & study aim	Study population & design	Study outcomes & implications
Abraham et al.[71] -Explore utility of SFN testing in patients with a clinical presentation suggesting SFN	*N* = 123 *M* = 55 ± 16 yrs/age *n* = 32 +DM Retrospective study	• Using the portable TSA-II NeuroSensory Analyzer (Medoc, Ramat Yishai, Isarel), participants with clinically suggestive SFN plus DM had significantly elevated vs. normal cooling thresholds (37%, 19%, respectively) & heat thresholds (67%, 22%, respectively) • Participants with clinically suggestive SFN plus DM had significantly reduced (37%) vs. normal (16%) LDIFlare (measure of SFN) values • Using Cohen's kappa coefficient, agreement between the different small-fiber testing modalities were significant; agreement was moderate between LDIFlare & cold testing thresholds (k = 0.52), fair between cooling & heat testing thresholds (k = 0.22), & poor between LDIFlare & heat testing thresholds (k = 0.11) for the entire sample
Alam et al.[72] - Compare diagnostic capability of CCM against skin biopsy & QST in patients with DSPN	*N* = 88 *n* = 30 T1D, -DSPN *M* = 38.8 ± 12.5 *n* = 31 T1D, +DSPN *M* = 53.3 ± 11.9 *n* = 27 HCs *M* = 41.0 ± 14.9 Cross-sectional	• ROC curve analyses used to define Wilcoxon estimate of AUROC & optimal cutoff values with associated sensitivity & specificity for CST & WST (TSA-II NeuroSensory Analyzer) • UROC for CST was 0.76 with an optimal cutoff of 25°**C**; sensitivity of 57% & specificity of 89% for diagnosing DSPN • AUROC for WST was 0.74 with an optimal cutoff of 38°**C**; sensitivity of 86% & specificity of 64% for diagnosing DSPN • AUROCs revealed moderate accuracy of CST & WST parameters
Azmi, et al.[73] -Assess whether baseline and follow-up measures of neuropathy, particularly small-fiber neuropathy, relate to changes in glucose tolerance over 3 yrs	*N* = 47 *n* = 30 IGT *M* = 60 ± 2.1 *n* = 17 Controls *M* = 62.3 ± 1.8 Longitudinal (3-yr FU)	• FU: CT & WT (TSA-II NeuroSensory Analyzer) values did not significantly change for participants who reverted to NGT, remained with IGT, or developed T2D at 3-yr FU • Findings suggest CT & WT are not responsive to changes in glucose tolerance status or T2D development
Courtin, at al.[74] -Investigate the potential of evaluating not only the threshold but also the slope of the psychometric functions for cold & warm detection	*N* = 30 *n* = 15 T2D *M* = 55 ± 4 age/yrs *n* = 15 HCs *M* = 53 ± 4 age/yrs Cross-sectional	• Using a Laser Stimulator Device (SIFEC, Ferrières, Belgium), ROC analysis revealed warm detection thresholds did not well discriminate between T2D participant & control groups at the wrist (AUC: 0.65) or foot (AUC: 0.67) • ROC analysis showed the spread of psychometric function for warm detection was also uninformative (AUC wrist: 0.59; AUC foot: 0.50) • Using a Thermal Cutaneous Stimulator (QST.Lab, Strasbourg, France), ROC analysis indicated both CDT (AUC wrist: 0.83; AUC foot: 0.80) & spread of psychometric function for cold detection (AUC wrist: 0.82; AUC foot: 0.84) displayed very good discriminative properties • Including both slope & threshold in ROC analysis, cold detection discrimination performance between T2D participants & HCs was further increased (AUC wrist: 0.89; AUC foot: 0.94) • Combining slope & threshold parameters of cold detection performance may yield better discriminative ability than relying solely on thresholds
Dhage, et al.[75] -Assess the longitudinal utility of different measures of neuropathy in patients with diabetes	*N* = 38 *n* = 19 +DM *M* = 52.5 ± 14.7 yrs/age (baseline) *n* = 19 HCs *M* = 47.4 ± 14.2 yrs/age (baseline) Longitudinal cohort study (*M* = 6.5 yrs FU)	• At baseline, QST (TSA-II NeuroSensory Analyser) measures of CPT, WPT, CIP, & WIP did not significantly vary between DM participants & controls • Compared to baseline, significant decreases in CPT were observed in DM participants at FU • CPT may serve as a biomarker of nerve damage in patients with DM
Fabry et al.[76] -Determine diagnostic value of skin biopsy, QST, Q-Sweat, LEP, ESC & AVCT for SFN diagnosis	*N* = 245 *M* = 50.4 ± 15.0 yrs/age *n* = 24, +DM *n* = 6, IGT *n* = 102 +SFN *n* = 90 -SFN Retrospective study	• Using the Thermotest (Somedic, Sollentuna, Sweden) device as the measure of QST, no significant difference was found between +SFN & -SFN groups • QST or Thermotest had a sensitivity of 72%, specificty of 39% & positive predictive value of 57% for SFN diagnosis • QST found to be most sensitive test for SFN diagnosis relative to IENFD, QSART (Q-Sweat, WR Medical Electronics, Minneapolis, USA), ESC (Sudoscan, Impeto Medical, Paris, France), LEP, & AVCT • Combining QST, IENFD, ESC & LEP yielded a sensitivity of 92%, specifity of 88%, & positive predictive value of 90% for diagnosing SFN

(continued)

Table 3. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Farooqi et al.[77] - Validate the performance of CDT to detect DSP in T2D	*N*=220, +DM *M*=63 ± 11 yrs/age *n*=52 Pre-clinical DSP *n*=139 +DSP *n*=29 Controls Cross-sectional	• Using the TSA-II NeuroSensory Analyzer to detect clinical DSP with CDT, AUC_{CDT} was 0.79, significantly higher than AUC_{HRV} & $AUC_{LDIFLARE}$ values; CDT (optimal threshold of ≤22.8°C) had a sensitivity of 64% & specificity of 83% in identifying clinical DSP with a positive predictive value of 87% • Using the TSA-II NeuroSensory Analyzer to detect pre-clinical DSP with CDT, AUC_{CDT} was 0.80, significantly higher than AUC_{HRV} & $AUC_{LDIFLARE}$ values; CDT (optimal threshold of ≤27.5°C) had a sensitivity of 83% & specificity of 72% in identifying pre-clinical DSP with a positive predictive value of 95% • CDT revealed good diagnostic performance for detection of clinical & pre-clinical DSP in T2D
Ferdousi, et al.[78] -Compare the utility of quantifying corneal nerve loss at the inferior whorl & central cornea to QST & NCS in the diagnosis & assessment of DPN severity	*N*=143 *n*=93 +DM *n*=51 –DPN *M*=57.68 ± 1.6 yrs/age *n*=47 Mild DPN *M*=60.16 ± 1.7 yrs/age *n*=45 Moderate to severe DPN *M*=64.1 ± 1.48 yrs/age *n*=30 Controls *M*=54.51 ± 2.3 yrs/age Cross-sectional	• ROC curve & Youden Index used to define the optimum cutoff point for WPT & CPT (TSA-II NeuroSensory Analyzer); WPT AUC 0.67, sensitivity 50%, & specificity 76%; CPT AUC 0.64, sensitivity 80%, & specificity 47% • CPT was significantly lower in patients with mild (19.52±1.47, p=0.02) and moderate to severe (18.99±1.55, p=0.01) neuropathy compared with controls (25.38±2.06) • WPT was significantly higher in patients with no (41.65±0.6, p=0.01), mild (43.47±0.6, p<0.0001) and moderate to severe (43.62±0.7, p<0.0001) neuropathy compared with controls (38.87±0.9) • While CPT & WPT, overall, had suboptimal performance values, progressive abnormalities in CPT & WPT were observed with increasing severity of DPN
Løseth et al.[79] - Evaluate progression of DPN & differences in the spectrum & evolution of large- and small-fiber involvement in patients with T1D & T2D over 5 yrs	*N*=59 *n*=35 T1D *M*=47.4 ± 12.0 yrs/age at 5 yr FU *n*=24 T2D *M*=57.8 ± 9.0 yrs/age at 5 yr FU Longitudinal	• Using Thermotest Type 1 (Somedic AB, Sösdala, Sweden) device for QST measurement, baseline values of CPT were elevated at baseline for participants with T1D (4.4 ± 4.4) & T2D (4.8 ± 3.8) • At 5-yr FU, CPT values increased significantly for participants with T2D (6.7 ± 5.3) but not for those with T1D (5.4 ± 5.3) • Yet, CPT z-scores, calculated to adjust for physiologic effects of age, height, & gender, did not reveal significant increases in CPT values for participants with T2D from baseline to 5-yr FU • Further research is indicated to identify if elevated CPT values are a biomarker for DN progression
Pfau et al.[80] -Assess the reliability/validity of "Q-Sense" (portable device) by comparing it with TSA II	*N*=204 *n*=83 +DM *n*=71 +DNP *n*=121 HCs *M*=32.9 ± 13.7 age/yrs Cross-sectional	• Agreement between Q-Sense & TSA II NeuroSensoryAnalyzer (both portable devices) was excellent for CDT (ICC=0.89) & WDT (ICC=0.90), moderate for HPT (ICC=0.53), & poor for CPT (ICC=0.31) • Sensitivity of Q-Sense to detect cold hypoesthesia was reduced in males >60 years • ROC curves for both devices were calculated, using skin biopsy results ("normal" vs. "pathologic") as reference measure, & resulting AUROCs were compared; statistical comparisons of AUROCs (related to TSA II & Q-Sense measurements, respectively) were non-significant for CDT, WDT, & TSL, revealing the non-inferiority of the Q-Sense, relative to TSA II, for thermal detection • Q-Sense is not advised to use for CPT thresholds & HPT thresholds should be used with caution. Q-Sense suitable for thermal detection thresholds (cutoff lowered to 18° C)
Pritchard et al.[81] -Determine if deficits in CNFL assessed using CCM can predict future onset of DPN	*N*=90 T1D, –DPN (baseline) 4-yr FU *n*=16 +DPN *M*=51 ± 14 yrs/age (baseline) *n*=64 –DPN *M*=42 ± 16 yrs/age (baseline) Longitudinal	• DPN developed in 16 participants (18%) after 4 yrs • Participants who developed DPN at 4-yr FU had significantly lower baseline values of CST & CPT (TSA-II NeuroSensory Analyzer) & significantly higher baseline values of WST & WPT (TSA-II NeuroSensory Analyzer) relative to those that did not develop DPN • For CST, AUROC was 0.77; sensitivity was 88% & specificity was 55% with a CST cutoff of 29.2°C • For CPT, AUROC was 0.68; sensitivity was 50% & specificity was 86% with a CPT cutoff of 0.2°C • For WST, AUROC was 0.71; sensitivity was 56% & specificity was 82% with a WST cutoff of 39.1°C • For WPT, AUROC was 0.68; sensitivity was 56% & specificity was 80% with a WPT cutoff of 49.5°C

(continued)

Table 3. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Ponirakis et al.[82] -Establish the reproducibility & diagnostic validity of NerveCheck for detecting DPN	*N* = 186 n = 130 +DM Med = 55.7 yrs/age IQR: 42.9–66.1 *n* = 74 +DM *n* = 28 +DPN *n* = 46 –DPN n = 56 controls Med = 43.6 yrs/age IQR: 35.7–53.1 Longitudinal	• Controls & DM participants tested 2 times (test-retest intervals: 1-8 weeks) with identification of intraclass agreement for NerveCheck (Phi Med Europe SL, Barcelona, Spain) CPT (0.86) & WPT (0.71) • Using ROC curve analysis, diagnostic accuracy for detecting DPN, against the TSA-II NeuroSensory. Analyzer, revealed AUCs for CPT (0.79) & WPT (0.72) • CPT sensitivity was 89% & specificity was 67%; WPT sensitivity was 75% & specificity was 66% • Findings indicate NerveCheck has good reproducibility & moderate diagnostic accuracy for detecting DPN
Ponirakis et al.[83] -Examine diagnostic performance of NerveCheck	*N* = 144 *n* = 74 +DM *n* = 33 +DPN *M* = 64.1 ± 1.79 yrs/age *n* = 41 –DPN *M* = 44.3 ± 2.19 yrs/age *n* = 70 Controls *M* = 41.8 ± 1.63 yrs/age Cross-sectional	• ROC curve analysis used to compare diagnostic accuracy of CPT & WPT against IENFD; AUC of CPT was 0.70 & WPT was 0.69; CPT sensitivity was 53% & specificity was 82%; WPT sensitivity was 56% & specificity was 81% • Diagnostic accuracy of NerveCheck is poor to good with reference to IENFD

Abbreviations: ACVT, autonomic cardiovascular tests; AUC, area under the curve; AUROC, area under receiver operator characteristic; CCM, corneal confocal microscopy; CDT, cold detection threshold; CIP, cold induced pain; CPT, cold pain threshold or cold perception threshold; CST, cold sensation threshold; CT, cold threshold; DM, diabetes mellitus; DNP, diabetic neuropathy; DPN, diabetic peripheral neuropathy; DSP, diabetic sensorimotor polyneuropathy; DSPN, diabetic symmetrical peripheral neuropathy; ESC, electrochemical skin conductance; FU, follow-up; HC, healthy control; HPT, heat pain threshold; HRV, heart rate variability; ICC, intraclass correlation coefficient; IENFD, intraepidermal nerve fiber density; IGT, impaired glucose tolerance; IQR, interquartile range; LDIFLARE, laser doppler imager flare; LEP, laser evoked potentials; M, mean; Med, median; NCS, nerve conduction study; NGT, normal glucose tolerance; QST, quantitative sensory testing; ROC, receiver operator characteristic; SFN, small fiber neuropathy; SNAP, sensory nerve action potential; SNCV, sural nerve conduction velocity; T1D, type 1 diabetes; T2D, type 2 diabetes; TSA, Thermal Sensory Analyzer; TSL, thermal sensory limen; VPT, vibration perception threshold; WDT, warm detection threshold; WIP, warm induced pain; WPT, warm pain or perception threshold; WST, warm sensation threshold; WT, warm threshold; yrs, years.

Contact Heat Evoked Potentials (CHEPs)

CHEPs examine the integrity of Aδ and C fibers by measuring cerebral responses to thermal pain stimuli. A heat evoked potential stimulator is used with a thermode placed on the lower extremity. A heat pulse is delivered from a baseline to increasing safe, warm temperatures. Heat stimuli are repeatedly applied to the same lower extremity area. Concurrently, CHEPs are recorded with electrodes placed on the vertex of the head. An evoked potential system generates waveform tracings reflecting responses in the cerebral cortex.[3,84-86]

The literature search identified one study meeting eligibility criteria for inclusion in the review of CHEPs.[87] The study sample was comprised of 255 adults with 188 diagnosed with neuropathy (38.5% had diabetes) and 57 controls. Tests of equality were performed to assess the area under the receiver operator characteristic (AUROC) curves with respect to the diagnostic accuracy of CHEPs (Medoc, Ramat Yishai, Israel) versus QST (TSA NeuroSensory Analyzer, Medoc, Ramat Yishai, Israel). Results revealed that CHEP amplitudes (AUC 0.79) had significantly greater accuracy realtive to the QST warm (AUC 0.71) but not cold (AUC 0.72) threshold for diagnosis of small-fiber neuropathy. Using a cutoff of 29.1 mV, CHEPs had a diagnostic sensitivity of 80.7% and specificity of 68.8% for DSPN.[87]

Corneal Confocal Microscopy (CCM)

The cornea is abundantly innervated by small thinly myelinated Aδ and unmyelinated C fibers, and thereby uniquely provides indirect assessment and quantification of small-fiber DSPN. CCM has emerged as a noninvasive, valid, reliable technique for assessing small-fiber DSPN.[88-90] CCM involves visualization, via image acquisition, of corneal microstructures. Analysis of corneal images allows for detection of small nerve fiber loss with assessment of corneal nerve fiber density (CNFD), nerve branch density (CNBD), and nerve fiber length (CNFL), among other corneal parameters.[91]

Since 2015, the literature search identified 32 studies meeting study criteria, including technological advancements of CCM (see Table 4).[72-73,75,78,81,92-118] Advancing CCM technology, automated quantification of corneal images was frequently examined with respect to its accuracy, validity, and reliability (reproducibility and repeatability) with very promising results reported.[72,93-98,104,105,107,109-110,113-115,118]. Compared to traditional manual methods, automated methods were found to be relatively equivalent with overall high levels of agreement.[92-94,96-98,107,110,113-115,118] With manual or automated methods for image quantification, CCM parameters tended to have moderate to excellent accuracy (as assessed by AUROC or AUC values) in detecting DSPN, including its levels of severity. However, sensitivies and specifities for CCM parameters tended to be highly variable and not uniformly adequate across studies.[72-78,95-98,103,110-112,116-117] Beginning evidence suggests CCM and IENFD may have roughly comparable performance in detecting DSPN although additional research is warranted.[72,96]

Further, the current longitudinal literature suggests CCM may predict incident DSPN, identify patients at high-risk for DSPN, and monitor progressive nerve damage over time.[73,75,81,101,106,108] Sampling adults with T1D, Pritchard et al. found, for example, that baseline CNFL predicted incident DSPN at 4-year follow-up. Participants who developed DSPN had significantly lower baseline CNFL (14.0 ± 4.1) relative to participants (16.2 ± 3.5) who did not develop small-fiber neuropathy.[81] Additional longitudinal research, reviewed in this study, support these findings, revealing reduced CNFL may be an important biomarker for future development of DSPN.[101,106,108]

Sudomotor Function Testing (SFT)

SFT is used to assess small-fiber DSPN.[3] SFT, a measure of autonomic function, may be assessed with quantitative sudomotor axon reflex testing (QSART), and newer approaches, including electrochemical skin conductance (ESC).[3,119-121] SFT non-invasively assesses C fiber function, specifically innervation of sweat glands.

QSART

QSART measures C fiber induced sweat production in predetermined sites (forearm, distal and proximal leg, and foot) with application of iontophoresis and measurement of sweat responses with iontophoretic stimulators.[119-120] Abnormal QSART test findings reveal reduced sweat volume or latency.[120] The literature search identified 2 studies specific to QSART technology and one related, novel technological advancement (see Table 5)[122-124] The Q-Sweat System (WR Medical Electronics, Stillwater, MN, USA) was found to have suboptimal sensitivity (58%), optimal specificity (100%) in one study while another documented lack of discriminatory power in identifying participants with and without DSPN and controls.[122-123]

Distinct, although related to traditional QSART, Loavenbruck et al. developed a brief, sensitive sweat test (SST) with nanoliter precision, using high-definition videography, to assess C fiber innervation in the foot, calf, thigh, and hand. In SST, the anatomical site being assessed has a small, handheld camera (with starch tape across its lens) pressed firmly, face down. *Acetylcholine (ACh)* gel, loaded in an anode iontophoresis capsule, is applied directly adjacent and lateral to the camera. Directly stimulated by ACh gel, affected sweat gland (SG) ducts secrete sweat, which is absorbed by the starch tape as small dark spots. Recorded dark spots accurately correspond with sweat volume. In comparing participants with neuropathy to controls, ROC analyses showed the greatest distinction between groups at the calf (directly stimulated rate/SG and total sweat had an AUC of 0.90 and 0.90, respectively) and foot (directly

Table 4. Corneal Confocal Microscopy (CCM)

Author(s) & study aim	Study population & design	Study outcomes & implications
Alam et al.[72] - Compare diagnostic capability of CCM against IENFD & QST in patients with DSPN	*N* = 88 *n* = 30 T1D, -DSPN *M* = 38.8 ± 12.5 *n* = 31 T1D, +DSPN *M* = 53.3 ± 11.9 *n* = 27 HCs *M* = 41.0 ± 14.9 Cross-sectional	• AUC for CNFD was 0.81 with an optimal cutoff of 25.0 no/mm^2, sensitivity of 77% & specificity of 79% for diagnosis of DSPN • AUC for CNBD was 0.67 with an optimal cutoff of 36.5 no/mm^2, sensitivity of 58% & specificity of 79% for diagnosis of DSPN • AUC for CNFL was 0.74 with an optimal cutoff of 16.8 mm/mm^2, sensitivity of 61% & specificity of 80% for diagnosis of DSPN • AUC for IENFD was 0.73 with an optimal cutoff of 4.5 fibers/mm, sensitivity of 61% & specificity of 86% for diagnosis of DSPN • CCM is a non-invasive method, with respectable performance, to identify small nerve fiber pathology & diagnose DSPN
Al-Fahdawi et al.[92] -Propose a robust, fast & fully automatic nerve segmentation & morphometric parameter quantification system for CCM images	*N* = 20, 498 images *n* = 12 +DM *M* = 58 ± 10 yrs/age *n* = 4 -DPN *n* = 5 mild DPN *n* = 3 moderate DPN *n* = 8 HCs *M* = 54 ± 7 yrs/age Cross-sectional	• For manually & automatically traced nerves, average tortuosity was 8.27 ± 7.18 & 6.7 ± 5.60, respectively, for controls; 20.11 ± 19.04 & 13.9 ± 12.79, respectively, for -DPN group; 37.52 ± 36.41 & 29.32 ± 28.36, respectively, for mild DPN group; & 40.45 ± 39.30 & 51.76 ± 50.64, respectively, for moderate DPN group • For manually & automatically traced nerves, average nerve length was 60.92 mm & 61.22 mm, respectively, for controls; 58.49 mm & 56.87 mm, respectively, for -DPN group; 57.08 mm & 56.87 mm, respectively, for mild DPN group; & 57.08 mm & 56.63 mm, respectively, for moderate DPN group • Across manually & automatically traced nerve methods, comparable results found for average nerve length values although average tortuosity values appear less consistent • Both manually & automatically traced nerve methods reveal increasing nerve tortuosity & decreased nerve length according to severity of DPN
Al Rashah et al.[93] -Assess repeatability CNM rate measurement in individuals with or without neuropathy	*N* = 14 *M* = 51.9 ± 13.8 yrs/age *n* = 5 +DM, +DN *n* = 5 +DM, -DN *n* = 4 HCs Longitudinal (3-week FU)	• Within & between observer repeatability of CNM within 4 different zones & CNM rate of the vertical section of the wide-field montage was outstanding with ICCs of 0.99 & 0.99, respectively • Repeatability of CNM rate of the vertical section of the wide-field montage within observers, when using semi-automated & fully automated image montaging software, was also outstanding with an ICC of 0.96 • With a laser-scanning CCM, CNM rate measurement shows impressive repeatability for within & between observers & when using manual, semi-automated, & fully automated image montaging
Azmi, et al.[73] -Assess whether baseline and follow-up measures of neuropathy, particularly small-fiber neuropathy, relate to changes in glucose tolerance over 3 yrs	*N* = 47 *n* = 30 IGT *M* = 60 ± 2.1 yrs/age *n* = 17 Controls *M* = 62.3 ± 1.8 yrs/age Longitudinal (3-year FU)	• FU: 10 IGT participants developed T2D & had significantly lower CNFD, CNBD, & CNFL at baseline compared to controls; IGT participants who developed T2D also had a further significant reduction in CNFL, IENFD, & MDL • FU: 15 participants had no change in IGT status & 5 participants returned to NGT with no significant baseline abnormality on CCM or IENFD • FU: IGT participants (n=15) showed a significant decrease in IENFD but no change in CCM • FU: Participants returning to NGT (n=5) showed a significant increase in CNFD, CNBD, & CNFL, but a significant decrease in IENFD • CCM may be an early marker of small-fiber neuropathy & allow for risk stratification of individuals with IGT likely to progress to T2D
Batawi et al.[94] - Study SCNP parameters by IVCCM using a new software technology	*N* = 29 *M* = 46 ± 20 yrs/age n = 22 +DM Cross-sectional	• Inter-operator reproducibility & intra-operator reproducibility ICCs, respectively, were: (1) NFLD 0.97 & 0.97; (2) NFL 0.97 & 0.97; (3) NF 0.90 & 0.93; (4) NT 0.97 & 0.96; (5) NBi 0.83 & 0.87; (6) NBr 0.81 & 0.87; (7) BD 0.92 & 0.95; (8) NBe 0.95 & 0.97; (9) NFT 0.73 & 0.88 • Semi-automated corneal nerve analysis showed excellent precision or reproducibility for evaluation of SCNP parameters with CCM
Brines et al.[95] -Using an automated methodology, compare sensitivity & specificity of NFD, NBD, NFL, & NFA for discriminating participants with neuropathy from NCs	*N* = 129 *n* = 21 -DN *M* = 37.1 ± 16.5 yrs/age *n* = 21 mild DN *M* = 55.9 ± 11.0 yrs/age *n* = 19 moderate DN *M* = 59.0 ± 11.3 yrs/age *n* = 20 severe DN *M* = 57.0 ± 14.6 yrs/age *n* = 48 NCs *M* = 46.2 ± 16.9 yrs/age Cross-sectional	• In participants with no or mild DN, relative to NCs, respectively, AUROC curves for NFD, NFB, NFL, NFA WxL, & NFA FIJI (≥0.70 – <0.85 range) were fair to good • In participants with moderate to severe DN, relative to NCs, respectively, AUROC curves for NFD, NBD, NFL, & NFA WxL (>0.80 – <1.0 range) were good to excellent • With DM participants collapsed into 1 group, cutoff points for discrimination of participants having DN from NCs were calculated from ROC curves; DM group cut point for NFD was 23.4 fibers/mm^2 with a sensitivity of 90% & specificity of 69%; DM group cut point for NBD was 23.4 branches/mm^2 with a sensitivity of 86% & specificity of 71%; DM group cut point for NFL was 12.3 mm/mm^2 with a sensitivity of 96% & specificity of 68%; DM group cut point for NFA FIJI was 19,128 μm^2/mm^2 with a sensitivity of 94% & specificity of 59% • Overall, automated methodology revealed good to excellent diagnostic performance in detecting moderate to severe DN & impressive ability to identify true positives for DN in DM participants

(continued)

Table 4. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Chen, et al.[96] -Determine the diagnostic performance of CCM (manual & automated methods) & IENFD for DSPN	*N* = 89 *n* = 17 T1D, +DSPN *M* = 59 ± 11 yrs/age *n* = 46 T1D, -DSPN *M* = 44 ± 13 yrs/age *n* = 26 CG *M* = 44 ± 15 yrs/age Cross-sectional	• AUCs: CNFD manual 0.82 & automated 0.80; CNFD manual S/S = 76% at EERP; CNFD manual S/S = 82%/71% at threshold of 24.0 (M ± 2 SDs); CNFD automated S/S = 70% at EERP; CNFD automated S/S = 60%/83% at threshold of 15.5 (M ± 2 SDs) • AUCs: CNFL manual 0.70 & automated 0.77; CNFL manual S/S = 71% at EERP; CNFL manual S/S = 59%/74% at threshold of 16.5 (M ± 2 SDs); CNFL automated S/S = 70% at EERP; CNFL automated S/S = 59%/80% at threshold of 10.5 (M ± 2 SDs) • AUCs: CNBD manual 0.59 & automated 0.70; CNBD manual S/S = 53% at EERP; CNBD manual S/S = 17%/96% at threshold of 15.0 (M ± 2 SDs); CNBD automated S/S = 59% at EERP; CNBD automated S/S = 29%/98% at threshold of 4.0 (M ± 2 SDs) • AUC of IENFD = 0.66; IENFD S/S = 65% at EERP; IENFD S/S = 53%/76% at threshold of 3.3 (M ± 2 SDs) • Overall, performance between CCM (manual & automated) & IENFD comparable
Chen, et al.[97] -Evaluate an automated software tool for nerve-fiber detection & quantification in CCM images, combining sensitive nerve-fiber detection with morphological descriptors	*N* = 176; 888 images *n* = 63 T1D, +DSPN *n* = 29 T1D, -DSPN *n* = 84 Controls Cross-sectional	• AUCs of ACNFD, ACNFL, & ACNBD were 0.76, 0.76, 0.68, respectively; ACNFD S/S = 65%, ACNFL S/S = 62%, & ACNBD S/S = 58% at EEP for discriminating +DSPN & -DSPN • AUCs of MCFND, MCNFL, & ACNBD were 0.79, 0.71, & 0.61, respectively; MCNFD S/S = 72%, MCNFL S/S = 66% & MCNBD S/S = 59% at EEP for discriminating +DSPN & -DSPN • AUCs of combined CCM automated & manual features were 0.74 & 0.78, respectively; CCM automated S/S = 71%; CCM manual S/S = 68% for discriminating +DSPN & -DSPN • Performance of automated quantification compared to manual quantification of corneal nerves in CCM images is relatively equivalent • Automated quantification provides a sensitive tool for identification of DSPN while improving speed & repeatability
Chen, et al.[98] -Evaluate the performance of previously established CCM parameters to a novel automated measure of corneal nerve complexity (ACNFrD)	*N* = 176 *n* = 84 AMCs *M* = 46 ± 15 yrs/age *n* = 29 T1D, +DSPN *M* = 63 ± 12 yrs/age *n* = 63 T1D, -DSPN *M* = 44 ± 15 yrs/age Cross-sectional	• AUROC curve for ACNFD was 0.77, ACNFL was 0.74, ACNBD was 0.69, & ACNFrD was 0.74; ACNFD S/S = 65% at EER; S/S = 63%/79% at threshold of 15.1(M ± 2 SDs); ACNFL S/S = 62% at EER; S/S = 62%/83% at threshold of 10.2 (M ± 2 SDs); ACNBD S/S = 58% at EER; S/S = 24%/98% at threshold of 3.3 (M ± 2 SDs); ACNFrD S/S = 65% at EER; S/S = 61%/78% at threshold of 1.45 (M ± 2 SDs) • AUROC curves were 0.79 for MCNFD, 0.71 for MCNFL, & 0.61 for MCNBD; MCNFD S/S = 72% at EER; S/S = 79%/71% at threshold of 23.8 (M ± 2 SDs); MCNFL S/S = 65% at EER; S/S = 55%/86% at threshold of 14.9 (M ± 2 SDs); MCNBD S/S = 59% at EER; S/S = 17%/96% at threshold of 13.8 (M ± 2 SDs) • ACNFrD performance comparable to automated & manual CNFD, CNBD, & CNFL in diagnosing patients with +DSPN or -DSPN • Automated & manual methods show good equivalency in accuracy
Dehghani et al.[99] - Determine alterations in CSNP over 4 yrs using IVCCM	*N* = 108 T1D, -PN (baseline) M = 43.9 ± 15.7 age/yrs (baseline) Longitudinal	• At 4-yr FU, mean CNFD (no./mm^2, 19.6 ± 6.9) was marginally significantly increased compared to baseline (18.3 ± 7.1) • At 4-yr FU, mean CNBD (no./mm^2, 29.1 ± 19.6) was significantly increased relative to baseline (24.2 ± 17.4) • At 4-yr FU, mean CNFL (mm/mm^2, 16.3 ± 3.7) did not significantly change from baseline (16.0 ± 3.8) • IVCCM may be useful for monitoring subclinical alterations in CSNP in T1D
Dell'Omo, et al.[100] -Measure the thickness & length of corneal nerves & peri-papillary RNFL thickness in patients recently diagnosed with T2D	*N* = 44 *n* = 22 new onset T2D *M* = 50.6 ± 6.74 age/yrs *n* = 22 HCs *M* = 50.8 ± 4.26 age/yrs Cross-sectional	• Evaluated by CCM, CNT & CNL were significantly lower in participants with new onset T2D than controls • Using SD-OCT, RNFL thickness in temporal quadrant was significantly lower in patients with T2D relative to controls • ICC values for intra-observer and inter-observer repeatability for CNT were 0.76 & 0.78 & for CNL 0.71 & 0.74, respectively • Reductions observed in CNL, CNT, & RNFL thickness suggest that CCM & SD-OCT may detect early markers of neuropathy in patients recently diagnosed with T2D • ICC values revealed good reliability
Dhage, et al.[75] -Assess the longitudinal utility of different measures of neuropathy in patients with diabetes	*N* = 38 *n* = 19 +DM *M* = 52.5 ± 14.7 yrs/age (baseline) *n* = 19 HCs *M* = 47.4 ± 14.2 yrs/age (baseline) Longitudinal cohort study (MFU = 6.5 yrs)	• At baseline, CNFD, CNBD & CNFL significantly reduced in DM participants vs. controls • Compared to baseline, CNFD, CNBD & CNFL significantly decreased in DM participants at FU • At baseline, NSP & NDS scores significantly higher & IENFD significantly lower in DM participants vs. controls • Compared to baseline, NSP & NDS scores significantly increased & IENFD significantly decreased in DM participants at FU • Change in CNFD, CNBD, & CNFL significantly correlated with change in IENFD • CCM, a rapid, non-invasive & reproducible ophthalmic imaging technique to objectively quantify small-fiber damage in DN, was found to longitudinally identify progressive nerve damage

(continued)

Table 4. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Edwards et al.[101] -Demonstrate DN development & progression in T1D individuals	*N*=38, T1D, -DN (baseline) Longitudinal cohort study (4-yr FU)	• CNFL identified 7 participants who had unfavorable corneal nerve changes from baseline to 4-yr FU • CNFL, relative to PNCV, CST, WST, VPT, NDS, & monofilament testing, consistently performed better • CNFL revealed the earliest, most sustained, & highest proportion of abnormal parameters indicative of PN development
Ferdousi et al.[102] - Identify longitudinal CNM changes in CC & IW relative to other DN measures	N = 36 n = 19 age-matched HCs M = 49.47 ± 13.25 yrs/age n=30 +DM *M*=54.08 ± 15.86 yrs/age (baseline) *n*=21 T1D *n*=9 T2D Longitudinal cohort MFU=3.6 ± 1.3	• In participants with DM, CNBD (mm/mm^2) & CNFL (mm/mm^2) were significantly reduced from baseline (57.72 ± 30.08; 21.77 ± 5.19, respectively) to FU (44.04 ± 23.69; 15.65 ± 4.7, respectively) • In participants with DM, IWL (mm/mm^2) & ANFL (CNFL + IWL/2; mm/mm^2) were also significantly reduced from baseline (24.69 ± 8.67; 23.26 ± 5.53, respectively) to FU (14.23 ± 6.13; 15.09 ± 4.48, respectively • Rate of annual decline in CNFL, IWL, & ANFL was significantly higher in patients with DM compared to controls • ICC showed good consistency between the changes per year in CNFL & IWL in participants with DM (ICC=0.78; 95% confidence interval, 0.56–0.88)
Ferdousi, et al.[78] -Compare the utility of quantifying corneal nerve loss at the inferior whorl & central cornea to QST & NCS in the diagnosis & assessment of DPN severity	*N*=143 *n*=93 +DM *n*=51 -DPN *M*=57.68 ± 1.6 yrs/age *n*=47 Mild DPN *M*=60.16 ± 1.7 yrs/age *n*=45 Moderate to severe DPN *M*=64.1 ± 1.48 yrs/age *n*=30 Controls *M*=54.51 ± 2.3 yrs/age Cross-sectional	• ROC curve & Youden index used to define optimum cutoff points for CNFD, CNBD, CNFL, & IWL; CNFD AUC 0.71, sensitivity 58%, & specificity 83%; CNBD AUC 0.70, sensitivity 69%, & specificity 65%; CNFL AUC 0.68, sensitivity 64%, & specificity 67%; IWL AUC 0.72, sensitivity 70%, & specificity 65% • CNFD & CNBD were significantly lower in patients with -DPN (26.61 ± 1.05 & 64.07 ± 4.39, respectively) & mild DPN (24.47 ± 1.09 & 58.49 ± 4.76, respectively) compared to controls (33.71 ± 1.3 & 81.52 ± 5.54, respectively); CNFD & CNBD were significantly lower in patients with moderate to severe DPN (22.4 ± 1.14 & 45.60 ± 4.5, respectively) relative to those with -DPN & controls • CNFL & IWL were significantly lower in patients with mild (20.84 ± 1.00 & 22.28 ± 1.31, respectively) & moderate to severe (19.27 ± 1.04 & 19.03 ± 1.36, respectively) DPN compared to controls (25.07 ± 1.27 & 31.69 ± 1.66, respectively); CNFL & IWL were significantly lower in patients with moderate to severe DPN relative to those with -DPN (23.31 ± 0.96 & 24.90 ± 1.26, respectively) • CCM identifies early & progressive corneal nerve loss at the inferior whorl & CC
Ferdousi, et al.[103] -Assess the diagnostic utility of CCM for DPN & risk factors for corneal nerve loss	*N*=490 *n*=149 T1D *n*=269 T2D *n*=72 HCs Cross-sectional	• CNFD, CNBD, & CNFL were significantly reduced in participants with T1D vs. those with T2D • ROC curve analysis for diagnosis DPN showed a very good AUC for CNFD at 0.81 with an optimal cutoff point of 29.40/mm^2; sensitivity was 73.5% & specificity was 74.4% • ROC curve analysis for diagnosis DPN showed a reasonable AUC for CNBD at 0.74 with an optimal cutoff point of 64.58/mm^2; sensitivity was 66.7% & specificity was 66.7% • ROC curve analysis for diagnosis DPN showed a reasonable AUC for CNFL at 0.73 with an optimal cutoff point of 24.00 mm/mm^2; sensitivity was 66.7% & specificity was 66.4% • CCM identified more severe corneal nerve loss in T1D patients relative to those with T2D & shows very reasonable diagnostic accuracy for DPN
Guimarães et al.[104] -Describe & validate an automatic approach to nerve tracing	*N*=30 *n*=24 pathologic group *n*=10 +DM *n*=6 HCs Cross-sectional	• Automatic nerve tracing, following a proposed algorithm, was assessed with respect to manual grading of CNT (high, mid, & low tortuosity classes) with a significant Spearman's rank correlation coefficient of 0.95 achieved • With setting 2 thresholds to distinguish between the 3 tortuosity classes, correct classification (93.3%) was yielded for the automatic compared to the manual approach • Nerve tracing results reveal the automatic method performed well although larger studies are needed to confirm results
Kalteniece et al.[105] -Assess the effect of a standardized protocol for image selection & number of images required for adequate quantification of CN pathology using IVCCM	*N*=35 obese &/or +DM *M*=49.97 ± 12.47 yrs/age Longitudinal	• In terms of inter-observer variability, ICC values for CNFD, CNBD, & CNFL were significant at 0.93, 0.96, & 0.95, respectively • With respect to intra-observer variability, ICC values for CNFD, CNBD, & CNFL were significant at 0.95, 0.97, & 0.97, respectively • For sample size variability, ICC values for CNFD, CNBD, & CNFL were significant at 0.94, 0.95, & 0.96, respectively • Bland-Altman plots showed excellent agreement for all parameters • 6 images were found to be adequate for the fully automated analysis • Implementing a standardized protocol to select IVCCM images results in high intra- & inter-observer reproducibility for all corneal nerve parameters
Lewis et al.106 -Determine reference distribution of annual CNFL change, prevalence of abnormal change in diabetes, & associated variables	*N*=794 *n*=399 T1D *M*=39.9 ± 18.7 yrs/age *n*= 191 T2D *M*=60.4 ± 8.2 *n*=204 Controls *M*=37.9 ± 19.8 yrs/age Secondary analysis of longitudinal observational study	• Participants with T1D (median FU of 3 visits over 4.4 yrs) had a mean annual change in CNFL (mm/mm^2) of -0.8%; T1D participants with RCNFL had a significant annual change in CNFL (-14.67 ± 11.46%) relative to T1D participants without RCNFL (2.58 ± 9.93%) • Participants with T2D (median FU of 3 visits over 5.3 yrs) had a mean annual change in CNFL of -0.2%; T2D participants with RCNFL had a significant annual change in CNFL (-11.49 ± 6.35%) compared to T2D participants without RCNFL (2.47 ± 7.33%) • RCNFL prevalence was 17% overall & similar by DM type (16.0% T1D, 19.4% T2D) • RNCFL was significantly more frequent in those with baseline DSP (47%) vs. those without baseline DSP (30%) • RCNFL may identify patients at high risk for DSP development & progression

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Table 4. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Li et al.[107] -Examine & compare fully-automated & manually measured corneal nerve fiber parameters in T2D patients with & without DPN	*N* = 152 *n* = 128 T2D *n* = 49 -DPN *M* = 67.12 ± 6.01 yrs/age *n* = 79 +DPN *M* = 70.15 ± 7.34 yrs/age *n* = 24 HCs *M* = 68.63 ± 5.19 yrs/age Cross sectional	• $CNFL_M$ & $CNBD_M$ in +DPN group were significantly lower than -DPN & HC groups • Likewise, $CNFL_{FA}$ & $CNBD_{FA}$ in +DPN group were significantly reduced relative to -DPN & HC groups • $CNFD_{FA}$, but not $CNFD_M$, was significantly reduced in +DPN group vs. HC group • Significant, positive correlations between manual & fully automated CNFL, CNFD, & CNBD were observed • Fully automated method slightly underestimated corneal nerve fiber parameters. • A progressive decrease in manual & fully automated CNFL, CNBD & CNFD accompanied the occurrence of DPN • Fully automated corneal nerve fiber parameter quantification may be a fast, objective way to detect DPN
Lovblom et al.[108] -Determine the predictive validity of a baseline IVCCM measure in identifying future DSP onset in patients with T1D	*N* = 65 T1D, -DSP *M* = 34 ± 15 yrs/age Longitudinal (mean 3.5 years FU)	• At FU, 54 (83%) remained without DSP & 11 (17%) developed DSP • New-onset cases of DSP had lower baseline CNFL & CNBD but higher baseline CNFT • CNFL: AUC was 0.78; optimal operating threshold of 14.9 mm/mm^2 with 82% sensitivity, 69% specificity, & 35% PPV • CNFT: AUC was 0.72; optimal operating threshold of 15.4 (tortuosity coefficient) with 73% sensitivity, 72% specificity, & 35% PPV • CNBD: AUC was 0.71; optimal operating threshold of 36.1 branches/mm^2 with 82% sensitivity, 50% specificity, & 25% PPV • CNFL may have applicability in identifying high-risk patients for DSP
Ostrovski et al.[109] -Determine inter- & intra-observer reproducibility of a novel automated analysis program vs. manual analysis	*N* = 46 *n* = 26 T1D *M* = 42.8 ± 16.9 yrs/age *n* = 20 controls *M* = 41.4 ± 17.3 yrs/age	• Inter-observer ICCs for $CNFL_M$, $CNFL_{SA}$, & $CNFL_{FA}$ were 0.73, 0.75 & 0.78, respectively, with no significant differences for 3-way comparisons; intra-observer ICCs were 0.72, 0.74, & 0.84, respectively, with $CNFL_{FA}$ reproducibility significantly higher than that of $CNFL_M$ & $CNFL_{SA}$ • Inter-observer & intra-observer ICCs for $CNFD_M$, $CNFD_{SA}$, $CNFD_{FA}$, $CNBD_M$, $CNBD_{SA}$, & $CNBD_{FA}$ were substantially lower compared to those for CNFL • Fully automated analysis preserves CNFL reproducibility despite an apparent measurement bias (underestimation) relative to the manual strategy of image analysis
Perkins et al.[110] - Establish concurrent validity & diagnostic thresholds in a large cohort of participants with & without DSP	*N* = 998 *n* = 516 T1D *M* = 42 ± 19 yrs/age *n* = 482 T2D *M* = 62 ± 10 yrs/age Cross-sectional, pooled multi-national consortium study	• In participants with T1D, $CNFL_A$ had an AUC of 0.77 & optimal threshold of 12.5 mm/mm^2 (73% sensitivity & 69% specificity) • In participants with T2D, $CNFL_A$ had an AUC of 0.68 & optimal threshold of 12.3 mm/mm^2 (69% sensitivity & 63% specificity) • In participants with T1D, AUC for $CNBD_A$ & $CNFD_A$ were 0.73 & 0.71, respectively • In participants with T2D, AUC for $CNBD_A$ & $CNFD_A$ were 0.66 & 0.52, respectively • In the total cohort, $CNFL_A$ had an AUC of 0.71 & optimal threshold of 12.3 mm/mm^2 (67% sensitivity & 66% specificity); AUC of $CNFL_M$ (0.70) vs. $CNFL_A$ was marginally, yet significantly lower although its optimal threshold value of 16.3 mm/mm^2 had similar operating characteristics • A lower $CNFL_A$ threshold value of $<$8.6 mm/mm^2 to rule in DSP & upper $CNFL_A$ threshold value of 15.3 mm/mm^2 to rule out DSP was associated with 88% specificity & 88% sensitivity • In the largest cohort to date, diagnostic validity & common diagnostic thresholds for CNFL in T1D & T2D established
Petropoulos et al.[111] - Compare ability of CNFD, CNFL, & IWL alone & in combination for diagnosis of DPN	*N* = 68 *n* = 53 +DM (T1D & T2D) *n* = 25 +DPN *M* = 60.1 ± 10.2 yrs/age *n* = 28 –DPN *M* = 42.4 ± 14.7 yrs/age *n* = 15 AMCs Cross-sectional	• For diagnosis of DPN, ROC curve analysis showed CNFL = 21.9 mm/mm^2 had an AUC of 0.75, sensitivity of 76%, & specificity of 65%; CNFD = 28.4 fibers/mm^2 had an AUC of 0.74, sensitivity of 68%, & specificity of 61%; IWL = 20.0 mm/mm^2 had an AUC of 0.70, sensitivity of 68%, & specificity of 67% • Combination of CNFL & IWL achieved an AUC of 0.75, sensitivity of 80%, & specificity of 71% for DPN • For inter & intra-observer agreement for IWL estimation, no significant difference between 2 separate observers (17.8 ± 8.5 vs. 17.7 ± 9.1 mm/mm^2) & no significant difference (17.8 ± 8.5 vs. 17.2 ± 8.0 mm/mm^2) when same observer assessed & reassessed IW center images from 1 dataset on 2 separate occasions • CNFD, CNFL, & IWL have comparable ability to diagnose DPN; combining IWL & CNFD may improve CCM diagnostic performance • Inter- & intra-observer agreement for IWL estimation was excellent
Pritchard et al.[81] -Determine if deficits in CNFL assessed using CCM can predict future onset of DPN	*N* = 90 T1D, -DPN (baseline) 4-yr FU *n* = 16 +DPN *M* = 51 ± 14 yrs/age (baseline) *n* = 64 -DPN *M* = 42 ± 16 yrs/age (baseline) Longitudinal	• DPN developed in 16 participants (18%) after 4 yrs • Baseline CNFL (mm/mm^2) predicted incident DPN at 4-yr FU • Participants who developed DPN at 4-yr FU had significantly lower baseline CNFL (14.0 ± 4.1) relative to participants (16.2 ± 3.5) who did not develop DPN • For CNFL, AUROC was 0.6 with a threshold cutoff of 14.1 mm/mm^2; sensitivity was 63% & specificity was 74% to predict DPN • CCM may predict DPN in T1D
Pritchard et al.[112] -Compare SNF damage in central cornea & whorl area in participants with DPN & examine accuracy of evaluating these 2 sites for DPN diagnosis	*N* = 187 *n* = 107 T1D *M* = 48.3 ± 15.1 yrs/age *n* = 25 +DPN *n* = 82 -DPN *n* = 80 Controls *M* = 37.0 ± 17.8 yrs/age Cross-sectional	• Participants with & without DPN had significantly lower $CNFL_{center}$ compared to controls (14.2 ± 3.5 & 16.7 ± 3.5 mm/mm^2 vs. 19.3 ± 3.0 mm/mm^2, respectively) • Participants with & without DPN had significantly reduced $CNFL_{whorl}$ relative to controls (15.4 ± 4.4 & 18.2 ± 3.9 mm/mm^2 vs. 22.1 ± 3.9 mm/mm^2, respectively) • For $CNFL_{center}$, AUC was 0.76; Youden Index cutoff point of $<$17.9 with sensitivity of 90% & specificity of 50% for detecting DPN • For $CNFL_{whorl}$, AUC was 0.77; Youden Index cutoff point of $<$18.6 with sensitivity of 80% & specificity of 60% for detecting DPN • SNF pathology comparable at corneal central & whorl anatomical sites • Quantification of CNFL from the corneal center is as accurate as CNFL quantification of whorl area for diagnosis of DPN

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Table 4. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Scarpa et al.[113] - Investigate whether CNN can be successfully used for corneal nerve multiple-image analysis	*N* = 100 participants, 600 confocal images *M* = 53 ± 13 yrs/age *n* = 50 +DM (T1D & T2D), +DN *n* = 50 AMHCs Cross-sectional	• Cross-validation used to evaluate a proposed algorithm for binary classification (healthy or pathological) of 100 participants (CNN training on 80 subjects & evaluation on the other 20, repeated 5 times) with 97% mean accuracy for CNN correct classification • Also, with a final classification derived for each participant (properly classified if both right & left eyes correctly classified), CNN revealed validity with a mean accuracy of 96% • With outstanding classification accuracy, the CNN is a highly promising, fully automated method of corneal confocal image analysis with strong potential to yield improved results obtained from traditional methods
Scarr et al.[114] -Evaluate agreement between manual & automated analysis protocols in controls & T1D & T2D participants with & without DSP	*N* = 456 *M* = 53 ± 18 yrs/age *n* = 139 T1D *n* = 249 T2D *n* = 68 Controls Cross-sectional	• For the study population, mean $CNFL_M$ (15.1 ± 4.9 mm/mm^2) was greater than mean $CNFL_A$ (10.5 ± 3.7 mm/mm^2) although values were highly correlated; absolute mean difference between $CNFL_A$ & $CNFL_M$ for the study population was -4.6 ± 2.6 mm/mm^2 & percentage difference was -29 ± 17%, representing underestimation bias by $CNFL_A$ • A similar pattern of correlations & underestimation bias was observed for $CNFL_M$ vs. $CNFL_A$ for T1D, T2D, & control groups • In participants with T1D, percentage difference between $CNFL_A$ & $CNFL_M$ for those with DSP was -27 ± 27%, & for those without DSP the percentage difference was -32 ± 13% although non-significantly • In participants with T2D, percentage difference between $CNFL_A$ & $CNFL_M$ for those with DSP was -28 ± 16%, & for those without DSP was -27 ± 16% although non-significantly • Weighted kappa statistic for agreement between tertiles of $CNFL_A$ & $CNFL_M$ was 0.62, indicating moderate to substantial agreement • $CNFL_A$ & $CNFL_M$ were significantly lower in T1D participants with DSP relative to those without DSP • $CNFL_A$ & $CNFL_M$ were not significantly lower in T2D participants with DSP compared to those without DSP • Although $CNFL_A$ underestimated $CNFL_M$, its bias was non-differential between participant groups & its relationship with DSP status was preserved • Determination of diagnostic thresholds specific to $CNFL_A$ requires further investigation
Schaldemose et al.[115] -Compare a new sampling method & AAC with established methods of corneal nerve quantification in patients with & without DSPN & HCs	*N* = 88 *n* = 62 T1D *n* = 17 +DSPN *M* = 59 ± 11 yrs/age *n* = 45 -DSPN *M* = 44 ± 13 yrs/age *n* = 26 HCs *M* = 44 ± 15 yrs/age Cross-sectional	• Using randomized & area adjusted method, $CNFD_M$ & $CNFL_M$ were significantly reduced in +DSPN group compared to both HC & -DSPN groups; $CNFL_M$ values were larger in -DSPN group relative to HCs • Using a randomized & area adjusted method, $CNFD_A$, $CNFL_A$ &, $CNBD_A$ were reduced significantly in +DSPN & -DSPN groups compared to HCs & lowest in the +DSPN group • Randomized sampling & adjusted area method with automated analysis showed that, among +DSPN participants, $CNFD_A$ (no./mm^2; 17.3 ± 12) had a higher mean than standard automated procedures (13.5 ± 9.1) with a significant difference of 28.1%; $CNFL_A$ (mm/mm^2; 12.3 ± 6.8) had a higher mean than standard automated procedures (8.8 ± 4.7) with a significant difference of 39.8%%; $CNBD_A$ (no./mm^2; 19.1 ± 14) had a higher mean than standard automated procedures (15.4 ± 12) with a significant difference of 24.0% • Randomized sampling & adjusted area method with automated analysis showed that, among -DSPN participants, $CNFD_A$ (no./mm^2; 28.2 ± 9.3) had a higher mean than standard automated procedures (22.6 ± 7.3) with a significant difference of 24.8%; $CNFL_A$ (mm/mm^2; 17.0 ± 4.2) had a higher mean than standard automated procedures (13.4 ± 3.3) with a significant difference of 26.9%%; $CNBD_A$ (no./mm^2; 31.1 ± 18) had a higher mean than standard automated procedures (26.2 ± 15) with a significant difference of 18.7% • Interobserver reliability testing revealed no significant difference in means for $CNFL_M$, $CNFD_M$, & $CNBD_M$ between the investigator & a blinded second observer • Randomized sampling method & area-dependent analysis objectively shows a reduction in corneal nerve parameters in diabetic patients with & without DSPN while providing unbiased corneal nerve quantification
Tummanapalli et al.[116] - Determine utility of CCM & tear neuromediator analysis in diagnosis of DPN	*N* = 70 *n* = 38 T1D *n* = 19 +DPN *M* = 44 ± 12 age/yrs *n* = 19 -DPN *M* = 37 ± 10 age/yrs *n* = 32 T2D *n* = 16 +DPN *M* = 58 ± 6 age/yrs *n* = 16 -DPN *M* = 52 ± 12 age/yrs Prospective, cross- sectional	• For DPN diagnosis in T1D, IWL had the best diagnostic performance (AUC 0.91, optimal diagnostic threshold of ≤12.93 mm/mm^2, 89% sensitivity, & 83% specificity), followed by CNFrD (AUC 0.89; diagnostic threshold ≤1.50, 89% sensitivity, & 72% specificity), CNFD (AUC 0.88, diagnostic threshold ≤22.46 no./mm^2, 83% sensitivity, & 83% specificity), IWNFrD (AUC 0.88, diagnostic threshold ≤1.46, 83% sensitivity, & 89% specificity), CNFL (AUC 0.87, diagnostic threshold ≤14.24 mm/mm^2, 89% sensitivity, & 78% specificity), CNBD (AUC 0.76, diagnostic threshold ≤26.17 no./mm^2, 72% sensitivity, & 72% specificity), & CTBD (AUC 0.75, diagnostic threshold ≤40.40 no./mm^2, 72% sensitivity, & 72% specificity) • For DPN diagnosis in T2D, CNFL had the best diagnostic performance (AUC 0.81, optimal diagnostic threshold ≤13.64 mm/mm^2, 81% sensitivity, & 81% specificity), followed by CNFrD (AUC 0.78, diagnostic threshold ≤1.48, 75% sensitivity, & 63% specificity), CNBD (AUC 0.76, diagnostic threshold ≤29.17 no./mm^2, 81% sensitivity, & 75% specificity) CNFD (AUC 0.76, diagnostic threshold ≤22.90 no./mm^2, 75% sensitivity, & 69% specificity), CTBD (AUC 0.76, diagnostic threshold ≤43.10 no./mm^2, 81% sensitivity, & 81% specificity), & IWNFrD (AUC 0.73, diagnostic threshold ≤1.47, 69% sensitivity, & 62% specificity) • In T1D & T2D, different corneal nerve parameters were identified, suggesting different disease processes across conditions

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Table 4. (continued)

Author(s) & study aim	Study population & design	Study outcomes & implications
Wang et al.[117] -Explore the application of CCM in DPN & other T2D chronic complications	*N* = 220 *n* = 100 T2D +DPN M= 56.2 ± 12.4age/yrs *n* = 72 -DPN *M* = 54.9 ± 11.1age/yrs *n* = 37 T2D +DN *n* = 89 T2D +DR *n* = 48 HCs *M* = 51.9 ± 14.9yrs/age Cross-sectional	• In participants with T2D, CNFL & CNBD were significantly lower than HCs, & similar in +DPN group compared to -DPN group • Using CCM to identify DPN, AUC for CNFD was 0.67 & optimal cutoff was 24.68 no./mm^2 (78% sensitivity, 53% specificity); AUC for CNFL was 0.70 & optimal cutoff was 15.32 mm/mm^2 (80% sensitivity, 60% specificity); AUC for CNBD was 0.68 & optimal cutoff was 39.0 no./mm^2 (85% sensitivity, 47% specificity) • This study provides more support for clinical use of CCM to diagnose DPN
Williams et al.[118] -Validate a DLA for corneal nerve segmentation in CCM images & compare to the widely used, validated automated image analysis software, ACCMetrics	*N* = 3865 confocal images of corneal SBP obtained from +DM individuals & HCs *n* = 120 confocal images from Italy *n* = 1578 confocal images from China *n* = 2137 confocal images from UK	• DLA, employing CNN with data augmentation, trained using a high-end graphics processor unit on 1698 images for automated quantification of the corneal SBP for DN diagnosis • DLA further tested on 2137 images for external validation with DLA ICCs superior to those for ACCMetrics for total CNFL (0.93 vs. 0.83), mean length per segment (0.66 vs. 0.33), number of branch points (0.89 vs 0.57), number of tail points (0.62 vs. 0.26), number of nerve segments (0.88 vs. 0.50) & fractals (0.93 vs 0.76) • DLA achieved an AUC of 0.83, specificity of 0.87, & sensitivity of 0.68 for the classification of participants without (*n* = 90) or with (*n* = 132) neuropathy • Results reveal DLA provides rapid & excellent localization performance for quantification of corneal nerve biomarkers • DLA model has potential for adoption into clinical screening programs for DN

Abbreviations: AAC, adjusted area calculation; ACNBD, automated corneal nerve branch density; ACNFD, automated corneal nerve fiber density; ACNFL, automated corneal nerve fiber length; ACNFrD, automated corneal nerve fiber fractal dimension; AMC, age-matched controls; AMHCs, age-matched healthy controls; ANFL, average nerve fiber length; AUC, area under the curve; AUROC, area under the receiver operator characteristic; BD, beading density; CC, central cornea; CCM, corneal confocal microscopy; CG, control group; CN, corneal nerve; CNBD, corneal nerve branch density; $CNBD_A$, corneal nerve branch density with automated analysis; $CNBD_{FA}$, corneal nerve branch density with fully automated analysis; $CNBD_M$, corneal nerve branch density with manual analysis; $CNBD_{SA}$, corneal nerve branch density with semi-automated analysis; CNFD, corneal nerve fiber density; $CNFD_A$, corneal nerve fiber density with automated analysis; $CNFD_{FA}$, corneal nerve fiber density with fully automated analysis; $CNFD_M$, corneal nerve fiber density with manual analysis; $CNFD_{SA}$, corneal nerve fiber density with semi-automated analysis; CNFL, corneal nerve fiber length; $CNFL_A$, corneal nerve fiber length with automated analysis; $CNFL_{center}$, corneal nerve fiber length at the central cornea; $CNFL_{FA}$, corneal nerve fiber length with fully automated analysis; $CNFL_M$, corneal nerve fiber length with manual analysis; $CNFL_{SA}$, corneal nerve fiber length with semi-automated analysis; CNFLwhorl, corneal nerve fiber length at the whorl; CNFrD, corneal nerve fractal dimension; CNFT, corneal nerve fiber tortuosity; CNL, corneal nerve length; CNM, corneal nerve migration; CNN, convolutional neural network; CNT, corneal nerve thickness or corneal nerve tortuosity; CSNP, corneal sub-basal nerve plexus; CTBD, corneal total branch density; DLA, deep learning algorithm; DM, diabetes mellitus; DN, diabetes neuropathy; DPN, diabetes peripheral neuropathy; DSP, diabetic sensorimotor polyneuropathy or distal symmetric polyneuropathy; DSPN, diabetes symmetrical peripheral neuropathy or diabetic sensorimotor polyneuropathy; EEP, equal error point; EER, equal error rate; EERP, equal error rate point; FU, follow-up; HCs, healthy controls; ICC, interclass correlation coefficient; IENFD, intraepidermal nerve fiber density; IGT, impaired glucose tolerance; IVCCM, in vivo corneal confocal microscopy; IWL, inferior whorl length; IWNFrD, inferior whorl nerve fractal dimension; M, mean; MCNBD, manual corneal nerve branch density; MCNFD, manual corneal nerve fiber density; MCNFL, manual corneal nerve fiber length; MDL, mean dendric length; MFU, mean follow-up; mm, millimeter; mm/mm^2, millimeter/square millimeter; mm^2, millimeters squared; NBD, nerve branch density; NBe, number of beadings; NBi, number of bifurcations; NBr, number of branches; NCs, normal controls; NDS, Neuropathy Disability Score; NFA FIJI, nerve fiber area determined by total number of pixels within the nerve plexus; NFA W×L, nerve fiber area determined by length times average width; NFD, nerve fiber density; NFL, nerve fiber length; NFLD, nerve fiber length density; NFT, nerve fiber tortuosity; NGT, normal glucose tolerance; no., number; no./mm^2, number/square millimeter; NSP, Neuropathy Symptom Profile,; NT, number of trunks; PN, peripheral neuropathy; PNCV, peroneal nerve conduction velocity; PPV, positive predictive value; QST, quantitative sensory testing; RCNFL, rapid corneal nerve fiber loss; RNFL, retinal nerve fiber layer; ROC, receiver operator characteristic; S/S, sensitivity/specificity; SBP, sub-basal nerve plexus; SCNP, sub-basal corneal nerve plexus; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography; SNF, small nerve fiber; T1D, type 1 diabetes; T2D, type 2 diabetes; VPT, vibration perception threshold; vs., versus; WST, warm sensation threshold; yr, year; yrs, years; μm^2, square micrometer.

Table 5. Quantitative Sudomotor Axon Reflex Testing (QSART).

Author(s) & Study Aim	Study Population & Design	Study Outcomes
Kamel et al.[122] -Assess the clinical utility of CSP, QSART, SSR & AFT in detection of SFN related to glycemic dysregulation	$N = 52$ $n = 26$ +SFN $n = 9$ T1D, $n = 9$ T2D $n = 8$ IGT $M = 50.8 \pm 2.6$ yrs/age $n = 26$ Controls $M = 48.9 \pm 2.6$ age/yrs Cross-sectional	• QSART (Q-Sweat System; WR Medical Electronics, Stillwater, MN, USA),) results showed a sensitivity of 58% & specificity of 100% • Sensitivity of the Q-Sweat System may have been improved by limiting the sample to T1D & T2D participants & more rigorous evaluation of sensitivity • Q-Sweat System revealed an optimal specificty (100%) although suboptimal sensitivity (58%)
Krieger et al.[123] -Evaluate performance of Sudoscan against QSART (Q-Sweat System) in diagnosing DPN	$N = 63$ $n = 27$ T2D, +DPN $M = 69 \pm 4.8$ yrs/age $n = 20$ T2D, -DPN $M = 66 \pm 5.8$ yrs/age $n = 16$ MCs $M = 64 \pm 5.1$ yrs/age Cross-sectional	• Q-Sweat System could not differentiate between the 3 groups (+DPN, -DPN, MCs) • Q-Sweat System showed poor discriminatory performance
Loavenbruck et al.[124] -Report a method that quantifies axon reflex sweating from individual SGs with nanoliter precision	$N = 72$ $n = 20$ +Neuropathy ($n = 11$ +DM) Aged 45–82 yrs $n = 52$ AACs Aged 21–88 yrs Cross-sectional	• Comparing +neuropathy to AAC groups, AUC of 0.90 achieved for directly & indirectly stimulated rate/SG & total sweat at the calf • AUC of 0.80 & 0.84, respectively, achieved for directly stimulated rate/SG & total sweat at the feet • AUC of 0.58 & 0.74, respectively, achieved for indirectly stimulated rate/SG & total sweat at the feet • Overall, SST shows impressive performance for quantifying axon reflex sweating from individual SGs with nanoliter precision

Abbreviations: AAC, age-adjusted control; AFT, autonomic function testing; AUC, area under the curve; AUROC, area under receiver operator characteristic; CSP, cutaneous silent periods; DM, diabetes mellitus; DPN, diabetic polyneuropathy; IGT, impaired glucose tolerance; M, mean; MCs, matched controls; QSART, quantitative sudomotor axon reflex testing; SFN, small fiber neuropathy; SG, sweat gland; SST, sensitive sweat test; T1D, type 1 diabetes; T2D, type 2 diabetes; yrs, years.

stimulated rate/SG and total sweat had an AUC of 0.80 and 0.84, respectively).[124]

ESC

ESC assesses the electrical potential of sweat glands to evaluate sudomotor function. ESC directly evaluates C fiber stimulated sweat gland function through measurement of sweat chloride concentrations using reverse iontophoresis and chronoamperometry.[125-127]

Since 2015, the literature search identified 14 studies evaluating ESC, namely Sudoscan (Impeto Medical, Paris, France; see Table 6).[51,76,123,128-139] Advancing earlier EZSCAN technology, Sudoscan is a POCD wherein testing requires that the patient place his/her hands and feet, respectively, on 2 stainless steal electrodes.[125-126] While the patient's hands and feet remain on the electrodes for 2 minutes, a computer records ESC values.[125]

Most studies revealed overall adequate to good performance of Sudoscan.[51,76,123,130-131,133-134,136,138-139] For example, sampling Mexicans with T2D, one study examined the performance of Sudoscan in predicting DSPN among 2 groups: (1) Mexicans with T2D for greater than 5 years; and (2) Mexicans with T2D for less than 5 years. In the first group, the AUROC curves for hands and feet ESC were 0.84 and 0.78, respectively, with the Michigan Neuropathy Screening Instrument as the reference. The sensitivity of abnormal hands or feet ESC for detection of neuropathy was 97%, while the positive predictive value was 87%. In the second group, AUROC curves of hands and feet ESC were 0.66 and 0.72, respectively. The sensitivity of abnormal hands or feet ESC for detection of neuropathy was 91%, while the positive predictive value was 88%.[130] These findings, coupled with the work of Goel et al,[134] suggest Sudoscan is a technology that may detect early DSPN. Sudoscan has also demonstrated respectable repeatability and reproducibility. Bordier and colleagues reported that, for feet, the ESC mean coefficient of variation for repeatability was $2.8 \pm 1.6\%$ in healthy controls and $6.9 \pm 6.3\%$ in participants with T2D, while the coefficients of variation for reproducibility were 3.1 ± 1.5 and $6.9 \pm 6.3\%$, respectively.[129]

Discussion

The diagnosis of DSPN is typically informed by a complete patient history and clinical exam. This approach is often sufficient to diagnose DSPN but not in its early asymptomatic and subclinical stages. Also, more advanced DSPN

Table 6. Electrochemical Skin Conductance (ESC).

Author(s) & Study Aim	Study Population & Design	Study Outcomes & Implications
Ang et al.[128] - Evaluate ESC as a reliable surrogate for early CAN	*N* = 77 *n* = 37 T1D *M* = 39 ± 8 yrs/age *n* = 40 HCs *M* = 38 ± 13 yrs/age Longitudinal	• Using Sudoscan (Impeto Medical, Paris, France) to measure ESC, no significant differences were observed in hands or feet of T1D participants relative to HCs at baseline • In T1D participants, mean ESC, as measured by Sudoscan, declined significantly from baseline to 12 months • While both hands & feet ESC declined over time, the significance of this finding is unclear and warrants further reliability testing
Binns-Hall et al.[51] -Evaluate feasibility one-stop microvascular screening service for early diagnosis of DSPN, painful DSPN, & at-risk diabetic foot	*N* = 236 *M* = 63.5 ± 14.1 yrs/age *n* = 231 T2D *n* = 5 T1D *n* = 84 + DPN *n* = 69 -DPN *n* = 83 unclassified	• Using Sudoscan, AUROC curve was 0.75 with an ESC threshold of ≤58.5 μS; sensitivity was 77.4% & specificity was 68.3% for detecting DSPN • Sudscan may be useful screening device with respectable performance values • On 3 different Sudoscan devices, 2 measurements were performed under usual testing conditions on T2D & HV participants
Bordier et al.[129] -Assess repeatability & reproducibility of Sudoscan in HVs & diabetic patients with a range of glycemic control	N = 32 n = 14 T2D M = 62 ± 9 yrs/age n = 18 HVs M = 37 ± 13 yrs/age Cross-sectional	• For hands ESC, in particpants with T2D, the mean repeatability SD was 4.3 μS (mean coefficient of variation was 7.1 ± 5.9%) & mean reproducibility SD was 4.5 μS (mean coefficient of variation was 7.4 ± 6.1%) • For hands ESC, in HVs, the mean repeatability SD was 3.1 μS (mean coefficient of variation was 4.2 ± 2.7%) & mean reproducibility SD was 3.2 μS (mean coefficient of variation was 4.3 ± 2.7%) • For feet ESC, in particpants with T2D, the mean repeatability SD was 4.3 μS (mean coefficient of variation was 6.9 ± 6.3%) & mean reproducibility SD was 4.3 μS (mean coefficient of variation was 6.9 ± 6.3%) • For feet ESC, in HVs, the mean repeatability SD was 2.1 μS (mean coefficient of variation was 2.8 ± 1.6%) & mean reproducibility SD was 2.3 μS (mean coefficient of variation was 3.1 ± 1.5%) • In participants with T2D, ICCs used to compare the 3 devices were 0.95 (0.89–0.98) & 0.88 (0.74–0.96) & for HVs were 0.87 (0.74–0.94) & 0.85 (0.71–0.93) for feet & hands, respectively • Findings establish that repeatability & reproducibility of ESC measurements are respectable in participants with T2D & HVs
Carbajal-Ramírez et al.[130] -Assess the accuracy of Sudoscan (feet & hands) compared to MNSI in a cross-sectional study of Mexicans with T2D	N = 221, Mexican n = 170 T2D < 5 yrs M = 58.6 ± 12.6 age/yrs n = 51 T2D > 5 yrs M = 63.8 ± 11.8 age/yrs Cross-sectional	• Evaluating the diagnostic accuracy of Sudoscan, in participants with T2D > 5 years, AUROC curve of hands & feet ESC were 0.84 & 0.78, respectively, with MINSI B as the reference; sensitivity of abnormal hands or feet ESC for detection of neuropathy was 97% • In participants with T2D < 5 years, AUROC curve of hands & feet ESC were 0.66 & 0.72 respectively; sensitivity of abnormal hands or feet ESC for detection of neuropathy was 91% • Sudoscan, which does not require any preparation, is noninvasive, easy & rapid to use in detecting P • Sudoscan may be useful in the early diagnosis of PN in T2D
Chae et al.[131] -Determine if Sudoscan can complement NCS & EMG in patients with LSR & PPN	*N* = 73 LE dysesthesia *n* = 34 Controls *n* = 18 LSR *n* = 21 PPN (57% + DM) *M* = 63.1 ± 10.8 yrs/age for + DM group Cross-sectional	• AUC was 0.78 for feet ESC; cutoff at 48 μS; sensitivity was 57.1% & specificity was 94.2% to detect PPN • At a 55 μS cutoff, hands ESC had a sensitivity of 71.4% & specificity of 78.8% to detect PPN • Sudoscan was found to have highly acceptable diagnostic accuracy for feet ESC with impressive specificity
D'Amato et al.[132] -Determine diagnostic value of the combined scores of composite autonomic symptom score 31, validated questionnaire for autonomic symptoms, CAN, & ESC	*N* = 102 DM; 65% T2D *M* = 57.1 ± 13.7 yrs/age Cross-sectional	• In assessing the diagnostic accuracy of Sudoscan, AUC of ESC feet was 0.69 for DPN diagnosis • Among participants with DPN, ESC had a sensitivity of 62% specificity of 67%, & positive predictive value of 67% • Findings reveal fair Sudoscan test performance
Fabry et al.[76] -Compare several methods of evaluating small sensory & autonomic nerve fibers	*N* = 245 *M* = 50.4 ± 15.0 yrs/age *n* = 24 + DM *n* = 6 + IGT *n* = 102 "Definite SFN" *n* = 90 "No SFN" Retrospective study	• Diagnostic performance of ESC (Sudoscan) & IENFD was evaluated by studying the normality or abnormality of each test according to the diagnosis of "Definite SFN" or "No SFN," respectively • ESC sensitivity was 60%, specificity was 89%, & positive predictive value was 86% for detecting SFN • IENFD sensitivity was 58%, specificity was 91%, & positive predictive value was 88% for detecting SFN • ESC or Sudoscan revealed significant differences between the "Definite SFN" & "No SFN" groups both in hands (60.2 ± 16.7 vs. 75.0 ± 8.9 μS) & feet (70.2 ± 16.5 vs. 81.6 ± 7.0 μS) • ESC & IENFD had comparable sensitivity, specificity, & positive predictive values
Gandecka et al.[133] -Evaluate sudomotor function & its relationship to metabolic control & diabetic complications	*N* = 485 Median = 41 yrs/age, IQR = 32–51 *n* = 404 T1D *n* = 84 Controls Case Control Study	• Participants with T1D had a significantly lower ESC (as measured by Sudoscan+) relative to controls • Discriminative value of feet ESC to identify patients with PN was slightly better than that of ESC in the hands: AUC 0.77 vs. AUC 0.72 • With a cutoff point of 79 μS or less for feet ESC (optimal Youden index), sensitivity was 72%, specificity was 68%, & Youden index was 0.4 • Reproducibility of Sudoscan (feet & hands ESC) was confirmed with a cutoff value ratio not significantly different from 0 & slope ratio close to unity
Goel et al.[134] -Determine efficacy of ECS in diagnosing early DPN when compared to VPT & DNS score	*N* = 523 T2D *n* = 110 + DPN *M* = 54.4 ± 11.9 yrs/age *n* = 413 -DPN *M* = 48.1 ± 11.4 yrs/age Cross-sectional	• AUC of the ROC plot for feet ESC (Sudoscan) was 0.88 & for VPT was 0.84 • Feet ESC, with a cutoff of < 60 μS, had a sensitivity of 85% & specificity of 85% for classifying DPN • VPT, with a cut-off of > 15 V, had a sensitivity of sensitivity of 72% & specificity of 90% for classifying DPN • Feet ESC measurement was superior to VPT testing for identifying patients with early DPN

(continued)

Table 6. (continued)

Author(s) & Study Aim	Study Population & Design	Study Outcomes & Implications
Jin et al.[135] -Evaluate whether SUDOSCAN has good diagnostic ability in DSPN & CAN	*N* = 180 T2D, Chinese *n* = 60 -DSPN *M* = 54.4 ± 11.3 yrs/age *n* = 120 +DSPN *M* = 59.8 ± 8.0 yrs/age Cross-sectional	• AUROC was 0.61, sensitivity was 89.8% & specificity was 41.2% to diagnose DSPN • Sudoscan is a sensitive test to detect DSPN in China & may be an effective screening tool in primary health care settings
Krieger et al.[123] -Evaluate performance of Sudoscan against QSART in diagnosing DPN	*N* = 63 *n* = 27 T2D, +DPN *M* = 69 ± 4.8 yrs/age *n* = 20 T2D, -DPN *M* = 66 ± 5.8 yrs/age *n* = 16 MCs *M* = 64 ± 5.1 yrs/age Cross-sectional	• For feet ESC (Sudoscan), AUROC curve was 0.71; cutoff ≤ 80.0 μS (optimal Youden index) with a sensitivity of 70% & specificity of 53% • For hand ECS, AUROC curve was 0.71; cutoff of ≤ 75.0 μS (optimal Youden index) with a sensitivity of 85% & specificity of 50% • Feet & hand ESC significantly lower in patients with +DPN as compared to MCs • Patients with +DPN also had lower hand ESC than patients with -DPN • Sudoscan shows poor to good performance in detecting DPN • Sudoscan has high potential as a DPN screening tool in patients with T2D
Novak[136] -Determine the relationship between ECS measurements & loss of small fibers in the skin	*N* = 81 +SFN *M* = 53.3 ± 17.3 yrs/age *n* = 48 SFN-I *n* = 33 SFN-AD *n* = 9 DM *n* = 2 IGT Prospective, blinded	• ESC (Sudoscan) of feet (M = 0.88 ± 0.35 μS/kg), among participants with abnormal IENFD, was significantly reduced relative to participants with normal IENFD (M = 1.17 ± 0.27 μS/kg) • ESC significantly correlated with IENFD but not symptom scores • AUROC ESC feet was 0.74, with IENFD as reference, while adjusting for weight • ESC shows acceptable performance with the gold standard as the reference, revealing it may be useful in detecting SFN
Porubcin et al.[137] - Evaluate diagnostic accuracy of ESC to detect abnormal SGNFD & IENFD	*N* = 210 *M* = 45.5 ± 16.1 yrs/age *n* = 132 SFN-I *n* = 78 SFN-AD *n* = 2 IGT Retrospective, blinded	• ESC (Sudoscan), adjusted for weight (ESC/kg), was significantly reduced in participants with abnormally low IENFD (normal/abnormal ESC/kg 1.20 ± 0.37/1.04 ± 0.33 μS/kg) • AUROC curve was 0.63 for ESC/kg in predicting abnormal IENFD; sensitivity was 69% & specificity was 55% • ESC/kg showed modest performance & accuracy to detect SFN in the diverse sample
Selvarajah et al.[138] -Assess if Sudoscan is a reliable screen for DPN in clinics	*N* = 70 *n* = 24 T1D, +DPN *M* = 52.1 ± 9.7 yrs/age *n* = 21 T1D, -DPN *M* = 40.6 ± 9.8 yrs/age *n* = 25 HVs *M* = 48.1 ± 16.4 yrs/age Cross-sectional	• Foot ESC (Sudoscan) was significantly lower in participants with +DPN compared to those with -DPN & HVs • AUROC curve for foot ESC was 0.85; foot ESC cutoff point ≤ 77.0 μS (optimal Youden index); sensitivity & specificity were 88% & 76%, respectively, for classifying DPN • Sudoscan, a non-invasive & quick test, may be used as an objective screening test for DPN in busy diabetic clinics
Sheshah et al.[139] -Evaluate if ESC at foot can detect DPN & risk of foot ulceration as compared to traditional methods	*N* = 296, Saudi Arabians *M* = 46.7 ± 11.2 age/yrs *n* = 272 T2D *n* = 24 T1D Cross-sectional	• Feet ESC (Sudoscan; threshold <50 μS for severe SMD) AUC was 0.73 & 0.73 to detect severe DPN & FU, respectively, with NDS as the reference; sensitivity (61%, 64%) & specificity (85%, 82%) for DPN & FU, respectively • Feet ESC (Sudoscan; threshold <70 μS) AUC was 0.66 & 0.65 to detect DPN & FU, respectively, with NDS as the reference; sensitivity 81% & 81% & specificity 51% & 49% for DPN & FU, respectively • Sudoscan, a simple & objective tool, may be used to detect DPN & risk of FU in patients with DM

Abbreviations: AUC, area under the curve; AUROC, area under receiver operator characteristic; CAN, cardiovascular autonomic neuropathy; DM, diabetes mellitus; DNS, Diabetic Neuropathy Symptom Scale; DPN, diabetic peripheral neuropathy or diabetic polyneuropathy; DSPN, diabetic distal symmetric peripheral neuropathy or distal symmetrical polyneuropathy; EMG, electromyography; ESC, electrochemical skin conductance; FU, foot ulceration; HC, healthy control; HVs, healthy volunteers; IENFD, intraepidermal nerve fiber density; IGT, impaired glucose tolerance; IQR, interquartile range; kg, kilogram; LE, lower extremity; LSR, lumbosacral radiculopathy; M, mean; MC, matched controls; MNSI B, Michigan Neuropathy Screening Instrument B; NCS, nerve conduction study; NDS, Neuropathy Disability Score; PN, peripheral neuropathy; PPN, peripheral polyneuropathy; QSART, quantitative sudomotor axon reflex testing; ROC, receiver operator characteristic; SFN, small fiber neuropathy; SFN-AD, small fiber neuropathy classified according to associated disorders; SFN-I, small fiber neuropathy classified as idiopathic; SGNFD, sweat gland nerve fiber density; T1D, type 1 diabetes; T2D, type 2 diabetes; VPT, vibration perception threshold; yrs, years; μS, microSiemens.

small- and large-fiber disease may present exclusively or together and sometimes without signs or symptoms.[4,39-42] Given DSPN may not present with clinical signs and symptoms, utilization of highly sensitive screening technologies may be warranted to promote early detection of DSPN. Also, when signs or symptoms are present, but the distinction between small- and large-fiber disease remains unclear, confirmation of the DSPN subtype may require diagnostic testing. NCS is recommended for confirming large-fiber DSPN.[3]

Advances in NCS technologies have yielded a very promising POCD, DPN-Check. DPN-Check assesses sural nerve conduction. Research suggests that DPN-Check, overall, has very respectable accuracy in detecting the presence and severity of DSPN.[51-52,56-59] Also, DPN-Check has strong reliability and good agreement with standard electromyography.[60] However, a few studies indicate the POCD may have measurement bias compared to standard NCS.[56,140] Yet, DPN-Check, approved by the Food and Drug Administration (FDA), is sufficiently accurate and reliable for use as a screening technology. The POCD is inexpensive ($500), provides rapid results, and does not require highly specialized training. DPN-Check has the potential to widen access to nerve conduction testing in primary care, internal medicine, and endocrinology practices although patients with abnormal or borderline results should undergo standard NCS.[56]

Typically preceding large-fiber DSPN, small-fiber DSPN has negative findings upon NCS testing.[3] The gold standard for small-fiber diagnostic testing is IENFD. IENFD may identify early DSPN.[141-142] Yet, this diagnostic technology is invasive and may be painful for patients. Serial skin biopsies for detecting early changes in IENFD may not be practical. More recent technological advances for small-fiber DSPN screening provide alternative, more rapid, non-invasive approaches – some of which show promise for early or asymptomatic, subclinical detection of small-fiber disease.

NerveCheck, a POCD, is an inexpensive ($500) QST device. It has demonstrated adequate to good reproducibility but mixed results with respect to diagnostic accuracy.[82-83] The TSA-II NeuroSensory Analyzer, while also having varying results with respect to performance, may discriminate between clinical and subclinical DSPN in line with prior QST research.[77,143-146] CHEPs has not advanced technologically and lacks practicality given its complex testing approach.

CCM technology has advanced, including automated image assessment. Prior and more current CCM research reveals its high promise to detect incident and early risk for DSPN [73,75,81,101,106,108,147-151] In the present study, CCM, compared to IENFD, was found to have fairly comparable performance.[72,96] A limitation of CCM is that it is currently considered investigational for the purposes of detecting DSPN, and thus, is an out-of-pocket patient expense although smartphone CCM may be on the horizon, which may reduce costs in tandem with automated image evaluation.

In terms of sudomotor function testing, technological advancements are also impressive. A novel POCD, using high-definition videography, assesses C fiber innervation in the foot, calf, thigh, and hand with a brief SST. Beginning data indicate that the POCD has respectable accuracy in detecting small-fiber DSPN.[124] Yet, evidence is lacking in SST's ability to detect asymptomatic or subclinical DSPN. Further rigorous research is needed prior to clinical adoption.

When considered with respect to past and more recent research, Sudoscan has a substantial evidence revealing it may potentially identify early DSPN (although this not its main use) and monitor DSPN progression over time.[51,76,123,130-131,133-134,136,138-139,152-154] Sudoscan also has adequate reproducibility and repeatability.[129,155-156] Sudoscan is approved by the FDA and may be reimbursed through proper billing. Sudoscan is thus a PCOD worthy of clinical adoption to detect and monitor DSPN in clinical settings, which may be accompanied by initial, confirmatory IENFD results.

While established and more recent technological advances may detect DSPN, it must be underscored that early detection of the disease is critical. At this time, IENFD (gold standard) and CCM have the strongest evidence for early detection of small-fiber disease, a precursor to large-fiber disease. The small-fiber technological screening devices reviewed may build on their respective research bases to further examine performance measures in detecting small-fiber DSPN in asymptomatic, subclinical populations. Furthermore, it appears that additional examination of normative values may be required, as indicated, for ethnic/racial, gender, and age groups to minimize the risk for bias in DSPN device outcomes data.

Conclusion

There is no cure for DSPN. Hence, its early detection is critical. Early, regular screening for DSPN is essential, particularly for small-fiber disease. Although IENFD is the gold standard for assessing small-fiber disease, innovative, non-invasive technologies, such as Sudoscan and particularly CCM, for early disease detection may be useful alternatives. Regardless of whether screening reveals small-fiber disease or not, healthy lifestyle interventions are warranted, if not ideally implemented earlier. Healthy lifestyle behaviors (weight loss, increased physical activity, and smoking cessation), may prevent, modify the progression, or mitigate symptoms of DSPN.[9,21,33,157-161] In T1D populations, tight glycemic control tends to delay or prevent DSPN whereas, in T2D populations, tight control, for some, may slow DSPN progression.[15,30,162-164] Optimization of blood pressure and lipid levels is also warranted.[22-25]

Abbreviations

ADA, American Diabetes Association; CCM, corneal confocal microscopy; CHEPs, contact heat evoked potentials; DSPN, distal symmetrical peripheral neuropathy; DTRs, deep tendon reflexes; ESC, electrochemical skin conductance; IENF, intra-epidermal nerve fiber density testing; NCS, nerve conduction study; QST,

quantitative sensory testing; QSART, quantitative sudomotor axon reflex testing; SFT, sudomotor function testing; T1D, type 1 diabetes; T2D, type 2 diabetes.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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