What was known before:

Keratoconus may continue to progress even after cross linkage (CXL) Identifying eyes that have progressed can be difficult Criteria to define progression vary, with no agreed definition

What this study adds:

The rate of keratoconus progression following CXL varies with the criteria adopted We have developed 95% Limits of Agreement for keratometry to account for all stages of keratoconus severity We have compared this method with results using standard definitions

# A comparison of keratoconus progression following collagen cross-linkage using standard or personalised keratometry thresholds

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Running header: Keratoconus progression

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**Abstract**

**Objective:** To define how estimates of keratoconus progression following collagen cross-linking (CXL) vary according to the parameter selected to measure corneal shape.

**Materials and Methods:** We estimated progression following CXL in 1677 eyes. We compared standard definitions of keratoconus progression based on published thresholds for Kmax, front K2, or back K2, or progression of any two of these three parameters, with the option of an increased threshold for Kmax values ≥55D. As corneal thickness reduces unpredictably after CXL, it was excluded from the principal analysis. We then repeated the analysis using novel adaptive estimates of progression for Kmax, front K2, or back K2, developed separately using 6463 paired readings from keratoconus eyes, with a variation of the Bland-Altman method to determine the 95% regression-based limits of agreement (LoA). We created Kaplan-Meier survival plots for both standard and adaptive thresholds. The primary outcome was progression five years after a baseline visit 9-15 months following CXL.

**Results:** Progression rates were 8% with a standard (≥1.5D) threshold for K2 or 6% with the static multi-parameter definition. With a ≥1D threshold for Kmax, the progression was significantly higher at 29%. With adaptive Kmax or K2, the progression rates were similar (20%) but less than with the adaptive multi-parameter method (22%).

**Conclusions:** Estimates of keratoconus progression following CXL vary widely according to the reference criteria. Using adaptive thresholds (LoA) to define the repeatability of keratometry gives estimates for progression that are markedly higher than with the standard multi-parameter method.

**Key words:** Cornea, keratoconus, corneal cross-linking, Kaplan-Meier estimate

## Introduction

Keratoconus is a common cause of visual disability in young people, with a prevalence in some populations estimated to be as high as 1:50.[1–3] It is characterised by progressive corneal thinning and distortion with visual loss.[4,5] Corneal cross-linking (CXL) is a photochemical treatment that can arrest progression.[6–9] However, estimates of treatment success vary (reported range 90.1% to 98.3%) in part due to the different definitions of progression adopted, with no consensus on the best parameters to use.[7,10–12] The heterogeneity of definitions of progression and inconsistent or absent reporting of key outcome measures, is highlighted in a recent systematic review.[13]

The primary options to identify keratoconus progression are to document an increase in corneal power, a reduction in corneal thickness, or a loss of visual acuity, considered singly or combined. Keratometry changes can incorporate either a single parameter, such as an increase in the front K2 of ≥1.5D or an increase in Kmax of ≥1D, with a single threshold applied across the full spectrum of disease severity. However, as anterior keratometry values increase, the measurement repeatability reduces.[14–17] A modification that recognises this phenomenon is to incorporate a second threshold, typically for a keratometry value of >55D, above which the threshold increases,[14] although with a low corneal power progression would still be missed if small (<1D), but repeatable, changes are ignored. A solution to this would be a personalised threshold that considers all grades of corneal power.

In this study, we compared estimates of keratoconus progression following CXL derived when we apply different criteria to a single dataset. We first used standard definitions of keratometry progression for Kmax, front K2, or back K2, or combinations of these keratometry values, with the option of an increased threshold for front K2 for values >55D. We then compared these

results with a novel estimate of progression based on the 95% regression-based limits of agreement (LoA) for all values of Kmax, front K2, or back K2. However, we excluded pachymetry from our estimates due to the unpredictable corneal thinning after CXL and measurement uncertainty from stromal compaction and light scatter.[6,18–20] We used Kaplan-Meier survival plots to compare the progression rates.

## Methods

Moorfields Eye Hospital NHS Foundation Trust approved the study (references CA17/CED/03 and 22/PR/0249), which complied with the Interventional Procedure Guidance (IPG466) of the National Institute for Health and Care Excellence (NICE) and adhered to the tenets of the Declaration of Helsinki. We based the first diagnosis of keratoconus on computerised corneal tomography parameters, such as the Belin-Ambrosio analysis of posterior corneal ectasia (Oculus HD, Optikgeräte GmbH, Wetzlar, Germany), evaluated by experienced clinicians based in a dedicated keratoconus clinic. For the cohort who had CXL we only included participants who were ≥13 years of age who had epithelium-off accelerated pulsed high-fluence CXL (30 mW/cm2, 1.5 sec on\off cycle, energy 7.2 J/cm2 (Avedro KXL, San Clemente, USA) between January 2014 and September 2021. We no longer use the Dresden protocol at our centre. We included both eyes if they met the inclusion criteria. Demographic data included age, sex, and self-identified ethnicity. Exclusion criteria included pregnancy or breastfeeding, uncontrolled ocular surface disease, or a minimum corneal thickness measurement before treatment of <375 µm. We also excluded patients with previous corneal surgery, pellucid marginal corneal degeneration or other ectatic corneal disorders. We routinely scheduled slit-lamp examination and Scheimpflug corneal tomography at 6 and 12 months after treatment and then as required for up to six years, with data recorded on an electronic spreadsheet. For the progression analysis, we defined the baseline visit as an examination 9 to 15 months after CXL.[21] We then recorded any change from the baseline keratometry to the subsequent measurements and

excluded eyes that did not have at least one valid scan after the baseline visit. We then generated Kaplan-Meier survival curves for all the parameters of interest, with progression defined as an increase in the parameter beyond the predefined thresholds (Table 1).

We used an overlapping dataset of repeat scans performed at the same visit for 9341 eyes with keratoconus to define the adaptive thresholds for keratometry. We selected the first two scans from each visit with an 'OK' Pentacam quality score (QS), so there was no variation in quality between eyes or pairs of scans. After exclusions, there were 6463 paired readings available for calculation of the LoA. We used a variation of Bland Altman analysis to generate regression-based limits of agreement (LoA) for the whole range of keratoconus severity for Kmax, front K2 and back K2 (Supplementary text); this is an accepted method when the standard deviation of repeated measurements varies according to the magnitude of the measurement.[22] Then, for each corneal parameter, we used steepening of keratometry above the 95% LoA as our definition of progression. We included pachymetry in our evaluation of the LoA because it is relevant when assessing suitability for repeat CXL, but it was excluded from our primary analysis of progression as CXL can induce corneal thinning. We excluded visual acuity as it was not measured objectively on multiple occasions at each visit and thus was not amenable to this method.

For statistical analysis, we performed regression-based Bland Altman analysis in RStudio version 1.3 (https://www.rstudio.com) and a non-parametric estimation of the risk of keratometric progression using the Kaplan-Meier method (Stata 17, StataCorp LP, Texas, USA). We used McNemar's test to compare corresponding eyes five years following the baseline visit to establish whether the results from any two definitions of progression were statistically significantly different.

## Results

We evaluated 5035 eyes that had CXL. Following exclusions, 1677 eyes (1217 patients) were available for survival analysis. Of these patients, 72% were male, with a self-declared non-white ethnicity in 373 (40%) of the 934 patients with available data. Figure 1 shows the reasons for exclusion from the survival analysis. At the baseline appointment 9 to 15 months after CXL the mean keratometry values were 57.7D for Kmax (standard deviation (SD) 8.0D, range 42.8D to 92.4D), 50.2D for front K2 (SD 5.2D, 36.7D to 74.4D), -7.6D for back K2 (SD 1.0D, -12.0D to 5.3D), and 447.8μm for minimum pachymetry (SD 40.7μm, 315μm to 579μm). Of the 1677 eyes in the dataset used for the survival analysis, 11.9% had a K2 at baseline of <45D (mild keratoconus).

Using 6463 paired readings of eyes, we generated v-shaped Limits of Agreement (LoAs) for each of the four corneal parameters. The associated regressions demonstrated statistical significance ($P<0.001$). The Bland Altman plots for Kmax, front K2 and back K2 and minimum corneal pachymetry are shown in Figure 2. For each plot, the red dashed lines represent the 95% LoA, which are v-shaped, with the LoA increasing as the value of mean Kmax and front K2 increases and the value of the back K2 and pachymetry decreases, suggesting that the repeatability of the readings reduces in more advanced disease. The LoA for each dioptre of keratometry for Kmax, front K2 and back K2 are shown in Supplementary Table 2.

The Kaplan-Meier survival curves for progression defined using six different keratometry indices (Table 1) are shown in Figure 3, with confidence intervals added (Supplementary Figure 4 A and B). The stepwise drop in survival at some points in the curves may result from predefined follow-up intervals. For the fixed keratometry definition of an increase in Kmax of ≥1D, the proportion of eyes that had progressed at five years after the baseline visit was the highest value in the series at 29%, or 18% if we increased the fixed threshold for Kmax to ≥1.5D (data

not shown). However, with a fixed definition of progression of an increase in K2 of ≥1.5D or the static multi-parameter definition of progression, the progressed proportion was lower at 8% and 6%, respectively. The results for all three thresholds were similar for the adaptive methods, with 22% of eyes progressing when we used the adaptive Kmax definition, 22% when we used the adaptive K2 definition, and 20% with the adaptive multi-parameter method. When we use the McNemar test to compare progression in these groups, we cannot conclude that the difference between adaptive K2 and adaptive Kmax are different (P=0.9468). However, the progression identified with the adaptive multi-parameter and adaptive K2 methods differ significantly (P<0.001).

When we performed a survival analysis for pachymetry with progression-defined thinning exceeding the adaptive threshold, there was an approximately 32% probability of progression five years after the baseline visit (Supplementary Figure 4C).

## Discussion

The primary method to identify keratoconus progression is to monitor for changes in corneal shape, particularly an increase in keratometry. However, we have shown that with the same dataset, different parameters, used singly or in combination, give widely different estimates. The accuracy of keratometry reduces as the cornea becomes more ectatic and using one threshold will not identify changes in keratometry with the same accuracy over the whole range of keratoconus severity.[15–17,23] As a result, with one threshold, there is a tendency to over-diagnose progression in steep corneas and miss a repeatable increase in keratometry in flat corneas. A partial solution to this problem is to use a higher threshold for more advanced disease.[14,15] We have refined this approach by identifying the regression-based 95% limits of agreement (LoA) for keratometry to derive thresholds that can be applied individually to all corneal curvature values. We have then used these adaptive thresholds to quantify keratometry changes in a

population following CXL and then compared the rate of progression with values obtained with standard methods and thresholds.[7,10,11,24,25] We have also incorporated a delayed time point for baseline observations to allow any acute changes of corneal shape following CXL to stabilise.[6,18–20]

Our results show that keratoconus can continue to progress after epithelium-off accelerated pulsed high-fluence CXL for at least five years following the baseline, but with a wide range (6% to 29%) in the estimates of progression depending on the parameter used. For example, with a static front K2 threshold of ≥1.5D, or the multi-parameter method, the number of eyes that had progressed five years after the baseline visit was similar at 6% and 8%, respectively. However, with a static Kmax threshold of ≥1.0D, the progression rate was much higher at 29%, although this reduced to 18% if we increased this threshold to ≥1.5D. In contrast, the results using the three adaptive thresholds were more uniform at 20% to 22%. Importantly, because there is no reference standard (ground truth) to define progression, we can only compare the results obtained with the different methods; we do not know which is the most accurate or best represents progression. It is also difficult to compare our estimates with other case series due to the variety of thresholds used in the literature, the lack of an agreed time-point for the baseline readings, and variation in the reported follow-up. Overall reported values have ranged between 2% and 20%,[7,26–32] and we previously reported that when measured from the time of treatment and with a static multi-parameter method, progression was between 1.9% and 2.4% two years after treatment.[7]

Monitoring for keratoconus progression after CXL is to determine whether the disease has stabilised or whether a repeat CXL is indicated. Multiple surgeon and patient factors can influence the decision to undergo retreatment, including patient reluctance following the experience of the first procedure with little patient-perceived benefit, insufficient residual stromal

thickness, and the relative lack of clinical outcome data to support the effect of repeat CXL. We found only a small number of reports of retreatment rates after CXL, which varied between 4 in 131 eyes (3%) to 45 in 230 eyes (20%).[25,33] Interestingly, in our series, despite a minimum value for progression at five years of 6%, only a minority of eyes (0.5%) had a repeat CXL, suggesting CXL retreatment is not a good proxy for keratometric progression after CXL and that different clinical criteria apply when considering treatment with primary CXL as opposed to repeat CXL. As yet, there is also no agreement on when to perform retreatment. However, the threshold differs from primary CXL, with criteria ranging from a >2D increase in Kmax within one year or an increase in Kmax of >1D at two subsequent follow-up visits more than one year following the primary treatment.[25,33]

The strengths of our study include the large sample size available to develop the keratometry LoAs and the large cohort with extended follow-up after CXL for validation. For the first time, we have quantified the effect of using different keratometry parameters on the estimates of progression. The limitations of this study are the high proportion of eyes with incomplete data and follow-up, a risk inherent when analysing data retrospectively. We do not know if the characteristics of the population censored from the survival curves are the same as the included data. Because of the high attrition rate, our results best serve as a comparative analysis of the included parameters as opposed to a statement of their relative utility to identify the actual rate of progression, which is unknown. We included older children and young adults, although there may be differences in their risk of progression. Although we confirmed that a proportion of eyes had thinned after CXL, it is unclear if this is an effect of CXL or the progression of keratoconus, and the role of pachymetry when monitoring for continued keratoconus progression after CXL is uncertain. Monitoring for a change is visual acuity, not included in this study, may also have a role in the detection of progression. We defined our new definitions of progression as keratometry crossing an adaptive threshold after one appointment; requiring sustained

progression across at least two examinations may be more accurate. Finally, an unknown proportion of the eyes in the original cohort with primary CXL may not have progressed even if they did not have this treatment.[10] These stable eyes would also be unlikely to progress further after their primary CXL.

In conclusion, a missed diagnosis of keratoconus progression can lead to visual loss. We have confirmed that the choice of parameter and the associated threshold used to define progression will affect estimates of treatment failure following CXL. With a single or multi-parameter threshold definition of keratoconus progression, the clinician could misclassify measurement error in advanced disease as progression and miss repeatable changes in keratometry in early disease. Therefore, we recommend adaptive thresholds as a consistent and personalised method to identify keratoconus progression. Until this data is incorporated into tomography summary displays, we encourage clinicians to refer to the estimates of the LoA for each dioptre of keratometry provided in Supplementary Table 2.

Supplemental material is available at Eye's website.

**Data availability statement:** Additional data are available from the corresponding author on reasonable request

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**Figure 1.** Reasons for exclusions from the survival analysis following collagen cross linking for progressive keratoconus. K keratometry

**Figure 2.** Bland-Altman plots for Kmax, front K2, back K2, and minimum pachymetry with 95% limit of agreement for 6463 paired readings. The red dashed lines show the 95% regression-based limits of agreement (LoA) for each parameter. The blue dashed lines on the Kmax and front K2 plots represent the standard thresholds defined in Table 1. The rug plots on the vertical and horizontal axes of each chart show the frequency of the data. For Kmax and front K2, the LoA increases as the mean keratometry value in dioptres increases. For back K2, the LoA increases as back corneal negative power (D) increases. The LoA for thinnest pachymetry is also greater for the thinner corneas. K keratometry.

**Figure 3.** Kaplan Meier survival curves based on 1677 eyes following corneal cross-linking and using six different definitions of progression. The results using the three adaptive methods give similar rates of progression (middle three lines). However, with the fixed threshold method, the use of Kmax gives a markedly higher rate (bottom line) compared to the K2 and multiparameter methods (top two lines), that both indicate a lower rate of progression than the adaptive methods. Two years after the baseline visit there were 1451 eyes at risk, 983 at 3 years, 674 at 4 years, and 307 at 5 years.

**Figure 4 (supplemental).** Survival plots with confidence intervals for the two general methods used to calculate progression

**Table 1.** Definitions of keratoconus progression based on fixed or adaptive thresholds

**Table 2 (supplemental).** 95% limits of agreement for Front K2, Back K2 and Kmax.
A) For the static methods there is overlap of the confidence intervals for the static single threshold K2 and the dual threshold multi-parameter method, but not for the static single threshold Kmax method. The survival rates calculated using the fixed threshold for K2 and the dual threshold multi-parameter methods are also similar, but both are significantly different from the fixed threshold Kmax method.
B) There is an overlap of the confidence intervals for the three adaptive thresholds. This suggests that there is not a statistically significant difference between the survival rates for the three adaptive threshold methods. However, when we use the McNemar test to compare progression in these groups, we cannot conclude that the difference between adaptive K2 and adaptive Kmax are different (P=0.9468). The progression identified with the adaptive multi-parameter method and the adaptive K2 methods are significantly different (P<0.001). K keratometry.
C. Survival analysis for pachymetry, with progression defined as thinning exceeding the adaptive threshold. There was an approximately 32% probability of progression five years after the reference visit.

**Supplementary Text.** Adaptive Thresholds: A variation of Bland Altman analysis was used to generate regression-based limits of agreement (LoA)

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