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GUIDELINES

Joint European Academy of Neurology–European Pain Federation–Neuropathic Pain Special Interest Group of the International Association for the Study of Pain guidelines on neuropathic pain assessment

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Abstract

Background and Purpose: In these guidelines, we aimed to develop evidence-based recommendations for the use of screening questionnaires and diagnostic tests in patients with neuropathic pain (NeP).

Methods: We systematically reviewed studies providing information on the sensitivity and specificity of screening questionnaires, and quantitative sensory testing, neurophysiology, skin biopsy, and corneal confocal microscopy. We also analysed how functional neuroimaging, peripheral nerve blocks, and genetic testing might provide useful information in diagnosing NeP.

Results: Of the screening questionnaires, Douleur Neuropathique en 4 Questions (DN4), I-DN4 (self-administered DN4), and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) received a strong recommendation, and S-LANSS (self-administered LANSS) and PainDETECT weak recommendations for their use in the diagnostic pathway for patients with possible NeP. We devised a strong recommendation for the use of skin biopsy and a weak recommendation for quantitative sensory testing and nociceptive evoked potentials in the NeP diagnosis. Trigeminal reflex testing received a strong recommendation in diagnosing secondary trigeminal neuralgia. Although many studies support the usefulness of corneal confocal microscopy in diagnosing peripheral neuropathy, no study specifically investigated the diagnostic accuracy of this technique in patients with NeP. Functional neuroimaging and peripheral nerve blocks are helpful in disclosing pathophysiology and/or predicting outcomes, but current literature does not support their use for diagnosing NeP. Genetic testing may be considered at specialist centres, in selected cases.

Conclusions: These recommendations provide evidence-based clinical practice guidelines for NeP diagnosis. Due to the poor-to-moderate quality of evidence identified by this review, future large-scale, well-designed, multicentre studies assessing the accuracy of diagnostic tests for NeP are needed.

KEYWORDS
diagnostic accuracy, diagnostic tests, neuropathic pain

INTRODUCTION

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system (https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Neuropathicpain). Besides clinical examination, diagnostic tests are useful in patients with suspected neuropathic pain, as they provide evidence of somatosensory nervous system damage.

The grading system for diagnosing neuropathic pain, issued by the International Association for the Study of Pain (IASP) [1], was proposed to determine the level of certainty in diagnosing neuropathic pain. For patients who report pain whose history suggests the presence of a neurological lesion or disease, a diagnosis of neuropathic pain is graded based on symptoms and signs as follows: neuropathic pain would be considered as "possible" if the patient reported pain distribution is neuroanatomically plausible, "probable" if there are, in addition, sensory signs in the painful territory, and "definite" if, additionally, the somatosensory lesion/disease can be documented using objective diagnostic tests.

Previous guidelines on neuropathic pain assessment issued by the European Federation of Neurological Societies and IASP [2, 3] investigated the usefulness of objective diagnostic tests for patients with suspected neuropathic pain. However, these guidelines neither used the now largely accepted GRADE system to assess the quality of the studies and elaborate recommendations, nor directly aimed at providing information on the accuracy of diagnostic tests. Therefore, these new neuropathic pain assessment guidelines plan to use GRADE for assessing quality and provide recommendations on the accuracy of diagnostic techniques.

The objectives of these neuropathic pain assessment guidelines are (i) to provide recommendations on the diagnostic value of established tools in the diagnosis of neuropathic pain, namely screening

questionnaires, quantitative sensory testing (QST), neurophysiological testing, skin biopsy, and corneal confocal microscopy (CCM) and (ii) to provide information on how less established techniques such as functional neuroimaging, peripheral nerve blocks, and genetic testing may contribute to the diagnosis of neuropathic pain.

METHODOLOGY

The appointed task force by the European Academy of Neurology (EAN), the European Pain Federation (EFIC) and the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP defined patient intervention comparison outcome (PICO) questions and performed a systematic literature review, using a standardized review (Appendix S1) and data extraction protocol (unpublished). The full reports of studies published in peer-reviewed journals between January 1966 and December 2020 were identified with searches of PubMed and the Cochrane Library.

Additional studies were identified from published reviews and the reference lists of selected papers. We included studies in English, providing information on diagnostic yield. Studies with fewer than 10 participants were excluded. The quality of the studies was assessed with the Quadas-2 [4].

These guidelines were developed in accordance with the recommendations of the GRADE Working Group (https://www.gradeworkinggroup.org/) and in line with the 2015 practical recommendations for proposing, planning, and writing neurological management guidelines by EAN task forces [5].

Two to three authors (Appendix S1) were responsible for extracting data from the literature review for each technique (screening questionnaires, quantitative sensory testing, neurophysiology, skin biopsy and corneal confocal microscopy, functional neuroimaging, peripheral nerve blocks and intravenous drug infusion tests, genetic investigations). For each technique, consensus on literature review and article selection was discussed through dedicated remote meetings. The search keywords used were adapted to the specificity of the different techniques (Appendix S1).

The outcome of interest was, for screening questionnaires, their accuracy in the diagnosis of neuropathic pain in comparison to clinical examination (with or without supporting diagnostic tests). For quantitative sensory testing, neurophysiology, skin biopsy, and corneal confocal microscopy, the outcome was the diagnostic yield for identifying damage to the somatosensory nervous system in patients with probable or definite neuropathic pain according to the grading system [1]. Articles not explicitly referring to the IASP Grading System were included if the task force participants considered that methods for patient inclusion adhered to the Grading System.

We devised specific PICOs for screening questionnaires and diagnostic techniques (Appendix S1). Given that peripheral nerve blocks, functional neuroimaging, and genetic testing are not commonly used to diagnose neuropathic pain in clinical practice, we did not directly aim at assessing their sensitivity and specificity in the diagnosis of neuropathic pain (although for peripheral nerve blocks we searched for studies indirectly providing evidence whether these procedures may confirm a diagnosis of neuropathic pain). Accordingly, PICOs for these techniques were adapted (Appendix S1).

In the assessment of diagnostic accuracy, we calculated the sensitivity and specificity and used random effects, bivariate model, which focuses on a summary estimate of sensitivity and specificity and provides prediction ellipses [6]. This is the preferred model for diagnostic test accuracy meta-analyses when we have one defined threshold value. The weight of each study was accounted for in the meta-analyses when possible. Following the GRADE approach, we considered the sample sizes of the individual studies when we were assessing the various domains of the evidence assessment. Because of the nature of the meta-analyses (diagnostic accuracy meta-analyses), for assessing the heterogeneity, we did not use the I^2 test, but observed the difference in the estimates among various studies observing the bivariate model figures (https://methods.cochrane.org/sdt/sites/methods.cochrane.org.sdt/files/uploads/Chapter%2010%20-%20Version%201.0.pdf). For plotting the sensitivity and specificity of the studies, we used RevMan and for the bivariate model the online platform MetaDTA (https://crsu.shinyapps.io/dta_ma/).

We also controlled whether covariates such as age, gender, and study design and quality, if applicable, affected diagnostic accuracy findings. For the GRADE evaluation, we set predefined preferred thresholds. The preferred sensitivity and specificity minimum threshold for noninvasive techniques, such as screening questionnaires, QST, neurophysiology, and CCM, was 70%; the preferred minimum threshold for skin biopsy was 80%.

Where possible, we calculated the positive predictive values (PPVs) and negative predictive values (NPVs), to assess the impact of false positive and false negative results in the population of interest. For this assessment, we assumed a 20% prevalence of neuropathic pain in a population of patients with chronic pain [7]. The overall quality of evidence for each outcome was assessed by the methodology subgroup of coauthors (A.T., K.A.).

The results of the literature search are presented in Appendix S1, and the results of the assessment of the diagnostic accuracy and the GRADE evaluation are presented in Tables S1–S9 and Figures 1–7. The covariates did not change the results of the meta-analysis, and therefore we did not include them in the analysis presentation.

The methodology subgroup (A.T., K.A.) proposed the recommendations, following the evidence-to-decision framework, and presented them to the rest of the task force participants. Consensus on the final recommendations was reached through email discussion and dedicated online meetings.

SCREENING QUESTIONNAIRES

Based on the assumption that some qualities of sensory perceptions may be indicative of neuropathic pain, screening questionnaires assess characteristic neuropathic pain symptoms (such as burning, tingling, sensitivity to touch, pain caused by light pressure,

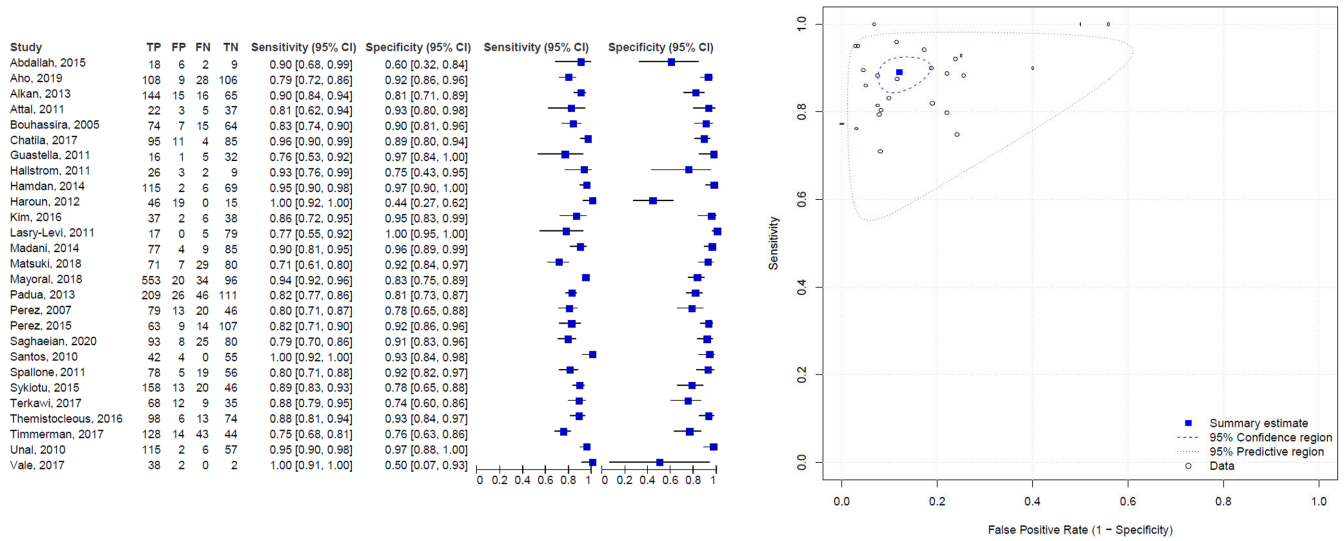


FIGURE 1 Left panel: Forest plot of sensitivity and specificity of the Douleur Neuropathique en 4 Questions (DN4) questionnaire in the diagnosis of neuropathic pain. These studies investigated the DN4 accuracy in patients with probable and definite neuropathic pain. Right panel: Summary receiver operating characteristic of DN4 diagnostic accuracy in the diagnosis of neuropathic pain. The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

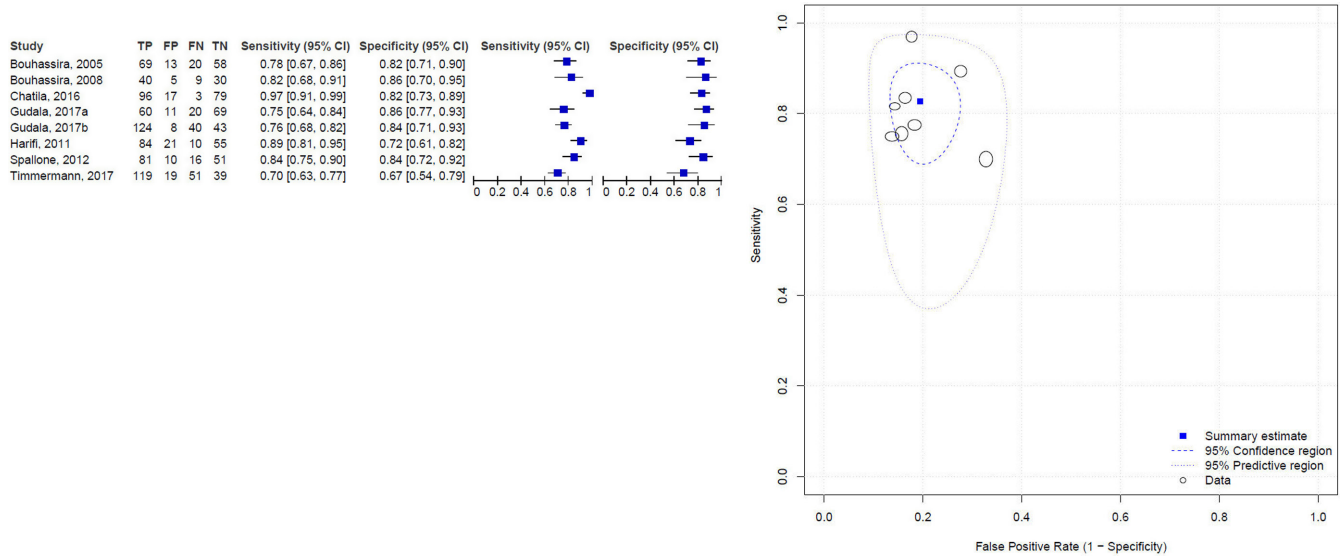


FIGURE 2 Left panel: Forest plot of sensitivity and specificity of the self-administered version of the Douleur Neuropathique en 4 Questions (I-DN4) questionnaire in the diagnosis of neuropathic pain. These studies investigated the I-DN4 accuracy in patients with probable and definite neuropathic pain. Right panel: Summary receiver operating characteristic of I-DN4 diagnostic accuracy in the diagnosis of neuropathic pain. The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

electric shock-like pain, pain to cold or heat, and numbness) and are designed to distinguish between neuropathic and nonneuropathic pain [8]. Some questionnaires also contain an optional clinician-completed element, usually in the form of a simple sensory examination. These patient-reported questionnaires, validated in more than 90 languages, helped to conduct large epidemiological surveys in different countries and are commonly used in pharmacological trials to select patients with neuropathic pain [8]. The screening questionnaires have been validated in patients with pain exclusively or predominantly at a single body location. They can also assess patients with two or three pain locations, provided they are administered with specific instructions and successively to the different pain areas. This appears less feasible in patients with multiple pain locations (i.e., more than three). Thus, screening tools should not be used for diagnostic purposes in patients with widespread pain for both practical and theoretical reasons.

Our data collection and analysis included only the most widely used screening questionnaires, namely the Leeds Assessment

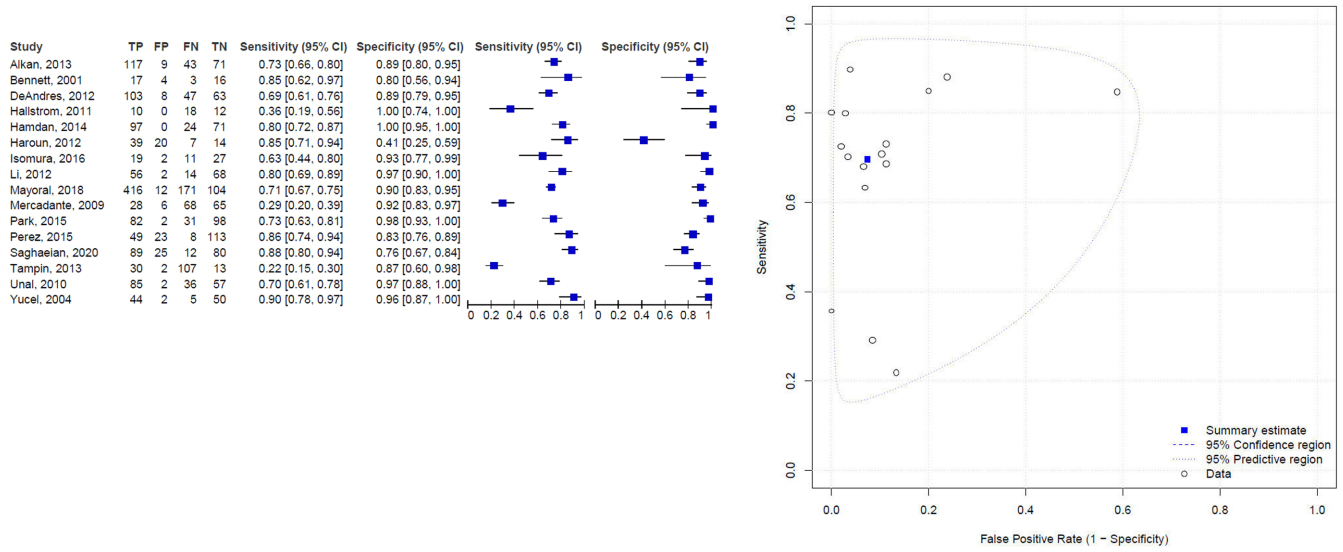


FIGURE 3 Left panel: Forest plot of sensitivity and specificity of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire in the diagnosis of neuropathic pain. These studies investigated the LANSS accuracy in patients with probable and definite neuropathic pain. Right panel: Summary receiver operating characteristic of LANSS diagnostic accuracy in the diagnosis of neuropathic pain. The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

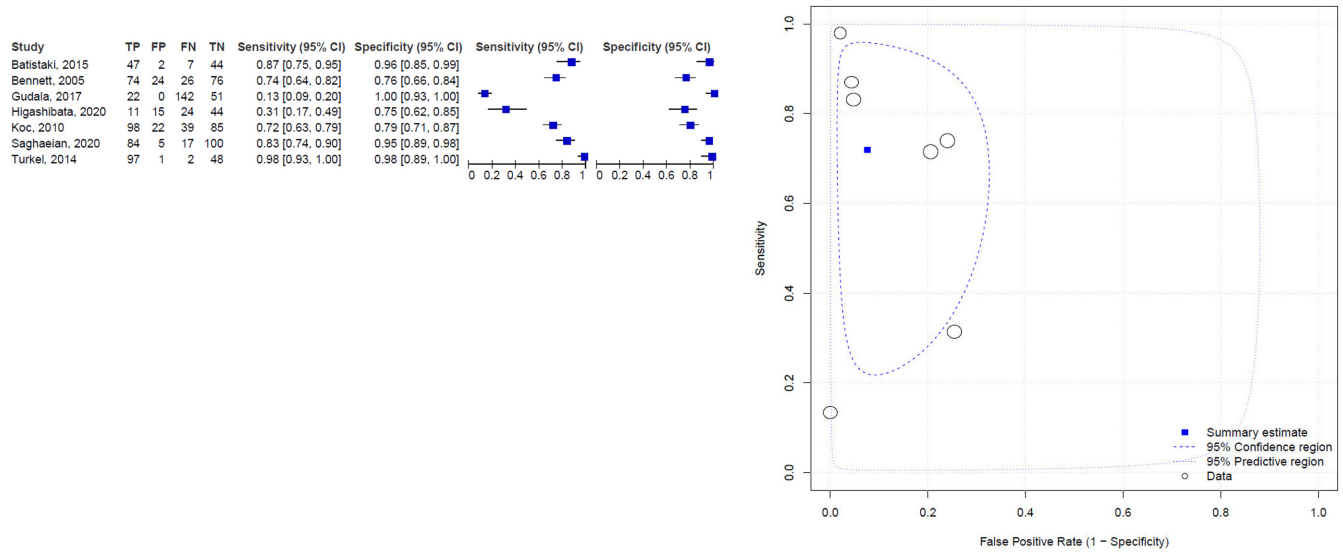


FIGURE 4 Left panel: Forest plot of sensitivity and specificity of the self-administered version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire in the diagnosis of neuropathic pain. These studies investigated the S-LANSS accuracy in patients with probable and definite neuropathic pain. Right panel: Summary receiver operating characteristic of S-LANSS diagnostic accuracy in the diagnosis of neuropathic pain. The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

of Neuropathic Symptoms and Signs (LANSS), the Douleur Neuropathique en 4 Questions (DN4), their self-administered versions (S-LANSS and I-DN4, respectively), and the PainDETECT [8]. We have therefore excluded the IDPain and Neuropathic Pain Questionnaire [9, 10], given that these screening questionnaires found a limited application in studies dealing with diagnostic accuracy [8]. The LANSS and the DN4 include sensory descriptors as well as the investigation of signs related to bedside sensory examination [11, 12]. Conversely, the PainDETECT, S-LANSS, and I-DN4 use only a patient-based questionnaire without the need of examinations by the physician [13–15]. Whereas LANSS and DN4 have a precise cut-off for defining that neuropathic pain is likely, the PainDETECT distinguishes a score ≥ 19, indicating likely neuropathic pain, and scores 12–18, indicating uncertain neuropathic pain.

For the DN4, we included 27 studies; pooled sensitivity was 0.89 (95% confidence interval [CI] = 0.86–0.92) and specificity was 0.88 (95% CI = 0.83–0.92; Figure 1). For the I-DN4, we included nine studies with a pooled sensitivity of 0.83 (95% CI = 0.75–0.88) and

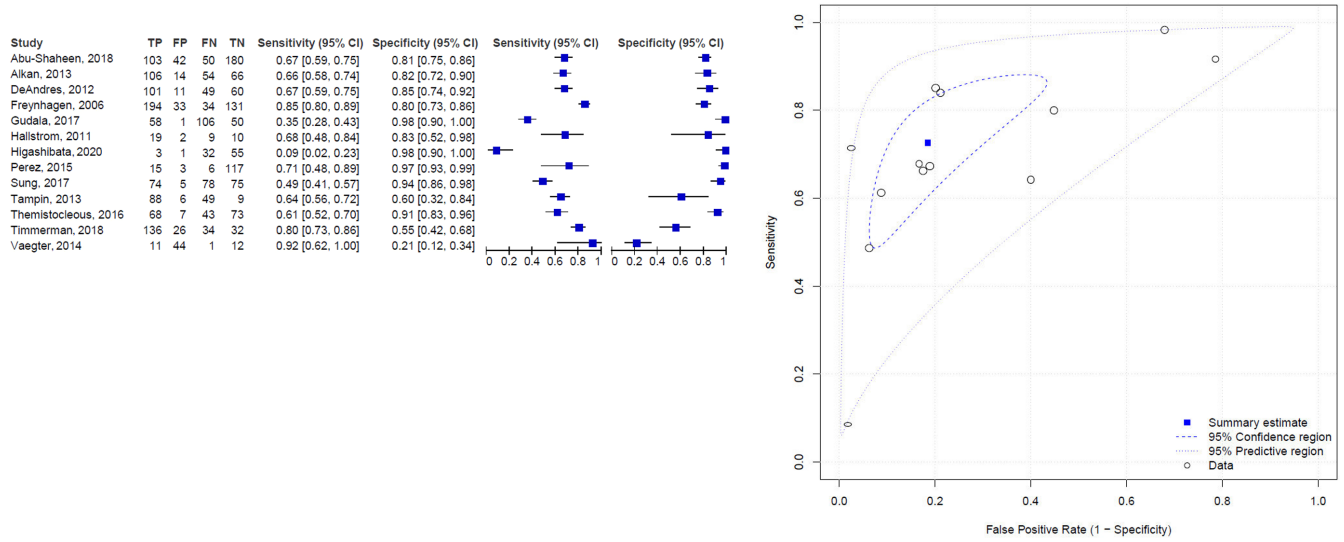


FIGURE 5 Left panel: Forest plot of sensitivity and specificity of the PainDETECT questionnaire in the diagnosis of neuropathic pain. These studies investigated the PainDETECT accuracy in patients with probable and definite neuropathic pain. Right panel: Summary receiver operating characteristic of PainDETECT diagnostic accuracy in the diagnosis of neuropathic pain. The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

specificity of 0.81 (95% CI = 0.76–0.84; Figure 2). For the LANSS, we included 16 studies, and the pooled sensitivity and specificity were 0.70 (95% CI = 0.70–0.70) and 0.93 (95% CI = 0.93–0.93; Figure 3). For the S-LANSS, we included seven studies; the pooled sensitivity was 0.72 (95% CI = 0.42–0.90) and specificity was 0.92 (95% CI = 0.81–0.97; Figure 4). For the PainDETECT, we included 13 studies with a pooled sensitivity and specificity of 0.73 (95% CI = 0.56–0.84) and 0.81 (95% CI = 0.66–0.91; Figure 5).

For the DN4, the certainty of the evidence was low (with sensitivity regarded as a critical outcome) and the main weakness in the studies included was the unclear blinding in one half of them. However, the results were consistent among the studies and the summary estimates were within the threshold of the predefined preferred sensitivity and specificity (Table S1).

For the I-DN4, the certainty of the evidence was very low due to unclear blinding and variability of the results among the studies (Table S2).

For the LANSS and S-LANSS, the certainty of the evidence was very low due to bias in blinding and variability of the results among studies. We considered the pooled estimates of the test accuracy for the S-LANSS analyses as imprecise, having wide CIs for the sensitivity (Tables S3 and S4).

The certainty of the evidence for the PainDETECT was very low due to bias in patient selection, variability of results among the different studies, and imprecision of summary estimates despite the substantial number of patients included (Table S5).

The certainty of the evidence of all tests was downgraded for indirectness of the population because in most of the studies the prevalence of neuropathic pain was higher than that in patients with chronic pain, as reported in epidemiological studies. This inconsistency might reflect the patients' enrolment at pain centres, where the patients have a higher probability of neuropathic pain.

The PPV of the questionnaires were generally low (implicating that the tests provide a high number of false positives), and the NPV was high for all questionnaires (implicating a low number of false negatives; Tables S1–S5). However, given the low certainty of the evidence, these results should be taken with caution, and future studies with a well-defined reference standard and population of interest should provide more information on the relevance of the current results.

Discussion

The usefulness of screening questionnaires for clinical purposes and epidemiological and pharmacological studies is well established [8]. They are easy to use and thus particularly suitable for assessing patients with suspected neuropathic pain in primary care and by specialists. The position of screening questionnaires in the NeuPSIG diagnostic algorithm has not been clearly defined; however, because they do not provide information or specific scoring for location or aetiology of pain, they are most useful to assist health care providers in detecting possible neuropathic pain in their patients. However, by ascertaining neuropathic pain-related symptoms in a structured and validated manner, such questionnaires can assist the health care professional in administering the NeuPSIG algorithm at stage 1 ("possible"), especially when used in combination with a symptom map to determine "neuroanatomically plausible" symptom localization.

Given their relatively high diagnostic accuracy (compared to clinical examination, with or without supporting diagnostic tests), the lack of undesirable effects, the low resources needed, and the availability in many languages [8], we recommend screening questionnaires in the diagnostic pathway for neuropathic pain. We did not consider the relatively low PPV as a critical issue, because the

TABLE 1 Quantitative sensory testing studies.

					Risk of Bias				Applicability		
Author	Condition	Abnormality criteria[a]	Patients, *n*	Frequency of QST abnormalities	Patient selection	Index test	Reference test	Flow and timing	Patient selection	Index test	Reference test
Probable neuropathic pain[b]											
Magda, 2002	SFN	1/3	14	100	☺	☺	☺	?	☹	☺	☺
Kvarnström (2003)	Painful neuropathies	2/6	12	91.7	☹	☺	☹	?	☹	☺	☹
Martin (2003)	Painful neuropathies	1/3	31	100	☹	☺	☹	?	☹	☺	☹
Leffler (2008)	Painful neuropathies	1/5	32	87.5	☺	☺	☹	?	☺	☺	☹
Konopka (2012a)	Painful neuropathies	3/13	81	55.6	☺	☹	☺	?	☺	☹	☺
Konopka (2012b)	Peripheral and central NP	3/13	84	67.9	☺	☹	☺	?	☺	☹	☺
Lefaucheur (2015)	Painful neuropathies	1/2	33	78.8	☹	☺	☹	?	☹	☺	☹
Landmann (2017)	SCI	3/13	13	84.6	☺	☹	☺	?	☹	☹	☺
Definite neuropathic pain[b]											
Maag (2008)	Painful neuropathies	3/13	10	70	☹	☹	☹	?	☹	☹	☹
Quiding (2013)	Painful neuropathies	2/9	27	100	☺	☺	☺	☹	☺	☺	☺
Tampin (2013)	Painful radiculopathy	3/13	23	65.2	☹	☹	☹	?	☹	☹	☹
Krøigård (2014)	Painful neuropathies	1/5	40	59.1	☺	☺	☹	?	☺	☺	☹
Krause (2016)	CPSP	L0G0 classification	50	96	☺	☹	☹	?	☺	☹	☹
Raputova (2017)	Painful diabetic neuropathy	1/10	23	79.7	☺	☹	☺	?	☺	☹	☺

Note: Risk of bias assessment: ☺, high risk; ☹, low risk; ?, unclear risk.Abbreviations: CPSP, central poststroke pain; NP, neuropathic pain; QST, quantitative sensory testing; SCI, spinal cord injury; SFN, small-fibre neuropathy.

[a]Number of abnormal parameters to identify patients with abnormal QST.

[b]The frequency of QST abnormalities is calculated in patients with a probable and definite diagnosis of neuropathic pain.

screening questionnaire can be easily applied and does not require high resources, and the undesirable effects of the subsequent tests (neurophysiology, skin biopsy, neuroimaging) are negligible. At the same time, the high NPV is an advantage, indicating a low number of false negative results. Whereas the results for DN4, I-DN4, and LANSS were consistent among the studies and the summary estimates generally within the threshold of the predefined preferred sensitivity and specificity, results for S-LANSS and PainDETECT varied among the different studies, with wide CIs for sensitivity and specificity. Accordingly, based on the quality of evidence and pooled sensitivity and specificity, we devised a strong recommendation for DN4, I-DN4, and LANSS, and a weak recommendation for S-LANSS and PainDETECT (Tables S1–S5).

Recommendations

We devised a strong recommendation for DN4, I-DN4, and LANSS, and a weak recommendation for S-LANSS and PainDETECT.

QUANTITATIVE SENSORY TESTING

QST uses standardized mechanical and thermal stimuli (e.g., graded von Frey hairs, pinprick stimuli, light touch, pressure algometers, quantitative thermotesting) to examine the nociceptive and non-nociceptive afferent pathways in peripheral nerves and the central nervous system. QST assesses and quantifies the loss of function (sensory deficits) as well as gain of function (positive signs). The standardized protocol for QST proposed by the German Research Network on Neuropathic Pain [16] is widely used for assessing patients with neuropathic pain. This protocol includes 13 parameters gathered from sensory testing procedures. An age-, gender-, and location-matched database for absolute and relative QST reference data, useful for clinical purposes, was established for healthy children, adolescents, and adults [17, 18]. This QST protocol has been applied for defining sensory profiles and establishing subgroups of patients with peripheral neuropathic pain of different aetiology [19]. The different sensory profiles, as assessed with QST, may be related to different pathophysiological mechanisms and may be useful in clinical trials to enrich the study population for treatment responders [19]. We identified 288 articles and eventually included 14 for the analysis of QST accuracy in different central and peripheral neuropathic pain conditions. To ease the interpretation of the results, we defined an abnormal QST if three of 13, two of six, or one of two tested parameters were abnormal. This approach probably increases the sensitivity if many tests are performed, but may affect their specificity, given that 5% of healthy subjects are expected to present with at least one abnormal QST value [20]. In the studies collected, the frequency of QST abnormalities in patients diagnosed with probable and definite neuropathic pain ranged from 55% to 100% and from 59% to 100% (overall median = 82%, interquartile range = 67.2%–97.0%; Table 1). Most studies, however, included only patients with neuropathic pain (only positive subjects at the standard reference test), and we did not find studies that reliably examined the QST sensitivity and specificity. This limitation probably reflects the position of QST in the diagnostic pathway for neuropathic pain. Commonly, this technique is part of the diagnostic criteria for neuropathic pain and the diagnosis cannot be made without sensory examination; hence, it is not possible to assess the sensitivity and specificity of QST, as there is no other reference standard for comparison.

Due to study design limitations, a pooled analysis was not appropriate. Instead, we formulated a descriptive assessment of the evidence, following the GRADE approach (Table S6). This assessment is based on the studies that compared the QST results with the reference standard in patients with probable and definite neuropathic pain, reflective of how QST is used in clinical practice.

Discussion

Although no study specifically investigated the diagnostic accuracy of the QST because sensory testing is an inherent part of the reference standard, the use of this technique in assessing somatosensory nervous system damage in patients with neuropathic pain is well established [1]. Previous recommendations based on expert opinion suggest using QST for a selective investigation of the nociceptive system and propose that in patients with painful small-fibre neuropathy the use of QST is an alternative to skin biopsy [20]. The studies collected showed that QST can identify somatosensory nervous system damage in most patients with neuropathic pain. QST is particularly useful for identifying functional somatosensory disturbances. In clinical practice, QST supports the diagnosis of probable neuropathic pain by robustly demonstrating sensory signs in a neuroanatomically plausible location. Therefore, we devised a weak recommendation for the use of QST in the diagnosis of neuropathic pain (Table S6).

Recommendations

We devised a weak recommendation for using QST to diagnose neuropathic pain.

CLINICAL NEUROPHYSIOLOGY

Various neurophysiological techniques are commonly used for assessing somatosensory nervous system function. Standard neurophysiological responses to electrical stimuli, such as nerve conduction studies and somatosensory-evoked potentials, do not specifically assess the nociceptive system. However, they are useful to demonstrate, locate, and quantify damage along the peripheral or central sensory pathways. Given that they are readily available in most neurophysiological departments and most peripheral and

central nervous system conditions simultaneously affect large- and small-diameter afferent fibres [21], nerve conduction studies and somatosensory-evoked potentials are considered the reference standard for documenting somatosensory nervous system damage. Nevertheless, we did not identify any study providing quantitative information on the sensitivity and specificity of these two techniques (Appendix S1) for the diagnosis of somatosensory system damage in patients with suspected neuropathic pain. Common reasons for exclusion were the circularity of their diagnostic yield (i.e., these techniques were used for the case definition), the lack of information on the frequency of abnormalities (e.g., the study provided only the mean data), and the lack of a reliable comparator (e.g., the reference standard was not clearly defined).

Several techniques are available to assess nociceptive system function, but they are not commonly used in clinical practice. Microneurography, using single-fibre recording from peripheral nerves, mostly provides information on unmyelinated C-fibres. Several studies showed that microneurography can identify nociceptive C-fibre abnormal functioning in patients with painful neuropathies [22]. However, microneurography is time-consuming, requires highly trained personnel, and lacks widely agreed abnormality criteria. Therefore, this technique may be appropriate for phenotyping patients with neuropathic pain, examining pain mechanisms, and verifying the drug modulation of C-fibre activity, but its usefulness in everyday clinical practice has not yet been proven.

The RIII flexion reflex and the corneal reflex are purely nociceptive reflexes. However, their use is limited to physiological and pharmacological studies of modulation of nociception, with no role in the clinical assessment of patients with neuropathic pain [3].

Quantitative sudomotor axon reflex has been studied in patients with painful neuropathy. This technique, though not assessing the somatosensory nervous system, provides information on sudomotor C-fibre function, which may indicate nociceptive C-fibre function [23].

Various neurophysiological techniques are available nowadays for the study of the nociceptive system [24]. One of the most used techniques is evoked potentials to nociceptive stimuli. These can be radiant or contact heat stimuli, which selectively activate nociceptors, giving rise to, respectively, laser-evoked and contact heat-evoked potentials [2]. Electrical stimulation of sensory axons, specifically the nociceptive fibres in the epidermis, has also been proposed [24]. However, its selectivity for activating nociceptive fibres remains unsettled and controversial [25]. There are different techniques devised for electrical stimulation, and several authors have reported on their utility by showing reduced evoked potential amplitude in patients suffering from pain compared to healthy subjects [26]. The particular device employed for electrical stimulation may determine specificity; although the nociceptive specificity of the surface concentric electrode has been challenged [25], intraepidermal concentric electrodes were shown to have similar latencies to laser-evoked potentials in intracortical human recordings [27].

In line with the previous guidelines issued by the EAN, we sought information on the evoked potentials obtained with laser and contact heat stimuli in patients with neuropathic pain [2]. We found three studies that fulfilled the inclusion criteria [28–30]. The authors investigated laser- or contact heat-evoked potentials in patients with small-fibre neuropathy and specifically addressed their sensitivity and specificity using skin biopsy as a comparator. The sensitivity ranges from 0.66 to 0.79 and the specificity is between 0.82 and 0.90 (Figure 6; Table S7). Given that we included for the analysis only three studies, collecting a relatively small sample of patients, we did not complete a pooled analysis.

We also collected and analysed the accuracy of trigeminal reflex testing, the established technique for diagnosing trigeminal neuralgia. Several studies showed that this technique has a high specificity for disclosing trigeminal nerve damage; a previous study reported a trigeminal reflex specificity of 99% in patients with iatrogenic damage to the mandibular nerves [31]. Guidelines for trigeminal neuralgia management issued by the EAN and the diagnostic grading for trigeminal neuralgia issued by the NeuPSIG recommend using trigeminal reflexes in patients with trigeminal neuralgia in cases where magnetic resonance imaging (MRI) is contraindicated or unavailable [32]. Trigeminal reflex testing is more accurate than MRI for detecting trigeminal neuropathy mimicking trigeminal neuralgia [33]. We have included in the analysis four studies providing information on the accuracy of trigeminal reflex testing in patients with trigeminal neuralgia. We found that the pooled sensitivity was 95% (95% CI = 0.58–1.00) with a very low certainty of evidence and the pooled specificity was 94% (95% CI = 0.90–0.97) with a low certainty of evidence (Figure 6; Table S8).

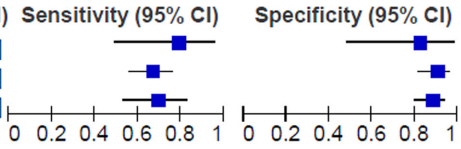
Discussion

Standard nerve conduction studies and somatosensory-evoked potentials do not provide information on the nociceptive system; nonetheless, we consider that they are the most useful tool for documenting and assessing somatosensory system damage of large myelinated fibres in patients with or without neuropathic pain [2].

Although different evoked potential techniques using electrical stimulation are currently available, their selectivity and reliability in the nociceptive system assessment are still controversial. Laser- and contact heat-evoked potentials are established techniques for investigating the nociceptive system in patients with neuropathic pain; they can detect minute, image-proven lesions within the nociceptive system [34]. Although the certainty of the evidence is very low, and the sensitivity is heterogeneous across the three studies included, these techniques have high specificity (critical outcome given that nociceptive evoked potentials are second-line tests). Accordingly, we devised a weak recommendation for using nociceptive evoked potentials in diagnosing neuropathic pain in patients with chronic pain, particularly when conventional neurophysiology is normal (Table S7).

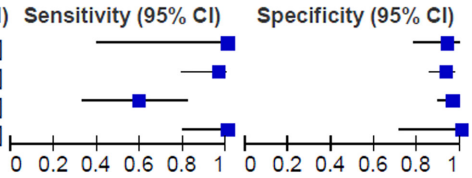
(a) Nociceptive evoked potentials accuracy in the diagnosis of neuropathic pain

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Di Stefano, 2017	11	2	3	9	0.79 [0.49, 0.95]	0.82 [0.48, 0.98]
Fabry, 2020	63	8	32	71	0.66 [0.56, 0.76]	0.90 [0.81, 0.96]
Lagerburg, 2014	29	12	13	85	0.69 [0.53, 0.82]	0.88 [0.79, 0.93]



(b) Trigeminal reflex testing accuracy in the diagnosis of secondary trigeminal neuralgia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cruccu, 1990	4	2	0	28	1.00 [0.40, 1.00]	0.93 [0.78, 0.99]
Cruccu, 2006	23	7	1	89	0.96 [0.79, 1.00]	0.93 [0.86, 0.97]
Kimura, 1983	10	4	7	89	0.59 [0.33, 0.82]	0.96 [0.89, 0.99]
Ongerboer, 1974	16	0	0	11	1.00 [0.79, 1.00]	1.00 [0.72, 1.00]



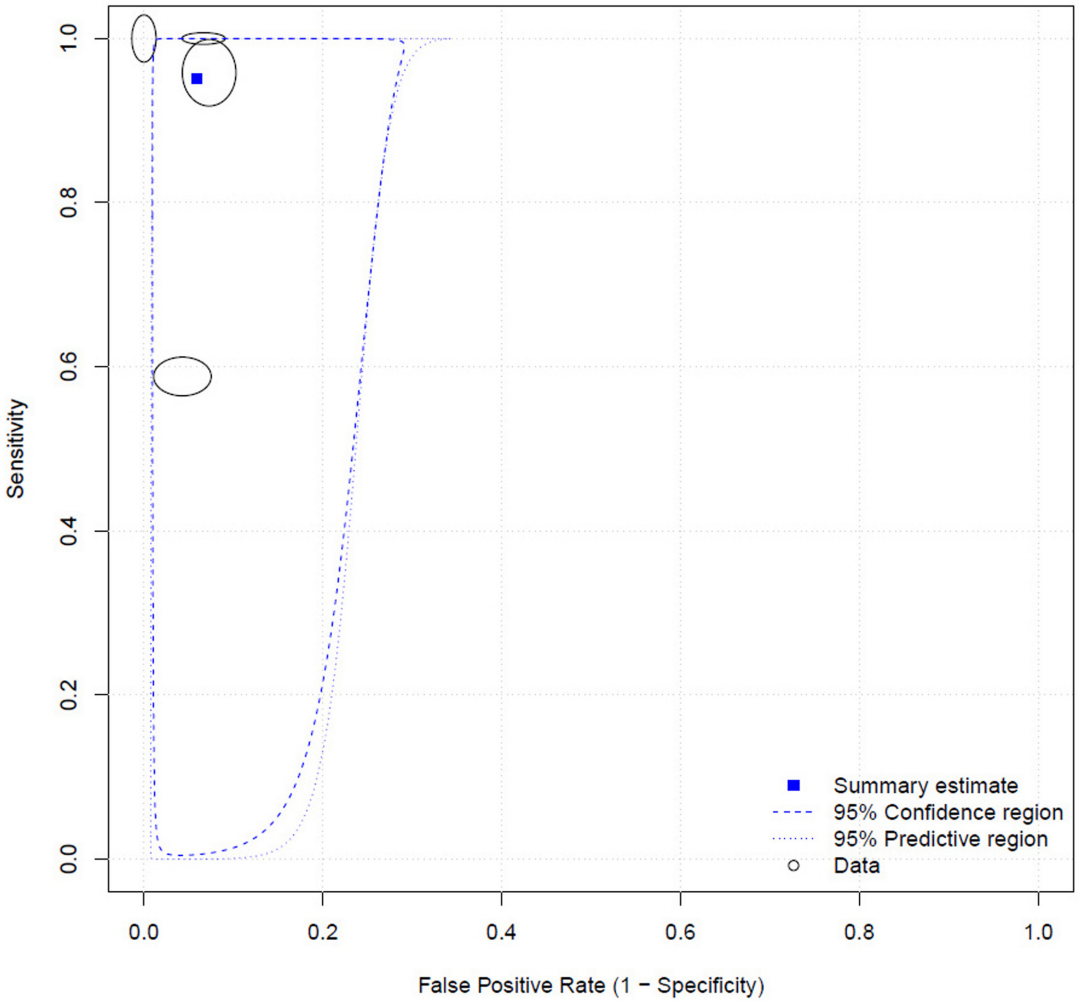


FIGURE 6 Diagnostic accuracy of neurophysiology. (a) Forest plot of sensitivity and specificity of the nociceptive evoked potentials (laser-evoked and contact heat-evoked potentials) in the diagnosis of neuropathic pain. The three studies included compared the diagnostic accuracy of nociceptive evoked potentials in patients with definite small-fibre neuropathy (diagnosis based on clinical examination and skin biopsy). (b) Forest plot of sensitivity and specificity of the trigeminal reflex testing in the diagnosis of secondary trigeminal neuralgia. In the studies included, magnetic resonance imaging was the reference standard diagnostic test (upper panel). Summary receiver operating characteristic of trigeminal reflex testing accuracy in the diagnosis of secondary trigeminal neuralgia is shown (lower panel). The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Concordant studies showed that trigeminal reflex testing is sensitive and specific for disclosing trigeminal damage. Therefore, due to the high diagnostic accuracy, we devised a strong recommendation for using trigeminal reflex testing to diagnose secondary trigeminal neuralgia (Table S8).

Recommendations

We devised a weak recommendation for using nociceptive evoked potentials (laser- and contact heat-evoked potentials) to diagnose neuropathic pain in patients with chronic pain.

Trigeminal reflex testing received a strong recommendation in diagnosing secondary trigeminal neuralgia.

SKIN BIOPSY

Skin biopsy is a technique that was implemented into clinical practice after the discovery of the neuron-specific protein PGP 9.5 [35] and its antibodies, which allowed the staining and quantification of small nerve fibres in skin biopsies [36]. This novel method to quantify small nerve fibres in skin biopsies was then proposed as one of the diagnostic measures for small-fibre neuropathy [37, 38], after extensive work had been done on standardizing methods and providing normative data [39–41]. For diagnostic purposes in peripheral neuropathy, a skin biopsy is commonly done at a distal site on the leg and a further biopsy is taken at a proximal site on the thigh; hence, a proximal site and a distal site can be assessed if a length-dependent process is suspected. Punch biopsy produces a sample of skin that includes the epidermis and the superficial dermis.

Of 207 studies identified by the search, six studies that mostly investigated patients with small-fibre neuropathy fulfilled the eligibility criteria for the meta-analysis. We found that in the included studies, the pooled sensitivity and specificity of skin biopsy in detecting the somatosensory system damage in patients with neuropathic pain were 0.84 (95% CI = 0.75–0.90) and 0.86 (95% CI = 0.70–0.94), respectively (Figure 7). Given the variability of the study designs and the selection of the reference population of healthy controls in some studies, we did not calculate the PPV and NPV. The certainty of the evidence was low for the sensitivity and very low for the specificity (Table S9).

Despite the high diagnostic accuracy of skin biopsy, there are approximately 12%–14% of patients with small-fibre neuropathy (as determined by a composite "reference standard") who show normal intraepidermal nerve fibre density in distal leg skin biopsies [42]. In some of these patients, microneurography or genetics is needed to make the final diagnosis [42]. Another approach has been to increase the sensitivity by using more parameters in skin biopsy than merely the intraepidermal nerve fibre density, for example, assessing dermal nerve fibres [43] or nerve fibre swellings [44], or the quantification of nerve fibre subtypes [45, 46]. Recent skin biopsy studies investigating possible pathological biomarkers of pain found that peptidergic and regenerating fibre immunostaining in patients with diabetic neuropathy is closely associated with neuropathic pain [45, 47]. However, there is not sufficient information about these techniques for clinical application.

Discussion

Skin biopsy collection, processing, and analysis should be done by experienced hands and in well-prepared settings, following published guidelines [39–41].

Because skin biopsy is minimally invasive and requires well-trained technicians, it should be considered based on well-founded clinical suspicion of small-fibre neuropathy or other neuropathic pain that less invasive methods cannot diagnose. Because the normative data on intraepidermal nerve fibre density from healthy controls differs between laboratories, intraepidermal nerve fibre density values should be compared to age- and gender-matched healthy controls from the same laboratory.

Although the certainty of the evidence for the test accuracy is very low, given its diagnostic accuracy and minor undesirable effects, we devised a strong recommendation for the use of skin biopsy in the diagnosis of neuropathic pain, particularly when probable neuropathic pain associated with small-fibre neuropathy is suspected and patients have unremarkable standard neurophysiological findings (Table S9). When skin biopsy is indicated, standardized methods for sample collection, processing, and reading should be followed, and the most recognized standardized procedures for skin biopsies in neuropathic pain should be observed [39–41].

Recommendation

The use of skin biopsy is strongly recommended in the diagnosis of neuropathic pain, particularly in patients with suspected small-fibre neuropathy.

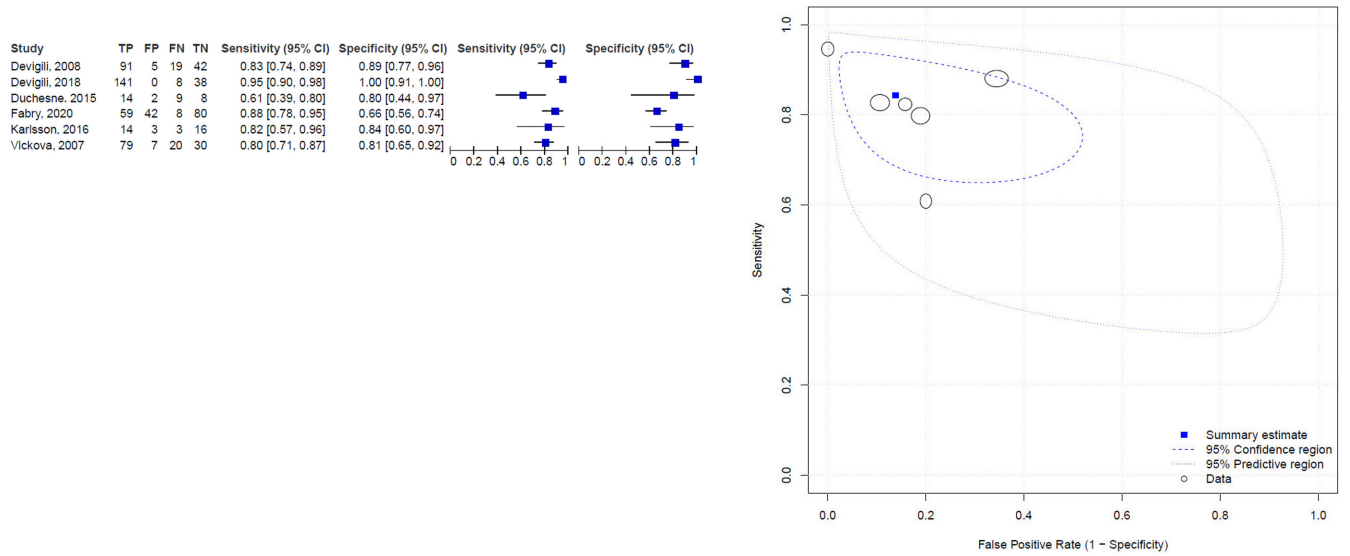


FIGURE 7 Left panel: Forest plot of sensitivity and specificity of skin biopsy in the diagnosis of neuropathic pain; the studies included compared the diagnostic accuracy of skin biopsy in patients with definite small-fibre neuropathy (diagnosis based on clinical examination and quantitative sensory testing/nociceptive evoked potentials). Right panel: Summary receiver operating characteristic of skin biopsy accuracy in the diagnosis of small-fibre neuropathy with neuropathic pain. The list of studies included is reported in Appendices S3 and S4. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

CORNEAL CONFOCAL MICROSCOPY

The corneal innervation consists of small myelinated Aδ- and C-fibres. CCM is a noninvasive, in vivo technique, useful for assessing corneal innervation and quantifying corneal nerve fibre damage in patients with peripheral neuropathies. This technique assesses different corneal nerve fibre parameters, namely the corneal nerve fibre length, the nerve fibre density, and the nerve fibre branching [48]. Several studies showed that in patients with diabetic neuropathy and sarcoidosis, corneal nerve fibre damage correlates with the severity of peripheral nerve damage assessed by neurophysiological and skin biopsy findings [49]. CCM parameters are sensitive to treatment indicating corneal nerve fibre repair. This has been shown in patients with diabetes after pancreas transplantation and the consequent improvement of risk factors associated with diabetic neuropathy [50] as well as in patients with sarcoidosis after specific pharmacological anti-inflammatory treatment [51]. In a study including 998 patients with type 1 and type 2 diabetes, corneal nerve fibre length, nerve fibre density, and nerve fibre branching had a sensitivity of 67%, 52%, and 66%, and a specificity of 66%, 68%, and 60% for detecting peripheral neuropathy (regardless of neuropathic pain) [48]. Applying CCM additionally to established small-fibre tests like skin biopsy and QST might increase the diagnostic sensitivity for small-fibre neuropathy, thus having the potential to contribute to a diagnosis of definite neuropathic pain [42].

We identified two articles addressing the diagnostic accuracy of CCM in patients with sarcoidosis-related small-fibre neuropathy and neuropathic pain. One study [52] provided a frequency of abnormality of 9%, 43%, and 28% for nerve fibre density, nerve fibre branching, and nerve fibre length, respectively. In 16 patients with evidence of small-fibre neuropathy after skin biopsy, the CCM sensitivity was 44% and the CCM specificity was 55% compared to skin biopsy. The other study found that the sensitivity and specificity of the three main CCM parameters ranged between 60% and 80% [49]. However, we did not pursue a GRADE assessment due to the low number of patients included and the unclear case definition of small-fibre neuropathy, with uncertainties regarding true positives and false negatives.

Comments

CCM represents a novel and promising tool for investigating small nerve fibre damage in patients with peripheral neuropathy. It is important, however, that trained examiners evaluate results and that ophthalmological abnormalities that lead to changes in the corneal subbasal plexus are excluded (e.g., dry eye syndrome, contact lens wearers, keratoconus, keratopathy, keratitis, ophthalmological surgery).

The current evidence on CCM accuracy in patients with neuropathic pain due to small-fibre damage is still inconclusive. Further studies with established comparators are still needed to verify the sensitivity and specificity of CCM in patients with neuropathic pain associated with small-fibre neuropathy.

PERIPHERAL NERVE BLOCKS

Given that in clinical practice peripheral nerve blocks are not typically used for the diagnosis of neuropathic pain, our search and analysis did not explicitly aim at collecting information on the sensitivity and specificity of these procedures. However, because the efficacy

of peripheral nerve blocks might be used to confirm a diagnosis of neuropathic pain, we searched for articles providing evidence that peripheral nerve blocks indirectly confirm a neuropathic pain diagnosis.

We identified six relevant studies providing information on how peripheral nerve blocks may help confirm a diagnosis of neuropathic pain. The six selected studies enrolling 175 patients assessed anaesthetic nerve blocks for genitofemoral neuralgia (one study), sciatica (three studies), cervical radiculopathy (one study), or pain due to focal nerve injury (one study). Four of these studies were part of (or mentioned in) previous systematic reviews aiming to assess the utility of diagnostic nerve blocks in patients with lumbar radiculopathy [53]. No data met our criteria concerning the supporting diagnostic value of intravenous injections or sympathetic blocks. Comparators (reference) included the response to surgery in two studies, imaging evidence of compression in two studies, a combination of spine imaging with a neurological examination in one study, and intraoperative findings in one study. In all cases, nerve blocks used local anaesthetics (lidocaine, bupivacaine, mepivacaine, and procaine).

Whereas one study found that retroperitoneal genitofemoral nerve block efficacy was relevant to the diagnosis of genitofemoral neuralgia [54], other studies have reported a limited or moderate role of nerve blocks, three of them in the diagnosis of lumbar radiculopathy [55–57] and one in the diagnosis of cervical radiculopathy [58]. One high-quality study conducted on 24 patients using a double-blind design assessing the predictive value of a diagnostic nerve block in focal nerve injury with neuropathic pain on the outcome of surgery found a low predictive value of placebo-controlled lidocaine blocks [59]. In general, sensitivity was high, except in two studies finding moderate sensitivity [55, 58], whereas specificity and diagnostic accuracy were low, except in the study of Yeom et al. [55].

Three studies were judged at high risk of bias [55–57], two had moderate risk [54–58], and one was considered as high quality [59]. Risks of bias were related to lack of blinded tests (except in the study of Malessy et al. [59]), patient selection, or concerns related to reference standards because surgery was predominantly performed in patients with positive responses to blocks or response to surgery was not considered [55–57]. Applicability was generally good for index tests and reference standards, except in the study in which reference standards were intraoperative findings [57].

Comments

The studies identified provide limited evidence to support using nerve blocks to diagnose neuropathic pain. Some procedures, such as intraforaminal nerve root blocks for cervical radiculopathy and genitofemoral blocks for genitofemoral neuralgia, may have a prognostic value for surgical success but need to be thoroughly examined in future controlled trials.

FUNCTIONAL NEUROIMAGING

Functional neuroimaging, specifically positron emission tomography and functional MRI, has been used to investigate changes in brain activity in response to various experimental stimuli inducing pain [60]. In clinical practice, functional neuroimaging is not used for diagnosing neuropathic pain. Accordingly, in our search and analysis, we aimed to assess how functional neuroimaging reflects somatosensory nervous system damage in patients with neuropathic pain.

We selected 91 articles on functional neuroimaging in patients with different neuropathic pain conditions. Most studies compared patients with or without neuropathic pain at the group level, without providing biomarkers able to discriminate patients with neuropathic pain at the individual level. Although in its present state, functional neuroimaging has no diagnostic value for patients with neuropathic pain, it provides useful insights into the pathophysiology of neuropathic pain to generate notions that may be subsequently tested for diagnostic purposes. Functional neuroimaging has generated useful results with tentative clinical usefulness for the most representative neuropathic pain qualities, namely, ongoing neuropathic pain and provoked pain (allodynia).

Several studies by different groups showed that patients suffering from ongoing neuropathic pain have a decrease in thalamic activity (metabolism, blood flow) contralateral to the painful side [61]. A functionally inhibited thalamus in chronic neuropathic pain is also supported by volume reduction in voxel-based morphometry, reduced neural functionality in MRI spectroscopy [62], and single-unit activity consistent with hyperinhibition [63]. The pathophysiological relevance of these thalamic changes to neuropathic pain development is underscored by their absence in nonneuropathic pain [62] and their reversibility with successful analgesia [64]. Although preliminary, recent studies showing functional connectivity changes between the thalamus and pain-related areas also support such plastic functional thalamic changes [65].

Provoked pain, in particular dynamic mechanical allodynia, is associated with characteristic quantitative changes, the most relevant being a cerebral response out of proportion to the actual intensity of the stimulus, that is, the response magnitude to gentle stroking becomes virtually identical to that triggered by painful stimuli in normal conditions [66]. Qualitative changes have been also reported, namely (i) transformation of thalamic resting hypoactivity into hyperactivity [67], (ii) topographical shift of activation from ventrolateral to medial nuclei [68], (iii) paradoxical activity enhancement of ipsilateral operculoinsular cortex, and (iv) lack of physiological reactivity of ventromedial prefrontal cortex [66].

A range of alterations in metabolite concentrations in subsets of patients with neuropathic pain has been described [69], sometimes pointing to glial-related alterations. This is likely to represent a productive avenue in the upcoming years.

Comments

Although not considered a diagnostic tool, functional imaging has provided relevant data to understand mechanisms underlying ongoing neuropathic pain and allodynia in humans.

GENETIC STUDIES OF NEUROPATHIC PAIN

In clinical practice, genetic testing has a diagnostic role in selected conditions. Our systematic research did not aim at collecting information on the diagnostic accuracy of genetic testing; we rather aimed at reviewing and summarizing the studies in humans that have investigated how genetic factors influence neuropathic pain.

There are a number of rare human monogenic neuropathic pain conditions. A twin study demonstrated a substantial contribution of genetic factors to common neuropathic pain conditions with heritability estimates of approximately 37% [70], arising from multiple genes.

Genetic analysis is currently employed in clinical practice in relation to specific phenotypes associated with rare monogenic pain disorders and is important for diagnosis, genetic/reproductive counselling, and also treatment selection. The best example of this phenomenon is mutations in the *SCN9A* gene encoding the voltage-gated sodium channel (VGSC) Nav1.7. Biallelic loss of function variants in *SCN9A* result in congenital insensitivity to pain [71]; conversely, more than 20 distinct rare gain of function variants have now been linked to inherited erythromelalgia [72]; a distinct set of rare gain of function *SCN9A* variants have also been shown to cause paroxysmal extreme pain disorder (PEPD).

More recently, small-fibre neuropathy has also been linked to rare variants in *SCN9a* (and other VGSCs), although these may be acting to increase risk of small-fibre neuropathy (rather than Mendelian inheritance), given the allele frequency in the general population. A recent systematic review summarized studies describing how gene variants contribute to neuropathic pain susceptibility [73]; we have updated this review here and eventually included 36 genetic studies (Table S10). More than 70% of the studies had applied a candidate gene association (CGA) approach and reported several genes that are mainly involved in immune responses, neurotransmission, ion channels, protein binding, receptor signalling, and metabolism. *COMT* [74], HLA-A, HLA-B, HLA-DRB1 [75], and *OPRM1* [76] genes are the most frequently reported candidate genes, but their role remains debated due to inconsistent replication. Although HLA genes achieved significance ($p = 0.05$) in a meta-analysis, these studies had a relatively small sample size and significant heterogeneity across studies [73]. Neither the genetic variant in *COMT* nor *OPRM1* achieved significance in the meta-analysis [73]. There have been several candidate genes, *GCH1* [77], *IL6* [78], *IL10* and *IL1R2* [79], *TNFA* [80], *SCN9A* [81], *CACNG2* [82], *SLC6A4* [83], *ACO1*, *B2M*, *BMP6*, *TF*, *CP*, *TFRC*, *FXN*, and *SLC11A2* [84], and *HTR2A* [85,86] found to be associated with neuropathic pain susceptibility in a single study each. Studies have also reported the association of *COMT* [74], *OPRM1* [86], *MMP1* [87], *KCNS1* [88], *TNFA* [89], and *P2RX7* [90] harbouring variants with increased pain intensity. The most recent study replicated only one variant in *P2RX7* associated with neuropathic pain in patients with herpes zoster [91]. All these studies suffer from insufficient power, replication, and inconsistent phenotyping. CGA studies have so far failed to find causative variants [90, 91]. To date, there are a very few hypothesis-free genome-wide association studies (GWASs) in this field. Two GWASs were performed in the same diabetic population using different phenotyping criteria and found suggestive variants near GFRA2 [92], *HMGB1P46* in females and near *ZSCAN20* in males [93]. Another GWAS of neuropathic pain in post-joint replacement patients identified one suggestive variant near *PRKCA* [94]. A meta-analysis of GWASs of sciatica found a genome-wide significant locus near NFIB [95]. A recent GWAS of neuropathic pain in head and neck cancer patients found four loci near *SNX8*, *PCP2*, *KNG1*, and *RORA* [96]. A large-scale GWAS in the UK Biobank identified 16 susceptibility loci for carpal tunnel syndrome, which often includes neuropathic pain [97]. However, these individuals were not screened for neuropathic pain. These findings warrant validation, and their potential biological roles are as yet unclear.

Comments

In this study, we have only examined genetic associations with neuropathic pain, rather than genetic associations with the inciting injurious event (such as disc degeneration or peripheral neuropathy). We acknowledge that there are inherited neuropathies (such as hereditary sensory neuropathy type-1, amyloid transthyretin amyloidosis, and Fabry disease) in which pain is a prominent feature, and these have been recently reviewed [98].

Genetic testing does not currently have a role in routine assessment of neuropathic pain. There is a role in specific monogenic disorders, such as erythromelalgia and PEPD, which have very clear phenotypes. At specialist centres, genetic testing may be considered in the case of small-fibre neuropathy if other causes have been excluded and particularly if there is a family history. Further genetic research, with large samples and clear phenotyping, may create a greater role for genetic testing in the future [99, 100].

NEUROPATHIC PAIN ASSESSMENT IN SPECIFIC PATIENTS' CATEGORY

Screening questionnaires have a low cost and do not require highly trained personnel; thus, they do improve care services for patients living in low-income countries or in rural areas lacking advanced health care facilities.

However, screening questionnaires as well as QST, requiring an active patient's cooperation, have limited applicability in vulnerable and noncommunicating patients. In patients with language or communication disorders and in those with cognitive impairment, the diagnosis of definite neuropathic pain should primarily rely on

TABLE 2 Summary of recommendations.

	Conditions	Studies included, *n*	Diagnostic accuracy		Strength of recommendation for use
			Sensitivity	Specificity	
Screening questionnaires					
DN4	All neuropathic pain conditions	27	0.89 (0.68–0.92)	0.88 (0.83–0.92)	Strong
I-DN4	All neuropathic pain conditions	9	0.83 (0.75–0.88)	0.81 (0.76–0.84)	Strong
LANSS	All neuropathic pain conditions	16	0.70 (0.70–0.70)	0.93 (0.93–0.93)	Strong
S-LANSS	All neuropathic pain conditions	7	0.72 (0.42–0.90)	0.92 (0.81–0.97)	Weak
PainDETECT	All neuropathic pain conditions	13	0.73 (0.56–0.84)	0.81 (0.66–0.91)	Weak
Quantitative sensory testing[a]	All neuropathic pain conditions	14	NA	NA	Weak
Nociceptive evoked potentials[b]	All neuropathic pain conditions	3	0.66–0.79	0.82–0.90	Weak
Trigeminal reflex testing	Trigeminal neuralgia	4	0.95 (0.58–1.00)	0.94 (0.90–0.97)	Strong
Skin biopsy	Neuropathic pain associated with small-fibre neuropathy	6	0.84 (0.75–0.90)	0.86 (0.70–0.94)	Strong
Corneal confocal microscopy	Neuropathic pain associated with small-fibre neuropathy	Insufficient and inconclusive evidence; further studies needed			
Functional neuroimaging	All neuropathic pain conditions	Not currently a diagnostic tool but could provide insight in pathophysiology; further studies needed			
Peripheral nerve blocks	Neuropathic pain associated with peripheral nervous system diseases	Intraforaminal nerve root blocks for cervical radiculopathy and genitofemoral blocks for genitofemoral neuralgia may have a prognostic value for surgical success; further studies needed			
Genetic testing	Neuropathic pain associated with peripheral nervous system diseases	Established role in monogenic disorders (e.g., erythromelalgia); it might be also considered in selected cases (e.g., "idiopathic" small-fibre neuropathy), but not for the routine assessment of neuropathic pain			

Note: Corneal confocal microscopy, functional neuroimaging, peripheral nerve blocks, and genetic testing did not undergo GRADE assessment to derive a strength of recommendation.Abbreviations: DN4, Douleur Neuropathique en 4 Questions; I-DN4, self-administered version of DN4; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; NA, not applicable; S-LANSS, self-administered version of LANSS.

[a]Pooled analysis of sensitivity and specificity not provided due to the characteristics of the studies selected for the analysis.

[b]Pooled analysis of sensitivity and specificity not provided due to the small sample of subjects included in the three studies selected.

techniques (e.g., neurophysiology and skin biopsy) providing an objective demonstration of somatosensory nervous system damage.

LIMITATIONS

Limited information on the sensitivity and specificity of the different diagnostic techniques assessing the somatosensory nervous system in patients with suspected neuropathic pain is currently available. Because a "reference standard" technique could not be introduced as a comparator in most studies, a precise calculation of sensitivity and specificity was not possible. Admittedly, a reference standard for the diagnosis of neuropathic pain is still an open issue. Neuropathic pain can result from a wide range of peripheral and central nervous system diseases; therefore, different techniques are alternatively used in the assessment of patients suspected of neuropathic pain. Because of reference standard unavailability, we applied a circular approach in the analysis of diagnostic accuracy, with a specific technique being the index test or the comparator depending on the specific analysis. For instance, the diagnostic accuracy of the neurophysiological techniques for peripheral neuropathic pain has been calculated having the skin biopsy as a comparator [29]; alternatively, in the diagnostic accuracy calculation for skin biopsy, skin biopsy was the index test, and a combination of other techniques (including neurophysiology) was the comparator [38]. Future clinical investigations based on longitudinal follow-up of patients with suspected neuropathic pain may identify a reliable "reference standard" to be used for studies assessing the accuracy of further objective tests. Additionally, we may suggest that due to the relatively well-documented accuracy of skin biopsy in patients with painful small-fibre neuropathy, this technique might be used as a reliable comparator in studies verifying more precisely the diagnostic yield of QST in a cohort of patients selected according to the grading system for the diagnosis of neuropathic pain.

An additional problem in assessing diagnostic test accuracy in patients with suspected neuropathic pain is the variable association between somatosensory nervous system damage and neuropathic pain. Consequently, the association between diagnostic test abnormalities and neuropathic pain is not always straightforward. For instance, patients may suffer from nociceptive pain in an area within the territory affected by an injury or disease involving the somatosensory nervous system. Examples include spasticity-related pain below the level of injury in a patient with incomplete spinal cord injury or plantar fasciitis in a patient with polyneuropathy. An accurate description of pain characteristics can most often orient diagnosis in these cases.

Admittedly, in some instances we have deviated from the recommendations of GRADE in terms of moving from quality/confidence of evidence to recommendations [101]. In general, guidelines for therapeutic approaches do not provide strong recommendations where the confidence/quality of evidence is low or very low. However, we believe that diagnostic guidelines have some specificities. In our guidelines, some of the PICOs that received low certainty of the evidence resulted in strong recommendations. The low certainty of the evidence in these studies reflected the bias in patient selection (case–control study designs), and indirectness, because most of them excluded specific conditions that may result in chronic pain. Accordingly, the prevalence of neuropathic pain in the study populations was much higher than 20%. However, in formulating the recommendations, apart from the quality of evidence, we considered other aspects, such as the benefits and harms of the diagnostic test, their cost, and the variability of sensitivity and specificity among the studies.

CONCLUSIONS AND FUTURE DIRECTIONS

These joint EAN-EFIC-NeuPSIG guidelines provide previously unreported information on the accuracy of commonly used diagnostic techniques in patients with neuropathic pain (Table 2). Admittedly, the available literature provides poor information on the diagnostic accuracy of most diagnostic tests. Standardizing the cutoff values for the various diagnostic techniques and establishing a reference standard for neuropathic pain will enable a more accurate summary of the results among various studies.

These guidelines are scheduled for updates. As new evidence that would fundamentally change the recommendations of the guidelines emerges, a new production task force will be formed, which may include members of the initial group, and the document will be updated following the EAN's guidance. The EAN Scientific Committee will regularly survey the validity of published guidelines and generally ask for revision every 5 years or less if deemed necessary.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain*. 2016;157(8):1599-1606.
2. Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol*. 2010;17(8):1010-1018. doi:10.1111/j.1468-1331.2010.02969.x
3. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain*. 2011;152(1):14-27. doi:10.1016/j.pain.2010.07.031
4. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
5. Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. *Eur J Neurol*. 2015;22(12):1505-1510.
6. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58(10):982-990. doi:10.1016/j.jclinepi.2005.02.022
7. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet*. 2021;397(10289):2082-2097.
8. Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. *Lancet Neurol*. 2018;17(5):456-466.
9. Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. *Clin J Pain*. 2003;19(5):306-314.
10. Portenoy R. Development and testing of a neuropathic pain screening questionnaire: ID pain. *Curr Med Res Opin*. 2006;22(8):1555-1565.
11. Bennett M. The LANSS pain scale: the Leeds assessment of neuropathic symptoms and signs. *Pain*. 2001;92(1–2):147-157.
12. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114(1–2):29-36.
13. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain*. 2005;6(3):149-158.
14. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*. 2008;136(3):380-387. doi:10.1016/j.pain.2007.08.013
15. Freynhagen R, Baron R, Gockel U, Tölle TR. PainDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22(10):1911-1920.
16. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German research network on neuropathic pain (DFNS): standardized protocol and reference values. *Pain*. 2006;123(3):231-243.
17. Blankenburg M, Boekens H, Hechler T, et al. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. *Pain*. 2010;149(1):76-88. doi:10.1016/j.pain.2010.01.011
18. Magerl W, Krumova EK, Baron R, Tölle T, Treede RD. Maier C reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. *Pain*. 2010;151(3):598-605.
19. Demant DT, Lund K, Vollert J, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain*. 2014;155(11):2263-2273.
20. Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain*. 2013;154(9):1807-1819.
21. Garcia-Larrea L, Hagiwara K. Electrophysiology in diagnosis and management of neuropathic pain. *Rev Neurol (Paris)*. 2019;175:26-37.
22. Serra J, Duan WR, Locke C, Solà R, Liu W, Nothaft W. Effects of a T-type calcium channel blocker, ABT-639, on spontaneous activity in C-nociceptors in patients with painful diabetic neuropathy: a randomized controlled trial. *Pain*. 2015;156(11):2175-2183.
23. Novak V, Freimer ML, Kissel JT, et al. Autonomic impairment in painful neuropathy. *Neurology*. 2001;56(7):861-868.
24. Lefaucheur JP. Clinical neurophysiology of pain. *Handb Clin Neurol*. 2019;161:121-148.

25. Perchet C, Frot M, Charmarty A, et al. Do we activate specifically somatosensory thin fibres with the concentric planar electrode? A scalp and intracranial EEG study. *Pain*. 2012;153(6):1244-1252.
26. Üçeyler N, Kahn AK, Kramer D, et al. Impaired small fiber conduction in patients with Fabry disease: a neurophysiological case-control study. *BMC Neurol*. 2013;24(13):47.
27. Hagiwara K, Perchet C, Frot M, Bastuji H, Garcia-Larrea L. Insular-limbic dissociation to intra- epidermal electrical Aδ activation: a comparative study with thermo-nociceptive laser stimulation. *Eur J Neurosci*. 2018;48(10):3186-3198.
28. Lagerburg V, Bakkers M, Bouwhuis A, et al. Contact heat evoked potentials: normal values and use in small-fiber neuropathy. *Muscle Nerve*. 2015;51(5):743-749.
29. Di Stefano G, La Cesa S, Leone C, et al. Diagnostic accuracy of laser-evoked potentials in diabetic neuropathy. *Pain*. 2017;158(6):1100-1107.
30. Fabry V, Gerdelat A, Acket B, et al. Which method for diagnosing small fiber neuropathy? *Front Neurol*. 2020;5(11):342.
31. Biasiotta A, Cascone P, Cecchi R, et al. Iatrogenic damage to the mandibular nerves as assessed by the masseter inhibitory reflex. *J Headache Pain*. 2011;12(4):485-488. doi:10.1007/s10194-011-0354-0
32. Bendtsen L, Zakrzewska JM, Abbott J, et al. European academy of neurology guideline on trigeminal neuralgia. *Eur J Neurol*. 2019;26(6):831-849.
33. Cruccu G, Pennisi EM, Antonini G, et al. Trigeminal isolated sensory neuropathy (TISN) and FOSMN syndrome: despite a dissimilar disease course do they share common pathophysiological mechanisms? *BMC Neurol*. 2014;19(14):248.
34. Convers P, Creac'h C, Beschet A, Laurent B, Garcia-Larrea L, Peyron R. A hidden mesencephalic variant of central pain. *Eur J Pain*. 2020;24(7):1393-1399.
35. Wilkinson KD, Lee KM, Deshpande S, Duerksen-Hughes P, Boss JM, Pohl J. The neuron-specific protein PGP 9.5 is a ubiquitin carboxyl-terminal hydrolase. *Science*. 1989;246:670-673.
36. Dalsgaard CJ, Rydh M, Haegerstrand A. Cutaneous innervation in man visualized with protein gene product 9.5 (PGP 9.5) antibodies. *Histochemistry*. 1989;92:385-390.
37. Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain*. 2008;131:1912-1925.
38. Devigili G, Rinaldo S, Lombardi R, et al. Diagnostic criteria for small fibre neuropathy in clinical practice and research. *Brain*. 2019;142:3728-3736.
39. Lauria G, Cornblath DR, Johansson O, et al. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. *Eur J Neurol*. 2005;12:747-758.
40. Lauria G, Hsieh ST, Johansson O, et al. European Federation of Neurological Societies/peripheral nerve society guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the peripheral nerve society. *Eur J Neurol*. 2010;17(903–12):e44-e49.
41. Provitera V, Gibbons CH, Wendelschafer-Crabb G, et al. A multicenter, multinational age- and gender-adjusted normative dataset for immunofluorescent intraepidermal nerve fiber density at the distal leg. *Eur J Neurol*. 2016;23(2):333-338.
42. Egenolf N, Zu Altenschildesche CM, Kreß L, et al. Diagnosing small fiber neuropathy in clinical practice: a deep phenotyping study. *Ther Adv Neurol Disord*. 2021;23(14):17562864211004318.
43. Karlsson P, Moller AT, Jensen TS, Nyengaard JR. Epidermal nerve fiber length density estimation using global spatial sampling in healthy subjects and neuropathy patients. *J Neuropathol Exp Neurol*. 2013;72:186-190.
44. Karlsson P, Gylfadottir SS, Kristensen AG, et al. Axonal swellings are related to type 2 diabetes, but not to distal diabetic sensorimotor polyneuropathy. *Diabetologia*. 2021;64(4):923-931.
45. Karlsson P, Provitera V, Caporaso G, et al. Increased peptidergic fibers as a potential cutaneous marker of pain in diabetic small fiber neuropathy. *Pain*. 2021;162(3):778-786.
46. Gylfadottir SS, Itani M, Kristensen AG, et al. Analysis of macrophages and peptidergic fibers in the skin of patients with painful diabetic polyneuropathy. *Neurol Neuroimmunol Neuroinflamm*. 2021;9(1):e111.
47. Galosi E, La Cesa S, Di Stefano G, et al. A pain in the skin. Regenerating nerve sprouts are distinctly associated with ongoing burning pain in patients with diabetes. *Eur J Pain*. 2018;22(10):1727-1734. doi:10.1002/ejp.1259
48. Perkins BA, Lovblom LE, Bril V, et al. Corneal confocal microscopy for identification of diabetic sensorimotor polyneuropathy: a pooled multinational consortium study. *Diabetologia*. 2018;61(8):1856-1861. doi:10.1007/s00125-018-4653-8
49. Brines M, Culver DA, Ferdousi M, et al. Corneal nerve fiber size adds utility to the diagnosis and assessment of therapeutic response in patients with small fiber neuropathy. *Sci Rep*. 2018;8(1):4734.
50. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, et al. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. *Diabetes*. 2013;62(1):254-260.
51. Dahan A, Dunne A, Swartjes M, et al. ARA 290 improves symptoms in patients with sarcoidosis- associated small nerve fiber loss and increases corneal nerve fiber density. *Mol Med*. 2013;19(1):334-345.
52. Oudejans LC, Niesters M, Brines M, Dahan A, van Velzen M. Quantification of small fiber pathology in patients with sarcoidosis and chronic pain using cornea confocal microscopy and skin biopsies. *J Pain Res*. 2017;26(10):2057-2065.
53. Beynon R, Elwenspoek MMC, Sheppard A, et al. The utility of diagnostic selective nerve root blocks in the management of patients with lumbar radiculopathy: a systematic review. *BMJ Open*. 2019;9:e025790.
54. Fritz J, Dellon AL, Williams EH, Rosson GD, Belzberg AJ, Eckhauser FE. Diagnostic accuracy of selective 3-T MR neurography-guided retroperitoneal genitofemoral nerve blocks for the diagnosis of genitofemoral neuralgia. *Radiology*. 2017;285:176-185.
55. Yeom JS, Lee JW, Park KW, et al. Value of diagnostic lumbar selective nerve root block: a prospective controlled study. *AJNR Am J Neuroradiol*. 2008;29:1017-1023.
56. North RB, Kidd DH, Zahurak M, Piantadosi S. Specificity of diagnostic nerve blocks: a prospective, randomized study of sciatica due to lumbosacral spine disease. *Pain*. 1996;65:77-85.
57. Schutz H, Lougheed WM, Wortzman G, Awerbuck BG. Intervertebral nerve-root in the investigation of chronic lumbar disc disease. *Can J Surg*. 1973;16:217-221.
58. Anderberg L, Annertz M, Rydholm U, Brandt L, Säveland H. Selective diagnostic nerve root block for the evaluation of radicular pain in the multilevel degenerated cervical spine. *Eur Spine J*. 2006;15(6):794-801. doi:10.1007/s00586-005-0931-5
59. Malessy MJA, de Boer R, Muñoz Romero I, et al. Predictive value of a diagnostic block in focal nerve injury with neuropathic pain when surgery is considered. *PLoS One*. 2018;13:e0203345.
60. Davis KD, Aghaeepour N, Ahn AH, et al. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. *Nat Rev Neurol*. 2020;16(7):381-400.
61. Peyron R, Garcia-Larrea L, Deiber MP, et al. Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. *Pain*. 1995;62(3):275-286.

62. Gustin SM, Wrigley PJ, Youssef AM, et al. Thalamic activity and biochemical changes in individuals with neuropathic pain after spinal cord injury. *Pain*. 2014;155(5):1027-1036.
63. Magnin M, Morel A, Jeanmonod D. Toward a unified theory of positive symptoms. *Neurophysiol Clin*. 2005;35(5-6):154-161.
64. Garcia-Larrea L, Maarrawi J, Peyron R, et al. On the relation between sensory deafferentation, pain and thalamic activity in Wallenberg's syndrome: a PET-scan study before and after motor cortex stimulation. *Eur J Pain*. 2006;10(8):677-688.
65. Chao CC, Tseng MT, Lin YH, et al. Brain imaging signature of neuropathic pain phenotypes in small-fiber neuropathy: altered thalamic connectome and its associations with skin nerve degeneration. *Pain*. 2021;162:1387-1399.
66. Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: a review. *Pain*. 2013;154(Suppl 1):S29-S43.
67. Casey KL, Morrow TJ, Lorenz J, Minoshima S. Temporal and spatial dynamics of human forebrain activity during heat pain: analysis by positron emission tomography. *J Neurophysiol*. 2001;85(2):951-959.
68. Peyron R, Faillenot I, Pomares FB, Le Bars D, Garcia-Larrea L, Laurent B. Mechanical allodynia in neuropathic pain. Where are the brain representations located? A positron emission tomography (PET) study. *Eur J Pain*. 2013;17(9):1327-1337.
69. Huynh V, Rosner J, Curt A, Kollias S, Hubli M, Michels L. Disentangling the effects of spinal cord injury and related neuropathic pain on supraspinal neuroplasticity: a systematic review on neuroimaging. *Front Neurol*. 2020;10:1413.
70. Momi SK, Fabiane SM, Lachance G, Livshits G, Williams FMK. Neuropathic pain as part of chronic widespread pain: environmental and genetic influences. *Pain*. 2015;156(10):2100-2106.
71. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature*. 2006;444(7121):894-898.
72. Bennett DL, Clark XAJ, Huang J, Waxman SG, Dib-Hajj SD. The role of voltage-gated sodium channels in pain signaling. *Physiol Rev*. 2019;99(2):1079-1151.
73. Veluchamy A, Hébert HL, Meng W, Palmer CNA, Smith BH. Systematic review and meta-analysis of genetic risk factors for neuropathic pain. *Pain*. 2018;159:825-848.
74. Xu J, Umlauf A, Letendre S, et al. Catechol-O- methyltransferase polymorphism Val158Met is associated with distal neuropathic pain in HIV- associated sensory neuropathy. *Aids*. 2019;33(10):1575-1582.
75. Chung HY, Song EY, Yoon JA, et al. Association of human leukocyte antigen with postherpetic neuralgia in Koreans. *Apmis*. 2016;124(10):865-871.
76. Cheng KI, Lin SR, Chang LL, Wang JY, Lai CS. Association of the functional A118G polymorphism of OPRM1 in diabetic patients with foot ulcer pain. *J Diabetes Complications*. 2010;24(2):102-108.
77. Zheng NN, Zhang RC, Yang XX, Zhong LS. Association of rs3783641 single-nucleotide polymorphism in GTP cyclohydrolase 1 gene with post-herpetic neuralgia. *J Dermatol*. 2019;46(11):993-997. doi:10.1111/1346-8138.15067
78. Noponen-Hietala N, Virtanen I, Karttunen R, et al. Genetic variations in IL6 associate with intervertebral disc disease characterized by sciatica. *Pain*. 2005;114(1–2):186-194.
79. Stephens K, Cooper BA, West C, et al. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. *J Pain*. 2014;15(2):169-180.
80. Kalliomäki ML, Sandblom G, Hallberg M, et al. Genetic susceptibility to postherniotomy pain. The influence of polymorphisms in the mu opioid receptor, TNF-α, GRIK3, GCH1, BDNF and CACNA2D2 genes. Scand. *J Pain*. 2016;12:1-6.
81. Li QS, Cheng P, Favis R, Wickenden A, Romano G, Wang H. SCN9A variants may be implicated in neuropathic pain associated with diabetic peripheral neuropathy and pain severity. *Clin J Pain*. 2015;31(11):976-982.
82. Nissenbaum J, Devor M, Seltzer Z, et al. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. *Genome Res*. 2010;20:1180-1190.
83. Cui W, Yu X, Zhang H. The serotonin transporter gene polymorphism is associated with the susceptibility and the pain severity in idiopathic trigeminal neuralgia patients. *J Headache Pain*. 2014;15(1):42.
84. Kallianpur AR, Jia P, Ellis RJ, et al. Genetic variation in iron metabolism is associated with neuropathic pain and pain severity in HIV-infected patients on antiretroviral therapy. *PLoS One*. 2014;9(8):e103123.
85. Sachau J, Bruckmueller H, Gierthmühlen J, et al. The serotonin receptor 2A (HTR2A) rs6313 variant is associated with higher ongoing pain and signs of central sensitization in neuropathic pain patients. *Eur J Pain*. 2021;25(3):595-611. doi:10.1002/ejp.1696
86. Olsen MB, Jacobsen LM, Schistad EI, et al. Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. *J Neurosci*. 2012;32(29):9831-9834.
87. Jacobsen LM, Schistad EI, Storesund A, et al. The MMP1 rs1799750 2G allele is associated with increased low back pain, sciatica, and disability after lumbar disk herniation. *Clin J Pain*. 2013;29(11):967-971. doi:10.1097/AJP.0b013e31827df7fd
88. Hendry L, Lombard Z, Wadley A, Kamerman P. KCNS1, but not GCH1, is associated with pain intensity in a black southern African population with HIV-associated sensory neuropathy: a genetic association study. *J Acquir Immune Defic Syndr*. 2013;63(1):27-30. doi:10.1097/QAI.0b013e318285cf36
89. Hendry LM, Wadley AL, Cherry CL, Price P, Lombard Z, Kamerman PR. TNF block gene variants associate with pain intensity in black southern Africans with HIV-associated sensory neuropathy. *Clin J Pain*. 2016;32(1):45-50.
90. Ursu D, Ebert P, Langron E, et al. Gain and loss of function of P2X7 receptors: mechanisms, pharmacology and relevance to diabetic neuropathic pain. *Mol Pain*. 2014;10(1):37.
91. Xing X, Bai Y, Sun K, et al. Identification of candidate genes associated with postherpetic neuralgia susceptibility. *Pain Physician*. 2020;23(3):E281-E288.
92. Meng W, Deshmukh HA, van Zuydam NR, et al. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. *Eur J Pain*. 2015;19(3):392-399.
93. Meng W, Deshmukh HA, Donnelly LA, et al. A genome- wide association study provides evidence of sex-specific involvement of Chr1p35.1 (ZSCAN20- TLR12P) and Chr8p23.1 (HMGB1P46) with diabetic neuropathic pain. *EBioMedicine*. 2015;2(10):1386-1393.
94. Warner SC, van Meurs JB, Schiphof D, et al. Genome-wide association scan of neuropathic pain symptoms post total joint replacement highlights a variant in the protein-kinase C gene. *Eur J Hum Genet*. 2017;44:1-6.
95. Lemmelä S, Solovieva S, Shiri R, et al. Genome-wide meta- analysis of sciatica in finnish population. *PLoS One*. 2016;11(10):1-18.
96. Reyes-Gibby CC, Wang J, Yeung SCJ, et al. Genome-wide association study identifies genes associated with neuropathy in patients with head and neck cancer. *Sci Rep*. 2018;8(1):1-7.

97. Wiberg A, Ng M, Schmid AB, et al. A genome-wide association analysis identifies 16 novel susceptibility loci for carpal tunnel syndrome. *Nat Commun*. 2019;10(1):1030.
98. Baron R, Dickenson AH, Calvo M, Dib-Hajj SD, Bennett DL. Maximizing treatment efficacy through patient stratification in neuropathic pain trials. *Nat Rev Neurol*. 2023;19(1):53-64. doi:10.1038/s41582-022-00741-7
99. Calvo M, Davies AJ, Hébert HL, et al. The genetics of neuropathic pain from model organisms to clinical application. *Neuron*. 2019;104(4):637-653.
100. Smith BH, Hebert HL, Veluchamy A. Neuropathic pain in the community: prevalence, impact, and risk factors. *Pain*. 2020;161(9):S127-S137.
101. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726-735. doi:10.1016/j.jclinepi.2013.02.003

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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