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Diagnostic accuracy of upper limb neurodynamic tests in the diagnosis of cervical radiculopathy

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Declaration of Conflict of Interests

The authors declare no conflict of interest for this article.

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1 Introduction

2 Cervical radiculopathy (CR) is a relatively common neurological disorder caused by 3 mechanical compression from a disc or other space-occupying lesion or from inflammation to 4 the nerve root (Anekstein et al, 2012) The annual incidence of CR is 107.3 per 100,000 for 5 men and 63.5 per 100,000 for women (Radhakrishnan et al, 1990). The clinical manifestations 6 of cervical radiculopathy may include pain, sensory deficits, motor deficits, diminished 7 reflexes, or combinations of these. Cervical radiculopathy typically is self-limiting with 75%– 8 90% of patients achieving symptomatic improvement or resolution within a year with 9 conservative care (Woods et al, 2015)

10 Although no gold standard exists as a reference standard for cervical radiculopathy, 11 magnetic resonance imaging (MRI) is the preferred diagnostic method (Mink et al, 2003), 12 since it can differentiate tumors, inflammation, visualize trauma, and the extensiveness of 13 disc, arthritic, neural, and vascular cervical pathologies. Electrodiagnostic tests are capable of 14 detecting clinically significant problems in many patients as well, although they are operator 15 dependent and variable methods and normative values are used in practice (Reza Soltani et al, 16 2014). Furthermore it may be negative if performed before denervation has occurred or when 17 re-innervation is complete (Ashkan et al, 2002). Cervical radiculopathy is considered a 18 'clinical diagnosis with imaging confirmation', and it is important to match valid clinical 19 signs with MRI findings and/or electrodiagnostic test results (Carette and Fehlings, 2005; 20 Kuijper et al, 2009).

There are numerous clinical tests used to diagnose cervical radiculopathy. Upper Limb neurodynamic tests ((ULNT) 1, 2a, 2b and 3), or also called upper limb tension test (ULTT), initially described by Elvey (Elvey, 1986), Butler (Butler, 2000) and Shacklock (Shacklock 1996), involve targeted sequences of movement that provoke mechanosensitivity of the nerve. The tests are performed by placing and releasing progressively more tension on the proposed component of the nervous system that is being tested. A recent systematic review (Thoomes
et al, 2017) concluded that "limited evidence for accuracy of physical examination tests for
the diagnosis of CR" exists.

29 Moreover, neurodynamic test procedures in studies that populated the aforementioned 30 systematic review used a variety of testing methods and results to determine a positive 31 finding. Three criteria has been advocated when testing: 1) reproduction of neurogenic pain-32 burning or lightning-like pain, tingling sensation in the neck and arm (Apelby-Albrecht et al, 33 2012), the patient's symptoms reproduced (Wainner et al, 2003), or reproduction of pain 34 (Ghasemi et al, 2013); 2) side to side range of motion difference (Wainner et al, 2003) or 35 side-to-side difference in painful radiation (Apelby-Albrecht et al, 2012); and 3) 36 increased/decreased symptoms with structural differentiation (Apelby-Albrecht et al, 2012) or 37 cervical structural differentiation with cervical spine movement alone (Wainner et al, 2003). 38 Interestingly, there is inconsistency in what is advocated to measure including conflicting 39 evidence for reproduction of any pain or discomfort (Apelby-Albrecht et al, 2012; Ghasemi 40 et al, 2013); and side to side range of motion comparisons (Nee et al, 2012). Most studies 41 advocate the use of structural differentiation, which involves directional movement of a 42 defined body region (e.g., neck side flexion) away from the area assessed to evaluate the 43 effect of mechanical force on the nervous system and its impact on the patient's symptoms. 44 In clinical practice, many clinicians have assessed the accuracy of neurodynamic tests 45 on two criteria as recommended by Nee et al (Nee et al, 2012) : 1) familiar patient's 46 pain/symptoms reproduced and 2) increased/decreased symptoms with structural 47 differentiation. Since we are unfamiliar with any studies that have included both findings in 48 the assessment of CR, we investigated the accuracy of four ULNTs in comparison against a 49 reference standard of medical history and MRI confirmation in patients with and without CR. 50 We hypothesized that the findings may provide insight on the role of ULNTs (e.g., screening

or confirmation) and that the more rigid definition of a positive test should improve the
specificity of the test findings. Further, combinations of test findings should result in more
diagnostic accuracy than individual tests alone.

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55 Materials and Methods

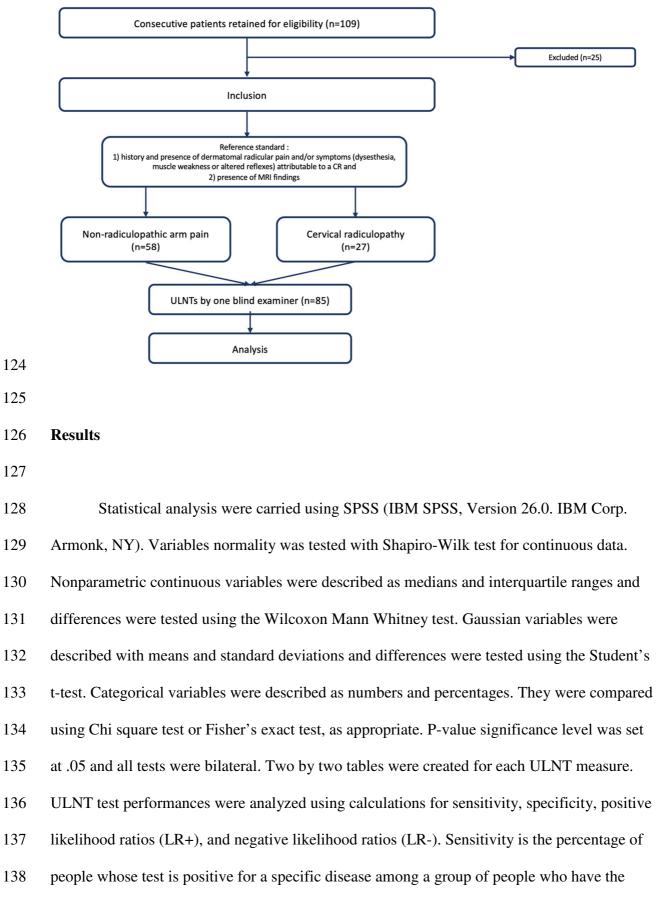
The study was a diagnostic accuracy study (prospective) design in which clinical testing occurred in a state of diagnostic uncertainty. The study followed the updated 2015 STARD reporting standards (Bossuyt et al, 2015). Patients were informed about the study and they gave their consent for participation before inclusion. The study was conducted in accordance with the Ethical principles and the Helsinki Declaration on research involving human subjects and was approved the French regulatory and ethics rules (n°2212189v0).

62 Participants were recruited from consecutive patients referred to a Neurosurgery 63 Department by a general practitioner or specialist from September 2017 to September 2019. 64 Each patient had a suspected neck disorder. Referred patients provided information and 65 questionnaires about pain intensity and neck disability. To be included patients had to be aged 66 18 to 65 years, reporting arm pain with or without neck pain of at least 3-months in duration. 67 In addition, they were required to have a self-reported pain score of at least 30mm and less 68 than 80 on a 100 mm visual analogue scale (VAS) (Horn et al, 2016) during the previous 24 69 hours, and had a self-reported score of at least 20% on the Neck Disability Index 70 questionnaire (NDI) (Masaracchio et al, 2013).

Subjects were excluded if they were unable to understand French, had suffered from a significant neck trauma at the time of the study (i.e., recent cranio-cervical trauma including cervical spine fracture), had a history of neck or arm surgery, inflammatory joint condition/arthritis, fibromyalgia, diabetes, pregnancy, cardiovascular, neurological, neoplastic or psychiatric pathology, cervical myelopathy, pyramidal or extrapyramidal pathology. 77 *Reference Standard:* The diagnosis of CR or a competing diagnosis was made by a single neurosurgeon with 15 years of experience from the consecutive patients included. 78 79 Cervical radiculopathy is a clinical diagnosis that is confirmed through imaging verification, 80 thus the diagnosis of CR was based on the following criteria: 1) history and presence of 81 dermatomal radicular pain and/or symptoms (dysesthesia, muscle weakness or altered 82 reflexes) attributable to a CR and 2) presence of MRI findings. MRI findings were specific 83 in their confirmation of nerve root compression or irritation by disc herniation or stenosis in 84 pre- or intra-foraminal space narrowing on the ipsilateral side and at the same or adjacent 85 level of radicular pain (Kuijper et al, 2008). The reference standard results were interpreted 86 without knowledge of the results of ULNT.

87 Index tests : Approximately one hour after the reference standard was provided by the 88 neurosurgeon, a single physiotherapist with 10 years of experience in neck pain management, 89 and advanced certification for orthopedic assessment evaluated the ULNT on each participant. 90 No intervention was allowed between the index test(s) and reference standard. The 91 physiotherapist was blind to the patient history, clinical/MRI findings and the diagnosis. The 92 index test results were interpreted without knowledge of the results of the reference standard 93 and the presence of CR. Before the tests, patients were instructed to communicate the onset 94 of any sensation such as stretch, tingling or pain anywhere in the arm or neck (Schmid et al, 95 2009). The patient was positioned supine without a pillow (Walsh 2005). The examiner 96 performed the ULNTs for that are purported for the median (ULNT1 and ULNT2a), radial 97 (ULNT2b) and ulnar (ULNT3) nerves (Figure 1) in randomized order using randomization 98 software. Upper limb neurodynamic testing was operated according to the standardized 99 sequence previously described (Butler, 2000; Nee et al, 2012; Schmid et al, 2009), with a 5-100 minute break between each test to avoid any pain sensitization by repeating tests (Walsh

101	2005). Passive movements were achieved to the end of range or until symptoms were
102	produced (Schmid et al, 2009). The non-symptomatic side was tested first for each ULNT for
103	familiarization with sensation/pain induced by tests. A ULNT was considered as positive if
104	both of the two following criteria were met:
105	- Reproduction of a familiar symptomatic complaint of arm pain and/or neck pain at
106	least partially (pain or dysesthesia including burning, or lightning-like pain, or
107	tingling sensation) (Nee et al, 2012);
108	- Structural differentiation: Once such a familiar complaint was provoked, structural
109	differentiation between neurogenic and non-neurogenic sources was performed by
110	the addition of sensitizing movements at a site distant to the pain: ipsilateral- or
111	contralateral cervical lateral flexion, elbow or wrist extension/flexion, or shoulder
112	girdle elevation (Appendix A) (Nee et al, 2012);
113	Tests were considered negative if each failed to meet the positive criteria identified above or
114	indeterminate if the patient was unable to tolerate the test of position to allow complete
115	execution of the test.
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123	Figure 1. Flow chart



139 disease (Cook et al, 2020). Specificity is the percentage of people whose test is negative for a

specific disease among a group of people who do not have the disease [22]. LR+ are the probability of a person with the disease testing positive divided by the probability of a person without the disease testing positive (Cook et al, 2020). LR- are the probability of a patient who has the condition of testing negative divided by the probability of a patient without the disease, testing negative (Cook et al, 2020).

145 We also calculated pretest probability, which is the probability of the condition being 146 present before the diagnostic result is known and is sample specific for those enrolled in our 147 study, and post-test probability with a positive and a negative finding on the ULNTs. Post-test 148 probability is the percentage chance of the condition being present after a positive or negative 149 finding for a ULNT. Generally, a positive test will increase the post-test probability of 150 diagnosing the condition (otherwise known as ruling in the diagnosis). In contrast, a negative 151 finding will generally decrease the post-test probability of diagnosing the condition 152 (otherwise known as ruling out the condition) (Cook et al, 2020).

153 We calculated sensitivity/specificity, LR+/LR-, and post-test probabilities with a 154 positive and a negative finding for the four individual ULNT tests and combinations of these 155 tests. When calculating combinations of findings, the clusters of tests were placed in 156 "conditions" (e.g., 1 of 4 is positive, 2 of 4 is positive, etc.) and evaluated for their abilities to 157 influence post-test probability change with each defined condition. For all analyses, we also 158 evaluated post-test probability change, which is the difference between the pre-test prevalence 159 and the post-test finding with a positive or a negative result (Cook et al, 2020). Since the 160 purpose of a test is to change the post-test probability of an accurate diagnosis, larger post-test 161 probability changes were considered to have the highest clinical utility. 95% confidence 162 intervals (95%CI) were calculated for all of these features.

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Between September 2016 to December 2018, 85 participants, from 109 individuals

165 who were screened, were enrolled in the study. Of the 85 participants, 27 (31.7%) were 166 diagnosed with CR, 42 with neck and non-radiculopathic arm pain, 12 with peripheral nerve 167 entrapment, and 4 with diffuse shoulder pain (Table 1). All participants received the same 168 reference standard and were included for analysis (Figure 1). Diagnostic accuracy of the 169 four individual ULNTs are presented in Table 2. All four of the tests were more specific, 170 than sensitive, with the ULNT3 demonstrating the highest specificity. None of the four tests 171 markedly influenced post-test probability with a positive or a negative finding, with post-test 172 probability changes from baseline prevalence ranging from 41.58% with a positive for 173 ULNT3 to 15.72% with a negative for ULNT 2a.

174

175	Table 1: Baseline	characteristics	of the	subjects	(n=85)
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Cervical	Non-radiculopathic	
radiculopathy	arm pain	
43.96 (8.94)	45.27 (9.74)	p = 0.61
1.66 (0.09)	1.67 (0.08)	p = 0.54
24.73 (3.91)	24.88 (4.97)	p = 0.74
93.25 (98.41)	70.51 (62.31)	p = 0.69
5.14 (1.58)	5.03 (1.53)	p = 0.73
38.16 (14.14)	43.07 (13.90)	p= 0.19
	radiculopathy 43.96 (8.94) 1.66 (0.09) 24.73 (3.91) 93.25 (98.41) 5.14 (1.58)	radiculopathy arm pain 43.96 (8.94) 45.27 (9.74) 1.66 (0.09) 1.67 (0.08) 24.73 (3.91) 24.88 (4.97) 93.25 (98.41) 70.51 (62.31) 5.14 (1.58) 5.03 (1.53)

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178

179 **Table 2:** Diagnostic Accuracy of Individual Upper Limb Neurodynamic Tests. Pre-test

180 Prevalence = 31.7%.

Sensitivity	Specificity	LR+ (95%	LR- (95%	Post-test	Post-test
		CI)	CI)	Probability	Probability with

					with a Positive Finding (95% CI)	Finding (95% CI)
ULNT 1	59.26 (38.80,	75.86 (62.83,	2.46 (1.41-	0.54 (0.33-	53.30 (39.55-	20.04 (13.28-
	77.61)	86.13)	4.27)	0.87)	66.46)	28.76)
ULNT 2a	70.37 (49.82,	72.41 (59.10,	2.55 (1.57-	0.41 (0.22-	54.20 (42.15-	15.98 (9.26-
	86.25)	83.34)	4.14)	0.75)	65.77)	25.82)
	,	,	,	,	,	,
ULNT 2b	55.56 (35.33,	75.86 (62.83,	2.30 (1.30-	0.59 (0.38-	51.63 (37.63-	21.49 (14.99-
	74.52)	86.13)	4.06)	0.92)	65.33)	29.92)
	,	,	,	,	,	,
ULNT 3	40.74 (22.39,	93.10 (83.27,	5.91 (2.07,	0.64 (0.46-	73.28 (48.99-	22.95 (17.59-
	61.20)	98.09)	16.87)	0.88)	88.65)	28.99)

Diagnostic accuracy of test conditions for combinations of ULNTs are presented in Table 3. Characteristically, with lower conditions (e.g., 1 of 4 is positive) values exhibit high sensitivity and low specificity, whereas higher conditions (4 of 4 are positive) values exhibit low sensitivity and high specificity. As expected, the condition of 1 out of 4 ULNT tests positive was the most sensitive combination whereas the condition of 4 out of 4 ULNT tests was the most specific. The condition of 1 out of 4 tests positive has the ability to "rule out" CR (LR-=0.08), exhibiting a post-test probability change of 28.12% with a negative finding. The condition of 4 of 4 tests positive had an infinite LR+ but there were only 3 cases in which all four tests were positive. The condition of 3 of 4 tests positive occurred in 12 of the 27 patients with CR and provided a LR+ of 12.89 and a post-test probability of 85.71 (post-test probability change of 54.01%). No adverse events from performing the index test or the reference standard were observed.
Table 3. Diagnostic Accuracy of Clustered Upper Limb Neurodynamic Test findings
 (Conditions). Pre-test Prevalence = 31.7%.

Sensitivity	Specificity	LR + (95%	LR- (95% CI)	Post-test	Post-test
				Probability	Probability with

			CI)		with a Positive Finding (95%	Finding (95%
1 of 4	96.30 (81.03,	46.55	1.80 (1.40,	0.08 (0.01,	CI) 45.51 (39.38-	CI) 3.58 (0.46-20.62)
Positive	99.91)	(33.34, 60.13)	2.32)	0.56)	51.84)	2.20 (0.10 20.02)
2 of 4	85.19 (66.27,	74.14 (60.96,	3.29 (2.07,	0.20 (0.08,	60.42 (48.99-	8.49 (3.59-18.83)
Positive	95.81)	84.74)	5.23)	0.50)	70.82)	
3 of 4	44.44 (25.48-	96.55 (88.09-	12.89 (3.10-	0.58 (0.41,	85,71 (59.06-	23.237 (18.57-
Positive	64.67)	99.58)	53.62)	0.81)	96.14)	28.82)
4 of 4	11.11 (2.35,	100.00 (93.84,	Inf.	0.89 (0.78.	100	29.23 (26.58-
Positive	29.16)	100.00)		1.02)		32.13)

²⁰³

205	Discu	ission

206 207

This study sought to determine the diagnostic accuracy of four ULNTs in identifying 208 209 CR in comparison with a reference standard of clinical diagnosis with MRI confirmation. 210 The study was performed in a situation of diagnostic uncertainty and used a more rigid 211 definition of what constitutes a positive test compared to previous studies [12-14]; the tests 212 also more closely matched how the tests are used in clinical practice. Findings were that 213 ULNTs when used in isolation did not lead to acceptable LR-, LR+ or post-test probability. 214 However, 3 out of 4 tests positive can rule in CR with a LR+ of 12.89. One of four positive 215 tests provided a LR- of 0.08 indicating that CR can be ruled out if no tests are positive. Of 216 the four tests, the ULNT3 influenced post-test probability the most with a positive test 217 (73.28%), whereas the ULNT2a influenced post-test probability the most with a negative 218 test (15.98%). 219

Each ULNT provided stronger LR+ values than LR-, thus influencing post-test probability
with a positive finding more notability than a negative finding. Our findings are markedly
different than those from Wainner et al. who found very low values of LR+ (<1.3) -
suggesting that they did not rule in - and moderately low LR- values (>0.12) - suggesting

224 they are better for ruling out (Wainner et al, 2003). Ghasemi and colleagues [14] failed to 225 report a LR+ (or a LR-) (Ghasemi et al, 2013) and our calculations from their sensitivity and 226 specificity values yielded LR+ values similar or worse than those of Wainner and associates 227 (Wainner et al, 2003). The differences in findings compared to those of others (Wainner et 228 al, 2003; Ghasemi et al, 2013) are likely related to the way we defined a positive index test 229 (familiar compliant that was altered by structural differentiation). In Wainner and 230 colleagues' study, an ULNT was defined as positive if only one of the following criteria 231 were present: reproduction of the patient's symptoms, or side to side range of motion deficit, 232 or structural differentiation using the cervical spine (Wainner et al, 2003). Ghasemi et al., 233 reported a positive finding if 'pain' occurred during testing (hasemi et al, 2013). Basing the 234 test outcome on one criterion alone as identified by those authors could lead to an increase 235 in false positive findings, thus decreasing specificity, and worsening the LR+ value 236 (Schiffman et al, 2014). Apelby-Albrecht et al. defined as positive if all the three following 237 criteria were met: reproduction of neurogenic symptoms according to a dermatomal pattern, 238 increased or decreased symptoms with structural differentiation, and a difference in painful 239 radiation between sides (Apelby-Albrecht et al, 2013). Our LR+ values are very similar to 240 previous findings by a recent systematic review (Thoomes et al, 2017) calculated from data 241 reported by Apelby-Albrecht et al (Apelby-Albrecht et al, 2013). However, in our study 242 ULNT was defined as positive according to two criteria and we include a more mixed 243 control group population (58 neck or shoulder pain, thoracic outlet syndrome and carpal 244 tunnel syndrome) than Apelby-Albretch (only 18 subjects with neck pain or carpal tunnel 245 syndrome) (Apelby-Albrecht et al, 2013). These findings highlight the importance to 246 clinicians of determining a positive ULNT based on symptom reproduction together with the 247 effects of structural differentiation, at least in diagnosing cervical radiculopathy.

249 In their recent systematic review of diagnostic tests for CR, Koulidis et al [25] concluded 250 that ULNTs could only be used as a "ruling out" strategy (Koulidis et al, 2019) based on 251 Apelby-Albrecht et al's data (Apelby-Albrecht et al, 2013). Conversely, in our sample, 252 ULNT when used in isolation were better at ruling in CR versus ruling out, yet clustering 253 the ULNT findings produced large changes in post-test probability with either a negative 254 finding or a positive finding. The condition of one of four positive tests yields a LR- of 0.08 255 (95%CI=0.01-0.56). This means that when none of the four ULNTs are positive it can rule 256 out CR with only a 3.58% chance that the patients in this sample had CR. Moreover, using 257 multiple combination of ULNT demonstrated that the condition of 3 of 4 positive tests 258 yielded a LR+ of 12.89 (95%CI=3.10-53.62) which means it can rule in CR with a post-test 259 probability of 85.71%. We recommend the use of 3 of 4 conditions over 4 of 4, since this 260 finding was uncommon and because the confidence intervals crossed 1.0 for the LR-261 analyses. 262 We are also the first to report post-test probability of a positive and negative finding with an 263 ULNT, an analysis omitted from past works (Apelby-Albrecht et al, 2013; Ghasemi et al, 264 2013). Post-test probability provides a better understanding of how markedly one's decision 265 is influenced by single, or combined, positive or negative test results. This is of particular 266 importance since the reporting of individual sensitivity and specificity values is not 267 recommended (Hegedus and Stern, 2009; Baeyens et al, 2019) and may yield conflicting 268 results for ruling in or ruling out conditions. 269 270 Study limitations 271 Although there is notable debate on an appropriate sample size for a diagnostic 272 accuracy study (Hajian-Tilaki, 2014; Bujang and Adnan, 2016), we feel compelled to

273	identify our sample of 85 (including 27 CR) as a potential limitation. A smaller sample size
274	may lead to less precision (e.g., wide confidence intervals). Only one clinician was involved
275	in determining the reference standard and another was involved in determining the ULNT.
276	Although the ULNT tester was blinded to the diagnosis of the patient, the transferability of
277	their findings is unknown, since we did not test interrater agreement. Future research is
278	needed to assessed the validity of ULNT with a larger sample of patients with CR and a
279	larger control group with similar symptoms (thoracic outlet syndrome, neck/shoulder pain,
280	peripheral nerve entrapment, etc.), and with more examiner and reference standards
281	including magnetic resonance neurography and small fiber function (Schmid et al, 2013).
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204	Conductors
284	Conclusions
284 285	Our results support past findings that the singular use of ULNT to rule in or rule out
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296	Table 1: Baseline characteristics of the subjects (n=85)
297	* Wilcoxon rank sum test
298	
299 300	Table 2: Diagnostic Accuracy of Individual Upper Limb Neurodynamic Tests. Pre-test
301	Prevalence = 31.7%.
302	1 to valence = 51.7%.
303	95%CI: Confidence interval at 95%
304	LR+: Positive likelihood ratio
305	LR-: Negative likelihood ratio
306	ULNT: Upper limb neurodynamic test
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308	
309	Table 3. Diagnostic Accuracy of Clustered Upper Limb Neurodynamic Test findings
310	(Conditions). Pre-test Prevalence = 31.7% .
311	
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313	LR+: Positive likelihood ratio
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# 329 Appendix A. Standard sequence of joint movements and suggested structural differentiation

330 maneuvers (sensitizing movements at a site distant to the pain) for each ULNT (Nee et al,

331 2012)

ULNT 1 (median nerve) :

- Shoulder girdle stabilization
- Shoulder abduction
- Wrist/finger extension
- Forearm supination
- Shoulder external rotation
- Elbow extension
- Structural differentiation: Cervical side bending or release wrist extension

ULNT 2a (median nerve) :

- Shoulder girdle depression
- Elbow extension
- Shoulder external rotation and forearm supination
- Wrist/finger extension
- Shoulder abduction
- Structural differentiation: Cervical side bending, or release shoulder girdle depression or release wrist extension

# ULNT 2b (radial nerve) :

- Shoulder girdle depression
- Elbow extension
- Shoulder external rotation and forearm pronation
- Wrist/finger flexion
- Shoulder abduction
- Structural differentiation : Release shoulder girdle depression or release wrist flexion

## ULNT 3 (ulnar nerve) :

- Wrist/finger extension
- Forearm pronation
- Elbow flexion
- Shoulder external rotation
- Shoulder girdle depression
- Shoulder abduction
- Structural differentiation : Cervical side bending, or release shoulder girdle depression or release wrist extension









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335	Abbreviations :
336	CR : Cervical radiculopathy
337	ULNT : Upper limb neurodynamic tests
338	MRI : magnetic resonance imaging
339	LR+ : Positive likelihood ratio
340	LR- : Negative likelihood ratio
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