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Determining Progression in Ectatic Corneal Disease

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Abstract: Before the advent of modern tomographic imaging and corneal cross-linking (CXL), diagnosis and treatment of ectatic disease were limited to disease severity where changes on the anterior corneal surface lead to visual complaints. Rigid contact lenses and/or penetrating keratoplasty addressed late stage disease, as identifying early or subclinical disease was not possible, or its need appreciated. The emergence of CXL as a viable treatment to alter the natural progression of keratoconus heightened the need for improved diagnostics.

Several methods have been described in the literature to evaluate and document progression in keratoconus, but there has been no consistent definition of ectasia progression. Newer imaging techniques (ie, tomography) allowed the detection of earlier ectatic disease, before visual loss and subjective complaints. The Belin ABCD classification/staging system was introduced on a Scheimpflug imaging system [Pentacam, (Oculus GmbH, Wetzlar, Germany)] to address previous shortcomings. The ABCD system utilizes 4 parameters: **A**nterior ("**A**") and posterior ("**B**" for **B**ack) radius of curvature taken from a 3.0 mm optical zone centered on the thinnest point, "**C**" is minimal **C**orneal thickness, and "**D**" best spectacle **D**istance visual acuity. The first 3 parameters (A, B, C) are machine-generated objective measurements that can be used to determine progressive change.

The staging system is not limited to a specific commercial entity and can be incorporated in any tomographic imaging system. The ABCD Progression Display graphically displays each parameter and shows when statistical change above measurement noise is reached. This should allow the clinician the ability to diagnose progressive disease at a much earlier stage than was previously possible, with the confidence that earlier intervention could prevent visual loss.

Key Words: cross-linking, ectatic disease, keratoconus, progression, tomography

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INTRODUCTION AND BACKGROUND

Keratoconus is a degenerative corneal disease of, as of yet, unknown etiology. It is normally a bilateral, although often highly asymmetric, condition that leads to corneal thinning, irregularly irregular astigmatism (corneal distortion) with subsequent decrease in both spectacle corrected visual acuity (CDVA) and uncorrected visual acuity (UCVA).[1–3] The prevalence and incidence vary greatly in different ethnicities and geographic areas, but also differs based on criteria used to make the diagnosis.[4] With increasing use of modern tomographic imaging and testing in different geographical regions of the world, keratoconus has been shown to be much more common than historical data would suggest, reaching nearly 5% of prevalence in a recent study.[5] In the past, treatments for keratoconus were limited to advanced disease when patients had already lost both CDVA and UCVA, as there was no treatment that could alter the natural course of this otherwise progressive disease.

Since past treatments were limited to treating late-stage disease, where changes on the anterior corneal surface lead to loss of visual function, classification systems, staging, or descriptors of the disease concentrated on the anterior corneal surface. Although multiple classifications have been proposed, the mostly commonly used historical grading is the Amsler-Krumeich (AK) system.[6] The AK system was developed over 70 years ago and predated modern imaging capabilities. It was based on central keratometry, apical corneal thickness measured by optical pachmetry, and spectacle refraction. The limitations of the AK system were recognized in the 2015 consensus document on keratoconus and ectatic corneal diseases which stated, *". . .. currently there is no clinically adequate classification system for keratoconus and that the historical Amsler–Krumeich classification fails to address current information and technological advances."*[7]

Similar to the limitations of the AK system, the most commonly used parameter to determine keratoconus progression has been maximum keratometry (K) reading (K*max*).[8–10] K*max* is a single point reading representing the maximum curvature typically taken from the axial or sagittal anterior corneal curvature map. K*max* has numerous limitations, which include: a single point reading is a poor descriptor of the cone morphology, a change in cone morphology (eg, a nipple cone progressing to a globular cone) can sometimes be associated with a reduction in K*max*, single point readings tend to have poor reproducibility, changes in K*max* do not correlate to changes in visual function, and K*max* is limited to the anterior corneal surface, ignoring the posterior cornea, thereby having no ability to detect early or subclinical disease or early progression.[11–16]

Others have proposed a series of complex keratometric indices to describe progression. These include: index of surface variance (ISV), demonstrating corneal surface irregularity; index of vertical asymmetry (IVA) measuring curvature symmetry with

TABLE 1. Previous Progression Parameters

Suggested Parameter	Value Representing Progression
Spherical power, and higher order irregular astigmatism	Positive rate of change per year
Spherical component, regular astigmatism,	Positive rate of change per year
K*max* (steepest K)	≥1.00 D increase
K*max*—K*min*	≥1.00 D increase
K*mean* (average of Kmax and K*min*)	≥0.75 D increase
Pachymetry	≥2% decrease in central thickness
Back optic zone radius of the best fitting contact lens	≥0.1 mm decrease
increase in the central K power	≥1.50 D increase from baseline
Manifest cylinder	Increase of ≥1.00 D in 24 mo
Manifest spherical equivalent change	≥0.50 D
ISV	Specific values for each KCN stage
IHA	Specific values for each KCN stage

IHA indicates index of height asymmetry; ISV, index of surface variance.

respect to the horizontal meridian; keratoconus index (KI), the ratio of mean radius value in the upper segment to mean radius value in the lower segment; central keratoconus index (CKI), the ratio of mean radius value in a peripheral ring to mean radius value in a central ring; index of height asymmetry (IHA), a calculation of height data symmetry between the superior and inferior areas with respect to the horizontal meridian; index of height decentration (IHD), representing the amount of decentration of elevation data in the vertical direction; and minimum radius of curvature (Rmin), the smallest radius of sagittal corneal curvature, representing the maximum steepness of the cone.[17] All of these suffer from the same limitation, their failure to recognize early or subclinical disease and the likelihood for visual loss to occur before documenting progression.

Other non−imaging-derived parameters investigated to detect progression include parameters such as: a reduction in central corneal thickness, loss of best-corrected distance visual acuity, change in spherical refraction, change in astigmatism, or changes in back curvature of a contact lens (Table 1).[12,15–21] Each of these parameters, however, fails to recognize early subclinical disease or its earliest progression. Additionally, subjective measurements such as visual acuity and/or refractions are known to be highly variable, especially in patients with ectatic disease.[3,17]

The need for a new system to describe the keratoconic cornea and specifically to determine the earliest signs of progression was made paramount with the introduction of corneal cross-linking (CXL). CXL was the first treatment with the potential to alter the natural disease progression and either slow, halt or even reverse the anatomic changes.[22–24] It has been theorized that early intervention with CXL, before a loss of visual function, could preserve vision by stabilizing the cornea prior to anterior surface changes. To do so, would require a mechanism to determine real progression at the earliest possible stage.[25]

Despite its known limitations, K*max* remains the most commonly used parameter to document both progressive disease and CXL efficacy. The limitations of K*max* were further highlighted by the 2015 consensus document which stated, "*Currently, there is no consistent or clear definition of ectasia progression*."[7] The same group went further and defined the minimal requirement for documented progression as at least 2 of the following, "*1. Steepening of the anterior corneal surface. 2. Steepening of the posterior corneal surface. 3. Thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point. The changes need to be consistent over time and above the normal variability (i.e., noise) of the measurement system*."[7]

Imaging systems, such as Placido-based imaging, cannot measure the posterior corneal surface necessary to identify early disease and detect early progression. Early tomographic systems also lacked the accuracy in measuring the posterior corneal surface that would be required to detect early or mild change.[7] Newer tomographic systems [both Scheimpflug and optical coherence tomography (OCT)] have the ability to image the entire anterior segment and the requisite accuracy needed to determine subtle progressive change.[26] Currently, Scheimpflug imaging is capable of greater corneal coverage than most commercially available OCT devices. It is also now understood the changes to the posterior cornea typically predate changes on the anterior surface and can often be seen in asymptomatic individuals with normal CDVA.[17,27–29]

Partly in response to the shortcomings outlined in the consensus document, and to incorporate the new data offered with tomographic imaging, the Belin ABCD classification was developed. The ABCD system uses 4 parameters: "A" represents the **A**nterior radius of curvature taken from a 3.0 mm optical zone centered on the thinnest point, "B" (for **B**ack) is the posterior radius of curvature from a 3.0-mm zone centered on the thinnest point, "C" is minimal **C**orneal thickness, and "D" is best spectacle **D**istance visual acuity. Each parameter is individually staged between 0 and 4. This system is currently available on the Oculus Pentacam (OCULUS GmbH, Wetzlar, Germany) (Table 2) (Fig. 1).[25]

TABLE 2. Belin ABCD Keratoconus Staging

ABCD Staging	A Anterior Radius of Curvature (3-mm Zone)	B Posterior Radius of Curvature (3-mm Zone)	C Thinnest Pachymetry, μm	D Spectacle Corrected Distance Visual acuity
Stage 0	>7.25 mm (<46.5 D)	>5.90 mm	>490	≥20/20 (≥1.0)
Stage 1	>7.05 mm (<48.0 D)	>5.70 mm	>450	<20/20 (<1.0)
Stage 2	>6.35 mm (<53.0 D)	>5.15 mm	>400	<20/40 (<0.5)
Stage 3	>6.15 mm (<55.0 D)	>4.95 mm	>300	<20/100 (<0.2)
Stage 4	<6.15 mm (> 55.0 D)	<4.95 mm	≤300	<20/400 (<0.05)

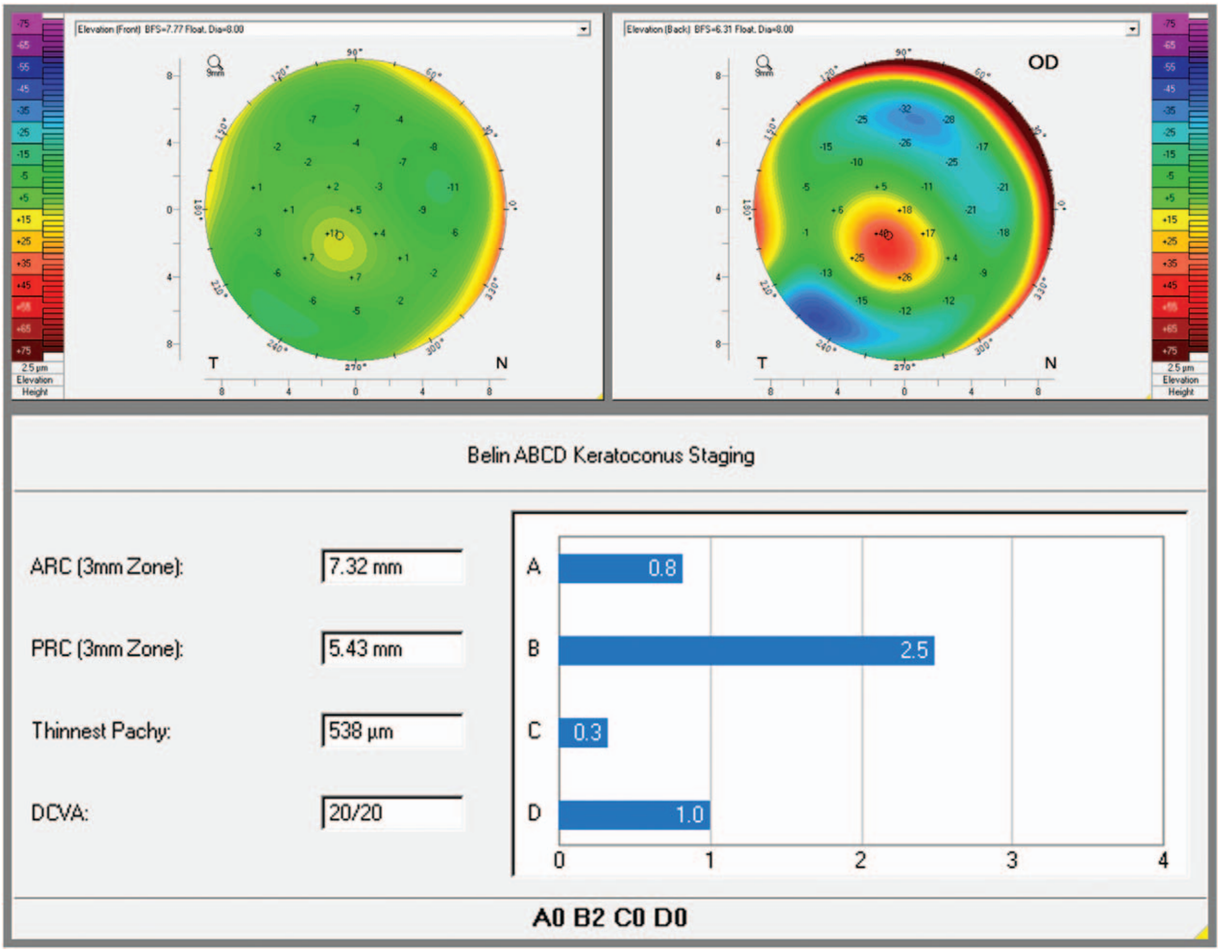

FIGURE 1. Composite showing anterior elevation (upper left) and posterior elevation (upper right). The maps show only minor changes on the anterior surface, but a prominent posterior ectasia on the posterior cornea. The ABCD staging is shown below. The staging is A0B2C0D0 indicating a "normal" anterior surface, normal corneal thickness (538 µm) and normal DCVA but a moderate posterior ectasia (B2). [All images are from Pentacam (OCULUS GmbH, Wetzlar, Germany)]. DCVA indicates uncorrected visual acuity.

In addition to a tomographic based classification system, having a standardized method to identify and document progression is similarly important as the decision to recommend treatments, such as CXL, is based largely on the progressive nature of the disease.[25,30]

The A, B, and C parameters from the ABCD display are machine-generated objective measurements that could serve as progression determinants. Each parameter is independently measured and includes both anterior and posterior corneal surfaces as well at the thinnest corneal pachymetry. Additionally, as opposed to the single point K*max*, the "A" and "B" parameters are more global, being measured over a 3-mm optical zone, and therefore should better reflect the nature of the cone. All 3 parameters are measured at the corneal thinnest point, as opposed to the corneal apex, as this better corresponds to the location of the cone.[25]

As both the "A" and "B" parameters were new parameters, measurement variability (ie, noise) was not known. To utilize these parameters as indicators of progression, the measurement noise needs to be determined as this allows us to separate true or real changes from measurement variance or noise.[30–32] Measurement noise of the 3 parameters [corneal thickness at the thinnest point, and anterior and posterior radius of curvature (ARC, PRC) taken from the 3.0-mm optical zone centered on the thinnest point], was determined in both normal and keratoconic populations.[29] It is well documented that measurement noise in pathologic corneas (eg, keratoconus) is higher than in normal eyes.[16] We chose to also sample a normal healthy population because of the clinical importance in determining progression in borderline, subclinical cases, or in early pediatric cases. Here, the normal patient variation is probably more applicable and more closely approximates very early disease than values determined from more advanced keratoconus cases.

Data were collected from both a normal population and keratoconic population. Both a pooled variance estimate and a one-sided confidence interval were computed using both SPSS version 23 (IBM Corp., Armonk, NY) and STATA 13 (StataCorp LP, College Station, TX). A one-sided confidence interval was chosen because progression is indicated by thinning and/or steepening of the anterior and/or posterior corneal surfaces. For each of these parameters (corneal thickness, ARC, PRC) a decrease would be indicative of progression.[30] Both 95% and 80% confidence intervals were determined (Table 3)[30–32] since the risk/benefit ratio for medical/surgical intervention would vary based on the age of the patient, family history, condition of the other eye, among others, and both the physician and patient's decisions could vary based on a multitude of factors including the risk aversion of the patient and/or surgeon.

TABLE 3. 80% and 95% One-sided Confidence Intervals for Corneal Thickness, ARC and PRC in Both Normal and Keratoconic Population

n = 252	80% One-Sided Confidence Interval	95% One-Sided Confidence Interval
Keratoconus "A" parameter	0.052	0.102
Keratoconus "B" parameter	0.053	0.104
Keratoconus "C" parameter	5.07	9.92
n = 135		
Normal "A" parameter	0.012	0.024
Normal "B" parameter	0.042	0.083
Normal "C" parameter	4.03	7.88

ARC indicates anterior radius of curvature; PRC, posterior radius of curvature.

ABCD PROGRESSION DISPLAY

The Belin ABCD Progression Display (Fig. 2) was designed to graphically display the ABCD parameters over time with their associated 80% and 95% confidence intervals for both the normal population database (broken green and solid green lines, respectively) and keratoconic population database (broken red and solid red lines, respectively).[25,31,32]

The baseline examination can be marked and the time of treatment indicated (eg, cross-linking) and shown by the black and white checkered line. As long as each examination meets internal quality checks, up to 8 examinations over time can be displayed and are automatically loaded by the Pentacam. Each parameter can then be examined over time and compared to the individual confidence intervals.[31,32] Since CDVA is user-entered and not a machine-generated parameter, the "D" parameter does not have confidence intervals indicated. In addition to the graphical display of the primary ABCD parameters, 10 supplementary tomographic/topographic parameters are shown in tabular form below the graphical display: [Belin-Ambrosio Enhanced Ectasia Display (BAD) "D", Progression Index Average (PIavg), Ambrosio Relational Thickness Maximum (ART*max*), K*max*, Q value 6.0 mm zone front, Q value 6.0 mm zone back, ISV, IVA, IHD, and the ABCD classification].

The ABCD Progression Display is designed to assist the physician and allow for earlier detection and documentation of progression. A recent study (*Vinciguerra R. submitted for publication*) found that more than half of patients, already scheduled for cross-linking (based on >1 D change), could have been identified as progressive on average 5 months earlier utilizing the ABCD progression display. Progression in this study was defined as at least 2 of the ABC parameters above the 80% confidence interval or one of the ABC parameters above the 95% confidence intervals using the more stringent keratoconus database (red gates on the display). The display can also analyze historical data and as such can be used to review past records.

CLINICAL COORELATES

Figure 3 shows 7-year historical data from a 15-year-old (on initial diagnosis) with moderately advanced keratoconus. Initial BAD final "D" was 11.02 progressing to 15.76 and initial K*max* of 56.8 progressing to 64.7. The graphical display of the ABC

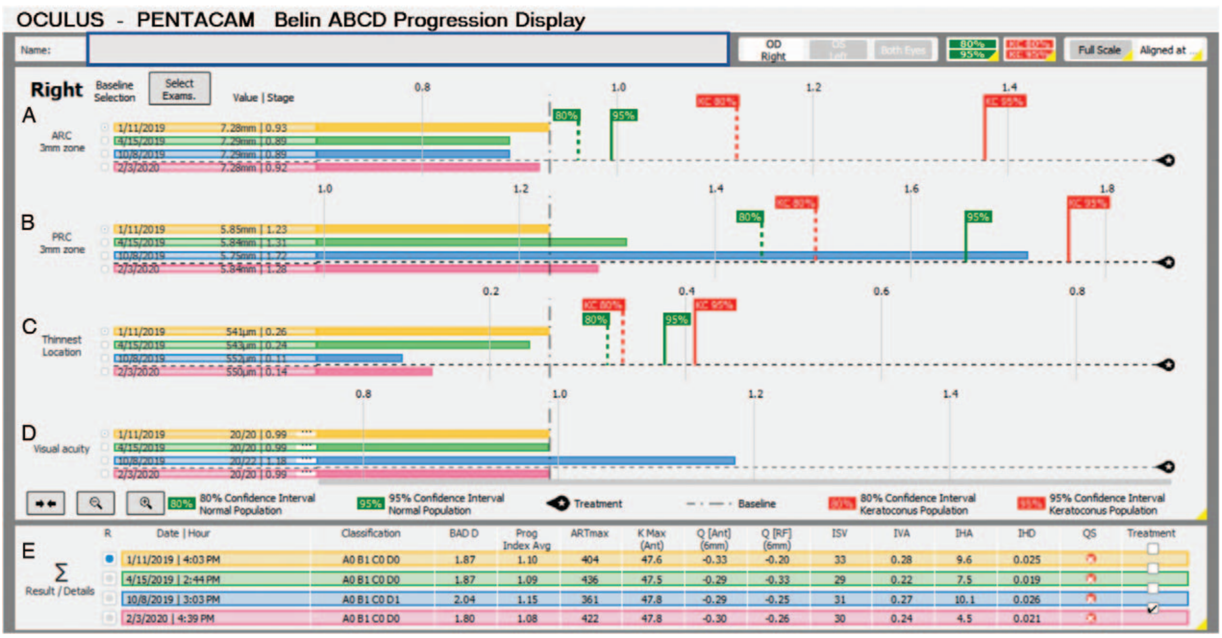

FIGURE 2. The Belin ABCD Progression Display. Four examinations are shown graphically over time. The first 3 are pretreatment (CXL) and the last examination is after CXL. This was a case of subclinical keratoconus (A0B1C0D, final "D" from the BAD of 1.87 at initial examination). Before CXL the anterior surface (A) was stable, but the posterior surface (B) change exceeded the 95% confidence interval for the normal population. All the confidence interval gates are removed after the CXL treatment. CXL indicates corneal cross-linking.

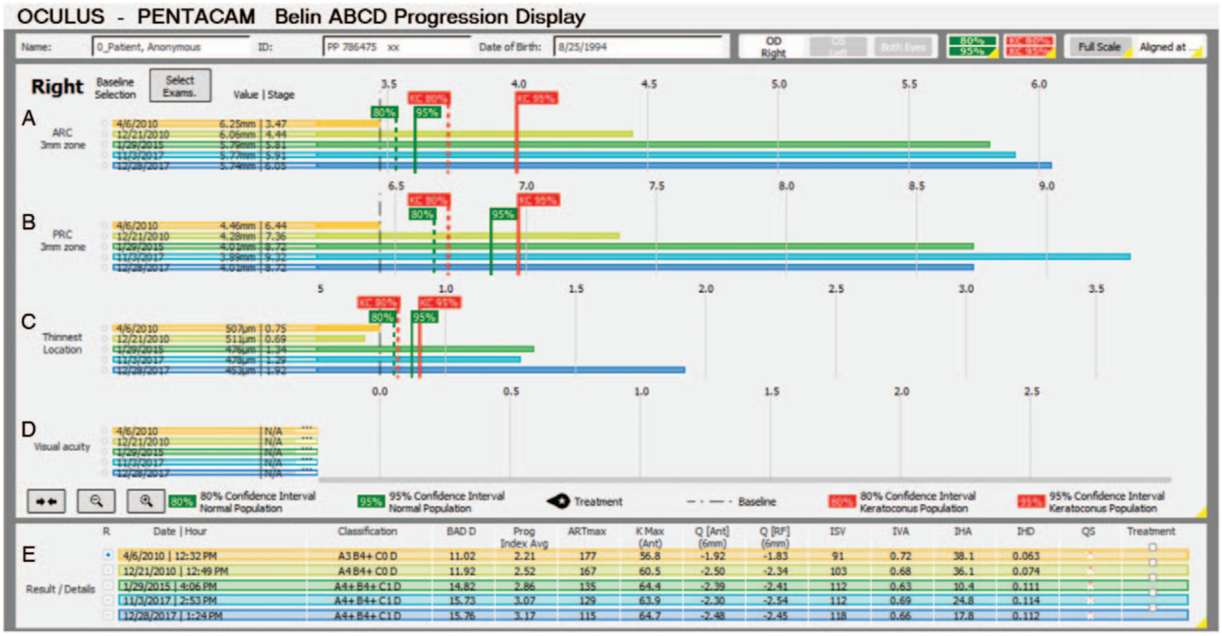

FIGURE 3. Fifteen-year-old patient on initial examination with advanced keratoconus (final "D" from the BAD of 11.02). Five examinations are displayed over a 7-year, 8-month interval showing progressive change on the anterior and posterior cornea and continued corneal thinning, all parameters well past the 95% confidence interval for both normal and keratoconic databases.

parameters (visual acuity was not entered) shows progressive change in all 3 parameters well past the 95% confidence intervals for both the normal (green) and keratoconic (red) population database.

Figure 4 shows a 13-month follow-up in a 15-year-old (on initial diagnosis) with early or subclinical disease. Initial final "D" from the BAD display is 2.92. Because of the young age and subclinical disease, only the green gates were selected by the user. Over the 13-month period (3 examinations) there is no significant change in K*max* or any of the anterior surface parameters. By the second examination, however, the "B" parameter (posterior corneal surface) shows a change above the 80% confidence interval and by the third examination well past the 95% confidence interval, documenting progressive change in spite of a stable K*max*.

Figure 5 shows two examinations, 15 months apart, from a 16-year-old patient with subclinical keratoconus. Initial final "D" from the BAD display was 2.77 progressing to 3.45, whereas the change in K*max* was just below the 1.0 D requirement used by most studies and insurance carriers. The progression display, however, documents progressive change in each of the 3 ABC parameters well past the 95% confidence intervals compared to the normal database (green gates). Although both red and green gates are displayed (machine default), the normal database is used

FIGURE 4. Thirteen-month follow-up of a 15-year-old with very early subclinical disease with an initial final "D" from the BAD of 2.92. Only the green gates are displayed since this is both a young patient and one with very early disease. In spite of a stable K*max*, the progression display shows highly significant progression on the posterior corneal surface.

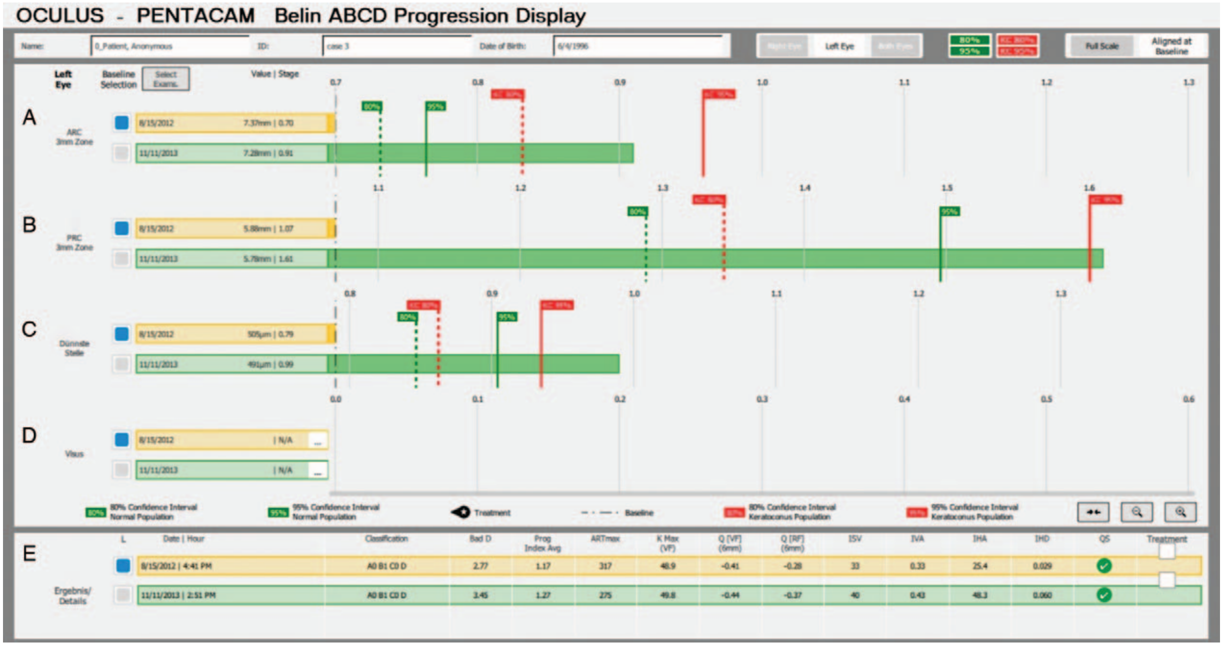

FIGURE 5. Two examinations 15 months apart in a 16-year-old with early ectatic change. The progression display shows highly significant change on both the anterior and posterior corneal surfaces as well and significant corneal thinning, in spite of a K*max* change below the standard 1.0 D change.

due to the young patient age and very mild nature of his ectatic change.

Figure 6 is of a 29-year-old with moderately advanced disease with initial final "D" from the BAD display of 7.36 and an initial K*max* of 51.2. The initial ABCD classification was A2B4C0 (visual acuity was not recorded). Four examinations over 16 months show only minimal change in the BAD display (final "D" 7.36 – 7.52) and K*max* actually decreasing from 51.2 to 50.3 diopters. While the "A" parameter shows no significant change, the change in the "B" parameter surpasses the 80% confidence interval, and the "C" parameter exceeds the 95% confidence interval.

The above examples highlight the limitations of using K*max* as the single determinant to document progression and as the sole requirement for insurance coverage. There is an apparent dissociation between changes in K*max* and the earliest detectable indicators of ectatic change. As there is increasing evidence that earlier intervention with CXL is associated with better outcomes

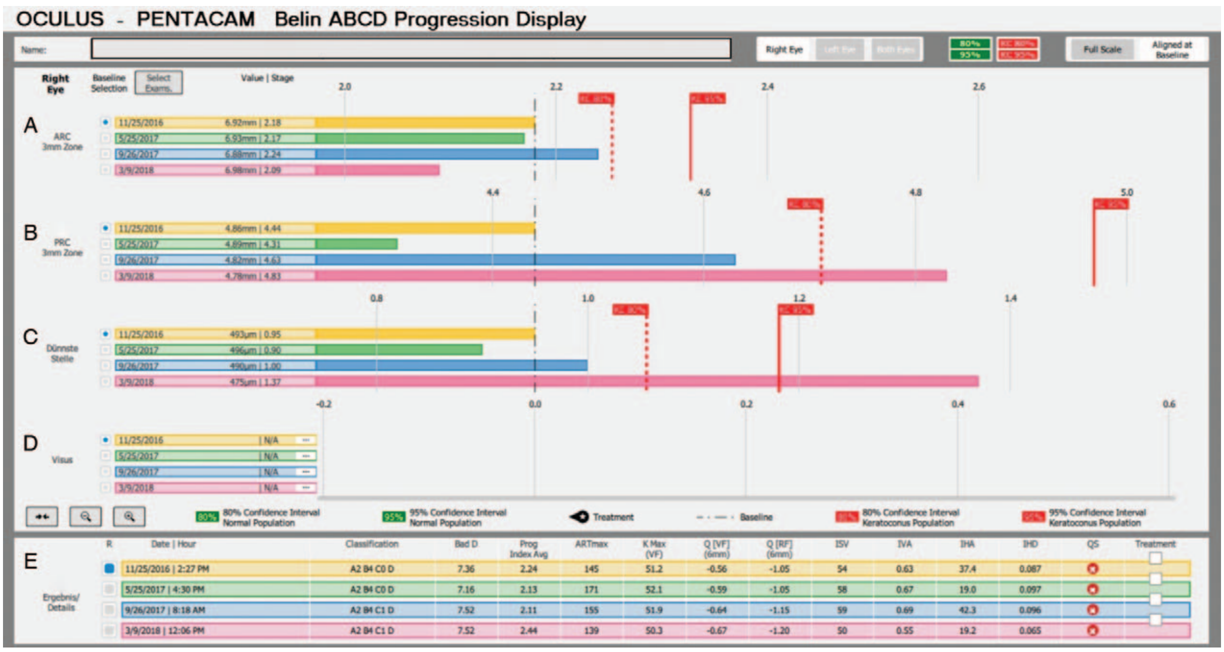

FIGURE 6. Twenty-nine-year-old patient with moderately advanced disease with an initial final ''D'' from the Bad of 7.36. The initial ABCD staging was A2B4C0 (visual acuity not recorded). Four examinations are shown over 16 months. There is minimal change in the final ''D'' (7.36 to 7.52), and K*max* shows a slight improvement (51.2–50.3), but the progression display shows significant progression on both the posterior cornea and corneal thickness.

TABLE 4. 80% and 95% One-sided Confidence Intervals for Corneal Thickness, ARC and PRC in Post-CXL Eyes

n = 41	80% One-Sided Confidence Interval	95% One-Sided Confidence Interval
Post-CXL "A" parameter	0.170	0.261
Post-CXL "B" parameter	0.136	0.208
Post-CXL "C" parameter	4.5	6.9

ARC indicates anterior radius of curvature; CXL, corneal cross-linking; PRC, posterior radius of curvature.

and fewer adverse events, there is a need for more robust progression determinants.

POST CROSS-LINKING EVALUATION

Although unequivocal data are missing on the exact turnover time of corneal collagen, corneal collagen undergoes a normal maturation and replacement, which raises the question of cross-linking's effective treatment duration. Although progression determinants for keratoconus before CXL have been established, less is known about the post-CXL natural course, and little is known about post-CXL progression and the possible need for repeat treatments. Currently, all the confidence interval gates on the Belin ABCD progression display are removed once a CXL treatment is performed (Fig. 2).

Post-CXL eyes, especially those submitted to protocols with epithelial removal (epi-off), undergo a healing response which can include tomographic changes, epithelial remodeling, corneal thickness changes, and haze formation.[33,34] Much of the healing response is thought to be complete by the end of the first post-operative year, but the exact time of stabilization is unknown and likely highly variable.[35] To determine appropriate progression parameters for post-CXL eyes, measurement noise after CXL had to be determined. In conjunction with the ELZA Institute (Zurich, Switzerland), the Ocular Cell Biology Group at the University of Geneva (Geneva, Switzerland) and the University of Arizona (Tucson, AZ), 41 eyes of 41 patients (average age 33 years, range 11–63) were enrolled. The average post-operative time since CXL was 13.5 months (range 9–23 months). All patients had a preoperative diagnosis of keratoconus without other comorbidities. Contact lens wear was discontinued a minimum of 1 week before measurements. Three separate and consecutive Pentacam measurements were taken, removing the patient from the device between each measurement. A minimum of 7.5 mm of corneal coverage and an acceptable Pentacam quality score was required for inclusion. Both pooled variance estimates and 1-sided confidence intervals were computed using SPSS version 23 and STATA 13 statistical software (same analysis used in current ABCD progression display). Both 80% and 95% one-sided confidence intervals were determined (Table 4).

Post-CXL data will be incorporated in the next iteration of the ABCD Progression Display (Fig. 7), where 80% and 95% confidence intervals for post-CXL changes will be shown by blue gates. These gates will only appear if a treatment (CXL) is marked and the post-CXL gates will only appear for the examinations after the treatment date. Of note and concern, however, is that our initial measurement noise post-CXL is significantly higher than the pretreatment values. This may reflect incomplete healing, residual haze, or a testing period that was too early post-CXL. We are currently evaluating patients at least 24 months post-CXL with additional and larger databases.

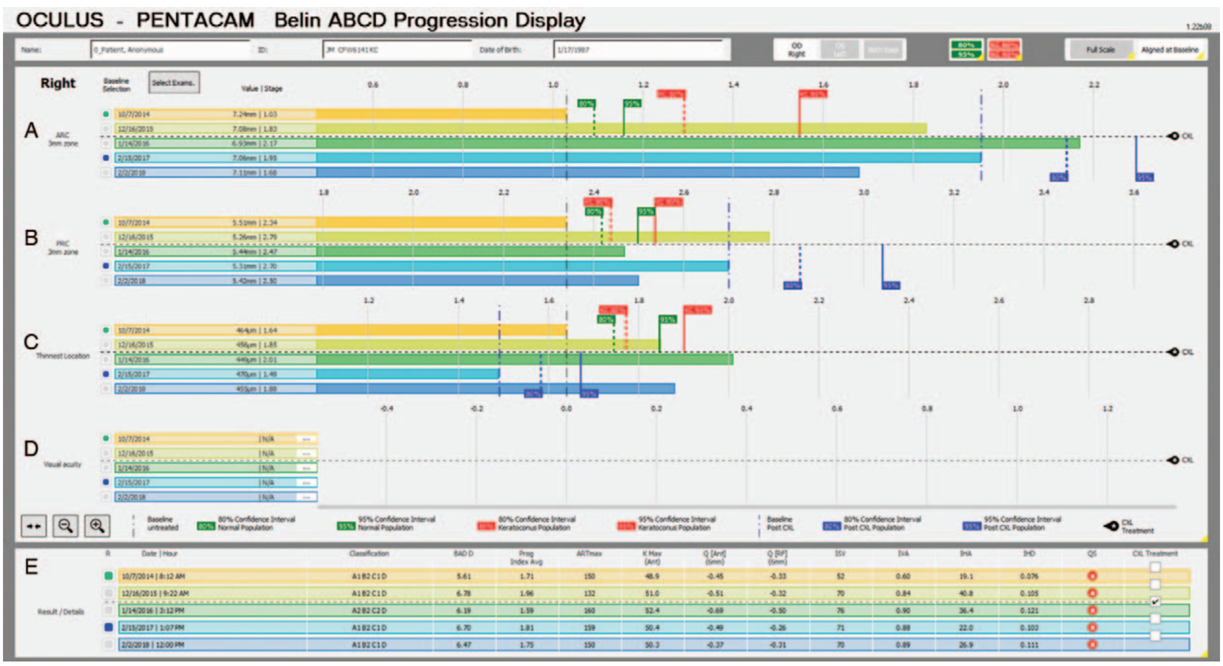

FIGURE 7. Beta version of the Belin ABCD progression display with the post-CXL confidence interval gates. The post-CXL gates are displayed in blue and appear under the dotted line (line indicated CXL treatment was performed). A new comparative baseline is also established as shown by the blue vertical dashed line. CXL indicates corneal cross-linking.

CONCLUSIONS

Multiple parameters and methods have been proposed to diagnose early ectatic disease and to define progressive disease. Nevertheless, the Global Consensus on Keratoconus and Ectatic Diseases (2015) stated that there is no consistent or clear definition of ectasia progression and acknowledged that specific quantitative data is lacking.[7] In this sense, a more global assessment of the cornea would be more appropriate.

The ABCD staging system incorporates anterior and posterior curvature, thinnest pachymetric values, and distance visual acuity. As it includes posterior curvature and thickness measurements based on the thinnest point, rather than apical measurements, this staging system better reflects the anatomical changes seen in keratoconus.[25] Moreover, corneal thickness, anterior and posterior quantitative curvature values can serve as suitable determinants for keratoconus progression.[30–32] The capacity for early diagnosis and determining progression at an earlier stage should allow for therapeutic intervention at an earlier stage, instead of later intervention with the potential for irreversible vision loss.

REFERENCES

1. Nottingham J. Practical Observations on Conical Cornea: and on the Short Sight, and Other Defects of Vision Connected with it. London: J Churchill; 1854.
2. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297–319.
3. Krachmer JH, Feder RS, Belin MW. Keratoconus and related non-inflammatory corneal thinning disorders. *Surv Ophthalmol*. 1984;28:293–322.
4. Castro-Luna G, Pérez-Rueda A. A predictive model for early diagnosis of keratoconus. *BMC Ophthalmol*. 2020;20:263.
5. Torres-Netto EA, Al-Otaibi WM, Hafezi NL, et al. Prevalence of keratoconus in paediatric patients in Riyadh, Saudi Arabi. *Br J Ophthalmol*. 2018;102:1436–1441.
6. Amsler M. Keratocone classique et keratocone fruste; arguments unitaires. *Ophtalmologica*. 1946;111:96–101.
7. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic disease. *Cornea*. 2015;34:359–369.
8. Wittig-silva C, Chan E, Islam FM, et al. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. 2014;121:812–821.
9. O'Brart DPS, Chan E, Samaras K, et al. A randomized, prospective to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen crosslinking to halt progression of keratoconus. *Br J Ophthalmol*. 2011;95:1519–1524.
10. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev*. 2015;3:CD010621.
11. Barbara R, Castillo JH, Hanna R, et al. Keratoconus expert Expert Meeting, London, 2014. *J Kerat Ect Cor Dis*. 2014;3:141–158.
12. Mahmoud AM, Nuñez MX, Blanco C, et al. Expanding the cone location and magnitude index to include corneal thickness and posterior surface information for the detection of keratoconus. *Am J Ophthalmol*. 2013;156:1102–1111.
13. De sanctis U, Loiacono C, Richiardi L, et al. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. *Ophthalmology*. 2008;115:1534–1539.
14. Tomidokoro A, Oshika T, Amano S, et al. Changes in anterior and posterior corneal curvatures in keratoconus. *Ophthalmology*. 2000;107:1328–1332.
15. Lopes BT, Ramos IC, Faria-Correia F, et al. Correlation of topometric and tomographic indices with visual acuity in patients with keratoconus. *J Kerat Ect Cor Dis*. 2012;1:167–172.
16. Guber I, McAlinden C, Majo F, et al. Identifying more reliable parameters for the detection of change during the follow-up of mild to moderate keratoconus patients. *Eye and Vis 4*. 2017;24. https://doi.org/10.1186/s40662-017-0089-3.
17. Kanellopoulos AJ, Asimellis Asimellis G. Revisiting keratoconus diagnosis and progression classification based on evaluation of corneal asymmetry indices, derived from Scheimpflug imaging in keratoconic and suspect cases. *Clin Ophthalmol*. 2013;7:1539–1548.
18. Suzuki M, Amano S, Honda N, et al. Longitudinal changes in corneal irregular astigmatism and visual acuity in eyes with keratoconus. *Jpn J Ophthalmol*. 2007;51:265–269.
19. Sandali O, El sanharawi M, Temstet C, et al. Fourier-domain optical coherence tomography imaging in keratoconus: a corneal structural classification. *Ophthalmology*. 2013;120:2403–2412.
20. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric corneal collagen cross-linking in children and adolescents. *J Refract Surg*. 2012;28:753–758.
21. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. *Invest Ophthalmol Vis Sci*. 2012;53:927–935.
22. Sorkin N, Varssano D. Corneal collagen crosslinking: a systematic review. *Ophthalmologica*. 2014;232:10–27.
23. Meiri Z, Keren S, Rosenblatt A, et al. Efficacy of corneal collagen cross-linking for the treatment of keratoconus: a systematic review and meta-analysis. *Cornea*. 2016;35:417–428.
24. Sklar JC, Wendel C, Zhang C, et al. Did collagen cross-linking reduce the requirement for corneal transplantation in keratoconus? The Canadian Experience. *Cornea*. 2019;38:1390–1394.
25. Belin MW, Duncan JK, Keratoconus. The ABCD Grading System. *Klin Monbl Augenheilkd*. 2016;233:701–707.
26. Ambrosio R, Belin MW. Imaging of the cornea: topography vs tomography. *J Refract Surg*. 2010;26:847–849.
27. Belin MW, Villavicencio OF, Ambrosio Jr . Tomographic parameters for the detection of keratoconus: suggestions for screening and treatment parameters. *Eye Contact Lens*. 2014;40(6):326–330.
28 Kanellopoulos AJ, Asimellis G. OCT corneal epithelial topographic asymmetry as a sensitive diagnostic tool for early and advancing keratoconus. *Clin Ophthalmol*. 2014;8:2277–2287.
29. Khachikian SS, Belin MW. Posterior elevation in keratoconus. *Ophthalmology*. 2009;116:816.
30. Duncan JK, Belin MW, Borgstrom M. Assessing progression of keratoconus: novel tomographic determinants. *Eye Vis (Lond)*. 2016;3:6.
31. Belin MW, Meyer JJ, Duncan JK, et al. Assessing progression of keratoconus & crosslinking efficacy: The Belin ABCD Progression Display. *Int J Kerat Ect Cor Dis*. 2017;6:1–10.
32. Belin MW, Duncan J, Ambrosio Jr , et al. A new tomographic method of staging /classifying keratoconus: The ABCD Grading System. *Int J Keratoconus Ectatic Dis*. 2015;4:85–93.
33. Belin MW, Lim L, Rajpal RK, et al. Corneal cross-linking: current USA status—Corneal Society Guidance Document. *Cornea*. 2018;37:1218–1225.
34. Grisevic S, Gilevska F, Biscevic A, et al. Keratoconus progression classification one year after performed crosslinking method based on ABCD Keratoconus Grading System. *Acta Inform Med*. 2020;28:18–23.
35. Imbornoni LM, McGhee CNJ, Belin MW. Evolution of keratoconus: from diagnosis to therapeutics. *Klin Monbl Augenheilkd*. 2018;235(6):680–688.

