

Investigating the diagnostic utility of non-invasive tear film stability and breakup parameters: A prospective diagnostic accuracy study

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4 **Short title:** Diagnostic profile of tear film breakup parameters

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49 **Research correspondence**

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51 Tear film stability assessment is recommended by the global consensus Tear Film and
52 Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) as an integral component to
53 the diagnostic workup for dry eye disease[1]. In recent decades, there has been growing
54 recognition of the destabilising effects of aqueous sodium fluorescein instillation[2, 3], and
55 non-invasive measurements of tear film breakup time have therefore been recommended in
56 preference[1, 4]. The Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany) is a
57 non-invasive instrument which provides automated measurements of various tear film
58 stability and breakup parameters, including first breakup time, average breakup time,
59 breakup time gradient, and maximum breakup area[1]. Although first and average breakup
60 time measurements are commonly used outcome measures in clinical trials and
61 epidemiological studies[1], the diagnostic utility of breakup time gradient and maximum
62 breakup area have received less attention in the current literature. The purpose of this
63 investigator-masked, prospective, diagnostic accuracy study was therefore to assess the
64 diagnostic performance of automated non-invasive tear film stability and breakup
65 parameters in detecting symptomatic dry eye.

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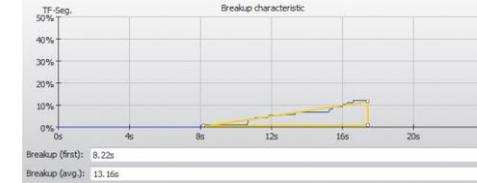
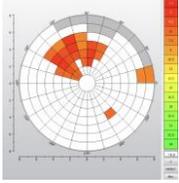
67 The study received institutional ethics committee approval and adhered to the tenets of the
68 Declaration of Helsinki. Participants were recruited through open advertisement from visitors
69 at the Royal Society Summer Science Exhibition between July 2 to July 8 2018 in London,
70 United Kingdom. Informed consent was provided electronically after reviewing the study
71 information. The sample size was pragmatically determined by the number of participants
72 enrolled during the recruitment period. Participants were assessed at a single location, and
73 ocular surface parameters were assessed on the left eye of each participant. The diagnostic
74 criteria for symptomatic dry eye required a Dry Eye Questionnaire (DEQ-5) score ≥ 6 , in
75 accordance to the recommendations of the global consensus TFOS DEWS II criteria[5]. Tear
76 film stability and breakup parameters were assessed using the Keratograph 5M, by an

77 investigator masked to the results of the symptomology questionnaire. Automated first
78 breakup time and average breakup time were recorded while the subject maintained fixation
79 and was requested to refrain from blinking. First breakup time represents the time taken for
80 the first breakup incident of the tear film to be detected, while average breakup time represents
81 the average time of all breakup incidents during an individual recording. Breakup time gradient
82 was derived from the breakup profile as the percentage area breakup per second and
83 maximum breakup area was reported as the count of the zones of breakup of <10.5 s on the
84 Keratograph breakup map (Table 1). The increment of <10.5 seconds was selected, as the
85 closest increment to the recommended non-invasive tear film breakup time threshold of 10
86 seconds, as per the global consensus TFOS DEWS II criteria [1]. Three readings for each
87 measurement were recorded and the arithmetic mean calculated in each case[1]. The
88 discriminative ability of tear film stability and breakup parameters measurements in detecting
89 symptomatic dry eye was determined by the area under the receiver operating characteristic
90 curve (C-statistic), the Youden-optimal diagnostic cut-off sensitivity and specificity values. All
91 tests were two-tailed and $p < 0.05$ considered significant.

92
93 The mean \pm SD age of the 1125 enrolled participants (707 females, 413 males, 5 other sex)
94 was 35 ± 21 years (range, 5 to 90 years), and 780 (69%) participants fulfilled the criteria for
95 symptomatic dry eye. None (0%) of the enrolled participants reported a background of
96 neuropathic pain conditions. Diagnostic accuracy values of non-invasive tear film stability
97 and breakup parameters in detecting symptomatic dry eye are presented in Table 1. The
98 discriminative ability for all non-invasive tear film stability and breakup parameters were
99 significantly greater than chance (all $p < 0.001$). The parameter demonstrating the highest
100 diagnostic performance was maximum breakup area (C-statistic 0.652), while the
101 discriminative ability for first and average breakup time were comparable (C-statistic 0.627
102 versus 0.611). The Youden optimal diagnostic cut-off for first breakup time was ≤ 8 seconds,
103 while the optimal threshold for average breakup time was ≤ 10 seconds.

104

105 **Table 1:** Diagnostic accuracy values of non-invasive tear film stability and breakup parameters in detecting symptomatic dry eye

	Non-invasive tear film breakup parameter			
	First breakup time (s)	Average breakup time (s)	Breakup time gradient (% area/s)	Maximum breakup area (zone count)
Median (IQR)	6.6 (4.2-10.8)	9.4 (6.3-14.4)	0.17 (0.06-0.44)	6 (3-10)
C-statistic, 95% CI	0.627 (0.593-0.662)	0.611 (0.576-0.646)	0.596 (0.561-0.632)	0.652 (0.618-0.686)
Discriminative significance (p-value)	<0.001	<0.001	<0.001	<0.001
Youden optimal diagnostic cut-off	≤8	≤10	≥0.17	≥6
Sensitivity, 95% CI (%)	61.9 (58.4-65.3)	63.1 (59.6-66.5)	54.8 (51.1-58.3)	55.9 (52.3-59.4)
Specificity, 95% CI (%)	52.2 (46.8-57.6)	52.5 (47.1-57.8)	58.6 (53.2-63.8)	65.8 (60.5-70.8)
Positive likelihood ratio, 95% CI	1.29 (1.14 -1.46)	1.33 (1.17-1.50)	1.32 (1.15-1.52)	1.63 (1.39-1.92)
Negative likelihood ratio, 95% CI	0.73 (0.64-0.84)	0.70 (0.61-0.81)	0.77 (0.69-0.87)	0.67 (0.60-0.75)
Tear film parameters (representative examples)	<p>Breakup (first)</p>  <p>Breakup (first): 8.22s Breakup (avg.): 13.16s</p>	<p>Breakup (average)</p>  <p>Breakup (first): 8.22s Breakup (avg.): 13.16s</p>	<p>Breakup gradient</p>  <p>Breakup (first): 8.22s Breakup (avg.): 13.16s</p>	<p><10.5s breakup zone count</p> 

106

107

108 This study compared the diagnostic performance of various non-invasive tear film stability
109 and breakup parameters obtained from the Keratograph, including first breakup time,
110 average breakup time, breakup time gradient, and maximum breakup area, for the detection
111 of symptomatic dry eye. The results demonstrated that all non-invasive tear film and breakup
112 parameters demonstrated discriminative abilities which were significantly greater than
113 chance.

114

115 Maximum breakup area was found to be the sole significant predictor variable, exhibiting the
116 highest diagnostic performance for the detection of symptomatic dry eye of the four tear film
117 breakup parameters considered independently or in combination. To our knowledge, this is
118 the first study to investigate the diagnostic utility of maximum breakup area in dry eye
119 disease, and the findings would suggest that dry eye symptoms is associated with both the
120 extent and speed of tear film breakup. Although conventional parameters used to assess
121 tear film stability focus on the speed and time by which the tear film breaks up[1-4, 6, 7], the
122 higher discriminative ability of maximum breakup area may suggest a closer correlation
123 between the extent and area of tear film breakup with dry eye symptoms. Future research is
124 therefore warranted to investigate whether the incorporation of maximum breakup area
125 measurement might yield additional diagnostic utility to the assessment of breakup time
126 alone.

127

128 Interestingly, first and average tear film breakup time measurements demonstrated
129 comparable discriminative performance, although the readings were not directly
130 interchangeable and exhibited different optimal diagnostic thresholds. The Youden optimal
131 cut-off for average breakup time was ≤ 10 seconds, which is similar to the diagnostic cut-off
132 of < 10 seconds recommended by the global consensus TFOS DEWS II diagnostic
133 methodology committee[1]. In contrast, the optimal threshold for first breakup time of ≤ 8
134 seconds was shorter, and these findings were similar to those reported by previous

135 diagnostic accuracy studies using the Ocular Surface Disease Index (OSDI) and the full
136 TFOS DEWS II criteria as reference standards[6, 7].

137

138 In conclusion, the results of this study showed that non-invasive first and average tear film
139 breakup time readings demonstrated comparable discriminative ability for the detection of
140 symptomatic dry eye, although the two measurements were not directly interchangeable and
141 exhibited different optimal diagnostic thresholds. Maximum breakup area was demonstrated
142 to be the non-invasive tear film parameter exhibiting the greatest discriminative
143 performance, and further research is required to assess whether its incorporation might yield
144 additional diagnostic utility to breakup time readings.

145 Disclosure statement

146

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149

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