# Pentacam HR Criteria for Curvature Change in Keratoconus and Postoperative LASIK Ectasia

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## ABSTRACT

**PURPOSE:** To determine criteria for keratoconus or postoperative LASIK ectasia progression or improvement based on Pentacam HR (Oculus Optikgeräte GmbH) measured steepest corneal curvature.

**METHODS:** Sixty-one eyes from 41 patients with keratoconus or postoperative LASIK ectasia were evaluated. Each eye was measured 5 times with the Pentacam HR during the same clinic visit and the random measurement variations of Rmin(back) and maximal keratometry (Kmax; mathematically linked to Rmin[front]) were statistically analyzed. Confidence levels for diagnosing true curvature change were determined for 3 typical clinical situations differing by the number of available Pentacam measurements.

**RESULTS:** With a single past and single present Pentacam HR measurement available (situation 1+1), the 95% confidence levels of true change for ΔKmax, ΔRmin(front), and ΔRmin(back) were 1.51 diopters (D), 0.162 mm, and 0.290 mm, respectively. With one prior and the average of five present Pentacam measurements (situation 5+1), the 95% confidence levels of true change for ΔKmax, ΔRmin(front), and ΔRmin(back) were 1.17 D, 0.126 mm, and 0.225 mm, respectively. With the average of five past and five present measurements (situation 5+5), the 95% confidence levels of true change for ΔKmax, ΔRmin(front), and ΔRmin(back) were 0.68 D, 0.072 mm, and 0.130 mm, respectively.

**CONCLUSIONS:** Steepest corneal curvature changed with 95% confidence if the difference between single past and present Kmax exceeded 1.51 D. With the advantage of five past and five present measurements, 95% confidence of real Kmax change occurs at a 0.68-D difference. [*J Refract Surg*. 2012;28(12):890-894.]

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Determining whether corneas with keratoconus or postoperative LASIK ectasia have worsened or improved after treatment such as intrastromal corneal rings and corneal collagen cross-linking (CXL) is an important issue. Wollensak et al[1] initially reported a flattening effect after CXL in patients with keratoconus as seen by the maximal keratometry (Kmax) reading measured by Technomed (Carl Zeiss Meditec, Jena, Germany) topography. Koller et al,[2] from the same institute, analyzed the effect of CXL on a large number of statistics generated using the Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) and showed that with CXL, the most statistically significant correlate of cross-linking effect was change of the steepest corneal curvature as described by Kmax or Rmin(front). Raiskup-Wolf et al,[3] also from the same institute, reported CXL-induced flattening of Kmax in a study of 241 patients with progressive keratoconus followed up to 6 years after treatment. They found an average flattening of steepest K of 2.68 diopters (D) in 142 patients at 1 year postoperative, 2.21 D in 66 patients at 2 years, and 4.48 D in 33 patients at 3 years postoperative. The work of that institute is statistically convincing, uses maximal corneal curvature as a metric, and shows that CXL changes continue to increase beyond 1 year. Many others, with the first corroborating study performed by Caporossi et al,[4] document the effect of CXL. But, as research continues with new CXL variations such as epithelium-on, chemically augmented epithelium-on, shorter exposure/higher ultraviolet A (UVA) intensity, and non-riboflavin CXL, it is important to assess the accuracy of the main CXL effect metric especially for the proof of effect in smaller, shorter duration CXL studies.

The repeatability of Pentacm HR Scheimpflug topography has been studied by a number of researchers.[5-7] Savini et al[8] studied the repeatability of Galilei Scheimpflug corneal

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topography (Ziemer Ophthalmic Systems AG, Port, Switzerland) curvature measurements, and their statistical methods are similar to our methods. However, these repeatability studies were not performed in ectatic corneas. Aside from the study by Koller et al,[2] in which 10 patients had repeated measurements and significant increase/decrease was determined to be ±1.00 D, no published studies have reported the accuracy of Scheimpflug-measured Kmax or related measurements in cases of known keratoconus or postoperative LASIK ectasia.

The purpose of this study was to determine a criterion to diagnose progression or improvement of keratoconus or postoperative LASIK ectasia.

## PATIENTS AND METHODS

Sixty-one eyes from 40 patients were included in the present study. Patients were all referred for possible participation in the US Food and Drug Administartion–monitored corneal collagen CXL clinical trial (NCT01325298) conducted in the office of one author (R.L.E.). The clinical trial was performed under written guidance and permission of the Institutional Review Board of Mercy Health System, Janesville, Wisconsin. All study patients gave consent to have measurements taken with the Pentacam HR (software version 6.1.7600) as part of the preoperative CXL eligibility examination.

Study patients discontinued contact lens wear for at least 2 weeks. Pentacam HR measurements were taken without use of topical anesthesia and with the patient keeping both eyes open. Five measurements per eye were taken in a single office visit with a break taken between each measurement in which the patient was instructed to sit back and shift in the chair and become repositioned for the next measurement. Patients were aligned, asked to blink several times, instructed to look at the red light inside the machine, instructed to blink again and hold still, and a picture was taken. Patients were instructed to close their eyes between shots for at least 10 seconds to moisten the eyes. The Pentacam device detects slight misalignment and instructs the technician on which way to move the alignmemt joy stick and fires instantly on good alignment. The Pentacam also comments on the quality of the picture noting "OK," "blinking," "nose," or "alignment." All Pentacam shots used in this study had an "OK" rating. The Pentacam was calibrated 2 months before the beginning of the study. Kmax was between 45.00 and 70.00 D in all cases as per the initial study protocol. Pachymetry exceeded 400 µm in all cases.

All eyes included in the present study had a history of worsening vision and increasing astigmatism or myopia associated with worsening keratoconus or postoperative LASIK ectasia.

The Pentacam HR measurement Kmax (and its mathematically related Rmin[front] [minimal radius of curvature of the corneal front surface]) and Rmin(back) (minimal radius of curvature of the corneal back surface) were analyzed using a double-repeated measures approach. Maximum keratometry (Rmin[front]) and Rmin(back) in the data set passed the Kolmogorov-Smirnov (D statistic) normality test, as there was no significant deviation from normality for each of the trial-by-eye combinations. For each of the dependent variables, Kmax (Rmin[front]) and Rmin(back), the mixed effects model included independent class variables for eye (right or left), trial (1-5), and the two-way interaction of eye and trial. The two-level compound symmetry variance/covariance structure was used such that the total variability from the data contained the inter-patient variability as well as the intra-patient variability, which was further decomposed into inter-eye variability within each patient and trial-to-trial variability within each eye of each patient. The trial-to-trial variability (within each eye and each patient) was used to characterize the probability distribution for the change over time.

In the actual data set, five trials per eye within each patient were conducted to increase the precision, as the average of the five trials was taken for the comparison of that at the next visit, which would also be averaged from five trials. However, fewer trials than five at each visit could have been conducted, but both the precision (benefit) and the cost decreased with the increased number of trials. Utilizing the data set, the precision for each of the potential scenarios from 1 to 5 trials at each visit was simulated and evaluated; the results were summarized in terms of relative efficiency based on the variances. The statistical analysis was carried out using SAS version 9.2 (SAS Institute, Cary, North Carolina).

After the estimation of the trial-to-trial variability was established, the standard error (SE) of the difference in means between two separate visits, each with multiple trials, could be derived. The SE is a function of the numbers of trials from both visits, where SE would be smaller for five trials per visit, as compared to less than five trials performed for each of the visits. Therefore, depending on the number of trials conducted for each of the visits for future studies (from 5+5 to 1+1), a *t* distribution could be established for the difference in means with the variability (characterized by SE), which depends on the number of trials per visit. The efficiency of the *t* tests was compared based on scenarios from 5+5 to 1+1 from two visits.

TABLE

**Probability That Pentacam HR Curvature Measurements Represent True Corneal Curvature Change Based on the Difference Between the Average of Past and Present Measurements**

| Probability (%) | Kmax | | | Rmin(front) | | | Rmin(back) | | | Rmin COMBO | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5+5 | 5+1 | 1+1 | 5+5 | 5+1 | 1+1 | 5+5 | 5+1 | 1+1 | 5+5 | 5+1 | 1+1 |
| 5 | 0.0216 | 0.0374 | 0.0483 | 0.0023 | 0.0040 | 0.0052 | 0.0041 | 0.0072 | 0.0093 | 0.0018 | 0.0032 | 0.0041 |
| 10 | 0.0433 | 0.0750 | 0.0969 | 0.0046 | 0.0080 | 0.0104 | 0.0083 | 0.0144 | 0.0186 | 0.0037 | 0.0064 | 0.0083 |
| 20 | 0.0873 | 0.1513 | 0.1953 | 0.0094 | 0.0162 | 0.0209 | 0.0168 | 0.0290 | 0.0375 | 0.0075 | 0.0129 | 0.0167 |
| 30 | 0.1328 | 0.2301 | 0.2971 | 0.0142 | 0.0246 | 0.0318 | 0.0255 | 0.0442 | 0.0570 | 0.0114 | 0.0197 | 0.0254 |
| 40 | 0.1808 | 0.3132 | 0.4043 | 0.0194 | 0.0335 | 0.0433 | 0.0347 | 0.0601 | 0.0776 | 0.0155 | 0.0268 | 0.0346 |
| 45 | 0.2061 | 0.3570 | 0.4609 | 0.0221 | 0.0382 | 0.0494 | 0.0396 | 0.0685 | 0.0885 | 0.0176 | 0.0305 | 0.0394 |
| 50 | 0.2326 | 0.4028 | 0.5200 | 0.0249 | 0.0431 | 0.0557 | 0.0446 | 0.0773 | 0.0998 | 0.0199 | 0.0345 | 0.0445 |
| 60 | 0.2909 | 0.5027 | 0.6489 | 0.0311 | 0.0538 | 0.0695 | 0.0557 | 0.0965 | 0.1245 | 0.0248 | 0.0430 | 0.0555 |
| 70 | 0.3574 | 0.6191 | 0.7992 | 0.0383 | 0.0663 | 0.0856 | 0.0686 | 0.1188 | 0.1534 | 0.0306 | 0.0530 | 0.0684 |
| 80 | 0.4420 | 0.7656 | 0.9884 | 0.0473 | 0.0820 | 0.1058 | 0.0848 | 0.1469 | 0.1897 | 0.0378 | 0.655 | 0.0846 |
| 90 | 0.5675 | 0.9829 | 1.2689 | 0.0608 | 0.1053 | 0.1359 | 0.1089 | 0.1886 | 0.2435 | 0.0486 | 0.0841 | 0.1086 |
| 95 | 0.6764 | 1.1715 | 1.5124 | 0.0724 | 0.1255 | 0.1620 | 0.1298 | 0.2248 | 0.2903 | 0.0579 | 0.1002 | 0.1294 |
| 98 | 0.8031 | 1.3910 | 1.7958 | 0.0860 | 0.1490 | 0.1923 | 0.1541 | 0.2670 | 0.3447 | 0.0687 | 0.1190 | 0.1536 |
| 99 | 0.8895 | 1.5407 | 1.9890 | 0.0953 | 0.1650 | 0.2130 | 0.1707 | 0.2957 | 0.3817 | 0.0761 | 0.1318 | 0.1702 |

*Note. The numbers in parentheses denote the number of measurements available in the past and present. Thus, (5+1) means five present and one past measurement are used.*

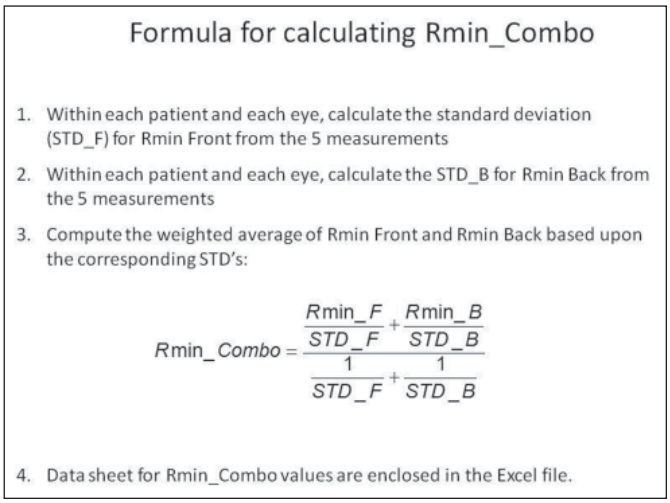


**Figure.** The COMBO statistic calculates the probability of corneal curvature change based on an optimized combination of both Rmin(front) and Rmin(back).

We created a combined statistic, "COMBO Statistic," for the evaluation of change in steepest corneal curvature. The statistic presented herein combined the front and back radii of curvature and normalized each according to their sample standard deviation. The method of calculating the COMBO statistic is presented in the Figure. Confidence values for the COMBO statistic appear in the Table.

## RESULTS

Among the tested patients, 30 were men and 11 were women. Patient age for the Pentacam statistical study ranged from 20 to 81 years. Although patients older than 60 were ineligible for CXL, their clinical data were used to evaluate the Pentacam. Of the 5 eyes of patients aged >60, 3 eyes were from patients with progressive keratoconus and 2 eyes from a patient with postoperative LASIK ectasia. Mean age of eyes measured was 41.5±13.5 years. Maximum keratometry ranged from 45.00 to 69.30 D with an average of 54.30±5.40 D.

The Kolmogorov-Smirnov test showed normality of data ($P$>.05 in all cases). The actual Kolmogorov-Smirnov statistic $P$ values were as follows: for trials 1, 2, 3, 4, and 5, respectively, Rmin(front) (left eye): >0.15 for all trials; Rmin(back) (left eye): 0.07, 0.12, >0.15, 0.06, and >0.15; Rmin(front) (right eye): >0.15 for all trials; and Rmin(back) (right eye): >0.15 for all trials.

Confidence levels in true change of Pentacam HR–measured Rmin(front), based on single past and single present (1+1), single past and five present (5+1), and

five past and five present (5+5) measurements appear in the Table. Maximum keratometry is a quantity calculated from Rmin(front). With a single measurement in the past and one in the present (1+1), corneal curvature change was 95% likely to have occurred when the difference of Pentacam HR Kmax readings exceeded 1.51 D (or Rmin[front] changed by 0.162 mm). When comparing the average of one past measurement and five present measurements, there was 95% confidence of true Kmax change when the difference between the average of the five current Kmax measurements and the single past measurements exceeded 1.17 D (or Rmin[front] changes by 0.126 mm). When comparing the average of five past measurements and five present measurements (5+5), true change of corneal curvature was 95% likely when the Kmax difference exceeded 0.676 D (Rmin[front] change of 0.072 mm).

The measurement Rmin(back) had greater inter-observational variation than Rmin(front). For Rmin(back), there was 95% confidence of true change in single past and single present Pentacam HR measurements (1+1) if the difference of Rmin(back) exceeded 0.290 mm. For one past and five present measurements (5+1), 95% confidence was achieved with a difference of 0.225 mm. When comparing the average of five past measurements and five present measurements (5+5), true change of corneal curvature was 95% likely if the difference of Rmin(back) was 0.130 mm.

## DISCUSSION

The prime purpose of this study was to provide a criterion for the diagnosis of curvature change in keratoconus and postoperative LASIK ectasia. Based on the results of this study, steepest corneal curvature in keratoconus and postoperative LASIK ectasia changed with 95% confidence when the difference between a single past and present Kmax exceeded 1.51 D. With the advantage of five past and five present measurements, 95% confidence of real Kmax change occurs at a 0.68-D difference in between the average of the past and the average of the present measurements.

The inter-observational variations in Kmax, Rmin(front), and Rmin(back) were greater in cases of keratoconus than in normal or normal postoperative LASIK corneas. This variation was due to the greater patient difficulty in seeing and looking at the red fixation light and the greater difficulty in alignment of irregular corneas. Thus, in keratoconus, corneal curvature could be erroneously diagnosed to have changed due to the disease or its treatment if the Pentacam HR repeatability data of normal or postoperative LASIK corneas were used to analyze change in corneas with keratoconus.[5]

### KMAX AND RMIN(FRONT)

To see the relationship between Kmax and Rmin(front), it should be mentioned as a point of review[9] that K, the dioptric power of the anterior surface of the cornea in air, is related to R, its radius of curvature by the equation:

$$K = (n_{air} - n_{cornea})/R$$

where $n_{air}$ is the index of refraction of air and $n_{cornea}$ is the index of refraction of the cornea.

### USING THE CRITERIA IN STUDIES AND IN CLINIC

Riboflavin-UVA CXL treatment has been performed with the epithelium intact,[10] but the effect of epithelium-on CXL has been debated.[11] The proponents state that the riboflavin penetration, although minimal, is sufficient for effect with the epithelium intact.[12] Future clinical trials with epithelium-off CXL with shorter exposure times and higher UVA light power, future trials of CXL with chemical augmentation of riboflavin penetration without epithelium removal, studies of CXL with other chemicals, and future trials of laser vision corrections combined with CXL will likely occur. It is our hope that the work in the current study will help in judging the effectiveness of CXL using the various methods. In addition, the criteria mentioned herein should aid the clinician in deciding whether an individual case of keratoconus is worsening without CXL treatment.

Pentacam HR measured steepest anterior corneal curvature Kmax (Rmin[front]) has less variability than the posterior steepest curvature (Rmin[back]). As evidence of statistical significance of changes of Kmax from CXL is available, because of the optical significance of anterior corneal curvature, and because we find Rmin(front) to be more repeatable than Rmin(back), we recommend the continued use of Kmax as a good single criterion to diagnose progression or improvement of keratoconus. The COMBO statistic presented herein may be more accurate than Kmax and therefore allows a more rapid diagnosis of corneal shape change. The important aspect of the COMBO statistic is that it includes information not only about the anterior corneal curvature but also the posterior corneal curvature. The COMBO statistic is more complicated, and the use of the website www.ICanSee.com for calculation is recommended.

### SOURCES OF MEASUREMENT ERROR

The slight linear and axial deviations in patient eye position do not affect the statistics of maximal curvature. But slight deviations in Pentacam-recorded corneal position of Kmax question the accuracy of subtraction mappings because those maps subtract data from correspond-

ing locations on the corneal reading that might not be the same spots. Patient head axial position may vary among measurements and patients may not look precisely at the same spot on the Pentacam fixation target. Because there are slight variations in the recorded position on the cornea, we prefer to use changes in magnitude of Kmax as the most accurate measure of corneal change. Subtraction elevation maps between different visits can be misleading and give a false notion of corneal change. Future Scheimpflug cameras may incorporate iris registration and pupil recognition to help correct these inaccuracies.

## Study Limitations

Our study had several limitations. First, we made only a small effort to consider possible diurnal variations in steepest corneal curvature. Three patients were seen both in the morning and in the afternoon for five Pentacam measurements and no diurnal trend was noted in the average of the Kmax data in those patients. If significant diurnal variation was present in eyes with keratectasia, it would increase the magnitude of the difference in sample values Kmax, Rmin(front), and Rmin(back) sufficient to achieve 95% confidence of true corneal shape change. Second, Kmax is a measurement that is dependent on measurement axis and that may change after any surgical intervention. We found that the precise recorded location of Kmax on the cornea varied slightly among multiple measurements in the same office visit. Another limitation of our study was that patients discontinued contact lens wear for only 2 weeks. Discontinuation for 1 month might have been better.

The inter-observational variations of Rmin(front) and Rmin(back) were found to be 39% correlated, meaning that the COMBO statistic is not as powerful as it could be if only the statistical deviations of Rmin(front) and Rmin(back) were statistically independent.

We recommend that all Pentacam HR studies on cross-linking effect state how many measurements were taken per patient pre- and postoperatively. We further recommend that decisions about whether an individual ectatic cornea has improved or worsened be based on the use of the confidence measures of corneal curvature change that are designed for ectatic corneas such as those expressed in the current study.

When keratoconus is diagnosed, we recommend five Pentacam HR measurements, not just one. However, sometimes keratoconus is not initially suspected or for some other reason only one past measurement is available. This study offers criteria to diagnose keratoconus change with only one past measurement and five current measurements.

## Author Contributions

*Study concept and design (R.L.E.); data collection (R.L.E., G.L.E.); analysis and interpretation of data (R.L.E., Y-.L.C.); drafting of the manuscript (R.L.E., Y-.L.C.); critical revision of the manuscript (R.L.E., G.L.E.); statistical expertise (Y-.L.C.); administrative, technical, or material support (G.L.E.)*

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