# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Medical technology guidance

## Assessment report overview

# The Neuropad test for the early detection of diabetic peripheral neuropathy

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem from scope

# 1      The technology

Neuropad (TRIGOcare International) is a point-of-care test for people with diabetes which detects sudomotor dysfunction (inadequate sweat production), which may indicate that a person is at risk of developing diabetic peripheral neuropathy (DPN). The 10-minute test is non-invasive and comprises a single-size colour-changing plaster containing cobalt chloride that is applied to the sole of each foot. A colour change from blue to pink indicates adequate sweat production and normal autonomic nerve function with a low risk of DPN. If colour changes partially, or remains blue, this indicates reduced sweating and sudomotor function which is associated with DPN and an increased risk of diabetic foot complications.

The Neuropad test can be done in a clinic by a healthcare professional during a routine foot check, or at home by the person themselves (or their carer). Neuropad is designed so it can be used in conjunction with other standard sensory neuropathy tests (such as the 10 g monofilament) or as a standalone test.

# 2      Proposed use of the technology

## 2.1      Disease or condition

Diabetic peripheral neuropathy (DPN) is a common long-term complication of diabetes, where high blood glucose levels damage the small blood vessels supplying the nerves to the hands and feet. DPN affects up to 50% of people with diabetes, with chronic, painful neuropathy affecting up to 26%, which increases the risk of foot ulceration and subsequent amputation. In England, around 2.5% of people with diabetes have foot ulcers at any given time (approximately 86,000 people) and there were around 6,000 lower limb amputations due to DPN in 2014/15. [1]

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[1] Diabetes UK Facts and Stats Dec 2015

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DPN may involve large nerve fibres, small nerve fibres, or both, affecting different sensation modalities. Large fibres affect motor function and sensation function for vibration and temperature. Small fibres constitute 80–91% of peripheral nerve fibres and control pain perception and autonomic sudomotor function. Small fibre neuropathy is the most common type of neuropathy in people over 50 years; it typically affects the lower limbs and often precedes large fibre neuropathy. 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 with the need for amputation.

## 2.2 Patient group

In the UK, an estimated 4.5 million people have diabetes: this is predicted to rise to 5 million people by 2025. DPN affects up to 50% of people with diabetes, with chronic, painful neuropathy affecting up to 26%, which increases the risk of foot ulceration and subsequent amputation. In England, around 2.5% of people with diabetes have foot ulcers at any given time (approximately 86,000 people) and there were around 6,000 lower limb amputations due to DPN in 2014/15.[2]

No training is required to administer Neuropad, nor does it require responses from the patient. Therefore people in community settings and those with cognitive or communication difficulties who have to respond to existing technologies were identified as relevant subgroups.

## 2.3 Current management

NICE's guideline on diabetic foot problems recommends that adults with diabetes have a risk assessment for diabetic foot problems on diagnosis; at least annually thereafter; whenever foot problems arise and on any admission to hospital. During the risk assessment, both feet should be examined for

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[2] Diabetes UK Facts and Stats Dec 2015

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multiple risk factors, including neuropathy, which should be tested using a 10 g monofilament as part of a foot sensory examination. If neuropathy is detected, a person's risk is classified as being moderate or high (depending on other comorbidities). This triggers referral to a foot protection service and an increased frequency of foot assessments.

Testing of sudomotor function to detect neuropathy is not included in NICE guidance. Tests for sensation that are not included in NICE guidance for detecting diabetic foot neuropathy in primary care include tuning fork, biothesiometer, and Neurotip. NICE guidance on Vibratip, a vibration perception device to detect neuropathy, states it shows potential but more research is needed.

Neuropad is the only self-testing device for sudomotor function available for use in a primary care or the home setting. More specialist tests are used in secondary care to detect small fibre neuropathy, including nerve conduction studies using electromyography, intraepidermal nerve fibre density biopsy, quantitative sudomotor axon reflex test (QSART), Sudoscan, corneal confocal microscopy and the NC-stat DPN check device for sural nerve velocity.

## 2.4    Proposed management with new technology

Neuropad is designed to be suitable for all people with diabetes to test for sudomotor dysfunction to detect DPN. The test can be used as an adjunct to the current 10 g monofilament test, which detects sensory DPN. The 10 g monofilament test is generally done in primary care by a trained healthcare professional as part of an annual foot check. Neuropad is claimed to be easy to perform and interpret, and so can also be done at home by the patient (or carer). This may allow for more regular self-testing without the inconvenience of attending a foot check clinic, as some patients do not always receive an annual foot check. The test may also be used instead of a monofilament test when this is inappropriate, such as people with communication difficulties and/or dementia.

# 3    Company claimed benefits and the decision problem

The claimed benefits and decision problem are reproduced in Appendix D. The company did not identify any variation from the scope. The EAC noted that the company's submission only partially covered the comparators and the outcomes specified in the scope. Table 1 in the assessment report details the EAC's view of how the submission aligns with the decision problem.

# 4    The evidence

## 4.1    Summary of evidence of clinical benefit

The company identified 43 studies on the technology from its literature searches. It excluded 33 studies and presented 10 studies, 8 published and 2 unpublished, see pages 33 to 38 of the company's clinical submission for further details.

The EAC developed its own search strategy and conducted its own searches for published, unpublished and grey literature on the technology. In total the EAC identified 18 studies which it considered relevant to the decision problem, 13 of which were available as full text articles, 5 of which were available in abstract form only. Table 2 summarises the overlap between the EAC and company's included studies.

Seventeen of the EAC's included studies investigated the diagnostic accuracy of Neuropad against a reference standard, and 1 reported its ability to predict the risk of foot ulceration. Additionally 1 study  looked at the reproducibility of results from using Neuropad, and 1 assessed the association between Neuropad testing and developing foot ulcers. The most common reference standard was the neuropathy disability score (NDS). All the studies were conducted prospectively, and were observational, cross sectional or longitudinal cohort studies.  For further details on the EACs included studies, see Table 5, in the assessment report.

**Table 2: Included studies, company and EAC**

| Studies | Type of publication | Type of study | Comment |
|---|---|---|---|
| **Included by EAC and company** | | | |
| *5 studies included by both* | *Full papers* | *Prospective, cross-sectional, observational studies* | *Quattrini (2008), Ponirakis (2014), Tentolouris (2008)* |
| | *Unpublished abstract or full text* | *Longitudinal prospective cohort* | *Tentolouris (2017)  Sanz (2016)* |
| **Included by company but excluded by EAC** | | | |
| *Ishabi (2013)* | *Full paper* | *Observational study* | *Performance of neuropad is not assessed, population does not fit the scope* |
| *Papanas (2011)* | *Full paper* | *Prospective, cross-sectional, observational cohort* | *Study population significantly overlapped with Manes et al. (2014).* |
| *Tentolouris (2010)* | *Full paper* | *Prospective observational cohort study* | *Included people with and without foot ulceration and results could not be separated* |
| *Tomesova (2013)* | *Full paper* | *Prospective cohort study* | *Outcomes do not assess the performance or impact of the Neuropad.* |
| *Tsapas (2014)* | *Full paper* | *Meta-analysis* | *Not a primary study* |
| **Excluded by company but included by EAC** | | | |
| | *Full papers* | *Prospective, cross-sectional, observational cohort* | *Aubert (2013), Freitas (2009), Kamenov (2010), Liatis (2007), Manes (2014), Mendivil (2016), Spallone (2009), Ziegler (2011& 12)* |
| | *Abstracts* | *Prospective, cross-sectional or longitudinal observational cohort* | *Didangelos (2006), Forth (2010), Marinou (2005), Tentolouris (2014)* |

The EAC noted that the studies included in the published meta-analysis

[Tsapas et al., (2014)] on which the company had relied in its submission had

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significant heterogeneity; specifically the studies used different reference standards and contained overlapping patient populations. The EAC therefore decided to conduct its own meta-analysis involving 5 studies, the details of which are described in the assessment report. The EAC considered the 5 studies used in its meta-analysis as well as the 2 published UK based studies [Ponirakis (2014) and Quattrini (2008)] to be the pivotal studies, and most informative to the evaluation. Table 3 below summarises the details of these studies.

The results of the EAC meta-analysis comparing Neuropad with NDS (NDS≥5) using 5 studies, (for further details, see pages 64 to 70 of the assessment report) were:

- Sensitivity: 89.4% (95%CI 83.2 to 93.5) $I^2$ = 84.2%

- Specificity: 60.3% (95%CI 50.9 to 69) $I^2$ = 92.5%

The values reported in the Tsapas et al. (2014) meta-analysis paper were:

- Sensitivity: 86% (95% CI 0.79 to 0.91), $I^2$ = 90.13%

- Specificity: 65% (95% CI 0.51 to 0.76), $I^2$ = 94.96%

The EAC concluded that while the study evidence showed that Neuropad may be more sensitive, but less specific than monofilament, there was not enough evidence to support a claim of superiority. Nor did the existing evidence support a claim of a similar sensitivity to neuropathy scoring systems [nerve conduction studies and the neuropathy disability score (NDS)] superior to that of monofilament or tuning fork. Insufficient evidence was found for the performance of Neuropad against vibration perception threshold testing (VPT), however unpublished evidence (Sanz et al. 2016 and Tentolouris et al 2017) indicated that the Neuropad may have a higher sensitivity but lower specificity than the NDS or a combination of VPT and monofilament for predicting future foot ulceration. No clear or conclusive evidence was found

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for the use of Neuropad as a screening test for early neuropathy or its use in patients with communication or language difficulties.

One study did assess the reproducibility of the Neuropad test and found very good overall agreement between the patient and healthcare professional. Most studies compared Neuropad against NDS, though thresholds used varied, were assessed to have a low bias, but a high level of heterogeneity in study methodology. The EAC noted that while Neuropad may theoretically be able to detect earlier stage neuropathy, in the current pathway this is of limited benefit, as action is only triggered when moderate or advanced neuropathy is detected.

**Table 3: Review of pivotal studies in the assessment report (reproduced from Table 5 in the assessment report)**

| Study and design | Participants/ population | Intervention & comparator | Outcome measures and follow up | Results | Withdrawals | Funding | Comments |
|---|---|---|---|---|---|---|---|
| Freitas et al (2009) Prospective, cross-sectional, observational cohort study | 40 (22 NDS confirmed neuropathy: 15 men, mean age 57.9, diabetes duration 15.4 yrs. 18 no neuropathy confirmed: 10 men, mean age 63.6 and DD 11.8 yrs)<br><br>Portugal | Neuropad Monofilament<br><br>Reference standard: NDS (≥6) | Sensitivity Specificity PPV NPV | Neuropad Sensitivity 100%, specificity 44%, PPV 69% NPV 100%<br><br>Monofilament Sensitivity 100%, specificity 38% PPV 59.38% NPV 100% | N/A | No external funding | Included in the Tsapas et al. meta-analysis Relatively small sample size. People with foot ulcerations were mentioned in the results section (as they had not been excluded a priori). |
| Kamenov et al (2010) Prospective, cross-sectional, observational cohort study | 264 (203 with type 2 diabetes; 126 male, 138 female; mean age 55.4+/-12.0; DM duration of | Neuropad Reference standards: NDS (≥3 and ≥6 | Sensitivity and specificity, PPV, NPV | NDS ≥3: Sensitivity = 76.3% Specificity = 56.1% PPV = 86.3% NPV = 39.5%<br><br>NDS ≥6: | | Unclear, tests provided by company | The scope comparators are used as the reference standard in this study. |

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| | 9.3+/-7.1 years)  DPN prevalence: 78.4% (207 out of 264)  One Bulgarian hospital | | | Sensitivity = 79.3% Specificity = 42.9% PPV = 62.8% NPV = 63.0% | | | | |
| Liatis et al (2007) Prospective, cross-sectional, observational cohort | 117 (108 type 2 diabetes; mean age 61.4; mean diabetes duration 10.9 years) | Neuropad Reference standard: NDS (≥5), NSS (≥3), VPT (DPN diagnosed when at least 2 tests indicate an abnormal result) | Sensitivity and specificity, PPV, NPV | Against NDS ≥5 Sensitivity = 86% (95%CI 80.0-92.0) Specificity = 67.2% (95%CI 59.0-75.0) PPV = 66.2% (95%CI 58.0-74.0) NPV = 86.5% (95%CI 80.0-92.0) | N/A | | Unclear | Reference test is a combination of scores. |
| Manes et al (2014) Prospective, cross-sectional, | 1010 (608 male, 402 female; mean age 63.9; diabetes | Neuropad Reference standard: NDS (≥6) | Sensitivity and specificity, PPV, NPV | Overall peripheral neuropathy Sensitivity = 74.6% | | | Unclear | Sudomotor dysfunction (a result of small nerve fibre damage) was assessed by NDS1, which is described by the authors as a component of the NDS specially |

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| observational cohort | duration 12.24 years)<br><br>Five diabetes clinics in Greece | | | Specificity = 36.1%<br>PPV = 48.5%<br>NPV = 63.8%<br><br>Small fibre:<br>Sensitivity = 85.6%<br>Specificity = 71.2%<br>PPV = 52.2%<br>NPV = 93.3% | | | dedicated small fibre dysfunction.<br>Two authors have served as advisory board members for the company |
| Tentolouris et al (2008) Prospective, cross-sectional, observational cohort | 156 (82 male, 7 type 1, age 59.6 ± 15.5 years)<br><br>Outpatient clinic in Greece | Neuropad Reference standard: NDS (≥5) and NSS (≥3). | Sensitivity and specificity, PPV, NPV<br><br>Reliability and reproducibility | Unclear comparator for NDS (no threshold described): sensitivity = 87% specificity = 66% PPV = 94% NPV = 79%<br><br>The k statistic to measure overall agreement between patient and health care provider of the IPN was "very good": 90.3% | | | The paper indicates it had similar results to Liatis, S., et al. (2007).<br><br>Evaluation of self-testing at home: The evaluation of the instructions and the test by the patients (median values, interquartile range) was as follows: easiness to understand the instructions for the use of the IPN 10.0 (9.0-10.0), easiness to use the IPN 10.0 (9.0-10.0), and easiness to evaluate the test as normal or abnormal 10.0 (8.0-10.0). |

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| | | | | agreement, k = 0.88 (95% CI 0.85–0.91). 20.5% people reported that they requested help to perform self-testing. | | | |
|---|---|---|---|---|---|---|---|
| Ponirakis et al (2014) Prospective, cross-sectional, observational cohort assessing | 127 (68 with type 1 diabetes and 59 with type 2 diabetes; 90 male, 37 female; mean age 57± 9.7 years) Diabetes clinic in UK hospital | Neuropad Multiple reference standards | Sensitivity, specificity, PPV, NPV | Against large fibre tests: NDS (=>3) Sensitivity: 70% Specificity: 50% PPV, NPV (%): 63, 57 Against small fibre tests: NDS score =>2 Sensitivity: 78% Specificity: 60% PPV, NPV (%): 34, 91 NDS ≥5 Sensitivity 85% Specificity 45% PPV 69% NPV 71% | | | UK study with a large number of comparisons with reference standards (for full list and outcomes see Table 5, AR) The NDS cut-off threshold is lower than in other selected studies Neuropad applied after callus removal |
| Quattrini (2008) Prospective, cross- | 57 (20 with type 1, and 37 with type 2 diabetes; | Neuropad Reference standard: NDS (≥5) | Sensitivity and specificity, PPV, NPV | Sensitivity 85% Specificity 45% PPV 69% NPV 71% | 4 (results missing) | Funding from NIH and | UK study with well described methodology. Relatively small sample size. |

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|---|---|---|---|---|---|---|---|
| sectional, observational cohort | mean age 56±1.4 years Diabetes clinic in UK hospital | | | | | Diabetes UK | Inconsistency in reporting NDS score cut-off for neuropathy/no neuropathy (5 out of 10, and ≥3) Neuropad was applied to plantar surface of the big toe, rather than, as per manufacturer recommendations, beneath the big or little toe on the plantar surface of the foot, , |

Abbreviations used: DPN = Diabetic peripheral neuropathy; PPV = positive predictive value; NPV = negative predictive value; NDS = Neuropathy disability score; NSS= Neuropathy symptoms score; VPT = Vibration perception test, NIH = National Institute of Health
+ In all the studies tabled, colour change of Neuropad was assessed 10 minutes after application

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## 4.2    Summary of economic evidence

The company submission did not identify any published economic evidence. The EAC replicated the company searches and undertook its own with a broader set of free-text terms and keywords, and using additional search engines. These also identified no economic evidence on the technology.

**De novo analysis**

The company submitted a Markov model with 6 month cycles using sensitivity and specificity values reported in the literature to model disease progression( (See figure 6 in the assessment report) over a 3 year time horizon, following a diagnosis or otherwise of neuropathy.

The EAC considered the company's model largely appropriate, but noted a number of issues with its structure. In practical terms the company had used a recursive decision tree to model the Markov transitions making it cumbersome and placing a practical limitation on its time horizon. The EAC considered the time horizon used of 3 years was insufficiently long enough to capture the long term impact of neurapthy, and used a 10 year time horizon and incorporated a death state. The model did not include patients who were false positives (wrongly diagnosed with neuropathy) and false negatives (wrongly diagnosed as not having neuropathy).

The EAC revised the company's model as shown diagramatically below. The EAC used a Markov model with 6 monthly cycles to simulate a cohort of 1000 patients newly diagnosed with diabetes. Patients entered the model following testing for neuropathy in one of four health states: true negaitve (No DPM), true positive (DPN), false negative (DPN), and false positive (no DPN). Patients were assumed to be tested for DPN in primary care during their annual diabetic check  if not previously diagnosed, and to have the same probability of DPN in repeated tests. Three main strategies were assessed:1) using Neuropad alone; 2) using monofilament alone; and 3) using

monofilament on neuropathy positive cases after Neuropad testing. The EAC additionally included a 'no testing' strategy to model the subgroup of patients with communication difficulties or cognitive impairment who would not be suitable for monofilament. It also undertook subgroup analysis for patients tested in the community using the same model structure, sensitivity and specificty of testing, with the assumption that positive tests are followed by a clinic referral including a monofilament test, the additional cost of which is that of undertaking the monofilament test. Other assumptions included that population mortality was independent of age, all patients enter a foot care programme after ulceration and upon testing positive for DPN, no further testing for DPN is conducted after a diagnosis of DPN, and ulceration of the ipsilateral foot does not occur after a major amputation.

**Figure 2: EAC's model with EAC additions shown in green font (reproduced from Figure 7 in the assessment report)**
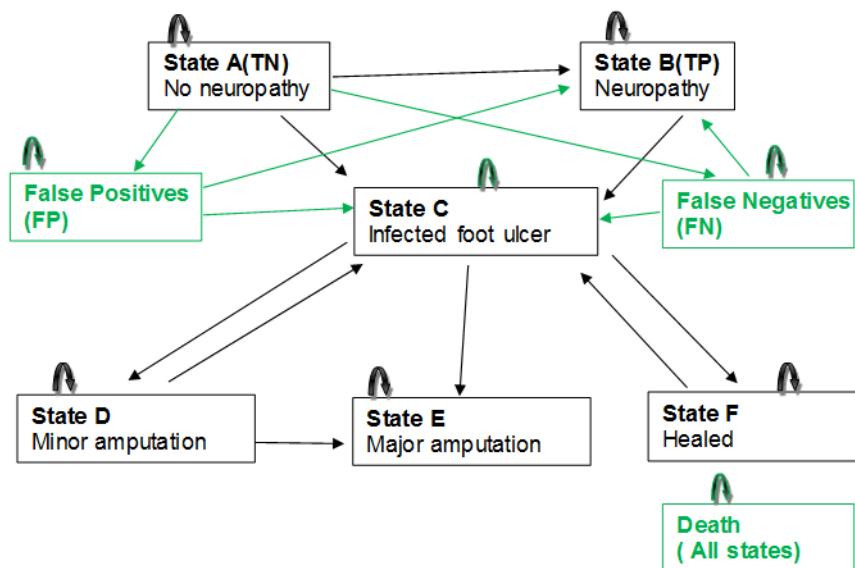


**Model parameters**

The EAC disagreed or noted anomalies with a significant number of the parameter values used in the company's model and used different values in its own. The addition of new states in the EAC model also led to the

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introduction of new parameters. The led to largely wholesale changes of the model parameters as the EAC constructed its revised model. Full details of all these changes and their rationale are provided in detail in the assessment report (see pages 93 to 113), and are summarised and tabulated below.

**Table 4: Clinical parameters used in the company's model and EAC revisions (reproduced from Table 10, assessment report)**

| | Sponsor's Estimate | Source | EAC Estimate | Source & Assumptions |
|---|---|---|---|---|
| **Clinical Parameters** | | | | |
| DPN Prevalence | 0.024 | Kostev et al (2014) | 0.024 | Kostev et al (2014) |
| Test Sensitivity (Neuropad) | 0.86 | Tsapas et al (2014) | 0.89 | EAC Meta-analysis |
| Test Specificity (Neuropad) | 0.65 | Tsapas et al (2014) | 0.60 | EAC Meta-analysis |
| Test Sensitivity (10g Monofilament) | 0.985 | Mythili et al (2010) | 0.84 | Willits et al(2015) |
| Test Specificity (10g Monofilament) | 0.55 | Mythili et al (2010) | 0.83 | Willits et al(2015) |
| Test Sensitivity (Neuropad + 10g Monofilament) | - | Applied sequentially if abnormal on Neuropad | 0.75 | Calculated : Sensitivity $_{Neuropad}$ * Sensitivity $_{Monofilament}$ |
| Test Specificity (Neuropad + 10g Monofilament) | - | Applied sequentially if abnormal on Neuropad | 0.93 | Calculated : Specificity $_{Neuropad}$ +( 1- Specificity $_{Neuropad}$)* Specificity $_{Monofilament}$ |
| Incidence of Neuropathy | 0.0237 | Unclear, though cited Ortegon et al (2004) | 0.0199 | Ortegon et al (2004) |
| No Neuropathy infected foot ulcer rate | 0.015 | Unclear, though cited Ragnarson et al(2001) | 0.0026 | Ortegon et al (2004) |
| No Neuropathy death rate | - | | 0.02 | Ortegon et al (2004) |
| False positive infected foot ucler rate* | - | | 0.00195 | Estimated by applying effectiveness(diabetic foot programme) |
| False positive death rate | - | | 0.02 | Assumed same as No neuropathy |

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| Neuropathy infected foot ulcer rate | 0.051 | Unclear, though cited Ortegon et al (2004) | 0.014 | Ragnarson et al(2001) |
| DPN Death rate | - | | 0.02 | Assumed same as No neuropathy |
| False negative infected foot ulcer rate^ | - | | 0.0187 | Estimated by applying effectiveness(diabetic foot programme) |
| Persistent infected foot ulcer | - | | 0.264 | HQIP (2017) |
| Infected foot minor amputation rate | 0.35 | Ragnarson et al(2001) | 0.13 | Promphers et al (2008) |
| Infected foot major amputation rate | 0.17 | Unclear, though cited Ragnarson et al(2001) | 0.05 | Promphers et al (2008) |
| Infected foot ulcer to healed | 0.40 | Ragnarson et al(2001) | 0.496 | Derived probability |
| Infected foot death rate | - | | 0.06 | Promphers et al (2008) |
| Minor amputation infected foot rate | 0.044 | Ragnarson et al(2001), but not included ulcers with critical ischaemia | 0.073 | Ragnarson et al (2001), including ulcers with critical ischaemia |
| Minor amputation major amputation rate | 0.17 | Ortegon et al (2004) | 0.17 | Ortegon et al (2004) |
| Minor amputation death rate | - | | 0.027 | Ragnarson et al (2001) |
| Major amputation death rate | - | | 0.12 | Ragnarson et al (2001) |
| Healed to infected foot rate | 0.039 | Unclear, though cited Ortegon et al (2004) | 0.073 | Ragnarson et al (2001), including ulcers with critical ischaemia |
| Healed death rate | - | | 0.027 | Ragnarson et al (2001) |
| Effectiveness of diabetic foot programme | - | | 0.25 | Ragnarson et al (2001) |
| Infected foot ulcer (hospitalization proportion) | - | | 0.40 | NICE(2015) |

The EAC agreed that the company's sources for transition probabilities (Ortegon et al. 2004; and Ragnarson et al. 2001) were appropriate, but noted anomalies and made revisions. Table 11 in the assessment report presents

the transition probabilities used in the EAC's revised model for the different health states applied to the 4 strategies considered by the EAC. The EAC introduced additional transitional probabilities for its added states. The transition probability for 'infected foot ulcer' to 'infected foot ulcer' was estimated to be 26.4%, based on the results from the national foot care audit (HQIP 2017).  The probability of death differed according to state the individual was transiting from (range, 2% to 12%), and was sourced directly or assumed from Ortegon et al (2004), Ragnarson et al (2001), and Promphers et al (2008) . The rates of infected foot ulcer for false positive and false negative patients used estimated effectiveness rates for the diabetic foot programme, derived from McCabe et al, (2008). Foot care audit data, HQIP (2017) provided the source for persistent foot ulcer rates.

## Costs and resource use

The EAC considered the sources used by the company as useful, but disagreed with the values used, made revisions and introduced additional costs. The EAC noted that the cost for a 10 g monofilament test used in the company's model, £16.80, refers to the cost of the reusable holder. It noted that the cost of a monofilament test in the MTEP assessment of VibraTip was estimated to be 7.6p (range 3.04-19p), which it considered more realistic. Based on expert advice the EAC assumed a diabetic nurse time of 1 minute to administer and interpret both tests, resulting in a revised estimate for a DPN examination using Neuropad of £8, and of using monofilament of 80p. The revised cost parameters used in the EAC model are summarised below in table 5.

## Table 5: Cost parameters used in the company's model and EAC revisions (reproduced from Table 12 in the assessment report)

| | Sponsor's Estimate | Source | EAC Estimate | Source & Assumptions |
|---|---|---|---|---|
| **Cost** | | | | |
| Neuropad | £7.28 | Sponsor list price | £8 | Sponsor, Curtis & Burns (2016) for staff cost |

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|---|---|---|---|---|
| Monofilament /examination | £16.80 | NICE briefing note, includes only the cost of the reusable holder | £0.80 | Willits et al (2015) , Curtis & Burns(2016) for staff cost |
| **Health state (6 month)** | | | | |
| No neuropathy (only annual diabetic check) | £125 | Green & Taylor (2016), not used in the model | £23.50 | Cutin & Burns(2016), staff cost for 30 minute consultation |
| Neuropathy (foot clinic) | £1,855 | Kerr(2017), these are cost of treating ulcers with no or mild infection | £325 | McCabe et al (1998), Estimated foot clinic cost |
| Infected foot ulcer (primary & community care) | £8,620 | Kerr(2017), rounded from £8,616 | £8,616 | Kerr(2017), weekly cost of £359 |
| Infected foot ulcer (hospitalization) | £3,277 | Kerr (2017), inconsistent estimates | £4,376 | Kerr (2017),weighted average of all foot ulcers grouped to ulcer-specific HRGs and other HRGs |
| Minor amputation + hospital rehabilitation | £11,512 | Kerr (2017) (£2,105). Also a transition cost of £ 9,407 (Ragnarson et al 2001) and a stump procedure cost has been added. | £6,329 | DOH (2016), weighted average for HRG codes YQ24A -YQ26C inclusive + HRG code VC14Z: Rehabilitation for Amputation of Limb |
| Minor amputation (post care) | £1,605 | Kerr (2017), stump procedure cost used as a post care | £384 | NICE (2016), monthly cost of £64 |
| Major amputation + hospital rehabilitation | £13,513 | Kerr (2017) (£4,106). Also a transition cost of £ 9,407 (Ragnarson et al 2001) and a stump procedure cost has been added. | £12,147 | DOH (2016), weighted average for HRG codes YQ21A - YQ22B inclusive + HRG code VC14Z: Rehabilitation for Amputation of Limb |
| Major amputation (post care) | £1,206 | Kerr (2017), stump procedure cost used as a post care | £2,508 | NICE (2016), monthly cost of £418 |

## Company results

The company's submission reported net monetary benefits which combines costs and utilities, in the company submission accrued QALYs were valued at £30k per QALY. The tabled figures have been recalculated using a cost consequence approach by the EAC which only considers monetary benefits. The figures show that using Neuropad was the cheapest option, with per patient costs over £1300 lower than the comparator technologies. The

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costings for the Neuropad + Monofilament comparator, assumed a Monofilament test was conditional on an abnormal Neuropad test.

**Table 6: Company base case results (reproduced from Table 9 in the assessment report)**

|  | Expected cost | Cost difference per patient |
|---|---|---|
| Neuropad (Technology) | £5,585 | - |
| 10g Monofilament (Comparator) | £6,954 | £1,369 |
| Neuropad + 10g Monofilament* (Comparator) | £6,944 | £1,359 |

The company conducted deterministic sensitivity analyses on a number of variables (health state costs, purchasing price of Neuropad and Monofilament, Transition probabilities and discount rate). The main finding of these analyses were that Neuropad was the optimal option until specificity fell below 55%, at which point the combined test strategy (monofilament conditional on an abnormal result of Neuropad) was the optimal (cheapest) option. For the care home subgroup, which the company modelled by assuming a higher prevalence of neuropathy, sensitivity analysis performed on the prevalence rate, found that Neuropad was always the optimal option.

The company concluded that Neuropad alone was the most cost effective option but it still saved money compared to monofilament testing when used in conjunction with monofilament. It also recommended, based on its modelling, that Neuropad be used as a home testing device for DPN, though it did not specifically model this setting.

**EAC revised model results**

The base case results for the EAC revised model are shown in Table 7, the cost savings are for the comparator compared with Neuropad.

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**Table 7: EAC base case results (reproduced from Table 14 in the assessment report)**

|  | 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 |

Using Neuropad alone is the most costly option, with no testing the cheapest. The EAC cautions however that the no testing option is likely to deliver inferior outcomes. It also expresses caution concerning its results for Neuropad + monofilament, which has applied the sensitivity of the two devices assuming that they are completely independent. This strategy saves money compared to Neuropad or monofilament alone by increasing specificity at the cost of sensitivity. As a result it may result in poorer outcomes that using either device alone.

The EAC conducted deterministic analyses on its base case results. This showed that changes to none of parameter changed the direction of the base case result, few had a noticeable impact on the results. None brought Neuropad close to cost equivalence, the closest being a cost difference of £495 compared to monofilament, when the specificity of Neuropad is assumed to be 69% (for further details see Appendix E of the assessment report)

The EAC conducted a structural sensitivity analysis where it assumed conditional independence, namely a patient could receive a different result at each re-test. This increased the cost of all strategies, except no testing, and the costs savings for the comparators compared with Neuropad.

**Conclusions**

With respect to the economic evidence the EAC concluded that the company model had inherent flaws and the revised EAC model addressed these. The

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revised EAC model, both base case analysis and sensitivity analyses showed that Neuropad was not cost-saving compared with the 10g monofilament test. If Neuropad is combined with the monofilament test there are cost savings but the EAC notes that the key parameters for this strategy are not clinically evidenced and are based on theoretical calculations. The EAC noted limitations to the cost modelling related to the assumptions in the model and the availability of data.

# 5      Ongoing research

The company identified 2 unpublished studies which were not identified in searches conducted by the EAC. The EAC identified 1 unpublished completed trial, for which no results were available (NCT00895440).

# 6      Issues for consideration by the Committee

## *Clinical evidence*

Key issues for consideration by the committee include:
- What are the most relevant and reliable estimates of sensitivity and specificity?
- The paucity of evidence for direct comparison of Neuropad with the 10g monofilament and other comparators;
- The promise offered by home or primary care use, as yet not supported by much identified evidence;
- The  promise offered of ease of use by the sub-groups identified in the scope:
    - People in community settings, as yet not supported by much identified evidence
    - People with communication difficulties or cognitive impairment, as yet not supported by much or any identified evidence.

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- The clinical relevance of early detection of neuropathy. The EAC noted the paucity of evidence and uncertainty on the benefits of the early detection of DPN. The evaluation has also highlighted a lack of evidence on the effectiveness and cost-effectiveness of foot care programmes.

## *Cost evidence*

Key issues for consideration by the committee include:

The company and EAC models did not agree about the cost-saving potential of this technology compared with standard care. Does the committee consider it is likely to be cost saving?

In the EAC model the combined treatment of Neuropad and monofilament was cheaper than either treatment alone however the EAC notes that there is no evidence to support this treatment and the results are based on a theoretical model which assumes that the tests are completely independent. The EAC considers that whilst the technologies test different neurological functions this is unlikely to be the case.

# 7      Authors

Neil Hewitt, Technical analyst
Bernice Dillon, Technical adviser
NICE Medical Technologies Evaluation Programme
October 2017

# Appendix A: Sources of evidence considered in the preparation of the overview

A      Details of assessment report:

- Bunce C, Chalkidou A, Goddard K et al., Neuropad test for the early detection of diabetic foot neuropathy (July 2017)

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B    Submissions from the following sponsors:

- Skrocketphytopharma (UK) Ltd

C    Related NICE guidance

- [Type 2 diabetes in adults: management.](#) (2016) NICE guideline NG28
- [Diabetic foot problems: prevention and management](#). (2016) NICE guideline NG19
- [Diabetes (type 1 and type 2) in children and young people: diagnosis and management](#). (2015) NICE guideline NG18.
- [Type 1 diabetes in adults: diagnosis and management.](#) (2016) NICE guideline NG17
- [Diabetes in pregnancy: management from preconception to the postnatal period](#). (2015) NICE guideline NG3
- [VibraTip for testing vibration perception to detect diabetic peripheral neuropathy](#) (2014) NICE medical technology guidance MTG22

**Under development**

NICE is developing the following guidance (details available from [www.nice.org.uk](http://www.nice.org.uk)):

- [Type 2 diabetes management](#). NICE guideline: standing committee update. Publication expected: December 2017

**NICE advice**

- [Diabetic foot problems](#) (2013) NICE Evidence Update 33
- [Training non-podiatrists to assess foot risk as part of an integrated foot service for people with diabetes](#) (2016) NICE shared learning database

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# Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

**Prof Michael Kirby**

Visiting Professor to the Faculty of Health & Human Sciences consultant to the Clinical Trials Coordinator,   Royal College of Physicians

**Ms Catherine Gooday**

Principal Podiatrist, Diabetes UK

**Dr Umesh Dashora**

Consultant Physician, Association of British Clinical Diabetologists

**Dr Andrew Holton**

Consultant Clinical Neurophysiologist, British Peripheral Nerve Society

**Prof Solomon Tesfaye**

Consultant Diabetologist, Royal College of Physicians

**Dr James Holt**

Consultant Neurologist, British Peripheral Nerve Society

**Dr Jonathan Roddick**

GP with a specialist interest in diabetes, Royal College of General Practitioners

**Dr Antonin Gechev**

Consultant Neurophysiologist, British Peripheral Nerve Society

- Two experts had direct involvement with the technology. One expert managed patients whom used Neuropad in another part of their care

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pathway, and 5 experts indicated they would like to use the technology but it is not currently available to them.

- The one expert who responded who had used the technology indicated that they found Neuropad useful in detecting neuropathy. Another expert who had not used the technology but was aware of it, did not consider it to be superior to monofilament. Finally one expert was interested in using Neuropad as a simple way to detect small fibre neuropathy in non-diabetic patients attending their neurology clinic.

- Two experts considered the technology to be a minor variation on existing technologies, 2 it a significant modification of an existing technology, and 4 that the technology is thoroughly novel

- There were uncertainties and differences in expert opinion as to the most appropriate use of the technology. Mostly commonly they saw its role as an adjunct to existing technologies and foot examinations where a diagnosis of neuropathy was uncertain, and in patients who could not interact with existing tests (e.g. those with cognitive impairment)

- Monofilament testing was the most commonly cited comparator. Other commonly cited comparators were neurothesiomenter and sympathetic skin response.

- Possible patient benefits identified included detecting neuropathy in patients unsuited to monofilament, providing earlier evidence of foot problems, and the ability to use it in the patient's home.

- Reductions in foot problems (ulcerations and amputations) were considered appropriate measures to determine the effectiveness of the treatment. The evidence for these benefits was considered to be limited to moderate.

- Possible benefits to the healthcare system were the ease of the test, ability to be performed in the patient's home, and potential to save money. Again the evidence for this was considered to be limited to moderate.

- The need for facilities and training to ensure the effective use of the technology was considered to be nil to minimal.

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- The majority of experts were of the opinion that NICE guidance on this technology would be useful

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# Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

- Diabetes UK
- Diabetes UK considered that if Neuropad could be shown to reduce the number of people who develop foot ulceration it would be of interest, but this would need to be proven in a clinical trial. It also noted that Neuropad has the potential to enable a faster diagnosis which is less open to interpretation than existing tests
- Diabetes UK identified people with physical disabilities, communication and language difficulties, learning difficulties, and mental health problems, as subgroups of patients who could benefit from the technology. These patient groups were also identified as having equalities issues that required special consideration.
- Possible disadvantages of the test were cited as being limited but identified as the need for training of healthcare professionals to ensure a correct diagnosis, and uncertainty on how the technology performs on different foot skin quality, such as on calluses.
- The increased cost of the technology compared to existing tests, was identified as an obstacle to its adoption. To overcome this there would need to be study evidence showing that this could be offset by potential benefits from earlier detections such as reductions in foot amputations and associated costs.

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# Appendix D: decision problem from scope

## *Claimed benefits*

The benefits to patients for Neuropad claimed by the company are:

- A simple test that can be done at home by the person with diabetes or in a clinic by a healthcare professional

- A colour-change objective result in 10 minutes that is easy to interpret

- Non-invasive, painless and safe

- Detection of neuropathy earlier than 10 g monofilament and vibration tests which is useful in identifying people with diabetes at the greatest risk of neuropathy.

The benefits to the healthcare system claimed by the company are:

- An inexpensive, simple to interpret objective test, with results obtained in 10 minutes that are recorded on the device

- No expertise, specialist equipment or staff needed to carry out the test: no expert intervention needed until the patient at risk is identified and followed up

- The test can be done at home by the patient, so no clinic appointments needed

- Detects neuropathy earlier than monofilament and vibration tests, so useful for the early identification of people with diabetes who are at the greatest risk of neuropathy.

The sustainability benefits claimed by the company are:

- A low carbon footprint with no energy use, no need for clinic visits or support staff

- No missed appointments as the test can be done at home and the results can be sent to a healthcare professional, electronically or by post.

| **Final scope issued by NICE** | |
|---|---|
| | |

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| Population | People with diabetes undergoing routine foot-care checks by health care workers in primary and secondary care settings and/or undertaking a DPN self-test in the home |
|---|---|
| Intervention | Neuropad |
| Comparator(s) | • 10 g monofilament<br>• Other sensation tests used in primary care (e.g. Vibratip, Neurotip, tuning fork, biothesiometer, Ipswich Touch Test)<br>• Standard neuropathy scoring systems used in primary care (e.g. Neuropathy Disability Score)<br>• Specialist small fibre neuropathy tests used in secondary care (nerve conduction tests, intraepidermal nerve fibre density biopsy, quantitative sudomotor axon reflex test (QSART), Sudoscan, corneal confocal microscopy, NC-stat DPN check)<br>(see also 'Cost analysis' below) |
| Outcomes | The outcome measures to consider include:<br>• Sensitivity and specificity in identifying diabetic peripheral neuropathy (DPN) compared to reference standard (standard neuropathy scoring or specialist secondary care tests)<br>• Patient experience and ease of use by patients and clinicians<br>• Reliability and reproducibility of use by patients and clinicians<br>• Total time to carry out test and obtain result<br>• Rates of GP surgery or hospital attendance<br>• Incidence of foot ulceration and/or amputation<br>• Device-related adverse events. |
| Cost analysis | Comparator(s): Costs will be considered from an NHS and personal social services perspective.<br>The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.<br>Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed. |
| Subgroups to be considered | • People in community settings<br>• People with communication difficulties or cognitive impairment |
| Special considerations, including those related to equality | Diabetes is a chronic condition that is covered under the Equality Act 2010. DPN is more common with increasing age and men may develop DPN earlier than women, but neuropathic pain causes more morbidity in women than in men. More secondary complications from DPN have been shown to occur in people of Hispanic or African American family origin.<br><br>The Neuropad test may be easier to use for people with communication difficulties, as it is an objective test that does not require assessment of subjective patient responses, unlike the vibration tests. This may allow for improved detection of diabetic neuropathy in children, people with mental health disabilities or people who have problems communicating. People with visual |

| | | |
|---|---|---|
| | impairments may need help to administer the Neuropad, so self-testing at home may not be possible in this subgroup. | |
| Special considerations, specifically related to equality issues | Neuropad is contraindicated for people with cobalt, nickel or chrome sensitivities and should not be placed on skin that is badly cracked, or has local inflammation or open wounds. | |
| | Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics? | No |
| | Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality? | No |
| | Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance? | No |

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