Supporting Dry Eye Diagnosis with a New Method for Noninvasive Tear Film Quality Assessment

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SIGNIFICANCE: Noninvasive high-speed videokeratoscopy equipped with specific software has shown potential for assessing the homeostasis of tear film, providing clinicians with a fast and consistent tool for supporting dry eye diagnosis and management.

PURPOSE: The purpose of this study was to evaluate the efficacy of a recently proposed method for characterizing tear film dynamics using noninvasive high-speed videokeratoscopy in assessing the loss of homeostasis of tear film.

METHODS: Thirty subjects from a retrospective study, of which 11 were classified as dry eye and 19 as healthy, were included. High-speed videokeratoscopy measurements were performed using E300 videokeratoscope (Medmont Pty., Ltd., Melbourne, Australia). Raw data were analyzed using a recently proposed method to estimate the dynamics of the tear film based on a fractal dimension approach. This method provides three time-varying indicators related to the regularity of the reflected rings: tear film surface quality indicator, breaks feature indicator, and distortions feature indicator. From each indicator, five parameters were extracted and analyzed, including noninvasive breakup time, mean value of the indicator in the stability phase, mean value of the indicator in the whole interblink interval, mean value of the indicator in the leveling phase, and the general trend of the time series. Receiver operating characteristic curves were used to determine the sensitivity and specificity of each parameter in dry eye detection.

RESULTS: The best discrimination performance between dry eye and healthy subjects was achieved with the breaks feature indicator noninvasive breakup time parameter, with an area under the curve of 0.85. For a cutoff value of 10 seconds, the sensitivity was 100% and the specificity was 84%.

CONCLUSIONS: The analyzed method improves the assessment of tear film homeostasis in comparison with previous high-speed videokeratoscopy methods showing higher potential in assisting dry eye diagnosis.

Dry eye disease is a frequently reported pathological condition of the ocular surface with an index of prevalence that ranges from 5 to 50%, depending on the demographics and the diagnostic criteria used.1 This wide variability on dry eye disease epidemiology could be attributed partly to the lack of a standardized definition and classification system. The Definition and Classification Subcommittee of the International Dry Eye Workshop II (2017), with the goal of creating an evidence-based classification, defined dry eye disease as a “multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”2

Tear film instability has been considered as one of the core mechanisms that causes dry eye disease.3 Consequently, the stability of the tear film lipid layer,4 assessed by noninvasively measured tear film breakup time, has been recommended, along with tear osmolarity and ocular surface staining, as one of the essential biomarkers of loss of tear homeostasis in dry eye disease.5,6 Etiologically, dry eye disease can be classified into two major groups: evaporative dry eye and aqueous-deficient dry eye; in both conditions, the stability of the tear film lipid layer is compromised.

Although the assessment of the stability of the tear film is one of the main tasks supporting dry eye diagnosis, there is no gold standard diagnostic tool or standardized clinical protocol available.6 Also, in the presence of a large number of tools and techniques, it is not evident, particularly in a clinical setting, which of them is the most appropriate.7–12 Hence, accurately assessing and monitoring the stability of tear film are a difficult task.13

Tear film stability can be assessed with the measurement of the tear film breakup time.14 Traditionally, it is measured by instilling a drop of fluorescein into the eye and determining the time until the appearance of the first dark growing spot on the tear film with the aid of a biomicroscope equipped with a yellow filter (such as Wratten12; Eastman Kodak Company, Rochester, NY). The fluorescein breakup time is invasive and subjective and has shown lack of reliability and repeatability. Likewise, the agreement between fluorescein breakup time and other clinical measures of dry eye is weak.15,16 It has been claimed that the preferred technique to assess the stability of the tear film should be noninvasive, quantitative, and objective.5,6

For this reason, in the past years, the development of noninvasive automatic measurement systems to assess the stability of the tear film in a more natural state has gained importance.8,17–20 In particular, the techniques that assess the quality of the tear film by the observance of morphological changes in the specular reflection of a grid pattern projected on the cornea have shown to be promising.21,22 One of those techniques is the high-speed videokeratoscopy, which could be viewed as an extension of the traditional static

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videokeratoscope. The videokeratoscope is a Placido disk topographer that projects a set of concentric rings onto the ocular surface. The regularity of the reflected pattern will depend, first of all, on the stability of the tear lipid layer. In high-speed videokeratoscopy, continuous captures of the reflected images from the cornea are recorded, providing dynamic information on changes in the tear film along with the time between blinks. High-speed videokeratoscopy is an accessible tool for clinicians, and it is easy to use. The development of specific software to analyze the recorded videos in an objective and automated fashion provides an added value to standard videokeratoscopy when assessing the tear film stability.

Different image processing techniques have been proposed to analyze high-speed videokeratoscopy recordings based on the analysis of the raw images provided by the instrument, and nowadays, several commercially available videokeratoscopes already incorporate an automated tear film analysis function. However, although the performance of these automated methods has been evaluated in dry eye subjects, there are only a few studies that have reported the sensitivity and specificity of these techniques to diagnose dry eyes. Also, the repeatability and agreement of the automated methods have been questioned. Recently, we have proposed a novel, automated, and objective technique that analyzes the recordings of high-speed videokeratoscopy to obtain an estimator of tear film surface quality and noninvasive breakup time. In this technique, the post-blink dynamics of the tear film are derived from a textural analysis of the videokeratoscopy recordings by means of computing the fractal dimension of the images. This method has been tested for subjects with healthy tear film, showing its utility in characterizing three different phases of tear film dynamics (i.e., leveling, stability, and evaporation, described previously by Braun et al. and estimating the noninvasive breakup time. Also, it was shown that the method based on fractal dimension provides estimates of tear film dynamics closely corresponding to the observable, by clinicians, deformations of Placido rings during an interblink interval.

The purposes of this study were to evaluate the proposed method of high-speed videokeratoscopy image analysis in cohorts of healthy and dry eye subjects and test its efficacy for supporting dry eye diagnosis.

**METHODS**

**Subjects and Data Acquisition**

Videokeratoscopy recordings from a previous study were analyzed with the algorithm proposed earlier to evaluate its performance in the assessment of tear homeostasis. That algorithm is based on textural analysis of Placido disk pattern. Data on the right eyes of 30 subjects were used (20 women and 10 men). Subjects were enrolled in the study voluntarily after informed consent was given. The study was approved by the Queensland University of Technology's research ethics committee and followed the tenets of the Declaration of Helsinki. An experienced clinician performed a clinical assessment of dry eye signs and symptoms. The tests included medical history, McMonnies questionnaire, slit-lamp examination, phenol red thread test of tear volume, and fluorescein tear film breakup time. A dry eye was diagnosed if the three following conditions were met: McMonnies test score of higher than 14, fluorescein tear film breakup time of less than 10 seconds, and corneal or conjunctival staining score of higher than 3. Note that the study preceded the Definition and Classification Subcommittee of the International Dry Eye Workshop II report. A detailed explanation of the clinical protocol and the clinical values for each group can be found in the work of Szczesna et al. Accordin to this classification, the cohort was divided into 11 dry eye and 19 healthy subjects.

Another masked clinician performed high-speed videokeratoscopy measurements with E300 videokeratoscope (Medmont Pty., Ltd, Melbourne, Australia) with a sampling frequency of 25 frames per second. Measurements were taken in suppressed blinking conditions. For that, patients were asked to look at the fixation target of the instrument, blink gently a few times, and maintain their eyes open as long as they could for a maximum time of 30 seconds. Three measurements per eye were taken with a 3-minute break between them. All the measurements were performed at approximately the same time of day in a room with monitored temperature and humidity. Measurements were performed from less to more invasive to avoid the disturbance of the tear film physiology in the subsequent tests.

**High-speed Videokeratoscopy Analysis**

High-speed videokeratoscopy recordings were stored and analyzed offline using a MATLAB-based (MathWorks Inc., Natick, MA) custom written algorithm to estimate the dynamics of the tear film. In the analysis, the texture (regularity) of the reflected Placido disk pattern is used to determine the stability of the tear film using a fractal dimension approach. An example of the appearance of breaks and distortions of the Placido disk reflection in a single high-speed videokeratoscopy frame is shown in Fig. 1.

The fractal dimension is a measure of texture roughness. High values of fractal dimension are related to more irregular structures, whereas values less than 1 are related to incomplete structures. The fractal dimension is highly correlated with human perception of texture and relatively insensitive to changes in image intensity and scaling. In previous work, it has been demonstrated that fractal dimension–based assessment of high-speed videokeratoscopy recordings is directly related to local morphological changes of the reflected pattern, thereby directly related to the regularity of the tear film. Briefly, the algorithm detects the interblink interval where the analysis is performed and uses an image block processing approach to compute the local fractal dimension of the images (i.e., the whole image is divided into small blocks, and the fractal dimension of each subimage is computed). Blocks are considered to have regular rings when the fractal dimension value is inside the interval of $1 \pm 0.18$. From this analysis, three time-series indicators for each detected interblink interval are obtained and used to describe the dynamics of the tear film:

1. **Breaks feature indicator:** this index is related to incomplete rings. For its calculation, all the blocks of each image having a fractal dimension value below the established interval are summed, and the inverse of this summation is equal to breaks feature indicator. Higher breaks feature indicator values correspond to a greater number of incomplete rings (e.g., broken rings; example shown in Fig. 2A).

2. **Distortions feature indicator:** this index is related to uneven rings. For its calculation, all the blocks of each image having a fractal dimension value above the established interval are summed, and this value corresponds to distortions feature indicator. Higher distortions feature indicator values correspond to a more irregular Placido disk pattern (example shown in Fig. 2B).
3. Tear film surface quality indicator: this general index is directly related to the stability of the tear film. It is composed of the weighted combination of breaks feature indicator and distortions feature indicator. The higher the tear film surface quality, the less regular the tear film is (example shown in Fig. 2C).

A detailed explanation about how the different indicators are computed and the determination of the limits can be found in previous work.\(^{33}\)

**Statistical Analysis and Data Processing**

For the three repeated measurements of the same eye, the median values were considered for the analysis. Data corresponding to the first second after a blink were removed to avoid the possible effect of the initial phase of the tear film dynamics (known as the leveling phase). The Shapiro-Wilk test revealed that the data were not normally distributed \((P < .05)\); accordingly, differences between medians groups were analyzed using the Mann-Whitney test for independent samples. \(P < .05\) was considered statistically significant.

To estimate the noninvasive breakup time, the remaining raw time-series data (omitting the first second) of each one of the three dynamic indicators (i.e., tear film surface quality, breaks feature indicator, and distortions feature indicator) were fitted with three different functions: a linear, a constrained bilinear, and a constrained linear-polynomial function. The bilinear and linear-polynomial functions are two-section functions. The former comprises two linear sections (Fig. 3C), whereas the latter comprises a linear section followed by a second-degree polynomial section (Fig. 3D). In both of those cases, a constraint is made so that the point where the first section ends must correspond to the point where the second section starts (red points in Figs. 3C, D; this is the constraining point) to avoid discontinuity between the sections in the model.

**FIGURE 1.** Appearance of the Placido disk pattern reflected on the ocular surface. (Left) Regular reflected rings from a stable tear film. (Right) Distorted reflected rings from a destabilized tear film. Red arrow indicates uneven rings, which would contribute to the distortions feature indicator, and white ellipse indicates broken rings, which would contribute to the breaks feature indicator.

**FIGURE 2.** Example of the time series of the three considered indicators and the corresponding fittings of a bilinear model: BFI (A), DFI (B), and TFSQ index (C). All three indicators are estimated from a high-speed videokeratoscopy recording of the same subject. The phases of tear leveling (gray shadowed area), stability (green line), deterioration (blue line), and the estimated breakup point (red dot) are demarcated. BFI = breaks feature indicator; DFI = distortions feature indicator; TFSQ = tear film surface quality.
Representative examples of the three fitting types can be seen in Fig. 3. The suitability of the fittings was assessed by computing Pearson correlation coefficient $r^2$ between the raw data and the fitting and testing the null hypothesis of equality in $r^2$ using the Fisher test. If the null hypothesis was not rejected ($P > .05$), the linear function was chosen; otherwise, the more appropriate constrained function (bilinear or linear-polynomial function) was fitted, using the constraining point as the estimated noninvasive breakup time.

The three different models (linear, constrained bilinear, and constrained linear-polynomial) were considered to precisely estimate the noninvasive breakup time under the changing characteristics of the individual tear film dynamics.37,38

In the case where a linear function was fitted, the estimated noninvasive breakup time was set to either 0 seconds if the slope of the linear function was greater than $10^\circ$ (Fig. 3B) or the duration of the interblink interval if the slope of the linear function was $10^\circ$ or less (no noninvasive breakup time was observed during the duration of the interblink interval; Fig. 3A).

In addition to the noninvasive breakup time, other parameters of each indicator (tear film surface quality, breaks feature indicator, and distortions feature indicator) were extracted and analyzed. These were as follows:

- **The mean value of the indicator along with the stability phase** (mean stability phase)
- **The mean value of the indicator along with all the considered interblink intervals omitting the first second after the blink** (mean interblink interval value)
- **The general trend of the indicator (slope)**

Mean values of the indicators in the different phases of the interblink interval are related to the overall quality of the tear film in the given phase. They are computed to clarify if the difference between dry eye and healthy subjects only lies in the noninvasive breakup time or if, on the contrary, there is also a difference in the quality of the tear film even when it is stable. On the other hand, the general trend of each indicator determines the speed with which the tear film evaporates. This metric is computed to explain if, once the tear film has been destabilized, the evaporation is quicker for dry eye subjects than that observed in healthy subjects.

The receiver operating characteristic curves were used to determine the sensitivity (true positive rate) and specificity (1 – false-positive rate) of the tested algorithm for dry eye diagnosis. To create receiver operating characteristic curves, the probability density function for healthy and dry eye subjects of each considered parameter was computed using a kernel density estimator with an Epanechnikov window.39 From each receiver operating characteristic curve, in addition to the sensitivity and specificity, other statistical parameters that provide information on the discrimination performance of the method were extracted.40 These were as follows:

- **Area under the receiver operating characteristic curve**, computed using trapezoidal numerical integration. It is bounded between 0 and 1. The closer to 1, the better the performance of a detector.
- **Cutoff value** optimizes the discrimination between healthy and dry eye subjects, determined as the point for which the
distance between the receiver operating characteristic and the diagonal is maximum.

- **Youden index**\(^4\) is defined as\(\gamma = \text{sensitivity} + \text{specificity} - 1\), so the closer to 1, the better the performance of a detector.
- **Discriminant power**\(^4\) is defined as: \(\text{DP} = \frac{1}{\log\left(\frac{\text{sensitivity}}{1 - \text{specificity}}\right) + \log\left(\frac{1 - \text{sensitivity}}{\text{specificity}}\right)}\), where \(\text{DP} < 1\) means poor discrimination, \(1 < \text{DP} < 2\) means limited discrimination, and \(\text{DP} < 3\) means fair discrimination, and values higher than 3 are considered good discrimination.

### RESULTS

The mean ± standard deviation of the interblink interval duration for normal and dry eye subjects was 24.2 ± 6.3 and 14.9 ± 8.6 seconds, respectively, and the difference was statistically significant (\(P < .0001\)). As a result of the fitting, the mean ± standard deviation of tear film surface quality noninvasive breakup time was 16.4 ± 8.3 seconds for healthy subjects and 8.6 ± 2.9 seconds for dry eye subjects.

Table 1 shows the descriptive statistics (median and interquartile ranges) for all the considered parameters and the \(P\) values for the Mann-Whitney test between healthy and dry eye subjects. With the exception of the mean stability and the mean interblink interval values for distortions feature indicator, all the parameters showed inferior tear film quality characteristics for the dry eye subjects. Statistically significant differences were found for the noninvasive breakup time assessed by all three indicators (i.e., tear film surface quality, breaks feature indicator, and distortions feature indicator), the slope of tear film surface quality and distortions feature indicator, and the mean stability phase value of breaks feature indicator.

The receiver operating characteristic curves were computed for all the parameters of each indicator. Table 2 summarizes the diagnostic power for those parameters with the best discriminative performance. The breaks feature indicator noninvasive breakup time showed to be the most powerful indicator in differentiating between healthy and dry eye subjects; the receiver operating characteristic of this parameter is shown in Fig. 4.

For a cutoff value of 10 seconds, the sensitivity is 100% and the specificity is 84% (subjects with breaks feature indicator noninvasive breakup time lower than 10 seconds are classified as dry eye subjects and higher than the healthy subjects). This means that, for a breaks feature indicator noninvasive breakup time greater than 10 seconds, a subject could be classified as healthy with certainty that there are no false negatives. Although this parameter is powerful enough to be a good classifier on its own, there is still a probability (16%) that a healthy subject is misclassified as a dry eye subject (false positive). Given that one of the characteristics of this method is that it provides multiple indicators, the rate of false positive can be decreased by performing a sequential analysis with another parameter. The proposed process is schematized in Fig. 5; thereby, for a subject to be classified as potentially having a dry eye, it needs to meet two conditions: a breaks feature indicator noninvasive breakup time of less than 10 seconds and a distortions feature indicator noninvasive breakup time of less than 11.1 seconds. Following this approach, in the representative cohort of this study, three healthy subjects had a breaks feature indicator noninvasive breakup time of less than 10 seconds, so they would be misclassified as dry eye subjects if the breaks feature indicator noninvasive breakup time cutoff value was taken into account as the only indicator. However, applying the proposed sequential analysis, the percentage of false positive would be reduced to 7.4%.

### DISCUSSION

Although dry eye is an ophthalmic disease affecting a large part of the population, a unified and reliable approach to its diagnosis is still missing.\(^3\) Traditional diagnostic tests are invasive, qualitative, and/or subjective, potentially leading to misdiagnosis and inaccurate treatment follow-up.\(^1\) Previous studies have demonstrated the utility in assessing tear film stability in dry eye diagnosis\(^43,44\) and the

| Indicator | Parameter | Healthy subjects | DE subjects |
|-----------|-----------|-----------------|-------------|
|           | Median | IQR | Median | IQR | \(P\) |
| TFSQ index | NIBUT (s) | 14.2 | 13.7 | 8.7 | 3.0 | .02* |
|           | Mean stability phase value | 43.6 | 9.7 | 51.4 | 10.5 | .21 |
|           | Mean interblink interval value | 49.093 | 12.4 | 51.5 | 12.8 | .44 |
|           | Slope (°) | 19.4 | 29.1 | 65.7 | 44.5 | .004* |
| BFI       | NIBUT (s) | 21.4 | 17.3 | 7.8 | 3.5 | .001* |
|           | Mean stability phase value | 39.7 | 6.1 | 44.6 | 9.6 | .05* |
|           | Mean interblink interval value | 40.0 | 8.1 | 44.6 | 10.2 | .19 |
|           | Slope (°) | 28.0 | 20.8 | 31.8 | 55.9 | .21 |
| DFI       | NIBUT (s) | 15.1 | 9.2 | 8.7 | 6.1 | <.0001* |
|           | Mean stability phase value | 53.0 | 43.8 | 42.6 | 27.6 | .21 |
|           | Mean interblink interval value | 64.6 | 43.5 | 47.3 | 45.0 | .87 |
|           | Slope (°) | 40.8 | 51.3 | 74.4 | 30.7 | .05* |

*\(P < .05\). BFI = breaks feature indicator; DFI = distortions feature indicator; IQR = interquartile range; NIBUT = noninvasive breakup time; TFSQ index = tear film surface quality index.
importance of using noninvasive and objective techniques owing to
the lack of repeatability and reproducibility of the traditional tests.²²,⁴⁵

Noninvasive and objective methods that allow for the assessment
of tear stability are already commercially available and implemented
in some videokeratoscopes (e.g., Oculus Keratograph [Oculus
Optikgerate, Wzlar, Germany]; Medmont E300 [Medmont Pty.,
LTD, Melbourne, Australia]; and Tear Stability Analysis System
(TSAS, Tomey Corporation, Aichi, Japan)). They are equipped with
specific software to estimate the noninvasive breakup time based
on the reflection of a pattern projected onto the ocular surface. How-
ever, dry eye diagnosis with such instruments is still challenging be-
cause, among other things, establishing the cutoff values between
healthy and unhealthy populations is difficult. Values of currently
available metrics are continuous, not showing dichotomous behavior
between dry eye and healthy subjects.

In this study, the capability to diagnose a dry eye of a recently pro-
posed method, which analyzes videokeratoscopy recordings, has
been tested. This method provides different dynamic indicators re-
lated to the regularity of the reflected pattern in videokeratoscopy
and thereby related to the dynamics and stability of the tear film.
The diagnostic ability of three indicators to arrive at the best detec-
tion criteria has been tested. The tear film surface quality noninva-
sive breakup time is the parameter that is directly related to the
first observed disturbance of the reflected rings (this is what a cli-
nician would note as the noninvasive breakup time), whereas the
breaks feature indicator noninvasive breakup time relates to completely
broken rings, and the distortions feature indicator noninvasive
breakup time relates to uneven rings.

The group mean tear film surface quality noninvasive breakup
time values for healthy and dry eye patients were 16.4 and
8.6 seconds, respectively. These values are slightly higher than
those found with the fluorescein breakup time for that group:
14.3 seconds for healthy subjects and 6.3 seconds for dry eye
subjects.²⁷ This fact has already been widely reported because
the stability of the tear film is affected by fluorescein.⁴³,⁴⁶,⁴⁷ Re-
cently, Downie²⁸ has found longer noninvasive breakup time values
using the same type of videokeratoscope but with a different image
analysis approach that is proprietary: 21.3 seconds for healthy sub-
jects and 13.4 seconds for dry eye subjects. Hence, when compar-
sing such results, it is important to consider not only the technique
used but also the approach followed to analyze the recorded se-
quences. In a study conducted by Abdelfattah et al.,³⁲ in which
they used Oculus Keratograph (K5M), they did not find statistically
significant differences between dry eye (mean noninvasive breakup
time of 8.2 seconds) and healthy (mean noninvasive breakup time
of 6.7 seconds) populations, showing in their case the powerless-
ness to dry eye diagnosis. Result discordance may be influenced by
the technical differences between E300 and K5M videokeratoscopes;
K5M has a lower number of mires, smaller corneal coverage, and
thicker rings, which presumably can result in less precise detection
of mire distortions. In contrast, Hong et al.²⁹ did find differences
using the K5M videokeratoscope, but lower values were reported
for noninvasive breakup time in healthy subjects (4.3 seconds)
and dry eye subjects (2.0 seconds). Many factors could have had
a role in noninvasive breakup time differences between the results
of Hong et al. and the ones obtained in this study. The first factor is
the technical characteristics of the instrument. Second, the image
analysis approach in K5M software is based on finding differences
in the brightness of the data points on the mire rings, whereas in

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**TABLE 2. Statistical parameters that determine the efficacy in dry eye diagnosis for the three considered parameters**

| Parameter | Sensitivity (%) | Specificity (%) | AUC   | Cutoff value | γ   | DP     |
|-----------|-----------------|-----------------|-------|--------------|-----|--------|
| BFI-NIBUT | 100             | 84              | 0.85  | 10 s         | 0.84| 4.71   |
| Slope TFSQ| 100             | 48              | 0.73  | 25°          | 0.48| 3.76   |
| DFI-NIBUT | 100             | 56              | 0.62  | 11.1 s       | 0.56| 3.94   |

AUC = area under the curve; BFI-NIBUT = noninvasive breakup time for breaks feature indicator; DFI-NIBUT = noninvasive breakup time for distortions feature indicator; DP = discriminant power; TFSQ = tear film surface quality index; γ = Youden index.

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**FIGURE 4.** The ROC curve for the BFI noninvasive breakup time parameter. BFI = breaks feature indicator; ROC = receiver operating characteristic.

**FIGURE 5.** Proposed schema for a dry eye sequential analysis. BFI-NIBUT = noninvasive breakup time for breaks feature indicator; DED = dry eye disease; DFI-NIBUT = noninvasive breakup time for distortions feature indicator.
this study, it is based on a morphological analysis of the deformation of the reflected Placido disk rings. Finally, the studied population was Asian, where higher prevalence of dry eye has been found.\(^{49}\)

In terms of dry eye detection, the breaks feature indicator noninvasive breakup time showed the best discrimination performance between dry eye and healthy subjects, with a sensitivity of 100% and a specificity of 84% for a cutoff value of 10 seconds and an area under the curve of 0.85. In Table 3, the results of the discrimination performance between dry eye and healthy subjects from different studies are summarized. Results show an improvement on the discrimination performance using this approach over that different approaches are measuring different characteristics of the instrument (e.g., number of rings, width of the rings, or area of coverage), but also, for the same instrument, on the criteria and dry eye definition used. Then the results will depend not only on the technical characteristics of the instrument (e.g., number of rings, width of the rings, or area of coverage), but also, for the same instrument, on the approach followed to analyze the images, because it is likely that different approaches are measuring different characteristics of tear film deformation. These pieces of evidence need to be taken into account that the criteria used to define dry eye subjects may vary between studies. Accordingly, those subjects who are close to the borderline between being healthy and having dry eyes may be included in different groups depending on the criteria and dry eye definition used. It is evident that high-speed videokeratoscopy-based assessment of tear homeostasis for supporting dry eye diagnosis is dependent on different factors. First, it has to be taken into account that different approaches are measuring different characteristics of tear film deformation. These pieces of evidence need to find a unified approach that can be applied to different instruments using high-speed videokeratoscopy technique, ensuring some consistency in the assessment of tear homeostasis.

### TABLE 3. Summary of published results of efficacy in dry eye detection

| Authors (year)                        | Instrument | NIBUT cutoff | AUC   | Sensitivity (%) | Specificity (%) | γ       | DP       |
|----------------------------------------|------------|--------------|-------|-----------------|-----------------|---------|----------|
| Szczesna et al. (2011)\(^{27}\)         | E300       | NR           | 0.72  | 79.0            | 72.0            | 0.51    | 1.24     |
| Alonso-Caneiro et al. (2011)\(^{26}\)  | E300       | NR           | 0.83  | 92.0            | 71.0            | 0.62    | 1.81     |
| Hong et al. (2013)\(^{29}\)            | K5M        | 2.65 s       | 0.82  | 84.1            | 75.6            | 0.60    | 1.54     |
| Downie (2015)\(^{28}\)                 | E300       | 12.1 s       | 0.92  | 81.5            | 94.4            | 0.76    | 2.38     |
| Yamaguchi et al. (2016)\(^{48}\)       | TSAS       | 5 s          | NR    | 77.8            | 70              | 0.48    | 1.16     |
| Current study                          | E300       | 10 s         | 0.85  | 100             | 84              | 0.84    | 4.71     |

AUC = area under the curve; DP = discriminant power; NR = not reported; γ = Youden index.

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