Diagnostic capacity of biomechanical indices from a dynamic bidirectional applanation device in pellucid marginal degeneration

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PURPOSE: To evaluate the diagnostic capacity of the keratoconus match index (KMI) and keratoconus match probability (KMP) classification from a dynamic bidirectional applanation device (Ocular Response Analyzer) in eyes with pellucid marginal degeneration (PMD).

SETTING: Department of Ophthalmology, University Clinics Saarland, Homburg, Germany.

DESIGN: Cross-sectional study.

METHODS: Pellucid marginal degeneration eligibility was confirmed by inferior peripheral thinning, corneal protrusion, and irregular astigmatism. The KMI and KMP parameters in PMD eyes (study group) were compared with those in normal eyes (control group). The KMI's overall predictive accuracy was assessed operating characteristic (ROC) curves. The relationship between KMI and corneal hysteresis (CH), the corneal resistance factor (CRF), and a series of Scheimpflug camera indices was evaluated with Spearman analysis (*r*).

RESULTS: The mean KMI in the study group (40 eyes) and control group (40 eyes) was 0.34 $\pm$ 0.43 (SD) and 0.95 $\pm$ 0.30, respectively ($P<.001$). The KMI correlated significantly with the CH, CRF, and most Scheimpflug camera indices. Regression analysis indicated that the index of height decentration ($r = -0.877$, $P<.001$) was the primary determinant of the KMI. Moreover, the KMP index identified 50.0%, 29.16%, and 20.83% of PMD eyes as ectatic, suspect for ectasia, and normal, respectively. The ROC curve analysis of the KMI parameter indicated a predictive accuracy of 94.8% (cutoff point 0.626; sensitivity 85.71%; specificity 90.1%).

CONCLUSIONS: The KMI seems to be a promising diagnostic index for PMD. In contrast, the KMP index identified a significant percentage of topographically defined PMD eyes as normal, limiting its diagnostic value in PMD.

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Pellucid marginal degeneration (PMD) is a degenerative noninflammatory ectatic corneal disorder that is clinically characterized by inferior peripheral corneal thinning, corneal protrusion above the point of maximum thinning, and subsequent against-the-rule irregular astigmatism on corneal topography.[1–6] Despite PMD's well-known clinical and topographic characteristics, diagnosis of early forms remains challenging, primarily due to the resemblance to inferior keratoconus and because specific diagnostic guidelines have not been introduced.[7]

The Ocular Response Analyzer dynamic bidirectional applanation device (Reichert Technologies) enables the measurement of the biomechanical parameters of corneal hysteresis (CH) and corneal resistance factor (CRF) in normal corneas and ectatic corneas in clinical settings.[8–11] In addition to these 2 parameters, the device's updated software (version 3.x) allows the measurement of 2 new parameters that are based on the distinct waveform characteristics in ectatic eyes. These new parameters are the keratoconus match index (KMI), which is the outcome of a calculation of 7 waveform scores representing the resemblance of the waveform in the examined eye against the same average waveform scores in ectatic eyes in the instrument's database, and the keratoconus match probability

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(KMP), which, based on the same 7 waveform parameters, shows how a certain cornea matches the reference population data of normal corneas, suspect corneas, and ectatic corneas.

Scheimpflug imaging is among the most prevalent and contemporary imaging modalities for the diagnosis and follow-up of ectatic disorders.[12–16] It is based on a rotating camera and a monochromatic slit light source that rotate together. Apart from topographic, pachymetric, and elevation maps, the system's software provides a series of ectasia-related indices commonly used in clinical settings.

An extensive literature review found no data on the diagnostic usefulness of Ocular Response Analyzer–derived parameters in eyes with PMD. Thus, the primary objective of this study was to assess the diagnostic capacity of the parameters in a cohort of PMD patients.

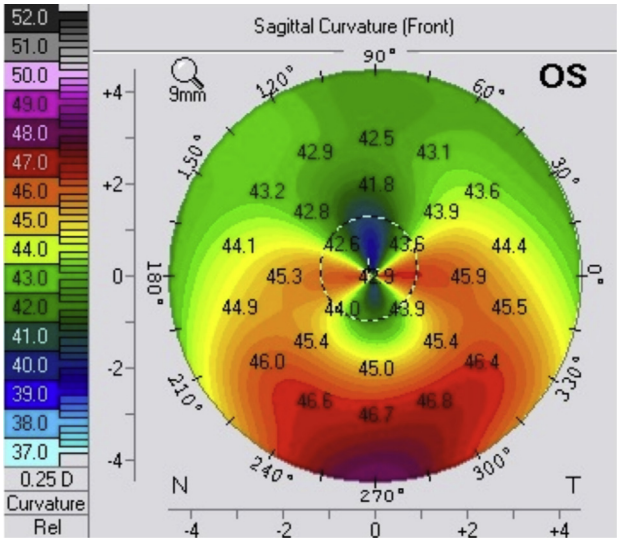

Figure 1. Scheimpflug imaging of an eye with PMD.

PATIENTS AND METHODS

This prospective noninterventional study was performed at the Department of Ophthalmology, University Clinics Saarland UKS, Homburg/Saar, Germany, between June 2011 and February 2012. The Institutional Review Board, University of Saarland, approved the protocol, and all participants signed a written consent form.

Study participants were recruited from the Cornea Service on a consecutive, if eligible, basis. Two study groups were formed. The PMD group (study group) included patients diagnosed with PMD. Inclusion criteria for enrollment in the PMD group were a slitlamp examination showing typical thinning of the inferior peripheral cornea with a region of normal cornea between the thinning and the limbus, corneal ectasia superior to the thinning with no indication of inflammation or deposits, and Scheimpflug-derived topography maps showing against-the-rule astigmatism with inferior steepening and a butterfly pattern (smiley or kissing birds) along the nasal and temporal hemimeridians (Figure 1). The control group consisted of refractive surgery candidates. Eligibility for participation in the control group was confirmed by a detailed ophthalmologic examination and consecutive topographies that excluded suspicion of ectatic or other corneal disorders.

The same general exclusion criteria applied to both groups. Among them were previous incisional eye surgery, corneal scars or opacities, a history of herpetic keratitis, severe dry eye, current corneal infection, glaucoma or suspicion of glaucoma, intraocular pressure–lowering treatment, pregnancy or nursing, and underlying autoimmune disease.

Data Collection

The same experienced operator (Z.G.) performed all Ocular Response Analyzer measurements (software version 3.01) in a consistent way. Specifically, the patient sat on a chair in front of the dynamic bidirectional applanation device. After successful fixation of the patient's eye on a red blinking target, the operator activated the device and a noncontact probe released an air puff. In brief, the air puff causes the cornea to move inward, past applanation, and into slight concavity. After milliseconds, the air pump shuts off, the pressure decreases, and the cornea returns to its normal state. The system monitored the entire process and produced a specific waveform. Three consecutive measurements were obtained, and the mean values of all parameters were calculated. If the measurements were of low quality (waveform score $<8/10$), the procedure was repeated until the acceptable criteria were met. Both ectasia-related indexes (KMI and KMP) and corneal biomechanical parameters (CH and CRF) were included in the analysis.

The same operator obtained all topographies using a Scheimpflug camera (Pentacam HR, Oculus Optikgeräte GmbH). Three consecutive scans were obtained, and the mean values of all parameters were calculated. Acceptable maps had at least 10.0 mm of corneal coverage. Images with extrapolated data in the central 9.0 mm zone were excluded. For the measuring procedure, patients were asked to blink and then look at the fixation device. When the image was of low quality (lid closure, insufficient fixation, or corneal coverage), the procedure was repeated until the acceptable criteria were met.

Statistical Analysis

Normality of the measured data was assessed with the Kolmogorov-Smirnov test, and parametric or nonparametric tests were applied accordingly. Differences between groups

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Table 1. Topographic and biomechanical characteristics by group.

	PMD Group		Control Group						
Parameter	Mean	SD	Mean	SD	*P* Value	Cutoff	AUC	Sensitivity	Specificity
KMI	0.34	0.43	0.95	0.30	<.001*	0.626	94.8	85.71	90.1
1CH	8.39	1.50	10.80	1.77	<.001*	9.1	94.0	81.82	90.91
CRF	7.83	1.97	10.18	2.08	<.001*	9.0	90.5	90.48	84.62
K1 anterior	42.51	4.63	43.46	2.14	.25	—	—	—	—
K2 anterior	50.68	4.66	44.58	1.88	<.001*	—	—	—	—
K mean anterior	46.13	4.17	44.00	1.95	.005*	—	—	—	—
K1 posterior	−5.67	0.87	−6.16	0.42	.002*	—	—	—	—
K2 posterior	−5.70	4.81	−6.54	0.36	.23	—	—	—	—
Kmean posterior	−6.37	0.73	−6.13	1.72	.55	—	—	—	—
CCT	511.58	60.00	550.26	34.79	.001*	—	—	—	—
TCT	471.11	103.40	542.55	39.98	<.001*	—	—	—	—
ISV	105.22	86.70	19.21	8.83	<.001*	—	—	—	—
IVA	1708.85	7245.72	0.15	0.10	.106	—	—	—	—
KI	1.25	0.27	1.02	0.02	<.001*	—	—	—	—
CKI	1.01	0.05	1.00	0.01	.268	—	—	—	—
IHA	23.01	26.86	4.45	4.50	<.001*	—	—	—	—
IHD	0.11	0.09	0.01	0.01	<.001*	—	—	—	—
Rmin	6.23	0.87	7.43	0.32	<.001*	—	—	—	—

AUC = area under the curve; CCT = central corneal thickness; CH = corneal hysteresis; CKI = central keratoconus index; CRF = corneal resistance factor; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; K = keratometry; K1 = keratometry in flat meridian; K2 = keratometry in steep meridian; KI = keratoconus index; KMI = keratoconus match index; PMD = pellucid marginal degeneration; Rmin = smallest radius; TCT = thinnest corneal thickness
*Statistically significant correlation

were evaluated using the Welch modified Student 2-sample *t* test and Wilcoxon signed-rank test, according to the normality of distribution of each parameter.

Receiver operating characteristic (ROC) curves were applied to determine the overall predictive accuracy of the CH, CRF, and KMI parameters as described by the area under the curve (AUC). These curves are obtained by plotting sensitivity versus 1-specificity, calculated for each value observed. An area of 100% suggests that the test perfectly discriminates between groups. The same approach was used to identify the cutoff points for each parameter to maximize the sensitivity and specificity in differentiating PMD eyes from normal eyes.

The Spearman correlation coefficient (*r*) was used to evaluate the degree of association between the KMI and tomographic parameters (Scheimpflug camera) and between the KMI and the biomechanical parameters (dynamic bidirectional applanation device). The impact of these indices on the KMI was assessed using multivariate regression analysis with stepwise forward selection ($P=.10$). Multivariate logistic regression was attempted to develop a diagnostic model for PMD that combines the dynamic bidirectional applanation device and the Scheimpflug camera parameters.

A *P* level less than 0.05 was considered statistically significant. All statistical analyses were performed with Medcalc software (version 9.6.2.0, Medcalc Software).

RESULTS

The study group consisted of 40 eyes that were randomly selected from 40 PMD patients when both eyes were eligible. The control group comprised 40 normal eyes. Table 1 shows comparative data for the biomechanical and topographic parameters in both groups. The CH and CRF parameters were statistically significantly lower in the study group than in the control group (both $P<.001$, Mann-Whitney *U* test). The mean KMI was also statistically significantly lower in the study group than in the control group ($P<.001$, Mann-Whitney *U* test). The only Scheimpflug camera parameters that were not statistically significantly different between the 2 groups were the central keratoconus index, the anterior keratometry (K) in the flat meridian, the posterior K in the steep meridian, the posterior mean K and the index of vertical asymmetry; all other indices were statistically significantly different between the 2 study groups (all $P<.01$, Mann-Whitney *U* test).

Table 2 shows the KMP distribution in the 2 study groups. Based on the KMP index, 12 PMD eyes (29.16%) and 9 control eyes (22.0%) were characterized as suspect for ectasia. Twenty PMD eyes (50.0%) were identified as ectatic; no eye in the control group was identified as ectatic.

The ROC curve analysis showed an overall predictive accuracy of 94.8% for the KMI. The cutoff point was 0.626 with a sensitivity of 85.71% and specificity of 90.1% (Figure 2). For the CH parameter, the cutoff

Table 2. Keratoconus match probability distribution by group.

Parameter	KMP Distribution (%)	
	PMD Group	Control Group
KMP normal	20.833	78.000
KMP suspect	29.167	22.030
KMP KC	50.000	0.000

KC = keratoconus; KMP = keratoconus match probability; PMD = pellucid marginal degeneration

point was 9.1 with a sensitivity of 81.82%, specificity of 90.91%, and AUC of 94%; for the CRF parameter, the cutoff point was 9 with a sensitivity of 90.48%, specificity of 84.62%, and predictive accuracy of 92.4% (Figures 3 and 4).

According to the Spearman analysis, the KMI was significantly correlated with CH, the CRF, and most Scheimpflug camera indices (Table 3). Nevertheless, regression analysis ($R^2 = 0.75$) showed that the index of height decentration (IHD) was the primary determinant of the variation in the KMI ($r = -0.877$, $P < .001$). Multivariate logistic regression was attempted to develop a diagnostic model for PMD that combines dynamic bidirectional applanation device–derived biomechanical indices and Scheimpflug-derived tomographic indices. The best model was expressed by the following formula:

$$\text{logit(p)} = -153.5\,\text{KMI} + 0.71\,\text{ISV} + 117.92\,\text{Rmin} - 681.9$$

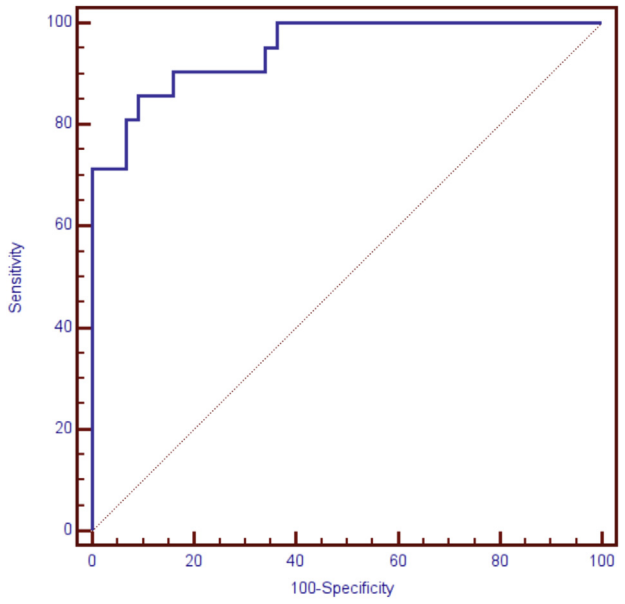

Figure 2. Results of the ROC analysis of KMI in PMD eyes.

where ISV is the index of surface variance and Rmin is the smallest radius (sensitivity 95.5%; specificity 93.48%; AUC 97.9%).

DISCUSSION

Pellucid marginal degeneration is a relatively rare thinning disorder of the inferior peripheral cornea that is typically identified in the second to fifth decades of life and progresses slowly.[3,7] Despite the idiopathic character of PMD, cases of iatrogenic PMD after laser

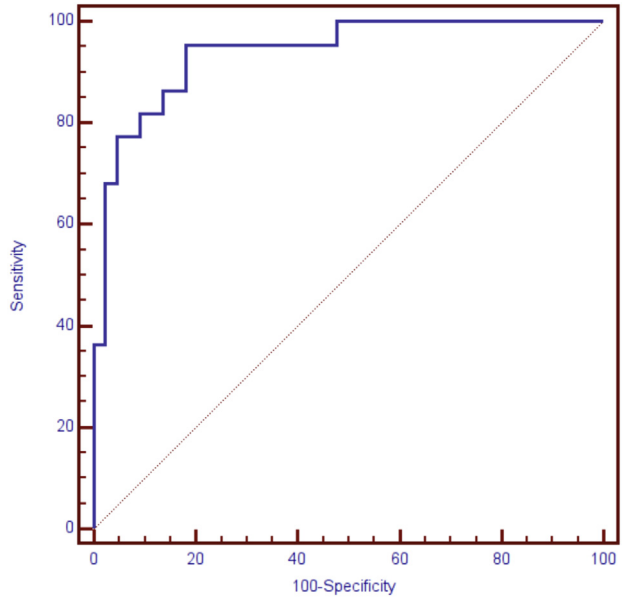

Figure 3. Results of the ROC analysis of CH in PMD eyes.

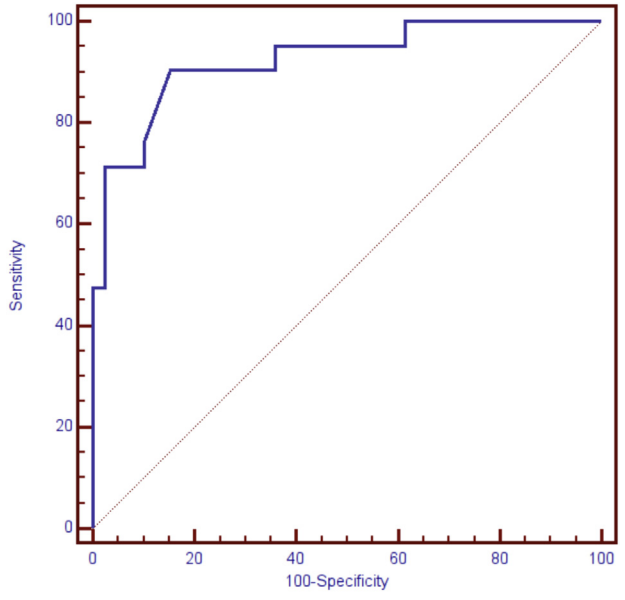

Figure 4. Results of the ROC analysis of the CRF in PMD eyes.

Table 3. Spearman analysis between KMI and biomechanical and topographic data.

Parameter	*r* Value	*P* Value
CH	0.4161	.0431*
CRF	0.5968	.0021*
ISV	−0.4485	.0541
IVA	−0.8024	.0001*
KI	−0.4957	.0309*
CKI	−0.5045	.0276*
IHA	−0.6395	.0032*
IHD	−0.7214	.0005*
Rmin	0.7472	.0002*
K1 anterior	−0.4405	.0591
K2 anterior	−0.7152	.0006*
Kmean anterior	−0.611	.0055*
K1 posterior	0.3165	.1868
K2 posterior	−0.03253	.8948
Kmean posterior	0.4924	.0322*
CCT	0.6353	.0035*
TCT	0.5294	.0198*

CCT = central corneal thickness; CH = corneal hysteresis; CKI = central keratoconus index; CRF = corneal resistance factor; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; K = keratometry; K1 = keratometry in flat meridian; K2 = keratometry in steep meridian; KI = keratoconus index; Rmin = smallest radius; TCT = Thinnest corneal thickness
*Statistically significant correlation

in situ keratomileusis (LASIK) have been described.[17] Moreover, despite recent advancements in the management of PMD,[18–23] no clearly defined diagnostic guidelines have been proposed, nor has a universally accepted classification system of the condition been developed.[7] Furthermore, although the role of contemporary diagnostic modalities such as the Ocular Response Analyzer dynamic bidirectional applanation device in the diagnosis and follow-up of other ectatic disorders, including keratoconus, has been thoroughly explored,[8–15] no related published data on PMD could be retrieved. Thus, in the present study, we attempted to assess the diagnostic potential of biomechanical parameters in eyes with PMD.

In addition to the well-known CH and CRF parameters, the updated software of the Ocular Response Analyzer (version 3.x) introduced 2 new ectasia-specific indices. These indices, the KMI and the KMP, are the mathematic representations of the device's waveform shape characteristics. Because, theoretically, certain eye pathologies share common waveform patterns, it is possible that they could be classified according to their biomechanical properties.

The KMI index is derived from 7 waveform scores representing the similarity of the waveform in the examined eye to the mean waveform scores in ectatic eyes in the machine's database. Apart from unpublished reports that suggest that normal KMI values are approximately 1 and normal ectatic KMI values are approximately 0, only 2 studies of this new parameter could be retrieved in the international literature.[24,25] Published data indicate a mean KMI value of 0.98, 0.20, and 0.41 in normal corneas, keratoconus corneas, and keratoconus-suspect corneas, respectively.[24,25] Furthermore, as indicated by ROC curve analysis, the KMI had a high diagnostic capacity in both keratoconus eyes and keratoconus-suspect eyes, with an overall predictive accuracy of 97.7% and 94.0%, respectively.[24,25] In the present study, we evaluated the KMI's diagnostic capacity in PMD corneas. The KMI differed significantly between control eyes and PMD eyes (0.95 ± 0.30 versus 0.34 ± 0.43, respectively) ($P < .001$, Mann-Whitney *U* test). Moreover, the ROC curve analysis of the KMI found an overall predictive accuracy of 94.8% with a sensitivity of 85.71% and specificity of 90.1%. The optimum cutoff point was estimated to be 0.626. As expected, the KMI correlated significantly with both biomechanical indices (CH, CRF) and most Scheimpflug camera–derived indices. Nevertheless, regression analysis distinguished IHD as the principal determining factor of the KMI. The IHD value is calculated from Fourier analysis of height values and reflects the degree of decentration in a vertical direction. Pellucid marginal degeneration traditionally presents high vertical decentration; therefore, the strong association between the IHD and KMI parameters further supports the diagnostic capacity of the KMI in eyes with PMD.

The KMP index represents the probability that a cornea is normal, suspect, or ectatic, with ectatic eyes being further classified as mild, moderate, or severe. In our study, the KMP index returned no false-positive results in the control group; however, it classified 22.0% as suspect for ectasia. Moreover, 20.0% of PMD eyes were characterized as normal (false-negative result) and 29.16% of them were classified as suspect. The relatively high percentage of KMP-classified suspect eyes in the normal group is consistent with previous published data for keratoconus,[24] possibly indicating the index has insufficiencies. Furthermore, unlike previous results for the KMP index in keratoconus, showing a false-negative probability of only 7%,[24] the index classified a significant number of clinically and topographically definite PMD corneas as normal, which further limits the diagnostic value of the index in discriminating PMD eyes from normal eyes.

The CH and CRF values showed statistically significant differences between normal corneas and PMD corneas (both $P < .001$, Mann-Whitney *U* test). Both

parameters had good predictive accuracy for PMD (AUC 94.0% and 92.4% for CH and CRF, respectively), with a cutoff point of 9.1 and 9.0, respectively.

Because this is the first study attempting to evaluate the diagnostic value of the Ocular Response Analyzer in PMD, no comparisons with the international literature could be attempted. Nevertheless, the KMI and KMP parameters are derived from the distinct waveform characteristics of the device's reference population of eyes with keratoconus, not with PMD. Therefore, it is yet to be determined whether PMD corneas share the same waveform patterns as keratoconic corneas or whether they possess distinct characteristics. Thus, the necessity of a new PMD-specific index is yet to be explored.

In conclusion, to our knowledge, this is the first study to report the diagnostic capacity of the Ocular Response Analyzer in eyes with PMD. Apart from the KMP index, the device's indices seem to efficiently differentiate PMD corneas from normal corneas. Thus, the indices should be considered as adjuvant diagnostic tools for PMD in cases in which the typical pattern of inferior thinning is present or probable as seen on slitlamp biomicroscopy, corneal tomography, or both. The primary drawback of the KMI is its average sensitivity. Possibly, custom waveform derivatives perform better in eyes with PMD.[26] However, our multivariate regression analysis suggests that biomechanical analysis of the cornea alone is inadequate for the diagnosis of PMD and that only combined models of biomechanical, tomographic, and topographic parameters provide adequate diagnostic capacity. Therefore, additional studies with larger cohorts are necessary to confirm our results and further explore the diagnostic role of the Ocular Response Analyzer and its new waveform-derived indices in cases of PMD.

WHAT WAS KNOWN

- The KMI provides additive diagnostic information in eyes with keratoconus and subclinical keratoconus. On the other hand, the KMP index classifies a significant percentage of ectatic eyes as normal and vice versa. However, biomechanical indices derived from dynamic bidirectional applanation have not been studied in eyes with PMD.

WHAT THIS PAPER ADDS

- The KMI can be considered an adjuvant diagnostic tool for PMD that has relatively high accuracy. The KMP had a poor ability to discriminate eyes with PMD from normal eyes. Combined models should be used to provide a high diagnostic capacity.

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