FAST TRACK ALGORITHM: HOW TO DIFFERENTIATE A "SCLERODERMA PATTERN" FROM A "NON-SCLERODERMA PATTERN"

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ABSTRACT

Objectives: This study was designed to propose a simple "Fast Track algorithm" for capillaroscopists of any level of experience to differentiate "scleroderma patterns" from "non-scleroderma patterns" on capillaroscopy and to assess its inter-rater reliability.

Methods: Based on existing definitions to categorise capillaroscopic images as "scleroderma patterns" and taking into account the real life variability of capillaroscopic images described standardly according to the European League Against Rheumatism (EULAR) Study Group on Microcirculation in Rheumatic Diseases, a fast track decision tree, the "Fast Track algorithm" was created by the principal expert (VS) to facilitate swift categorisation of an image as "non-scleroderma pattern (category 1)" or "scleroderma pattern (category 2)". Mean inter-rater reliability between all raters (experts/attendees) of the 8th EULAR course on capillaroscopy in Rheumatic Diseases (Genoa, 2018) and, as external validation, of the 8th European Scleroderma Trials and Research group (EUSTAR) course on systemic sclerosis (SSc) (Nijmegen, 2019) versus the principal expert, as well as reliability between the rater pairs themselves was assessed by mean Cohen's and Light's kappa coefficients.

Results: Mean Cohen's kappa was 1/0.96 (95% CI 0.95-0.98) for the 6 experts/135 attendees of the 8th EULAR capillaroscopy course and 1/0.94 (95% CI 0.92-0.96) for the 3 experts/85 attendees of the 8th EUSTAR SSc course. Light's kappa was 1/0.92 at the 8th EULAR capillaroscopy course, and 1/0.87 at the 8th EUSTAR SSc course.

Conclusion: For the first time, a clinical expert based fast track decision algorithm has been developed to differentiate a "non-scleroderma" from a "scleroderma pattern" on capillaroscopic images, demonstrating excellent reliability when applied by capillaroscopists with varying levels of expertise versus the principal expert and corroborated with external validation.

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168   **KEYWORDS**

169   EULAR Study Group on Microcirculation in Rheumatic Diseases, capillaroscopy, reliability,

170   "scleroderma patterns", novices, experts, algorithm.

ABBREVIATIONS

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172 ACR   *American College of Rheumatology*

173 CI   *Confidence Interval*

174 EULAR   *European League Against Rheumatism*

175 EULAR SG MC/RD   *EULAR Study Group on Microcirculation in Rheumatic Diseases*

176 EUSTAR   *European Scleroderma Trials and Research group*

177 NVC   *nailfold videocapillaroscopy*

178 SSc   *systemic sclerosis*

1. INTRODUCTION

The "scleroderma pattern" on capillaroscopy has been incorporated into the 2013 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria, as well as in criteria to facilitate a (very) early diagnosis of systemic sclerosis (SSc) (1-3). Its importance is based on the fact that the combination of a "scleroderma pattern" and SSc specific antibodies has the highest performance characteristics to discern in a Raynaud's phenomenon population who will and who will not develop SSc (4).

In 1973 and more detailed in 1981, Maricq et al. was the first to describe key capillary abnormalities of a "scleroderma pattern" using "wide-field" capillary microscopy as "enlargement of capillary loops, loss of capillaries ('loop drop-out'), disruption of the normal capillary architecture and haemorrhages" (5, 6). Moreover, in her seminal quantitative study she measured with the stereomicroscopic technique the apical diameter of "definitely enlarged" capillaries, and found a mean apical diameter of 47.7μm ± 5.8 to be specific for scleroderma spectrum diseases (7). This finding was adopted and further developed by Cutolo et al. who likewise defined "giant capillaries" with the nailfold videocapillaroscopic (NVC) technique as homogeneously enlarged capillaries with a normal shape and apical diameter over 50μm (8). The presence of these giant capillaries on NVC is interesting, as it allows distinction between SSc and non-SSc with over 95.6% specificity (9, 10). Of note, giant capillaries are the hallmark of the "early" and "active" scleroderma patterns, whilst the "late" scleroderma pattern is characterised by the combination of severe loss of capillaries combined with abnormal shapes ("[neo-] angiogenesis") (7, 8).

Even though the classification of a capillaroscopic image as "scleroderma pattern" or not has a high inter-rater reliability between trained capillaroscopists, to the untrained rheumatologist this

202   classification may be very challenging (11-13). One of the reasons may be the vast variety of

203   non-specific abnormalities of capillaroscopic characteristics (i.e. of capillary density, capillary

204   dimension, capillary morphology and haemorrhages) that may be found in the general

205   population (see below and in Supplementary File 1).

206   To facilitate the non-trained capillaroscopist in easily classifying an image as "scleroderma

207   pattern" or "non-scleroderma pattern", the EULAR Study Group on Microcirculation in

208   Rheumatic Diseases (EULAR SG MC/RD), a non-profit international network of expert centres

209   established in 2014 which has as its main (research) focus to facilitate standardization of

210   different non-invasive techniques, decided to create a swiftly trainable decision tree, the "Fast

211   Track algorithm", based on existing definitions to categorise capillaroscopic images into the

212   category of "scleroderma patterns" or into the category of "non-scleroderma patterns".

213   Additionally, the EULAR SG MC/RD decided to assess the reliability of raters using this

214   decision tree to classify capillaroscopic images. The key advantage of a fastly trainable, reliable

215   decision tree would be that any capillaroscopist of any level of experience would be able to use

216   this, knowing that he/she would rate likewise to a principal capillaroscopy expert, without the

217   need to evaluate each single capillaroscopic characteristic that can be evaluated in

218   capillaroscopy for research aims (see below and Supplementary File 1).

2. METHODS

2.1. "Fast Track algorithm"

Based on the standard interpretation of capillaroscopic images by the EULAR SG MC/RD, more specifically of the following capillaroscopic characteristics: capillary density, capillary dimension, presence of abnormal capillary shapes and presence of haemorrhages (see Supplementary File 1) and based on the key elements of the "scleroderma pattern", a decision tree (i.e. the "Fast Track algorithm") was consented by two founding members of the EULAR SG MC/RD (VS, MC) (see Figure 1). The "Fast Track algorithm" consists of three easy rules: 1) Rule number 1: the presence of ≥ 7 capillaries (capillary density) AND the absence of giant capillaries (capillary dimension) allows the rater to call the capillaroscopic image a "non-scleroderma pattern (category 1)"; 2) Rule number 2: the presence of giant capillaries or the presence of an extremely lowered capillary density (≤ 3 capillaries) in combination with abnormal shapes (= "late" scleroderma pattern) allows the capillaroscopist to call the capillaroscopic image a "scleroderma pattern (category 2)"; 3) Rule number 3: if the image does not meet rule number 1 or rule number 2 then the image is automatically classified as a "non-scleroderma pattern (category 1)" (see Figure 1).

2.2. Capillaroscopic images

Thirty representative NVC images (i.e. 14 images with "scleroderma pattern" and 16 with "non-scleroderma pattern") with good visibility, acquired by an optical probe videocapillaroscope equipped with a 200x magnification contact lens, were randomly selected from all NVC examinations of patients referred to the Ghent University Scleroderma Unit between December 2017 and June 2018 (see Supplementary File 2 for the examination set with all capillaroscopic

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images). In the distal row, the apical diameter of dilated capillaries was reported by a trainee (MG), who had been trained by the principal expert (VS). All images were proofread by the principal expert (VS). Categorisation of images as "scleroderma pattern" or "non-scleroderma pattern" had been executed by the principal expert (VS).

2.3. Procedure of teaching the "Fast Track algorithm" and examining the raters

In the first part of this international multicentre study, a 45 min lasting lecture ("Capillaroscopy in daily practice") was given at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa (September 2018) to 141 attendees, more specifically 6 experts in capillaroscopy and 135 attendees with varying levels of experience in capillaroscopy: 68 "novices", 53 "moderately experienced" and 14 "experienced" (see Table 1). In this lecture the EULAR SG MC/RD standardly assessed capillaroscopic characteristics (capillary density, capillary dimension, abnormal morphology and haemorrhages) were explained step by step by the principal expert (VS) and for the attendees' information an overview of all possible combinations of each of the capillaroscopic characteristics resulting into either "scleroderma patterns" or oppositely "non-scleroderma patterns" was taught both theoretically and applied to exemplary images (see Supplementary File 1 and 3). The "Fast Track algorithm" was applied to each capillaroscopic image and explained by the teacher, the principal expert (VS). Hence, in this interactive way, the audience was stimulated to actively learn the "Fast Track algorithm" (see Figure 1). After the teaching lecture, the attendees had the picture of the "Fast Track algorithm" at hand during the examination (see Figure 1). In addition, the PowerPoint slide of the "Fast Track algorithm" had also been projected in the room during the whole examination (see Figure 2A and 2B). The exams existed of 16 pages, containing two capillaroscopic images

265   per page (see Supplementary File 2). Next to an image the attendee was asked to choose

266   between two options by applying a cross, i.e. more specifically category 1 ("non-scleroderma

267   pattern") or category 2 ("scleroderma pattern") (see Supplementary File 2). Collaboration

268   between attendees to execute the exam was not allowed. Two trainees (AV, MG) of the

269   principal expert (VS) as well as the principal expert (VS) and the senior author (MC) supervised

270   the room to avoid any collaboration between attendees in taking the exam. Of note, the raters

271   (experts and attendees) were asked to attest their levels of expertise in capillaroscopy into one

272   of the following categories: "novices" (no experience), "moderately experienced" (< 5 years of

273   experience with capillaroscopy) and "experienced" raters (> 5 years of experience with

274   capillaroscopy).

275   In a second time, as an external validation, this procedure was repeated during the 8th European

276   Scleroderma Trials and Research group (EUSTAR) course on SSc in Nijmegen (February 2019)

277   on 88 attendees, more specifically 3 experts and 85 attendees with varying levels of knowledge

278   of capillaroscopy: 47 "novices", 29 "moderately experienced" and 9 "experienced" (see Table

279   2).

280

281   **2.4. Statistical analysis**

282   Inter-rater agreement for each rater versus the principal expert (VS), i.e. "mean index of

283   reliability", was calculated for the group of experts, "novices", "moderately experienced" raters

284   and "experienced" raters, both at the 8th EULAR course on capillaroscopy in Rheumatic

285   Diseases and for reasons of external validation, as well at the 8th EUSTAR course on SSc. To

286   this end, the mean Cohen's kappa value was reported, which is estimated by taking the mean

287   of all Cohen's kappa statistic scores between raters and the principal expert (VS) (see Figure

288   3A) (14).

289   Additionally, the agreement between all possible rater pairs, irrespective of the principal expert

290   (VS), was reflected through reporting the Light's kappa. Hence, conceivably, if the algorithms

291   should be representative for the experts (other than the principal expert) then the Light's kappa

292   should be high in between the experts (see Figure 3B) (14).

293   Thirdly, to get an idea of the percentage of raters at both courses which had a nearly perfect

294   agreement, which is a kappa of > 0.8 versus the principal expert (VS), the distribution of the

295   individual kappa's was calculated (15).

3. RESULTS

3.1. Raters

Six expert raters (MC, AH, FI, VR, AS, VS [principal expert]) and 135 attendees (68 "novices", 53 "moderately experienced" and 14 "experienced" raters, from 43 different countries) participated at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 3 expert raters (MC, MV, VS [principal expert]) and 85 attendees (47 novices, 29 moderately experienced and 9 experienced raters, from 22 different countries) participated at the 8th EUSTAR course on SSc.

3.2. Inter-rater reliability

The mean index of reliability (i.e. mean Cohen's kappa) based on 30 images was 1 for the expert raters present at the 8th EULAR course on capillaroscopy in Rheumatic Diseases (n=6) and 1 for the expert raters present at the 8th EUSTAR course on SSc (n=3). The mean index of reliability was 0.96 (95% Confidence Interval [CI] 0.95-0.98) for the attendees of the 8th EULAR course on capillaroscopy in Rheumatic Diseases (n=135) and 0.94 (95% CI 0.92-0.96) for the attendees of the 8th EUSTAR course on SSc (n=85). Subgroup analysis according to the level of experience of the attendees, demonstrated a mean Cohen's kappa of 0.98 (95% CI 0.96-0.99) and 0.93 (95% CI 0.90-0.96) for "novices" (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively), 0.96 (95% CI 0.93-0.99) and 0.94 (95% CI 0.89-0.98) for "moderately experienced" raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively) and 0.93 (95% CI 0.85-1) and 0.97 (95% CI 0.92-1) for "experienced" raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively).

319   Inter-rater agreement for each possible combination of rater pairs (i.e. Light's kappa),

320   irrespective of the principal expert (VS), based on the 30 images was 1 for the expert raters

321   present at the 8th EULAR course on capillaroscopy in Rheumatic Diseases (n=6) and 1 for the

322   expert raters present at the 8th EUSTAR course on SSc (n=3). The inter-rater agreement for

323   each possible combination of rater pairs, irrespective of the principal expert was 0.92 for the

324   attendees of the 8th EULAR course on capillaroscopy in Rheumatic Diseases (n=135) and 0.87

325   for the attendees of the 8th EUSTAR course on SSc (n=85). Subgroup analysis demonstrated a

326   Light's kappa of 0.95 and 0.87 for "novices" (at the 8th EULAR course on capillaroscopy in

327   Rheumatic Diseases and 8th EUSTAR course on SSc respectively), 0.91 and 0.88 for

328   "moderately experienced" raters (at the 8th EULAR course on capillaroscopy in Rheumatic

329   Diseases and 8th EUSTAR course on SSc respectively) and 0.84 and 0.94 for "experienced"

330   raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR

331   course on SSc respectively).

332

333   **3.3. Percentage of raters with high agreement versus the principal expert**

334   The distribution of the individual kappa's showed that 95% of raters at the 8th EULAR course

335   on capillaroscopy in Rheumatic Diseases in Genoa and 89% of raters at the 8th EUSTAR course

336   on SSc in Nijmegen had a kappa of > 0.8 versus the principal expert (VS).

4. DISCUSSION

This is the first international multicentre study to step forward to the need to find an easy rule of thumb decision tree (i.e. the "Fast Track algorithm") to categorise capillaroscopic images as "scleroderma pattern" or "non-scleroderma pattern". A principal expert (VS) had first classified 30 images, taken with a nailfold videocapillaroscope with a 200x magnification, as "scleroderma pattern" or "non-scleroderma pattern", the latter comprising perfectly normal images but also images with non-specific abnormalities. Then, in two renowned international training courses (the 8th EULAR course on capillaroscopy in Rheumatic Diseases and the 8th EUSTAR course on SSc) course raters (experts and attendees of different level of experience ["novices", "moderate experienced", "experienced"]) had been trained in 45 minutes by the principal expert to categorise images in the exact same way as the principal expert through exemplary teaching the "Fast Track algorithm". Subsequently, both in the pilot study at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa, as well as in the external validation study at the 8th EUSTAR course on SSc in Nijmegen, an excellent inter-rater reliability, not only versus the principal expert rater (mean Cohen's kappa) but also in between the raters themselves (Light's kappa) was found in categorising capillaroscopic images as "scleroderma pattern" or as "non-scleroderma pattern". Hence, we strongly feel that this "Fast Track algorithm" may be used safely as a teaching tool in daily practice to capillaroscopists with any level of experience, with the aim to have certainty to categorise a capillaroscopic image as a "scleroderma pattern" in the same way that an expert rater does.

This swiftly trainable and reliable decision tree is important, certainly as the "scleroderma pattern" is a criterion in the new 2013 ACR/EULAR classification criteria for systemic sclerosis (3). Correct attribution (vis à vis a principal expert as repère point) of a capillaroscopic image

360   to the "scleroderma pattern" category is key to correctly denote a patient to meet the criterion

361   of "abnormal capillaroscopy" of the 2013 ACR/EULAR criteria (3).

362   One of the advantages of the "Fast Track algorithm" is that only simple capillaroscopic

363   characteristics were needed to teach the raters, more specifically, capillaroscopic characteristics

364   that have attested through literature to have a high inter-rater reliability: "capillary density"

365   (number of capillaries), "giant capillaries" (capillaries with an apical diameter ≥ 50 µm) and

366   "abnormal shapes" (13, 16-24). Rather than trying to train the eye of the rater to interpret

367   capillaroscopic images according to any combination of all existing capillaroscopic

368   characteristics that are being used nowadays in research which may be quite challenging to the

369   untrained capillaroscopists (see Supplementary File 1), with the "Fast Track algorithm" the

370   capillaroscopist only has to check three rules which automatically lead him/her to a correct

371   categorisation, more specifically into a "scleroderma pattern or "non-scleroderma pattern".

372   Additionally, we want to draw attention to the fact that the aim of this study was not to assess

373   discriminatory characteristics of capillaroscopy to differentiate between healthy controls,

374   primary Raynaud's patients and patients with secondary Raynaud's phenomenon due to SSc.

375   Landmark work on this issue has already been done (4, 25, 26). Moreover, such a research

376   question would have needed a totally different statistical approach with calculation of receiver

377   operating curves and calculation of sensitivity and specificity of capillaroscopy to discriminate

378   healthy controls and primary from secondary Raynaud's phenomenon due to SSc. In contrast,

379   our intention was to assess an expert designed decision tree, the "Fast Track algorithm", with

380   the aim to enable every capillaroscopist of any level of experience to differentiate within groups

381   of clinically relevant capillaroscopic patterns, more specifically between "the scleroderma

382   patterns" versus the "non-scleroderma patterns".

5. CONCLUSION

For the first time, a clinical expert based fast track decision algorithm has been developed to differentiate a "non-scleroderma" from a "scleroderma pattern" on capillaroscopic images. This algorithm demonstrated an excellent reliability when applied by capillaroscopists with varying levels of expertise versus the principal expert, at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa and corroborated with external validation at the 8th EUSTAR course on SSc in Nijmegen.

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703 **TABLES AND FIGURES**

704 **Table 1: Mean Cohen's kappa (95% CI) and Light's kappa for the groups of raters at the**

705 **8th EULAR course on capillaroscopy in Rheumatic Diseases (Genoa 2018).**

706 **Table 2: Mean Cohen's kappa (95% CI) and Light's kappa for the groups of raters at the**

707 **8th EUSTAR course on SSc (Nijmegen 2019).**

708

709

710 **Figure 1: The "Fast Track algorithm".**

711 **Figure 2: Examination setting.**

712 **Figure 3: Inter-rater agreement assessed by kappa coefficients.**

713

714 **Table 1: Mean Cohen's kappa (95% CI) and Light's kappa for the groups of raters at the**

715 **8th EULAR course on capillaroscopy in Rheumatic Diseases (Genoa 2018).**

Group of raters	Mean Cohen's kappa (95% CI)	Light's kappa
Expert raters (n=6)	1	1
Attendees (n=135)	0.96 (0.95 – 0.98)	0.92
- *"Novices" (n=68)*	0.98 (0.96 – 0.99)	0.95
- *"Moderately experienced" (n=53)*	0.96 (0.93 – 0.99)	0.91
- *"Experienced" (n=14)*	0.93 (0.85 – 1)	0.84

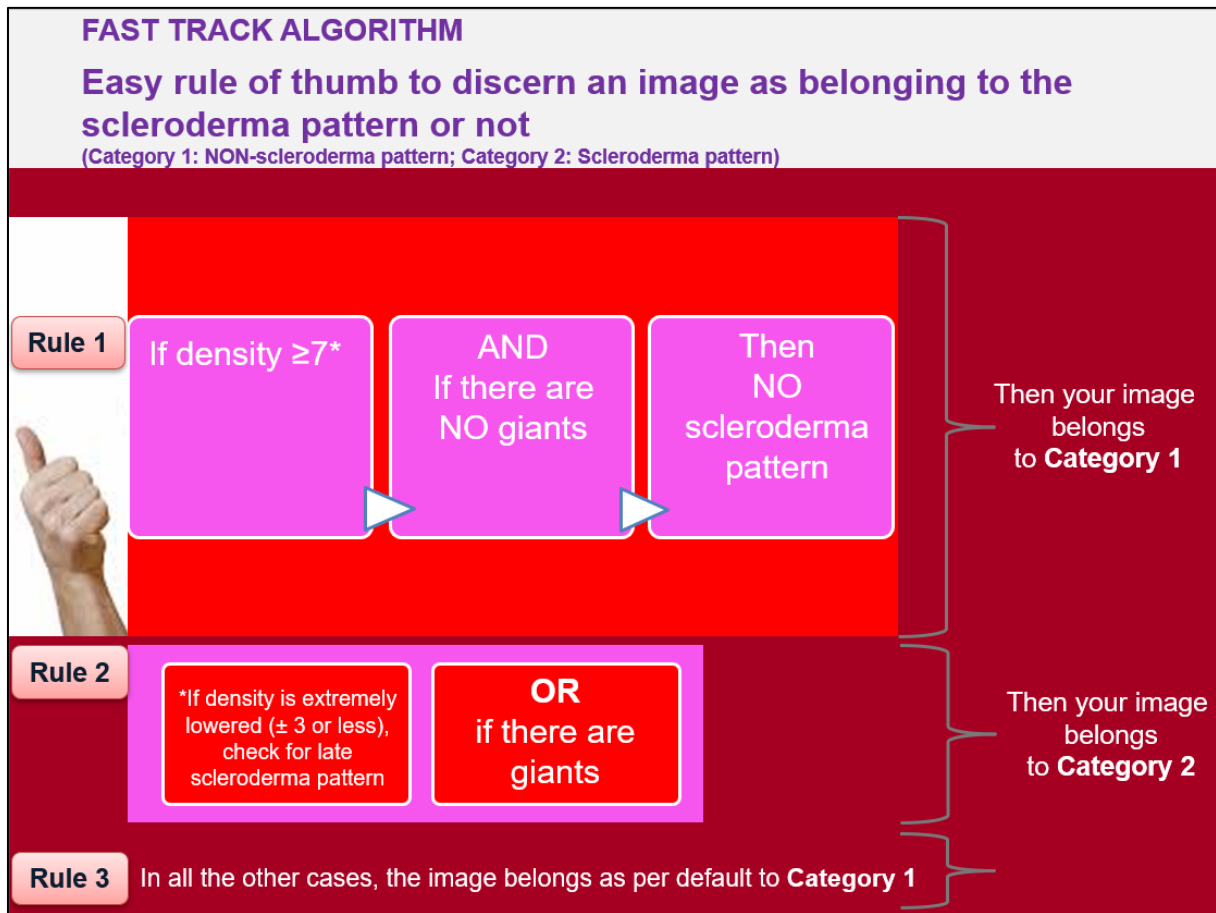716 *CI: Confidence Interval.*

717

38

718 **Table 2: Mean Cohen's kappa (95% CI) and Light's kappa for the groups of raters at the**

719 **8th EUSTAR course on SSc (Nijmegen 2019).**

| Group of raters	Mean Cohen's kappa (95% CI)	Light's kappa
Expert raters (n=3)	1	1
Attendees (n=85)	0.94 (0.92 – 0.96)	0.87
- *"Novices" (n=47)*	0.93 (0.90 – 0.96)	0.85
- *"Moderately experienced" (n=29)*	0.94 (0.89 – 0.98)	0.88
- *"Experienced" (n=9)*	0.97 (0.92 – 1)	0.94

720 *CI: Confidence Interval.*

721

722 **Figure 1: The "Fast Track algorithm".**

FAST TRACK ALGORITHM

Easy rule of thumb to discern an image as belonging to the scleroderma pattern or not
(Category 1: NON-scleroderma pattern; Category 2: Scleroderma pattern)

Rule 1 If density ≥7* AND If there are NO giants Then NO scleroderma pattern → Then your image belongs to **Category 1**

Rule 2 *If density is extremely lowered (± 3 or less), check for late scleroderma pattern OR if there are giants → Then your image belongs to **Category 2**

Rule 3 In all the other cases, the image belongs as per default to **Category 1**

723

724   The Fast Track algorithm" consists of three easy rules: 1) **Rule 1**: a capillary density ≥ 7

725   capillaries AND the absence of giant capillaries allows the rater to call the capillaroscopic

726   image a "non-scleroderma pattern (category 1)"; 2) **Rule 2**: an extremely lowered capillary

727   density (≤ 3 capillaries) in combination with abnormal shapes (i.e. "late scleroderma pattern")

728   OR the presence of giant capillaries allows the capillaroscopist to call the capillaroscopic image

729   "a scleroderma pattern (category 2)"; 3) **Rule 3**: if the image does not meet rule number 1 or

730   rule number 2 then the image is automatically classified as a "non-scleroderma pattern

731   (category 1)".

732 **Figure 2: Examination setting.**
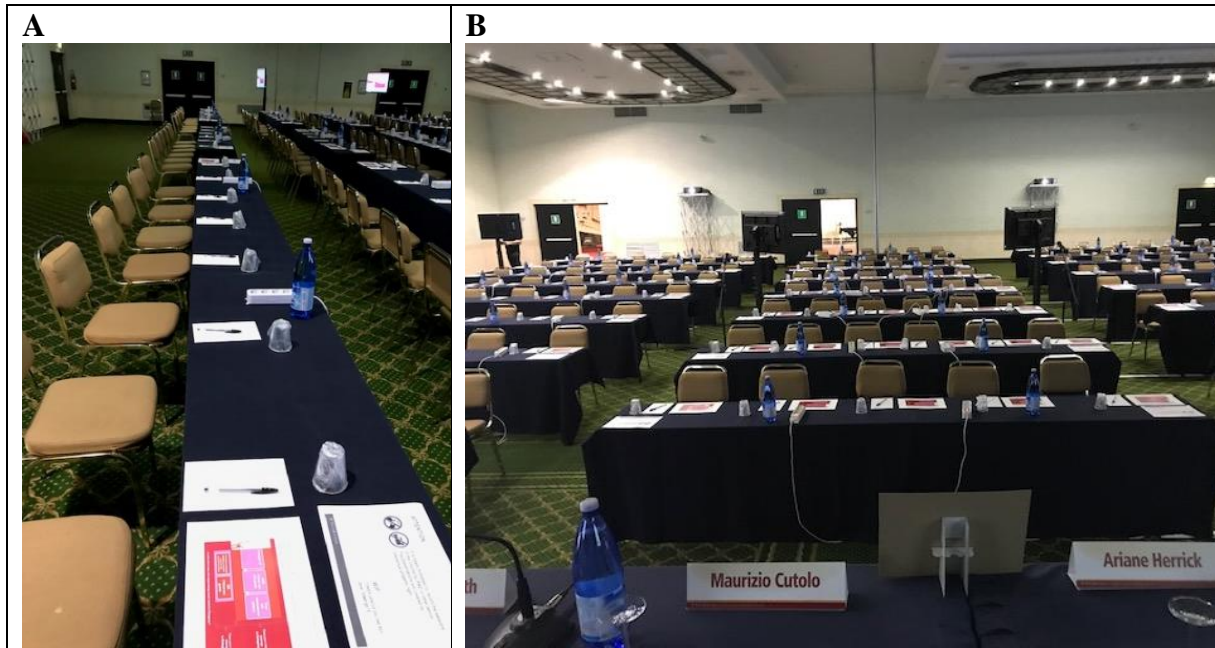
733 After the teaching lecture, the PowerPoint slide of the "Fast Track algorithm" was projected in

734 the room during the whole examination (A) and the attendees had the picture of the "Fast Track

735 algorithm" at hand during the examination (B).

736 **Figure 3: Inter-rater agreement assessed by kappa coefficients.**
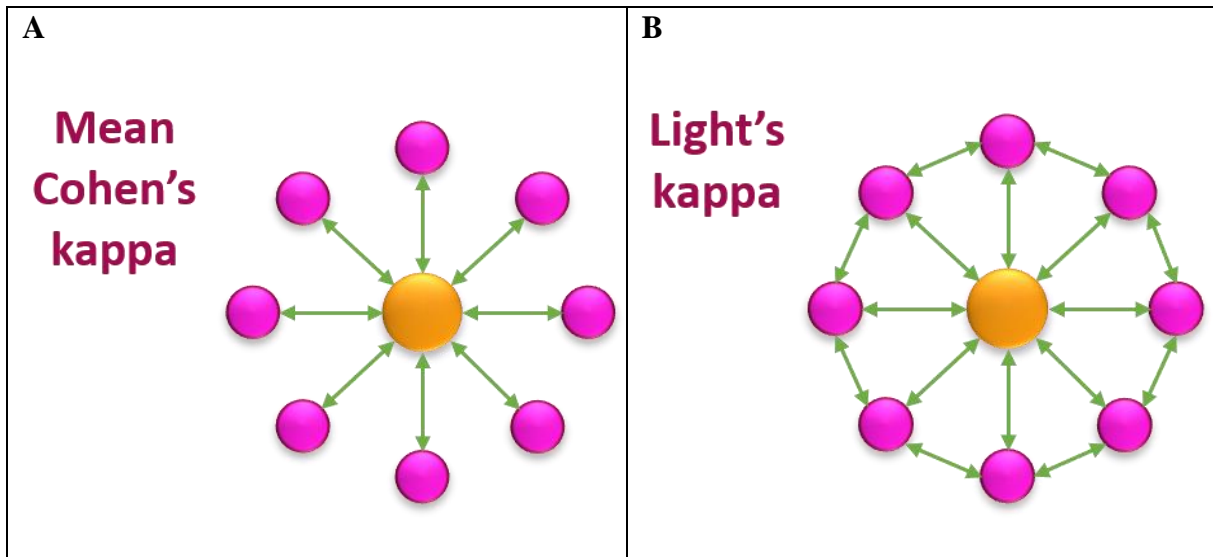
737 Inter-rater agreement was assessed by calculating kappa coefficients, i.e. the mean Cohen's

738 kappa (A) and Light's kappa (B). A) **Mean Cohen's kappa** was calculated to obtain the inter-

739 rater agreement for each rater (expert/ attendees/ "novices"/ "moderately experienced"/

740 "experienced") versus the principal expert (VS). B) **Light's kappa** was calculated to obtain the

741 inter-rater agreement for each possible combination of agreement between raters and the

742 principal expert (VS).

KEY MESSAGES

- The EULAR SG MC/RD created as first a clinical expert based fast track decision algorithm to categorize capillaroscopic images.

- Using the "Fast Track algorithm", non-trained capillaroscopists can discern a "non-scleroderma" from a "scleroderma pattern".

- Multicenter evaluation of the "Fast Track algorithm" shows excellent inter-rater reliability for categorizing capillaroscopic images.

750 **SUPPLEMENTARY FILES**

751 **Supplementary File 1: Standard capillaroscopic characteristics that are being evaluated**

752 **by the EULAR Study Group on Microcirculation in Rheumatic Diseases.**

753 **Supplementary File 2: Examination set.**

754 **Supplementary File 3: Application of the "Fast Track Algorithm" to exemplary images**.