National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT318 Neuropad for detecting early diabetic peripheral neuropathy

Consultation comments table

Final guidance MTAC date: Friday 16 February 2018

There were 26 consultation comments from 6 consultees:

- 1 public
- 1 company
- 1 private sector professional
- 2 NHS professionals
- 1 other

The comments are reproduced in full, arranged in the following groups (**some comments contain multiple issues and have been split**):

- Benefit of early detection of DPN/ Neuropad testing
- Appropriateness of using monofilament as a comparator
- Benefit in vulnerable groups/ those unable to engage with existing tests
- Miscellaneous

Benefit of early detection of DPN/ Neuropad testing

Comment Number	Consultee ID	Role	MTCD Section	Comment	NICE / EAC response
1	1	Public	1.1	If there is uncertain clinical benefit in the early detection of DPN (that is, earlier than can be achieved by other tests), then there is no need for Neuropad. What is the basis for making this statement? Surely early detection of anything is beneficial. See also 4.5	Thank you for your comment. The committee considered that there were potential benefits from the detection of pre-clinical DPN but they were uncertain. The committee considered that research into the wider benefits of detecting pre-clinical 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. The committee considered this comment carefully and decided not to change this section but to replace early DPN with pre-clinical DPN for clarity.
2	1	Public	4.5	DPN can be prevented and sometimes reversed if detected early (5th line) ' this statement completely contradicts the comment in 1.1 which stated that the clinical benefits of early detection of DPN are uncertain. Section 4.5 is quite positive about the usefulness of Neuropad for older and frailer patients but then seeks to negate this view with the final sentence about the lack of published evidence. This is a common theme in the report; commenting on the lack of published evidence for things that are clearly obvious and, in my opinion, reflects the unbalanced make-up of the team that compiled the report.	Thank you for your comment. The committee was aware of the benefits of the gylcemic control and received expert advice about the recent evidence showing the possibility of prevention and in somecases arrest of DPN when detected at the pre-clinical stage. The committee discussed the phrase ‘sometimes reversed’ in section 4.5 with the experts and decided to remove it.. Section 4.5 considers one aspect of the committee’s discussion, the

Comment Number	Consultee ID	Role	MTCD Section	Comment	NICE / EAC response
					potential value of this technology to a vulnerable patient group who do not currently access foot clinics. Section1.1 is the committee's recommendation based on consideration of the company's case for adoption, the associated evidence and the committee discussions and thus should be read in the context of the whole document. The committee considered this comment carefully and decided not to change this section but to remove sometimes reversed.
3	1	Public	4.3	I suggest the authors read 4.5 in their own report - 'The clinical experts also explained that DPN can be prevented and sometimes reversed if detected early'. If that isn't a benefit then what is? 4.3 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. Neuropad is not intended as a replacement for the monofilament test. This is a repeated mis-understanding by the report authors. 4.3 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. It's rather disturbing to think that clinical management is rigidly guided by out of date definitions. If new technology can improve	Thank you for your comment. In sections 1, 4.3 and 4.5 of the guidance the committee acknowledges that the benefits of detecting pre-clincal DPN are unclear but merit further research. These sections also explain that the benefits of detecting pre-clinical DPN are unproven for Neuropad, and it is unclear how they would be realised in the existing care pathway. The committee recognised the importance of research into the benefits of detecting preclinical DPN and how to address the deficiencies in the care pathway in section 4.11. The committee considered this comment carefully and decided to updates sections 1, 4.3 and 4.5 to

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				management decisions, then existing guidelines need to be updated accordingly. This is a deeply worrying situation.	improve the clarity of their considerations.
4	1	Public	-	There is also a very significant contradiction - the report mentions several times that there is doubt as to whether early detection of DPN is clinically beneficial, casting doubt on the usefulness of Neuropad's ability to do this. However, and this is a direct quote - The clinical experts also explained that DPN can be prevented and sometimes reversed if detected early. That certainly seems like a potential clinical benefit. I have seen the product and was extremely impressed with its ease of use and categorical colour change. It is a true innovation and patients with diabetes deserve to have it available.	Thank you for your comment. Please see the response to comment 2. The committee considered that there were potential benefits from the detection of pre-clinical DPN but they were uncertain. The committee considered that research into the wider benefits of detecting pre-clinical DPN and how to address the deficiencies in the care pathway in section 4.11. The committee considered this comment carefully and decided to update sections 1 and 4.5 to improve the clarity of their considerations.
5	3	NHS Professional	-	My understanding of what Neuropad should be used for is as follows: A screening tool for the detection of early diabetic neuropathy based on its ability to detect sudomotor dysfunction which is an early manifestation of autonomic neuropathy (small fibre problem) which is part of the neuropathic process. It is not designed to be used as a replacement for the 10g monofilament test (currently advocated by NICE for the detection of neuropathy). The added value of Neuropad is: 1 ' a positive Neuropad result when used with the 10g monofilament which if negative provides a ‘warning signal' that early changes in nerve function are occurring and that aspects of	Thank you for your comment

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				future diabetes care (surveillance and monitoring) should be influenced to minimise further damage and improve clinical outcomes ' in essence, it provides an opportunity for early intervention.	
6	3	NHS Professional	-	My other specific comments are: 1.1 I was concerned to see that MTAC place no value on the early detection of nerve damage in someone with diabetes; surely, even in the absence of well-designed clinical trial evidence (probably because of exclusion of older people) there is value of early detection (as stated by clinical experts) as it assists in the care plan, allows a greater focus on preventative care, and supports those who might not be able to attend regularly for feet examination ' reversing early damage can have a potentially major impact on a person's life in terms of their future quality of life and well-being.	Thank you for your comment Please see response to comment number 1
7	5	Company	-	2. Concerning the validity of testing for diabetic peripheral neuropathy (DPN), the purpose of the Neuropad guidance is not to reappraise the utility of DPN testing and therefore this is and should be completely outside the scope. In fact the validity of DPN testing has already been appraised in NICE guidance NG19 where monofilament was recommended, may we point out, despite the lack of clinical evidence for its adoption and use. The draft NICE Neuropad guidance recommendations contradict much of those of the NG19 recommendations and considerations in this area, and significantly the NG19 guideline development group (GDG) and committee is made up of diabetes foot experts and not principally analysts, healthcare economists and non-foot care specialists. We feel that it is not at all helpful to the wider diabetes community to face conflicting NICE guidance on this important issue which may we remind NICE is devastating for patients with diabetes and extremely costly to our NHS. https://www.nice.org.uk/guidance/ng19/evidence/full-guidance-pdf-15672915543 In particular, we also wish to draw the committee’s attention to	Thank you for your comment The development of this guidance is focussed on the potential patient and system benefits of using Neuropad. The committee considered there was insufficient evidence to demonstrate the benefits of using Neuropad in the current NHS system. It recognised that the benefits of detecting pre-clinical DPN were uncertain but merited research (see sections 1.3 and 4.11), and heard from experts that NG19 did not deal with these patients but those with later stage DPN In the cost modelling the company and the EAC models compared Neuropad

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				Table 17 on page 63 of NG19 – final - which states: 'The GDG considered the predictive accuracy of the different scores and tools. The group agreed that they would be prepared to accept lower specificity in exchange for higher sensitivity in order to ensure all patients at risk are included in the correct risk categories. The group felt that false positives were preferable to false negatives given the impact that foot ulcer can have on a person's life." The EAC has drawn attention to the number of false positives that may occur with Neuropad testing yet as stated above false positives are 'preferable' to the GDG experts in diabetic foot care who developed NG19. Moreover, the draft Neuropad guidance states that: '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.' Again, this is because the EAC have compared monofilament with Neuropad which are two completely different tests. To make ourselves abundantly clear, the following is an extract from one of our submitted evidential studies (Papanas et el 2011): 'Neuropad is a sweat test and detects sudomotor dysfunction as a result of small fibre dysfunction in diabetic patients and indicates both functional and structural denervation in the feet of diabetic patients. Neuropad testing response strongly correlates to other tests for small fibre neuropathy like IENFD. Neuropad is not a test of large fibre damage as present in sensory neuropathy. Small fibre damage may precede large fibre damage. But Neuropad is not comparable to monofilament and doesn't detect large fibre neuropathy. 'The invariably lower specificity than sensitivity is due to the fact that Neuropad is abnormal in about one third of patients with clinical examination negative for neuropathy [using tests for sensation]. It has been proposed that this result may be ascribed	with 10 g monofilament and also explored the scenario of combining the Neuropad and 10 g monofilament tests. However the EAC highlighted that there is no evidence on which to base the performance of a combination test strategy. The existing cost models combine the independent results of each test. The committee decided not to change the recommendations but to amend sections 1 to improve the clarity.

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				to earlier diagnosis of neuropathy by means of Neuropad® before conventional clinical signs become positive.' Neuropad is not intended as a replacement for the monofilament test. For reference, our de novo healthcare economic model actually modelled three different combinations: Neuropad alone, 10g SWME alone and Neuropad and 10g SWME together. Our model showed that using Neuropad and 10g SWME together saved £9.75 per patient and reported QALY gains compared to monofilament alone.	
8	5	Company	-	8. (a) The draft guidance and report states that 'The clinical benefits of detecting early diabetic peripheral neuropathy are uncertain but merit further research.' We find this very surprising as it implies that early detection of disease isn't necessarily useful which flies in the face of accepted medical and public health principles and practice. However, the clinical experts appointed by NICE and who advised the EAC 'explained that DPN can be prevented and sometimes reversed if detected early.' This seems entirely contradictory and it would appear that expert clinical opinion is not only being ignored but effectively reversed. We now wish to draw to your attention the two landmark studies in diabetes: the Diabetes Control and Complications Trial (DCCT) (n=1441) and the United Kingdom Prospective Diabetes Study (UKPDS). In the DCCT which is a highly regarded independent study in patients with Type 1 diabetes the investigators found that 'Intensive therapy during the DCCT significantly reduced the risk of DPN and CAN [cardiovascular autonomic neuropathy] at DCCT closeout (64% and 45%, respectively, $P < 0.01$). The prevalence and incidence of DPN and CAN remained significantly lower in the DCCT intensive therapy group compared with the DCCT conventional therapy group through EDIC year 13/14.' And that 'The persistent effects of prior intensive therapy on neuropathy measures through 14 years of EDIC largely mirror those observed for other diabetes complications. DCCT/EDIC provides important information on the influence of glycemic control, and the clinical course of diabetic neuropathy, and, most important,	Thank you for your comment. Please see response to comments 1,2 and 4. The committee was aware of the benefits of the gylcemic control and received expert advice about the recent evidence showing the possibility of prevention and in somecases arrest of DPN when detected at the pre-clinical stage. The committee considered that benefits of detecting pre-clinical DPN merit further research. b) The study by Tentolouris et al. 2008 was considered by the EAC in the assessment report. It noted that this study assessed the reliability of the Neuropad, finding that there was a 90.3% overall agreement between the patient and the heathcare professional scoring. However, the study provides no evidence that this translates to better clinical outcomes for the patient or benefit for the healthcare system. The committee considered that there

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				on how to prevent neuropathy in type 1 diabetes.' Neuropathy and Related Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study http://care.diabetesjournals.org/content/37/1/31 In the landmark prospective observational study UKPDS study (n=4585) the investigators found that 'The incidence of clinical complications was significantly associated with glycaemia. Each 1% reduction in updated mean HbA1c was associated with reductions in risk of 21% for any end point related to diabetes (95% confidence interval 17% to 24%, P<0.0001), 21% for deaths related to diabetes (15% to 27%, P<0.0001), 14% for myocardial infarction (8% to 21%, P<0.0001), and 37% for microvascular complications (33% to 41%, P<0.0001). No threshold of risk was observed for any end point.' DPN is in fact a microvascular complication of diabetes. The investigators concluded that 'In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycaemia. Any reduction in HbA1c is likely to reduce the risk of complications, with the lowest risk being in those with HbA1c values in the normal range (<6.0%).' Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC27454/ (b) To reiterate, the draft Neuropad guidance report states that '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.' This is an incorrect statement. In fact there is a published study by Professor Tentolouris and colleagues and this was provided to NICE in our original clinical submission. It is important evidence and the study was published in a high impact	is no published evidence on the benefits of Neuropad specifically in a community setting. It refers to a community-based study as a potential research area in section 4.10. The EAC noted that the Tentelouris 2008 study noted that 20% of the patients who used Neuropad at home, particularly those who are older or had kinetic and/or visual impairment reported that they requested help for self-testing. The EAC reviewed the studes referred to in this comment. It did not identify any new relevant evidence. Some studies were already part of the assessment and others were outside the scope of the assessment. The committee considered this comment and decided to amend section 1 and section 4.7 to improve the clarity of its considerations.

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				diabetes journal, Diabetes Care. The study (n=156) was 'To evaluate the relative reliability between patient and health care provider of the Neuropad test in the diagnosis of peripheral neuropathy and the ease of use of the test.' In other words, the question was how well did home testing correlate with clinic based testing? The primary outcomes were: 'The agreement between patient and health care provider in the evaluation of Neuropad as normal (n = 92) or abnormal (n = 49) was 90.3%. The k statistic to measure overall agreement between patient and health care provider as normal or abnormal was very good (0.88 [95% CI 0.85–0.91]). 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 Neuropad 10.0 (9.0–10.0), and easiness to evaluate the test as normal or abnormal 10.0 (8.0–10.0). Patients were asked to report whether they required any help for self-examination. A total of 32 patients (20.5%) reported that they requested help to perform self-testing. 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 Neuropad 10.0 (9.0-10.0), easiness to use Neuropad 10.0 (9.010.0), and easiness to evaluate the test as normal or abnormal 10.0 (8.0-10.0).' Tentolouris N, Achtsidis V, Marinou K, Katsilambros N. Evaluation of the self-administered indicator plaster Neuropad for the diagnosis of neuropathy in diabetes. Diabetes Care. Feb 31(2):236-7 (2008) We would also like to point out that our new UK patient instructions for the application of the Neuropad test at home are NHS compliant and are easy to follow for people who can read plain English. In addition, we have also commissioned a voiced and sub-titled animation for patients to show them how the test is applied and conducted at home and what do with their results. This animation could easily be translated into other languages and is compatible for all computer-based and smart phone devices and social media applications. In addition, the simplicity of conducting the test and the	

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				importance of the categorical colour charge is not given sufficient merit. Monofilament testing cannot be carried out by a person without trained help.	
9	5	Company	-	6. The following is also important additional evidence. It highlights why Neuropad detects neuropathy earlier than the neuropathy disability score (NDS) because the NDS does not assess autonomic function. Malik R, Veves A, Tesfaye S, Smith G, Cameron N, Zochodne D, Lauria G; on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. Small Fiber Neuropathy: Role in the diagnosis of Diabetic Sensorimotor Polyneuropathy Res Rev. 2011 Jun 22. doi: 10.1002/dmrr.1222.	Thank you for your comment. The EAC reviewed this study and concluded that it is out of scope of the assessment. The committee considered this comment and decided not to change the guidance.
10	5	Company	-	12. The following is an extract from a recently published paper: 'The lack of programs designed to prevent/eliminate DFUs is troubling, this in spite of the known impact these DFUs have on amputation requirements, increasing healthcare costs, and overall quality of life. The paucity of such programs, even in larger academic healthcare centers, may be related to the perception of a clear lack of economic benefit. Studies have been few and far between, and prior Markov models have not demonstrated a potential for overall savings, where cost effectiveness has been shown. The difference in this study from past offerings is this one looked at differing degrees of effectiveness (risk reductions ranging from 5% to 25%), assigning costs to each and determining a likely cost threshold for determining the need for preventive measures. One important limitation stated by the authors was separating low-risk from moderate- to high-risk patients, which may cause those higher risk populations to lose favor due to increased costs of prevention. An examination of the overall population as a whole would have been warranted to help support better utilization of prevention of diabetic foot ulcers and subsequent complications. If little else, there is certainly a need to encourage preventive programs as a means to reduce these high costs of care.' Barshes NR, Saedi S, Wrobel J, Kougias P, Kundakcioglu OE, Armstrong DG. A model to estimate cost-savings in diabetic foot ulcer prevention efforts. J Diabetes Complications. 2017;31(4):700-7. Epub 2017/01/21. doi:	Thank you for your comment The EAC has highlighted issues about foot care programmes in section 7 (Implications for research) of the assessment report: "The evaluation has highlighted a lack of evidence on the effectiveness and cost-effectiveness of foot care programmes. An intuition that such preventative care will reduce costs does not appear to be borne out by the modelling undertaken by the EAC. Given the scale of DPN an evaluation of the effectiveness and cost-effectiveness of foot care programmes is overdue." The cited paper (Barshes et al 2017) is a study on Diabetic Foot Ulcers done in the US, and does not involve any Neuropad evaluation and hence is not within scope for this assessment. The 17% prevalence refers to diabetic population and 2.4% refers to newly

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				10.1016/j.jdiacomp.2016.12.017. PubMed PMID: 28153676. We also wish to draw your attention to three important points contained in the above paper: · The prevalence of neuropathy the authors used (17%) is far higher than the one we applied in our de novo economic model (2.4%). · The costs the authors use are generally higher than the ones we used in our model however the EAC stated that our estimates were sometimes quite high. May we point out that the data we applied in our model were taken from the report written by Marion Kerr (2017) for Diabetes UK which are more up to date than the data used by the EAC. Kerr M. Diabeteic Foot care in England: an economic study. Insight Healthcare Economics on behalf of Diabetes UK, January 2017 https://digital.nhs.uk/article/1330/-Report-highlights-need-for-early-intervention-for-diabetic-foot-ulcers · The Authors highlight the need for prevention and early detection programmes. Neuropad supports them because it provides a means to detect diabetic neuropathy earlier than existing primary care tests that diagnose late.	diagnosed diabetics, which is more relevant for the model. Health care costs are usually high in US compared to UK, and the EAC has used costs that are more relevant to the UK setting. The EAC has acknowledged that Kerr (2017) is a reasonable source for UK health costs estimation but where more recent estimates (eg NHS reference costs) are available, the EAC has used those. The EAC has provided a rationale in its report where it has replaced the company's estimates with new estimates(see Resource identification, measurement and valuation section) The committee considered this comment and decided not to change the guidance.
11	6	Health professional (within NHS)	-	The EAC's meta-analysis demonstrates low specificity of 60.3% (95% CI 50.9 to 69) because this reflects the method used to diagnose 'DPN'. This is like comparing 'apples with oranges'. Using a neuropathy disability score (NDS) of 5 or more does not identify patients with early neuropathy, but those with moderate to severe neuropathy. Because Neuropad identifies small fibre and hence early neuropathy, this leads to the low specificity, because it will identify an abnormality in patients with a milder neuropathy who will not have an NDS >5. Hence the good sensitivity but poor specificity of Neuropad. The committee have therefore erroneously concluded that Neuropad testing is less effective as a diagnostic test for DPN than 10 g monofilament testing. The 10g monofilament detects advanced neuropathy i.e. NDS >5, with greater specificity as it correctly identifies those with advanced neuropathy as opposed to the Neuropad, which identifies early small fibre neuropathy. If	Thank you for your comment. The majority of the studies testing the diagnostic accuracy of Neuropad that align to the scope and were included in the assessment report used as a reference standard an NDS score equal or above 6. Specifically, 4 studies stated that they used ≥3 (Forth et al. 2010, Kamenov et al. 2010, Mendivil et al. 2016, Ponirakis et al. 2014), 2 studies used ≥5 (Liatis et al. 2007, Quattrini et al. 2008) and 5 used ≥6 (Aubert et al. 2013, Forth et al. 2010, Freitas et al. 2009, Kamenov et al. 2010, Manes et al. 2014) as 1 or multiple cut off thresholds. The

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				you were to use a reference test which identifies early neuropathy then the sensitivity of the 10g monofilament would be low and one would conclude that the 10g monofilament is not an effective diagnostic test for early DPN. The whole strategy of using the 10g monofilament to identify those with DPN is flawed as it actually identifies moderate to severe neuropathy and the 'high risk foot'. The cost-effectiveness of using the monofilament for DPN screening is also based on no clear evidence. It has been proposed that by using the 10g monofilament to identify those at 'high risk of foot ulceration', one can provide education and prevent ulceration/amputation. This assumption is however flawed and is based in consensus1 rather than evidence2. There is no evidence that educating patients at high risk of foot ulceration prevents foot ulceration/amputation3. This approach would be analogous to using a drop in visual acuity due to advanced retinopathy being adopted to assess early retinopathy, as opposed to digital retinal fundus screening which detects early retinopathy and has significantly reduced diabetes as the leading cause of blindness in working age adults in England. Similarly, if we were to use an eGFR of <30 and advanced nephropathy we would equally see no benefit in relation to progression to ESRF. We therefore employ ACR as a means to identify early incipient nephropathy. NICE need to reconsider the whole approach of what they are identifying in relation to neuropathy. If it is early neuropathy then there is irrefutable evidence that the 10g monofilament is not fit for purpose and Neuropad or alternative technologies such as corneal confocal microscopy4,5,6 should be considered. References 1. Edwards K, Borthwick A, McCulloch L, Redmond A, Pinedo-Villanueva R, Prieto-Alhambra D, Judge A, Arden N, Bowen C. Evidence for	threshold cut-off for NDS was unclear in 1 study (Marinou et al. 2005). The EAC reviewed all eligible studies in alignment with the scope in the assessment report and noted the following: • The studies that compared Neuropad against an NDS score ≥3 and ≥6 showed similar sensitivity and specificity for the two thresholds. • Tentolouris et al. 2014 reported that the adjusted odds ratio of NDS>6 versus NDS<6 for foot ulceration was 8.5 (CI 3.3-21.7). The odds ratio for foot ulceration was not increased significantly (p=0.09) in those having mild neuropathy (NDS 3-5) vs. those having no neuropathy, therefore, dismissing the claim that diagnosis of early stage neuropathy is predictive of future foot ulceration. • The EAC also highlighted that the monofilament was used as a comparator in two of the included studies not as a reference test. The EAC concluded that there is adequate evidence to support the claim that using a different NDS cut off will lead to improved specificity of the Neuropad and better clinical outcomes. The committee considered this comment and decided not to change the guidance.

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				current recommendations concerning the management of foot health for people with chronic long-term conditions: a systematic review. J Foot Ankle Res. 2017 Nov 22;10:51. 2. van Netten JJ, Price PE, Lavery LA, Monteiro-Soares M, Rasmussen A, Jubiz Y, Bus SA; International Working Group on the Diabetic Foot. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. Diabetes Metab Res Rev. 2016 Jan;32 Suppl 1:84-98. 3. Dorresteijn JA, Kriegsman DM, Assendelft WJ, Valk GD. Patient education for preventing diabetic foot ulceration. Cochrane Database Syst Rev. 2014 Dec 16;(12):CD001488. 4. Terkelsen AJ, Karlsson P, Lauria G, Freeman R, Finnerup NB, Jensen TS. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. Lancet Neurol. 2017 Nov;16(11):934-944. 5. De Clerck EE, Schouten JS, Berendschot TT, Kessels AG, Nuijts RM, Beckers HJ, Schram MT, Stehouwer CD, Webers CA. New ophthalmologic imaging techniques for detection and monitoring of neurodegenerative changes in diabetes: a systematic review. Lancet Diabetes Endocrinol. 2015 Aug;3(8):653-63. 6. Hossain P, Sachdev A, Malik RA. Early detection of diabetic peripheral neuropathywith corneal confocal microscopy. Lancet. 2005 Oct 15 21;366(9494):1340-3.	

Appropriateness of using monofilament as a comparator

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12	1	Public	3.6	A recurring error throughout the document ' Neuropad is not intended as a replacement for the monofilament test.	Thank you for your comment Section 3.6 compares Neuropad against a number of comparators which were specified in the scope and included in the companies submission.
13	1	Public	4.1	If no direct comparative data are available, then what is the basis for the statement that Neuropad 'appears to be less effective'? Also, as already stated, Neuropad is not an alternative test to the monofilament so this statement is incorrect and meaningless.	Thank you for your comment. The EAC review of the evidence demonstrates there is no direct head to head comparisons. The comparison was made against the neuropathy disability score, a commonly used reference standard
14	1	Public	-	I consider this to be a very poorly constructed report which perpetuates a significant error. The authors keep referring to Neuropad as a replacement for the 10g monofilament test, which it is not. This was made very clear in the initial submission so why is this so hard to understand?	Thank you for your comment. Monofilament is currently the test used in this group of patients and was considered an appropriate comparator in the scope which was consulted on, along with a number of other comparators.
15	5	Company	-	On behalf of the sponsor and the manufacturer we wish to raise the following important issues concerning the Neuropad draft NICE guidance and accompanying report: 1. The external assessment centre (EAC) have again used the wrong comparator. For clarity, Neuropad is not intended to replace monofilament but to complement it and this was stated correctly in the final NICE scope (see section 1, line 10). For reasons unknown to us this has been changed by the EAC without even prior discussion with and certainly without the agreement of the sponsor or manufacturer which for the record we would not have agreed to accept as it is an inappropriate comparator. This has led to the EAC coming to a series of wrong	Thank you for your comment. The comparators this assessment of Neuropad are specified in the scope. The EAC has noted in various sections of the assessment report that Neuropad is indicated as an adjunctive test to complement other standard diagnostic tests, which are administered by an appropriate healthcare professional. Therefore, routine testing (for example, using the monofilament) would still be carried

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				conclusions including those relating to false positives and the costs associated with them. This is completely unacceptable and has as a result led to the development of inadequate draft guidance concerning Neuropad. https://www.nice.org.uk/guidance/gid-mt513/documents/final-scope	out and the Neuropad test is an addition to the clinical pathway rather than a replacement of any component. In the cost modelling the EAC considered 3 main strategies :1) using Neuropad alone; 2) using monofilament alone; and 3) using monofilament on neuropathy positive cases after Neuropad testing. The committee considered this comment carefully and decided not to change the guidance.
16	3	NHS Professional	-	2. I am concerned that the draft NICE guidance on Neuropad appears to be at variance with the previously published NG19 recommendations, and that the draft guidance appears to suggest that Neuropad is being advocated as a replacement for the monofilament test although my understanding is that this is not the case and I wonder if at some stage during this evaluation process (e.g at the EAC stage), an error has occurred perhaps due to the continuing EAC's misunderstanding of the role of Neuropad? (I note this is incorrectly considered in 3.6, 4.1, 4.3) 4.1 I am rather concerned that the draft guidance makes the following conclusion: Neuropad testing appears to be less effective as a diagnostic test for DPN than 10 g monofilament testing and yet in the previous sentence, it states: Furthermore, although no direct comparative data are available, the point is that if there have been no comparative data, NICE are not entitled to say that one test is superior to another! Conclusions	Thank you for your comment 10 g monofilament is currently the test used in this group of patients and was considered an appropriate comparator in the scope which was consulted on, along with a number of other comparators. In their assessment of the evidence, the EAC had to focus on the comaprators presented in the evidence relevant to the scope. The sentence refers to the absence of comparative evidence and the observation is based on its comparison against NDS≥5 discussed in the same section

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				As a clinician that has had a significant focus on improving the well-being and diabetes care of older people with diabetes, and someone who recognises the high levels of vulnerability this population has to diabetic foot disease, I want to see tests/procedures that can also be utilised in those least able to care for themselves. I feel that the Neuropad test deserves an opportunity to be used within the NHS with NICE approval for the early detection of diabetic nerve damage in the feet.	
17	5	Company	-	5. We strongly disagree with the statement that 'Neuropad is less effective' than monofilament. How can this statement be made when the draft states that there are no comparable data? We can compare sensitivity and specificity values, for example, but they don't lead to the conclusion that Neuropad is less effective. Moreover, in our de novo economic analysis we provided the EAC with data on health gains in a three-year model: SWME alone reports 2.2898 QALYs per patient, Neuropad alone leads to 2.3213 QALYs per patient; and SWME together with Neuropad report 2.2903 QALYs per patient. In a recent paper published in the BMJ the durability of monofilaments was assessed. It found that monofilaments tend to fatigue with repeated use, and a 24 hour recovery period is recommended after 100 compression cycles. The paper also advises clinicians to replace a monofilament after three months of regular use. http://www.bmj.com/content/359/bmj.j5064	Thank you for your comment NICE generally adopts a cost-consequences approach for evaluating medical technology programmes (NICE 2011). For these methods, only the cost and resource consequences need to be modelled. Utilities need not be included to estimate the net benefit. The committee does consider QoL in its judgements on clinical effectiveness, where relevant evidence is available, but the technology needs to be cost saving. For this report, the EAC has considered only the cost of the technology and comparators and the resulting cost-savings. As there is uncertainty around the usage of 10g monofilament, the EAC used estimates from a previous MTEP assessment of VibraTipTM (Willits et al 2015). They estimate a monofilament to have a useful life of 200 patients before requiring replacement.

Benefit in vulnerable groups/ those unable to engage with existing tests

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18	1	Public	4.4	The first line Neuropad may be particularly beneficial for use in patients implies that the clinical experts do agree that Neuropad 'works'. What is the basis for the cited 5 to10% estimate in line 5? It seems quite low. Last line ' to decide whether using a sticking plaster at home is easier that going to a clinic hardly needs a clinical trial.	Thank you for your comment The estimate of between 5% and 10% of patients with diabetes having difficulty engaging with monofilament testing due to cognitive impairment or communication difficulties was provided by the experts who advised the Committee. The text in 4.4 has been amended to clarify that this percentage relates to the total population with diabetes.
19	3	NHS Professional	-	Reference to the Consultation: Neuropad for detecting early diabetic peripheral neuropathy - In development [GID-MT513] Expected publication date: 10 May 2018 I have read the draft guidance and feel that the true value and utility of Neuropad has been significantly underestimated and in fact, I am concerned that this guidance (produced by your MTAC committee at NICE) may not have received sufficient input/expertise from practising clinicians regularly working with people with diabetes and from my perspective, evidence of working with older vulnerable patients. For example, I would have to ask questions about the likely composition of such a group, e.g. was a working primary care physician (GP) or a actively working podiatrist members of the committee that met on Friday 20th October 2017? As a clinical academic I recognise the importance of supporting recommendations with a sound evidence base. Whilst I understand that Neuropad has been used in many clinical studies and a meta-analysis, I would think that the sponsor	Thank you for your comment Details of the committee and their specialisms can be found on our website. The committee was also advised by clinical experts who attended the meeting and had experience of the technology and this area of health care.

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				clearly recognises that further studies are generally needed such as practical observational study exploring the feasibility and clinical use/advantages of Neuropad in older community-dwelling patients with diabetes including those who do not regularly attend foot clinics. However, I also feel that the evidence base for the 10g monofilament is not as strong as this NICE guidance suggests and this tool clearly requires further evaluation. In fact, in NG19, the monofilament tool was selected despite a poor evidence base. Clinically, in my view, the monofilament test cannot be solely relied upon to diagnose diabetic peripheral neuropathy.	
20	3	NHS Professional	-	2 ' the Neuropad tool may be the only valid measure of nerve damage when a patient with diabetes has significant/severe communications difficulties, a history of dementia or mental health disease, severe frailty and care home residency ' these are substantial populations of people with diabetes* and should not be EXCLUDED from opportunities to have early intervention to maintain foot health (and who are unlikely to attend foot health clinics, see 4.5) ' otherwise, neglect of detecting early nerve damage can have devastating effects on their future quality of life. Exclusion from a procedure or test that can have some worthwhile benefit and is feasible to use in such a population (when other NICE-approved tests cannot be used) is an example of lack of equality and equity which I see as a major cause of concern! *Based on my clinical experience, audit information, research work, I estimate that in the community, as many as 25% of older adults with diabetes above the age of 70y would have a reduced ability to participate with an assessor in a comprehensive examination of feet, and in care homes (where 1 in 4 residents have diabetes based on my earlier work) about 40-50% of these would not be able to participate successfully (see 4.4). It is important to remember that diabetic neuropathy is one of the major risk factors for the development of foot ulcers which precede amputation and in an older person, can have	Thank you for your comment The committee considered this group of patients in its evaluation but noted that no evidence was presented for benefit in these patients. The committee also heard from the clinical experts that a positive Neuropad test alone would not currently lead to a change in management. The committee considerd it was unclear how the test would improve treatment without changes to the clinical pathway beyond the scope of this committee. Please see sections 4.3, 4.4, and 4.5 for further details. The committee considered this comment and decided to amend section 4.4 to clarify that the expert advisers patient estimate of 5% to 10% of patients have cognitive impairment or communication

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				devastating consequences on mobility, ability to self-care and quality of life. In addition, a person with diabetes may have many years of neuropathic damage being present before clinical signs become apparent or disabling ' this alone indicates that early detection of nerve damage might enable interventions (better foot care, blood glucose and lipids control, etc) to reduce the development of major symptoms ' I appreciate that the evidence is low but the good clinical practice element here is fundamental! It is also fundamental to appreciate that autonomic damage (as detected by the Neuropad) also contributes to the higher risk of foot ulcers (Vinik AL eta al, Diabetic neuropathy in older adults. Endocrinol Metab Clin North Am 2013; 42: 747-87	difficulties relates to the total population with diabetes.
21	5	Company	-	3. We wish again to draw to the attention of the MTAC committee the important vulnerable patient subgroup comprising people with communication and cognitive impairments who cannot respond to monofilament testing because the test is subjective and requires a patient response. This we regard as a major equality issue as these people cannot access the annual foot test which is specified in NICE guideline NG19. In addition, referral for those found to be at moderate/high risk is encouraged by a	Thank you for your comment. A number of population groups were identified by the scope as having potential special considerations for equality and they were discussed in the EAC's assessment report in page 27.

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				NICE quality standard, and this is so important that it is payment-incentivised for primary care doctors in the most recent Quality and Outcomes Framework (QOF). https://www.nice.org.uk/guidance/qs6/chapter/Quality-statement-5-Referral-for-adults-at-moderate-or-high-risk-of-diabetic-foot-problems In addition, see also https://www.nice.org.uk/standards-and-indicators/qofindicators/the-percentage-of-patients-with-diabetes-with-a-record-of-a-foot-examination-and-risk-classification-1-low-risk-normal-sensation-palpable-pulses-2-increased-risk-neuropathy-or-absent-pulses-3-high-risk-neuropathy-or-absent-pulses-plus-deformity-or-skin-ch	The committee considered the potential benefits of the use of Neuropad to people who are unable to access foot clinics in section 4.5. The committee considered this comment and decided not to change the guidance.

Miscellaneous

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22	1	Public	4.7	This is a superfluous comment which looks suspiciously like a further attempt to introduce aspects of negativity into the report. All medical devices need to have good instructions and existing Neuropad packaging already complies.	Thank you for your comment. Section 4.7 describes the committee considerations about the potential use of the technology in the community. The committee considered this comment and decided not to change the guidance.
23	2	Private Sector Professional	-	Clinicians at Shuropody have been using the Neuropad for some time in carrying out diabetic assessments. The feedback from other podiatrists has been very good, with a number of my colleagues impressed by its ease of use within a clinical setting and its accuracy at aiding a diagnosis of autonomic neuropathy. This has enabled the team to commuicate with the patients GP quickly to highlight the patients risk of neuropathy and managing the patients needs accordingly. Overall, an excellent diagnostic tool!	Thank you for your comment

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24	4	Healthcare Other	-	People with diabetes are mainly in charge of their own healthcare, with support and guidance from NHS professionals. For those who have the wherewithal, and the interest, it seems that this product could help improve diabetic footcare with the potential to prevent amputations by identifying problems early. The fact that it can be used at home and that is is so simple to use can only be of benefit.	Thank you for your comment
25	5	Company	-	4. NICE guideline NG17 (Type 1 diabetes) and NG28 (Type 2 diabetes) both refer to autonomic neuropathy as a complication of diabetes yet offer no scientific or clinical means of detecting it. In fact the T2D guidelines merely state that clinicians should 'think about the possibility of autonomic neuropathy…' which is vague advice to say the least. NG19 which is the specific foot care guideline doesn't even mention it, nor dryness of the skin of the feet specifically but it does mention callus which is not necessarily the same thing. It appears that more recent GDGs involved in NG17 and NG28 are aware of the usefulness of detecting autonomic neuropathy (though offer no means of doing so) yet NG19 does not even mention it. This is clearly something that needs to be addressed.	Thank you for your comment The assessment report highlights the lack of UK guidance regarding the management of early stage DPN as follows ''The EAC is unaware of UK guidance for management of early stage DPN (which is less likely to be accompanied by loss of protective sensation and therefore more likely to lead to a low foot risk classification).'' Please note that the aim of the MTEP programme is to issue guidance on the single technology being assessed. Comments on NICE guidelines, such as NG17 and NG18, should be directed to the relevant guideline team.
26	5	Company	-	7. The draft also mentions the potential value of running a number of new studies including 2 new longitudinal studies with at least 5 years' follow up whilst conveniently ignoring the 3 independently designed and conducted longitudinal cohort studies of up to 5 years duration that have already reported and which NICE originally accepted as bona fide evidence when we presented our clinical submission. Most recently, a study presented at the specialist Diabetic Foot Study Group (DFSG) of the European Association for the Study of Diabetes (EASD) in Stuttgart, Germany, in September 2016 provides further evidence of the high sensitivity that Neuropad has for the prediction of future foot ulceration in people with diabetes. The prospective study conducted by lead investigator Dr Irene Sanz Corbalán and colleagues enrolled 263 patients consecutively	Thank you for your comment The abstract by Sanz-Corbalan et al (2016) was included by the EAC and the summary of the results and critical appraisal are included in the assessment report. The paper was inappropriate for inclusion in the meta-analysis because of the way the comparator (monofilament and biothesiometer) results were reported. The full text publication does not

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				from the Diabetic Foot Unit of the Complutense University of Madrid between July 2011 and April 2015. Subjects were followed up for a mean duration of 41.55 ± 3.5 [35-48] months. Diabetic patients without an active foot ulcer were classified by the International Working Group of Diabetic Foot (IWGDF) risk stratification system. Diabetic neuropathy was evaluated according to the results of the Semmes-Weinstein Monofilament (SWM) or Biothesiometer and using the Neuropad® sudomotor function test (referred to in the study as the SFT). Results showed that 60 (22.8%) patients developed a diabetic foot ulcer (DFU) during a mean follow-up of 41.55 ± 3.5 [35-48] months. 10 (16.7%) patients who were not diagnosed as having diabetic neuropathy by the SWM/Biothesiometer and were classified into the group risk 0 (without risk for developing a foot ulcer) went on to develop a foot ulcer during follow-up. In contrast, all patients who tested positive for sudomotor dysfunction, and despite some having a 0 risk using conventional sensory tests, went on to develop DFU during the follow-up period. SFT was considered an independent and statistically significant factor in the final Cox regression model of DFU prediction during the follow up [p=0.002; HR: 4.3 (CI: 1.7-11.1)]. The diagnostic prediction model regarding the development of diabetic foot ulcer in follow-up showed that SWM/Biothesiometer had 83.33% sensitivity and 50.74% of specificity whilst Neuropad® demonstrated 100% sensitivity and 31.53% specificity for future foot ulceration. The investigators concluded that Neuropad identifies earlier and with greater accuracy patients with diabetes that are at risk of developing DFU compared with the standard neurological sensory tests. The results of this research add to the evidence base that sudomotor function should be included as a risk factor in the classification system for diabetic foot disease because the standard sensory tests under-diagnose the overall risk for ulceration. The study will be published. This is important evidence that we wish again to draw to NICE's attention. Link: http://dfsg.org/fileadmin/user_upload/files/DFSG/2016/ID8_Posterpresentation_P53.pdf	change any of the conclusion reached based on the abstract. Similarly, the abstract by Tentolouris et al (2014) was included in the assessment report, however the method of reporting the results precluded it from being used in the the meta-analysis. Tentolouris et al (2010) was critically appraised in the assessment report and excluded because the patient population was outside of the scope. The committee considered this information and decided not to change the guidance.

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				Secondly, another important study which has now reported also appears to have been 'misplaced' by the EAC. This study was first presented as a poster at EASD 2015, Stockholm, Sweden. It has 8 years of follow up from 2005 until 2013. The lead investigator is Professor N Tentolouris, University of Athens, Greece. 'Background and aims: Foot ulceration in patients with diabetes is a serious complication associated with increased morbidity, mortality and healthcare cost and is the main cause of amputation. The prevalence of foot ulcers is 4% to 10%, and the annual population-based incidence is 1.0% to 4.1%. Prevention of foot ulceration and consecutively amputation begins with identification of those at risk. Well-established risk factors for foot ulceration are previous foot ulceration and lower extremity amputation, long duration of diabetes, poor glycemic control, and severity of diabetic neuropathy, foot deformities and visual impairment. Cross-sectional data have shown that dryness of the skin of the feet assessed by either sympathetic skin response or Neuropad testing has been associated with foot ulceration in patients with diabetes. In addition, Neuropad testing has a high performance for the diagnosis of diabetic peripheral neuropathy and is proper for self-testing. The aim of the present prospective multicenter study was to examine the association between Neuropad testing with foot ulceration in patients with diabetes. 'Material and methods: A total of 308 patients with diabetes (155 females and 153 males; 280 with type 2 diabetes; mean age 62.8 ± 11.3 years; mean diabetes duration 12.4 ± 9.7 years) with no history of foot ulceration were recruited in the study from the year 2005 until the year 2013. At baseline participants were evaluated for neuropathy status using the neuropathy disability score (NDS). Patients with NDS 0-2 were considered as having no neuropathy, those with NDS 3-5 as having mild neuropathy and those with NDS ≥6 as having severe neuropathy. In addition Neuropad testing was performed and the results were evaluated as normal or abnormal based on complete colour change of the test after 10 min of application. 'Results: At baseline, 148 patients (48.1%) did not have neuropathy, 82 (26.6%) had mild neuropathy and 78 (25.3%) had severe neuropathy. Neuropad testing was normal in 128 (41.6%)	

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				and abnormal in 180 (58.4%) patients. The mean follow-up time was 5.5 ± 2.5 years. During this time, 55 (17.9%) patients developed foot ulcers. After adjustment for age, gender and duration of diabetes, abnormal Neuropad testing at baseline was associated with increased odds (OR, 95% confidence intervals) for foot ulceration [OR 4.2 (1.8-9.8)]. Similarly, the adjusted OR of NDS ≥ 6 for foot ulceration was [8.5 (3.3-21.7)]. 'Conclusion: Abnormal Neuropad testing is associated with a 4-fold higher risk for foot ulceration. Neuropad testing can be included in the screening tests for the prevention of foot ulceration in patients with diabetes. Finally, an earlier study (Tentolouris 2010) examined the association between the moisture status of the skin of the feet using the Neuropad gtest with foot ulceration in subjects with diabetes in 379 patients with diabetes. The investigators concluded that 'An abnormal Neuropad response correlates with foot ulceration in subjects with diabetes. This finding, if confirmed prospectively, suggests that the Neuropad test may be included in the screening tests for the prediction of foot ulceration.' Clearly, the aforementioned 2 studies have confirmed the usefulness of Neuropad testing as a means of identifying earlier patients at risk of diabetic foot ulceration. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858186/	
27	5	Company	-	9. The neuropathy disability score (NDS) is not a 'gold-standard' test. Corneal confocal microscopy (CCM) and intra epidermal nerve fibre density (IENFD) are. Both have been used as Neuropad comparators with statistically significant positive published results. This has not been properly taken into account. These are both complex and expensive tests that are not even routine in a specialist hospital environment.	Thank you for your comment. The EAC assessment report describes in pages 72 nd 73,the various tests used as reference standards to test the diagnostic accuracy of Neuropad. The EAC noted that from the studies that were within the scope, only 1 study by Quattrini et al (2008) used the IENFD as a reference standard. None of the included studies used the CCM as a reference standard. The committee considered this comment and decided to amend the

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					text in section 4.10 to refer to the NDS as a reference standard.
28	5	Company	-	11. The EAC's meta-analysis came to the same conclusions as the dismissed independent published Tsapas et al. (2014) one. The sensitivity of >89% is good and this has been stated correctly in the draft guidance however it has not been given sufficient importance.	Thank you for your comment The results of the EAC meta-analysis were fully considered by the committee and their considerations about the strength of the evidence are described in 4.1 of the guidance.
29	5	Company	-	Concluding remarks We wish to conclude with the following requests which are that the draft or eventual final guidance is a fit and proper document that actually reflects the published NICE scope (which it does not), that it reflects the very serious patient need and potential patient benefits of the earlier identification of complications (which it is at best ambiguous about) and that it actually reflects the published and un-published evidence that has been submitted to NICE as part of the MTEP process (which it does not).	Thank you for your comment