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Diagnostic Ability of Conventional Dry Eye Tests and their Correlation with Ocular Surface Temperature

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Abstract

Objective: To study the diagnostic ability of conventional dry eye tests and their correlation with ocular surface temperature (OST) and derive the best combined objective tests for dry eye.

Methods: This was a single visit study included a few conventional dry eye tests on 62 dry eye and 82 control subjects: symptom evaluation, fluorescein break-up time (FBUT), corneal epithelial staining (CES), non-invasive break-up time (NIBUT) and tear meniscus height (TMH). OST was recorded using NEC TH9260 thermo tracer and six temperature metrics of the extreme nasal conjunctiva was studied including the temperature 10 seconds after eye opening (T4-10). Diagnostic ability was assessed by calculating sensitivity and specificity and area under the receiver operating characteristics curve (AUC).

Results: No correlation (Pearson's coefficient, -0.203 to 0.209; $p>0.05$) was found between Mscore, Scount, FBUT and CES with any of the temperature metrics. However, CES correlated significantly with TMH ($r=0.276$; $p=0.030$) and inversely correlated significantly with FBUT ($r=-0.258$; $p=0.043$). Values of Mscore at 8 were found to give sensitivity of 87.1% (95% CI: 76.2 to 94.3%) and specificity of 92.7% (84.8 to 97.3%). Values of Scount at 1 were found to give sensitivity of 93.6% (84.3 to 98.2%) and specificity of 65.9% (54.6 to 76.0%). Values of FBUT at 2 s were found to give sensitivity of 58.1% (44.9 to 70.5%) and specificity of 87.8% (78.7 to 94.0%). Values of CES at grade 2 were found to give sensitivity of 71% (58.1 to 81.8%) and specificity of 59.8% (48.3 to 70.4%). Combining CES with T4-10 (series) had increased the AUC to 78% with sensitivity and specificity of 92.3% and 42.7% respectively.

Conclusion: This work validated the ability of Mscore, Scount, FBUT and CES in diagnosing dry eye and further confirmed the discordance between its signs and symptoms. Combining CES with T4-10 (series) can be future objective tests for dry eye.

Keywords: Correlation; Dry eye diagnosis; Conventional dry eye tests; Ocular surface temperature; Temperature metrics; Sensitivity; Specificity

Introduction

While there are many tests available for dry eye disease (DED), it is well understood that eye care practitioners generally rely on a battery of tests for its diagnosis [1]. Surveys on DED diagnostic testing indicate that there is no one single test which dominates [2] although many practitioners rank symptom reporting as their preferred test [2,3]. Conventional clinical tests for DED diagnosis include fluorescein tear break-up time, corneal fluorescein staining, and meibomian gland evaluation [3] and it is generally agreed that there is a lack of consistency between such measures [2,3]. The situation is further complicated in that DED is multifactorial, determining the cause of dry eye with minimal clinical signs is difficult, and there is a lack of correlation between symptoms and objective tests [4,5]. It is unlikely that a single test can provide a complete assessment of DED [6] and in recent international workshops, multiple tests have been advocated for DED diagnosis therapy evaluation [7,8].

Alterations to tear film stability is generally accepted as a key feature of DED [7]. Ocular surface temperature (OST) measurement with infrared (IR) ocular thermography is indicative of the tear film and its stability [9,10]. Ocular thermography has been used to study DED [9,11-19] with three studies reporting on its diagnostic ability [16,18,19] with inconsistent results. We have also considered the application of IR ocular thermography in screening mild to moderate DED. We determined that a region of the ocular surface showing the greatest diagnostic potential was the extreme nasal conjunctiva, especially when evaluated ten seconds after eye opening [20]. In common with our previous reports [20], we refer to this region in this manuscript at 'T4'. We have not previously considered the correlation between T4 with dry eye symptoms and conventional objective clinical dry eye tests; furthermore the diagnostic performance of combining this form of thermographic measure with conventional approaches has not previously been studied. As such, the current study was designed to address both of these issues.

Materials and Methods

Subjects

The research protocol was approved by the Singapore National Health Group (NHG) Domain-Specific Review Board (DSRB) and the Singapore Polytechnic ethics review committee and the work adhered to the tenets of the Declaration of Helsinki. A total of 62 dry eye (mean ± standard deviation age 48 ± 10 years; 14 males and 48 females) and 82 control subjects (aged 44 ± 7 years; 35 males and 47 females) were recruited. Informed consent was obtained from each subject at study enrolment. The inclusion criteria for the dry eye subjects were as described previously [21]: use of tear replacement therapy and had either a fluorescein tear break-up time of 10 sec or less [22], or a Schirmer I test result of less than 10 mm in 5 min [12] along with presence of corneal or conjunctiva staining. All dry eye patients were screened and diagnosed by an ophthalmologist at Khoo Tech Puat Hospital eye clinic prior to starting the study. Classification of mild or moderate and severe patients was based on a composite disease severity index, derived from the Dry Eye Workshop severity scale [23]. Control subjects were those not using tear replacement therapy or any topical medication and without signs or symptoms of dry eye. All subjects were required to have not worn contact lenses for at least two years prior to enrolment. Subjects were excluded from the control group if they had Schirmer I test result of less than 10 mm in 5 min or fluorescein tear break-up time of 10 sec or less. Subjects with any anterior ocular anomalies (e.g. current ocular infection, allergy or ptosis), those undergone surgery or taking any medication that could affect the tear film or who were currently pregnant or breastfeeding were also excluded [21].

Procedures

In this single visit study, a number of practitioner-preferred [2] conventional clinical tests were performed on both eyes: symptom evaluation using McMonnies dry eye questionnaire (Mscore) and symptoms count (Scount), Fluorescein break-up time (FBUT), fluorescein corneal epithelial staining (CES), non-invasive break-up time (NIBUT) and the lower tear meniscus height (TMH).

McMonnies dry eye questionnaire (DEQ) was used in this study as it is long-standing, widely used and reported to be efficient to screen DED [24]. Indeed, it is regarded as the "gold standard" questionnaire for dry eye and is statistically reliable and repeatable [25]. Subjects were interviewed to complete the McMonnies DEQ consisting of 12 questions [26] and the total score was calculated using the DEWS dry eye diagnostic template [7]. On the other hand, Scount was the number of symptoms based on McMonnie's DEQ Q2 (soreness, scratchiness, dryness, grittiness, burning) [26,27] with each symptom afforded a score of one point, to a maximum of five.

A Topcon DC-1 slit lamp biomicroscope was used to assess the anterior ocular health, FBUT, CES and TMH. A drop of fluorescein sodium HCL was instilled on the subject's eye and the cornea and tear film were assessed using cobalt blue light, viewed through a yellow barrier filter (Wratten #12) for FBUT and CES. FBUT was the time taken for the first dark spot to appear after a complete blink as suggested by previous workers [28]. FBUT was recorded on both eyes and the average of the first three readings was used. CES was recorded and graded according to Lemp's scale. We opted for Lemp's scale rather than the van Bijsterveld system [29] or the Oxford system [30] because it is widely used and has been adopted as a standard by the National Eye Institute/Industry Workshop [31]. According to Lemp's scale, the cornea is divided into 5 regions, with each being graded from 0 to 3. The scores for the 5 regions were summed up and recorded. In this study, fluorescein was used to assess corneal staining as it has been reported as being highly sensitive for dry eye diagnosis [32].

NIBUT was measured using a computerized High-Speed videokeratoscope (Medmont E300) which uses 32 rings and over 15,000 measurement points over a wide area of the human cornea, with Medmont studio version 4.12.0 (Medmont International Pty Ltd. Australia). We employed the method reported by Iskander et al. [33] who analysed tear film stability in the inter-blink interval, and measured tear film break-up time. While fixating at the center of a series of red placido rings, the subjects blink normally, closed for 3 sec, open widely and hold blink for 10 sec. NIBUT was recorded as the time required for the first appearance of distorted HSV mires. A number of repeated measures were recorded for both eyes and the average of the best three readings was used.

TMH was photographed using IMAGEnet software (Topcon medical systems, Inc., Oakland, NJ) and measured as reported by Kwong et al. [34]. The slit lamp eye piece and illumination lamp were positioned perpendicular to the lower tear meniscus. Subjects were asked to look straight ahead while a 1 mm conical beam at 25X magnification and medium illumination was placed at the center of the lower tear meniscus. TMH readings were measured using calibrated software (Adobe Photoshop CS2).

OST was recorded using NEC TH9260 thermo tracer using a previously-described method which has been shown to be repeatable when assessing healthy and dry eyes [21]. Six temperature metrics was used which related to the temperature of the extreme nasal conjunctiva (T4). These were the temperature immediately on eye opening and five and ten seconds after opening (T4-0, T4-5, T4-10) and then three metrics related to exponential curve fit of the change in temperature of this location after eye opening (T4-A, T4-S and T4-GR).

These latter variables represent the output variables when a one phase exponential curve is fitted to T4 temperature *vs.* time using JMP version 12.1.0 (http://www.jmp.com; SAS Institute Inc., USA) according to the model:

Temperature = a + b*Exp (c*time).

where 'a' represents the asymptote of the best fit curve ('T4-A'), 'b' is the 'scale' ('T4-S') and 'c' is the 'growth rate' ('T4-GR').

Statistical analysis

Data on 62 dry eye and 82 control subjects were tabulated and analysed. Only data obtained from right eye were used in the analysis to prevent difficulties arising when non-independent data were collected from both eyes [35].

Correlation between T4 metrics and signs and symptoms for dry eye

Unpaired t-tests (two-tailed) were first performed to explore differences between dry eye and control subjects for each of the conventional clinical test. Multivariate analysis followed by Pearson correlation test were then performed on dry eye subjects using JMP version 12.1.0 (http://www.jmp.com; SAS Institute Inc., USA) to explore correlations between T4 metrics with dry eye symptoms and conventional objective clinical tests. All the above analysis was done at

95% confidence. Multivariate statistical methods enabled analysis of complex datasets where several outcomes variables are measured and known to be related and to have an effect on each other and is useful to explain complex clinical situations in simpler ways [6]. In this sort of analysis, large datasets are recommended and sample sizes are often said to be appropriate when the number of subjects is 5 or even 10 times the number of outcome measures [6]. As we had 12 main outcomes measures in the current study, a minimum of 60 subjects should be available.

Diagnostic ability of conventional clinical tests and combining with T4 metrics

Diagnostic ability of the conventional clinical tests was evaluated in terms of their sensitivity, specificity and area under the receiver operating characteristics curves (AUC). Cutoff values, discrimination power (DP) [36] and Youden's index (Y) [37] for all tests were also studied as described in the previous report [20]. The clinical tests with best performance were combined with T4 metrics to ascertain if AUC of the combined tests could be improved. Deriving the best combination of conventional and thermographic tests was undertaken by using the Solver function of Microsoft Excel (Microsoft Excel 2013, USA). The analysis was developed for each dataset in order to reduce the dimensionality of the variables down to one or two factors combining these variables and determine the best detector(s).

Results

Mean and standard deviations of the values obtained on the six conventional clinical tests for DED in dry eye and control subjects are shown in Table 1. Significant differences were found between the two groups on four tests: FBUT, CES, Mscore and Scount (unpaired t-test, p<0.0001) at 95% CI. Dry eye subjects had significantly shorter FBUT but greater CES, Mscore and Scount as compared to control subjects.

Tests	Dry eye	Control	p values
FBUT (sec)	2.6 ± 2.2	4.5 ± 2.4	<0.0001**
NIBUT (sec)	2.6 ± 3.8	2.5 ± 3.5	0.794
TMH (mm)	0.18 ± 0.08	0.19 ± 0.09	0.566
CES (grade)	2.7 ± 3.0	1.0 ± 1.6	<0.0001**
Mscore	10.2 ± 3.4	2.4 ± 2.5	<0.0001**
Scount	2.0 ± 1.1	0.5 ± 0.7	<0.0001**
Data are the mean ± SD			

Table 1: Results of conventional clinical tests in dry eye and control subjects.

Correlation between T4 metrics and signs and symptoms for dry eye

No correlation was found between FBUT, CES, Mscore and Scount with any of the T4 metrics in dry eye (Pearson's coefficient, -0.203 to 0.209; p>0.05) or control subjects (Pearson's coefficient, -0.223 to 0.194; p>0.05).

Within the dry eye subjects, there were some correlations between the six conventional clinical tests. Results shown that CES correlated significantly with TMH (Pearson's coefficient, r=0.276; p=0.030) and inversely correlated significantly with FBUT (Pearson's coefficient, r=-0.258; p=0.043) (Table 2). However, both correlations were weak. Symptoms (Mscore and Scount) for dry eye did not correlate with any of the objective tests studied. FBUT was not correlated with NIBUT although both measured tear film stability (Pearson's coefficient, r=-0.085; p=0.547) (Table 2).

Variable	by Variable	r values	Lower 95%	Upper 95%	p values
NIBUT	FBUT	-0.085	-0.347	0.190	0.547
TMH	FBUT	-0.059	-0.304	0.194	0.649
	NIBUT	0.084	-0.191	0.346	0.551
CES	FBUT	-0.258	-0.477	-0.008	0.043*
	NIBUT	-0.023	-0.291	0.249	0.870
	TMH	0.276	0.028	0.492	0.030*
Mscore	FBUT	-0.121	-0.360	0.133	0.350
	NIBUT	0.247	-0.025	0.485	0.074
	TMH	0.152	-0.101	0.387	0.237
	CES	0.128	-0.126	0.366	0.322
Scount	FBUT	-0.035	-0.282	0.217	0.790
	NIBUT	0.112	-0.163	0.371	0.426
	TMH	0.016	-0.235	0.265	0.901
	CES	-0.010	-0.259	0.240	0.937
*p<0.05					

Table 2: Correlation among conventional clinical tests for dry eye subjects.

Diagnostic ability of conventional clinical tests and combining with T4 metrics

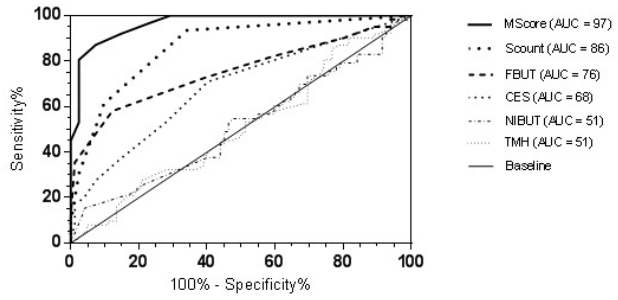

Figure 1: Discrimination of dry eye subjects by conventional clinical tests. AUC are shown on the legend.

Figure 1 shows the ROC curves for the six conventional clinical tests. From each of the ROC curves, AUC was extracted using trapezoidal numerical integration. Mscore provided the greatest AUC at 97% suggesting good diagnostic accuracy with AUC above 90% [38]. Scount and FBUT had AUC of 86% and 76%, respectively, suggestive

of moderate accuracy with AUC lies between 70 to 90%. The rest of the tests (CES, NIBUT and TMH) had AUC below 70 indicating low accuracy [38]. Table 3 shows a summary of AUC, sensitivity and specificity in descending order of test performances based on Youden's index and discrimination power.

Conventional tests	AUC, % (95% CI)	Cutoff values	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Y	DP
Mscore	97 (94 to 99)	>7	87.1 (76.2 to 94.3)	92.7 (84.8 to 97.3)	79.8	2.45
Scount	87 (81 to 93)	>0.5	93.6 (84.3 to 98.2)	65.9 (54.6 to 76.0)	59.4	1.84
FBUT (sec)	76 (67 to 84)	<2.5	58.1 (44.9 to 70.5)	87.8 (78.7 to 94.0)	45.9	1.27
CES (grade)	68 (60 to 77)	>1	71.0 (58.1 to 81.8)	59.8 (48.3 to 70.4)	30.7	0.71
TMH (mm)	51 (41 to 61)	<0.25	85.5 (74.2 to 93.1)	23.2 (14.6 to 33.8)	8.7	0.32
NIBUT (sec)	51 (41 to 62)	<0.4	54.7 (40.5 to 68.4)	52.4 (41.1 to 63.6)	7.2	0.16

Table 3: Test effectiveness of the conventional clinical tests. AUC, sensitivity, specificity, Youden's index (Y), discrimination power (DP) and the selected cutoff values are shown.

For T4 temperature measured after 10 seconds of eye opening (T4-10), AUC was 73%, similar to FBUT and CES (Figure 2). Table 4 shows a summary of AUC, sensitivity, specificity and test performances of the tested objective tests, when applied singly and in combination. Combining T4-10 with CES increased AUC to 78% in the expression of 0.30 T4-10+0.78 CES, with sensitivity and specificity of 92.3% and 42.7% respectively. Combining T4-10 with CES and FBUT increased AUC slightly to 79% in the expression of 0.30 T4-10+0.65 CES+0.01 FBUT with sensitivity and specificity of 92.3% and 45.1% respectively. ROC curves of the combined tests are shown in Figure 2. FBUT adds very little to the AUC overall, T4-10 and CES was a good combination.

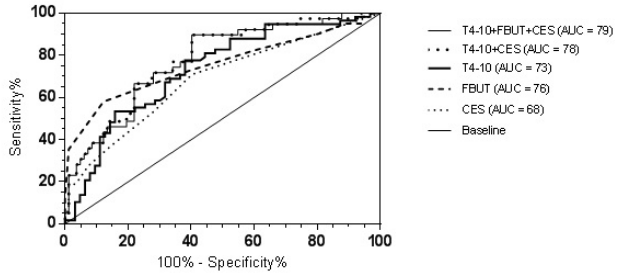

Figure 2: Discrimination of dry eye subjects by single *vs.* combined objective tests. AUC are shown on the legend.

Tests	AUC, % (95% CI)	Cut off Values	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Y	DP
Single Tests						
T4-10	73 (64 to 82)	<34.6°C	77.6 (64.7 to 87.5)	61.9 (48.8 to 73.9)	39.5	1.05
FBUT	76 (67 to 84)	<2.5 sec	58.1 (44.9 to 70.5)	87.8 (78.8 to 94.0)	45.9	1.27
CES	68 (60 to 77)	>grade 1	71.0 (58.1 to 81.8)	59.8 (48.3 to 70.4)	30.7	0.71
Combined tests						
T4-10 and CES	78 (69 to 87)	<34.6°C and >grade 1	92.3 (79.1 to 98.4)	42.7 (31.8 to 54.1)	35.0	1.21
T4-10, CES and FBUT	79 (67 to 86)	<34.6°C and >grade 1 and <2.5 sec	92.3 (79.1 to 98.4)	45.1 (34.1 to 56.1)	37.4	1.26

Table 4: Test effectiveness of single *vs.* combined objective tests in the diagnosis of dry eye. AUC, sensitivity, specificity, Youden's index (Y), discrimination power (DP) and the selected cutoff values are shown.

Discussion

For the conventional methods, Mscore of 8 and above, Scount of 1 and above, FBUT of 2 s or less and CES of 2 or more were able to differentiate DED subjects from controls. NIBUT and TMH, on the other hand, were not able to do so. All dry eye patients were mild to moderate with no inflamed meibomian glands. We recognise that many disease severity criteria are confounded by complex disease subtypes and a lack of standardisation, and the selection of single criteria for assessment of disease severity is therefore fraught with difficulties [7].

Correlation between T4 metrics and signs and symptoms for dry eye

Although we have previously demonstrated that the T4 metrics have some utility in differentiating dry eyes *vs.* controls, the present study was in agreement with Fujishima et al. [14] i.e., no correlation was found between OST with individual dry eye signs or symptoms.

Our study findings were in accordance to Kamao et al. [18]'s study who found no correlation between FBUT with conjunctival temperature. Changes in OST can be contributed by tear film instability and rapid tear evaporation [9,18]. Others have reported contrary findings. According to Kamao et al. [18] and Versura et al. [39], corneal temperature was found to be low in dry eye patients and decrease in temperature correlated significantly with tear break-up time, subject's age, subjective discomfort symptoms and enhanced evaporation in evaporative dry eye (EDE) [39]. Although the dry eye cohort in our study had significantly shorter FBUT, the differences in results could be due to (1) our focus on the conjunctiva in this work, not the cornea and (2) our subjects were mostly mild to moderate dry eyes and not solely consist of EDE subtypes with enhanced evaporation as reported by Versura et al. [39].

It is noteworth that findings on correlation between OST and dry eye tests are inconsistent and contradictory. Su et al. [40] reported a strong correlation between areas of tear film break-up with areas of lower temperature and suggested relationship between tear film break-up and evaporation in subjects with normal tear film. However, when the study was repeated on dry eye patients, no such relationship was observed [41]. In another study on normal subjects, rates of ocular surface cooling was found to be positively correlated to fluorescein tear thinning and break-up [42-45]. Simultaneous imaging of OST and fluorescein adopted in these studies [46-48] indicated some improvements in methodology to study OST and tear film behaviour at the same time. Pattmöller et al. [43], on the other hand, reported no correlation between corneal temperatures with other ocular parameters such as corneal thickness, endothelial cell density and anterior chamber depth in normal subjects.

Our study confirmed the discordance between signs and symptoms for DED [4,5,44-47]. Indeed, it was reported that up to 40% of patients had symptom and clinical sign discordance [46]. A more recent study has shown that dry eye symptoms aligned more closely to non-ocular pain, depression and post-traumatic stress disorder than tear film parameters [48].

Studies on correlation among conventional clinical tests for dry eye have been undertaken for many years [4,5,22,44-47,49-52] with inconsistent results. Such findings confirmed the complexity of DED and how the disease is multifactorial, depending on the dry eye subtypes, symptom questionnaire used and population studied [53]. Additionally, there are age- and gender-related, cultural, and ethnic influences on symptoms [54,55]. We noted that CES was correlated with TMH and inversely correlated with FBUT which is in agreement with reports from Tung et al. [56] and Nichols et al. [51], respectively. However, these findings could be due to possible type I errors when doing data analysis on multiple tests.

Diagnostic ability of conventional clinical tests and combining with T4 metrics

In this report, AUC was used as an indicator for test accuracy [38] whilst Youden's index and DP were used as indicators for test performance [57]. Sensitivity is the proportion of actual positives (i.e. dry eye subjects) that are correctly identified, while specificity is the proportion of actual negatives (i.e. control subjects) that are correctly identified [58].

Symptom evaluation

Our results were in agreement with previous studies that McMonnies DEQ has good test performance with sensitivity varying between 87% and 98% and specificity between 87% and 97% [22,26,59]. The variations in estimates of sensitivity reported in the literature could be due to differences in experimental population, the criteria used for dry eye classification and different scoring methods as well as variation in cutoff values ranging from 8 to 19 [24,26,59]. Of course, high sensitivity values are expected given the importance of symptom assessment in the diagnosis of DED. Scount can be a supplementary test as it was part of the McMonnies DEQ; our results found that patients presented with one symptom out of the five stated in McMonnie's DEQ Q2 (soreness, scratchiness, dryness, grittiness, burning) [26,27] can be suspected of having dry eye. Due to lack of gold standard for DED diagnostic criteria, it was not surprise to observe high correlation (and high AUC) in symptom evaluation. There could be non-dry eye patients presented with similar symptoms due to other disease (neuropathic pain, etc).

FBUT and CES

Our findings on FBUT and CES was in agreement to Downie et al. [3] report suggesting that FBUT and CES can be treated as key clinical objective tests with good sensitivity and specificity. Cutoff value for CES in our study was similar to that reported in the literature [60], with higher sensitivity but lower specificity. Lemp et al. [60] reported that only 1 in 4 severe dry eye subjects showed little or no evidence of staining. DED can present without keratitis [61] and therefore it is possible to have very little CES present in dry eye patients. Findings for FBUT vary across the literature due to different cutoff values; our study has derived reasonable good sensitivity and specificity with cutoff <2.5 sec.

NIBUT and TMH

FBUT and NIBUT were poorly correlated, consistent with Cho and Douthwaite [49] study. Variation in findings for NIBUT in the literature can generally be explained by the range of different techniques employed [62-64]. NIBUT measured using high-speed video keratoscope in the current study seem to give lower sensitivity and specificity than other work has reported. Differences in subject gender and ethnicity may also cause variation in results [52]. Our subjects were mainly Asian, so our findings may be different from those studied primarily on Caucasian eyes. Reports on TMH have also been contradictory, again due to differences in the measurement techniques, ranging from photographing an optic section of the inferior tear meniscus [65] to using anterior segment optical coherence tomography [66]. Our findings were similar to Kwong and Cho report, using the [34] using the same technique.

Combining thermography findings with conventional measures

We demonstrated good diagnostic power when CES was combined with the T4-10 thermographic measure as two clinical measures, in conjunction with routine symptomatology. In particular it is of note

that thermography provided similar outcomes to FBUT, with both tests indicative of the stability of the tear film.

FBUT assessment, of course, requires a high degree of clinical skill and the use of fluorescein drops or strips. On the other hand, thermography provides a near-immediate non-invasive assessment. As thermography has similar test accuracy to FBUT and CES, symptomatology with thermography can be future dry eye diagnostic tests for non-clinician.

We note that there are various problems when comparing findings across the dry eye literature. In particular, selection and spectrum bias [6] is a concern. All the dry eye patients in the current study were of mild to moderate severity which might point towards some selection bias in our cohort [67]. However, any bias was minimised by carefully adopting the same recruitment and assessment techniques for all subjects, as advocated by Tomlinson et al. [6].

In common with previous work, this article supports that multiple tests for dry eye disease are more useful than single tests [6,8]. We have demonstrated that a simple, single, thermographic measure provides similar diagnostic power to more complex clinical approaches. The themographic apparatus employed in this work was relatively large and expensive. However, simpler, hand-held models are now available and at a cost which is affordable for potential use. The findings of the current work indicate that the application of portable thermography equipment for clinical diagnosis should be further explored.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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