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Evidence-based guideline: Neuromuscular ultrasound for the diagnosis of ulnar neuropathy at the elbow

Steven J. Shook MD, MBA[1,2] | Matthew Ginsberg MD[3] | Pushpa Narayanaswami MD[4] | Roy Beekman MD, PhD[5] | Andrew H. Dubin MD, MS[6] | Bashar Katirji MD[7] | Bharathi Swaminathan MD[8] | Robert A. Werner MD, MS[9] | Michael S. Cartwright MD[10]

[1]American Association of Neuromuscular & Electrodiagnostic Medicine, Rochester, Minnesota, USA

[2]Department of Neurology, Neuromuscular Center, Cleveland Clinic, Cleveland, Ohio, USA

[3]Department of Neurology, Akron Children's Hospital, Akron, Ohio, USA

[4]Department of Neurology, Neuromuscular Division, Beth Israel Deaconess Medical Center, Boston, Ohio, USA

[5]Department of Neurology, Zuyderland Medisch Centrum, Sittard-Geleen, The Netherlands

[6]Department of Physical Medicine & Rehabilitation, University of Florida, Gainesville, Florida, USA

[7]Neurological Institute, University Hospitals, Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

[8]Department of Physical Medicine and Rehabilitation, Chicago Medical School, North Chicago, Illinois, USA

[9]Michigan Medicine, Ann Arbor VA Health System, Ann Arbor, Michigan, USA

[10]Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

Correspondence
Steven J. Shook, American Association of Neuromuscular & Electrodiagnostic Medicine, 2621 Superior Drive NW, Rochester, MN 55901, USA.
Email: policy@aanem.org

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Abstract

Introduction/Aims: The purpose of this literature review is to develop an evidence-based guideline for the use of neuromuscular ultrasound in the diagnosis of ulnar neuropathy at the elbow (UNE). The proposed research question was: "In patients with suspected UNE, does ulnar nerve enlargement as measured with ultrasound accurately identify those patients with UNE?"

Methods: A systematic review and meta-analysis was performed, and studies were classified according to American Academy of Neurology criteria for rating articles for diagnostic accuracy.

Results: Based on Class I evidence in four studies, it is probable that neuromuscular ultrasound measurement of the ulnar nerve at the elbow, either of diameter or cross-sectional area (CSA), is accurate for the diagnosis of UNE.

Recommendation: For patients with symptoms and signs suggestive of ulnar neuropathy, clinicians should offer ultrasonographic measurement of ulnar nerve cross-sectional area or diameter to confirm the diagnosis and localize the site of compression (Level B).

KEYWORDS
electromyography, mononeuropathy, ulnar nerve, ulnar neuropathy at the elbow, ultrasound

1 | INTRODUCTION

Ulnar neuropathy at the elbow (UNE) is the second most common mononeuropathy of the upper extremity, with a population incidence of about 3 in 10 000 person-years, and a prevalence of up to 6%, although in some populations it may be higher.[1-3] Diagnosis may be based on history and physical examination, and aided by electrodiagnostic studies. Examination generally demonstrates numbness of digits 4 and 5 and the medial hand, and weakness or atrophy of ulnar innervated muscles. However, there is clinical overlap with cervical radiculopathies and brachial plexopathies, as well as ulnar neuropathies at the wrist. Electrodiagnostic studies are also confounded by difficulty with localization, especially with axon loss lesions that are not associated with focal slowing or conduction block.[4]

Neuromuscular ultrasound has been increasingly used as a cost-effective[5] aid in the diagnosis of several neuromuscular conditions, but has been particularly helpful in entrapment mononeuropathies.[6] The most commonly evaluated ultrasonographic parameter is the size of the nerve, as determined by diameter or cross-sectional area (CSA). The first evidence-based guideline for neuromuscular ultrasound was published for the diagnosis of carpal tunnel syndrome, and proposed a Level A recommendation for measurement of median nerve CSA at the wrist for the diagnosis of carpal tunnel syndrome.[7] Several recent reviews and meta-analyses have evaluated neuromuscular ultrasound for the diagnosis of UNE.[8-10] However, a systematic review based on the American Academy of Neurology (AAN) criteria for assessing diagnostic accuracy studies has not been performed. The purpose of this systematic review was to apply these rigorous criteria to the current literature and provide recommendations on the use of ulnar nerve CSA or diameter for the diagnosis of UNE.

2 | METHODS

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) convened an expert panel of physicians specializing in neuromuscular neurology and physical medicine and rehabilitation to address this issue. The panel was selected to represent a broad range of expertise related to neuromuscular ultrasound. All panel participants had expertise in the clinical and electrodiagnostic assessment of UNE.

In June 2018, PubMed was used to search Medline to identify all potential abstracts. The search terms "cubital tunnel syndrome OR ulnar neuropathies OR ulnar neuropathy OR ulnar mononeuropathy OR ulnar neuropathy compression syndrome OR ulnar nerve" were combined with the terms "ultrasound OR ultrasonography OR sonogram OR sonography." This produced 713 articles from 1966 to June 2018. The titles and abstracts of those articles were reviewed for relevance by two of the present authors (S.S. and M.C.), which yielded 93 articles for full review. Fourteen were excluded, including 13 identified as review articles without original data, and 1 due to having no English language translation available for review. No additional articles were identified after reviewing the references from the review articles.

To be included in this study, an article had to describe the use of ultrasonography of the elbow in patients having clinical and/or electrodiagnostic evidence of UNE. We found that 49 articles were not relevant to our research question. The remaining 30 articles were rated by two expert panel members according to criteria set by the AAN.[11] Articles pertaining to the accuracy of measurement of the ulnar nerve at the elbow for the diagnosis of UNE were assessed using the AAN criteria for rating an article on diagnostic accuracy. Studies with the highest levels of evidence (Class I and II) are discussed in the text and summarized in the evidence tables. At each step in the process, disagreements were arbitrated by a third expert panel member.

Compatible with the analytic framework recommended by the AAN, the ideal study type to assess the question of diagnostic accuracy of ultrasound of the ulnar nerve would be a prospective, controlled, cohort survey of a population of patients meeting a clearly defined reference standard for the diagnosis of UNE, with blinding of the ultrasonographer to patient type. The panel required a stated reference standard for the diagnosis of UNE, which had to include clinical and/or electrodiagnostic criteria. Electrodiagnostic criteria were expected to be compatible with the practice parameter that was developed jointly by the Quality Assurance Committee of the AAEM and the Quality Standards Subcommittee of the AAN.[4]

The guideline development panel utilized overall accuracy (OA) as a measure of test validity. An OA of over 70% was considered acceptable and supportive of neuromuscular ultrasound as an accurate test for the diagnosis of UNE (accuracy = sensitivity × prevalence + specificity × [1 −prevalence]), consistent with the prior AANEM evidenced-based guideline: "Neuromuscular Ultrasound for the Diagnosis of Carpal Tunnel Syndrome."[7]

Evidence-based conclusions and recommendations were developed using the modified Delphi approach. Based on rationale derived from synthesis of the systematic review, panel members anonymously completed Modified Delphi Process Questionnaires. Responses were collated and reviewed by an independent assessor to determine the strength of agreement and to develop a final consensus.

3 | RESULTS

3.1 | Accuracy of neuromuscular ultrasound

We identified relevant articles pertaining to the accuracy of neuromuscular ultrasound in the diagnosis of UNE. Four were graded as Class I.[12-15] None were graded Class II. The remaining 26 were graded Class III[16-27] or Class IV.[28-41]

Of the 12 articles graded Class III, we found 11 with spectrum bias. By panel definition, a "narrow-spectrum" study included only patients who had UNE by reference standard and normal, healthy controls. Studies employing a case-control design with a "narrow spectrum" of patients were graded Class III. The author of one article was contacted to clarify issues pertaining to the control group, but no response was received after repeated efforts.

TABLE 1 Class I studies–reference standard: Electrodiagnostic criteria

First author	Year	Clinical criteria–UNE	EMG criteria
Beekman[12]	2004	**UNE** Sensory loss in the ulnar dermatome Motor weakness in the proximal ulnar myotome **UNE possible (EMG required)** Normal examination *or* sensory loss in the ulnar dermatome only *or* sensory loss + motor weakness in the hand	Dutch Neurophysiological Society/AAEM **Localized UNE** *One or more* of the following abnormalities: • Reduction of the CMAP from BE/AE 16% (block) • MNCV across the elbow of <46 m/s (slowing) • MNCV at 15 m/s slower AE/forearm (diff slowing) • Spontaneous activity in FCU and/or FDP muscles
Pompe[14]	2012	**UNE** Sensory loss in the ulnar dermatome + weakness in the proximal ulnar myotome *or* distal weakness + sensory disturbance **UNE possible (EMG required)** Normal Examination *or* sensory loss in the ulnar dermatome only *or* sensory loss + motor weakness in the hand	Dutch Neurophysiological Society/AAEM **Localized UNE** *One or more* of the following abnormalities: • Reduction of the CMAP from BE/AE 16% (block) • MNCV across the elbow of <46 m/s (slowing) • MNCV at 15 m/s slower AE/forearm (diff. slowing) • Spontaneous activity in FCU and/or FDP muscles
Omejec[15]	2015	**UNE** Forearm ulnar muscle weakness + sensory loss in ulnar dermatome *or* intrinsic hand ulnar muscle weakness + sensory loss, including the ulnar dorsal cutaneous branch **UNE suspected (EMG required)** Palmar sensory loss and weaknessor isolated weakness or sensory loss **UNE less likely** Normal examination	**Localized UNE** *One or more* of the following abnormalities: • MNCV < LLN across elbow (ADM, FDI) • Amplitude drop across elbow > ULN (ADM, FDI)
Ellegaard[13]	2015	Not applicable	**Localized UNE** Danish National Group Criteria CV across elbow CV forearm Change in CV across elbow-forearm Conduction block

Abbreviation: AAEM, American Association of Electrodiagnostic Medicine; ADM, abductor digiti minimi muscle; AE, above elbow; BE, below elbow; CMAP, compound motor action potential; CV, conduction velocity; EMG, electromyography; FDI, first dorsal interosseous muscle; FCU, flexor carpi ulnaris muscle; FDP, flexor digitorum profundus muscle; LLN, lower limit of normal; MNCV, motor nerve conduction velocity; UNE, ulnar neuropathy at the elbow

Of the 11 Class III articles with spectrum bias, we found 5 that also treated measurements of CSA for bilateral elbows in control patients as independent observations. This technique violates the assumptions of most statistical tests and may increase the possibility of a false-positive result.[42] Inadequate masking was identified as the determining factor in one retrospective Class III article, and was also present in four of the Class III articles with spectrum bias.

Of the 14 articles graded Class IV, all received this rating because of failure to report sufficient information to determine measures of diagnostic accuracy (sensitivity and specificity, or a likelihood ratio).

Studies meeting Class I level of evidence were conducted in different outpatient neurology and neurophysiology departments of teaching hospitals in Europe (ie, 2 in The Netherlands, 1 in Slovenia, and 1 in Denmark). There is no reason to believe that the same patients would have been included in more than one of the studies, based on diversity of location and study periods. Exclusion criteria were fairly consistent across the studies; presence of acute elbow trauma, prior elbow surgery, diabetes, hypothyroidism, rheumatoid arthritis, polyneuropathy, and motor neuron disease precluded participation in one or more of these studies.

All Class I studies were prospective, blinded, used appropriate reference standards, and included measures of diagnostic accuracy. Three studies were designed in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) initiative criteria.[43] One study utilized a similar methodology.[44] Three studies used combined clinical and electrodiagnostic criteria to diagnose UNE, and identified one group as "probable UNE," in which clinical examination was consistent with UNE, no alternative diagnosis was identified, but electrodiagnostic criteria for UNE were not met. For consistency, the panel chose to analyze "probable UNE" cases as UNE in all Class I studies for diagnostic accuracy calculations.

Regarding nerve measurement methodology, two studies used CSA of the ulnar nerve, one included both CSA and nerve diameter, and one used ulnar nerve diameter only. All nerve measurements were obtained within and excluding the hyperechoic epineurium. Three studies also included the measurement of a "swelling ratio," comparing the CSA of the ulnar nerve at the elbow with a location proximal and/or distal to the elbow segment. Clinical, electrodiagnostic (Table 1), and ultrasonographic (Table 2) criteria differed among the studies, but all were judged as valid by the reviewing panel.

3.2 | Summary of Class I studies

From May 1998 to May 2002, Beekman et al[12] conducted a prospective cohort study of 123 patients (136 arms) with symptoms or signs of UNE. Clinical and electrodiagnostic assessments classified participant arms as either definite UNE or probable UNE, or as a patient control (normal electrodiagnostic studies and normal/nonlocalizing clinical exam findings). Electrodiagnostic guidelines from the Dutch Neurophysiological Society and AAEM were used to localize ulnar neuropathy at the elbow. Index ultrasound testing was limited to ulnar nerve diameter measurements. UNE cases were identified by an ulnar nerve diameter measurement exceeding either 2.5 mm at the medial epicondyle (ME), 2.6 mm at 2 cm proximal to the ME, or 2.7 mm at 2 cm distal to the ME. Comparing definite and probable UNE cases (n = 91) and the remaining patient controls (n = 45), ultrasound identified UNE with a sensitivity of 80% and a specificity of 91%. Receiver-operating characteristic (ROC)-curve analysis found the optimal cutoff value of >2.5 mm at any of the three levels measured, with a sensitivity of 81% and specificity of 91%.

Pompe and Beekman[14] studied 191 patients from August 2009 to September 2010 for whom UNE was considered in their differential diagnosis based on referring symptoms. Clinical and electrodiagnostic criteria were identical to the prior Class I study by Beekman et al. Ultrasonography testing assessed maximum diameter and CSA of the ulnar nerve at the elbow, diameter or CSA at one or more of the three predetermined levels around the elbow, as well as an upper and lower arm swelling ratio. ROC analysis was conducted to identify optimal cutoff values to discriminate cases (including both definite and probable UNE) from patient controls. Sensitivities and specificities for cutoffs included maximum diameter >2.9 mm (68% and 79%, respectively), maximum CSA >8 mm^2 (74% and 72%), upper arm swelling ratio >2.1 (60% and 74%), and forearm swelling ratio >2.3 (65% and 79%), respectively. The study concluded that ultrasonographic measurements of ulnar nerve diameter, CSA, and swelling ratio have comparable diagnostic accuracy.

Omejec et al[15] studied a cohort of 109 patients from April 2012 to October 2013 with UNE symptoms. Of note, their study blended 49 healthy control patients from a previous study.[25] The authors were contacted to obtain their original data, which allowed the panel to separately evaluate the prospectively recruited cohort independently from the healthy controls. Patient arms (n = 113) were categorized as either definite UNE, probable UNE, or alternative diagnosis, based on clinical and electrodiagnostic criteria. Ulnar short-segment nerve conduction studies (SSNCSs) were recorded from both the first dorsal interosseous and abductor digiti minimi muscles. Electrodiagnostic localization to the elbow required either a motor nerve conduction velocity below the lower reference limit and/or an amplitude drop across the elbow greater than an upper level reference limit. Diagnosis of UNE by ultrasound required a CSA in excess of the upper reference limit at any one of six standardized elbow locations, or a ratio of the largest CSA at the elbow divided by a CSA measurement 6 cm proximal to the medial epicondyle >1.65. The CSA of the ulnar nerve at the level of the medial epicondyle exceeded 11 mm^2 in the majority of cases. Definite and probable UNE cases (n = 98) were compared with patient controls including 12 symptomatic arms found to have alternative diagnoses, and three arms with symptoms but normal EMG and

TABLE 2 Class I studies–ultrasound criteria

First author	Year	Ultrasound frequency range	Ultrasound measurement location	Ultrasound-UNE cutoff
Beekman[12]	2004	5-10 MHz	Medial epicondyle (ME) 2 cm proximal to ME (P2) 2 cm distal to ME (D2) Middle-upper arm (ratio) Middle forearm (ratio)	ROC curve derived from patients (UNE + probable UNE) and patient controls; largest diameter ≧2.5 mm at any of three levels
Pompe[14]	2012	5-16 MHz	Medial epicondyle (ME) 2 cm proximal to ME 2 cm distal to ME Mid upper arm Mid forearm	ROC curve derived from patients (UNE + probable UNE) and patient controls; largest CSA ≥8 mm^2 at any of three levels
Omejec[15]	2015	13 MHz	Medial epicondyle (ME) 2 cm proximal to ME (P2) 4 cm proximal to ME (P4) 6 cm proximal to ME (P6) 2 cm distal to ME (D2) 4 cm distal to ME (D4)	CSA enlarged at any 1 of 6 locations: • ME > 11.0 mm^2 • P2 > 12.2 mm^2 • P4 > 9.6 mm^2 • P6 > 8.0 mm^2 • D2 > 8.6 mm^2 • D4 > 10.0 mm^2 • Or largest CSA/P6 > 1.65
Ellegaard[13]	2015	18 MHz	Medial epicondyle	ROC curve derived from patients and patient controls; CSA > 11 mm^2 at sulcus

TABLE 3 Class I studies–ultrasound for the diagnosis of UNE accuracy summary

First author	Year	Number with UNE	Number without UNE	Prevalence	Sensitivity	Specificity	Accuracy
Beekman[12]	2004	91	45	66.9%	81.0%	91.0%	84.3%
Pompe[14]	2012	137	54	71.7%	74.0%	72.0%	73.4%
Omejec[15]	2015	98	15	86.7%	64.3%	60.0%	63.7%
Ellegaard[13]	2015	29	12	70.7%	72.4%	75.0%	73.2%

Note: These data incorporate the US-UNE cutoff from Table 2 for each study.

clinical examination. The presence of ulnar nerve enlargement at the elbow at any one of six locations around the elbow or an increased swelling ratio resulted in a sensitivity of 64.3% and a specificity of 60.0%.

Finally, the Class I study by Ellegaard et al between September 2012 and May 2013[13] studied a group of 80 consecutive patients with suspected UNE based on clinical symptoms, evaluated with NCS and ultrasound. Nerve conduction studies were used as the sole reference standard. Within the final cohort of 41 patients (19 of the 80 consecutive patients were excluded by study criteria, and 20 declined to be studied), UNE cases were electrodiagnostically defined according to criteria developed by the Danish National Group (EMG database).[45] Positive ultrasound cases were defined as both CSA at the sulcus >9.8 mm^2 and one or more abnormal ratio (comparing the sulcus to the upper arm, forearm, and/or wrist). ROC analysis found the optimal cutoff value for ultrasound was 11 mm^2, yielding a sensitivity of 72.4% and a specificity of 75.0%. The cutoff was not influenced by age, height, weight, or BMI.

3.3 | Summary of Class I evidence

To ensure an up-to-date literature review, our panel replicated the PubMed search methodology to include articles published from June 2018 to October 2020. The search yielded 168 additional abstracts for review, and 12 additional potentially relevant articles were evaluated. No additional Class I or Class II articles were identified.

Sensitivity in Class I studies ranged from 64.3% to 81.0%, and specificity ranged from 60.0% to 91.0%. Three of the four Class I studies met this criterion for acceptable accuracy (Table 3).

OA ranged from 63.7% to 84.3%, and was highest in the studies using a single cutoff value derived from ROC-curve analysis, including a diameter of >2.5 mm or CSA >8 mm^2 at any one of three levels from 2 cm distal to 2 cm proximal to the medial epicondyle. Lower OA (63.7%) was found in the Omejec et al study, which used both clinical and electrodiagnostic criteria to identify UNE cases, and a higher ulnar nerve cutoff (eg, >11 mm^2 at the medical epicondyle) ranging from 6 cm proximal to 4 cm distal to the medial epicondyle. Interestingly, a CSA cutoff of >11 mm^2 was used by Ellegaard et al, resulting in an OA of 73.2%, which may in part be attributed to the fact that the latter study used purely electrodiagnostic criteria to define UNE cases.

Overall accuracy has some limitations as a single measure of test validity, as it is impacted by prevalence. The prevalence may be affected by the study criteria for UNE and in turn influence the diagnostic accuracy.[46] Likelihood ratios (LRs) are clinically useful measures of diagnostic accuracy, indicating the magnitude by which a test result raises (positive LR) or lowers (negative LR) the pretest probability of a disorder. LRs are not influenced by disease prevalence. An LR of 1 indicates that the post-test probability is the same as the pretest probability.

We calculated the positive and negative LR (LR^+ and LR^-) of ultrasound for diagnosis of UNE in the four Class I studies. Inverse-variance random-effects meta-analyses of the LR^+ and LR^- of the four studies were then performed. The meta-analysis identified a combined LR^+ of 3.018 (95% confidence interval [CI], 1.634-5.576; $I^2 = 66\%$), consistent with a small increase in likelihood of disease. The wide LR^+ CI reflects imprecision. The LR^- of 0.359 (95% CI, 0.24-0.538; $I^2 = 67\%$) is indicative of a small decrease the in the likelihood of disease, with fair precision.

4 | DISCUSSION

Based on Class I evidence in four studies it is probable that neuromuscular ultrasound measurement of the ulnar nerve at the elbow, either of diameter or CSA, is accurate for the diagnosis of UNE.

Recommendation: For patients with symptoms and signs suggestive of ulnar neuropathy, clinicians should offer ultrasonographic measurement of ulnar nerve CSA or diameter to confirm the diagnosis and localize the site of compression (Level B).

5 | CONCLUSION

Ultrasound is a cost-effective,[5] noninvasive adjunctive test that adds diagnostic accuracy to the clinical and electrodiagnostic (EDx) evaluation for UNE. Ultrasound may also reveal specific pathology not identifiable by clinical or EDx examination alone, and may aid in localization. Based on the available Class I evidence, the accuracy of neuromuscular ultrasound is not sufficient to replace clinical examination or EDx.

Neuromuscular ultrasound should be performed and interpreted by clinicians experienced with the technique. Guidelines for neuromuscular ultrasound training have been published elsewhere.[47] American Board of Electrodiagnostic Medicine–certified physicians have the option of demonstrating their ultrasound knowledge and skill by obtaining a Certificate of Added Qualification.

Ideal UNE cutoffs for nerve CSA, diameter, and swelling ratio could not be determined by the available Class I evidence. Evidence supports obtaining ulnar nerve diameter or CSA within the hyperechoic epineurium, at the level of the medial epicondyle and across the elbow segment spanning from at least 2 cm proximal to 2 cm distal to the medial epicondyle. These studies did not provide evidence that a swelling ratio increases the accuracy of ultrasound for the diagnosis of UNE. Overall, scanning protocols and reference values for the ulnar nerve should be established by each laboratory prior to using neuromuscular ultrasound for the diagnosis of UNE.

6 | RECOMMENDATIONS FOR FUTURE RESEARCH

1. A standard research definition for UNE is needed. In 1999, the AAEM published a practice parameter for electrodiagnostic studies in UNE, which reported sensitivities of electrodiagnostic studies ranging from 37% to 86% and specificities of 95%, based on extensive literature review.[4] It is reasonable to conclude that reliance solely on electrodiagnostic criteria may yield false-negative results, especially in patients with mild lesions or nonlocalizing axon loss lesions.[29] Although electrodiagnostic studies will continue to play an important role in the diagnosis of UNE, a standardized set of clinical criteria to localize ulnar neuropathy at the elbow will facilitate comparison and meta-analyses of future studies.
2. A standardized protocol for using neuromuscular ultrasound in the diagnosis of UNE should be developed. This should include definition of the optimal cutoffs and sites of ulnar nerve diameter or CSA measurement. Reproducible measurement of nerve diameter within flattened or ovoid nerve segments needs to be more clearly defined.
3. Further research should assess the gamut and prevalence of structural abnormalities that may cause UNE. Ultrasound has been shown to complement the clinical and electrodiagnostic evaluation of patients with mononeuropathies in general, changing management by identifying potentially surgically amenable pathology in 26% of patients in one review.[48] One review identified cases of UNE caused by snapping of the medial head of the triceps muscle, accessory muscles (eg, anconeous epitrochlearis muscle), ganglia at the elbow, osteophytes, or tumors.[8] Additional study is needed.
4. The role of ultrasound as an initial screening test for ulnar neuropathy at the elbow in patients with clinical symptoms and signs needs to be studied. Currently, there is sufficient evidence to recommend ultrasound as an adjunct to clinical examination and electrodiagnostic studies.
5. Future studies should assess the relative benefit, harm, and cost of performing nerve conduction studies, needle EMG, and ultrasound in patients with symptoms suggestive of UNE, and whether neuromuscular ultrasound changes treatment strategies and outcomes.

DISCLAIMER

This statement has been provided as an educational service of the AANEM. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care of a particular neurological problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodology. The AANEM recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all the circumstances involved. The clinical context section is made available place the evidence-based guidelines into perspective with current practice habits and challenges. No formal practice recommendation should be inferred.

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