Complex clinical pathways: assessing the value of a device for detecting diabetic peripheral neuropathy

Kate Goddard, Mark Pennington, Muralikrishnan R. Kartha, Tom Macmillan, Catey Bunce, Jennifer A Summers, Stephen Keevil and Anastasia Chalkidou

Citation: Goddard K, Pennington M, Kartha MR et al (2020) Complex clinical pathways: assessing the value of a device for detecting diabetic peripheral neuropathy. *The Diabetic Foot Journal* 23(1): 16–20

Article points

1. The King's Technology Evaluation Centre (KiTEC) undertook a value assessment of the Neuropad device (TRIGOcare International) for detecting preclinical diabetic peripheral neuropathy (DPN).
2. Neuropad has potential benefits for patients who have difficulty engaging with standard testing for DPN.
3. However, there was insufficient evidence from patient groups in which standard testing for DPN is a challenge.
4. Neuropad detects sub-normal sweat function but the clinical importance of this in current NHS care pathways is poorly defined.
5. This research highlights the importance of producing evidence supporting a clearly defined position within the current clinical pathway.

Key words

- Clinical pathway
- Device assessment
- Diabetic peripheral neuropathy

Authors

Author details on page 20

The Neuropad device (TRIGOcare International) was evaluated by the King's Technology Evaluation Centre to inform a new National Institute for Health and Care Excellence (NICE) medical technology guideline. NICE promotes the adoption of clinically and cost-effective medical devices by the NHS in England through the work of the Medical Technologies Evaluation Programme and Diagnostics Assessment Programme. Manufacturers notify NICE when their medical device meets the eligibility criteria for entry to the programme. If the technology is selected by NICE, the manufacturer submits clinical and economic evidence for evaluation. This article describes the challenges encountered during an assessment of a simple device that had been proposed for a complex clinical pathway.

In the UK, an estimated 1 in 15 people have diabetes; this is predicted to reach more than 5 million people by 2035. Diabetic peripheral neuropathy (DPN) affects up to 50% of people with diabetes, with chronic, painful neuropathy which increases the risk of foot ulceration and subsequent amputation, affecting up to 26% of people with diabetes (Ziegler, 2010). In England, around 2.5% of people with diabetes have foot ulcers at any given time (between 70,000 and 90,000 people) and around 8,500 leg, toe or foot amputations are carried out in England every year (Diabetes UK, 2019).

DPN may involve large nerve fibres, small nerve fibres or both, affecting different sensation modalities. Small fibre neuropathy typically affects the lower limbs and often precedes large fibre neuropathy.

Sudomotor axons are small nerve fibres that control the activity of sweat glands. Sudomotor dysfunction is indicative of diabetic autonomic neuropathy, which can result in foot ulceration. A lack of sweating can cause the skin to crack, leading to an increased risk of infection. If untreated, this can cause sepsis and gangrene, which can subsequently require amputation.

Current pathway

Currently, people with diabetes are offered foot checks every year. During a physical examination, 10 g monofilament testing is used to test for DPN and the clinical risk of future complications. Patients who test positive for DPN at foot checks are considered to be at moderate or high risk of foot complications and are referred to community podiatrists for ongoing foot care.

The NICE guideline on diabetic foot problems recommends that adults with diabetes have a risk assessment for diabetic foot problems on diagnosis and at least annually thereafter (NICE, 2015). Further risk assessments should be carried out whenever foot problems arise and on any admission to hospital. During the risk assessment, both feet should be examined for multiple risk factors. These include neuropathy, which should be tested using a 10 g monofilament as part of a foot sensory examination.

If neuropathy is detected, the person is classified as being moderate or high risk, depending on other comorbidities. This triggers referral to a foot protection service and an increased frequency of foot assessments.

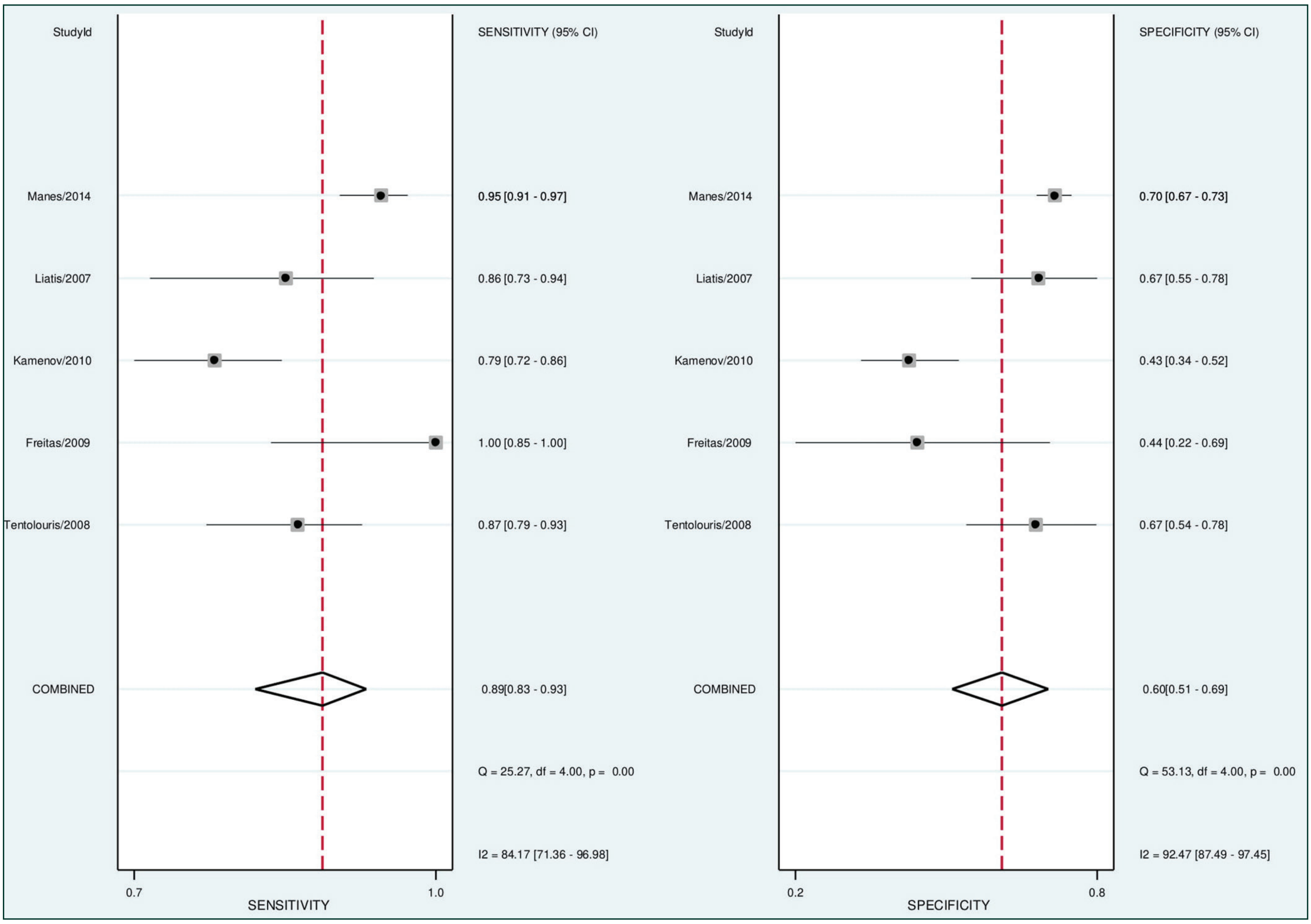

Figure 1. Forest plot of Neuropad versus Neuropathy Disability Score ≥ 5.

The current NICE guideline does not include testing sudomotor function to detect neuropathy.

Neuropad

Neuropad (TRIGOcare International) is a point-of-care test that detects inadequate sweat production. The test comprises of a small plaster that is placed on the sole of the foot for 10 minutes. The plaster contains cobalt chloride, which changes colour from blue to pink in the presence of normal sweat production. If the plaster does not turn fully pink, sudomotor function may be impaired. At the time of the report publication, the sponsor has used the list price of £7.28 as the cost of Neuropad per patient.

The test could help detect that a person is in the preclinical stages of developing DPN. It may be particularly valuable for use in people who cannot be screened using the standard 10 g monofilament, such as people with cognitive or communication difficulties and those who require testing in community settings.

The Neuropad test can be done in clinic by a healthcare professional during a routine foot check, or at home by the person or their carer. Neuropad is used in conjunction with other standard sensory neuropathy tests (such as the 10 g monofilament) to improve the detection of diabetic foot neuropathy. No training is required to administer Neuropad, nor does it require verbal responses from the patient.

Neuropad is the only self-testing device for sudomotor function available for use in primary care and community settings. There are more specialised tests used in secondary care to detect small fibre neuropathy, including nerve conduction studies using electromyography, intraepidermal nerve fibre

Table 1. Results of the EAC meta-analysis of Neuropad versus Neuropathy Disability Score (≥5).

Meta-analysis	Studies	Pooled population	Sensitivity	Specificity
Neuropad vs Neuropathy Disability Score ≥5	*n*=5	*n*=1,587	89.4% (83.2–93.5%) I^2: 84.2% (95%CI: 71.4–97.0%)	60.3% (50.9–69%) I^2: 92.5% (95%CI: 87.5–97.4%)

Table 2. Base case results of cost modelling.

	Expected cost/patient	Cost saving/patient
Neuropad	£3,893	
10g monofilament	£3,118	£775
Neuropad + 10g monofilament	£2,818	£1,075
No testing	£2,101	£1,792

density biopsy, quantitative sudomotor axon reflex test, Sudoscan, corneal confocal microscopy and the NC-stat DPN check device for sural nerve velocity.

Aims

The aim of the assessment was to evaluate the clinical and economic effectiveness of the Neuropad point-of-care test for detecting preclinical DPN in people with diabetes. This article presents a summary of the evaluation for Neuropad (NICE, 2018).

Methods

The manufacturer of Neuropad submitted clinical and economic evidence for the device to NICE, including a cost model of the consequences of adoption. This was independently evaluated by King's Technology Evaluation Centre (KiTEC), an external assessment centre commissioned by NICE.

In addition, KiTEC carried out its own systematic review of the evidence on Neuropad for detection of preclinical DPN. A meta-analysis was carried out, pooling data from the best quality studies reporting diagnostic accuracy. KiTEC developed a revised cost model to address flaws in the manufacturer's model. In addition, NICE carried out a consultation with diabetes experts.

Results of the assessment report

The evidence for Neuropad consisted of 18 studies, of which 13 were full text articles and five were abstracts (Aubert et al, 2013; Didangelos et al, 2006; Forth et al 2010, Freitas et al, 2009; Kamenov et al, 2010; Liatis et al, 2007; Manes et al, 2014; Marinou et al, 2005; Mendevil et al, 2016; Ponirakis et al 2014; Quattrini et al, 2008; Sanz-Corbalán et al, 2018; Spallone et al, 2009; Tentoulouris et al, 2008; Tentolouris et al, 2014; 2017; Ziegler et al, 2011; 2012). All were prospective observational, cross-sectional or longitudinal cohort studies. Of the 18 studies, 17 investigated the diagnostic accuracy of Neuropad against a reference standard and one reported its ability to predict the risk of diabetic foot ulceration. In addition to examining diagnostic accuracy, one study looked at the reproducibility of results when using Neuropad and three assessed the association between Neuropad test results and the development of foot ulcers.

While the evidence indicated that Neuropad may be non-inferior to the monofilament and may have higher sensitivity (though less specificity), there was insufficient robust head-to-head evidence to support superiority. A meta-analysis was conducted using five studies (Liatis et al, 2007; Tentoulouris et al, 2008; Freitas et al, 2009; Kamenov et al, 2010; Manes et al, 2014). This analysis used a bivariate random-effects model in STATA 14 (*Figure 1*).

The pooled values used the published data or were back-calculated by KiTEC, and compared Neuropad with the Neuropathy Disability Score (NDS) at a threshold of ≥5 in a pooled diabetic population of *n*=1,587 (*Table 1*). NDS is a standard neuropathy scoring system which is a composite of vibration perception (evaluated with a 128Hz tuning fork), temperature perception at the dorsum of the foot (evaluated with the cold/hot tip of the same tuning fork), ability to discriminate sharp from dull after a pinprick or ability to detect a 10g force exerted with a monofilament, and Achilles reflex (normal or reduced).

Neuropad may have a higher sensitivity, but lower specificity, than NDS ≥5 for diagnosing diabetic peripheral neuropathy. A high amount of heterogeneity was found in the meta-analysis outcomes as indicated by the I^2 values.

No published economic evidence was found. Cost modelling showed that Neuropad testing incurred additional costs over a 10-year time horizon compared with all other comparators (*Table 2*). Using Neuropad alone is the most costly option, with no testing the cheapest.

Discussion

The assessment report results were discussed in a NICE committee. The following issues arose when discussing the potential adoption of Neuropad in the NHS.

Clinical effectiveness

Although no direct comparative data were available for the 10 g monofilament, the review concluded that Neuropad may have had higher sensitivity than the current standard of care (10 g monofilament), but less specificity. The evidence provided for Neuropad was insufficient to support its effectiveness as an alternative test to 10 g monofilament for detecting DPN.

Study population

One of the claimed benefits of Neuropad is the potential to test people who have difficulty engaging with DPN testing. It is estimated that between 5% and 10% of all people with diabetes may have difficulty engaging with 10 g monofilament testing (NICE, 2018). Because Neuropad testing does not need patient feedback, it may be of particular value for people with cognitive impairment or communication difficulties. A test which can be carried out in the community may also be of particular value to people with limited access to foot clinics. However, no evidence was found which examined these populations or settings, therefore the effectiveness in the most relevant population and setting could not be assessed.

Pathway positioning

Currently, the existing care pathway includes interventions that are only triggered by clinically apparent DPN (ie, moderate or advanced), so the benefit of detecting preclinical DPN is unclear. Because it is uncertain how well autonomic testing (such as testing for sudomotor dysfunction) predicts progressive neuropathy or the development of complications, it is not included in current DPN scoring systems. This means that it is unclear, on the basis of current evidence, what role, if any, Neuropad testing may have in diabetic foot risk assessment and referral practice. Within the existing pathway, a positive Neuropad test alone would not lead to a change in management, because it would not alter the definition of risk status. A patient diagnosed with preclinical DPN using Neuropad testing could be offered more attentive foot care, but it is unclear as to whether this would lead to beneficial clinical consequences to any extent.

Costs

The committee noted that Neuropad's low diagnostic specificity meant that its use alone would increase the rate of false-positive results for DPN. Because of the current uncertainty about whether patients with diagnosed preclinical DPN would benefit from referral to a foot care service, the committee decided that a positive result with Neuropad would probably lead to further 10 g monofilament testing. No clinical evidence was found to support the benefits of a dual-testing approach (using 10 g monofilament and Neuropad). The committee concluded that the cost modelling for Neuropad is uncertain, but that it is most likely that Neuropad testing alone would be cost incurring compared with conventional testing with a 10 g monofilament.

Conclusion

During the assessment, the overall clinical opinion suggested that Neuropad had potential benefits for patients who have difficulty engaging with DPN testing. On the basis of the available evidence and the current pathway, it was concluded that Neuropad testing would be unlikely to affect foot risk assessment and referral practice. To enable a thorough assessment of the benefits of a technology, it is crucial that its relevance to clinical pathways is well-defined and that the evidence presented matches the population and setting of the proposed benefits.■

Authors

Kate Goddard is Health Technology Assessor, King's Technology Evaluation Centre, King's College London, UK; Mark Pennington is Senior Lecturer in Health Economics, King's Technology Evaluation Centre, King's College London, UK; Muralikrishnan R. Kartha is Senior Health Economist, King's Health Economics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK; Tom Macmillan is Health Technology Assessor and Information Specialist, King's Technology Evaluation Centre, King's College London, UK; Catey Bunce is Reader in Medical Statistics, School of Population Health and Environmental Sciences, King's College London, UK; Jennifer A Summers is PostDoctoral Research Fellow in Medical Statistics, King's Technology Evaluation Centre, King's College London, UK; Stephen Keevil is Professor of Medical Physics, King's Technology Evaluation Centre, King's College London, UK; Anastasia Chalkidou is Associate Director, King's Technology Evaluation Centre, King's College London, UK

Aubert CE, Le Doeuff J, Lajou J et al (2013) Influence of peripheral arterial occlusive disease on the Neuropad® test performance in patients with diabetes. *Diabet Med* 30(5): 178–84

Diabetes UK (2019) *Us, Diabetes and a Lot of Facts and Stats*. London: Diabetes UK. Available at: https://bit.ly/3a0e0SN (accessed 24.02.2020)

Didangelos T, Zografou I, Papageorgiou A et al (2006) Validation of a new diabetic autonomic neuropathy bedside test (Plaster) vs. the MNSI, monofilament of 10 gr test and biothesiometer. *Diabet Med* 23(Suppl 4): 78

Forth R, Vere J, Tentolouris N et al (2010) Use of Neuropad in the diagnosis of diabetic peripheral neuropathy. Uppsala, Sweden: Diabetic Foot Study Group

Freitas C, Carvalho A, Melo-Rocha G et al (2009) The Neuropad test in the screening of peripheral neuropathy in diabetic patients [in Portuguese]. *Acta Med Port* 22(6): 729–34

Kamenov ZA, Petrova JJ, Christov VG (2010) Diagnosis of diabetic neuropathy using simple somatic and a new autonomic (Neuropad) tests in the clinical practice. *Exp Clin Endocrinol Diabetes* 118(4): 226–33

Liatis S, Marinou K, Tentolouris N et al (2007) Usefulness of a new indicator test for the diagnosis of peripheral and autonomic neuropathy in patients with diabetes mellitus. *Diabet Med* 24(12): 1375–80

Manes C, N. Papanas N, Exiara T et al (2014) The indicator test Neuropad in the assessment of small and overall nerve fibre dysfunction in patients with type 2 diabetes: a large multicentre study. *Exp Clin Endocrinol Diabetes* 122(3): 195–9

Marinou K, Maggana S, Liatis S et al (2005) Usefulness of the indicator plaster neuropad for the diagnosis of peripheral and autonomic neuropathy in patients with diabetes mellitus. *Diabetologia* 48(Suppl 1): A360

Mendivil CO, Kattah W, Orduz A et al (2016) Neuropad for the detection of cardiovascular autonomic neuropathy in patients with type 2 diabetes. *J Diabetes Complications* 30(1): 93–8

National Institute for Health and Care Excellence (2015) *Diabetic foot problems: prevention and management*. London: NICE. Available at: https://www.nice.org.uk/guidance/ng19 (accessed 17.02.2020)

National Institute for Health and Care Excellence (2018) *Neuropad for Detecting Preclinical Diabetic Peripheral Neuropathy*. London: NICE. Available at: https://www.nice.org.uk/guidance/mtg38 (accessed 17.02.2020)

Ponirakis G, Petropoulos IN, Fadavi H et al (2014) The diagnostic accuracy of Neuropad for assessing large and small fibre diabetic neuropathy. *Diabet Med* 31(12): 1673–80

Quattrini C, Jeziorska M, Tavakoli M et al (2008) The Neuropad test: a visual indicator test for human diabetic neuropathy. *Diabetologia* 51(6): 1046–50

Sanz-Corbalán I, Lazaro-Martinez JL, Garcia-Morlaes E et al (2018) Advantages of early diagnosis of diabetic neuropathy in the prevention of diabetic foot ulcers. *Diabetes Res Clin Pract* 146(2018): 148–54

Spallone V, Morganti R, Siampli M, et al (2009) Neuropad as a diagnostic tool for diabetic autonomic and sensorimotor neuropathy. *Diabet Med* 26(7): 686–92

Tentolouris N, Achtsidis V, Marinou K, Katsilambros N (2008) Evaluation of the self-administered indicator plaster neuropad for the diagnosis of neuropathy in diabetes. *Diabetes Care* 31(2): 236–7

Tentolouris N, Papanas N, Panagoulias G et al (2014) The association between Neuropad testing with foot ulceration in diabetes. *Diabetologia* 57(Suppl 1): S471

Ziegler D (2010) Diabetic peripheral neuropathy. In: Holt RIG, Cockram CS, Flyvbjerg A et al (eds.) *Textbook of Diabetes* (4th edn.) Oxford: Wiley-Blackwell

Ziegler D, Papanas N, Rathmann W et al (2012) Evaluation of the Neuropad sudomotor function test as a screening tool for polyneuropathy in the elderly population with diabetes and pre-diabetes: the KORA F4 survey. *Diabetes Metab Res Rev* 28(8): 692–7

Ziegler D, Papanas N, Roden M (2011) Neuropad: Evaluation of three cut-off points of sudomotor dysfunction for early detection of polyneuropathy in recently diagnosed diabetes. *Diabet Med* 28(11): 1412–5