NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

Neuropad for detecting early diabetic peripheral neuropathy

The National Institute for Health and Care Excellence (NICE) is producing guidance on using Neuropad for detecting early diabetic peripheral neuropathy in the NHS in England. The medical technologies advisory committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the public. This document should be read along with the evidence base (see Sources of evidence considered by the committee).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Note that this document is not NICE's final guidance on Neuropad for detecting early diabetic peripheral neuropathy. The recommendations in section 1 may change after consultation. After consultation the committee will meet again to consider the evidence, this document and comments from public consultation. After considering these comments, the committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the medical technologies evaluation programme process guide and medical technologies evaluation programme methods guide.

Key dates:

- Closing time and date for comments: 17:00 20 December 2017

Issue date: November 2017

- Second medical technologies advisory committee meeting: 16 February 2018

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

1 Draft recommendations

1.1 The case for adopting Neuropad to detect early diabetic peripheral neuropathy is not supported by the evidence. There is limited evidence for its effectiveness, and no published evidence to support its use in patients who are likely to benefit most from its use, such as those unable to engage with or access conventional testing. The clinical benefits of detecting early diabetic peripheral neuropathy are uncertain but merit further research.

1.2 Cost modelling is uncertain because of the uncertainties in the evidence of clinical effectiveness, but suggests that using Neuropad costs more than conventional testing with a 10 g monofilament. This is mainly because of the cost consequences of the high rate of false-positive results associated with Neuropad.

Issue date: November 2017

2 The technology

Description of the technology

2.1 Neuropad (TRIGOcare International) is a point-of-care test for use in people with diabetes. The test detects sudomotor dysfunction (inadequate sweat production), which may indicate that a person is in the early stages of developing diabetic peripheral neuropathy (DPN). The 10-minute test is non-invasive, and involves applying a single-size plaster to the sole of the foot. The plaster contains cobalt chloride, which changes colour as it absorbs sweat. The colour changing from blue to pink indicates normal sweat production and implies preserved autonomic nerve function. If the plaster stays blue or does not turn fully pink, it is assumed that there is reduced sweating which carries with it 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 can be used either as a standalone test or in conjunction with other standard sensory neuropathy testing.

2.2 Neuropad is a class I diagnostic device. The cost of Neuropad stated in the company's submission is £7.28 (excluding VAT).

2.3 The summary claimed benefits of Neuropad in the case for adoption presented by the company are that it:

- is simple and can be done at home by the person with diabetes or their carer, or in a clinic by a healthcare professional
- is non-invasive, painless and safe
- provides results in 10 minutes that are easy to interpret

- can detect DPN earlier than monofilament and vibration tests, so is useful for the early identification of people at the greatest risk of complications.

Current management

2.4 NICE's guideline on diabetic foot problems recommends that adults with diabetes should have a risk assessment for diabetic foot problems at diagnosis, at least every year thereafter, whenever foot problems arise and at the time of any admission to hospital. During the risk assessment, both feet should be examined for any risk factors, including manifestations of DPN, which should be tested using a 10 g monofilament as part of a foot sensory examination. If DPN is detected, a person's risk is classified as being moderate or high (depending on the presence or absence of other comorbidities). This should trigger referral to a foot protection service and more frequent subsequent foot assessments.

2.5 The NICE guideline does not refer to testing for sudomotor function as part of detecting DPN, but sensory testing in primary care is done using tuning forks, a biothesiometer or Neurotip. NICE medical technologies guidance on VibraTip for testing vibration perception to detect DPN states that the technology shows potential but more research is needed.

3 Evidence

Summary of clinical evidence

3.1 The evidence for Neuropad assessed by the external assessment centre (EAC) comprised 18 studies, of which 13 were full text articles and 5 were abstracts. Of the 18 studies, 17 investigated the diagnostic accuracy of Neuropad against a reference standard

and 1 reported its ability to predict the risk of diabetic foot ulceration. In addition to examining diagnostic accuracy, 1 study looked at the reproducibility of results when using Neuropad and 3 assessed the association between Neuropad testing and developing foot ulcers. The most common reference standard used was the neuropathy disability score. All the studies were prospective observational, cross-sectional or longitudinal cohort studies. For full details of the clinical evidence, see section 3 of the assessment report.

EAC's analysis of the clinical evidence

3.2 The EAC considered that the 2 published UK studies (Ponirakis et al. 2014 and Quattrini et al. 2008) were fully relevant to the scope. The EAC also did a meta-analysis of 5 diagnostic accuracy studies that used a neuropathy disability score of 5 or more as the reference standard: Freitas et al. 2009, Kamenov et al. 2010, Liatis et al. 2007, Manes et al. 2016 and Tentolouris et al. 2008.

3.3 The EAC concluded that Neuropad may be more sensitive in detecting DPN than conventional 10 g monofilament testing, but it is less specific. Furthermore, it stated that detecting early DPN may be of limited clinical benefit because the current care pathway includes steps only after detecting moderate or advanced DPN.

Summary of economic evidence

3.4 No relevant published economic evidence was identified by the company or EAC. The company submitted a Markov model with 2 comparisons: Neuropad testing compared with 10 g monofilament testing, and Neuropad testing compared with Neuropad testing then 10 g monofilament testing. The time horizon of the model was 3 years. The EAC made a number of changes, including:

adding the implications of false-negative and false-positive results; adding a death state; extending the time horizon to 10 years; and adding a third comparison of Neuropad testing with no testing. For full details of the economic evidence, see section 4 of the assessment report.

EAC's analysis of the economic evidence

3.5 The EAC disagreed with a number of the sources used to generate parameter values in the company's model. It also noted discrepancies between the values used in the model and those quoted in the referenced sources. Moreover, the EAC considered the cost of 10 g monofilament testing in the model had been overestimated because it included the cost of the reusable holder. For full details of the EAC's changes to the company's economic model, see sections 4.2 and 4.3 of the assessment report.

3.6 Results from the EAC's revised model showed that Neuropad testing incurs additional cost compared with all other comparators:

- £775 per patient compared with 10 g monofilament testing
- £1,075 per patient compared with Neuropad testing then 10 g monofilament testing
- £1,792 per patient compared with no testing.

The EAC did sensitivity analyses which showed that Neuropad testing alone was not cost saving in any considered scenario.

4 Committee discussion

Clinical effectiveness

4.1 The evidence for the diagnostic accuracy of Neuropad comprises longitudinal observational studies that mainly compared testing in terms of neuropathy scoring systems (most commonly the

neuropathy disability score) when diagnosing DPN. The committee was aware that the EAC had rejected the study by Tsapas et al. (2014, a meta-analysis identified by the company) because of overlapping populations in the studies included and differences in the reference standards used, and had instead done its own meta-analysis. The committee noted that the results from the EAC's meta-analysis showed that Neuropad has a sensitivity of 89.4% (95% confidence interval [CI] 83.2 to 93.5) and a specificity of 60.3% (95% CI 50.9 to 69), when using a neuropathy disability score of 5 or more as a reference standard. Based on this, the committee concluded that Neuropad demonstrates good sensitivity but poor specificity as a diagnostic test for DPN. Furthermore, although no direct comparative data are available, Neuropad testing appears to be less effective as a diagnostic test for DPN than 10 g monofilament testing. The committee concluded that the current evidence for Neuropad is insufficient to support its effectiveness as an alternative test to 10 g monofilament for DPN.

Pathway positioning

4.2 The clinical experts advised the committee that patients with diabetes are offered foot checks every year, during which physical examination, 10 g monofilament testing and other vibration testing are used to test for DPN and therefore the clinical risk of future complications. The clinical experts explained that patients identified with evidence of DPN and at moderate or high risk of foot complications are then referred to community podiatrists for ongoing foot care.

4.3 The clinical experts explained that Neuropad and 10 g monofilament test different nerve fibres and functions: Neuropad testing detects sudomotor dysfunction, which is a feature of small

fibre and early DPN, whereas 10 g monofilament testing detects the loss of fine touch, which is a feature of later DPN. They explained that it is uncertain how well autonomic testing (such as sudomotor dysfunction) predicts neuropathy, so it is not included in DPN scoring systems. This means that it would be difficult to understand, on the basis of current evidence, how Neuropad testing may affect risk assessment and referral practice. For example, clinicians may still want to use 10 g monofilament testing to confirm DPN, and Neuropad would not replace it on the basis of the current evidence. Furthermore, the clinical experts advised that a positive Neuropad test alone would not lead to a change in management, because it would not alter the current definition of risk status in a patient with diabetes. A patient diagnosed with early DPN may be offered more attentive foot care, but it is unclear to what extent this may lead to beneficial clinical consequences. As a result, the committee concluded that further research to better understand the possible benefits of detecting early DPN, and on the best way of managing early DPN when it is detected, would be helpful.

Patient selection

4.4 The clinical experts explained that Neuropad may be particularly beneficial for use in patients who have difficulty in engaging with testing for DPN. Monofilament testing requires the patient to confirm when they feel a fine touch on their foot or toes, but some people with cognitive impairment or who struggle to communicate may find this difficult. The clinical experts estimated that between 5% and 10% of patients with diabetes may have difficulty engaging with 10 g monofilament testing for these reasons. The committee acknowledged that Neuropad testing does not require the same level of patient engagement and therefore may be of

particular value in these patients, but there is no published evidence to support this.

4.5 The committee also heard that some patients such as older and frailer people may not be able to easily access foot clinics. The clinical experts explained that type 2 diabetes, which accounts for 90% of all diabetes, is much more common in older people. Many of these patients do not always attend their yearly foot checks and so do not have the benefit of foot care programmes. The clinical experts also explained that DPN can be prevented and sometimes reversed if detected early, so limited access to regular testing may increase the risk of DPN in a vulnerable patient group. The committee acknowledged that a test such as Neuropad, which can be done easily in the community, may be of particular value to people with limited access to foot clinics. However, it also noted that there is currently no published evidence available to support this.

NHS considerations

4.6 The clinical experts stated that Neuropad could be considered a potential part of a community-delivered DPN detection and management service. However, they acknowledged that for this to be successful, changes would be needed to other important elements of delivering community healthcare to people with diabetes. Having considered the existing deficiencies in DPN detection and foot care services, the committee concluded that, on the basis of current evidence, addressing these deficiencies would likely be more beneficial than introducing the use of Neuropad testing in the community.

4.7 The committee considered the importance of foot preparation before Neuropad testing in order to ensure a reliable result. It

heard from the clinical experts that the foot needs to be completely dry and that the test strip not be placed on calluses or dry skin for the result to be meaningful. It concluded that instructions would need to be worded clearly to avoid misleading results if Neuropad testing were introduced into the community.

Cost savings

4.8 The committee noted the differences between the company's and EAC's revised cost models and their base-case estimates. It agreed with the EAC's changes and concluded that the revised model most accurately represented the cost consequences of adopting Neuropad.

4.9 The committee noted that Neuropad's low diagnostic specificity (based on the evidence presented) means that its use alone would increase the rate of false-positive results in DPN testing. The clinical experts explained that patients with a positive Neuropad test result may not be referred to a specific foot care programme, but the committee was concerned about the potential cost and clinical consequences of a higher rate of mistaken DPN diagnoses. It observed that a positive result with Neuropad would probably lead to further 10 g monofilament testing for confirmation. The committee understood that the results for this strategy in the model should be treated with caution, because the EAC model assumed that the 2 tests were done completely independent (that is, the sensitivity and specificity of the 10 g monofilament test were not affected by the results of the Neuropad test). The committee was also aware there was no evidence for such a testing approach. It concluded that the cost modelling for Neuropad is uncertain, but it is likely that Neuropad testing alone is cost incurring compared with conventional testing with a 10 g monofilament.

Potential research

4.10 In its assessment report, the EAC identified a number of possible priorities for future research on the comparative effectiveness of Neuropad against monofilament testing, and on the effectiveness of foot care programmes. The clinical experts also highlighted areas for future research that could be considered. They described the value of a multicentre, longitudinal study with at least 5-years' follow-up, comparing how well point-of-care testing strategies (including Neuropad) predict future diabetic complications, using a gold standard (such as the neuropathy disability score). The experts also described a potential community-based study that could explore the use of Neuropad in detecting early DPN and improving access to DPN diagnostic and treatment services.

4.11 The committee considered that research into the wider benefits of detecting early DPN and how to address the deficiencies in the care pathway would be most valuable, but acknowledged that these are issues beyond the scope of this assessment. Such research would also help to confirm the promise, or otherwise, of Neuropad in the early detection of DPN.

Peter Groves
Chair, medical technologies advisory committee
November 2017

7 Committee members and NICE project team

Committee members

This topic was considered by the medical technology advisory committee which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal) and a technical adviser.

Neil Hewitt
Technical analyst

Bernice Dillon
Technical adviser

Jae Long
Project manager

ISBN: