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ORIGINAL ARTICLE

Independent Population Validation of the Belin/Ambrósio Enhanced Ectasia Display: Implications for Keratoconus Studies and Screening

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ABSTRACT

With advances in technology and imaging, finding diagnostic criteria that are both sensitive and specific for keratoconus while using the latest corneal imaging modalities is paramount. The Belin/Ambrósio enhanced ectasia display final 'D' index, tested on an independent population, illustrated excellent false positive rates for refractive screening while eliminating 99% of keratoconus corneas. A false positive rate of 0% is achieved with a final 'D' of 2.69, meeting the more stringent criteria for treatment studies.

Keywords: Keratoconus, Ectasia, Tomography, Cornea, Imaging, Refractive surgery, Cross-linking, Scheimpflug, Placido, Topography.

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INTRODUCTION

Prior to refractive surgery the diagnosis of keratoconus was based on the distortion of the anterior cornea and the resultant decrease in visual acuity. Treatments, both surgical and non-surgical were based on visual loss, a fairly late sequelae. Steep and distorted keratometry, corneal striae and scarring, and loss of best corrected spectacle visual acuity were hallmarks of keratoconus and represent advanced manifestations of the ectatic process.[1,2] Refractive surgery, however, put new stresses on the cornea and revealed what was previously viewed as 'normal' could, if biomechanically stressed, could undergo progressive ectatic change.[3-6]

More recently, treatments, such as cross-linking, have moved the timing of intervention from the late stage to earlier in the disease process. Cross-linking is being utilized to stabilize an ectatic cornea at the earliest signs of visual loss.[7-9] Conceivably, however, the most efficacious timing may be prior to any visual loss, which requires an accurate diagnosis at a much earlier stage than was previously necessary or possible.[10]

Quoted figures and estimates of keratoconus fall between 50 and 230 per 100,000 with variations across different populations and complicated by different criteria used for the diagnosis.[2] The challenge most face is diagnosing early ectatic disease before apparent clinical manifestations. Although almost all ophthalmologists routinely screen patients prior to refractive surgery using corneal imaging, many have difficulty identifying abnormalities indicative of early keratoconus.[11] The problem is amplified by the lack of a concise definition of early, suspected or 'form fruste' keratoconus.

Marc Amsler in 1938 used photographic placido disk to describe early corneal topographic changes and coined the term 'form fruste keratoconus'.[12,13] 'Subclinical keratoconus' is described as early preclinical keratoconus only detectable by diagnostic examinations such as corneal tomography. Topographic and/or tomographic features suspicious for keratoconus are described as 'keratoconus suspect' especially if there are no clinical signs or history of keratoconus.

The Amsler-Krumeich classification of keratoconus is based on disease evolution. The severity of keratoconus is classified into 4 stages with the central K value having significant importance. Mean central K readings of < 48 Diopters (D) in addition to eccentric steepening and mild myopia and astigmatism indicate stage I disease. Stage II disease has mean central K readings < 53D and increasing myopia and astigmatism with absence of scarring. Stage III disease has mean central K readings of > 53D, myopia and

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astigmatism from 8 to 10D and minimum corneal thickness of 300 to 400 microns. Finally, stage IV disease is indicated by central corneal scarring with mean central K readings > 55D with unmeasurable refractions.[14]

There are several other index-based systems that utilize Placido-based topographic criteria. These indices include: Pathfinder Corneal Analysis, keratoconus percentage index (KISA%),[15] and KPI and KCI indices from Maeda and Klyce,[16,17] and I-S value.[18]

Rabinowitz utilized computer-assisted videophotokeratoscopy to devise indices used in an attempt to identify early keratoconus.[15] These indices were central keratometry (K), inferior-superior (I-S), and the keratoconus percentage index from each eye examined under videokeratograph.[18] The KISA index was derived from 2 additional indices besides central K and I-S, the astigmatism index (AST) which quantifies the degree of regular corneal astigmatism, and SRAX index, an expression of the irregular astigmatism.[15]

Maeda and Klyce[16] utilized the keratoconus prediction index (KPI) a calculation from 8 quantitative videokeratography-derived indices. These indices include: SimK1 (major axis), SimK2 (minor axis), surface asymmetry index, differential sector index, opposite sector index, center/surround index, and analyzed area.[16]

All of the above, however, were limited to imaging the anterior corneal surface and additionally relied on a single central corneal thickness value. Further advances in technology and imaging devices, including but not limited to rotating Scheimpflug optical cross-sectional analysis, confocal microscopy, optical coherence tomography, very high-frequency ultrasound, and biomechanical analysis have added additional diagnostic criteria to assist the clinician in diagnosing ectatic disease.[19,20]

The Belin/Ambrósio Enhanced Ectasia Display (BAD) was initially released for the Pentacam (OCULUS GmbH, Wetzlar Germany) in 2008. The display was designed to combine elevation data from the anterior and posterior cornea with pachymetric data in an effort to provide a more comprehensive display for keratoconus and ectasia screening. The initial release (BAD 1) showed anterior and posterior elevation with a standard 8 mm best fit sphere (BFS) reference surface, with an enhanced reference surface (ERS), and the numerical change between the two. The enhanced reference surfaces utilizes the standard BFS but modifies it by eliminating a variable 3.5 to 4 mm zone surrounding the thinnest point on the cornea. The exact exclusion zone size is determined by the astigmatism magnitude and is not operator selected. In a normal or keratoconic population (i.e. nonsurgically altered) the ERS is flatter than the standard BFS and results in an amplification of positive elevations. Since, the exclusion zone surrounds the thinnest portion of the cornea, eyes with significant ectasia (positive elevation) have a greater flattening of the ERS compared to the standard BFS, while normal eyes have an ERS that more closely mimics the standard BFS. The numerical difference between the elevation data going from the BFS to the ERS should therefore show greater change in eyes with ectasia. The BAD 1 also displayed the full pachymetric map as well as two pachymetric progression graphs, the 'corneal thickness spatial profile' (CTSP) and the 'percentage thickness increase' (PTI). The BAD 1 also displayed the following individual parameters; corneal thickness at the apex and thinnest point, distance between the apex and thinnest point, progression index (minimal, average and maximum) and a display quality check.

The second release (BAD II) (2010) reported the standard deviations from a large normative database of five parameters Df (change in anterior elevation from BFS to ERS), Db (change in posterior elevation), Dp (pachymetric progression), Dt (pachymetric value at the thinnest point), and Dy (vertical displacement of the thinnest point from the apex). These five parameters were then utilized in a regression analysis with the normative database and a known keratoconic database. The final 'D' represents how the examined cornea varies from 'normal' when compared to the keratoconic group.

The current version (BAD III) (2012) (Fig. 1) added four additional parameters to the original regression analysis (K_{max}, anterior and posterior elevation at the thinnest point and Ambrósio relational thickness maximum (ART_{max}). ART_{max} is the maximal progression index divided by the thinnest pach. Additional individual parameters, not utilized in the regression analysis, were also added; steep and flat simulated keratometry (K1 and K2) and Q value. The final 'D' was further refined with additional testing against a population of so-called unilateral or highly asymmetric keratoconic patients.

The current study seeks to validate the BAD III using two new populations (both normative and keratoconic) that were not used in the original regression analysis (i.e. independent retest population) and to evaluate both individual BAD parameters as well as the final 'D' in their performance for both screening (i.e. exclusion) potential (e.g. refractive surgery screening) and for studies (i.e. inclusion) on keratoconus (e.g. cross-linking).

MATERIALS AND METHODS

The validation normative database consisted of 341 adults (682 eyes) details of which have been previously described.[21] All patients had a normal ocular examination, a best corrected visual acuity of 20/20 or better and no family history of ectatic disease. Only simple and compound myopic patients were

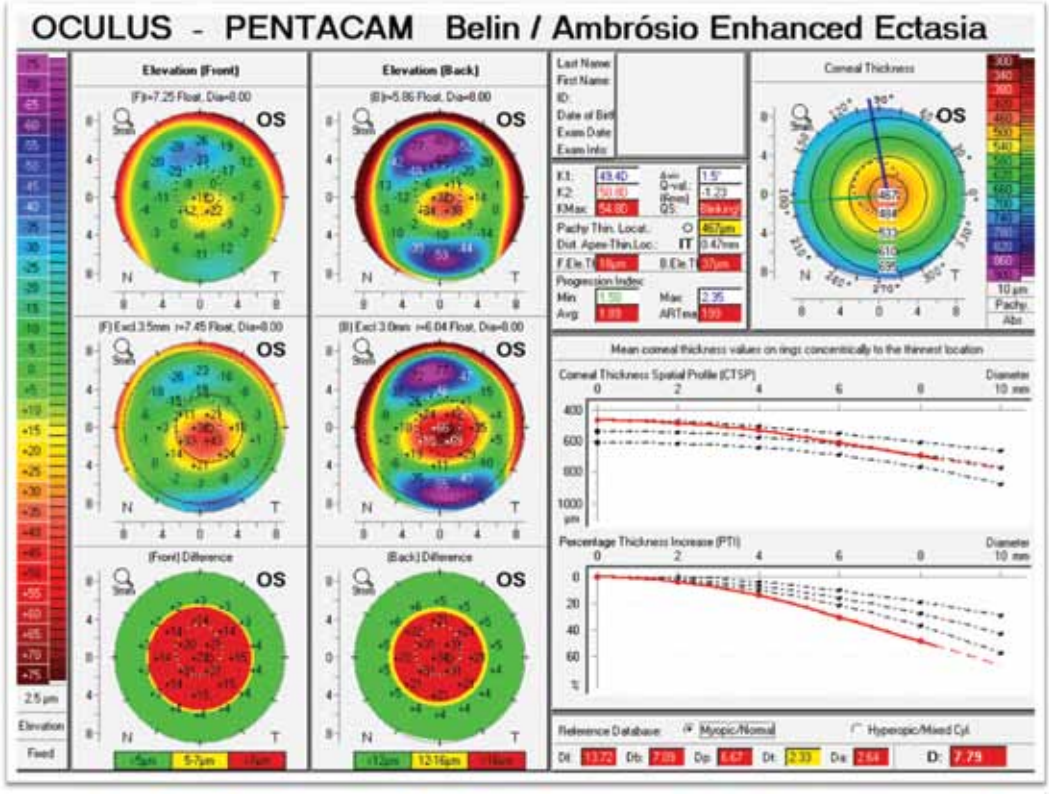


Fig. 1: BAD III sample display of keratoconus. Both anterior and posterior elevation maps show positive islands of elevation (upper elevation maps) that are amplified with the enhanced reference surface (middle elevation maps) and the lower display shows that the difference is significant. The upper-right pachymetric map reveals a thin cornea (thinnest point 467) with highly abnormal pachymetric progression graphs (both CTSP and PTI). Other individual parameters that are flagged as abnormal include K_{max}, Front and Back elevation at the thinnest point, PI_{avg}, and ART_{max}. The final 'D' for this cornea is 7.79.

included (range –0.5D to –10D). Patients were included whether they proceeded to refractive surgery or not. All exams were independently examined by two fellowship trained refractive surgeons (MWB and RA). All patients had at least 3 years of clinically uneventful follow-up. Clinically uneventful follow-up was defined as no loss of one or more lines of vision, or an increase in astigmatism by 0.5D or the need for an enhancement. All exams had at least 9 mm of coverage with a minimum of 8 mm nonextrapolated data and an internal Pentacam quality check indicating no issues. One eye per patient was randomly selected for the initial analysis.

To minimize bias, the keratoconic data base (74 patients (147 eyes)) was provided by an outside research department, Oftalmosalud Instituto de Ojos (Lima, Peru). All examining physicians at the institute are fellowship trained corneal specialists (MAH, LI). They were contacted based on a prior published paper describing a large keratoconic patient population.[22] Instructions were limited to providing a keratoconic database with at least 8 mm of coverage on Pentacam examination. Complete U12 files were provided. This database was then reviewed by MWB and RA only to exclude exams that did not meet quality standards. Eyes that had any prior surgical alteration were eliminated.

Individual patient data were imported into an Excel file using a specially designed extraction program. The following parameters were analyzed: Minimal central corneal thickness, K_{max}, Df (change in front elevation from standard BFS to enhanced BDS), Db (change in back elevation from standard BFS to enhanced BFS), Front elevation at the thinnest point, Back elevation at the thinnest point, PIavg (pachymetric progression index), ART_{max} (Ambrosio relational thickness), final 'D'. All elevation values were referenced against a BFS taken from the central 8 mm of the cornea. The final 'D' is a derived parameter based on a regression analysis designed to distinguish between normal and ectatic corneas and was based on a prior (i.e. initial) study population.[23,24] Each individual parameter and the final 'D' were then analyzed for screening potential (e.g. refractive surgical screening) using a one-sided 95% and 97.5% confidence interval (i.e. a 5% and 2.5% false positive rate) and for inclusion potential for keratoconic studies using a 95 and 97.5% capture rates and a 99.9% normal exclusion rate (0.1% false positive). Finally the screening values and inclusion values were compared.

RESULTS

Six hundred eighty-two eyes of 341 patients (177 female/164 male) were analyzed for the normative database with an age range of 18 to 68 years. Racial data were not identifiable, but the vast majority of the study population was white. One

eye of each patient was randomly selected as each eye is not viewed as an independent variable (details of this normative database were previously published (J Cat Refract Surg 2013;39(11):1707-1712).

One hundred forty-seven eyes of 74 keratoconic patients were analyzed with an age range of 12 to 58 years. All patients were screened at the Oftalmosalud Instituto de Ojos, Lima, Peru and are assumed to be native. Both eyes (one eye received cross-linking and was excluded) were included in the analysis, since, the purpose of the study was to determine the potential to identify ectatic disease.

The mean, standard deviation and range of each parameter are shown in Table 1. The actual distribution for each parameter and final 'D' are shown in shatter graphs (Figs 2A to I). The insert shows only the region of overlap between the normal and keratoconic population.

Refractive surgery screening entails examining an assumed normal population to identify potential at risk patients. This often involves not only trying to identify patients with true disease, but also identifying outliers, whom may or may not have disease, but are assumed to be at higher risk or in whom risk data analysis is lacking. We arbitrarily selected at 95 and 97.5% one-sided confidence interval (accepting a 5% and 2.5% false positive rate) for the normal population as representative of a reasonably risk adverse screening. Each of the 8 individual parameters and the final 'D' are shown in Table 2 with both the representative screening gates and the percentage of keratoconus patients that would be incorrectly included as 'normal' (false negatives). The worst performing individual parameter was minimal corneal thickness which would include up to 43.5% of the keratoconic population, while the best performing parameter was the final 'D' which included <1% of the keratoconic group.

Conversely, one can examine a 95 and 97.5% keratoconus capture rate. The results are shown in Table 3 with the associated gates and percentage of normal eyes that would be included (false positives). The worst performing individual parameter in this scenario is the front elevation at thinnest with a false positive rate of 98.1%, and the best performing parameter is the final 'D' with a zero false positive rate at the 95% keratoconic capture rate.

Treatment studies, as opposed to screening to exclude disease, requires a totally different set of parameters to insure that the majority of those entered into a trail actually have the disease being studied. Table 4 shows the keratoconus capture

Table 1: Mean, standard deviation, and range for 9 tomographic parameters in normal and keratoconus population (all elevation values referenced of a BFS from the central 8.0 mm zone) (Pentacam, OCULUS GmbH)

		Normal	*Keratoconus*
Eyes		341	147
Minimal pach	Mean	539	473
	Std.	30.7	50.3
	Range	459 to 622	156 to 564
K_{max}	Mean	45.3	54.9
	Std.	1.47	8.23
	Range	40.9 to 51.3	44.8 to 106.7
Df	Mean	–0.07	9.2
	Std.	1.01	6.92
	Range	–1.86 to 4.02	–1.1 to 37.7
Db	Mean	–0.10	6.69
	Std.	0.9	5.60
	Range	1.5 to 3.77	–0.52 to 40.5
Elev front thin	Mean	1.7	18.3
	Std.	1.6	11.0
	Range	–3.0 to 8.0	–3 to 52
Elev back thin	Mean	4.1	39.8
	Std.	4.10	25.59
	Range	–8 to 18	–3.0 to 162
PI_{avg}	Mean	0.92	2.09
	Std.	0.13	1.97
	Range	0.53 to 1.36	0.82 to 22.8
ART_{max}	Mean	473	209.9
	Std.	84.3	81.5
	Range	253 to 893	4 to 557
D	Mean	0.69	7.49
	Std.	0.58	5.56
	Range	–1.25 to 2.61	1.55 to 54.77

Table 2: Sample refractive screening using 5 and 2.5% false positive rates with accompanying percentage of keratoconus eyes included

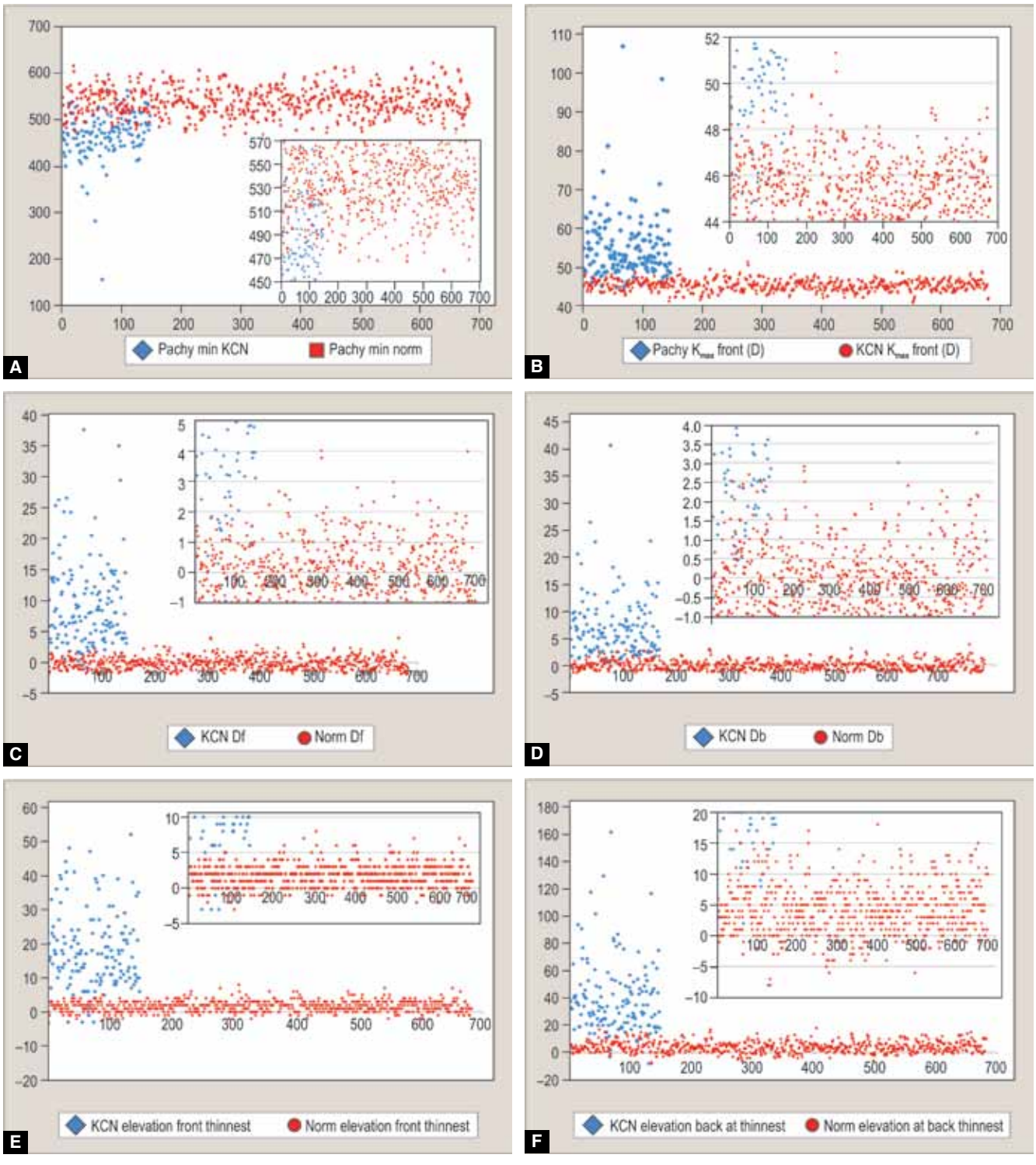
	95% CI/KCN included(%)	*97.5% CI/KCN included(%)*
Minimal pach	489/38.1%	480/43.5%
K_{max}	47.7/9.5%	48.1/10%
Df	1.66/6.8%	2.14/10%
Db	1.63/11%	2.05/15%
Elev front thinnest	4.0/4.8%	5.0/6.1%
Elev back thinnest	12.0/6.1%	13.0/6.1%
PI_{avg}	1.14/4.1%	1.18/6.1%
ART_{max}	353/4.8%	332/8.8%
Final D	1.65/0.7%	1.88/0.7%

Table 3: Percentage of normals included for each parameter, if 95 and 97.5% of keratoconic eyes are included

	95% CI/normal included(%)	*97.5% CI/normal included(%)*
Minimal pach	538/49%	558/73%
K_{max}	46.1/31%	45.3/55%
Df	1.43/8.2%	–0.2/50%
Db	1.0/13%	0.48/23%
Elev front thinnest	4.3/3.5%	–1.7/98.1%
Elev back thinnest	11.3/5.7%	6.3/25%
PI_{avg}	1.17/3.2%	1.08/12%
ART_{max}	354/5.3%	376/11%
Final D	2.69/0%	2.26/0.6%

Table 4: Percentage of keratoconus eyes included for each parameter, if 99.9% of normal eyes are excluded

	Minimal pach	*K_{max}*	*Df*	*Db*	*Elev front thinnest*	*Elev back thinnest*	*PI_{avg}*	*ART_{max}*	*Final D*
99.9% normal exclusion	459	51.3	4.02	3.77	8	18	1.36	253	2.61
% KCN capture	33%	63%	74%	65%	87%	87%	85%	71%	95%



Figs 2A to F

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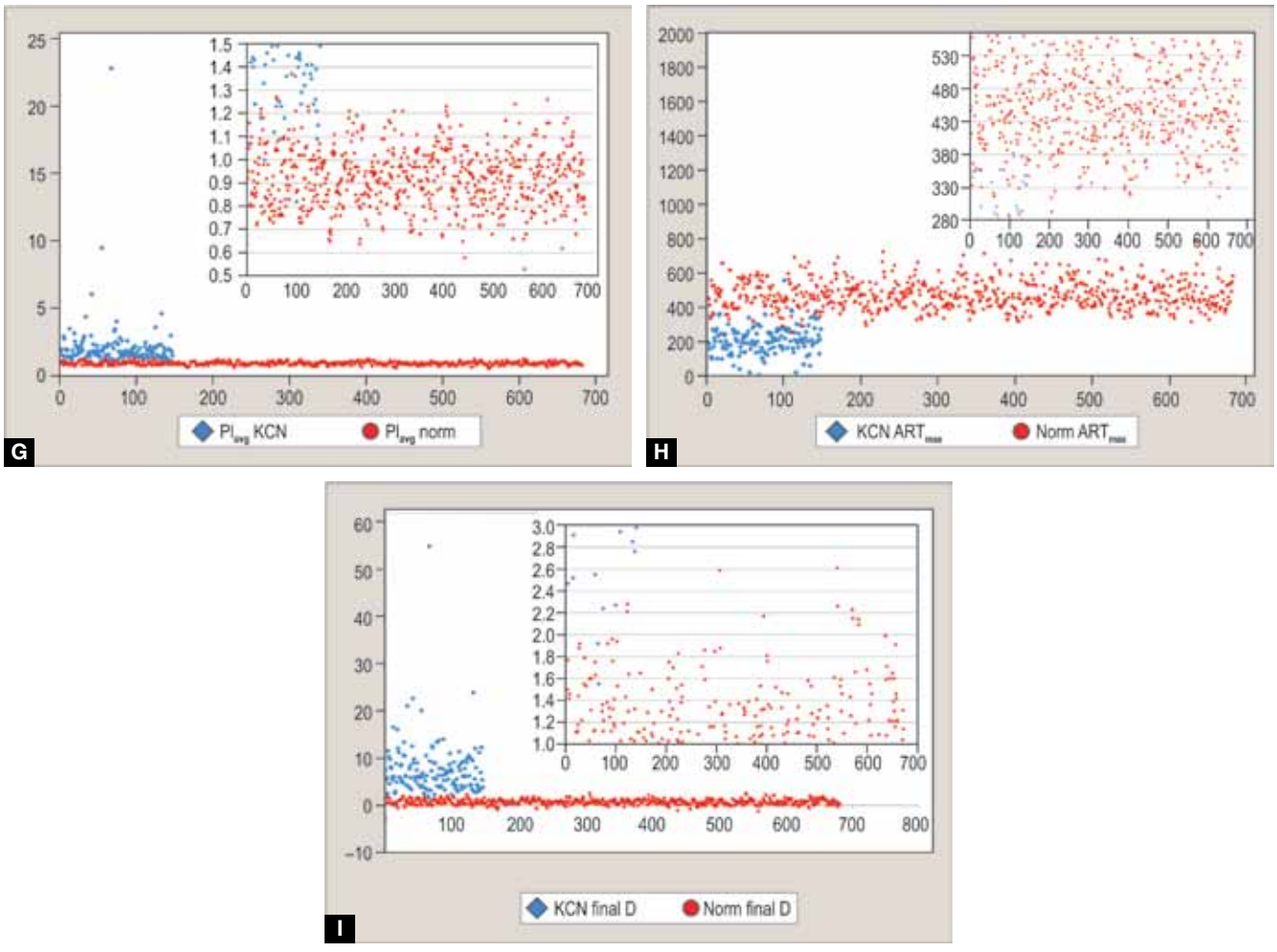

Figs 2A to I: Individual Scatter graphs of the 8 individual parameters minimal pachymetry, K_{max}, Df (front elevation difference), Db (back elevation difference), elevation front thinnest, elevation back thinnest, PI_{avg}, ART_{max}) and the final overall reading 'D'. The smaller insert graphs display only the area of overlap between the normative population (red) and the keratoconus population (blue)

percentage if one excludes 99.9% (0.1% false positive) of normal patients. Minimal pachymetry is the worst performing parameter, capturing only one-third of the keratoconic group, while the final 'D' performs the best with a 95% capture rate.

DISCUSSION

An optimal screening test for refractive surgery should be relatively simple and quick to perform and to be able to identify 'abnormals' with an acceptable degree of false positives. Rates of keratoconus range from 1/400 to 1/2,000, the latter being oft quoted for an US population. These rates probably underestimate the frequency of keratoconus seen in a refractive screening population which tends to pre-select myopes, contact lens wearers and individuals dissatisfied with their vision, all of which are more common in keratoconic individuals.[25] We arbitrarily selected a 95 and 97.5% one-sided confidence interval for the normal population and reported the percentage of a keratoconic population that would be included (false negative) (Table 2) and a 95 and 97.5% keratoconus detection rate and report the accompanying percentage of false positives (i.e. normals) associated with that detection rate (Table 3). These values will also vary based on geographic variation in the incidence of keratoconus as well as individual surgeon's choice for screening parameters. The final 'D,' based on a regression analysis of all the parameters, is the best performing screening parameter with values of 1.65/1.88 associated with a 95 and 97.5% confidence interval with an acceptable false negative rate of less than 1%.

As opposed to screening normal patients for disease, inclusion studies for treating keratoconus (e.g. cross-linking) require a completely different set of parameters. Unfortunately, this has typically not been done in studies treating early or 'form-fruste' disease.[26] For example, if one chooses the 95% keratoconus detection rate the accompanying false positive rate of the best performing individual parameter (ART_{max}) is 5%. If you used this parameter to determine entrance into a clinical trial, then you would have 49 normal patients misdiagnosed as abnormal for every true keratoconic

(assuming a 1/1,000 incidence), making treatment efficacy claims problematic. Only the final 'D' appears to have adequate discriminatory potential to screen for treatment (i.e. inclusion) studies. In practice, most parameters would likely perform better taking into account additional screening by family history and perhaps other ancillary testing.

This study analyzed the ability of the BAD display to separate a normal population from a keratoconic population. The study utilized two new databases that were not utilized in the initial regression analysis (retest population). The study validates the BAD's final 'D' as the most useful of the nine parameters tested and the only one with sufficient discriminatory potential to serve both for refractive screening and for treatment protocols (though at very different gates). Separating a normal population from a known keratoconic population is very different from assessing risk or screening for potential post-LASIK ectasia. Surgical patients at increased risk may not have currently measurable risk factors or may only exhibit evidence of subclinical keratoconus (i.e. normal anterior surface in the presence of posterior ectasia and/or abnormal pachymetric progression). Our keratoconic study population was heavily weighted toward moderate disease with observable anterior changes with an average topographical keratoconus classification (TKC) score of 1.94 and only 6/147 eyes classified as early or subclinical disease. The TKC score relies solely on anterior corneal shape and is designed to mimic similar placido based keratoconus classifications.[27,28] Future work with earlier and/or subclinical disease should allow for further refinement.

CONCLUSION

The Belin/Ambrósio enhanced ectasia display final 'D' shows excellent potential for use in both refractive screening and for treatment inclusion studies albeit at significantly different gates.

The final 'D' is a product of a multivariate regression analysis and validation tested was performed using two (normal and keratoconic) independent retest populations. No tested individual parameters performed sufficiently to function in a similar manner. Final 'D' values of 1.65 and 1.88 were associated with a 5 and 2.5% false positive rate, reasonable for refractive screening while eliminating over 99% of known keratoconus corneas, while a final 'D' of 2.69 had a 0% false positive rate which should be required for treatment studies.

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