NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of MTG 38: Neuropad for detecting preclinical diabetic peripheral neuropathy

This guidance was issued in September 2018.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Decision

Amend the guidance (the guidance is amended but the factual changes proposed have no material effect on the recommendations) to reflect the new evidence on Neuropad (guidance review options see Appendix 1).

The external assessment centre's (EAC) review of the clinical evidence can be found in the review report.

2. Original objective of guidance

To assess the case for adoption of Neuropad for detecting preclinical diabetic peripheral neuropathy.

3. Current guidance

1.1 The case for adopting Neuropad to detect preclinical diabetic peripheral neuropathy is not supported by the evidence. Neuropad detects sub-normal sweating in patients with diabetes but the clinical importance of this in current NHS care pathways is poorly defined. There is insufficient evidence to support the use of Neuropad in patients in whom 10 g monofilament testing for diabetic peripheral neuropathy is not possible.

1.2 Cost modelling is uncertain because of the limited clinical-effectiveness evidence. Using Neuropad instead of 10 g monofilament testing would likely increase costs because Neuropad has a lower specificity for detecting diabetic peripheral neuropathy. Further research is needed on the benefits and consequences of detecting preclinical diabetic peripheral neuropathy.

4. Rationale

The original guidance did not recommend Neuropad for detecting preclinical diabetic peripheral neuropathy. For the 2021 guidance review, there is no change to the technology, the care pathway and the cost of the technology since MTG38 was published. The new clinical evidence was reviewed and the guidance needs amending to reflect the new evidence.

5. New evidence

The search strategy from the original assessment report was re-run. References from April 2017 to September 2021 were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of new evidence are summarised in section 5.4.

The EAC identified no results for “Neuropad” in the FDA MAUDE database. The EAC found no MHRA safety notices for “Neuropad”.

5.1 Technology availability and changes

The technology is still available to the NHS. No functional change has been made to the technology. The company noted that a smartphone app (feet4life) has been developed. The app allows recording self-testing results at home. The app is not a medical device because it does not measure or diagnose but records data. The CE mark is unchanged and the company said Neuropad now has a UKCA mark.

5.2 Clinical practice

The NICE pathway on diabetes covers children, young people and adults. Since the publication of MTG38 Neuropad.

There have been no changes to relevant NICE guidelines since the publication of MTG38 in 2018, and the current NICE guideline on diabetic foot problems does not include testing sudomotor function to detect neuropathy. The EAC and experts also identified no changes to care pathways or clinical guidelines, relating to Neuropad, since the publication of the guidance.

In May 2022 the National Advisory Panel for Care Home Diabetes (NAPCHD) published a strategic document based on expert opinion, which mentions Neuropad as a simple objective method that could be used to document early signs of neuropathy in care homes. The development of the strategic paper involved a range of stakeholders across clinical and other professional groups and also representatives from the CQC and the RCGP.

5.3 NICE facilitated research

None.

5.4 New studies

Since the publication of MTG38, there is new evidence on the use of Neuropad. The EAC identified 9 studies that are relevant to the original scope, including 8 studies that provided clinical evidence, and 1 study that provided economic evidence. The clinical studies by study design include:

- 3 cross-sectional studies (Chicharro-Luna et al. 2021, Gomez-Banoy et al. 2017, and Lorenzini et al. 2020 [abstract only in English]);
- 3 cohort studies (Panagoulias et al. 2020, Sanz-Corbalan et al. 2018, Tesic et al. 2017 [abstract only]);
- 1 case-control study (Vagvolgvi et al. 2021) comparing patients with type 1 diabetes and matched controls;
- 1 diagnostic accuracy study (Zografou et al. 2020).

There was heterogeneity among the studies in the choice of comparator, with many studies using multiple tests to diagnose diabetic peripheral neuropathy which indicates variation in the care pathway. 4 studies compared the diagnostic accuracy of Neuropad with standard care (the 10g monofilament test), varying from 24.3% (Gomez-Banoy et al 2017) to 95% (Zografou et al. 2020). Other comparators reported included sensation tests (VibraTip, n=1, tuning fork test, n=4, biothesiometer, n=3) and standard neuropathy scoring systems (neuropathy disability score, n=2; neuropathy symptom score, n=1; Michigan Neuropathy Screening Instrument (MNSI), n=2).

A cost-effectiveness study was published after the original guidance (Rodriguez-Sanchez et al. 2020). The model was a variant of the model in the original guidance. One additional health state (death) was added to this model but other changes proposed by the EAC in the assessment were not addressed in the model; for example, the model included those testing positive for neuropathy and people with true and false positive were not modelled separately. The study applied a cost-effectiveness approach, reporting costs and health gains of using Neuropad compared with the 10g monofilament test alone or a combination of Neuropad and the 10g monofilament test

The EAC clinical evidence review also assessed 5 specific objectives:

Objective 1: Has new evidence defined the clinical pathway? If so, how is Neuropad positioned in the care pathway?

The EAC found that a multi-centre prospective cohort study which included 367 people across 4 countries, was the only study which included people from the UK (alongside patients from Bulgaria, Greece and Serbia; the breakdown per country was not provided) (Panagoulias et al. 2020). This study compared Neuropad with symptoms as assessed by Neuropathy Symptom Score (NSS), signs assessed by Neuropathy Disability Score (NDS), and vibration perception threshold assessment with biothesiometer, all included in different combinations. This study did not include 10g monofilament or VibraTip as comparators. Given the large range of reference tests identified in the newly

available evidence, the EAC would conclude that the clinical pathway remained undefined.

Objective 2: Is there new clinical evidence to support the use of Neuropad in people in whom 10 g monofilament testing for diabetic peripheral neuropathy would be used?

Evidence from 4 studies reported the use of Neuropad compared with 10g monofilament alone for diagnosing diabetic peripheral neuropathy. Reported sensitivity ranged between 24.3% (Gomez-Banoy et al. 2017, n=93) and 95% (Zografou et al. 2020, n=174). Reported specificity ranged between 29% (Lorenzini et al. 2020, n=42) and 94.2% (Gomez-Banoy et al. 2017, n=93). The authors of Gomez-Banoy et al. (2017) acknowledged that their reported prevalence of diabetic peripheral neuropathy in people with type 2 diabetes is lower than that reported in similar populations (although this may not influence sensitivity and specificity). But it is unclear to the EAC why the sensitivity and specificity reported by this study were outliers to the other studies. The EAC considers it possible that the authors have reported their sensitivity and specificity in the incorrect columns, but as no raw numbers were reported for the individual components of the MNSI, this was not verified. The EAC did contact the corresponding author of the study for clarification, on 15/12/2021, but the authors did not respond.

Because the evidence reported a wide variation in sensitivity and specificity for Neuropad, compared with monofilament the EAC considered the new evidence was not robust to support the use of Neuropad in those who would currently undergo testing with monofilament.

Objective 3: Considering new clinical evidence, has the estimated effect in the EAC original meta-analysis changed?

The meta-analysis in Tsapas et al. (2014) was rejected in the original assessment report due to study heterogeneity such as different reference standards used. The EAC of the original assessment report did its own meta-analysis, including 5 studies resulting in a pooled sensitivity and specificity of 89.4% and 60.3%, respectively, against NDS (NDS≥5) as a reference

standard (noting that there was high heterogeneity in the outcomes). One of the 5 included studies compared Neuropad with monofilament (Freitas et al, 2009). Although the patient populations in these 5 studies were largely similar in terms of age, there was a mix of patients with type 1 and type 2 diabetes, with this breakdown not reported fully in all studies.

The EAC did not consider it appropriate to update the meta-analysis because of the study heterogeneity (population, reference standard, thresholds) across the new evidence. There are now 5 studies comparing Neuropad with 10 g monofilament, including Freitas et al. (2009) identified in the evidence review for the original assessment report, but the EAC considered these studies to be too heterogeneous. The 5 studies had different proportions of people with type 1 or type 2 diabetes, one study (Chicharro-Luna et al. 2021) included only people with a 10-year history of diabetes, and one study was explicitly in a population group with chronic kidney disease (Tesic et al. 2017). The EAC considered that each of these variations may alter the pre-test probability of diabetic foot neuropathy. Additionally, some studies did not report sufficient data to perform a meta-analysis, especially Chicharro-Luna et al. (2021) which reported results for left and right feet separately, rather than for individual patients. Due to the differences in tested populations, and reporting concerns, the EAC has not conducted a meta-analysis to combine overall sensitivity and specificity.

Objective 4: Has new clinical evidence demonstrated any population groups who are most likely to benefit from using Neuropad?

The study by Zografou et al. (2020) reported that Neuropad was a useful screening tool for diagnosing diabetic peripheral neuropathy in terms of time saving and objectivity during clinical examination and educational benefit for the patient. However, none of the included studies explicitly measured and compared the time taken with Neuropad versus a comparator, and none of the new evidence demonstrated particular benefit for specific patient groups.

One clinical expert stated that Neuropad is superior to other screening tests as it could not require a response from the patient, and would therefore be

beneficial in people who are frail, housebound, in residential care, have sensory loss, dementia or where communication is otherwise difficult. There is no published evidence to support this claim.

Objective 5: Has new economic evidence addressed issues identified in the sponsor's original economic submission?

Several issues were identified with the company's de novo model during the original assessment, including:

- use of a cost-effectiveness analysis rather than a cost-consequences analysis;
- exclusion of negative cases of neuropathy from further modelling following diagnosis, which places people with false-negative results at risk of untreated ulcers;
- combination of both true and false-positive results into a single state, which was considered inappropriate as people with false-positive are at lower risk of ulceration; and
- exclusion of a death state, which is relevant as mortality is increased in patients with infected foot ulcers, particularly following amputation.

The KiTEC EAC of the original assessment report had addressed these concerns in their updated economic model.

An economic study was published after the publication of the original guidance (Rodriguez-Sanchez et al. 2020). It included a cost-effectiveness Markov model from a healthcare provider perspective in England. This study reported that the combination of Neuropad and 10g monofilament (when compared with 10g monofilament alone) was cost saving by £1,049 per patient and resulted in 0.044 QALY gain. Cost-savings remained during deterministic and probabilistic sensitivity analysis. The study reported that using Neuropad alone was not cost-effective when compared to 10g monofilament alone.

The EAC reviewed the newly available economic study and noted that it is cost-effectiveness analysis. The true positive and false positive results were

considered together, although cases with no neuropathy were able to transition to a state of “infected foot ulcer” and a death state was included. The EAC does not consider the study to fully address the issues outlined by KiTEC EAC. The committee understood that the results of this dual-testing strategy in the KiTEC EAC model should be treated with caution, because it assumed that the 2 tests are done completely independently (that is, the sensitivity and specificity of the 10 g monofilament test are not affected by the results of the Neuropad test). The committee was also aware there is no evidence to support the merits of such a dual-testing approach at the original guidance development. The results of Rodriguez-Sanchez et al. (2020) are consistent with the findings presented in the original assessment report, and the EAC concludes that the economic case remains the same.

5.5 Cost update

There is no change made to the cost of the technology. The EAC did not conduct an analysis of costs.

6. Summary of new information and implications for review

The company provided a review of the new evidence on Neuropad (6 studies). All are included in the IS search result. Five of the 6 studies were included in this review. Fernández-Torres et al. (2020) was not included because this is a systematic review, in which 3 primary studies assessed peripheral neuropathy using Neuropad: 2 studies (Ponirakis et al.2014; Spallone et al.2009) were included in the assessment report of the original guidance and 1 study (Papanas et al. 2007) was not in the EAC assessment report. But Papanas et al. (2011) was excluded from the original assessment because its study population overlapped with Manes et al. (2014). Panagoulias et al.(2020) was included in this review

The EAC has considered the evidence from 8 clinical studies, and 1 economic study using Neuropad for detecting diabetic peripheral neuropathy. It concluded that the new evidence does not sufficiently address the 5 specific objectives set for the review.

The EAC found that the new evidence was heterogeneous and it did not help to clarify the position of Neuropad in the care pathway. When using 10 g monofilament as a reference standard, the sensitivities and specificities of Neuropad reported in the new evidence varied widely. The EAC did not consider the use of meta-analysis to be appropriate because of the study heterogeneity. The EAC noted that no adverse events were identified in the literature.

An economic study was identified, which reported the use of Neuropad to be cost saving when used in conjunction with the 10 g monofilament test when compared to the 10 g monofilament test alone. This is the same conclusion stated in the original assessment report for Neuropad. As the cost of Neuropad has not changed since the original guidance, and no significant new evidence has been identified, the cost case has not been updated at this time.

Overall, the EAC concluded that the newly available studies are not compelling for updating the guidance. Although none of the evidence reported benefits for particular patient subgroups, one clinical expert highlighted that Neuropad is superior to other screening tests because it does not rely on a response from the patient, and this should be addressed in future research. Therefore, the EAC considered that Neuropad could be a useful diagnostic tool in, for example, a subgroup of patients who are unable to comprehend or respond to current methods of testing for diabetic peripheral neuropathy.

An amendment to the guidance is recommended to reflect new evidence on the use of the technology.

7. Implementation

The company said that the technology is available to the NHS. None of the experts was aware of Neuropad use in the NHS.

8. Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were raised in the original guidance. Potential equality issues concerning the problems individuals with cognitive impairment or communication difficulties have in accessing existing tests were covered in detail by the committee lead and equalities expert, and discussed by the committee in the guidance development. It was decided that no action was required.

Review proposal sign off:
Anastasia Chalkidou, Associate Director Medical Technologies Evaluation Programme and Interventional Procedures Programme, 4th August 2022

Contributors to this paper:

Technical analyst:	YingYing Wang
Technical adviser:	Paul Dimmock
Associate Director:	Anastasia Chalkidou
Project Manager:	Sharon Wright
Coordinator:	Joanne Heaney

Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	Yes
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	Yes
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant NICE work

Published

NICE guidelines

- Type 2 diabetes in adults: management (2015) NICE guideline NG28
- Diabetic foot problems: prevention and management (2015) 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 (2015) NICE guideline NG17
- Diabetes in pregnancy: management from preconception to the postnatal period (2015) NICE guideline NG3
- Type 2 diabetes: prevention in people at high risk (2012) NICE public health guideline PH38
- Type 2 diabetes prevention: population and community-level interventions (2011) NICE public health guideline PH35

NICE quality standards

- Diabetes in children and young people (2016) NICE quality standard QS125
- Diabetes in pregnancy (2016) NICE quality standard QS109
- Diabetes in adults (2011) NICE quality standard QS6

NICE technology appraisals and highly specialised technologies

- NICE has published 15 technology appraisal guidance related to diabetes.

NICE medical technologies guidance

- Neuropad for detecting preclinical diabetic peripheral neuropathy (2018) NICE medical technologies guidance MTG38

- VibraTip for testing vibration perception to detect diabetic peripheral neuropathy (2014) NICE medical technologies guidance MTG22
- The Debrisoft monofilament debridement pad for use in acute or chronic wounds (2014) Medical technologies guidance MTG17

NICE diagnostic guidance

- Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (2016) NICE diagnostics guidance DG21

NICE interventional procedures guidance

- Implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes (2015)
- NICE Interventional procedures guidance IPG518
- Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus (2008) NICE Interventional procedures guidance IPG257
- Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy (2008) NICE Interventional procedures guidance IPG274

NICE pathways

- NICE Pathway (2021) Type 1 diabetes in adults
- NICE Pathway (2020) Diabetes in pregnancy
- NICE Pathway (2020) Type 2 diabetes in adults
- NICE Pathway (2020) Diabetes in children and young people
- NICE Pathway (2020) Preventing type 2 diabetes
- NICE Pathway (2019) Foot care for people with diabetes

In development

NICE guidelines

- Type 2 diabetes in adults: management (update). NICE guideline. Publication expected February 2022. This guidance will partially update the following: NG28.

- Diabetes update. NICE guideline. Publication expected: TBC. This guidance will partially update the following: NG3, NG17, NG28, NG18.

NICE technology appraisals and highly specialised technologies

- NICE is currently developing 5 technology appraisals for treating diabetes.

Registered and unpublished trials

The EAC searched for "Neuropad" on clinicaltrials.gov on 23/11/2021 and identified 2 studies: one of unknown status (NCT01896648 estimated study completion June 2016, however last updated in 2013), 1 completed (NCT00895440, with links to 2 publications Papanas *et al.* 2008 and Papanas *et al.* 2005; which would have been considered within the original MTG38 published in 2018). The company did not share any details of any ongoing studies.

Referemce

Chicharro-Luna E, Pomares-Gómez FJ, Ortega-Ávila AB, Coheña-Jiménez M, Gijon-Nogueron G. Variability in the clinical diagnosis of diabetic peripheral neuropathy. Prim Care Diabetes. 2020; 14(1): 53-60

Chicharro-Luna E, Ortega-Avila AB, Requena-Martínez A, Gijon Nogueron G. Concordance between sudomotor disorder and the clinical diagnosis of diabetic peripheral neuropathy, according to various clinical guidelines. Prim Care Diabetes. 2021 Oct; 15(5): 853-8

Fernandez-Torres, R., et al. (2020). "Instruments of choice for assessment and monitoring diabetic foot: A systematic review." Journal of Clinical Medicine 9(2): 602

Freitas, C., A. Carvalho, G. Melo-Rocha, et al. (2009) "O teste com NEUROPAD: Na deteccao precoce da neuropatia periferica do doente diabetico (THE NEUROPAD TEST In the Screening of Peripheral Neuropathy in Diabetic Patients)." Acta Medica Portuguesa 22(6): 729-734

Gomez-Banoy, N., *et al*. Screening tests for distal symmetrical polyneuropathy in Latin American patients with type 2 diabetes mellitus. Archives of endocrinology and metabolism. 2017; 61(5): 470-75

Kamenov, Z. A., J. J. Petrova and V. G. Christov. Diagnosis of diabetic neuropathy using simple somatic and a new autonomic (Neuropad®) tests in the clinical practice. Experimental and Clinical Endocrinology and Diabetes. 2010; 118(4): 226-233

Lorenzini N, Díaz C, Quintana T. Prueba diagnóstica de disfunción sudomotora en la detección precoz de la neuropatía diabética [Sudomotor dysfunction diagnostic test for early detection of diabetic neuropathy]. Rev Med Chil. 2020; 148(1): 54-9 [abstract]

Manes, C., N. Papanas, T. Exiara, et al. (2014) "The indicator test Neuropad in the assessment of small and overall nerve fibre dysfunction in patients with type 2 diabetes: a large multicentre study." Experimental & Clinical Endocrinology & Diabetes 122(3): 195-199

Panagoulias GS, Eleftheriadou I, Papanas N, *et al.* Dryness of Foot Skin Assessed by the Visual Indicator Test and Risk of Diabetic Foot Ulceration: A Prospective Observational Study. Front. Endocrinol. 2020; 11: 625

Papanas N., Giassakis G., Papatheodorou K., Papazoglou D., Monastiriotis C., Christakidis D., Maltezos E. Use of the new indicator test (Neuropad) for the assessment of the staged severity of neuropathy in type 2 diabetic patients. Exp. Clin. Endocrinol. Diabetes Off. J. Ger. Soc. Endocrinol. Ger. Diabetes Assoc. 2007;115:58–61

Ponirakis, G., I. N. Petropoulos, H. Fadavi, et al. (2014) "The diagnostic accuracy of Neuropad® for assessing large and small fibre diabetic neuropathy." Diabetic Medicine 31(12): 1673-1680

Rodríguez-Sánchez B, Peña-Longobardo L, Sinclair A. Cost-effectiveness analysis of the Neuropad device as a screening tool for early diabetic peripheral neuropathy. European Journal of Health Economics. 2020; 21: 335-49

Sanz-Corbalan I, Lazaro-Martınez J, Garcıa-Morales E, *et al.* Advantages of early diagnosis of diabetic neuropathy in the prevention of diabetic foot ulcers. Diab Res and Clin Prac. 2018; 146; 148-54

Spallone, V., R. Morganti, M. Siampli, et al. (2009) "Neuropad as a diagnostic tool for diabetic autonomic and sensorimotor neuropathy." Diabetic Medicine 26(7): 686-692

Tesic DS, Papanas N, Stokic E, Mitrovic M, Bajkin I, Icin T *et al.* Sudomotor examination should be regularly performed in patients from predialysis stage (CKD4) but also after transplantation to detect nerve regeneration. Diabetologia. 2017; 60(1supplement1): 460 [abstract]

Tsapas, A., A. Liakos, P. Paschos, *et al*. A simple plaster for screening for diabetic neuropathy: A diagnostic test accuracy systematic review and meta-analysis. Metabolism: Clinical and Experimental. 2014; 63(4): 584-592

Vágvölgyi A, Maróti Á, Szűcs M, Póczik C, Urbán-Pap D, Baczkó I *et al.* Peripheral and Autonomic Neuropathy Status of Young Patients With Type 1 Diabetes Mellitus at the Time of Transition From Pediatric Care to Adult-Oriented Diabetes Care. Front Endocrinol (Lausanne). 2021; 12: 719953

Zografou I, Iliadis F, Sambanis C, Didangelos T. Validation of Neuropad in the Assessment of Peripheral Diabetic Neuropathy in Patients with Diabetes Mellitus Versus the Michigan Neuropathy Screening Instrument, 10g Monofilament Application and Biothesiometer Measurement. Curr Vasc Pharmacol. 2020; 18(5): 517-22