Review report of MTG38: Neuropad for detecting preclinical diabetic peripheral neuropathy

This medical technology guidance was published in September 2018.

All medical technology guidance is usually reviewed 3 years after publication unless NICE become aware of significant new information before the expected review date.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance will be updated, amended, remain unchanged (static list) or withdrawn.

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1. Original objective of guidance

To assess the clinical and cost effectiveness of Neuropad for detecting preclinical diabetic peripheral neuropathy.

2. Current guidance recommendations

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.

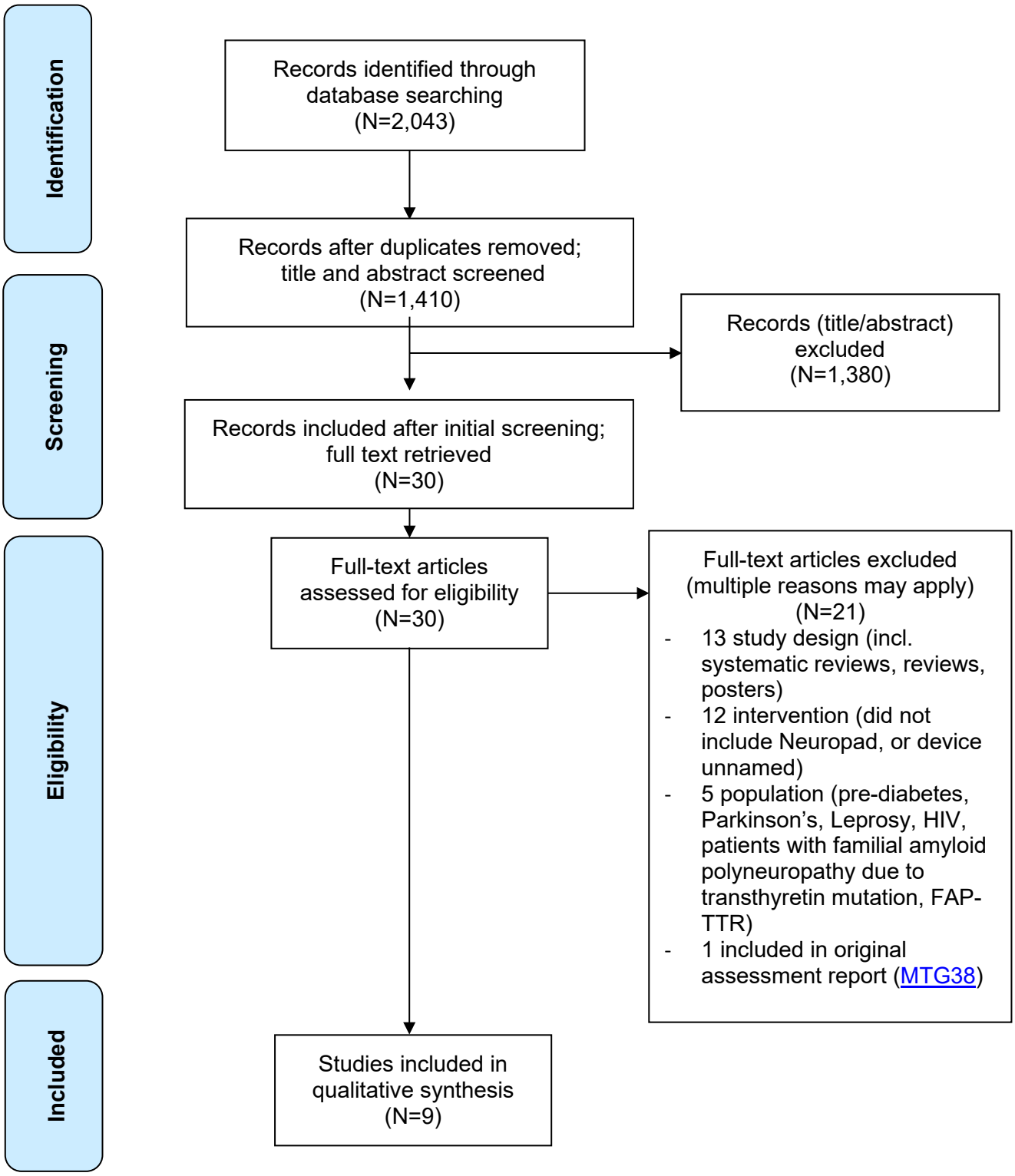
1.2 Cost modelling is uncertain because of the limited clinical-effectiveness evidence. Using Neuropad instead of 10 g monofilament testing would likely increase costs because Neuropad has a lower specificity for detecting diabetic peripheral neuropathy. Further research is needed on the benefits and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

3. Methods of review

NICE Information Services (IS) repeated the original search strategy used for MTG38, with revised dates (April 2017 to September 2021). The IS search identified 2,043 references, reducing to 1,410 references after deduplication, and shared a reference library (in standard research information system, RIS, format) with the EAC. A total of 1,410 titles and abstracts were sifted by a single reviewer (KK) and 30 were found to be potentially within the scope of the original guidance (NICE MTG38 Scope, 2017). The full text articles for these studies were retrieved and assessed for inclusion against the scope (KK). A total of 21 were excluded on full text review (Appendix B1), with 9 studies remaining for further analysis.

A summary of the sifting and selection process of the EAC literature search is reported in Figure 1.

Figure 1: PRISMA diagram illustrating EAC literature search



The company provided a list of six published studies, all of which were identified in the gIS search. The company did not provide details of any ongoing studies. The EAC considered a total of nine papers (including two abstracts and one economic study) in scope, see Appendix B2.

4. New evidence

4.1. Changes in technology

The company has confirmed that the technology has not changed, and that Neuropad is available on the NHS Drugs Tariff. The current Declaration of Conformity for this Class I non-sterile device is valid until 31/12/2024. The company has applied for registration with the MHRA (pending).

The company has advised that they have developed a Smartphone App, feet4life, which would allow patients or their carers to record results of tests at home and transmit them to healthcare professionals. The company advised that the feet4life App is not a medical device as it acts as a data recording tool only, and that the intention is for it to be made available free of charge to patients who are home testing with Neuropad. The app is available for Android and Apple phones.

4.2. Changes in care pathways

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 NICE pathway on diabetes covers children, young people and adults, and includes other relevant pathways and guidance identified by NICE Information Services, as listed in Appendix A.

The EAC and experts also identified no changes to care pathways or clinical guidelines, relating to Neuropad, since the publication of the guidance. However, one clinical expert, who chairs the National Advisory Group on Care Home Diabetes, indicated they were currently involved in drafting a strategic document that will recommend the use of Neuropad in care home residents with diabetes, as an alternative to the Ipswich Touch Test.

Relevant guidance is summarised in Appendix A.

4.3. Results from the MTEP research commissioning workstream

Medical Technology Guidance (MTG38, 2018) states that "*Further research is needed on the benefits and consequences of detecting preclinical diabetic peripheral neuropathy*." The EAC is not aware of any research commissioned by the MTEP to inform the guidance review.

4.4. New studies

Of the nine studies identified as being in scope, eight provided clinical evidence, and one provided economic evidence. Of the eight clinical studies, tabulated in Appendix B2, seven were comparative and all were reported, or assumed by the EAC, as being prospective, including:

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

Studies ranged in size between n=42 (Lorenzini *et al*. 2020) and n=367 (Panagoulias *et al*. 2020) patients. Participants were reported across most studies only as having diabetes, although Tesic *et al*. (2017) included some participants without diabetes, but with other kidney diseases that may cause neuropathy. All studies were in healthcare settings (or assumed to be, if not reported), such as outpatient clinics, foot clinics, and diabetes centres. None reported use in a home setting. Additionally, none of the included studies explicitly reported use in patient groups that might be most likely to benefit from the use of the technology; for example, those who are frail, housebound, living in residential care homes, or with sensory loss, dementia, or difficulty communicating.

Comparators

There was no single comparator in any of the studies, with all using multiple tests to diagnose diabetic peripheral neuropathy which indicates variation in the care pathway. The most common comparators (reference tests) in line with the final scope included:

- 10g monofilament test (N=4 studies), Table 1a. Results for the 10g monofilament test, when used in conjunction with sensation tests, are given in Table 1b.

- Other sensation tests (for example, VibraTip [N=1 studies], tuning fork test [N= 4 studies], biothesiometer [N=3 studies]), Table 1b. Although listed in the scope, no studies reported using Neurotip or the Ipswich Touch Test.

- Standard neuropathy scoring systems (Neuropathy Disability Score [N=2 studies], Neuropathy Symptom Score, [N=1 studies]), Table 1c. Michigan Neuropathy Screening Instrument (MNSI) [N=2 studies] was also used, but it is not clear to the EAC how widely this is used in the UK.

- No studies described the use of Neuropad compared with the specialist small fibre neuropathy tests (for example, nerve conduction tests, intraepidermal nerve fibre density biopsy, quantitative sudomotor axon reflex test, Sudoscan, corneal confocal microscopy, NC-stat DPN check).

One additional study compared the use of Neuropad with the development of an ulcer (Sanz-Corbalan *et al.* 2018); whilst the comparator was out of scope the study was included and treated as a single-arm cohort.

Sensitivity and specificity

The majority of studies (N=6) considered the diagnostic performance of Neuropad, Table 1a, 1b, and 1c. All reported on the performance of Neuropad alone, and Panagoulias *et al*. (2020) also considered the performance of

Neuropad used in conjunction with the Neuropathy Disability Score (NDS) and vibration perception assessment using a biothesiometer. Four of the six studies compared Neuropad with a monofilament test. Reported sensitivity of Neuropad alone, when compared with monofilament alone ranged between 24.3% (Gomez-Banoy *et al*. 2017) and 95% (Zografou *et al*. 2020). Specificity of Neuropad, when compared with monofilament alone ranged between 29% (Lorenzini *et al*. 2020) and 69% (Zografou *et al*. 2020). Neuropad was also compared with single vibration perception tests, with sensitivity ranging from 29.2% for VibraTip (Gomez-Banoy *et al*. 2017), to 73.0% for biothesiometer (Zografou *et al*. 2020), and specificity ranging from 81.0% for biothesiometer (Zografou *et al*. 2020) to 86.4% for VibraTip (Gomez-Banoy *et al*. 2017). The EAC acknowledges that these sensitivities and specificities cover a wide range, influenced by the results reported by Gomez-Banoy *et al*. (2017). This is explored further below, in response to the Objectives.

Chicharro-Luna *et al*. (2021) compared Neuropad with combinations of tests and reported sensitivities ranging between 85% and 100%, and specificities ranging between 32% and 37% (Table 1b). For patients who developed ulcers, Panagoulias *et al*. (2020) compared Neuropad, either alone or with other tests, with a diagnosis made solely using the Neuropathy Disability Score or Neuropathy Symptom Score. Sensitivity ranged between 33% when diagnosis required both Neuropad and vibration perception testing to be abnormal, and 91% when diagnosis required either Neuropad or vibration perception testing to be abnormal. Specificity ranged between 41% when diagnosis required Neuropad or vibration perception testing to be abnormal, and 89% when diagnosis required both Neuropad and vibration perception testing to be abnormal.

Vagvolgyi *et al.* (2021) reported that no significant differences were detected with Neurometer, Neuropad, and 10g monofilament between patients with type 1 diabetes (n=29) and controls (n=30), however no tabulation of results was provided.

Table 1a: Studies (N=4) comparing Neuropad (index test) against 10g monofilament alone (reference test)

Study	No. of patients	Index test	Reference test	Sensitivity	Specificity	Likelihood ratios (positive)	NPV	PPV	Accuracy
Chicharro-Luna *et al.* (2021)	n=111	Neuropad only	10g monofilament	Right: 88% Left: 89%	Right: 37% Left: 33%	Right: 1.40 Left: 1.33	NR	NR	NR
Gomez-Banoy *et al.* (2017)	n=93	Neuropad only	10g monofilament	24.3%*	94.2%*	NR	61.2%	76.9%	NR
Lorenzini *et al.* (2020)†	n=42	Neuropad only	10g monofilament	94%	29%	NR	NR	NR	NR
Zografou *et al.* (2020)	n=174	Neuropad only	10g monofilament	95%	69%	NR	NR	NR	78%

Abbreviations: NR, not reported: NPV, negative predictive value; PPV, positive predictive value.
†Abstract only, full test in Spanish.
*the EAC has noted that the narrative description of sensitivities of 10g monofilament and 128Hz tuning fork, when compared to MNSI are ranked differently to the results described in Table 4 of the Gomez-Banoy *et al.* (2017) paper. The EAC assumes that the sensitivity and specificity of NeuroPad versus 10g monofilament described in Table 2 of Gomez-Banoy *et al.* (2017) may also be incorrect and has approached the author for clarification. The results from this study should be interpreted with caution.

Table 1b: Studies (N=3) comparing Neuropad (index test) against other sensation tests (for example Vibratip, reference test)

Study	No. of patients	Index test	Reference test	Sensitivity	Specificity	Likelihood ratios (positive)	NPV	PPV	Accuracy
Chicharro-Luna *et al.* (2021)	n=111	Neuropad only	Monofilament **and** pinprick	Right: 85% Left: 100%	Right: 35% Left: 32%	Right: 1.3 Left: 1.47	NR	NR	NR
		Neuropad only	Monofilament **and** tuning fork	Right: 90% Left: 90%	Right: 37% Left: 32%	Right: 1.43 Left: 1.32	NR	NR	NR
		Neuropad only	Monofilament **and** Achilles reflex	Right: 84% Left: 88%	Right: 32% Left: 34%	Right: 1.32 Left: 1.33	NR	NR	NR
		Neuropad only	Monofilament **and** cotton wisp	Right: 88% Left: 100%	Right: 36% Left: 32%	Right: 1.38 Left: 1.48	NR	NR	NR
Gomez-Banoy *et al.* (2017) *	n=93	Neuropad only	128 Hz tuning fork	39.0%	82.9%	NR	63.2%	64.0%	NR
		Neuropad only	Ankle reflex	60.9%	71.2%	NR	69.8%	62.5%	NR
		Neuropad only	VibraTip	29.2%	86.4%	NR	60.8%	63.1%	NR
Zografou *et al*. (2020)	n=174	Neuropad only	Biothesiometer	73%	81%	NR	NR	NR	76%

Abbreviations: NR, not reported; NPV, negative predictive value; PPV, positive predictive value
* These results should be interpreted with caution, as the EAC has concerns relating to the reporting of results in this paper, as highlighted in the footnote to Table 1a.

Table 1c: Studies (N=3) comparing Neuropad (index test) against Standard neuropathy scoring systems used in primary care (reference test)

Study	No. of patients	Index test	Reference test	Sensitivity [95% CI]	Specificity [95% CI]	Likelihood ratios (negative)	Likelihood ratios (positive)	NPV [95% CI]	PPV [95% CI]	Area under ROC [95% CI]	Accuracy
Gomez-Banoy *et al.* (2017) *	n=93	Neuropad only	5-item MNSI	66.6%	63.8%	NR	NR	84.6%	39.0%		
Panagoulias *et al.* (2020)	n=308	Neuropad only	NDS from 3 to 5, and NSS≥5, or NDS≥6 irrespective of neuropathic symptoms.	87 [87 to 95]%	49 [42 to 54]%	0.27 [0.1 to 0.5]	1.67 [1.4 to 2.0]	94 [89 to 97]%	27 [24 to 30]%	0.675 [0.620 to 0.727], p<0.001	NR
		Neuropad **and** high NDS	NDS from 3 to 5, and NSS≥5, or NDS≥6 irrespective of neuropathic symptoms.	40 [27 to 54]%	87 [83 to 91]%	0.69 [0.6 to 0.9]	3.16 [2.0 to 5.0]	87 [84 to 89]%	41 [30 to 52]%	0.637 [0.580 to 0.691], p=0.023	NR
		Neuropad **or** high NDS	NDS from 3 to 5, and NSS≥5, or NDS≥6 irrespective of neuropathic symptoms.	85 [73 to 96]%	47 [41 to 54]%	0.31 [0.2 to 0.6]	1.63 [1.4 to 1.9]	94 [89 to 97]%	26 [23 to 29]%	0.664 [0.609 to 0.717], p<0.001	NR
		Neuropad **and** high VPT measured with biothesiometer	NDS from 3 to 5, and NSS≥5, or NDS≥6 irrespective of neuropathic symptoms.	33 [19 to 49]%	89 [83 to 93]%	0.76 [0.6–0.9]	2.86 [1.6 to 5.2]	84 [81 to 86]%	42 [29 to 57]%	0.606 [0.536 to 0.672], p=0.04	NR
		Neuropad **or** high VPT measured with biothesiometer	NDS from 3 to 5, and NSS≥5, or NDS≥6 irrespective of neuropathic symptoms.	91 [78 to 97]%	41 [34 to 49]%	0.23 [0.1 to 0.6]	1.55 [1.3 to 1.8]	95 [87 to 98]%	29 [25 to 32]%	0.660 [0.592 to 0.724], p=0.0001	NR
		Neuropad **and** NDS of	NDS from 3 to 5, and NSS≥5, or NDS≥6	84 [71 to 92]%	59 [53 to 65]%	0.28 [0.2 to 0.5]	2.03 [1.7 to 2.5]	94 [90 to 97]%	31 [27 to 35]%	0.713 [0.659 to 0.763],	NR

Study	No. of patients	Index test	Reference test	Sensitivity [95% CI]	Specificity [95% CI]	Likelihood ratios (negative)	Likelihood ratios (positive)	NPV [95% CI]	PPV [95% CI]	Area under ROC [95% CI]	Accuracy
		between 3 and 5	irrespective of neuropathic symptoms.							p<0.001	
Zografou *et al*. (2020)	n=174	Neuropad only	MNSIQ	78%	92%	NR	NR	NR	NR	NR	83%
		Neuropad only	MNSIE	73%	90%	NR	NR	NR	NR	NR	78%

Abbreviations: MNSI, MNSIQ Michigan Neuropathy Screening Instrument; MNSIE, Michigan Neuropathy Screening Instrument Examination; MNSIQ, Michigan Neuropathy Screening Instrument Questionnaire; NDS, Neuropathy Disability Score; NR, not reported; NPV, negative predictive value; NSS, Neuropathy Symptom Score; PPV, positive predictive value; VPT, vibration perception threshold

* These results should be interpreted with caution, as the EAC has concerns relating to the reporting of results in this paper, as highlighted in the footnote to Table 1a.

Patient experience and ease of use

None of the updated evidence reported on this outcome.

Reliability and reproducibility

None of the updated evidence reported on this outcome.

Total time to carry out test and obtain result

The methodology of most studies allowed a ten-minute period for Neuropad to change colour and considered incomplete or absent colour change at this point to indicate diabetic peripheral neuropathy (Chicarro-Luna *et al.* 2021; Panagoulias *et al.* 2020; Gomez-Banoy *et al.* 2017), as per manufacturer's instructions. One abstract (describing a prospective single-arm cohort of 199 patients) by Tesic *et al*. (2017) reported time to complete colour change, as an outcome variable, Table 2. Tesic *et al.* (2017) reported a significant association between Neuropad time and chronic kidney disease of stage 3 or 4 (Odds Ratio, OR 1.14 [95%CI 1.09 to 1.19], p=0.000), and mortality (OR 1.05 [1.02 to 1.08], p=0.001).

Table 2: Time to complete Neuropad colour change reported by Tesic *et al*. (2017) in different patient groups.

Patient group	No. of patients	Time to complete colour change in minutes (SD)
Patients with type 2 diabetes, stage 3 chronic kidney disease [*G1]	n=25	8.9 (5.8)
Patients with diabetes on haemodialysis, patients without diabetes but with nephroangiosclerosis on haemodialysis, and patients on haemodialysis for other reasons [*G2a-c]	n=82	26.8 (8.2)
Transplant recipients, some with diabetes [*G3a]	n=26	9.1 (7.6)
Patients with diabetes, and glomerular filtration rate ≥90ml/min/1.73m^2 [*G3b]	n=56	11.3 (7.4)
Abbreviations: SD, standard deviation; *group name assigned in Tesic *et al.* (2017)		

Rates of GP surgery or hospital attendance

None of the updated evidence reported on this outcome.

Incidence of foot ulceration or amputation

Three studies reported the incidence of foot ulceration or amputation (Sanz-Corbalan *et al*. 2018; Tesic *et al*. 2017; Panagoulias *et al*. 2020). Sanz-Corbalan *et al*. (2018) reported the development of diabetic foot ulcers in 60 patients (22.8%), in a median time of 6.2 months after the first examination. In the subgroup of 27 patients with diabetes and on haemodialysis and followed up to 5 years, Tesic *et al*. (2017) reported ulceration or minor amputation in 5, and major amputation in 6 patients. In the subgroup of 56 patients with diabetes with glomerular filtration rate of at least 90 ml/min/1.73m^2, ulceration or minor amputation was reported in 13 patients and major amputation in 1 patient. Only 1 patient with diabetes and stage 3 chronic kidney disease (a subgroup of 25 patients) had a major amputation. Panagoulias *et al*. (2017) reported diabetic foot ulcers in 55/308 (17.86%) patients during the 6-year follow up period, and Kaplan-Meier analysis showed the proportion to be

significantly higher in those with an abnormal Neuropad result (p<0.001), at 48/180 versus 7/128 of those with normal Neuropad result. The authors used univariate Cox-regression analysis to show that the risk for foot ulceration increased significantly with an abnormal Neuropad result (p<0.001), with a hazard ratio of 4.57 (95% CI 2.07 to 10.11). Multivariate Cox-regression analysis, controlling for age, gender and diabetes duration, also indicated an increased risk of ulceration for those with abnormal Neuropad results, with a hazard ratio of 3.319 (95% CI 1.460 to 7.545; p=0.004). Panagoulias *et al*. (2020) also reported 7 amputations (6 minor and one below the knee amputation), giving an overall amputation incidence of 2.27% over 6 years.

Device-related adverse events

None of the updated evidence reported on this outcome.

Objectives

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

The study by Panagoulias *et al.* (2020), a multi-centre prospective cohort study which included 367 patients across 4 countries, was the only study which included patients from the UK (alongside patients from Bulgaria, Greece and Serbia; the breakdown per country was not provided). 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 is still 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?

As reported previously, four additional studies were identified that compared Neuropad against 10g monofilament alone in the diagnosis of 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). It is unclear to the EAC why the sensitivity and specificity reported by Gomez-Banoy *et al.* 2017 are outliers to the other studies. The authors acknowledge that their reported prevalence of diabetic peripheral neuropathy in patients with type two diabetes is lower than that reported in similar populations (although this may not influence sensitivity and specificity). The patients within this study had a higher mean (SD) age of 75.8 (7.3) years and the authors claim it is possible that the diagnostic performance of the tests used would change in a younger population. 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. However, the EAC did contact the corresponding author of the study for clarification, on 15/12/2021, and is awaiting their response.

One of the clinical experts highlighted a systematic review and meta-analysis (Wang *et al*. 2017) reporting on the diagnostic accuracy of a 10 g monofilament for diagnosing DPN using nerve conduction studies as the reference standard. Authors reported a pooled sensitivity of 53% (95% CI 32% to 74%) and specificity of 88% (95% CI 78% to 94%) across 8 trials for 10g monofilament. The authors reported heterogeneity in the evidence base, in terms of how monofilaments were used (location and number of testing sites, and threshold values for diagnosis), reported issues relating to how many times a single monofilament can be used, recovery time needed between patients, and the impact of changes in temperature or humidity. The study concluded that its clinical use cannot be encouraged based on the currently available evidence, and a randomised controlled trial should be conducted. Given this, and the wide ranges reported for sensitivity and specificity for Neuropad, compared with monofilament, the EAC does not

consider the new evidence sufficiently 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 EAC did not consider the meta-analysis presented in the original Assessment Report to be robust, and identified issues relating to study heterogeneity. At the time, the Tsapas *et al*. (2014) meta-analysis was rejected in the original assessment report due to study heterogeneity, including the variety in reference standards used. The EAC of the original assessment report had gone on to include, in the same analysis, studies with two different reference standards: monofilament, and NDS. Only one of the five included studies compared Neuropad with the monofilament, and although all five studies used NDS as a comparator, the thresholds applied were either undefined or varied between NDS of at least three, and NDS of at least six. In one of the included studies, the exact comparator was not reported in “Appendix B: Data table”, but included in the meta-analysis summary as using NDS. Whilst the patient populations in the included studies were largely similar in terms of age, there was a mix of patients with type one and type two diabetes, with this breakdown not reported fully in all studies. The EAC queries the inclusion of Kamenov *et al.* (2010) which studied a population of inpatients with diabetes. Although reported disease duration was similar to other studies included in the previous meta-analysis, this population could potentially differ significantly from the populations reported in the other studies, in terms of disease state and general health. The EAC also noted that statistical effects, namely confidence intervals, were not reported in the majority of the included studies. On the basis of the study heterogeneity (population, reference standard, thresholds) across the newly identified evidence, the EAC did not consider it appropriate to update the meta-analysis to include any new evidence identified from this review. Although there are now five studies comparing Neuropad with 10 g monofilament, including Freitas *et al*. (2009) identified in the evidence review for the original Assessment Report, the EAC also considers these studies to be too heterogeneous. The five studies report different proportions of patients with

type 1 or type 2 diabetes, one study (Chicharro-Luna *et al*. 2021) included only patients with a ten year history of diabetes, and one study was explicitly in a patient group with chronic kidney disease (Tesic *et al.* 2017), and the EAC considers that each of these variations may alter the pre-test probability of diabetic foot neuropathy. Additionally, some studies lack sufficient reporting of results to reconstruct the 2x2 tables needed to perform meta-analysis, especially Chicharro-Luna *et al*. (2021) which reported results for left and right feet separately, rather than for individual patients. It is also likely, given the poor reporting highlighted elsewhere in this report, that studies would be excluded from the meta-analysis following the necessary critical appraisal using QADAS or STARD, Due to the differences in tested populations, and reporting concerns, the EAC has not conducted 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 new evidence 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.

However, one expert stated that Neuropad is superior to other screening tests as it does not require a response from the patient, and is therefore beneficial in patients who are frail, housebound, in residential care, have sensory loss, dementia or where communication is otherwise difficult. There is, however, no published evidence to support this claim.

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

Only one additional economic study was identified; a cost-effectiveness Markov model by Rodriguez-Sanchez *et al.* (2020), reporting 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. A number of issues were identified with the company's *de novo* model during the development of the original Assessment Report, including:

- use of a cost-effectiveness framework rather than cost-consequences;
- exclusion of negative cases of neuropathy from further modelling following diagnosis, which places false negative cases at risk of untreated ulcers;
- combination of both true and false positive results into a single state, which was considered inappropriate as false positive cases 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 EAC authoring the original Assessment Report had addressed these concerns in their updated economic model. The newly available economic study by Rodriguez-Sanchez *et al*. (2020) is a cost-effectiveness analysis, and is therefore out of scope for the MTEP process. 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 during the production of their original Assessment report, and as the findings of Rodriguez-Sanchez *et al*. (2020) are consistent with the findings presented in the original Assessment Report, the EAC therefore concludes that the economic case remains the same. Further details of the economic study are reported in Appendix B3.

4.5. Ongoing trials

The EAC searched for "Neuropad" on clinicaltrials.gov on 23/11/2021 and identified two studies: one of unknown status (NCT01896648 estimated study

completion June 2016, however last updated in 2013), one completed (NCT00895440, with links to two publications Papanas *et al.* 2008 and Papanas *et al.* 2005; which would have been considered within the original MTG38 published in 2018), Appendix C. The company did not share any details of any ongoing studies.

4.6. Changes in cost case

The company has confirmed that the price has been held at £7.28 per Neuropad pack (excluding VAT) which comprises two test plasters.

4.7. Other relevant information

The EAC identified no results for “Neuropad” in the FDA MAUDE database on 23/11/2021. The EAC found no MHRA safety notices for “Neuropad” on 23/11/2021.

5. Conclusion

The EAC has considered eight clinical studies, and one economic study in its review of new evidence to support the use of Neuropad for detecting diabetic peripheral neuropathy, and notes that the new evidence does not sufficiently address any of the specific objectives identified for this review. The EAC found that the new evidence was sufficiently heterogeneous that 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 were wide ranging, and heavily influenced by the results reported in the Gomez-Banoy *et al*. (2017) study, which appeared to be an outlier by comparison with the others. No reason was found for this, and as raw numbers were not reported, its accuracy was not verified by the EAC. The EAC did not consider the use of meta-analysis, presented in the original Assessment Report, to be appropriate, given the study heterogeneity, and therefore did not update this to include any of the new evidence. A clinical expert highlighted a meta-analysis by Wang *et al*. (2017) which suggests that 10 g monofilament may not be an appropriate reference standard for diagnosing diabetic peripheral neuropathy.

Only a single 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 10 g monofilament test alone. This is the same conclusion stated in the original Assessment Report for Neuropad. Conducting two tests would likely have time implications in NHS practice. 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.

Panagoulias *et al*. (2017) found a significant association between a positive Neuropad result, and the development of an ulcer, however overall evidence for later patient outcomes is lacking. The EAC notes that no adverse events were identified in the literature, but overall, the EAC does not consider that the newly available evidence is compelling evidence 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 concludes 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.

Appendix A – Relevant guidance

NICE guidance – published

NICE guidelines (clinical, public health, social care, medicine practice guidelines, safe staffing)

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 interventional procedures, medical technologies or diagnostics guidance

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

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

Implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes (2015)

NICE Interventional procedures guidance IPG518

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

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

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator, and NICE CKS

Aptiva for painful diabetic neuropathy (2017) NICE Medtech innovation briefing MIB119

NICE has published 8 Medtech Innovation Briefings related to diabetes.

NICE has published 9 Evidence Summaries related to diabetes.

NICE has published 3 Key therapeutic topic documents related to diabetes.

NICE guidance – 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 quality standards

None identified

NICE technology appraisals and highly specialised technologies

NICE is currently developing 5 technology appraisals for treating diabetes.

NICE interventional procedures, medical technologies or diagnostics guidance

None identified

NICE pathways

None identified

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator, and NICE CKS

None identified

Guidance from other professional bodies

None identified

Appendix B1 – Excluded studies

#	Citation	Reason for exclusion
1.	Adam, M., *et al*. (2017). "Computer aided diagnosis of diabetic foot using infrared thermography: A review." Computers in Biology and Medicine **91**: 326-336.	Study design (review), Intervention (does not include Neuropad)
2.	Akinci, G., *et al*. (2021). "Diabetic neuropathy in children and youth: New and emerging risk factors." Pediatric Diabetes 22(2): 132-147.	Study design (review), Intervention (does not include Neuropad)
3.	Azzopardi, K., *et al*. (2018). "Hidden dangers revealed by misdiagnosed diabetic neuropathy: A comparison of simple clinical tests for the screening of vibration perception threshold at primary care level." Primary Care Diabetes **12**(2): 111-115.	Intervention (does not include Neuropad)
4.	Bonhof, G. J., *et al*. (2017). "Patterns of small and large fiber dysfunction in painful and painless diabetic polyneuropathy." Diabetologia **60**(1supplement1): 450.	Study design (poster)
5.	Bonhof, G. J., *et al*. (2019). "Assessment of sudomotor dysfunction using neuropad and sudoscan in diabetic polyneuropathy." Diabetologie und Stoffwechsel **14**(supplement1): 50-s51.	Study design (poster)
6.	Faselis, C., *et al*. (2020). "Microvascular Complications of Type 2 Diabetes Mellitus." Current Vascular Pharmacology **18**(2): 117-124.	Study design (review), Intervention (does not include Neuropad)
7.	Fealey, R. D. (2018). "Thermoregulation in neuropathies." Handbook of Clinical Neurology **157**: 777-787.	Study design (review), Intervention (does not include Neuropad)
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.	Study design (systematic review): - Papanas et al. 2007 (excluded from AR overlapping populations); - Ponirakis et al. 2014 (included in AR); - Spallone et al. 2009 (included in AR)
9.	Fernandez-Torres, R., *et al*. (2020). "Clinician assessment tools for patients with diabetic foot disease: A systematic review." Journal of Clinical Medicine **9**(5): 1487.	Study design (systematic review of scoring systems), Intervention (does not include Neuropad)
10.	Gujjar, P. and Y. S. Ravikumar (2020). "Early Detection of Neuropathy in Prediabetes with Special Reference to Vibration Perception Threshold and Autonomic Function Tests." The Journal of the Association of Physicians of India **68**(1): 49.	Intervention (device not named)
11.	Gylfadottir, S. S., *et al*. (2019). "Painful and non-painful diabetic polyneuropathy: Clinical characteristics and diagnostic issues." Journal of Diabetes Investigation **10**(5): 1148-1157.	Study design (review), Intervention (does not include Neuropad)

#	Citation	Reason for exclusion
12.	Khurana, R. K. and C. Russell (2017). "The spoon test: a valid and reliable bedside test to assess sudomotor function." Clinical autonomic research : official journal of the Clinical Autonomic Research Society **27**(2): 91-95.	Intervention (does not include Neuropad)
13.	Kirthi, V., *et al*. (2021). "Prevalence of peripheral neuropathy in pre-diabetes: a systematic review." BMJ open diabetes research & care **9**(1).	Study design (systematic review): - Ziegler et al. 2012 (included in AR) Population (pre-diabetes)
14.	Laroussi, S., *et al*. (2021). "Idiopathic Parkinson's disease and sensory disorders: A complication of dopatherpy or an intrinsic feature of the disease." Movement Disorder **36**(suppl1): 421.	Population (Parkinson's)
15.	Laurin, K. L. and P. D. Blanchard (2019). "Sensitivity and specificity of the Neuropad for distal sensory peripheral neuropathy (DSPN) in subjects with HIV-Infection: A case controlled observational study." International Journal of Osteopathic Medicine **31**: 1-6.	Population (HIV: excluded patients with diabetes)
16.	Li, J., *et al*. (2019). "Correlations among Diabetic Microvascular Complications: A Systematic Review and Meta-analysis." Scientific Reports **9**(1): 3137.	Study design (systematic review), Intervention (does not include Neuropad)
17.	Shabeeb, D., *et al*. (2018). "Electrophysiological measurements of diabetic peripheral neuropathy: A systematic review." Diabetes & Metabolic Syndrome **12**(4): 591-600.	Study design (systematic review), Intervention (does not include Neuropad)
18.	Tentolouris, N., *et al*. (2008). "Evaluation of the self-administered indicator plaster neuropad for the diagnosis of neuropathy in diabetes." Diabetes Care **31**(2): 236-237.	Included in original assessment report
19.	Wagenaar, I., *et al*. (2017). "Early detection of neuropathy in leprosy: a comparison of five tests for field settings." Infectious diseases of poverty **6**(1): 115.	Population (Leprosy: excluded patients with diabetes)
20.	Wang, F., *et al*. (2017). "Diagnostic Accuracy of Monofilament Tests for Detecting Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis." Journal of Diabetes Research **2017**: 8787261.	Study design (systematic review), Intervention (does not include Neuropad)
21.	Zouari, H. G., *et al*. (2019). "Assessment of autonomic innervation of the foot in familial amyloid polyneuropathy." European Journal of Neurology **26**(1): 94-e10.	Population (patients with familial amyloid polyneuropathy (FAP) due to transthyretin (TTR) mutation)

Appendix B2 – Clinical evidence

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Chicharro-Luna *et al.* (2021) Spain	Prospective cross sectional study (n=111), single centre. Intervention: sudomotor dysfunction assessed by Neuropad. Comparators: 5.07 Sensifil monofilament (sensory response); 128 Hz Rydel-Seiffer tuning fork (vibratory sensitivity); Neuropen (pain sensitivity); cotton wisp (tactile sensitivity); Achilles reflex assessed by tapping tendon with hammer.	Participants aged at least 18 years, with at least a 10 year history of diabetes mellitus. Recruitment dates not reported. Participants with distal foot amputation or significant hyperkeratosis in the forefoot area preventing the placement of Neuropad were excluded. Setting: Endocrinology clinic	Neuropad colour change, result of monofilament test, result of monofilament test plus pinprick, result of monofilament test plus tuning fork, result of monofilament test plus Achilles reflex, result of monofilament test plus cotton wisp.	Comparators and setting described more fully in Chicharro-Luna *et al*. 2020.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Gomez-Banoy *et al.* (2017) Colombia	Prospective cross-sectional study (n=93), single centre. Interventions: Neuropad and VibraTip (out of scope). Comparators: Distal symmetrical polyneuropathy (DSPN) defined by Michigan Neuropathy Screening Instrument (MNSI) clinical score greater than 2; 128 Hz tuning fork; 10g monofilament; ankle reflex; VibraTip.	Participants were aged at least 18 years, with type 2 diabetes based on the American Diabetes Association, and outpatients belonging to the "Program for the Prevention of Diabetes Complications". Recruitment dates not reported. Participants with neuropathy from other etiology, active neoplastic or autoimmune disease, acute exacerbation of chronic disease or pregnant were excluded. Setting: University (Faculty of Medicine)	Test sensitivity, specificity, positive and negative predictive values.	

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Lorenzini *et al.* (2020) Chile	Prospective cross-sectional study (n=42), single centre. Intervention: Neuropad Comparators: 10g monofilament test; surface sensitivity assessed with a brush; pain perception (measurement method not reported); thermal discrimination (measurement method not reported); 128 Hz tuning fork for deep sensitivity.	Type 2 diabetic patients. Recruitment dates not reported. Setting: Not reported	Test sensitivity, specificity.	Full text only available in Spanish.
Panagoulias *et al.* (2020) Bulgaria, Greece, Serbia, UK	Prospective cohort study (n=367), 7 centres. Intervention: Neuropad Comparators: DPN assessment based on history and physical examination (symptoms assessed by Neuropathy Symptom Score; signs assessed by Neuropathy Disability Score [NDS]); vibration perception threshold assessment with biothesiometer (n=210, 4 clinics only).	Adult participants attending outpatient diabetes clinics. Recruitment from January 2012 to December 2017. Setting: Outpatient diabetes clinics	Primary: Association between dryness of foot skin, assessed by Neuropad, and risk for diabetic foot ulcer. Secondary: Diagnostic performance of Neuropad and other established modalities for foot ulceration prediction. Follow up: Every three to six months, or if a foot injury occurred.	

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Sanz-Corbalan *et al.* (2018) Spain	Prospective cohort study (n=263). Intervention 1: Diagnosis of DPN made by Neuropad (reported as method B) Intervention 2: Diagnosis of DPN made by Semmes-Weinstein Monofilament (SWM) or biothesiometer (reported as method A, not in scope) Comparator: Development of foot ulcer	Participants between 18 and 75 years with previous diagnosis of type 1 or 2 diabetes mellitus. Recruitment for 12 months from July 2011. Setting: diabetic foot unit	Primary: Ulceration Secondary: Test sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio. Follow up: Until first foot ulceration, or April 2015.	Unclear reporting as to whether method A was one intervention OR the other, or both interventions.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Tesic *et al.* (2017) Serbia	Single-arm prospective cohort study (n=199). Intervention: Severity of foot pathology assessed by NDS plus Neuropad, colour Doppler, ulcer or amputation.	Type 1 and 2 diabetic patients with stage 3 chronic kidney disease (glomerular filtration rate [GFR] between 30 ml/minute/1.73m^2 and 59 30 ml/minute/1.73m^2), on haemodialysis, or with GFR of at least 90 ml/minute/1.73m^2; non-diabetic patients with nephroangiosclerosis on haemodialysis, or on haemodialysis for other reasons; and transplant recipients. Setting: not explicitly reported	Mortality, Neuropad time to colour change, ulcerations, amputations (minor or major). Follow up at five years.	Patients also have chronic kidney disease

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Vagvolgyi *et al.* (2021) Hungary	Case control study (n=29 cases; n=30 controls), single centre. Interventions: cardiovascular function testing (heart rate response to deep breathing and standing up, and blood pressure response from lying to standing up); sensory nerve testing using Neurometer, Neuropad, 128 Hz Rydel-Seiffer graduated tuning fork, SWM, Tiptherm, questionnaire; fasting venous blood and urine samples; transthoracic echocardiography.	Young patients with type 1 diabetes mellitus transitioning from paediatric to adult diabetes care, with age-matched controls. Recruitment between September 2019 and February 2020. Setting: University medical department	Difference in results of tests between cases and controls.	Inclusion and exclusion criteria relating to age not reported, but mean age in the case group was 22.4 years; control group 21.5 years.
Zografou *et al.* (2020) Greece	Diagnostic accuracy study (n=174). Intervention: Neuropad Comparators: self reported MNSI Questionnaire; MNSI Examination (including visual foot inspection, vibratory perception and ankle reflex testing); 10g monofilament testing; vibration perception threshold assessment with biothesiometer.	Patients with diabetes under the age of 75 years. Recruitment dates not reported. Setting: diabetes centre	Test specificity, sensitivity, accuracy.	

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Abstract only Abbreviations: DPN, diabetic peripheral neuropathy; NDS, neuropathy disability score; DSPN, distal symmetrical polyneuropathy; MNSI, Michigan Neuropathy Screening Instrument; SWM, Semmes-Weinstein Monofilament;				

Appendix B3 – Economic evidence

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
Rodriquez-Sanchez *et al.* (2020) UK	Cost-effectiveness study using Markov model from healthcare provider perspective; 6 month cycle length, time horizon 3 years, 3.5% discount rate applied. 7 healthcare states: no neuropathy, neuropathy, infected foot ulcer, minor amputation, major amputation, healed foot, death. All patients are tested prior to entry into the model and placed into one of four health outcomes to	People of any age with diabetes (including type 1, type 2, and rarer types) without a prior diagnosis of peripheral neuropathy, an active ulcer, a previous ulcer, a previous amputation, or other causes such as low levels of vitamin B12, kidney disease, and thyroid problems. The authors report that this would be around 80% of patients, as 20% will have a prior diagnosis of neuropathy.	Interventions: Neuropad or 10g monofilament, or Neuropad and 10g monofilament.	Clinical parameters from published evidence and expert opinion where needed. Cost parameters from published evidence and NICE guidance. No staff time, training or infrastructure costs were included. Cost per patient or per use was also neglected for both screening tools due to uncertainty in the number of times monofilament would be used. Only direct medical costs were considered. Costs were assigned to amputations in the cycle in which they	Compared with standard care (10g monofilament only), the combination of Neuropad plus 10g monofilament is the dominant strategy, leading to savings of £1,049.26 per patient and 0.044 QALY gain. Results were found to be consistent across sensitivity analysis. 100% probability of Neuropad plus 10g monofilament being dominant, regardless of the willingness to pay threshold. However Neuropad alone was never cost-effective when compared with 10g monofilament.	DSA and PSA reported. Authors report source of monofilament sensitivity and specificity as not reporting the corresponding 95% CI, which was not the case,

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
	represent DPN (true positive), No DPN (true negative), false positive, DPN (false negative).			occurred, and subsequent cycles, to model ongoing care.		

Appendix C – Details of studies and ongoing trials

Study identification	Study design	Population	Intervention Comparator	Outcomes [Time frame]	Status
Sexual dusfunction in Type 2 diabetic women NCT01896648 Italy	Observational, cohort (n=306) Estimated study completion June 2016 [No results posted]	Type 2 diabetic women (aged 18 years and older). Exclusion criteria: previous surgery for hysterectomy or ovariectomy, hormone replacement	Data collection: history, physical exam, assessment of glycemic variability, Female Sexual Function Index, blood and urine, clinical and instrument exam of foot (Neuropad)	Primary: Female sexual function index [12 months] Secondary: Prevalence of sexual dysfunction risk factors [36 months], Correlation between sexual dysfunction and diabetic neuropathy [36 months]	Unknown Last update posted: July 2013

Study identification	Study design	Population	Intervention Comparator	Outcomes [Time frame]	Status
Role of indicator test (Neuropad) in detecting diabetic neuropathy NCT00895440 UK	Observational, cross-sectional (n=139) Actual study completion: June 2013	Type 1 or Type 2 diabetics with and without peripheral neuropathy (painless and painful) and Charcot neuroarthropathy, and non-diabetic subjects. Exclusion criteria: patients with allergy to any metal, peripheral vascular disease (defined as the absence of two or more foot pulses and an ankle brachial index of <0.8), renal failure (serum creatinine>130 micromol/l), foot ulceration or cellulitis or osteomyelitis, patients taking drugs that affect sweating (corticosteroids, antihistamines, psychoactive drugs), chronic alcohol use, B12 deficiency (presence of anaemia, raised mean corpuscular volume, past history of abnormal B12 levels, treatment with B12), patients with any skin conditions affecting their feet (neurodermatitis, psoriasis, scleroderma, Raynaud syndrome, hyperhydrosis, acrocyanosis)	Neuropad Subgroups: 1) Diabetic patients without neuropathy 2) Diabetic patients with painless neuropathy 3) Diabetic patients with painful neuropathy 4) Diabetic patients with Charcot neuroarthropathy 5) Control non-diabetic subjects	Primary: Identify patients with peripheral neuropathy with the Neuropad indicator test [6 months]	Completed Links to 2 studies included: - Papanas *et al.* (2008) - Papanas *et al.* (2005)

Appendix D – References

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