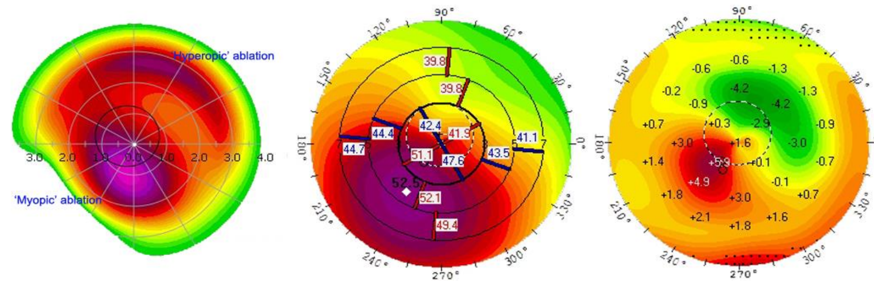
Cornea cross-linking. Indications, applications, results, complications and evolving technology.

A. John Kanellopoulos, MD[1,2]



1: Laservision.gr Clinical & Research Eye Institute, Athens, Greece
2: New York University Medical School, NY, NY

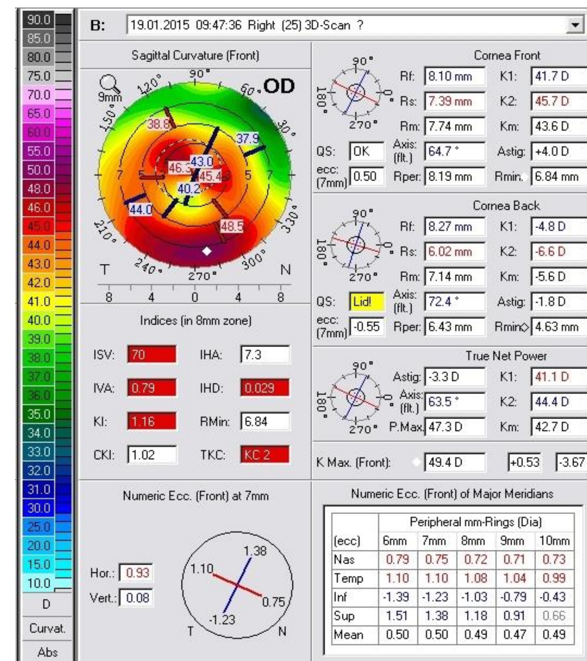
Financial disclosure:
Kanellopoulos: Consultant for Alcon, Avedro, Allergan, i-Optics, Keramed, Zeiss, ISP surgical

When and how to CXL?

- How do we screen for keratoconus?
- What is the familiar predisposition for KCN?
- How do we document progression?
- What is is the optimal pediatric and adult CXL technique?
- Potential complications specific to pediatric pts

How do we screen for keratoconus?

- Cornea imaging essential, do not rely on acuity, refraction and/or biomicroscopy!
- Anterior curvature asymmetry indices very sensitive
- Corneal pachymetry maps
- Corneal epithelial mapping maybe the most sensitive!!!



How do we screen for keratoconus?

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Open Access Full Text Article — ORIGINAL RESEARCH

Revisiting keratoconus diagnosis and progression classification based on evaluation of corneal asymmetry indices, derived from Scheimpflug imaging in keratoconic and suspect cases

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Clinical Ophthalmology
25 July 2013
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Anastasios John Kanellopoulos[1,2]
George Asimellis[1]

[1]Laservision.gr Eye Institute, Athens, Greece; [2]New York University School of Medicine, New York, NY, USA

Purpose: To survey the standard keratoconus grading scale (Pentacam®-derived Amsler–Krumeich stages) compared to corneal irregularity indices and best spectacle-corrected distance visual acuity (CDVA).

Patients and methods: Two-hundred and twelve keratoconus cases were evaluated for keratoconus grading, anterior surface irregularity indices (measured by Pentacam imaging), and subjective refraction (measured by CDVA). The correlations between CDVA, keratometry, and the Scheimpflug keratoconus grading and the seven anterior surface Pentacam-derived

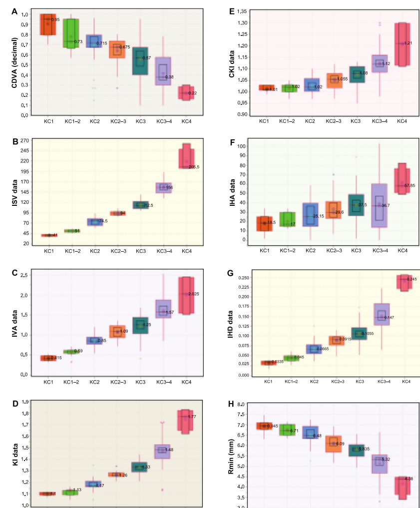

Figure 2 Box plots of measured parameters versus keratoconus grading, as produced by the Oculyzer™ software, showing median level (indicated by □), average symbol (□), 95% median confidence range box (black line boxes), and interquartile intervals range box (red line boxes). (**A**) CDVA versus keratoconus grading. (**B**) ISV versus keratoconus grading. (**C**) IVA versus keratoconus grading. (**D**) KI versus keratoconus grading. (**E**) CKI versus keratoconus. (**F**) IHA versus keratoconus grading. (**G**) IHD versus keratoconus grading. (**H**) Rmin versus keratoconus grading.
Abbreviations: CDVA, best spectacle-corrected distance visual acuity; CKI, central keratoconus index; IHA, index of height asymmetry; IHD, index of height decentration; ISV, index of surface variance; IVA, index of vertical asymmetry; KC1, keratoconus grading Stage I; KC1–2, keratoconus grading Stage I–II; KC2, keratoconus grading Stage II, KC2–3, keratoconus grading Stage II–III; KC3, keratoconus grading Stage III; KC3–4, keratoconus grading Stage III–IV; KC4, keratoconus grading Stage IV; KI, keratoconus index; PI, prediction interval; Rmin, minimum radius of curvature.

In Vivo Three-Dimensional Corneal Epithelium Imaging in Normal Eyes by Anterior-Segment Optical Coherence Tomography: A Clinical Reference Study

Anastasios John Kanellopoulos, MD,† and George Asimellis, PhD**

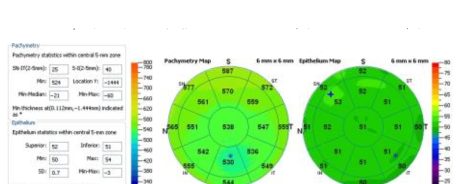

FIGURE 1. Details from the analysis software main report, showing corneal and epithelial 3-dimensional pachymetry maps over the 6-mm corneal diameter. The symbol * indicates the thickness minimum (both corneal and epithelial maps), and the symbol + indicates the thickness maximum (epithelial map only).

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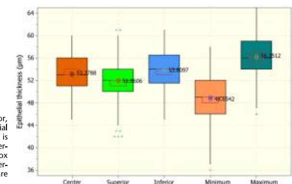
FIGURE 2. Box plot describing central, superior, inferior, minimum, and maximum epithelial thickness for all 373 cases. The median level is displayed numerically and indicated by ⊗, average by ⊕, the 95% median confidence range box by the red borderline, and the interquartile intervals range box by the black borderline. All units are in micrometers.



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Open Access Full Text Article — ORIGINAL RESEARCH

Comparison of high-resolution Scheimpflug and high-frequency ultrasound biomicroscopy to anterior-segment OCT corneal thickness measurements

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Clinical Ophthalmology
19 November 2013
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Anastasios John Kanellopoulos[1,2]
George Asimellis[1]

[1]Laservision.gr Eye Institute, Athens, Greece; [2]New York University Medical School, New York, NY, USA

Background: The purpose of this study was to compare and correlate central corneal thickness in healthy, nonoperated eyes with three advanced anterior-segment imaging systems: a high-resolution Scheimpflug tomography camera (Oculyzer II), a spectral-domain anterior-segment optical coherence tomography (AS-OCT) system, and a high-frequency ultrasound biomicroscopy (HF-UBM) system.

Methods: Fifty eyes randomly selected from 50 patients were included in the study. Inclusion

Table 2 Comparative statistics for the three pairs of imaging modalities examined

	HF-UBM versus AS-OCT	AS-OCT versus Oculyzer II	Oculyzer II versus HF-UBM
Estimated mean of the differences (μm)	+19.06	−12.20	−6.86
Estimated SD of the differences (μm)	±12.62	±10.01	±9.85
95% CI for mean difference (μm)	(15.47, 22.65)	(−15.05, −9.35)	(−9.66, −4.06)
t-test of mean difference =0 (versus not =0) *t*-value (μm)	+10.68	−8.61	−4.92
t-test of mean difference =0 (versus not =0) *P*-value	<0.0001	0.0002	0.0003
Coefficient of determination (r^2)	0.830	0.895	0.893
Coefficient of linearity	0.8412	0.9295	1.006

Abbreviations: CCT, central corneal thickness; AS-OCT, anterior-segment optical coherence tomography; HF-UBM, high-frequency ultrasound biomicroscopy; CI, confidence interval.

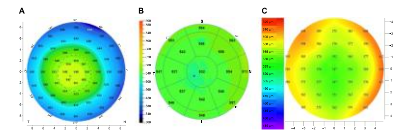

Figure 1 Corneal thickness maps of a cornea from the same subject obtained sequentially on the same day by (**A**) Oculyzer II Scheimpflug camera, (**B**) OptoVue AS-OCT, and (**C**) Artemis II HF-UBM. We observe "thinner measurements" of corneal thickness (eg, centrally) by the AS-OCT versus the Scheimpflug and the HF-UBM (~15 μm).
Abbreviations: AS-OCT, anterior-segment optical coherence tomography; CCT, central corneal thickness; HF-UBM, high-frequency ultrasound biomicroscopy.

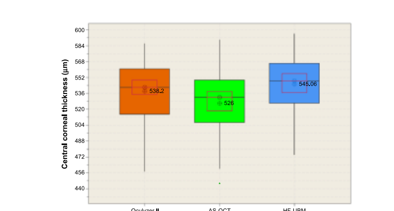

Figure 2 Corneal thickness measurement by the three modalities in the form of box plots. Median level is indicated by ⊗, average by ⊕, the 95% median confidence range box by the red borderline, and the interquartile intervals range box by the black borderline.
Abbreviations: AS-OCT, anterior-segment optical coherence tomography; HF-UBM, high-frequency ultrasound biomicroscopy.

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Open Access Full Text Article — ORIGINAL RESEARCH

Correlation between epithelial thickness in normal corneas, untreated ectatic corneas, and ectatic corneas previously treated with CXL; is overall epithelial thickness a very early ectasia prognostic factor?

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Clinical Ophthalmology
22 May 2012
Number of times this article has been viewed

Anastasios John Kanellopoulos[1,2]
Ioannis M Aslanides[3]
George Asimellis[1]

[1]Laservision Eye Institute, Athens, [2]Emmetropia Mediterranean Eye Clinic, Crete, Greece, [3]New York University School of Medicine, NY, USA

Purpose: To determine and correlate epithelial corneal thickness (pachymetric) measurements taken with a digital arc scanning very high frequency ultrasound biomicroscopy (HF UBM) imaging system (Artemis-II), and compare mean and central epithelial thickness among normal eyes, untreated keratoconic eyes, and keratoconic eyes previously treated with collagen crosslinking (CXL).

Methods: Epithelial pachymetry measurements (topographic mapping) were conducted on 100 subjects via HF UBM. Three groups of patients were included: patients with normal eyes (controls), patients with untreated keratoconic eyes, and patients with keratoconic eyes treated with CXL. Central, mean, and peripheral corneal epithelial thickness was examined for each

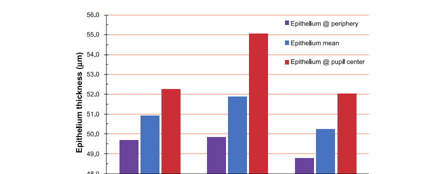

Figure 7 Epithelium thickness across the three study groups, at the periphery, mean, and pupil center.
Abbreviation: KCN, keratoconus.

surprise that while the epithelial center was, on average, thicker by only 1.3 μm compared to the mean, on several occasions it was thicker compared to the nasal, temporal, inferior, or superior points by up to 10 μm. This conclusion is also supported by the fact that the periphery epithelium thickness value of 49.7 μm was closer to the mean (50.9 μm) than to the pupil center (52.3 μm).

We note that the standard deviation of the measurements (±3–4 μm) is comparable to the accuracy and precision of the instrument, as established by our investigation, and thus epithelial thickness variations of ±4–4 μm, as it is the case, might be observed differently even on the same eye. An example of a control patient who demonstrated a thicker epithelium at the pupil center is shown in Figure 6. In one instance the central epithelium was elevated by 9 μm (51 μm–42 μm), while in a subsequent examination of the same eye, the difference between the same points was recorded as only 6 μm (54 μm–48 μm).

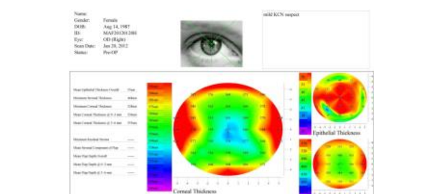

Figure 8 Corneal and epithelial thickness maps of a KCN patient.
Note: A significantly thicker epithelium over the pupil center is observed.
Abbreviation: KCN, keratoconus.

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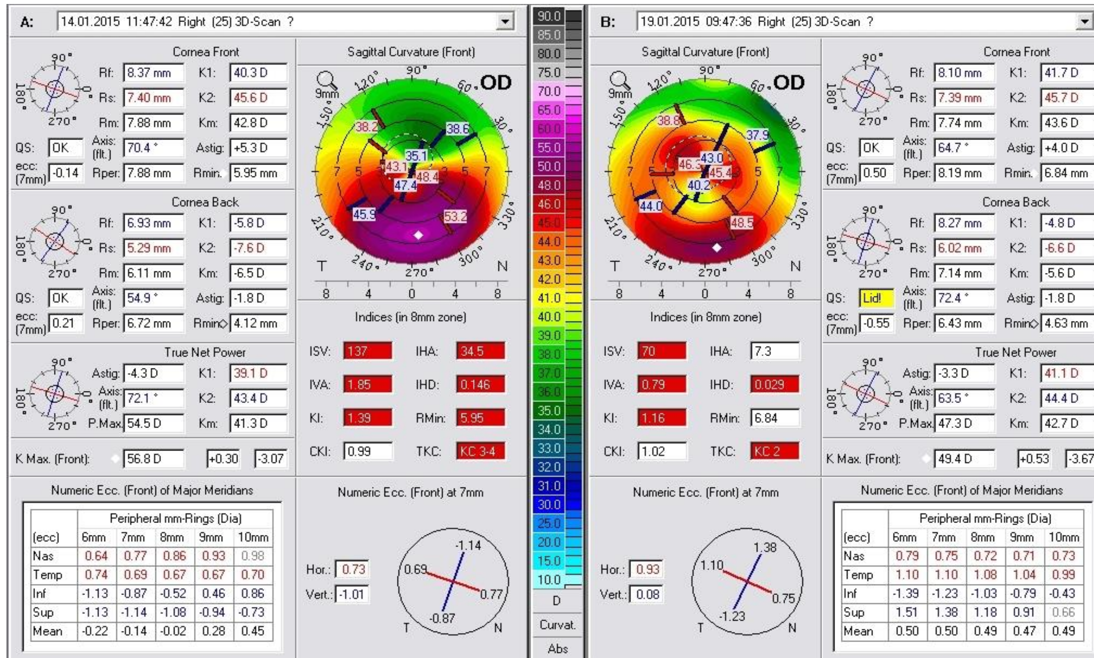
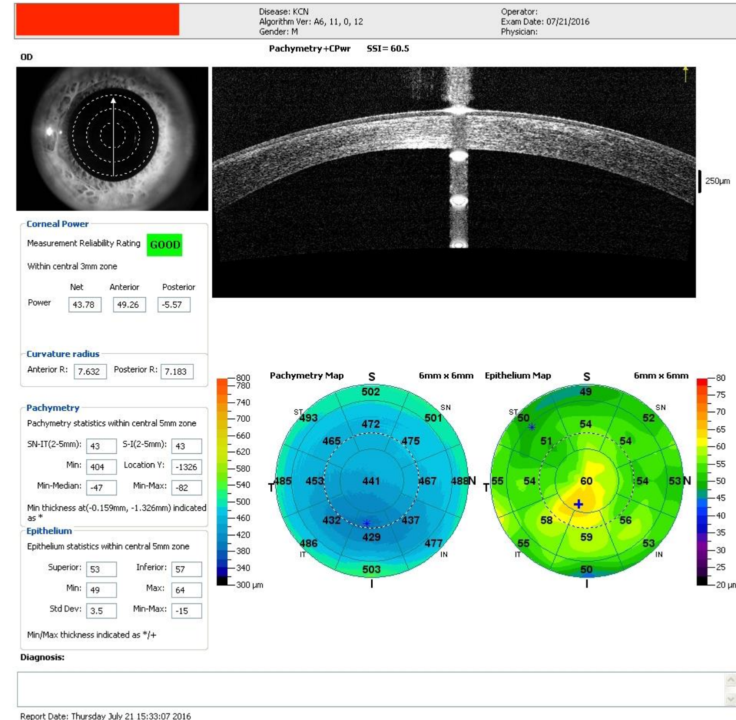
Topometric indices comparison,
as we reported IHD (index of height decentration)
and ISV (index of surface variance) the most pivotal





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First Name: Eleni
ID: 68823
Date of Birth: 17.01.1965 Eye: Right
Exam Date: 16.03.2016 Time: 16:39:40
Exam Info:

Cornea Front

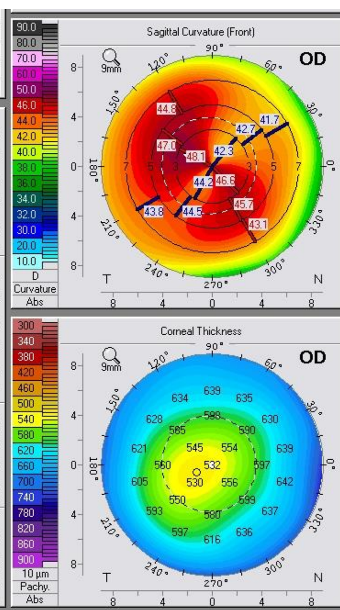
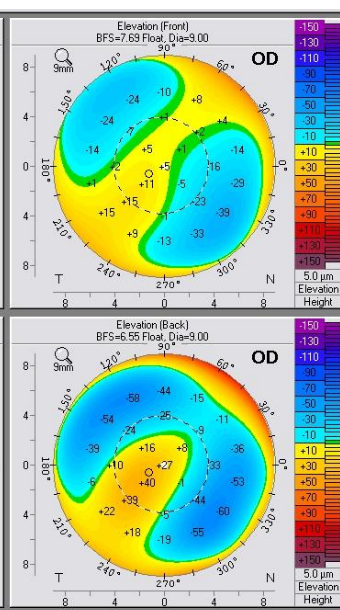
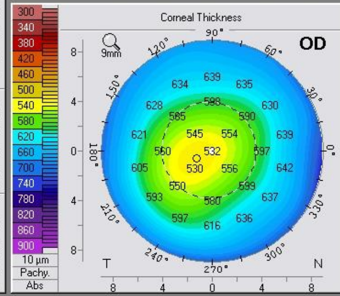
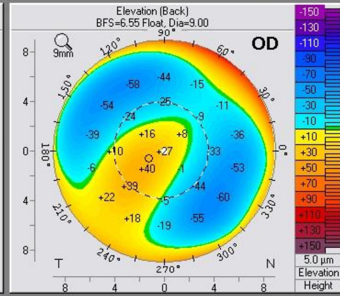
	Rf: 7.81 mm	K1: 43.2 D		
	Rs: 7.16 mm	K2: 47.2 D		
	Rm: 7.48 mm	Km: 45.1 D		
QS: OK	Axis: (flt.) 55.3 °	Astig: +3.9 D		
ecc: (7mm) 0.80	Rper: 8.15 mm	Rmin: 7.00 mm		

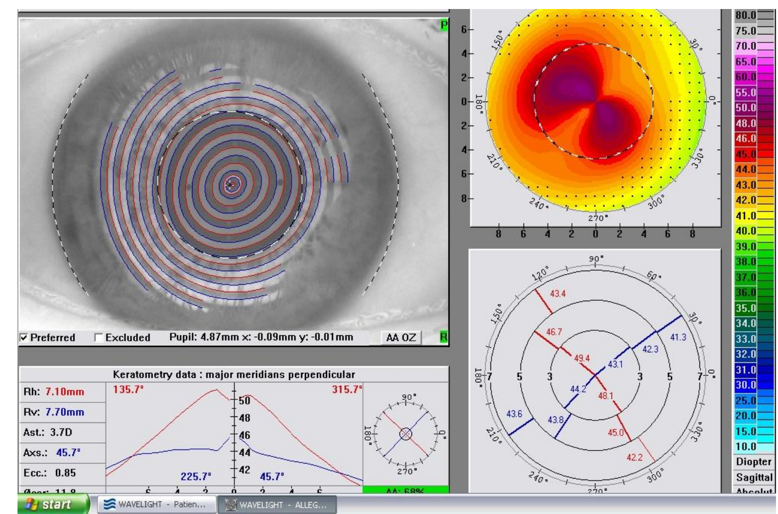
Cornea Back

	Rf: 6.34 mm	K1: -6.3 D		
	Rs: 5.53 mm	K2: -7.2 D		
	Rm: 5.94 mm	Km: -6.7 D		
QS: OK	Axis: (flt.) 42.2 °	Astig: +0.9 D		
ecc: (7mm) 1.01	Rper: 7.10 mm	Rmin: 5.12 mm		

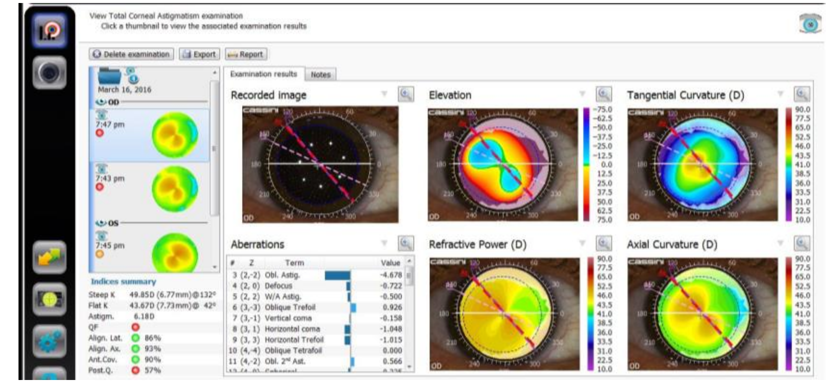
	Pachy:	x[mm]	y[mm]
Pupil Center: +	531 µm	-0.13	+0.03
Pachy Apex:	532 µm	0.00	0.00
Thinnest Locat.: O	527 µm	-0.64	-0.28
K Max. (Front):	48.2 D	-1.00	+0.50

Cornea Volume:	58.1 mm³	KPD:	+1.9 D
Chamber Volume:	132 mm³	Angle:	24.8 °
A. C. Depth (Int.):	2.67 mm	Pupil Dia:	3.86 mm
Enter IOP	IOP(Sum): +0.9 mmHg	Lens Th.:	



Normal?



51yoM, has decrease in CDVA
And increasing astigmatic correction

Right / OD

Exam Date: 03/16/2016 19:33:35

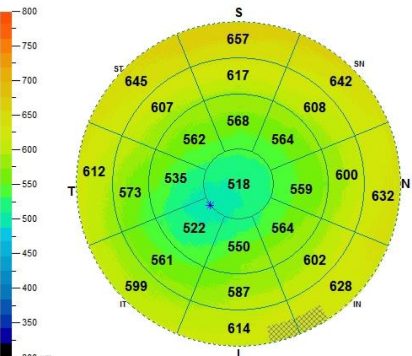
PachymetryWide OU Report

28 Signal Strength Index 30

Left / OS

Exam Date: 03/16/2016 19:34:28

Pachymetry Map

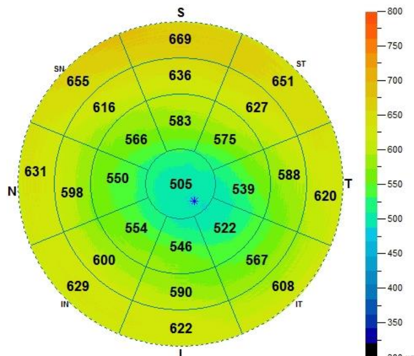


Pachymetry

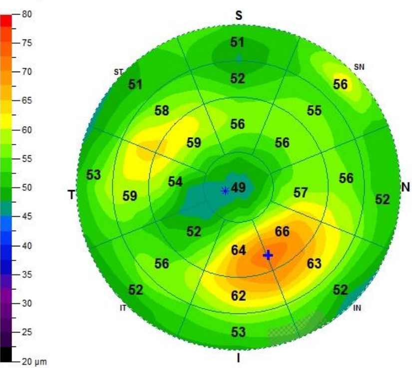
Pachymetry statistics within central 5mm

	OD	OS		OD	OS
SN-IT(2-5mm):	42	44	S-I(2-5mm):	18	37
Min:	503	490	Location Y:	-586	-486
Min-Median:	-44	-56	Min-Max:	-83	-118

Min thickness indicated as *



Epithelium Map

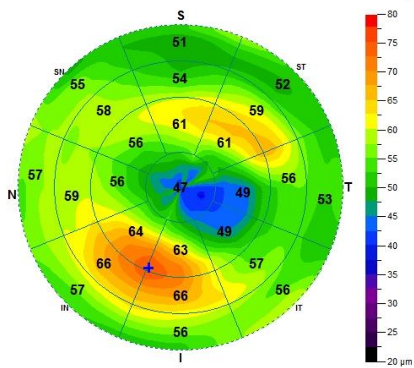


Epithelium

Epithelium statistics within central 7 mm

	OD	OS		OD	OS
S (2-7mm):	54	57	I (2-7mm):	63	65
Min:	46	41	Max:	72	74
Std Dev:	5.4	7.0	Min-Max:	-26	-33

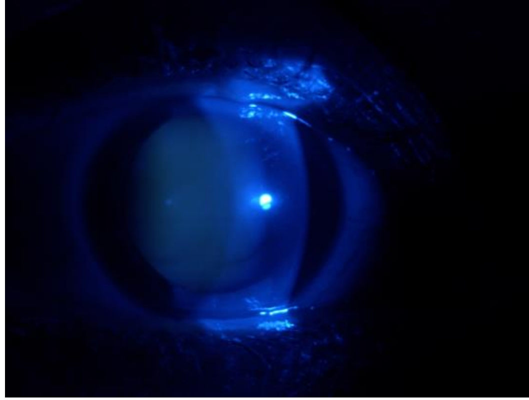
Min/Max thickness indicated as */+



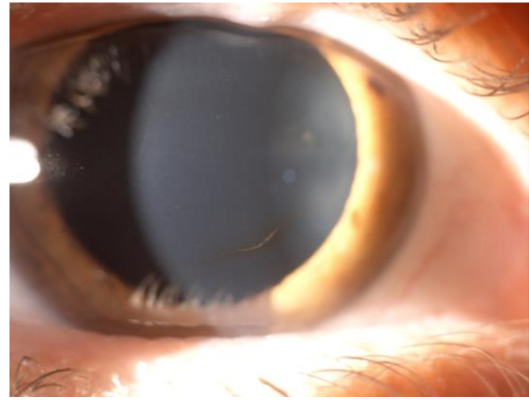
Stroma Map

Print

optovue



Normal?



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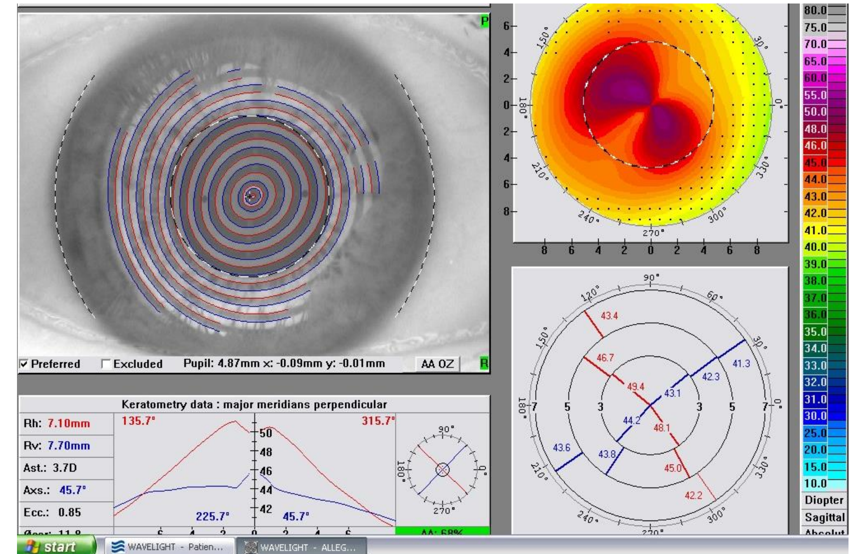
What is the familiar predisposition for KCN?

- 12% reported so far
- Almost 100% in the Greek population when tomography and epithelial mapping is used-may be similar in the eastern Mediterranean basin and the Middle East
- Keratoconus should be considered a family disease
- LASIK vs. Surface ablation in family of known KCN patient's

How do we document progression?

- Again corneal imaging crucial
- Ideally tomography (Scheimpflug-based, anterior segment OCT)
- Corneal thickness mapping change
- Corneal epithelial mapping

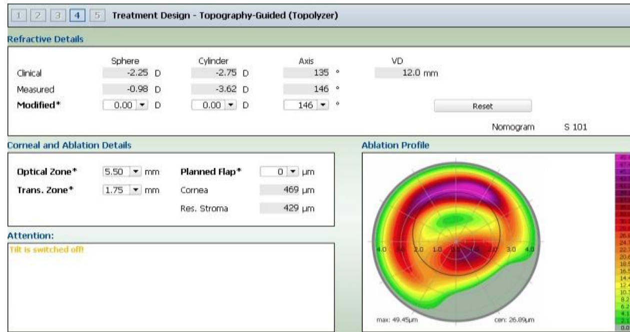


What is is the optimal pediatric and adult CXL technique?

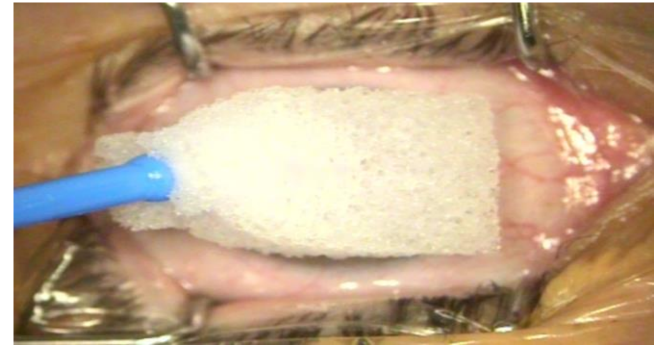
- Epithelium-off CXL the gold standard (Dresden protocol)
- Athens Protocol (Partial topo-guided PRK+CXL) the most effective in our hands
- Epi-on CXL may offer significant less morbidity especially in ped pts if proven effective enough
- Intracorneal ring segments + CXL

The Athens Protocol 4 steps after TMR has been done:

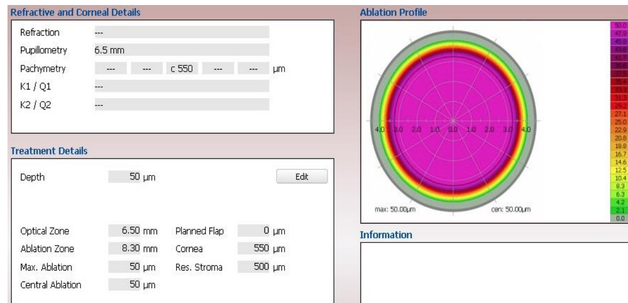
same day partial topo-PRK > PTK > MMC > CXL (6mW/cm² x 15 min)



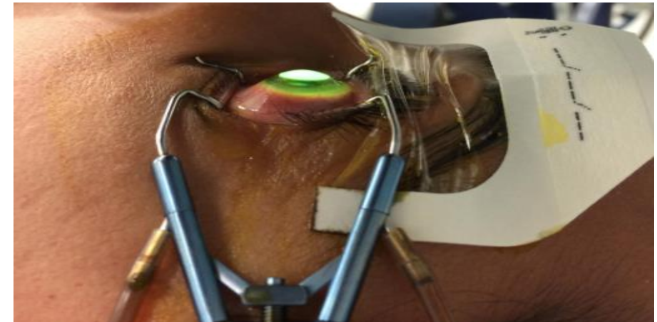
Step 1: Topo-guided partial PRK



Step 3: MMC 0.02% for 30sec



Step 2: PTK @ 50µm



Step 4: CXL 6mW/cm²

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The Athens Protocol: combining same-day partial topo-guided PRK normalization with higher fluence CXL for keratectasia.

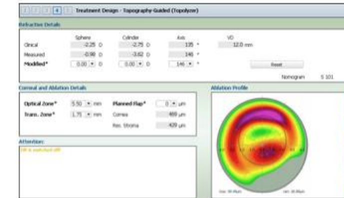
CXL combined with excimer-laser partial photorefractive keratectomy may offer stable, reliable, improved visual rehabilitation, in addition to potentially increased biomechanical strengthening. We have shown that same-session partial topo-guided PRK with CXL is more effective than sequential PRK after earlier CXL in a large comparative case series. The refractive effects of the combined, same-day treatment were impressive: the majority of patients obtained a CDVA of 20/40.

The Athens Protocol Design & Procedure

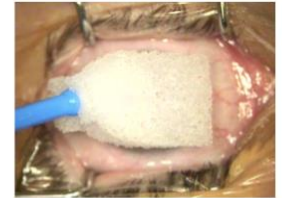
This procedure known today as the Athens Protocol has evolved since we introduced it to include sequentially, same-session, excimer-laser epithelial debridement (50 μm), partial topography-guided excimer-laser stromal ablation, and high-fluence UVA (6 mW/cm^2), accelerated (15') CXL. The evolution of the Athens Protocol involves employment of cyclorotation compensation with the highly irregular topo-guided partial PRK as a first step to be followed by a 50μm PTK that accounts for epithelial removal as a second step (Figure 1). Last MMC and the CXL complete the protocol.

The Athens Protocol 4 steps:

same day partial topo-PRK > PTK > MMC > CXL (6mW/cm^2 x 15 min)

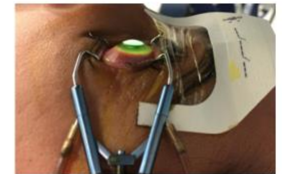


Step 1: Topo-guided partial PRK



Step 3: MMC 0.02% for 30sec

Step 2: PTK @ 50μm



Step 4: CXL 6mW/cm^2

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Designing the Ablation Pattern

The most challenging part of the Athens Protocol is the design of excimer-laser ablation pattern. As this is not a refractive procedure, the priority is the maximal 'normalization' of the irregular anterior corneal surface that the thinned cornea permits. Therefore, the aim of the design is dual: to reduce the large curvature of the cone area and attempt to 'relocate' this steeper area to a more central location by steepening the flattened central cornea next to the cone. Evaluation of an ablation pattern (figure 2 left) and its comparison to the preoperative curvature data (figure 2 middle) illustrates the key distinct areas of this specific ablation pattern: the paracentral cone location; this is the 'myopic ablation' component.

The second is the 'hyperopic ablation' component, corresponding to the 'antipode' of the cone. The purpose of this second 'hyperopic' component is to create an artificial 'elevation' gradient to the cone diagonal location. Together, these two different keratomileusis patterns combined, results in dramatic reduction of corneal asymmetry, correlating clinically with the postoperative marked CDVA increase. Of course this may not be absolutely necessary in patients that had or can tolerate RGP and/or scleral contact lenses. It has proven nevertheless in our hands the most stable, predictable tool in addressing severe visual morbidity associated with moderate to advanced keratoconus in young adults in Southern Europe. The fact that globally, Athens Protocol-type procedures have become the treatment of choice has justified our findings.

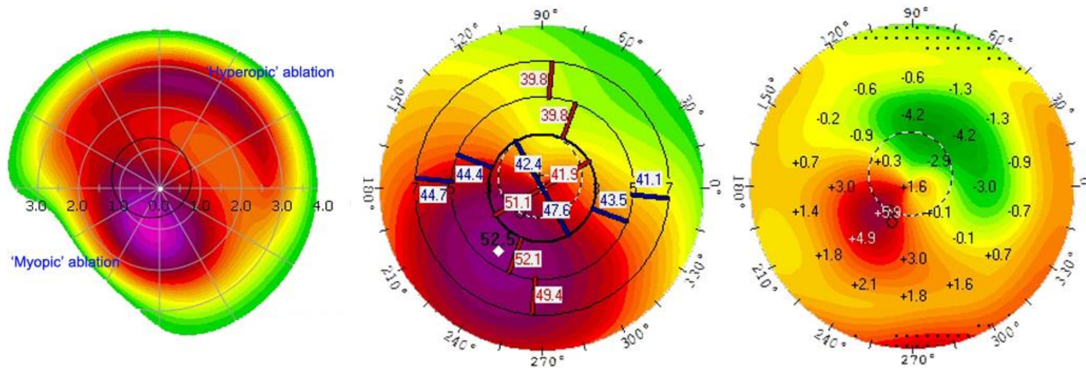
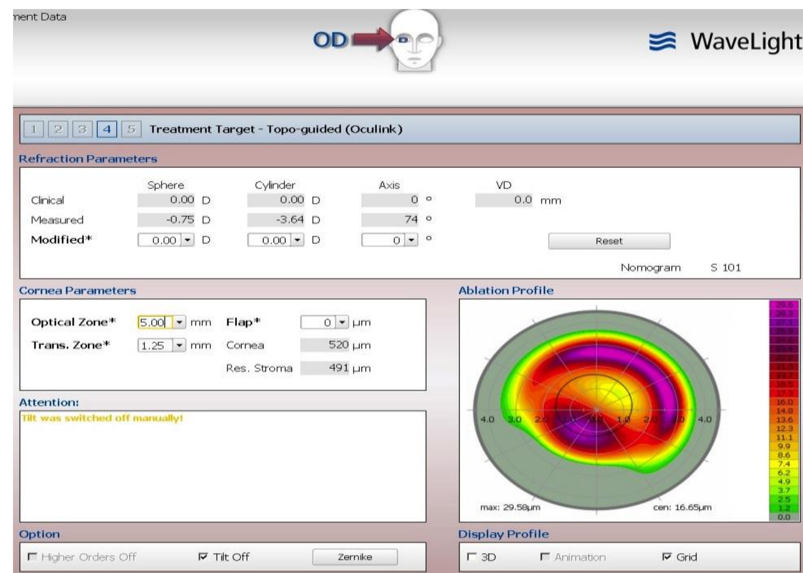


Figure 2: Left, topography-guided ablation pattern design; middle, pre-operative topography; right, difference between pre- and six months postoperative topography. The difference correlates angularly to the intended ablation pattern showing the myopic (red) and 'hyperopic' (green) components of the achieved result.

Clinical benefits

We have reported and published extensively early results, late stability and visual rehabilitation, and even recently, pediatric case with 7 and 10-year outcomes along with rare complications.

We have suggested at its inception, that the **topography-guided** ablation be limited to normalization and 50um max depth, a baseline that most investigators and clinicians have followed subsequently. This allows for **PARTIAL** treatment of the cylinder and sphere anticipating some correction by the CXL process as well. On the right such an attempt with refractive goal set at 0 for both sphere and cylinder: the software attempts to flatten the cone and simultaneously place an arc of “hyperopic” treatment away from the cone in order to steepen the paracentral flatter cornea and thus “normalize” the corneal surface power will less tissue removal from the central cornea.



Athens Protocol: Stabilization and cornea normalization
UDVA from 20/200 to 20/50, CDVA from 20/60 to 20/25

	A: 14.01.2015 11:47:42 Right (25) 3D-Scan ?	B: 19.01.2015 09:47:36 Right (25) 3D-Scan ?	Difference A - B
K1	40.3 D	41.7 D	-1.4 D
K2	45.6 D	45.7 D	-0.1 D
Axis (flat)	70.4 °	64.7 °	+5.7 °
Astig	+5.3 D	+4.0 D	+1.3 D
ecc (7mm)	-0.14	0.50	-0.64
QS	OK	Lid!	
Pupil Center: Pachy	455 µm	444 µm	+12 µm
Pupil Center: x[mm]	-0.27	-0.36	+0.10
Pupil Center: y[mm]	+0.65	+0.32	+0.34
Thinnest Locat.: Pachy	400 µm	380 µm	+20 µm
Thinnest Locat.: x[mm]	-0.75	-0.53	-0.21
Thinnest Locat.: y[mm]	-0.67	-1.15	+0.47
Chamber Volume	210 mm³	209 mm³	+1 mm³
Angle	39.9 °	-39.2 °	+79.1 °
A. C. Depth (Int.)	3.45 mm	2.86 mm	+0.58 mm
Pupil Dia	2.39 mm	2.90 mm	-0.51 mm
IOP(cor)			
Lens Th.			
Map	Sagittal Curvature (Front)	Sagittal Curvature (Front)	Sagittal Curvature (Front)

Exam: Curvature, Abs (D) — Curvature, Rel (0.25 D)

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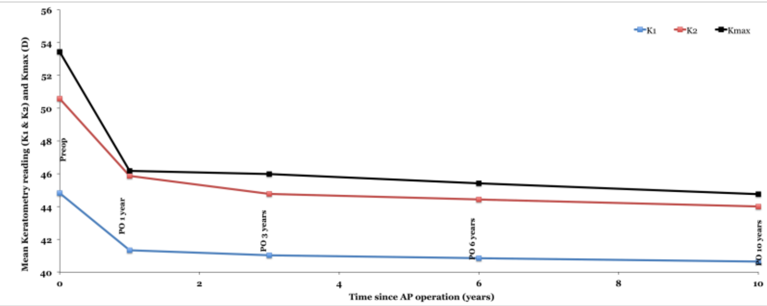
10 year Visual Acuity Changes:



K flat and K steep decreased significantly postoperatively (K2 steep meridian, 47,5±8,81D) and remained stable during the follow-up period.

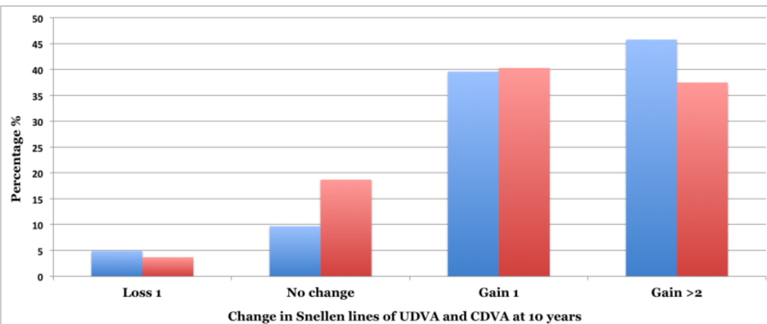


TABLE 1

Refractive, Pachymetric and Topographic parameters

Parameters (Mean Values)	Preoperative	Postoperative 1 year	Postoperative 10 years	P value[(a)]	P value[(b)]	P value[(c)]
UDVA (decimal)	0.19±0.17	0.53±0.21	0.55±0.19	<.01	<.01	.52
CDVA (decimal)	0.59±0.21	0.80±0.17	0.81±0.19	<.01	<.01	.63
CCT (um)	468.74±35.05	391.14±40.07	395.42±32.21	<.01	<.01	.31
IHD (um)	0.117±0.061	0.072±0.038	0.074±0.031	<.01	<.01	.62
K_1 (D)	44.82±2.95	41.33±3.77	40.64±2.95	<.01	<.01	.08
K_2 (D)	50.57±2.80	45.87±2.70	44.00±3.22	<.01	<.01	<.01
Kmax (D)	53.43±2.97	46.17±1.18	44.75±2.14	<.01	<.01	<.01

Abbreviations: UDVA = Uncorrected Distance Visual Acuity; CDVA = Corrected Distance Visual Acuity; CCT = Central Corneal Thickness; IHD = Index of Height Decentration; K1 = K-flat meridian; K2 = K-steep meridian

P value[(a)] at 1 year compared to preoperative values.

P value[(b)] at 10 years compared to preoperative values.

P value[(c)] at 1 year compared to 10 years postoperatively values.

Spherical equivalent:

-4.5 (±3.2) to -1.55 (±2.75)D

UDVA: 0,2 to 0,55 (decimal);

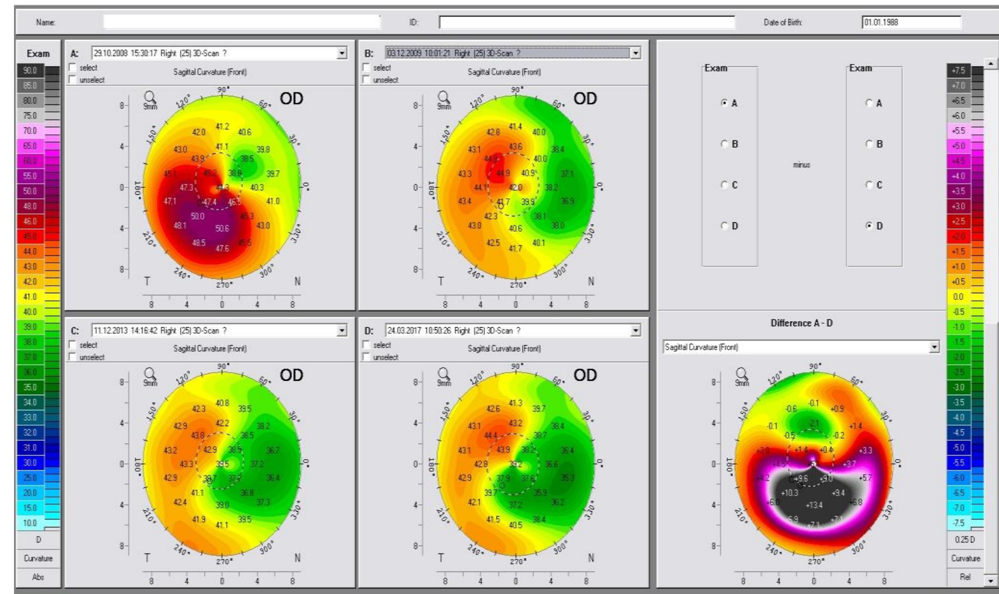
CDVA: 0,38 to 0,61 (decimal);

Steepest keratometry:

59,5± 7.72 to 47,5± 8.81,

IHD Index: 0,285 to 0,074,

Thinnest cornea: 468±27 to 395±32 µm.



17 pts. functioned without

21 with spectacles and/or soft contact lenses.

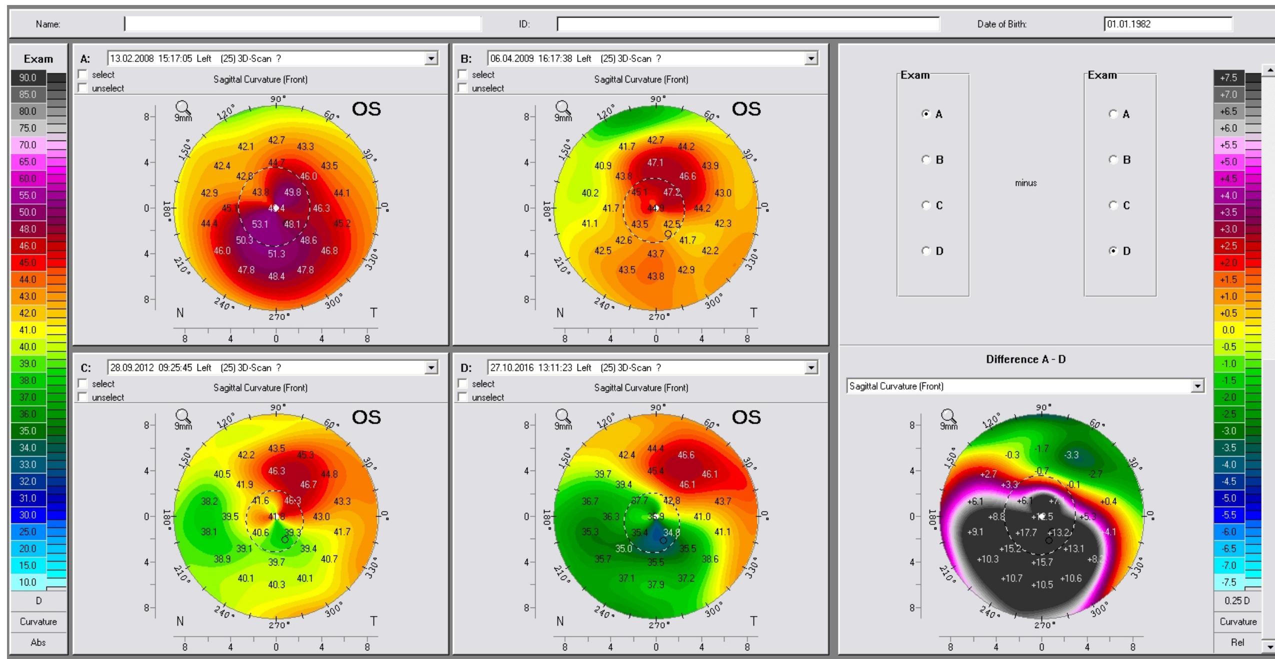
6 pts. required rigid or scleral lenses.

All eyes did not show further progression.

One hundred forty one eyes (97.9%) showed cone reduction

3 cases developed long term cone over-flattening!

Three eyes showed progression at 10 years follow-up as documented by corneal topography:



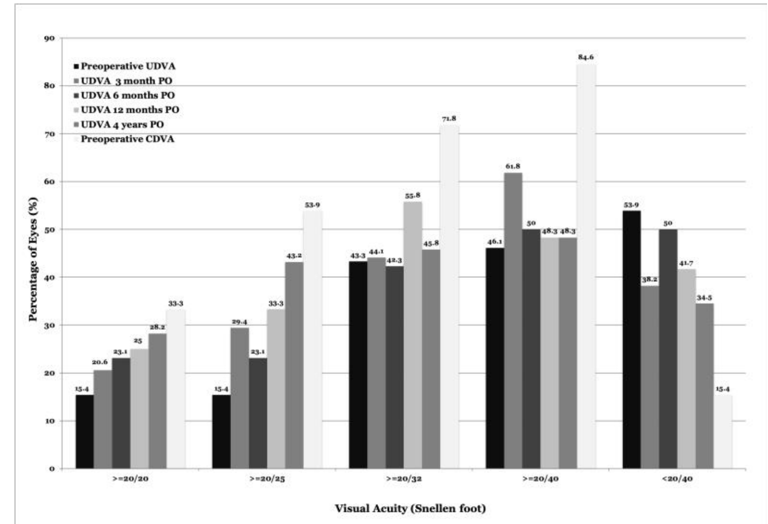
Case 2. A) Preoperative Pentacam tomography reveals inferocentral steep cone (Kmax: 53.10D) (Rx: -0.50 -2.00@135, CDVA 20/20) **B)** One year following AP/OS, the Pentacam shows superior steepening Kmax: 47.2D with a reduced inferocentral reading K: 43.50D. Rx: +1.00 -0.75@140 CDVA: 20/32, UCDVA: 20/40 **C)** At 4 years postoperative, Pentacam reveals an inferocentral flattening K:39.30D while the superior corneal power remains stable Kmax: 46.70D. Rx: +1.50 -2.25@135 CDVA: 20/32, UCDVA: 20/40 **D)** At 10yrs postoperative the inferocentral corneal power shows flattening Kmin: 34.80D, meanwhile the superior Kmax readings are 46.60D. Rx: +4.75 -1.75@75 CDVA: 20/50, UCDVA: 20/63

Long-term stability with the Athens Protocol (Topography-Guided partial-PRK combined with CXL), in pediatric keratoconus patients.

This prospective study included 39 keratoconic eyes of 21 patients aged under 18 years of age with clinical and imaging evidence of keratoconus progression. Partial topography-guided excimer laser ablation in conjunction with high-fluence CXL was performed to all patients according to the Athens Protocol. UDVA, CDVA, refraction, keratometry, endothelial cell density, topography and tomography using both Scheimplug and OCT were evaluated for 4-years postoperatively.

Results

At 4-years postoperatively, there was significant improvement in mean UDVA from 0.51±0.31(decimal) to 0.65±0.26(decimal; P<.05). Mean CDVA improved from 0.71±0.22(decimal) preoperatively to 0.81±0.19(decimal; P<.05), respectively. Mean flat keratometry (K1) and mean steep keratometry (K2) were reduced from 44.95±3.71D and 49.32±5.05D respectively preoperatively to 43.14±2.95D and 46.28±4.87D (P<.05) at 4-years. The mean anterior maximum keratometry (Kmax) was reduced from 56.81±2.94D preoperatively to 48.11±3.17D at 48 months. The mean Index of Height Decentration (IHD) was 0.105±0.054um preoperatively and 0.049±0.024(P<.05) at 4-years postoperatively. Mean preoperative corneal thickness at the thinnest point was 436.66±42.63um preoperatively, 392.50±45.68um at 12-months postoperatively and 418.42±17.01um at the 4-year follow up. Late onset deep corneal haze was encountered in 2 cases at least 1-year after the procedure; a potential intrinsic complication of this technique in pediatric patients.



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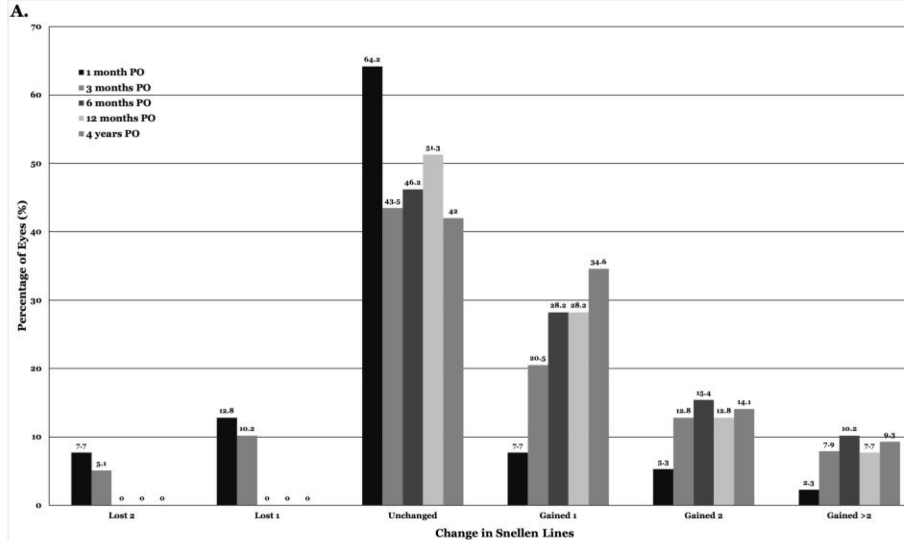
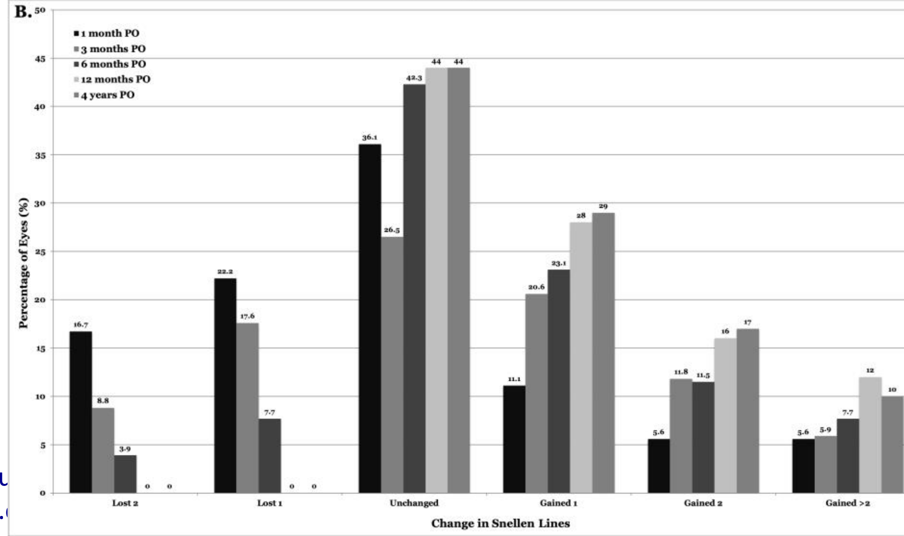
A. Percentage of eyes with gain/loss in Snellen lines of UDVA at 1 month, 3, 6, 12 months and 4 years postoperatively.

B. Percentage of eyes with gain/loss in Snellen lines of CDVA at 1 month, 3, 6, 12 months and 4 years postoperatively.



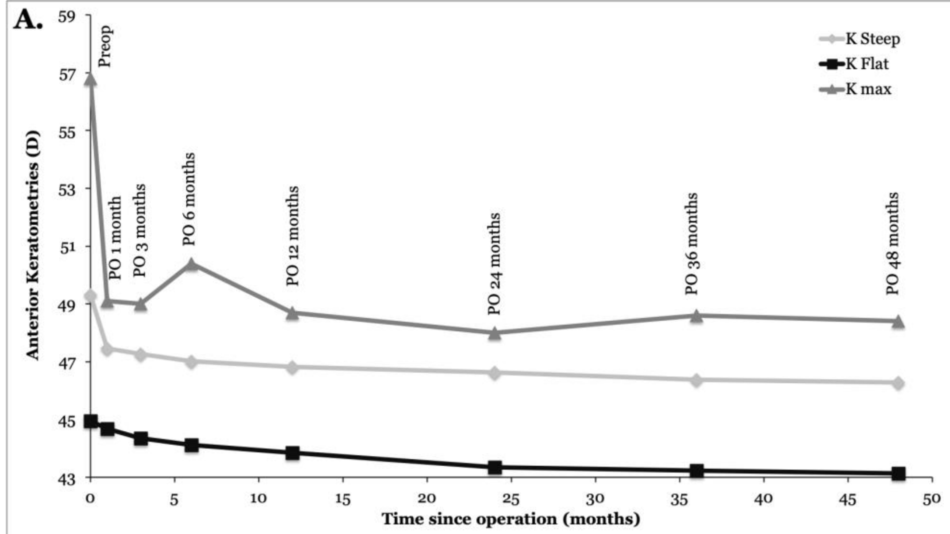


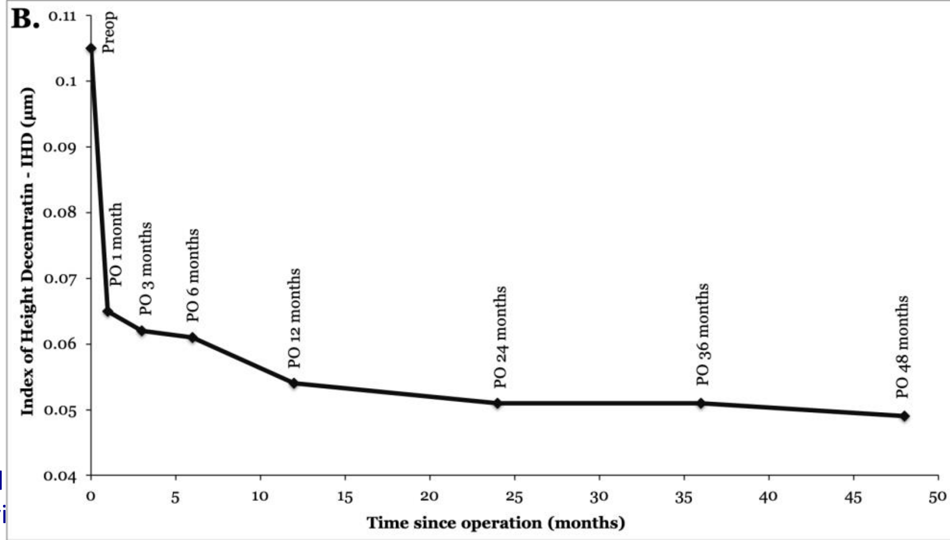
Athens Protocol appears to result in postoperative improvement in both UDVA and CDVA. Average gain/loss in visual acuity was consistently positive, starting from the first postoperative month, with gradual and continuous improvement toward the 4-year visit.

Keratometric Regression

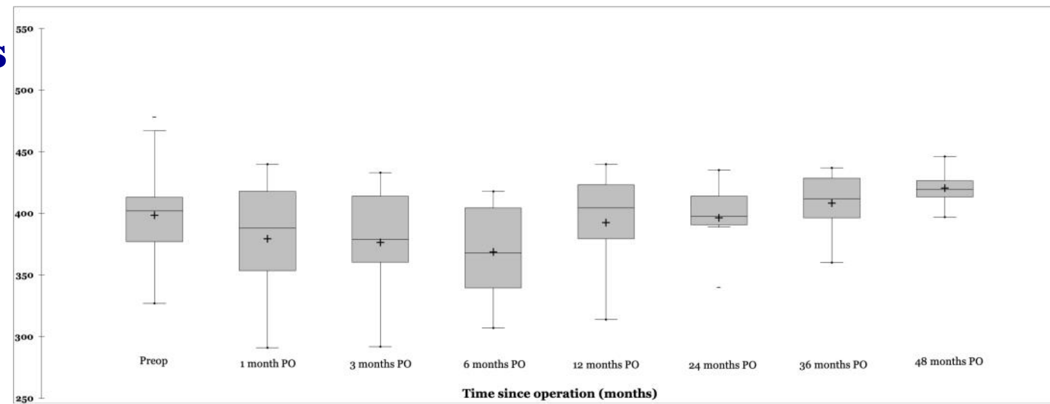
The keratometric values and index of height decentration were reduced in the pediatric patients, particularly in the postoperative 1st month (statistically significant). After the 1st month, until the 48th month, the mean data results were statistically not significant.

Index of Height Decentration Regression

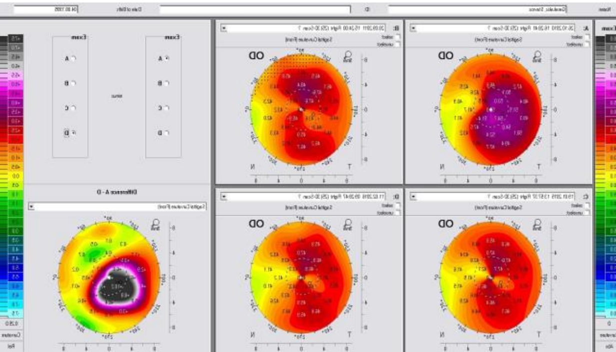




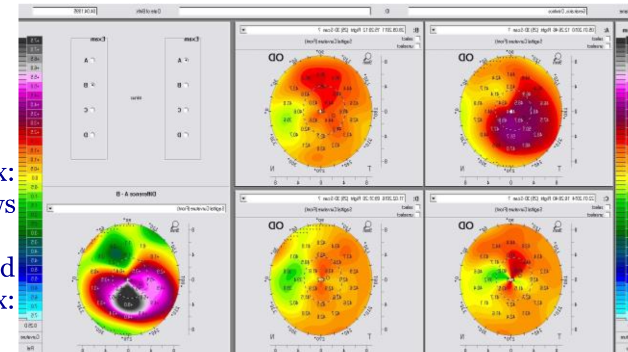
Pachymetric Changes



15 years old Identical Twins



Case 1. (Left) A) Preoperative Pentacam tomography reveals central steep cone (Kmax: 54.7D) (Rx: 0.00 -1.00@20, CDVA 20/32, UCDVA: 20/40) B) One year following AP/OS, the Pentacam shows greater symmetry and reduced steepness of corneal shape Kmax: 48.40D. Rx: plano -1.50 @20 CDVA: 20/25, UCDVA: 20/25 C) At 5 years postoperative, we have even grater symmetry and reduced steepness Kmax: 47.7D. Rx: plano -1.50 @20, CDVA: 20/25, UCDVA: 20/25. D) At 6 years postoperative, Kmax: 47.0D. Rx: plano -1.50 @15, CDVA: 20/25, UCDVA: 20/25.



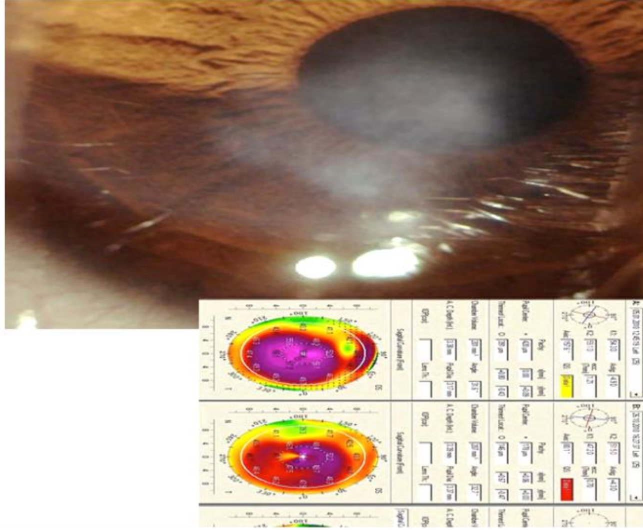
Case 2. (Right) A) Preoperative Pentacam tomography reveals central steep cone (Kmax: 51.7D) (Rx: +0.75 -4.50@40, CDVA 20/32, UCDVA: 20/63) B) One year following AP/OS, the Pentacam shows greater symmetry and reduced steepness of corneal shape Kmax: 45.30D. Rx: -0.50 -0.25 @35 CDVA: 20/25, UCDVA: 20/25 C) At 5 years postoperative, we have even grater symmetry and reduced steepness Kmax: 45.6D. Rx: +0.75sph, CDVA: 20/25, UCDVA: 20/25. D) At 6 years postoperative, Kmax: 43.6D. Rx: plano, CDVA: 20/20, UCDVA: 20/25.

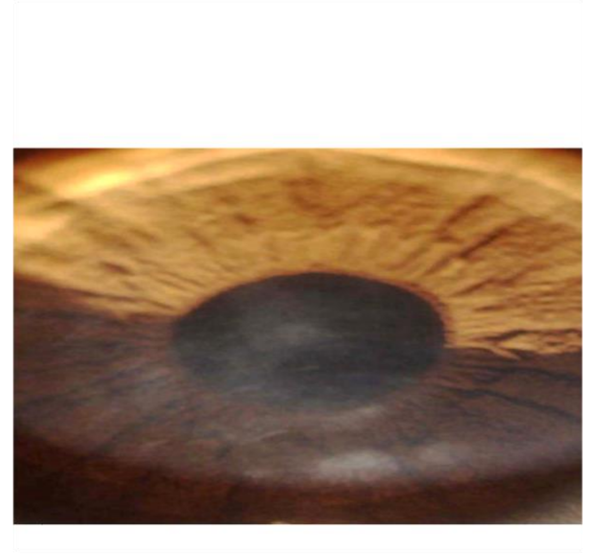
Potential complications specific to pediatric pts

- Bandage contact lens use a specific concern
- Delayed epithelial healing also a concern
- UV-related post-CXL stromal scarring a potential pediatric-specific complication
- Continued eye-rubbing may cause recurrence

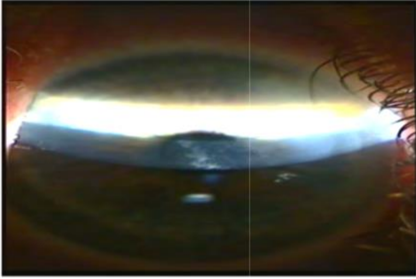
Potential complications specific to pediatric pts

-Late stromal have with UV exposure maybe specific to pediatric pts-

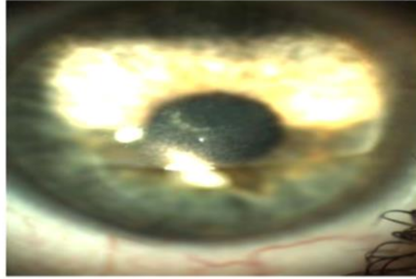




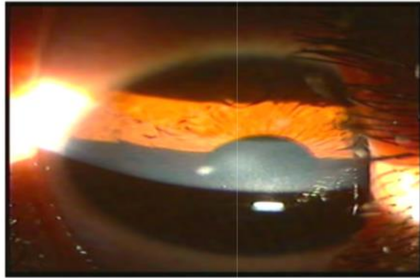
Potential complications specific to pediatric pts



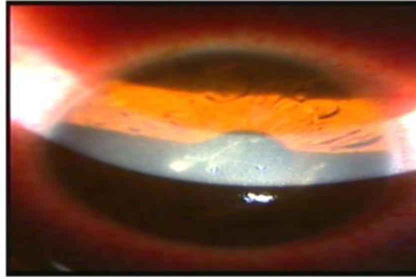
Haze



Salzman's-like nodule(s) can persist to 3 months postop



Faint Scar and white spot



Delayed epithelial healing with white spots

When to CXL: early!

- Screen for keratoconus efficiently
- Strong familiar predisposition for KCN!
- Document progression efficiently!
- Use the optimal pediatric and adult CXL technique of your expertise
- Be aware of complications specific to ped pts especially trisomy 21!

•Alternative treatments:

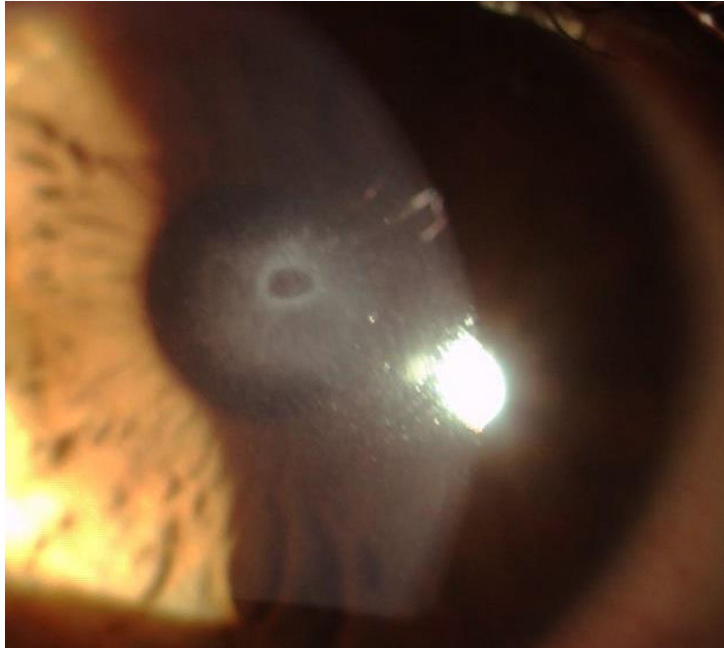
- ✓ CXL alone
- ✓ Contact lenses: RGPs and/or Scleral lenses
- ✓ Intracorneal ring segments
- ✓ Allograft inlays?
- ✓ Lamellar keratoplasty
- ✓ Penetrating keratoplasty

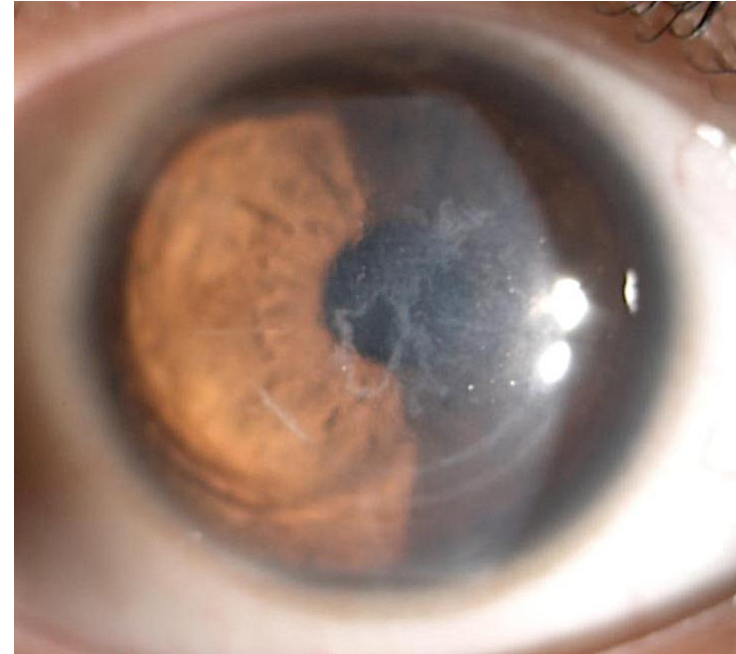
Early Complications

- Postoperative pain
- Immune intrastromal ring
- Delayed epithelial healing
- Salzmann-like epithelial scarring

Early immune-like ring

Delayed epithelial healing





Delayed epithelial healing

80
60
40
20
0

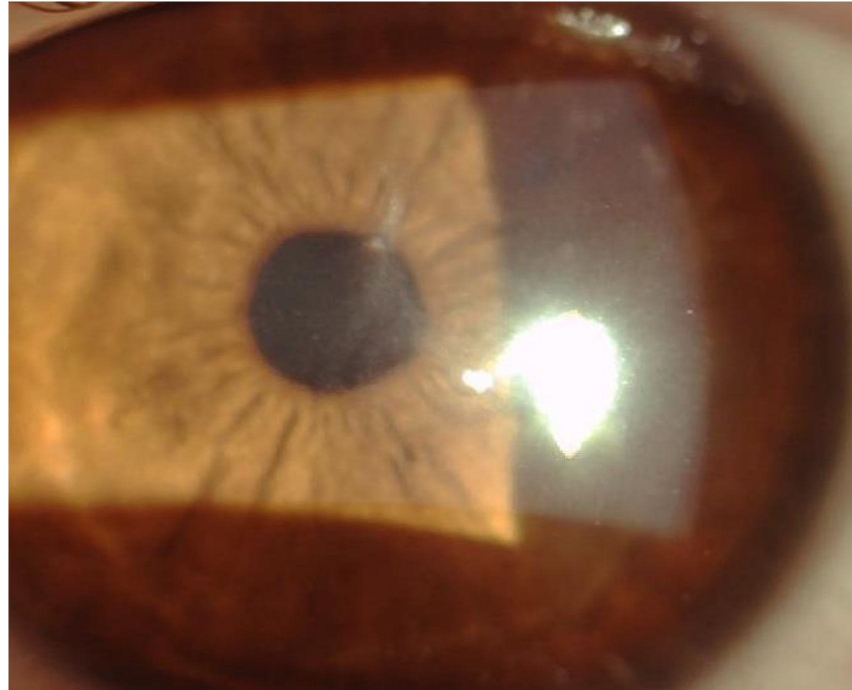
% cases

6 7 8 9 10

Day

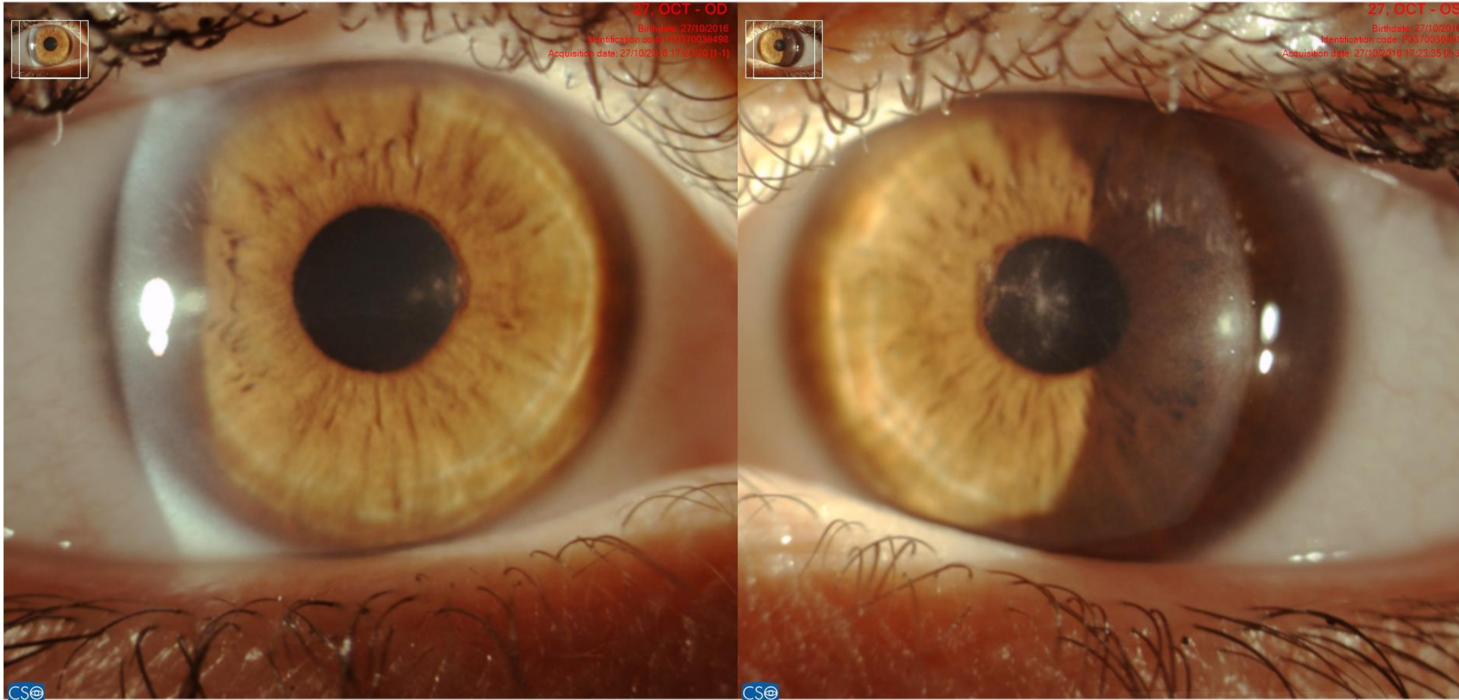
% cases with delayed epithelial healing

Salzmann-like surface hyaline deposits



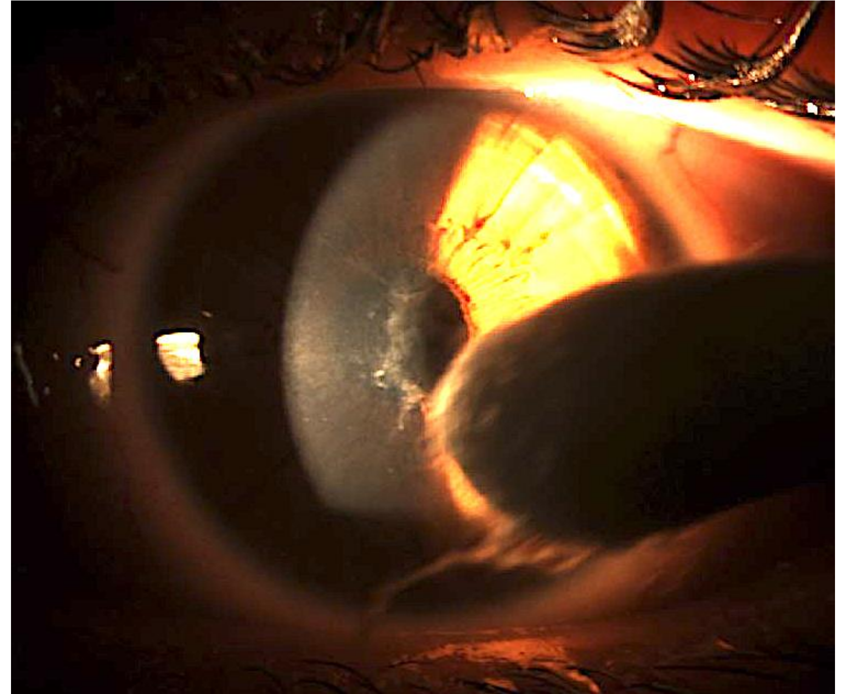
Potential complications: **elevated white epi spots**

1-remove at slit-lamp 2-may hold-off on steroids for a few days, 3-Bandage CL , BCL



Management

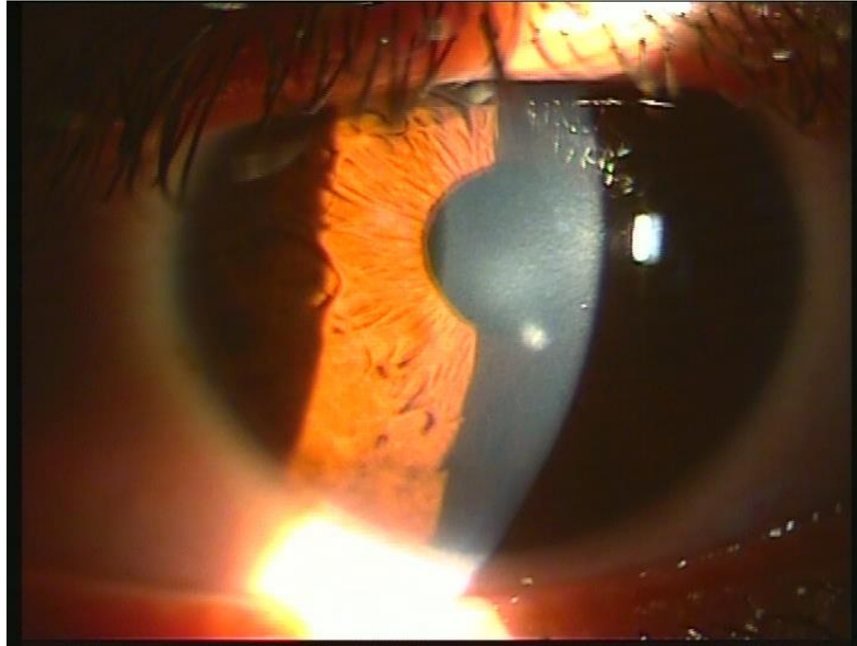
- Lubrication
- Bandage contact lens
- Autologous serum topical administration
- Hold-off steroids
- Surgical removal



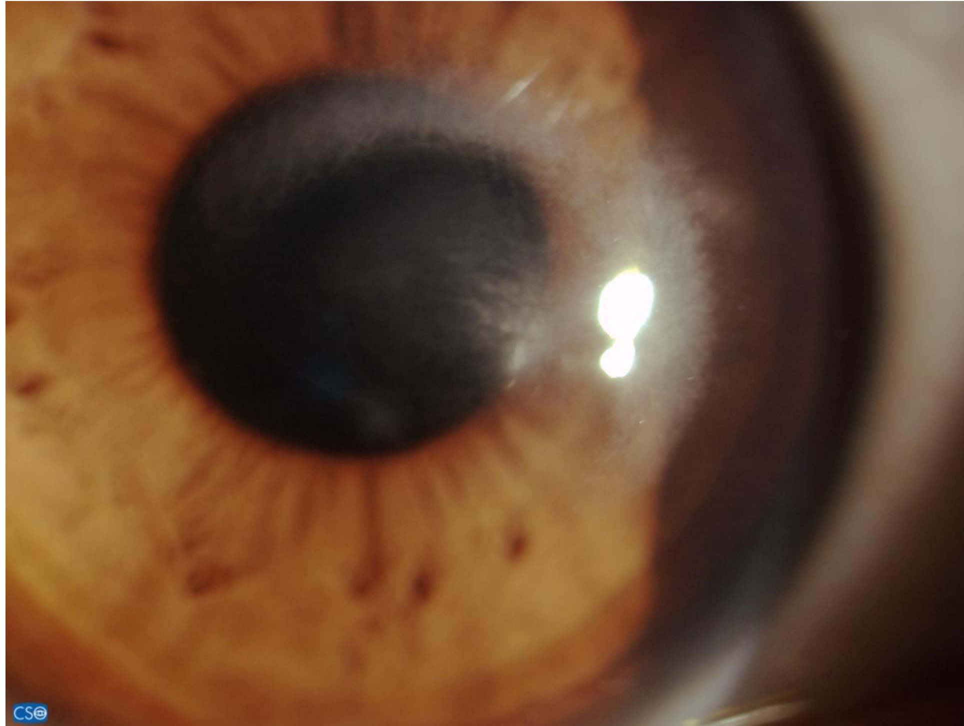
Late Complications

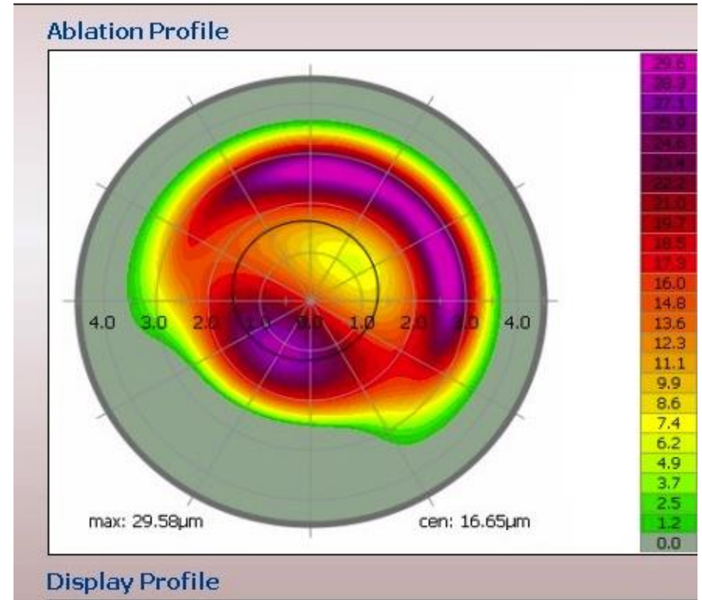
- Subepithelial corneal scar (2.9%, n = 12)
- Stromal haze (3.8%, n = 16)
- Ectatic progression (1.7%, n = 7)
- Overcorrections: 1.2%, n=5

Mild Subepithelial corneal scar

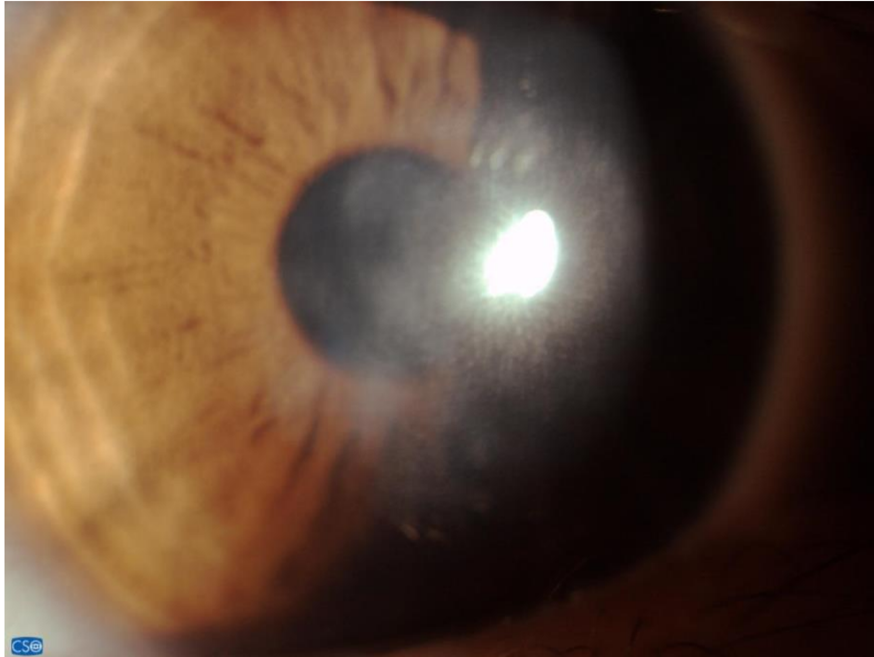


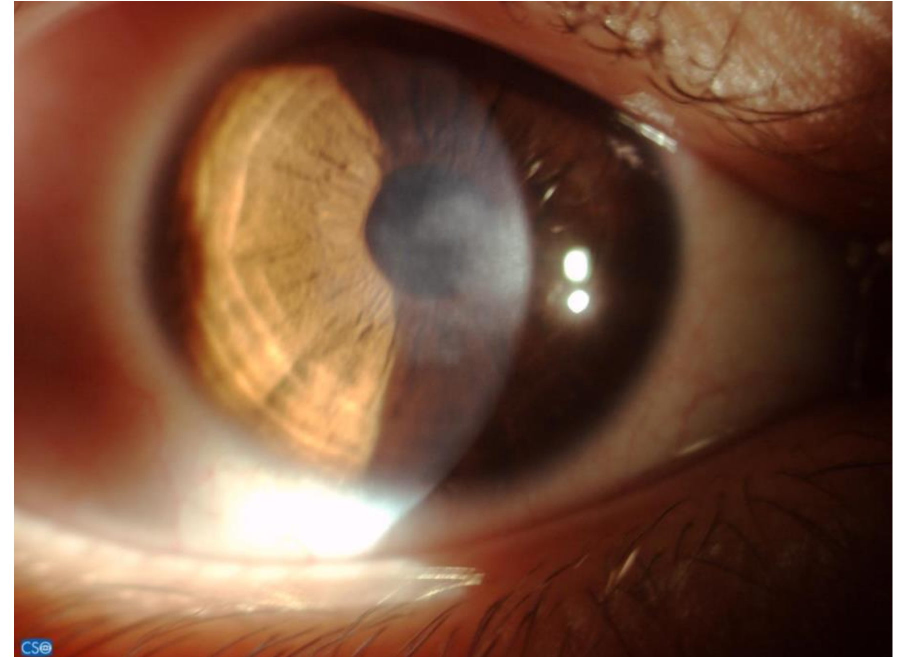
Subepithelial corneal scar and haze related to the normalization ablation



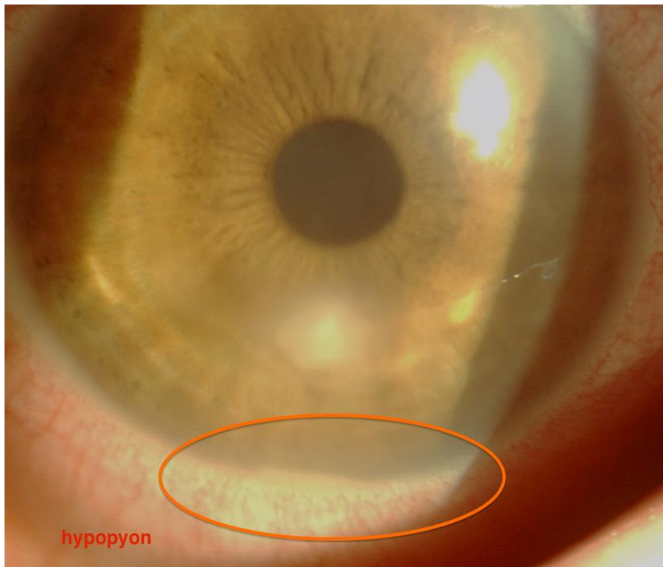


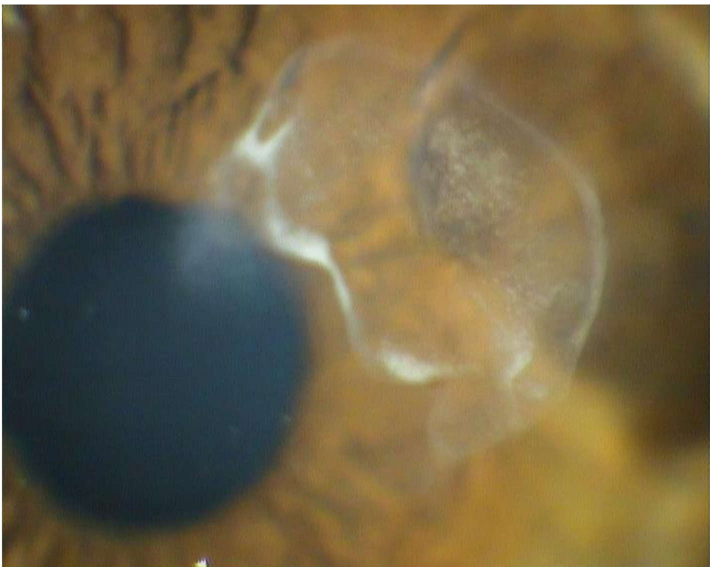
Deep diffuse Stromal haze





Other Infectious Complications: Keratitis





Stromal melt

Unknown potential risks

Long-term ocular surface disease (limbal stem cell def)
Conjunctival squamous cell Ca
Endothelial toxicity
Cataractogenesis
Interference with IOP measurements

Conclusions:

CXL has proven the standard of care internationally and lately in the US for progressive keratoconus and ectasia.

CXL alone achieves significant (1-3 diopters) corneal normalization.

In patients that are contact lens intolerant combining topography-guided partial PRK and CXL has proven in our hands (short term and in over 10 years follow-up) and the subsequent global experience to be safe and effective in enhancing visual rehabilitation.

Clinicians should be cautioned in overcorrecting, potential for delayed healing and/or scarring and the significance of effective ablation plan delivery.

Our current CXL protocols

- **Athens Protocol:** topo partial PRK +15'x 6mw/cm^2
- **LASIK Xtra: 1' (60") 30mW/cm^2 all hyperopes**

Epi-on CXL: 0.25% ribo + 30mW

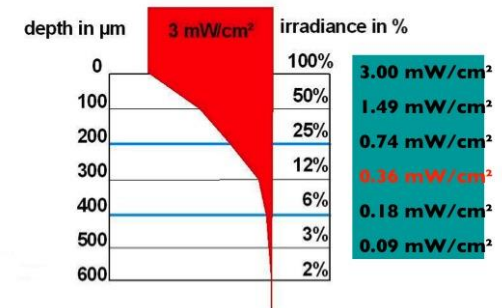
- **Infection: 0.25% riboflavin + 20mW/cm^2 /7,2 Joules**

CXL early!, but should be aware:

- Screen for keratoconus efficiently not every abnormal topography is KCN that will progress
- Strong familiar predisposition for KCN!
- Document progression efficiently!
- Use the optimal pediatric and adult CXL technique of your expertise
- Manage complications early and effectively

From our Athens team: CXL contributions

- 2nd team to CXL - 2002
- Combining high fluence CXL with topo-guided reshaping of irregular corneas - 2005
- Higher fluence - 2006
- CXL and Kpro - 2006
- Intrastromal treatments through femto-pockets - 2007 (
- LASIK Xtra - 2008 *(ESCRS)*
- LASIK Xtra for hyperopia - 2011 *(ASCRS)*
- Combining CXL and AK - 2012 *(ESCRS)*
- Refractive CXL - 2013 *(AAO)*
- Modified Athens Protocol - 2015



Over the last 13 years we have treated over 3000 cases of KCN and ectasia with CXL combined with partial topo-guided PRK: The Athens Protocol.

J Cornea 2007

WAVELIGHT - ALLEGRETTO WAVE TOPOLYZER

A 17.10.03 07:25 Left | B 19.11.04 11:54 Left | C A minus B | D treatment plan

E 20.02.06 15:13 Left | F B minus E | G 17.10.03 07:25 Right | H 19.11.04 11:54 Right

CASE REPORT

Collagen Cross-Linking (CCL) With Sequential Topography-Guided PRK

A Temporizing Alternative for Keratoconus to Penetrating Keratoplasty

A. John Kanellopoulos, MD†‡ and Perry S. Binder, MS, MD§*

Purpose: To assess the effectiveness of ultraviolet A (UVA) irradiation–induced collagen cross-linking (CCL) on keratoconus (KC) progression.

Methods: A patient with bilateral, progressive KC underwent UVA irradiation (3 mW/cm^2 for 30 minutes) after topical 0.1% riboflavin drops over a deepithelialized cornea. Twelve months later, a topography-guided penetrating keratoplasty (PRK; wavelight 400 Hz Eye-Q excimer) was performed in 1 eye for a refractive error of −3.50 −4.00 × 155 by using an attempted treatment of −2.50 −3.00 × 155. At all postoperative follow-up visits to 18 months, uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), pachymetry, and topography were performed.

Results: In the treated left eye, the UCVA after the UVA CCL improved from 20/100 to 20/80, and the BSCVA improved from 20/50 to 20/40. Eighteen months after the topography-guided PRK, the UCVA was 20/20, and the BSCVA was 20/15, with a refractive error of Plano −0.50 × 150. The cornea was clear, and the endothelial cell count remained unchanged. The untreated right mate eye continued to progress during the same period.

Conclusions: The significant clinical improvement and the apparent stability of more than a year after UVA CCL, and subsequent PRK compared with the untreated mate eye, seems to validate this treatment approach for KC. An adjusted nomogram may be considered in the ablation of cross-linked cornea tissue to avoid overcorrections.

Key Words: keratoconus, cornea ectasia, surgical management, collagen cross-linking, ultraviolet A, riboflavin, customized topography-guided cornea ablation, visual rehabilitation

(*Cornea* 2007;26:891–895)

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Keratoconus is a bilateral, nonsymmetric, and noninflammatory progressive corneal degeneration. Its incidence has been thought to be 1 in 2000 in the general population,[1] but the increased number of eyes undergoing screening for laser refractive surgery suggests the prevalence may be higher. It can be diagnosed at puberty, with up to 20% of the eyes progressing to the extent that penetrating keratoplasty is indicated.[2] Although spectacles and contact lenses can provide useful vision in many cases, there are several surgical options for those cases that can no longer benefit from them: implantation of intracorneal ring segments (Intacs or Ferrera rings),[3] lamellar keratoplasty,[4] or penetrating keratoplasty.[2] Other ectatic corneal disorders such as Pellucid marginal degeneration[5] and post-LASIK ectasia[6] require similar treatment approaches. Although penetrating keratoplasty for ectatic corneal disorders is highly successful, many eyes require contact lenses to correct the unpredictable topographic changes that are associated with sutures and postsuture abnormal corneal shapes, and sometimes the contact lens is not successful.[7]

In recent years, basic laboratory studies and subsequent clinical studies have suggested that by increasing the collagen cross-linking (CCL) of the corneal stromal collagen, one is able to increase the stiffness (biomechanics?) of the cornea with attendant stabilization of the normally progressive corneal disorder.[8–16] We present a case of bilateral progressive keratoconus that underwent unilateral CCL followed by PRK with an excellent outcome.

CASE REPORT

A 26-year-old male patient had been treated with gas-permeable contact lenses for 8 years before his presentation. Because of debilitating giant papillary conjunctivitis he was no longer able to wear the contact lens; spectacles were unable to provide functional vision because of poor vision and asthenopia. At the time of his examination, his uncorrected visual acuity (UCVA) was 20/40 in the right eye and 20/100 in the left eye, and his best spectacle-corrected visual acuity (BSCVA) was 20/15 OD (manifest refraction −0.75 −0.75 × 165) and 20/50 OS (manifest refraction −3.75 −4.50 × 155). The keratometry readings were as follows: OD, 43.25 × 10/44.25 × 100; OS, 45.50 × 05/48.50 × 95 (Topolyzer; Wavelight, Erlagen, Germany).

Slit-lamp examination of the right eye failed to show clinical findings associated with keratoconus such as a Fleischer ring, Vogt striae, or a noticeable excessive thinning of the central or paracentral cornea. The central pachymetry was 520 μm (Orbscan II; Bausch and

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CXL followed 6 months later by a partial tPRK

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We have reported early, interim and 10 year data in dozens peer-reviewed publications

ORIGINAL ARTICLE

Corneal Refractive Power and Symmetry Changes Following Normalization of Ectasias Treated With Partial Topography-Guided PTK Combined With Higher-Fluence CXL (The Athens Protocol)

Anastasios John Kanellopoulos, MD; George Asimellis, PhD

ABSTRACT

PURPOSE: To investigate preoperative and postoperative anterior and posterior keratometry and simulated corneal astigmatism in keratoconic eyes treated with collagen cross-linking combined with anterior surface normalization by partial topography-guided excimer ablation (the Athens Protocol).

METHODS: Anterior and posterior corneal keratometry were measured by Scheimpflug imaging for 267 untreated keratoconic eyes. Following treatment, they were assessed 1 year postoperatively.

RESULTS: Before treatment, average anterior keratometric value was 47.06 ± 6.02 diopters (D) for flat and 51.24 ± 6.75 D for steep. The posterior keratometric values were -6.70 ± 0.99 D (flat) and -7.67 ± 1.15 D (steep). Anterior astigmatism was on average with-the-rule (-1.97 ± 6.21 D), whereas posterior astigmatism was against-the-rule (+0.53 ± 1.02 D). The posterior and anterior astigmatism were highly correlated (r^2 = 0.839). After treatment, anterior keratometric values were 43.97 ± 5.81 D (flat) and 46.55 ± 6.82 D (steep). Posterior keratometric values were -6.58 ± 1.05 D (flat) and -7.69 ± 1.22 D (steep). Anterior astigmatism was on average with-the-rule (-1.56 ± 3.80 D), whereas posterior astigmatism was against-the-rule (+0.45 ± 1.29 D). The statistically significant (P < .05) keratometric changes indicated anterior surface flattening -3.09 ± 2.67 D (flat) and -4.19 ± 2.96 D (steep). The posterior keratometric changes were not statistically significant (P > .05).

CONCLUSIONS: Before treatment, there was a strong correlation between posterior and anterior corneal astigmatism. After treatment, statistically significant anterior keratometric values flattened. The posterior surface keratometric values did not demonstrate statistically significant postoperative change: there was minimal posterior change, despite the significant anterior surface normalization.

[*J Refract Surg.* 2014;30(5):342-346.]

Keratoconus assessment employs indicators such as keratometric values, inferior-superior index, skew percentage, astigmatism, and the KISA% index.[1] Acceptable quantitative keratometric criteria include central corneal refractive power larger than 47.2 diopters (D), inferior-superior dioptric asymmetry larger than 1.2 D, and simulated astigmatism, expressed as the difference between steep and flat keratometric values greater than 1.5 D.[2] The steep and flat meridian keratometric values correspond to the smaller and larger anterior corneal curvature radius, respectively.

Corneal cross-linking (CXL) is an in vivo intrastromal photo-oxidative technique with riboflavin and ultraviolet-A light aiming to address the advancing corneal ectasia and, consequently, the keratoconus progression. With CXL, additional covalent bonding between stromal collagen can be achieved, which stabilizes the collagen framework structure.[3] The remodeling effects of CXL on the cornea can be described by the reduction of mean anterior surface keratometric values.[4] Few studies have been published on the quantitative link between anterior and posterior keratometric values in keratoconic eyes or particularly on the postoperative effects of CXL on either corneal surface.

This study aims to investigate the distribution of and relationship between anterior and posterior corneal keratometric values and simulated anterior and posterior astigmatism on a large group of clinically diagnosed, untreated keratoconic eyes, and the 1-year postoperative effects on both anterior and posterior keratometric values and astigmatism induced by a combined procedure known as the Athens Protocol,[5,6] which intends to arrest the keratoconus progression and normalize the anterior corneal surface.

From Laservision.gr Eye Institute, Athens, Greece (AJK, GA); and New York University School of Medicine, New York, New York (AJK).

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The authors have no financial or proprietary interest in the materials presented herein.

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ORIGINAL ARTICLE

Keratoconus Management: Long-Term Stability of Topography-Guided Normalization Combined With High-Fluence CXL Stabilization (The Athens Protocol)

Anastasios John Kanellopoulos, MD; George Asimellis, PhD

ABSTRACT

PURPOSE: To investigate refractive, topometric, pachymetric, and visual rehabilitation changes induced by anterior surface normalization for keratoconus by partial topography-guided excimer laser ablation in conjunction with accelerated, high-fluence cross-linking.

METHODS: Two hundred thirty-one keratoconic cases subjected to the Athens Protocol procedure were studied for visual acuity, keratometry, pachymetry, and anterior surface irregularity indices up to 3 years postoperatively by Scheimpflug imaging (Oculus Optikgeräte GmbH, Wetzlar, Germany).

RESULTS: Mean visual acuity changes at 3 years postoperatively were +0.38 ± 0.31 (range: -0.34 to +1.10) for uncorrected distance visual acuity and +0.20 ± 0.21 (range: -0.32 to +0.90) for corrected distance visual acuity. Mean K1 (flat meridian) keratometric values were 46.56 ± 3.83 diopters (D) (range: 39.75 to 58.30 D) preoperatively, 44.44 ± 3.97 D (range: 36.10 to 55.50 D) 1 month postoperatively, and 43.22 ± 3.80 D (range: 36.00 to 53.70 D) up to 3 years postoperatively. The average Index of Surface Variance was 98.48 ± 43.47 (range: 17 to 208) preoperatively and 76.80 ± 38.41 (range: 7 to 190) up to 3 years postoperatively. The average Index of Height Decentration was 0.091 ± 0.053 µm (range: 0.006 to 0.275 µm) preoperatively and 0.057 ± 0.040 µm (range: 0.001 to 0.208 µm) up to 3 years postoperatively. Mean thinnest corneal thickness was 451.91 ± 40.02 µm (range: 297 to 547 µm) preoperatively, 353.95 ± 53.90 µm (range: 196 to 480 µm) 1 month postoperatively, and 370.52 ± 58.21 µm (range: 218 to 500 µm) up to 3 years postoperatively.

CONCLUSIONS: The Athens Protocol to arrest keratectasia progression and improve corneal regularity demonstrates safe and effective results as a keratoconus management option. Progressive potential for long-term flattening validates using caution in the surface normalization to avoid overcorrection.

[*J Refract Surg.* 2014;30(2):88-92.]

Keratoconus is a degenerative bilateral, noninflammatory disorder characterized by ectasia, thinning, and irregular corneal topography.[1] The disorder usually has onset at puberty and often progresses until the third decade of life, may manifest asymmetrically in the two eyes of the same patient, and can present with unpredictable visual acuity, particularly in relation to corneal irregularities.[2] One of the acceptable options[3] for progressive keratoconus management is corneal collagen cross-linking (CXL) with riboflavin and ultraviolet-A.[4]

To further improve the topographic and refractive outcomes, CXL can be combined with customized anterior surface normalization.[5-7] Our team has developed a procedure[8,9] we have termed the Athens Protocol,[10] involving sequentially excimer laser epithelial debridement (50 µm), partial topography-guided excimer laser stromal ablation, and high-fluence ultraviolet-A irradiation (10 mW/cm²), accelerated (10', or minutes) CXL. Early results[11] and anterior segment optical coherence tomography quantitative findings[12] are indicative of the long-term stability of the procedure.

Detailed studies on postoperative visual rehabilitation and anterior surface topographic changes by such combined CXL procedures are rare,[13-16] particularly those reporting results longer than 1 year. This study aims to investigate safety and efficacy of the Athens Protocol procedure by analysis of long-term (3-year) refractive, topographic, pachymetric, and visual rehabilitation changes on clinical keratoconus management with the Athens Protocol in a large number of cases.

PATIENTS AND METHODS

This clinical study received approval by the Ethics Committee of our Institution and adhered to the tenets of the Declaration

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Dr. Kanellopoulos is a consultant for Alcon/WaveLight. The remaining author has no financial or proprietary interest in the materials presented herein.

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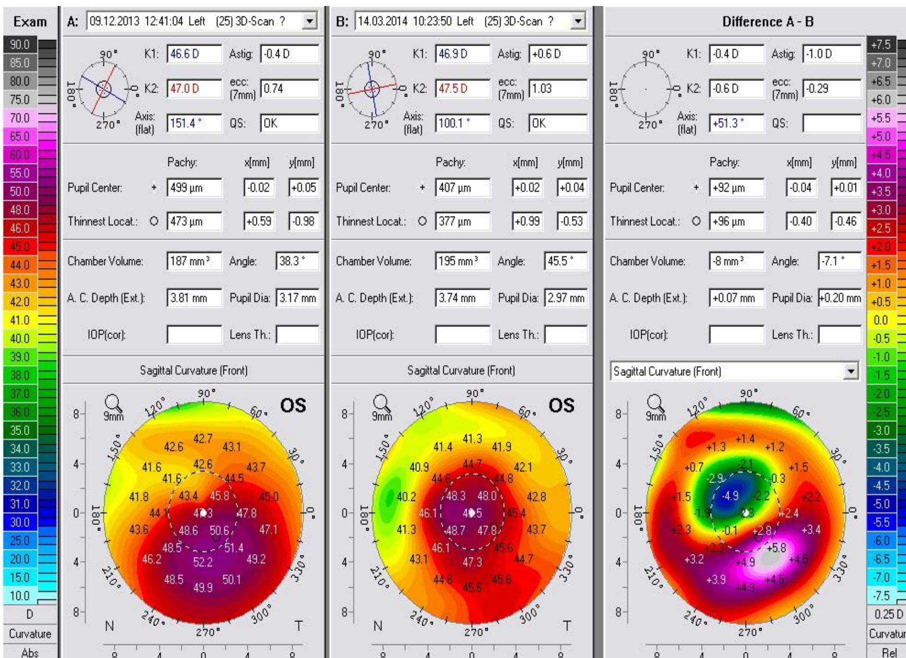

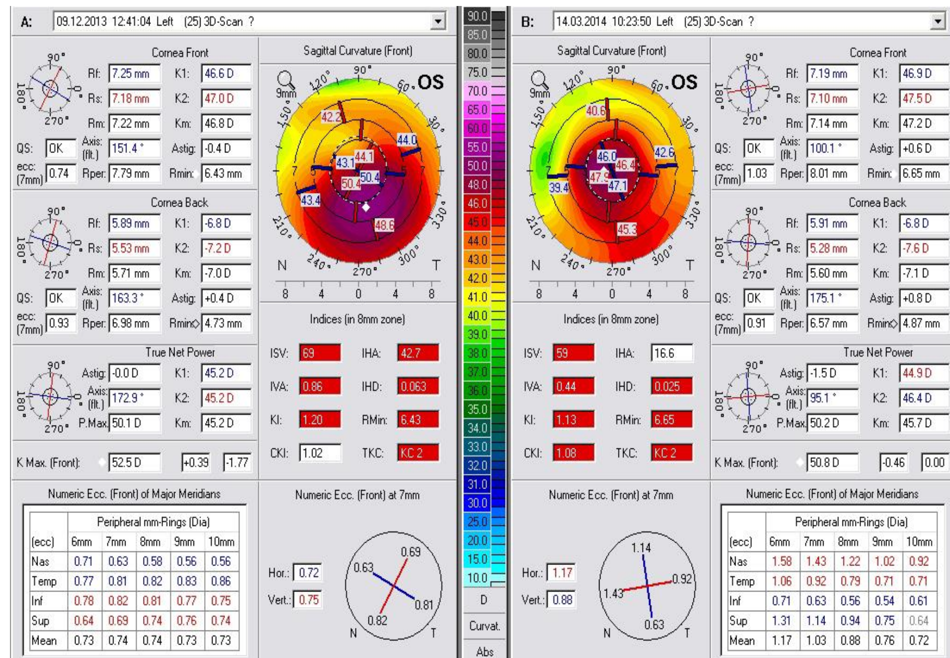

Peripheral mm-Rings (Dia) (A)	6mm	7mm	8mm	9mm	10mm
Nas	0.71	0.63	0.58	0.56	0.56
Temp	0.77	0.81	0.82	0.83	0.86
Inf	0.78	0.82	0.81	0.77	0.75
Sup	0.64	0.69	0.74	0.76	0.74
Mean	0.73	0.74	0.74	0.73	0.73

Peripheral mm-Rings (Dia) (B)	6mm	7mm	8mm	9mm	10mm
Nas	1.58	1.43	1.22	1.02	0.92
Temp	1.06	0.92	0.79	0.71	0.71
Inf	0.71	0.63	0.56	0.54	0.61
Sup	1.31	1.14	0.94	0.75	0.64
Mean	1.17	1.03	0.88	0.76	0.72

Case presentation of a 30-year old male patient subjected to the Athens Protocol procedure. Pre-operatively, the patient's best correction was -1.00 S -2.75 C x 98, CDVA with this refraction was 0.65 decimal. Six-months postoperatively, the patient has just 1.50 D of myopia, with zero cylinder. His CDVA with this refraction is 1.0 decimal. Top, sagittal curvature data, pre-operative (left), thee-month post-operative (center) and difference (right). Bottom, topometric comparison. Note the significant reduction occurring in all anterior-surface asymmetry indices, particularly in the index of height decentration (IHD) from 0.063 to 0.025.

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Key Kanellopoulos ectasia questions::

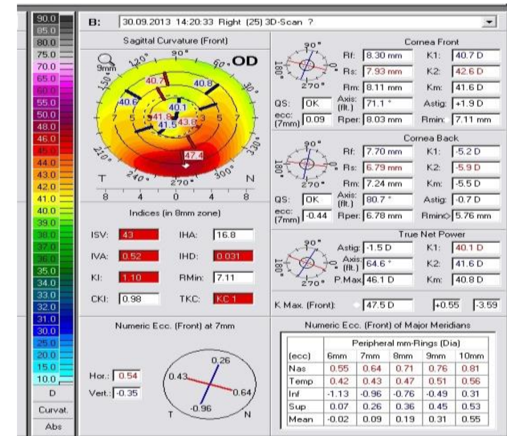
- Does the thickness change first or does curvature change first?
- Does anterior curvature change first or posterior?
- Are corneas with "weaker" biomechanics in risk for ectasia? - or is there a "break" point in biomechanics different for EACH cornea in destabilizing it?

Visual rehabilitation of ECTASIA:

- Spectacles, Contacts, INTACS, DALK, PK!
- CXL
- Combined technique: CXL+tgPRK
- Implantation of phakic IOLs in cases with high residual myopia and/or anisometropia
- CXL prior to a phakic IOL will produce a more stable ground for calculating the refractive error
- Other

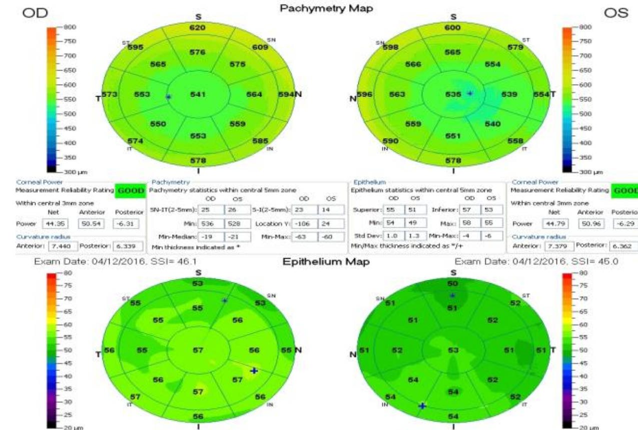
Currently sensitive criteria:

- Topometric asymmetry indices IHD and ISV
- Pachymetric asymmetry; Scheimpflug, OCT
- ART – Max = TP / PPI – Max (essentially "steep" cornea pachymetry change)
- Epithelial profiles
- Biomechanical measurements-Brillouin

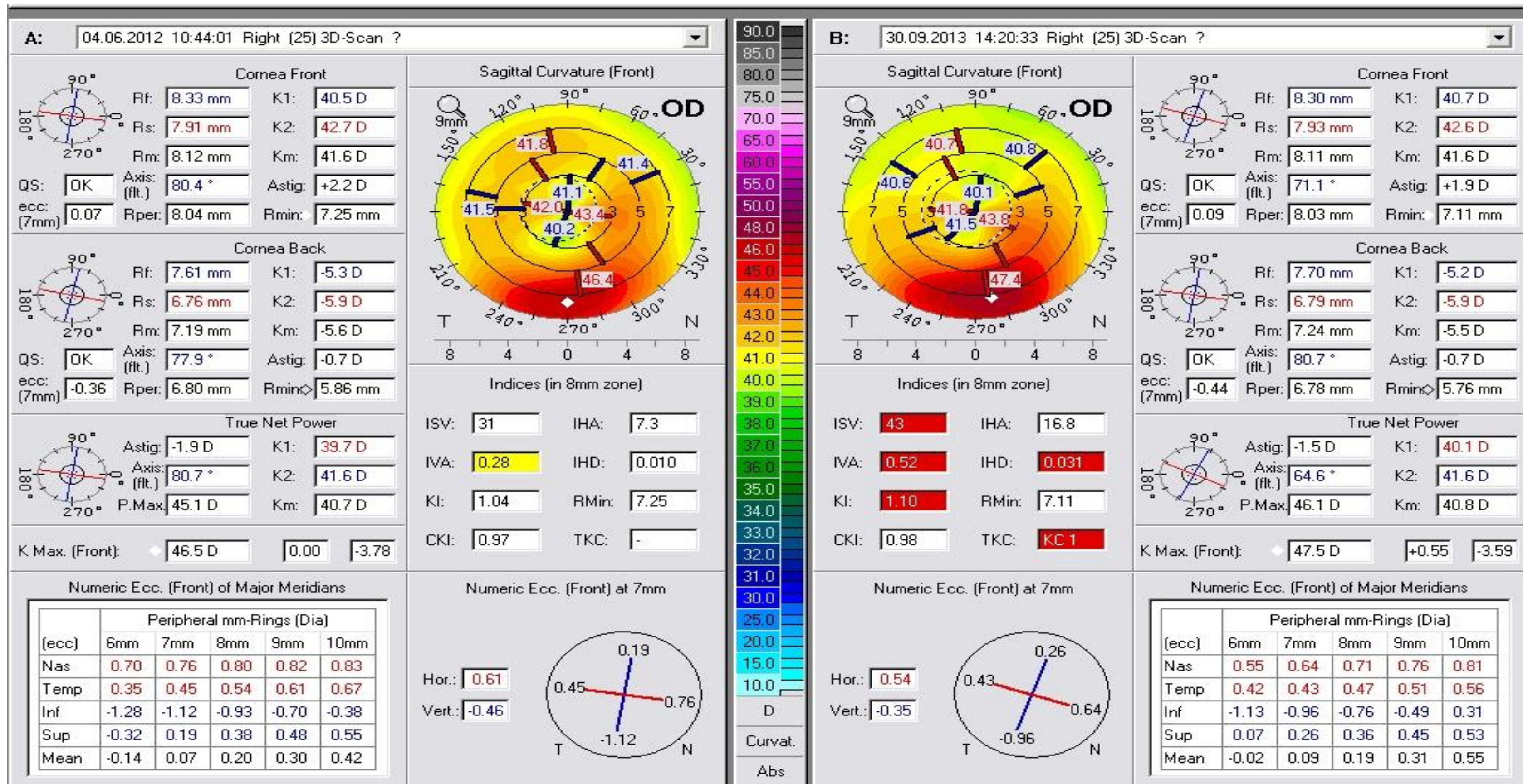


My Clinical practice:

- Asymmetry indices Topometric indices IHD, ISV
- Pachymetric norms and asymmetry changes
- Epithelial remodeling
- Biomechanical measurements?
- View all topos in correlation with Biomicroscopy!
- Family topos important!



Most topometric asymmetry indices worse!



Is this KCN?

OCULUS - PENTACAM

Field	Value	Field	Value
Last Name:	Lake		
First Name:	Brian		
ID:	40806		
Date of Birth:	06/04/1959	Eye:	Right
Exam Date:	04/23/2014	Time:	12:35:51
Exam Info:			

Cornea Front

Rh:	7.41 mm	K2:	45.6 D
Rv:	7.55 mm	K1:	44.7 D
Rm:	7.48 mm	Km:	45.1 D
QS: OK	Axis: (flat) 55.9 °	Astig:	0.9 D
Q-val.: (30°) -0.37	Rper: 7.98 mm	Rmin:	6.88 mm

Cornea Back

Rh:	6.38 mm	K1:	-6.3 D
Rv:	6.03 mm	K2:	-6.6 D
Rm:	6.21 mm	Km:	-6.4 D
QS: OK	Axis: (flat) 179.5 °	Astig:	0.4 D
Q-val.: (30°) -0.31	Rper: 6.60 mm	Rmin:	5.89 mm

	Pachy:	x[mm]	y[mm]
Pupil Center:	514 µm	-0.32	+0.18
Pachy Apex:	519 µm	0.00	0.00
Thinnest Locat.:	509 µm	-0.86	+0.60
K Max. (Front):	49.0 D	+0.07	-2.18

Cornea Volume:	59.2 mm³	KPD:	+1.1 D
Chamber Volume:	111 mm³	Angle:	30.5 °
A. C. Depth (Int.):	2.47 mm	Pupil Dia:	2.77 mm
Enter IOP	IOP(cor):	Lens Th.:	

Refractive

Sagittal Curvature (Front) — OD

Elevation (Front) — BFS=7.72 Float, Dia=8.00 — OD

Corneal Thickness — OD

Elevation (Back) — BFS=6.30 Float, Dia=8.00 — OD

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Post-LASIK ectasia?

OCULUS - PENTACAM

Last Name:	Lake		
First Name:	Brian		
ID:	40806		
Date of Birth:	06/04/1959	Eye:	Right
Exam Date:	04/23/2014	Time:	12:35:51
Exam Info:			

Cornea Front

		Rh:	7.41 mm	K2:	45.6 D
		Rv:	7.55 mm	K1:	44.7 D
		Rm:	7.48 mm	Km:	45.1 D
QS:	OK	Axis: (flat)	55.9 °	Astig:	0.9 D
Q-val.: (30°)	-0.37	Rper:	7.98 mm	Rmin:	6.88 mm

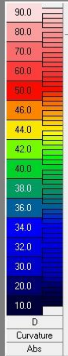
Cornea Back

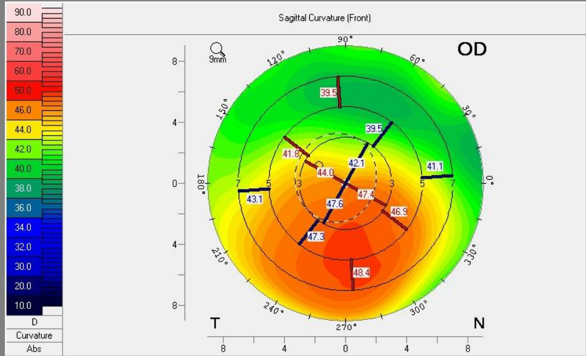
		Rh:	6.38 mm	K1:	-6.3 D
		Rv:	6.03 mm	K2:	-6.6 D
		Rm:	6.21 mm	Km:	-6.4 D
QS:	OK	Axis: (flat)	179.5 °	Astig:	0.4 D
Q-val.: (30°)	-0.31	Rper:	6.60 mm	Rmin:	5.89 mm

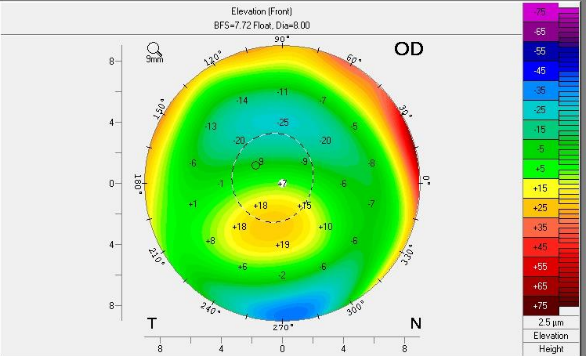
	Pachy:	x[mm]	y[mm]
Pupil Center:	514 µm	-0.32	+0.18
Pachy Apex:	519 µm	0.00	0.00
Thinnest Locat.:	509 µm	-0.86	+0.60
K Max. (Front):	49.0 D	+0.07	-2.18

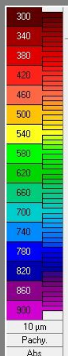
Cornea Volume:	59.2 mm³	KPD:	+1.1 D
Chamber Volume:	111 mm³	Angle:	30.5 °
A. C. Depth (Int.):	2.47 mm	Pupil Dia:	2.77 mm
Enter IOP	IOP(cor):	Lens Th.:	

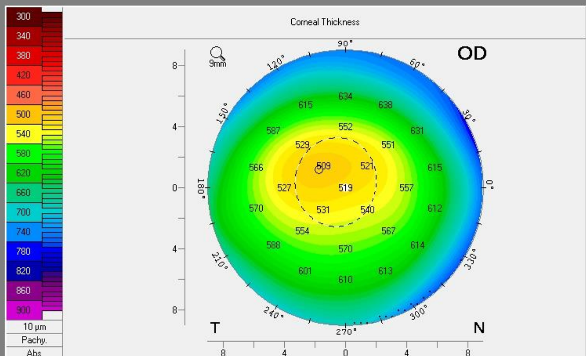
Refractive

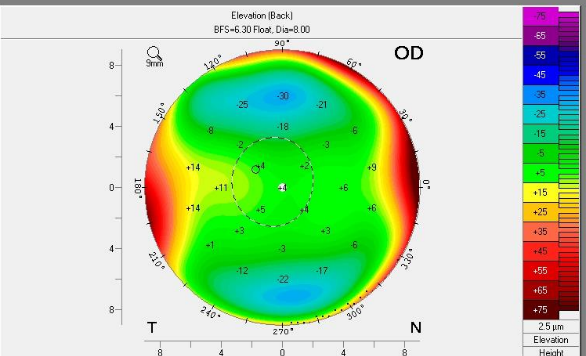












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Is this keratoconus progressing?

	A: 04.06.2012 10:44:01 Right (25) 3D-Scan ?	B: 30.09.2013 14:20:33 Right (25) 3D-Scan ?	Difference A - B
K1	40.5 D	40.7 D	-0.2 D
K2	42.7 D	42.6 D	+0.1 D
Axis (flat)	80.4 °	71.1 °	+9.3 °
Astig	+2.2 D	+1.9 D	+0.3 D
ecc (7mm)	0.07	0.09	-0.02
QS	OK	OK	
Pupil Center: Pachy	572 µm	560 µm	+12 µm
Pupil Center: x[mm]	-0.33	-0.32	-0.02
Pupil Center: y[mm]	+0.12	+0.11	0.00
Thinnest Locat.: Pachy	553 µm	537 µm	+16 µm
Thinnest Locat.: x[mm]	-0.69	-0.70	+0.01
Thinnest Locat.: y[mm]	-1.78	-1.88	+0.10
Chamber Volume	197 mm³	188 mm³	+9 mm³
Angle	40.9 °	40.8 °	+0.1 °
A. C. Depth (Ext.)	3.82 mm	3.74 mm	+0.08 mm
Pupil Dia	2.62 mm	3.10 mm	-0.47 mm
IOP(cor)			
Lens Th.			

Sagittal Curvature (Front) — OD

Athend Protocol outcomes:

From stage 3 KCN to NONE Average K from 48.5 to 44 Refraction -2.5-4.5@155 (20/70) to -1-1.5@10 (20/20)

A: 21.09.2009 10:27:52 Left (25)

Cornea Front

Rh: 7.25 mm	K1: 46.6 D
Rv: 6.67 mm	K2: 50.6 D
Rm: 6.96 mm	Km: 48.5 D
QS: OK / Axis: 138.4°	Astig: -4.1 D
ecc (7mm): 0.74 / Rper: 7.54 mm	Rmin: 6.06 mm

Cornea Back

Rh: 5.93 mm	K1: -6.7 D
Rv: 5.04 mm	K2: -7.9 D
Rm: 5.49 mm	Km: -7.3 D
QS: OK / Axis: 146.7°	Astig: +1.2 D
ecc (7mm): 0.87 / Rper: 6.55 mm	Rmin: 4.51 mm

True Net Power

Astig: -3.3 D	K1: 45.5 D
Axis: 136.0°	K2: 48.8 D
P.Max: 53.3 D	Km: 47.2 D

Sagittal Curvature (Front)

Indices (in 8mm zone)

ISV: 92	IHA: 49.4
IVA: 1.08	IHD: 0.080
KI: 1.25	RMin: 6.06
CKI: 1.03	ABR: 2.0

Keratoconus Level Topogr.

KK 2-3

Numeric Ecc. (Front) at 7mm

Hor.: 0.66 Vert.: 0.81

Numeric Ecc. (Front) of Major Meridians

(ecc)	6mm	7mm	8mm	9mm	10mm
	Peripheral mm-Rings (Dia)				
Nas	0.75	0.63	0.56	0.54	0.55
Temp	0.58	0.69	0.76	0.81	0.85
Inf	0.75	0.82	0.88	0.92	0.96
Sup	0.86	0.80	0.76	0.74	0.77
Mean	0.73	0.74	0.74	0.75	0.78

B: 19.11.2010 11:15:39 Right (25)

Sagittal Curvature (Front)

Indices (in 8mm zone)

ISV: 39	IHA: 17.0
IVA: 0.40	IHD: 0.019
KI: 1.06	RMin: 7.06
CKI: 1.01	ABR: 0.0

Keratoconus Level Topogr.

KK possible

Numeric Ecc. (Front) at 7mm

Hor.: 0.45 Vert.: -0.05

Cornea Front

Rh: 7.78 mm	K1: 43.4 D
Rv: 7.54 mm	K2: 44.8 D
Rm: 7.66 mm	Km: 44.1 D
QS: OK / Axis: 25.3°	Astig: -1.4 D
ecc (7mm): 0.20 / Rper: 7.77 mm	Rmin: 7.06 mm

Cornea Back

Rh: 6.33 mm	K1: -6.3 D
Rv: 5.67 mm	K2: -7.0 D
Rm: 6.00 mm	Km: -6.7 D
QS: OK / Axis: 21.6°	Astig: +0.7 D
ecc (7mm): 0.65 / Rper: 6.45 mm	Rmin: 5.24 mm

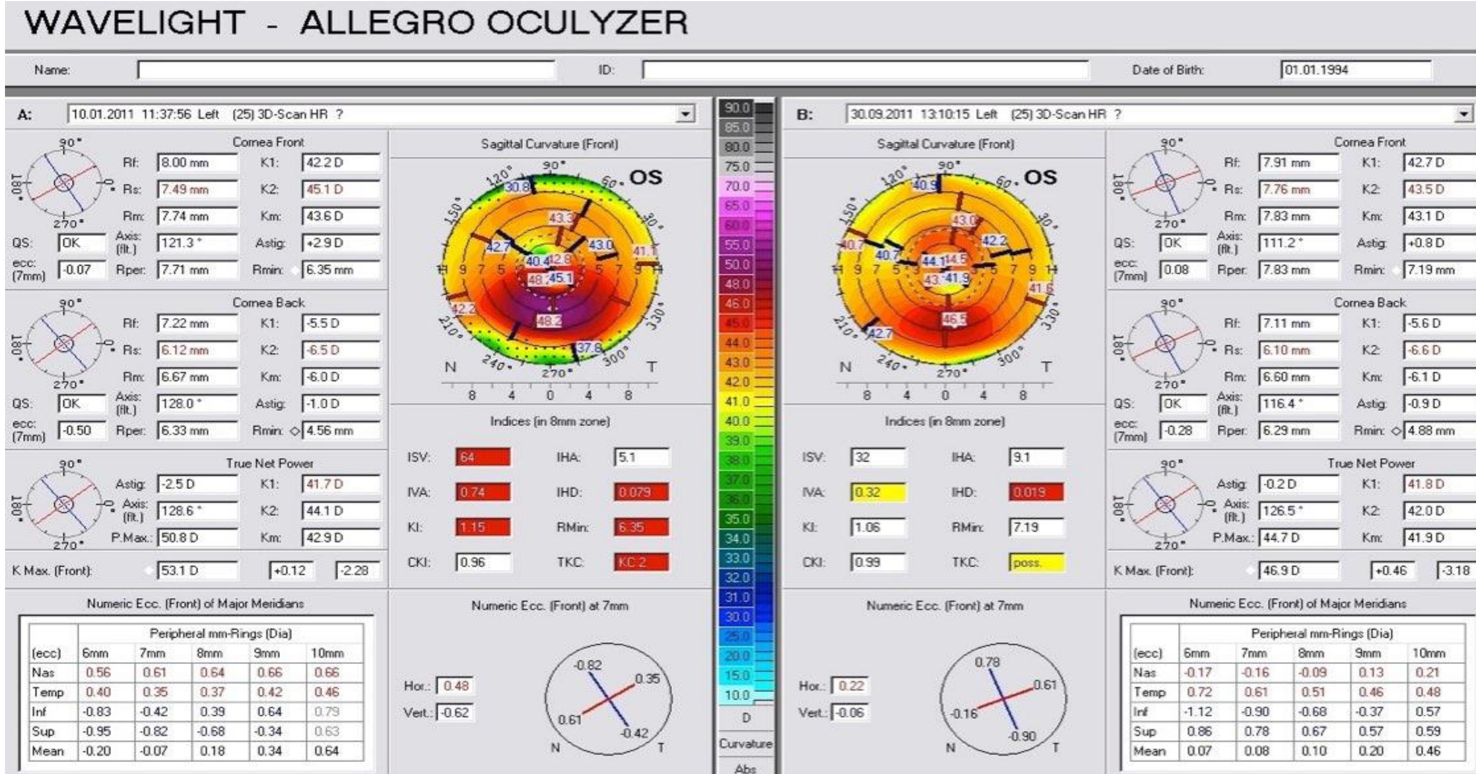
True Net Power

Astig: -0.7 D	K1: 42.2 D
Axis: 25.3°	K2: 42.9 D
P.Max: 46.0 D	Km: 42.6 D

Numeric Ecc. (Front) of Major Meridians

(ecc)	6mm	7mm	8mm	9mm	10mm
	Peripheral mm-Rings (Dia)				
Nas	0.76	0.49	-0.13	-0.36	-0.31
Temp	0.45	0.41	0.42	0.48	0.56
Inf	-0.69	-0.50	0.10	0.55	0.78
Sup	0.46	0.41	0.42	0.48	0.59
Mean	0.24	0.20	0.20	0.29	0.41

Athens Protocol outcomes: may induce myopia!
Refraction from +0.75-3.50@10 (20/60) to -0.75-0.75@170 (20/20) due to improvement of the topometric parameters.

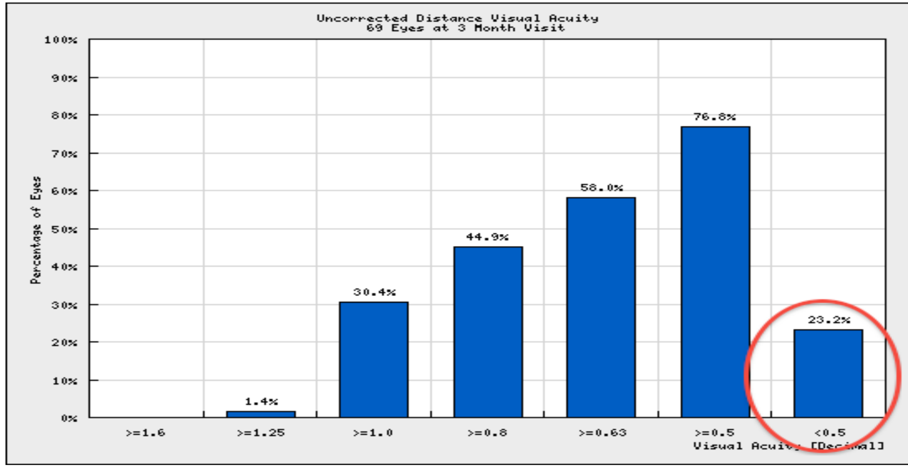


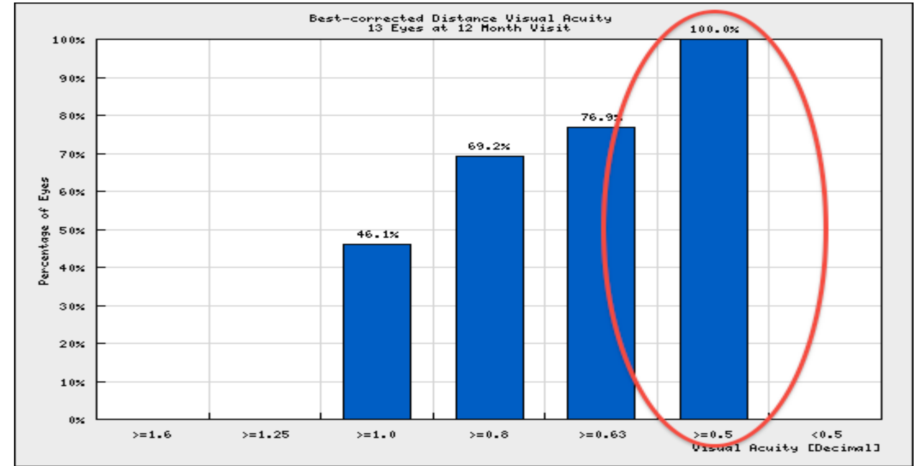
(ecc)	6mm	7mm	8mm	9mm	10mm
Nas	0.56	0.61	0.64	0.66	0.66
Temp	0.40	0.35	0.37	0.42	0.46
Inf	-0.83	-0.42	0.39	0.64	0.79
Sup	-0.95	-0.82	-0.68	-0.34	0.63
Mean	-0.20	-0.07	0.18	0.34	0.64

(ecc)	6mm	7mm	8mm	9mm	10mm
Nas	-0.17	-0.16	-0.09	0.13	0.21
Temp	0.72	0.61	0.51	0.46	0.48
Inf	-1.12	-0.90	-0.68	-0.37	0.57
Sup	0.86	0.78	0.67	0.57	0.59
Mean	0.07	0.08	0.10	0.20	0.46

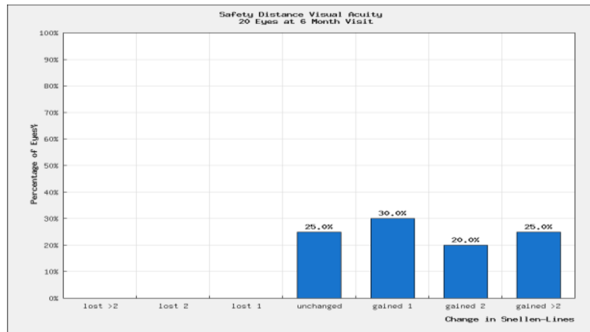
Athens Protocol:

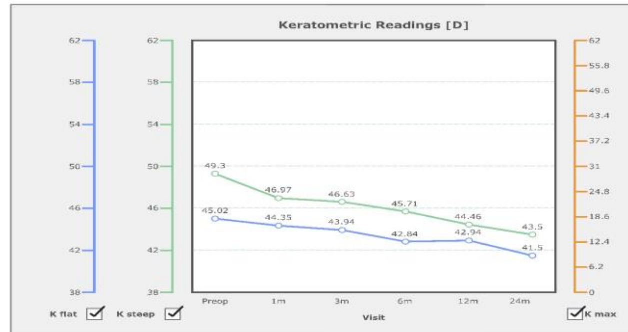
Some improvement in UCVA, dramatic improvement in BSCVA: 98% of cases at least 20/40!)





Athens Protocol: safety





Athens Protocol:

Keratometric change over 24 months, progressive flattening this finding makes challenging the prediction of refractive correction

New York University School of Medicine

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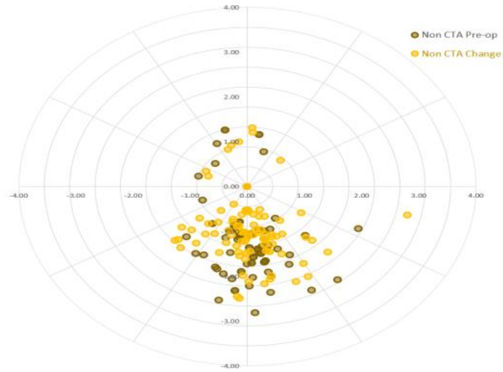
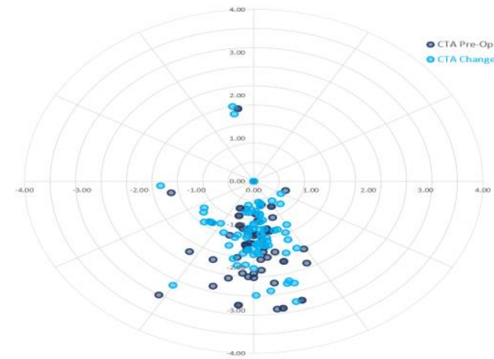
Comparative Results 220 Athens Protocol eyes treated with the EX500 excimer (Alcon/Wavelight) without and with cyclorotation adjustment.

No CTA



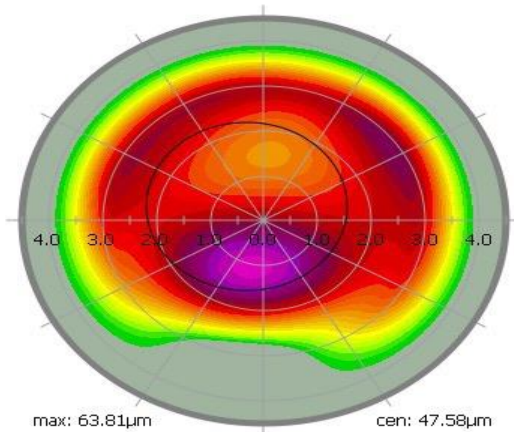


CTA

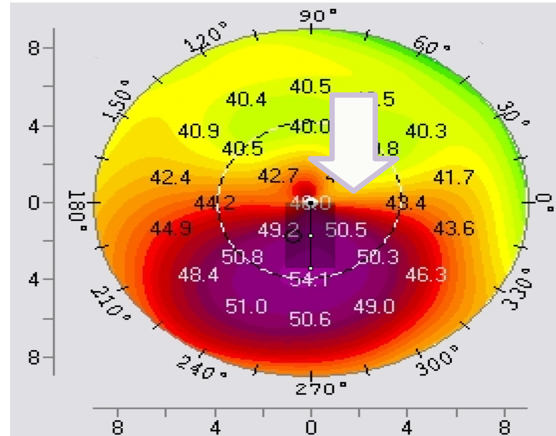
	group-A	(Vario/cyclo)	group-B	(Oculyzer II, non-cyclo)
	Δϑ (°)	WΔϑ (mm)	Δϑ (°)	WΔϑ (mm)
average	7.18	3.43	14.50	10.23
st. dev	± 7.53	± 4.76	± 12.65	± 15.15
min	0	0.00	0	0.00
max	34	21.41	49	80.56
Confidence Intervals				
0.95	± 1.77	± 1.12	± 2.64	± 3.21
0.99	± 2.35	± 1.49	± 3.49	± 4.25
p-value between groups	0.0058	0.0015		

Novel software to access on the cornea, planned vs. acchieved normalization in the aplicatiom of the Athens Protocol in Keratoconus (topo-guided PTK normalization+CXL)

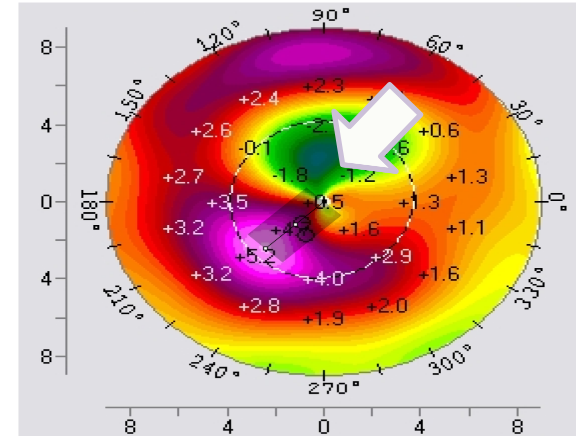
Actual achieved normalization analysis In a 2 dimensional analysis



(r_p, ϑ_p)



(r_d, ϑ_d)



$$\Delta\vartheta = |\vartheta_p - \vartheta_d|$$

$$W\Delta\vartheta = \Delta\vartheta \cdot \Delta r$$

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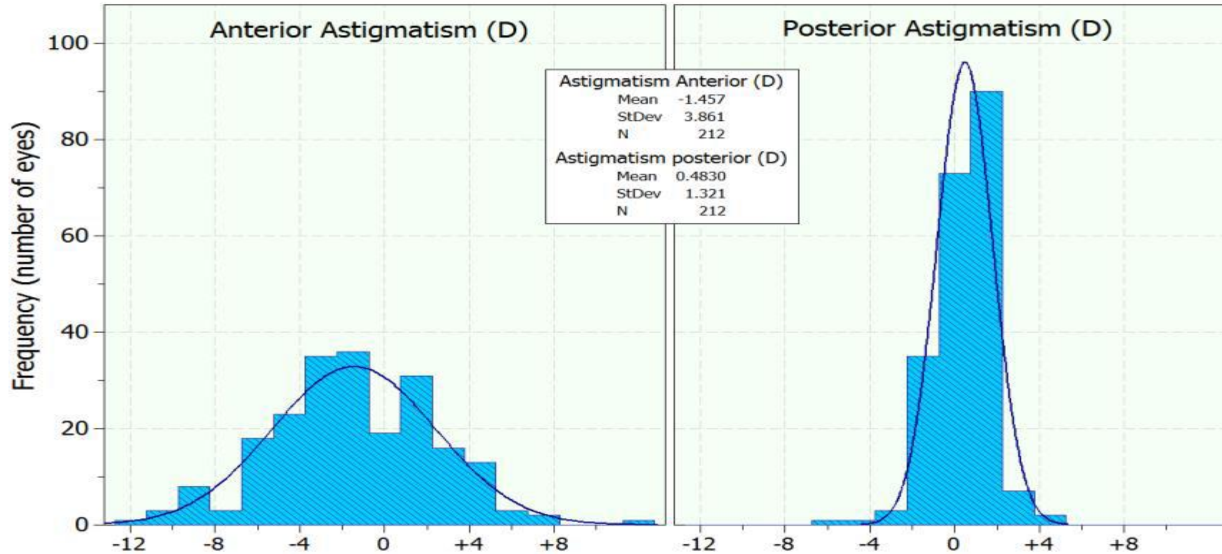
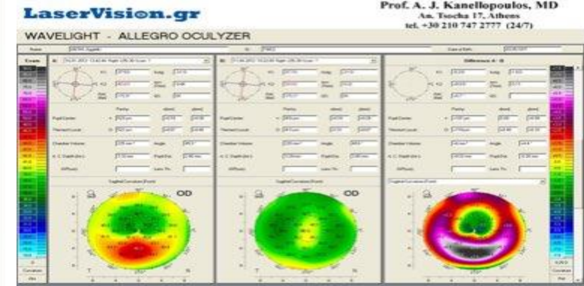
Athens Protocol: improved anterior corneal profile, but what about the posterior?





Ex-vivo comparison of epi-off 3, 9, 18, 30, 45mW/cm2
Over 30mW/cm2 no CXL takes place!!!

MS NO: CORNEA-D-15-00976

Cross-linking Biomechanical Effect in Human Corneas by Same Energy, Different UV-A Fluence: An Enzymatic Digestion Comparative Evaluation

Anastasios J. Kanellopoulos, MD,† Yannis L. Loukas, PhD,‡ and George Asimellis, PhD**

Purpose: To evaluate ex vivo the possible difference in corneal cross-linking (CXL) biomechanical effect of different ultraviolet-A (UV-A) irradiances.

Methods: The study involved 25 human donor corneas, randomly allocated to 5 groups (n = 5 each). CXL was applied with UV-A irradiances of 3, 9, 18, 30, and 45 mW/cm^2, maintaining equal cumulative energy dose of 5.4 J/cm^2. UV-A was delivered on half of the cornea. The nonirradiated halves served as controls. Specimens were subjected to collagenase-A enzymatic digestion. The time to complete dissolution in each specimen was recorded.

AU3

Results: Time to dissolution in group-A (3 mW/cm^2 for 30 minutes) was 321 ± 13.4 minutes (range: 300–330) compared with 171 ± 8.2 (range: 165–180) for their control. In group-B (9 mW/cm^2 for 10 minutes), it was 282 ± 19.6 minutes (range: 270–315) compared with 177 ± 6.7 (165–180) for their control. In group-C (18 mW/cm^2 for 5 minutes), it was 267 ± 19.6 minutes (range: 240–285) compared with 177 ± 7.7 (range: 165–180) for their control. In group-D (30 mW/cm^2 for 3 minutes), it was 252 ± 12.5 minutes (range: 240–270) compared with 180 ± 10.6 minutes (range: 165–195) for their control. In group-E (45 mW/cm^2 for 2 minutes), it was 204 ± 17.1 minutes (range: 180–225) compared with 186 ± 8.2 minutes (range: 180–195) for their control.

Conclusions: The data in this ex vivo human corneal study indicate that the biomechanical effect of CXL studied by resistance to enzymatic digestion in human corneas is comparable between irradiances of 9, 18 and 30 mW/cm^2 and seems to be reduced at a fluence of 45 mW/cm^2.

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From the *Laservision.gr Clinical and Research Eye Institute, Athens, Greece; †Department of Ophthalmology, NYU Medical School, New York, NY; and ‡Neoscreen Laboratory, Athens, Greece.

AU2

A. J. Kanellopoulos holds consultant/advisory positions at Alcon/WaveLight, Allergan, Avedro, i-Optics, Keramed, and ISP Surgical. The remaining authors have no funding or conflicts of interest to disclose.

Design and conduct of the study (A.J.K., G.A.); collection (G.A., Y.L.L.), management (A.J.K.), analysis (G.A., Y.L.L.), and interpretation of the data (A.J.K., G.A., Y.L.L.); manuscript preparation (G.A.), manuscript review (A.J.K., G.A., Y.L.L.), and manuscript approval (A.J.K.).

Reprints: Anastasios J. Kanellopoulos, MD, Laservision.gr Clinical and Research Eye Institute, 17 Tsocha St, Athens 11521, Greece (e-mail: ajk@brilliantvision.com).

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Key Words: corneal cross-linking, keratoconus, high-irradiance CXL, corneal biomechanics, high-energy CXL, reciprocity law, Bunsen–Roscoe law, collagenase-A, enzymatic digestion, accelerated CXL, rapid CXL

(*Cornea* 2016;00:1–5)

Corneal cross-linking (CXL) has been clinically used for stabilizing progressive keratectasia for more than a decade.[1–3] This photochemical reactive process is induced by peak 370-nm ultraviolet-A (UV-A) radiation absorbed by riboflavin, a photosensitive vitamin B2 molecule, with an absorption maximum at 365 nm.[4] The procedure is broadly accepted to result in corneal biomechanical strengthening not only in advanced keratoconus[5–7] but also in early-stage[8] and iatrogenic keratectasia.[9,10]

Collagenase has been known to contribute to break down of collagen in the corneal stroma.[11] This collagenase-related breakdown is a vigorous biochemical process that has been used as an indirect metric of corneal biomechanical properties.[12,13] The stabilizing biochemical effect of CXL may be thus reflected by an increased amount of resistance to collagenase digestion.[14,15] CXL-treated porcine corneas have demonstrated nearly double the dissolution time after pepsin, trypsin, and collagenase digestion.[16–19]

The original (standard) Dresden CXL protocol introduced epithelial removal and 30-minute corneal soaking with a dextran-based 0.1% riboflavin solution. UV-A illumination settings were 30 minutes with an irradiance of 3 mW/cm^2, corresponding to a dissipated energy of 5.4 J/cm^2.[1,20,21]

We have subsequently introduced higher fluence, same-energy protocols, and many other investigators have subsequently introduced a multitude of CXL protocols currently in use internationally. The rationale of these protocols has been justified by the Bunsen–Roscoe reciprocity law,[22] which states a certain biological effect is directly proportional to the total radiant exposure (energy dose), irrespective of application time.[23] The reported limitations of the reciprocity law may indicate that there exists a range of applicability of how much the clinical UV-A radiation may be increased (and correspondingly, the application time shortened), which may need to be further investigated.

Despite their widespread clinical practice, a thorough clinical comparative validation of these approaches has not yet been published. The quantitative CXL effect between several of these protocols still remains elusive. The enzymatic

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Time to Disolution (min)

350
300
250
200

3 mW/cm2 for 30 min
9 mW/cm2 for 10 min
18 mW/cm2 for 5 min
30 mW/cm2 for 3 min
45 mW/cm2 for 2 min

3 mW/cm2/30 min
9 mW/cm2/10 min
18 mW/cm2/5 min
30 mW/cm2/3 min
45 mW/cm2/2 min

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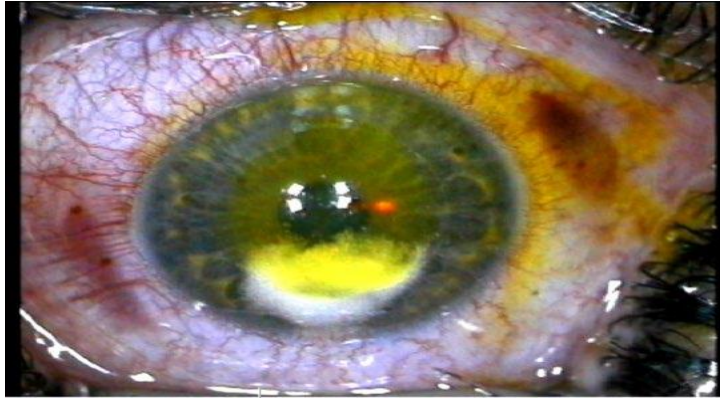
Introduction of riboflavin in a femto-pocket



NEW TECHNIQUE

Collagen Cross-linking in Early Keratoconus With Riboflavin in a Femtosecond Laser-created Pocket: Initial Clinical Results

Anastasios John Kanellopoulos, MD

HYPEROPIC LASIK+CXL

A drop of 0.1% riboflavin sodium phosphate solution, just prior to its spread over the exposed stromal bed

Topography-guided Hyperopic LASIK With and Without High Irradiance Collagen Cross-linking: Initial Comparative Clinical Findings in a Contralateral Eye Study of 34 Consecutive Patients

Anastasios John Kanellopoulos, MD; Jonathan Kahn, MD

ABSTRACT

PURPOSE: To evaluate the safety and efficacy of intrastromally applied collagen cross-linking (CXL) in a comparative contralateral eye study of topography-guided femtosecond laser–assisted hyperopic LASIK.

METHODS: Thirty-four consecutive patients with hyperopia and hyperopic astigmatism elected to have bilateral topography-guided LASIK and were randomized to receive a single drop of 0.1% sodium phosphate riboflavin solution under the flap followed by 3-minute exposure of 10 mW/cm^2 ultraviolet A (UVA) light with the flap realigned in one eye (CXL group) and no intrastromal CXL in the contralateral eye (no CXL group). All eyes were treated with the WaveLight FS200 femtosecond laser and WaveLight EX500 excimer laser (Alcon Laboratories Inc). Refractive error and keratometric, topographic, and tomographic measurements were evaluated over mean follow-up of 23 months.

RESULTS: Preoperatively, mean spherical equivalent refraction was $+3.15\pm1.46$ diopters (D) and $+3.40\pm1.78$ D with a mean cylinder of 1.20 ± 1.18 D and 1.40 ± 1.80 D and mean uncorrected distance visual acuity (UDVA) (decimal) of 0.1 ± 0.26 and 0.1 ± 0.25 in the CXL and no CXL groups, respectively. At 2 years postoperatively, mean spherical equivalent refraction was -0.20 ± 0.56 D and $+0.20\pm0.40$ D with mean cylinder of 0.65 ± 0.56 D and 0.76 ± 0.72 D and mean UDVA of 0.95 ± 0.15 and 0.85 ± 0.23 in the CXL and no CXL groups, respectively. Eyes with CXL demonstrated a mean regression from treatment of $+0.22\pm0.31$ D, whereas eyes without CXL showed a statistically significant greater regression of $+0.72\pm0.19$ D ($P=.0001$).

CONCLUSIONS: Topography-guided hyperopic LASIK with or without intrastromal CXL is safe and effective, with greater long-term efficacy (less regression) in eyes with CXL. Our data suggest that the regression seen with hyperopic LASIK may be related to biomechanical changes in corneal shape over time. [*J Refract Surg*. 2012;28(11 Suppl):S837-S840.]
doi:10.3928/1081597X-20121005-05

The evolution of laser vision correction technology has made the treatment of myopia, hyperopia, and astigmatism more accurate. Numerous studies of hyperopic LASIK have been reported,[1-7] and as the WaveLight Allegretto Wave laser (Alcon Laboratories Inc, Ft Worth, Texas) was introduced, reports of wavefront-optimized hyperopic LASIK have also been published.[8,9] We previously reported the use of topography-guided excimer laser ablations for hyperopia and their advantage in correcting angle kappa.[10,11]

Recently, we published a report on a large cohort of topography-guided hyperopic LASIK with long-term follow-up.[12] In this study, we found a higher level of safety and efficacy when treating hyperopia and hyperopic astigmatism with topography-guided LASIK. Nevertheless, between 1 and 2 years postoperatively a consistent level of regression was noted. We theorized that this was due to a progressive flattening effect, and not due to latent hyperopia and/or accommodation loss, because the regression was consistent with a reduction of the amount of "steepening" of corneal shape achieved initially.

We also introduced the concept of high irradiance, short exposure corneal collagen cross-linking (CXL)[13] and prophylactic CXL in myopic LASIK several years ago,[14] and recently reported the long-term safety and efficacy of these therapies. In the present study, we have attempted to evaluate the effect of "prophylactic" CXL in the long-term stability and safety of hyperopic topography-guided LASIK.

PATIENTS AND METHODS

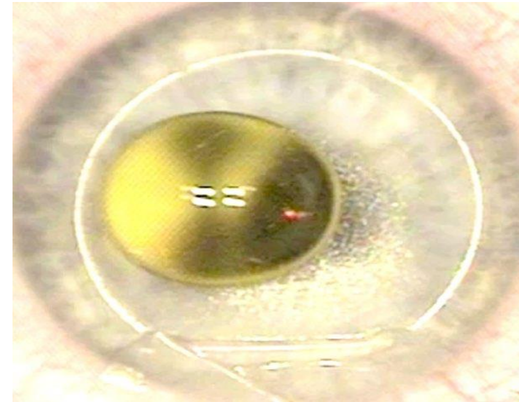
All patients signed informed consent prior to treatment following the protocol set forth by the Declaration of Helsinki.

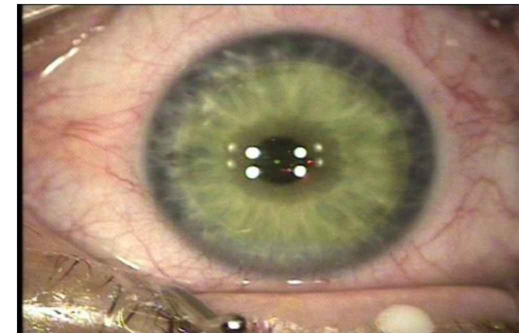
From the Department of Ophthalmology, New York University Medical School, New York, New York (Kanellopoulos, Kahn); and LaserVision.gr Eye Institute, Athens, Greece (Kanellopoulos).

Dr Kanellopoulos is a consultant to Alcon Laboratories Inc. Dr Kahn has no financial interest in the materials presented herein.

Presented in part at the American Society of Cataract and Refractive Surgery annual meeting; April 20-24, 2012; Chicago, Illinois.

Correspondence: Anastasios John Kanellopoulos, MD, LaserVision.gr Eye Institute, Tsocha 17 Ampelokipi, 11527, Athens, Greece. Tel: 30 210 7472 777; Fax: 30 210 7472 789; E-mail: ajk@brilliantvision.com





" profile Hyperopic" oz 6-9mm
"hyperopic PTK" 6-9oz 30 microns

KXL2 - Treatment Report

Patient:

ID: 020229

D.O.B.: 04-Jan-1983

Notes:

avedro

The World Leader in Corneal Cross-linking Science

OD Exam Date: 23-Jul-2013 18:44:50

No.	Shape Type	Time (mm:ss)	Total Energy (J/cm²)	X Position (mm)	Y Position (mm)	Axis (degs.)	Dim. 1 (mm)	Dim. 2 (mm)	Arc (degs.)
1	Circle	10:00	6.0	0.0	-0.0		7.0		

Indices

K's at 3mm:

Avg. K (D):

Pupil Ø (mm):

Limbus Ø(mm):

Min. Pachy (μ).:

Additional Notes

Treatment Power: 10 mw/cm² - Continuous.

Version: 1.0.7.0

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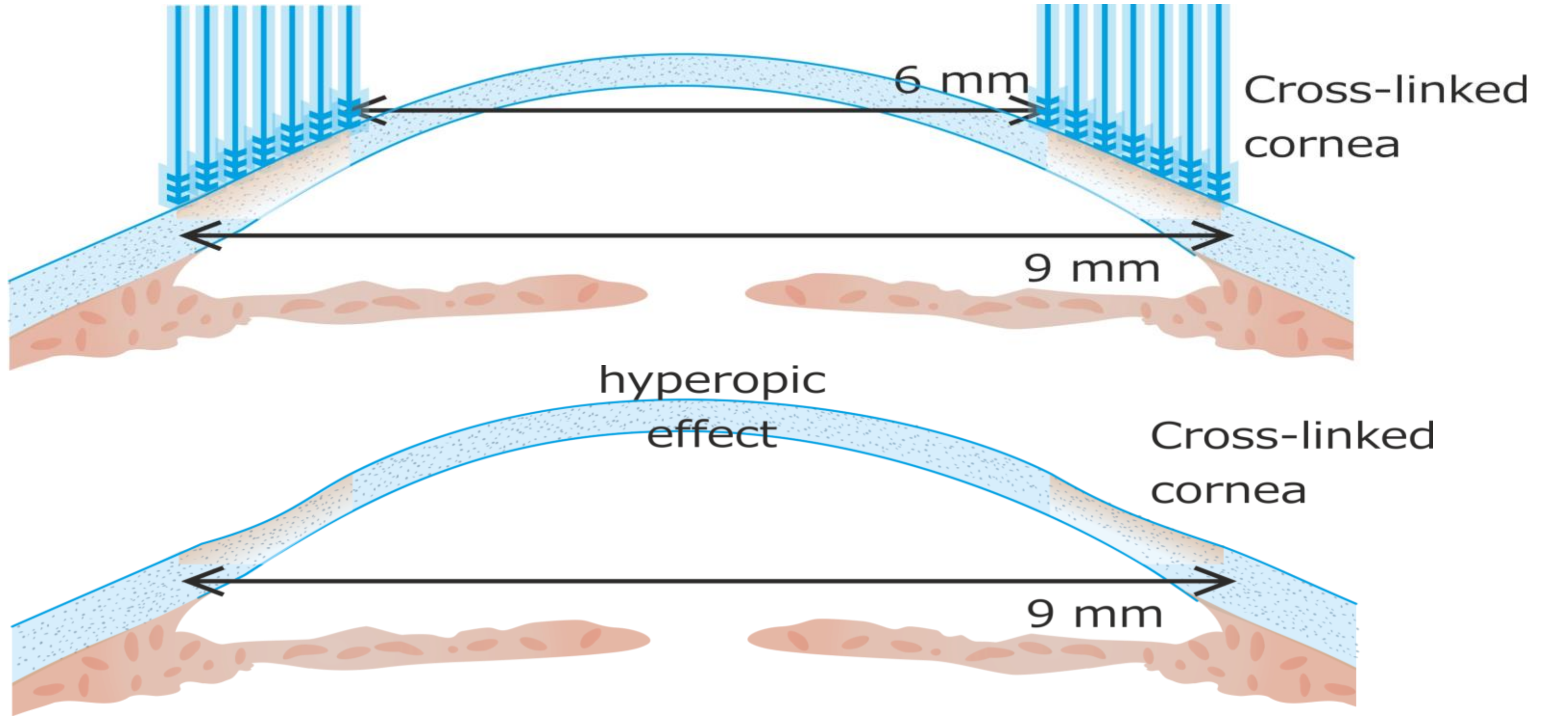
Cross-linked cornea

9 mm

6 mm

The myopic shift
(hyperopia-presby treatment)



2 years PiXL (CXL) myopic treatments **4D flattening !**

	OD (1)	OD (2)	Difference
K1	45.0 D	43.0 D	+1.9 D
K2	45.2 D	43.4 D	+1.8 D
Axis (flat)	51.3°	175.3°	-124.0°
Astig	+0.2 D	-0.3 D	+0.6 D
ecc (7mm)	0.54	-0.15	+0.69
QS	OK	OK	
Pupil Center Pachy	515 µm	485 µm	+31 µm
Pupil Center x[mm]	-0.37	-0.27	-0.10
Pupil Center y[mm]	-0.02	-0.06	+0.04
Thinnest Locat. Pachy	511 µm	482 µm	+29 µm
Thinnest Locat. x[mm]	-0.80	-0.58	-0.22
Thinnest Locat. y[mm]	-0.33	-0.32	-0.01
Chamber Volume	98 mm³	102 mm³	-4 mm³
Angle	32.0°	33.2°	-1.3°
A. C. Depth (Int.)	2.31 mm	2.32 mm	-0.01 mm
Pupil Dia	2.98 mm	3.42 mm	-0.43 mm
IOP(cor)			
Lens Th.			

USB connection problematic! Please wait.

Sagittal Curvature (Front)

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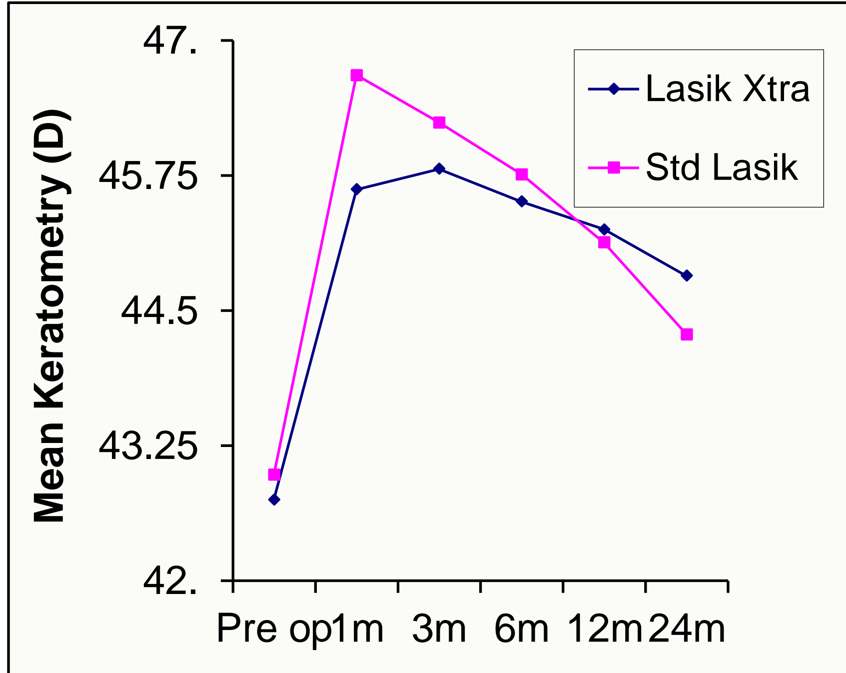
Conclusions higher fluence CXL

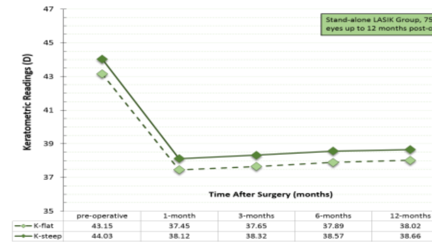
- CXL can sterilize the stroma higher fluence and higher riboflavin % may be useful
- The apoptosis of keratocytes may have unknown benefit to epithelial hyperplasia and risks
- Potential endothelial toxicity
- Potential limbal cell cell and/or goblet cell toxicity from collateral Rib+ interaction
- CXL may prove to be the standard collagen stabilizer and adjunct disinfectant in LASIK, PRK and even cataract surgery
- Appears to be more effective if Type I model of CXL holds true
- Customised fluence and riboflavin concentration may personalize CXL as a biomechanical stromal modulator for many applications:
- May prevent regression in hyperopia
- LASIK Xtra appears to have only potential advantages
- May become the standard of care for PRK (reduce scarring, epithelial hyperplasia)

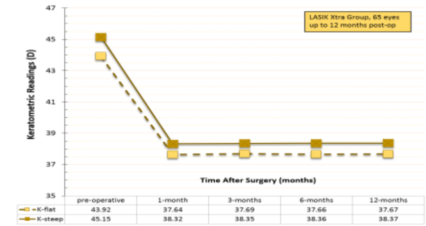
Comparison of Keratometric Stability compelling evidence that LASIK Xtra works and maybe a necessary adjunct in hyperopic LASIK

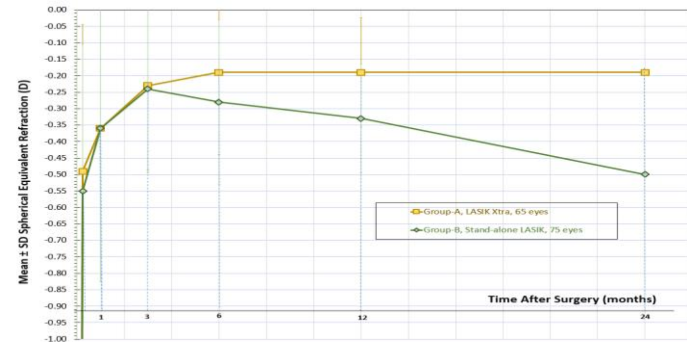


Kanellopoulos AJ, Kahn J: JRS November 2012

LASIK Vs LASIK Xtra in high myopia - 24 months







Placido topo data of hyperopic PiXL (CXL) treatments:

Left: difference, center : after, right: before

minus

23.01.14 13:20:55 Left

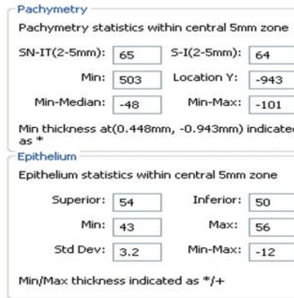
24.07.13 13:15:21 Left

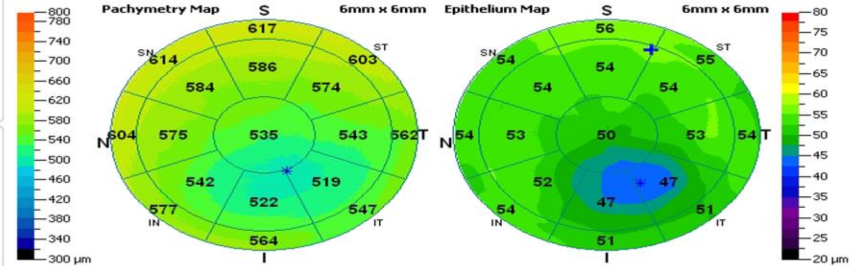
minus

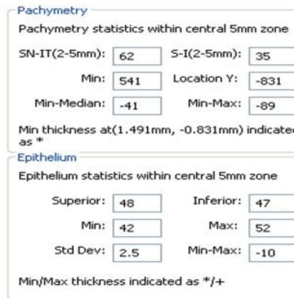
22.01.14 14:46:02 Left

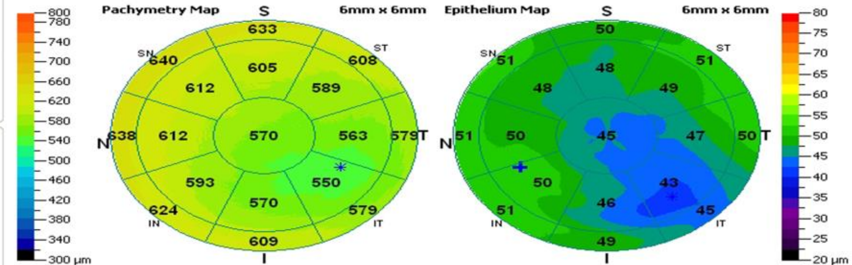
24.07.13 12:39:07 Left

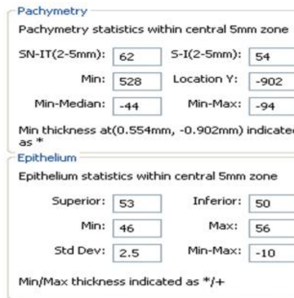
Transepi toric CXL:
1-8 month validation
of transepithelial Toric PiXL!

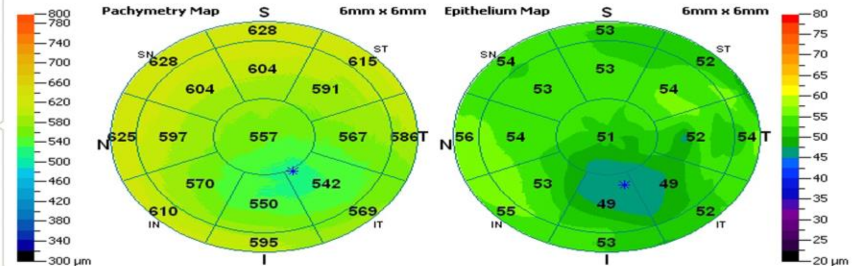








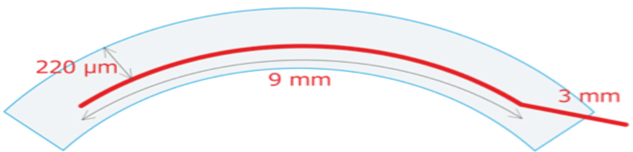




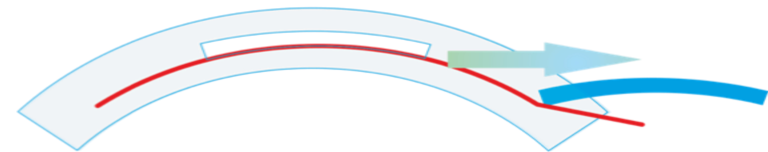
2014: laboratory work establishing ex-vivo in-situ CXL effect in a SMILE simulation all femto procedure.

Two-surface intra-lamellar bed corneal dissections were performed within a 5.5 mm optical zone. The lenticule was extracted through a 3.5 mm wide superior canal. High-fluence CXL was conducted in the pocket created.

A: posterior lamellar bed cut

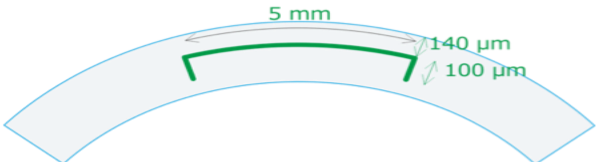


D: Intra-lamellar button extraction

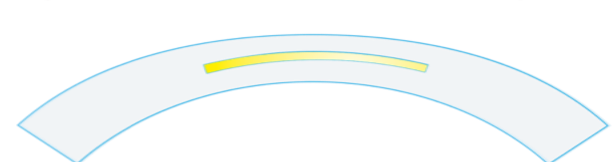


B: anterior lamellar cut

5 mm

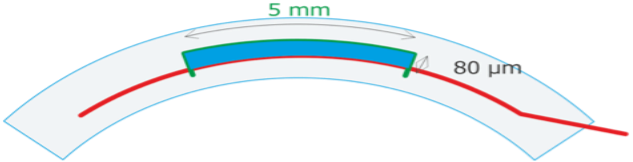


E: Injection of riboflavin within the pocket

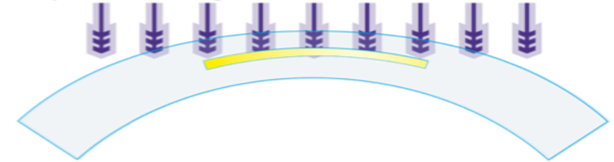


C: Intra-lamellar button creation

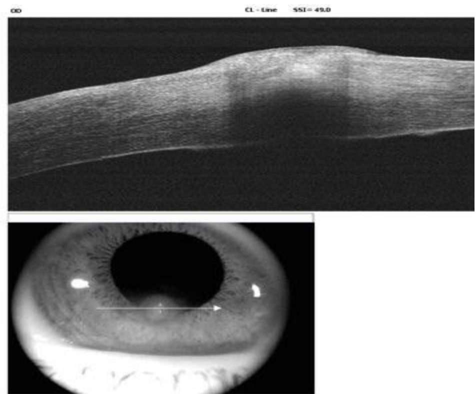
5 mm

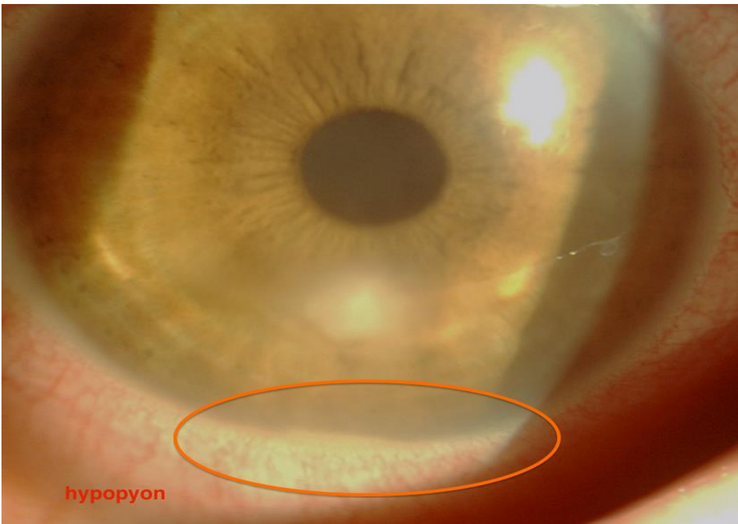


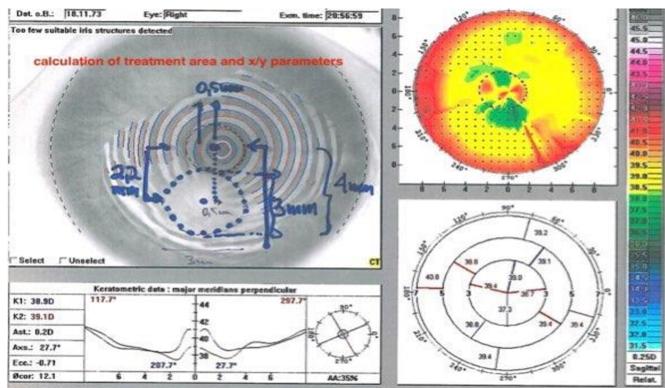
F: Superficial high-fluence UV-A illumination



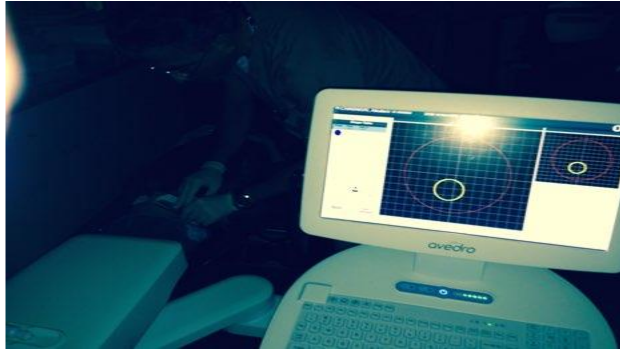
Infectious Keratitis in a 38y/o F MD and right designing a x/y topo-guided CXL focal intervention with the KXL-II device



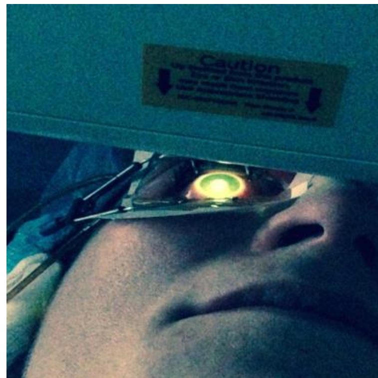


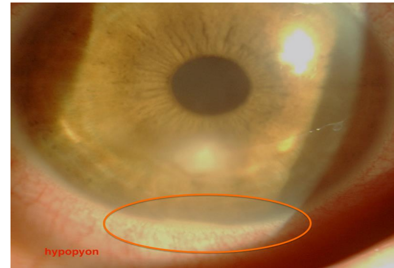


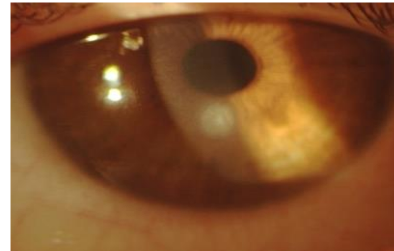
The actual application of topo-customized CXL treatment in **infectious keratitis.**

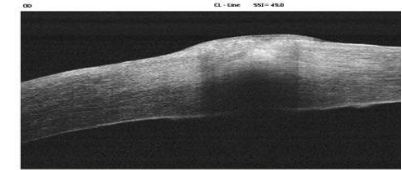


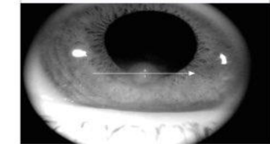
20mW/cm²˒ 7.2J continuous for 10’

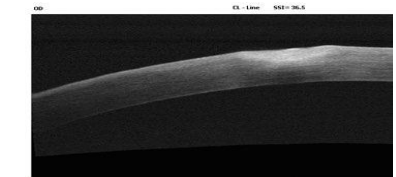


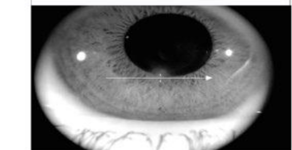






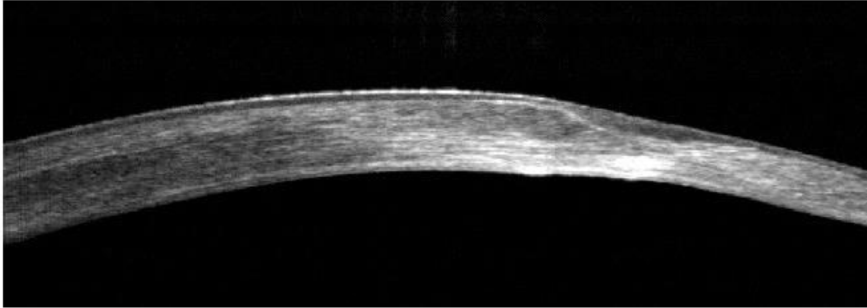


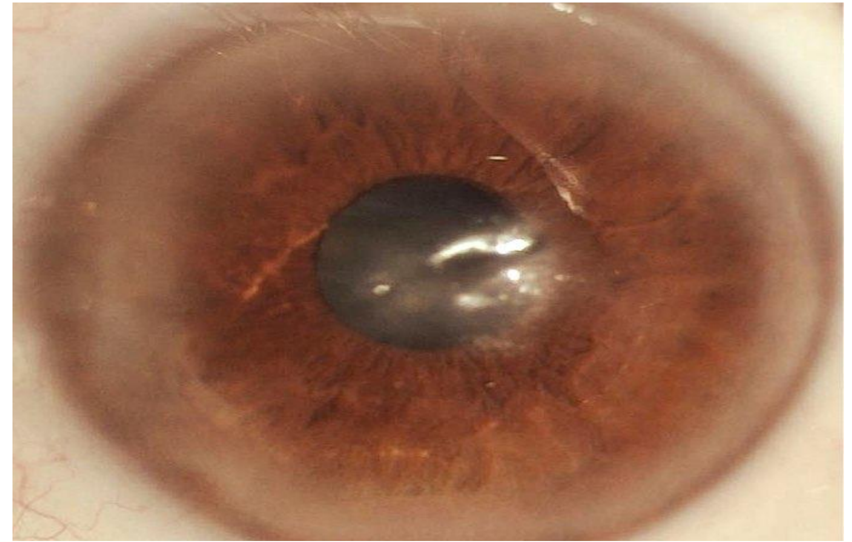




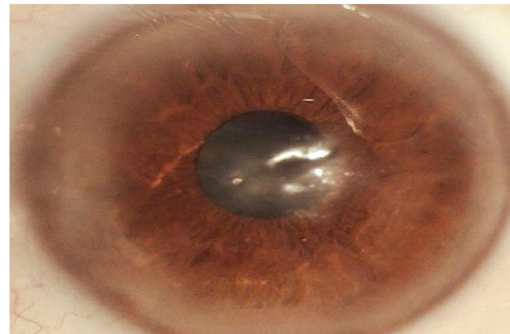
Resoltion of nebular infiltrate by day 1!!!

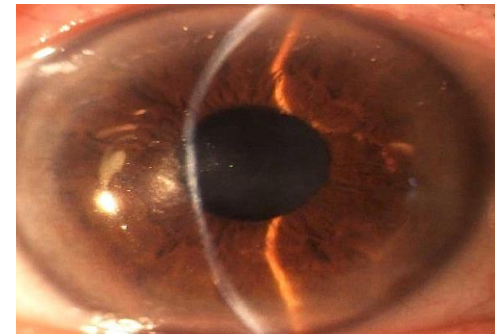
Severe scar of the cornea
BCVA 20/200,
Lamellar or PK?





From 20/200 to 20/40!





Initial ex-vivo evaluation of flap-less, femto-second laser-assisted simulation of myopic Refractive Lens Extraction, stabilized with high-fluence CXL

Materials employed in the study

Human donor corneas (Eye Bank for Sight Restoration, NY),

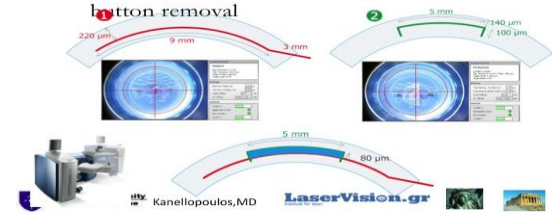
Lamellar Cuts: Femtosecond laser (FS200, Alcon/WaveLight),

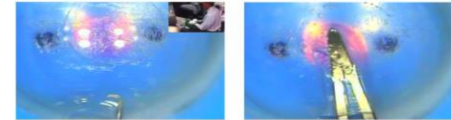
In-situ Cross Linking: High-fluence device (KXL, Avedro),

Keratometry: Scheimpflug imaging (Pentacam, Oculus),

Pachymetry: Anterior-Segment OCT (AS-OCT, RtVue100, Optovue),

Biaxial load cell-based analysis: Biotester 5000, CellScale





Clinical Ophthalmology

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ORIGINAL RESEARCH

Management of progressive keratoconus with partial topography-guided PRK combined with refractive, customized CXL – a novel technique: the enhanced Athens protocol

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Clinical Ophthalmology

Anastasios John Kanellopoulos[1,2]

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[2]Department of Ophthalmology, NYU Medical School, New York, NY, USA

Purpose: To report a novel application of partial topography-guided photorefractive keratectomy combined with topographically customized, higher fluence, and variable pattern corneal cross-linking applied on the same day of the treatment of keratoconus.

Methods: A topography-guided partial photorefractive keratectomy treatment of maximum 30 μm over the thinnest cone area was applied initially followed by a 7 mm, 50 μm phototherapeutic keratectomy treatment to address epithelial removal. 0.02% Mitomycin C was applied for 20 seconds and then the exposed stroma was soaked with 0.1% riboflavin solution for 5 minutes. The cornea was then treated with a customized, variable-pattern and 20 mW/cm² fluence for a total of 5–10 J, and up to 15 J of energy was delivered with the KXL-II device employing an active tracker. The center of the pattern that received the 15 J was topography-matched with the thinnest area of the cone. Visual acuity, refractive error, cornea clarity, keratometry, topography, pachymetry with a multitude of modalities and endothelial cell density were evaluated over 36 months.

Results: Keratoconus was stabilized in all cases. The severity of keratoconus stage by Amsler–Krumeich criteria improved from an average of 3.2 (1–4) to 1.8 (0–3). Uncorrected distance visual acuity changed from preoperative 20/80 to 20/25 at 6 months. A maximum astigmatic reduction of 7.8 D (5.3–15.6), and a significant cornea surface normalization (an index of height decentration improvement from 0.155 [±0.065] to 0.045 [±0.042]) were achieved by 1 month and remained relatively stable for 36 months postoperatively. Two cases delayed full reepithelialization for up to 9 days.

Conclusion: This paper introduces a novel technique in order to maximize the refractive normalization effect along with ectasia stabilization in young keratoconus patients. This may facilitate the use of less tissue ablation, in comparison to utilizing a homogeneous UV light beam for corneal cross-linking in Athens Protocol cases. It broadens the number of potential candidate cases that would have been limited to employ this technique due to tissue thickness limitations.

Keywords: corneal ectasia, corneal irregularity-normalization, therapeutic excimer ablation

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Introduction

Corneal cross-linking (CXL) has been employed for many years as a means of stabilizing cornea ectasia.[1–6] It has been introduced and reported for the use of higher fluence UV light for accelerated CXL in keratoconus.[7,8] Among the multitude of treatments and technique variations applied, CXL has almost invariably documented results in

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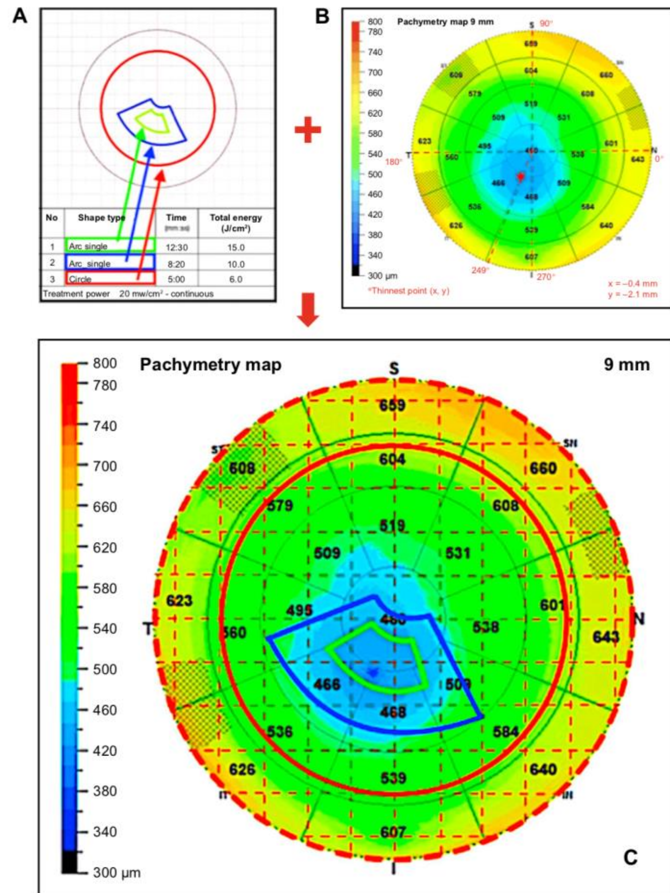


Figure 1 Illustration of the customized CXL treatment.

Notes: (**A**) The customized CXL patterns, the fluence of delivery was set to 20 mW/cm². Upon commencement of the UV treatment the initial circular pattern (red) of 7 mm diameter was treated for a total of 6 Joules delivered over 5 minutes, then the device "focused" its further continuous treatment of 20 mW/cm² fluence over the intermediate arc pattern (blue) centered on the thinnest point of the cornea, this part of the treatment was an added 3 min and 20 seconds to finally have the device "focus" on the smallest arc pattern (green) that was also centered on the thinnest part of the cornea, as defined by the anterior segment OCT thickness map shown on (**B**) and for an additional 4 minutes and 10 seconds. This area was treated during the red pattern period (5 minutes) and the blue pattern period (an additional 3 min and 20 seconds) and as noted above for an additional final 4 minutes and 10 seconds to complete a TOTAL amount of continuous energy delivered of 15 Joules. The relative time exposures and energy delivered for each pattern is noted in map 1A. Map 1B illustrates the definition of the (x, y) Cartesian coordinates on the anterior segment OCT thickness map of the cornea, that would serve as the center of the two smaller arc customized treatment profiles, in respect to the pupil center, the "target" for the tracker of the KXL-II device during customized UV light pattern delivery. (**C**) The map illustrates the superimposition of the treatment patterns on the thickness map mentioned above.

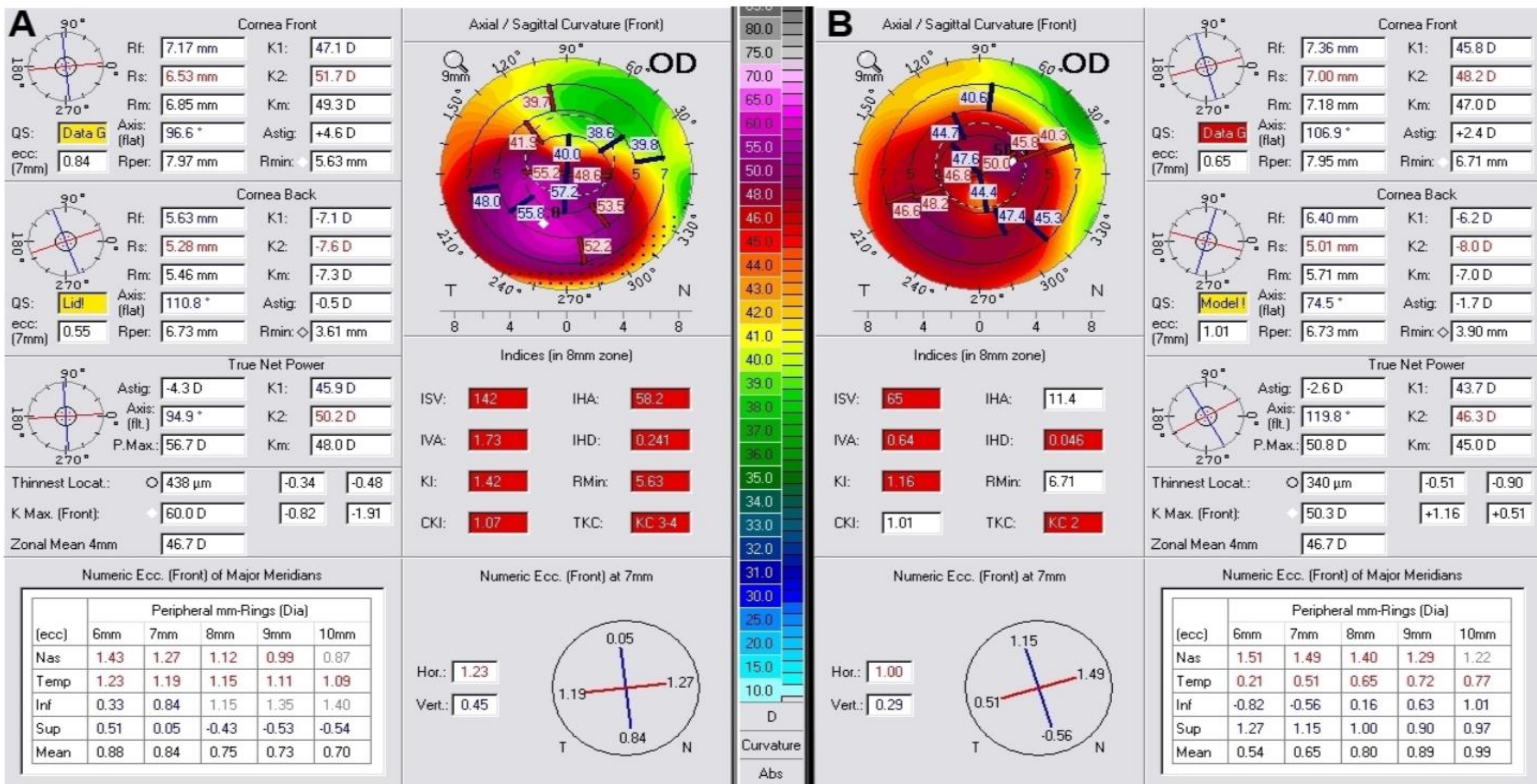


Figure 3 Topometric difference map comparing the anterior curvature parameters and asymmetry indices prior (**A**) to and 6 months postoperatively (**B**): all parameters have improved dramatically, transforming the ectatic cornea to a significantly more regular form.

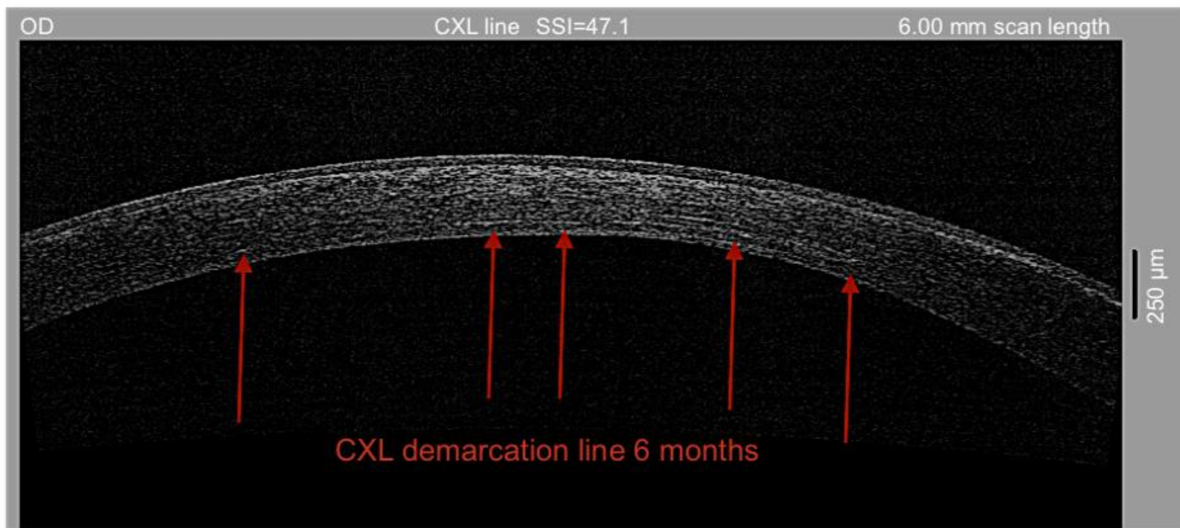
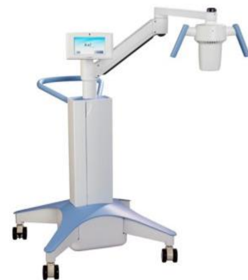


Figure 4 Anterior-segment OCT cross-section image of the treated cornea at 6 months post-operatively.
Notes: The hyper-eflectivity in the stroma, described as the "CXL line" suggests the depth and width of CXL effect. The CXL demarcation line is visualized and underlined with the red arrows testablishing indirectly a very "deep" CXL-effect, with 9 mm width with this novel technique.
Abbreviations: CXL, corneal cross-linking; OCT, optical coherence tomography.

Our current CXL protocols



Athens Protocol: topo partial PRK +15'x 6mw/cm^2

- **LASIK Xtra: 1' (60") 30mW/cm^2 all hyperopes**
- **PRK Xtra: 1' (90") 30mW/cm^2**
- **TransepiCXL: 0.25% ribo + 30mW X 3'**
- **Infection: 0.25% riboflavin + 20mW/cm^2 /7,2 Joules**
- **PiXL 0.25% ribo + 30mW/cm^2 7.2-20 Joules**

Conclusions

- **Alternative treatments:**
  - ✓ CXL alone
  - ✓ Contact lenses: RGPs and/or Scleral lenses
  - ✓ Intracorneal ring segments
  - ✓ Allograft inlays?
  - ✓ Lamellar keratoplasty
  - ✓ Penetrating keratoplasty

ORIGINAL ARTICLE

Corneal Refractive Power and Symmetry Changes Following Normalization of Ectasias Treated With Partial Topography-Guided PTK Combined With Higher-Fluence CXL (The Athens Protocol)

Anastasios John Kanellopoulos, MD; George Asimellis, PhD

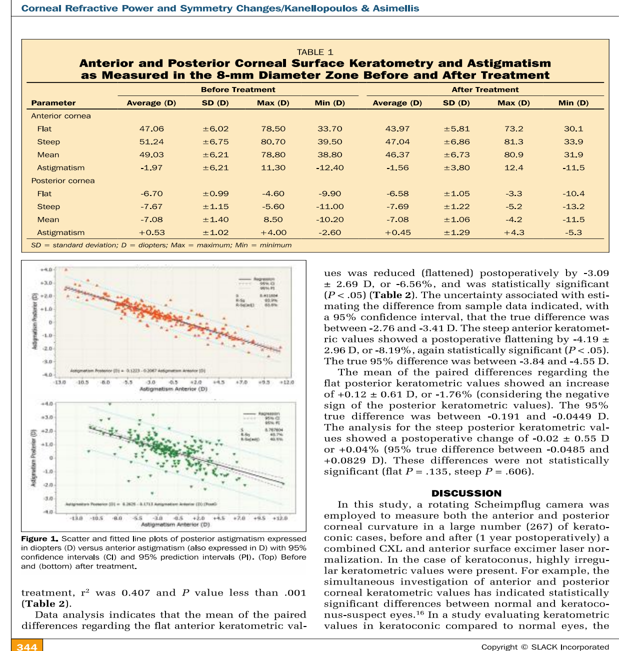


TABLE 1
Anterior and Posterior Corneal Surface Keratometry and Astigmatism as Measured in the 8-mm Diameter Zone Before and After Treatment

Parameter	Before Treatment Average (D)	Before Treatment SD (D)	Before Treatment Max (D)	Before Treatment Min (D)	After Treatment Average (D)	After Treatment SD (D)	After Treatment Max (D)	After Treatment Min (D)
Anterior cornea								
Flat	47.06	±6.02	78.50	33.70	43.97	±5.81	73.2	30.1
Steep	51.24	±6.75	80.70	39.50	47.04	±6.86	81.3	33.9
Mean	49.03	±6.21	78.80	38.80	46.37	±6.73	80.9	31.9
Astigmatism	-1.97	±6.21	11.30	-12.40	-1.56	±3.80	12.4	-11.5
Posterior cornea								
Flat	-6.70	±0.99	-4.60	-9.90	-6.58	±1.05	-3.3	-10.4
Steep	-7.67	±1.15	-5.60	-11.00	-7.69	±1.22	-5.2	-13.2
Mean	-7.08	±1.40	8.50	-10.20	-7.08	±1.06	-4.2	-11.5
Astigmatism	+0.53	±1.02	+4.00	-2.60	+0.45	±1.29	+4.3	-5.3

SD = standard deviation; D = diopters; Max = maximum; Min = minimum

Figure 1. Scatter and fitted line plots of posterior astigmatism expressed in diopters (D) versus anterior astigmatism (also expressed in D) with 95% confidence intervals (CI) and 95% prediction intervals (PI). (Top) Before and (bottom) after treatment.

treatment, r^2 was 0.407 and P value less than .001 (**Table 2**).

Data analysis indicates that the mean of the paired differences regarding the flat anterior keratometric values was reduced (flattened) postoperatively by -3.09 ± 2.69 D, or -6.56%, and was statistically significant ($P < .05$) (**Table 2**). The uncertainty associated with estimating the difference from sample data indicated, with a 95% confidence interval, that the true difference was between -2.76 and -3.41 D. The steep anterior keratometric values showed a postoperative flattening by -4.19 ± 2.96 D, or -8.19%, again statistically significant ($P < .05$). The true 95% difference was between -3.84 and -4.55 D.

The mean of the paired differences regarding the flat posterior keratometric values showed an increase of +0.12 ± 0.61 D, or -1.76% (considering the negative sign of the posterior keratometric values). The 95% true difference was between -0.191 and -0.0449 D. The analysis for the steep posterior keratometric values showed a postoperative change of -0.02 ± 0.55 D or +0.04% (95% true difference between -0.0485 and +0.0829 D). These differences were not statistically significant (flat $P = .135$, steep $P = .606$).

DISCUSSION

In this study, a rotating Scheimpflug camera was employed to measure both the anterior and posterior corneal curvature in a large number (267) of keratoconic cases, before and after (1 year postoperatively) a combined CXL and anterior surface excimer laser normalization. In the case of keratoconus, highly irregular keratometric values were present. For example, the simultaneous investigation of anterior and posterior corneal keratometric values has indicated statistically significant differences between normal and keratoconus-suspect eyes.[16] In a study evaluating keratometric values in keratoconic compared to normal eyes, the

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Conclusions

- ✓ The Athens Protocol (partial topo-guided PRK combined with CXL) appears to be safe, predictable, and effective in ectasia stabilization, and visual rehab over 12 years later.
- ✓ Clinicians should be cautioned in overcorrecting, potential for delayed healing and/or scarring and the significance of effective ablation plan delivery.

ORIGINAL ARTICLE

Corneal Refractive Power and Symmetry Changes Following Normalization of Ectasias Treated With Partial Topography-Guided PTK Combined With Higher-Fluence CXL (The Athens Protocol)

Anastasios John Kanellopoulos, MD; George Asimellis, PhD

ABSTRACT

PURPOSE: To investigate preoperative and postoperative anterior and posterior keratometry and simulated corneal astigmatism in keratoconic eyes treated with collagen cross-linking combined with anterior surface normalization by partial topography-guided excimer ablation (the Athens Protocol).

METHODS: Anterior and posterior corneal keratometry were measured by Scheimpflug imaging for 267 untreated keratoconic eyes. Following treatment, they were assessed 1 year postoperatively.

RESULTS: Before treatment, average anterior keratometric value was 47.06 ± 6.02 diopters (D) for flat and 51.24 ± 6.75 D for steep. The posterior keratometric values were -6.70 ± 0.99 D (flat) and -7.67 ± 1.15 D (steep). Anterior astigmatism was on average with-the-rule (-1.97 ± 6.21 D), whereas posterior astigmatism was against-the-rule (+0.53 ± 1.02 D). The posterior and anterior astigmatism were highly correlated (r^2 = 0.839). After treatment, anterior keratometric values were 43.97 ± 5.81 D (flat) and 46.55 ± 6.82 D (steep). Posterior keratometric values were -6.58 ± 1.05 D (flat) and -7.69 ± 1.22 D (steep). Anterior astigmatism was on average with-the-rule (-1.56 ± 3.80 D), whereas posterior astigmatism was against-the-rule (+0.45 ± 1.29 D). The statistically significant (P < .05) keratometric changes indicated anterior surface flattening -3.09 ± 2.67 D (flat) and -4.19 ± 2.96 D (steep). The posterior keratometric changes were not statistically significant (P > .05).

CONCLUSIONS: Before treatment, there was a strong correlation between posterior and anterior corneal astigmatism. After treatment, statistically significant anterior keratometric values flattened. The posterior surface keratometric values did not demonstrate statistically significant postoperative change: there was minimal posterior change, despite the significant anterior surface normalization.

[*J Refract Surg*. 2014;30(5):342-346.]

Keratoconus assessment employs indicators such as keratometric values, inferior-superior index, skew percentage, astigmatism, and the KISA% index.[1] Acceptable quantitative keratometric criteria include central corneal refractive power larger than 47.2 diopters (D), inferior-superior dioptric asymmetry larger than 1.2 D, and simulated astigmatism, expressed as the difference between steep and flat keratometric values greater than 1.5 D.[2] The steep and flat meridian keratometric values correspond to the smaller and larger anterior corneal curvature radius, respectively.

Corneal cross-linking (CXL) is an in vivo intrastromal photo-oxidative technique with riboflavin and ultraviolet-A light aiming to address the advancing corneal ectasia and, consequently, the keratoconus progression. With CXL, additional covalent bonding between stromal collagen can be achieved, which stabilizes the collagen framework structure.[3] The remodeling effects of CXL on the cornea can be described by the reduction of mean anterior surface keratometric values.[4] Few studies have been published on the quantitative link between anterior and posterior keratometric values in keratoconic eyes or particularly on the postoperative effects of CXL on either corneal surface.

This study aims to investigate the distribution of and relationship between anterior and posterior corneal keratometric values and simulated anterior and posterior astigmatism on a large group of clinically diagnosed, untreated keratoconic eyes, and the 1-year postoperative effects on both anterior and posterior keratometric values and astigmatism induced by a combined procedure known as the Athens Protocol,[5,6] which intends to arrest the keratoconus progression and normalize the anterior corneal surface.

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The authors have no financial or proprietary interest in the materials presented herein.

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