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# A simple plaster for screening for diabetic neuropathy: A diagnostic test accuracy systematic review and meta-analysis

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ABSTRACT

*Objective.* Neuropad is an adhesive indicator test applied at the plantar surface of the foot that detects sweating through color change. We examined the diagnostic accuracy of this simple plaster as triage test for screening for clinically relevant diabetic sensorimotor polyneuropathy in adult outpatients with type 1 or type 2 diabetes.

*Materials/Methods.* Systematic review and meta-analysis of diagnostic accuracy studies. We searched Medline, Embase, Cochrane Library, Biosis Previews, Web of Science, Scopus and gray literature without date or language restrictions. We pooled estimates of sensitivity and specificity, and fitted hierarchical models to produce summary receiver operating characteristic curves. We assessed methodological quality of included studies utilizing the Quality Assessment of Diagnostic Accuracy Studies 2 tool.

*Results.* Eighteen studies with 3470 participants met the inclusion criteria. Average sensitivity and specificity were 86% (95% CI 79 to 91) and 65% (95% CI 51 to 76) respectively. Likelihood ratios (LRs) were LR+ = 2.44 and LR− = 0.22. Subgroup analyses per reference standard utilized provided similar estimates. Most studies were at risk of bias for patient selection and use of index or reference test, and had concerns regarding applicability due to patient selection.

*Conclusion.* The adhesive indicator test has reasonable sensitivity and could be used for triage of diabetic neuropathy to rule out foot at risk. Patients who tested positive should be referred to specialized care to establish a definite diagnosis. There is insufficient evidence for effectiveness on patient-important outcomes and cost-effectiveness of implementation in the diagnostic pathway compared with the standard clinical examination.



*Abbreviations:* DNI, Diabetic Neuropathy Index; DOR, Diagnostic Odds Ratio; DSPN, Diabetic Sensorimotor Polyneuropathy; HSROC, Hierarchical Summary Receiver Operating Curve; LR, Likelihood Ratio; NDS, Neuropathy Disability Score; MDNS, Michigan Diabetic Neuropathy Score; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

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## 1. Introduction

Diabetic sensorimotor polyneuropathy (DSPN) affects approximately 10% of patients with newly diagnosed type 2 diabetes and 40% of patients with diabetes overall [1–3]. Risk increases with duration of diabetes, lack of glycemic control, and presence of cardiovascular complications [4,5]. Treatment is based on restoration of tight glycemic control, which delays progression of DSPN, and symptomatic management of painful symptoms [6]. There has been significant inconsistency regarding definition of DSPN due to lack of unanimously accepted diagnostic criteria and utilization of multiple diagnostic modalities [7,8]. Recent reports have therefore introduced the use of separate case definitions for epidemiological studies, and clinical research. The case definition introduced for clinical practice and for field or epidemiologic studies is based solely on clinical criteria (possible or probable clinical diabetic sensorimotor polyneuropathy) [7,8].

Existing evidence supports the clinical relevance of screening for clinical DSPN according to Wilson and Jungner criteria [9,10]. DSPN is an important health problem, with a high prevalence and high rate of complications. It is associated with an increased incidence of diabetic ulcers, Charcot's neuroarthropathy and > 50% of all limb amputations [1,11,12]. Timely and appropriate intervention has been shown to significantly reduce diabetic ulcers and amputations [13]. The natural history of the disease is adequately understood, and it has indeed a latent stage during which it can be diagnosed and treated in facilities available. Recent guidelines suggest annual screening for DSPN and clinical examination of lower extremities and feet in patients with diabetes, advocating diagnosis of DSPN by means of simple clinical tests [6,14,15]. This may represent a significant burden for primary care services that could be reduced by implementation of a simple and accurate triage test.

Neuropad (TRIGOCare International, Wiehl-Drabenderhöhe, Germany) is an adhesive indicator test that contains the blue complex salt anhydrous cobalt II chloride, which in the presence of water absorbs six water molecules and changes color to pink, hence detecting sweating through color change. It is a simple test that can be used even by patients themselves to diagnose sudomotor dysfunction and peripheral neuropathy [16]. Following removal of socks and shoes and a 10-min acclimatization period in room temperature (20 °C–25 °C), the plaster is applied to the sole at the level of the first through second metatarsal heads. It is assessed 10 min later for color change. Results are classified as normal if there is complete color change (from blue into smooth pink), or as abnormal if there is incomplete change (from blue into patchy blue) or no change at all.

In the present systematic review we assessed Neuropad as a triage test [17] for screening for clinically relevant DSPN that poses feet at risk for ulceration [2]. Our review question focused on outpatients with diabetes, who could then undergo a thorough, specialized, and more accurate diagnostic evaluation.

## 2. Methods

The systematic review was based on a prespecified protocol developed by the coauthors. Deviations from the protocol were minimal and only due to amount of data available, restricting the analysis planned. Methods and results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement [18].

### 2.1. *Eligibility criteria*

For our review we adopted the case definition of clinical DSPN for field or epidemiologic studies (possible or probable DSPN) [19] and the respective diagnostic criteria [7,8]. We included studies in adult outpatients with type 1 or type 2 diabetes, irrespective of duration of disease, or number of study participants. We excluded studies conducted in high-risk populations (e.g., patients with diabetic ulcers). Due to the lack of a unique "gold standard", we considered all studies that assessed the accuracy of the plaster for clinical DSPN utilizing an acceptable reference standard (Neuropathy Disability Score (NDS), Michigan Diabetic Neuropathy Score (MDNS), Diabetic Neuropathy Index (DNI), San Luis Valley Diabetes Study tool, Neuropathy Impairment Score in the Lower Limbs, or composite examination scores combining multiple individual examination findings) [1,7,20–23]. When multiple reference standard cut-off values were available, we focused on the most clinically relevant threshold (i.e. NDS $\geq$ 6) to predict patients at risk for foot ulceration [2]. We included both cohort type and case–control type accuracy studies [24]. We excluded prognostic accuracy studies.

### 2.2. *Data sources and searches*

We conducted a comprehensive search of multiple electronic databases, including Medline via Pubmed, Embase via OvidSP, Biosis Previews, Cochrane Library, Web of Science and Scopus, without imposing any date, language, or document type restrictions. The index test is very specific in its name and use, and unique (no similar tests). Thus, in order to generate a list of studies as comprehensive as possible, we only used the brand name of the diagnostic test under investigation without combining it with the disease it is intended to detect or potential reference standards. This approach was adopted based on a relevant suggestion from the Cochrane diagnostic test accuracy review group [25] and following consultation with two independent healthcare librarians. Moreover, it was verified in preliminary searches, which demonstrated significant inconsistencies in the key concepts described by authors and database indexers, and lack of other patterns of text words and database subject headings to further increase the comprehensiveness of the search strategy. We also searched for relevant systematic reviews and gray literature in multiple databases (Medion, OpenSIGLE, DARE, HTA and ARIF) and did an extensive search for unpublished studies in relevant websites and abstract books of relevant meetings. Finally, we sought to identify additional records by subjecting all included studies to a forward citation search and searching their reference lists, exploring the website of the manufacturing pharmaceutical company, and contacting researchers and experts in the field. Literature sources searched are listed in detail in Appendix 1. Our search was last run on April 22nd, 2013.