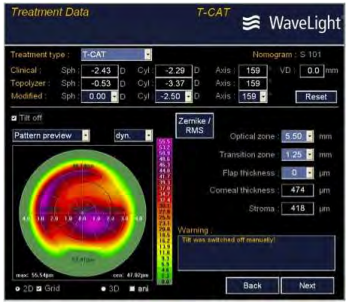
Combining Advanced Laser Applications with Collagen Crosslinking



Anastasios John Kanellopoulos, MD

Director, Laservision.gr Institute, Athens, Greece

Clinical Professor NYU Medical School, NY

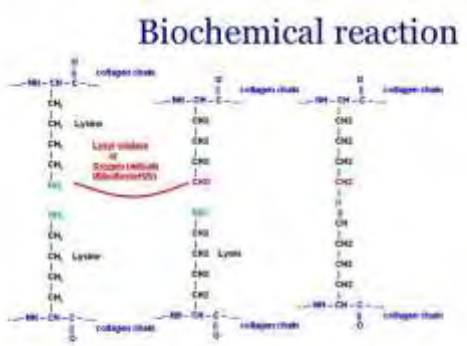
Disclosures: Alcon, Avedro, B&L, Wavelight, Ocular Therapeuti

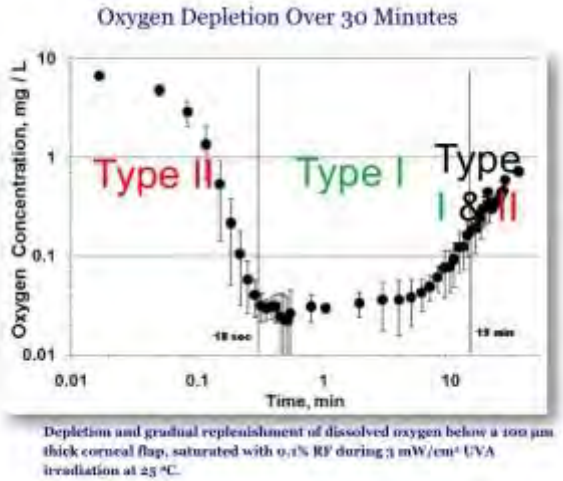
New York University School of Medicine

2-Do you understand how CXL works?

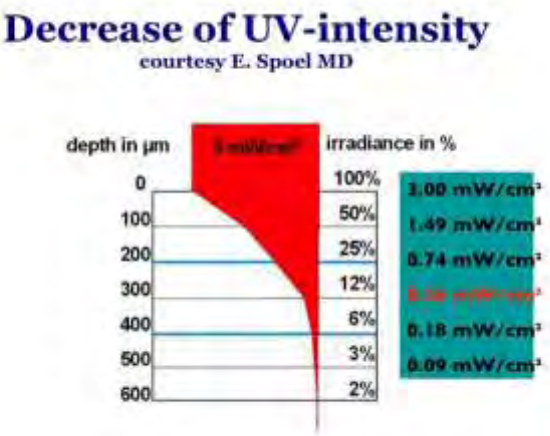
a-YES

B-no





Depletion and gradual replenishment of dissolved oxygen below a 100 µm thick corneal flap, saturated with 0.1% RF during 3 mW/cm² UVA irradiation at 25 °C.



3-How long do you think CXL lasts?

a:1 year

b:2-3 years

c:3-5 years

D: >10 years

4-What is the worst complication of CXL?

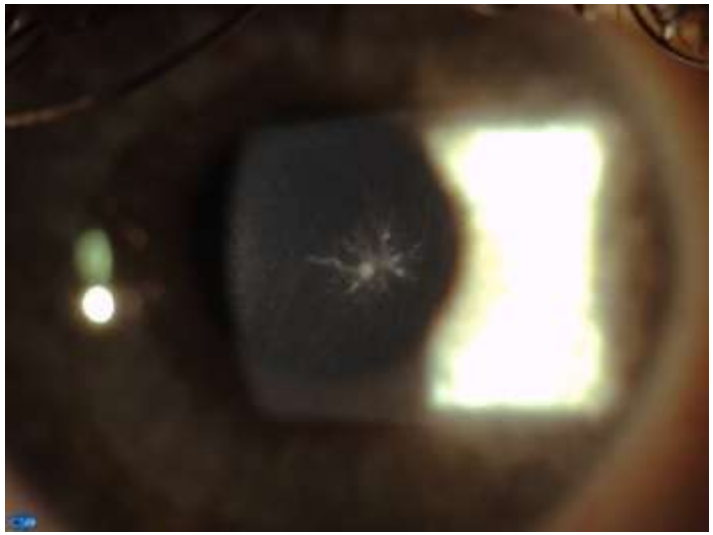
a-Infectious keratitis

b-cornea scarring

c-cornea melt

d-dry eye

e recurrence of ectasia



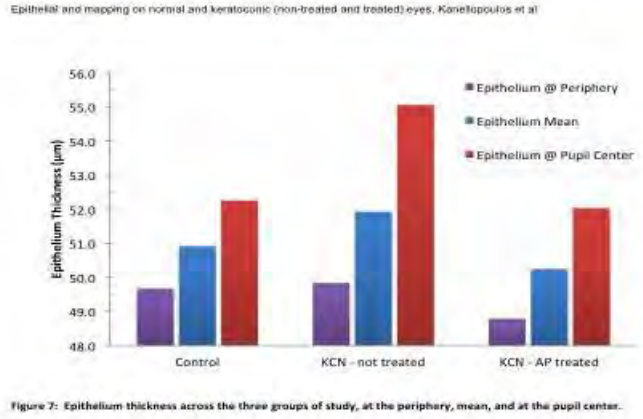
5-If CXL is offered early enough, can it eradicate clinical keratoconus?

a-yes

b-no

c-I do not know

Epithelial thickness: nl-KCN-KCNcxl'ed



Livestream to watch all our topo-guided + CXL surgeries of the last 6 months:

http://www.livestream.com/laservision or livestream.com/laservision

- A. John Kanellopoulos, MD
- Director, Laservision.gr Institute, Athens, Greece
- Clinical Professor NYU Medical School, NY

New York University School of Medicine

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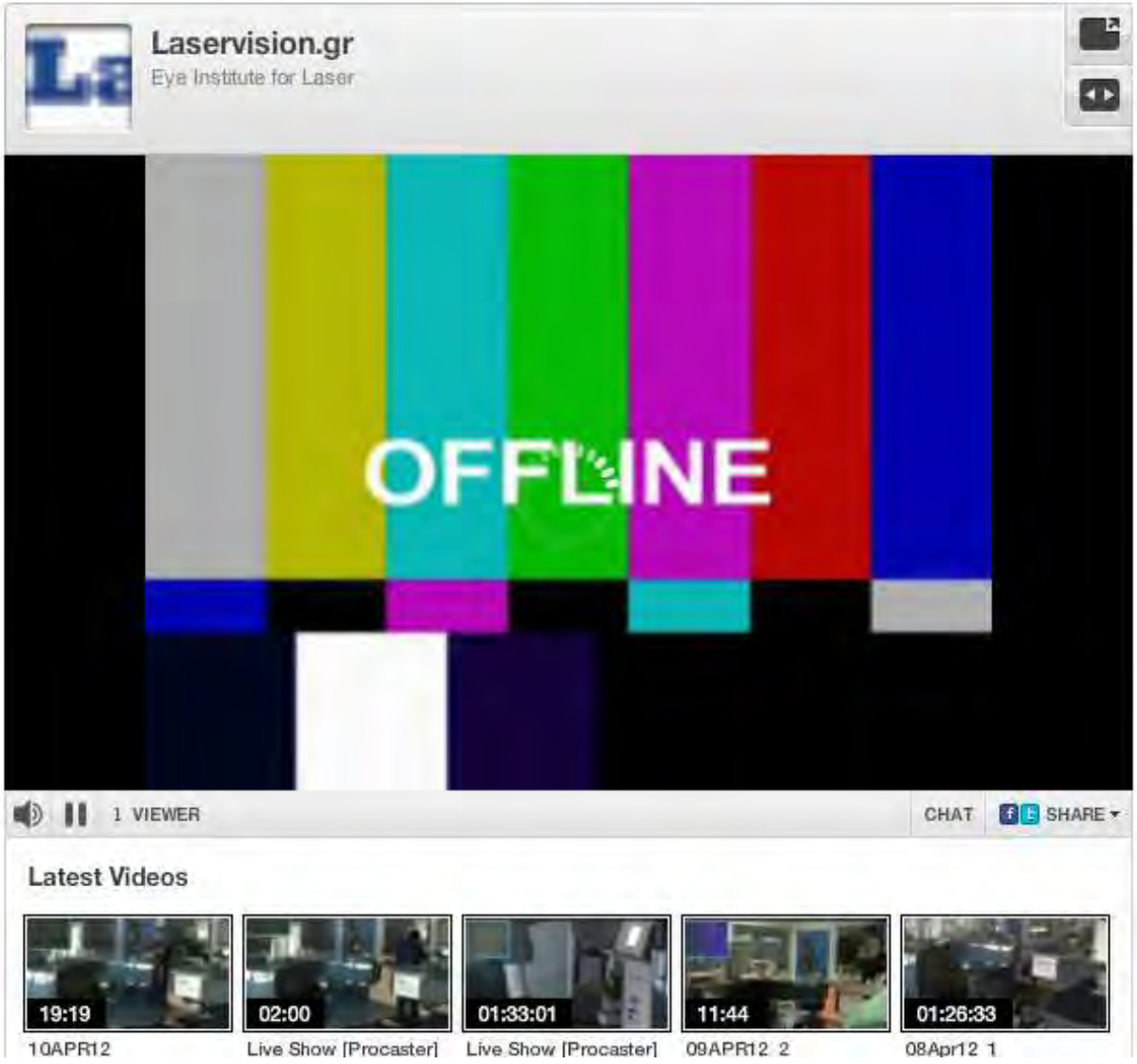

We introduced the concept of topography-guided excimer laser normalization of highly irregular corneas.

This is not just “PRK” it is a phototherapeutic normalization based on the proprietary Wavelight (Alcon) driven platform

Managing Highly Distorted Corneas

A John Kanellopoulos MD

The corneal surface is the principal refracting element of the eye the air- o-tear film in erface is responsible for the major-ity of refraction of light entering the eye.[1] Any change to this surface dramatically changes the refraction which is what is accomplished in refracti e surgery. Likewise any irregularity in this surface dramatically affects the quality of ision. This may be the problem in eyes with decentered and/or sma l op ical zone ablations in these cases the cornea acts like a multifocal lens and causes une en d stribution of ligh . As a consequence pat ents experience loss of BSCVA and contrast sensiti ity and haloes and starbursts around objects. These symp oms are especially annoying during scotopic and/or mesopic conditions when the pupil dilates and exposes more of the irregular cornea.[1 3 4 6 10-14]

Methods and Results

We ha e pre iously presented and published our experience in utilizing wa efront[1] as well as topography-guided[2] excimer ablations in order o treat highly irregular corneas such as eccentric pre ious ablations kera oconus and post LASIK ectas as. To correct these irregularities surgeons ha e gone to customized forms of ablation which include wa efront-guided ablat ons as well as techniques of opography-guided treatment.[3 9]

We ha e been working with the topography-guided plat-form by Wa elight (Erlangen Germany) o er he last four years. This proprietary software utilizes topographic da a from the linked topography de ice (Topolyzer-Wa elight Erlagen Germany). It by default permits the consideration of eight topographies (of predetermined threshold accuracy) a erages he data and enables the surgeon to adjust desired postoperati e cornea asphericity to include or not tilt cor-rection and to adjust sphere cylinder axis and treatment zone.

The mechanism of topography-guided ablation is he fit-ting of an ideal cornea shape (usually a sphere) under the present topography map with the ablat on of issue in between. The ad antages of topography-guided treatments o er wa efront-guided treatments include the following

1. It can be used in highly irregular corneas that are beyond the limits of wa efront measuring de ices.
2. It can be used in cases that ha e media opaci y such as in eyes with corneal scars since its measurements are based solely on the surface.
3. S nce it is based on the corneal surface it is heoreti-cally possible to factor in the asphericity (Q alue) and maintain the natural aspheric shape of the cornea.

Recent studies ha e demonstrated that there is a shift in the pupillary center between normal (photopic) and dark-adapted (mesopic scotopic state). Therefore topography-guided treatments would hold grea er accuracy on deli ery to the cornea since they are captured with the photopic pupil the same as in the treatment. The major d sad antage of topography-guided ablat on is that ignores the rest of the refracti e media since it concentrates mainly on the corneal contour. This may induce some refracti e surprises pre i-ously encountered when utilizing this techn que. One example of this would be in the reatment to widen the op ical zone of pre iously myopic pat ents. The treatment would require the laser to flatten a broader area of the cornea and therefore ablate tissue periphera ly this ablation pattern w ll resemble a hyperopic treatment and thus will cause some amount of

Figure 1. This is he pre and post LASIK opography (1 and 2 respecti ely) of an rregular cornea ha ing topography-guided LASIK wi h the TCAT Wa elight platform. The cornea irregulari y was caused by an old contact lens-rela ed bacterial ulcer. The difference map (1 minus 2) demonstrates he highly irregular flattening achi ed by he topography-guided treatment.

Figure 1. Display of topographies. **1**, Corneal topography of this case when first seen by the authors, with central cornea ectasia and midperiphery flattening as an effect of the Intacs that were present. At this point, best spectacle-corrected visual acuity (BSCVA) is 20/200. **2**, Corneal topography 2 months after the removal of Intacs and 1 month after combined ultraviolet radiation and riboflavin treatment to achieve collagen cross-linking. The central steepening is still present, and the effect of the Intacs removal relative to the previous image is appreciated mostly at the midperiphery, which appears steeper now. At this point, BSCVA is 20/200. **Bottom center**, An estimated corneal topographic ablation pattern as a laser treatment plan of the topography-guided procedure. It is notable that this ablation pattern is highly irregular, with a deeper ablation plan just inferior to and right of the center, which matches, however, the central cornea irregularity in the previous topographies. **4**, Corneal topography 6 months after topography-guided photorefractive keratectomy. The central cornea appears more regular and much flatter. At this point, BSCVA and UCVA are 20/20⁻. **Bottom left**, Comparison map depicting the result of subtraction of corneal topography 4 (final result) from corneal topography 1 (state of the complication when we encountered it). Impressively, the difference resembles the topography-guided ablation pattern (bottom center), demonstrating effectively the specificity of this treatment in reducing the pathogenic cornea irregularity, which, we theorize, contributed to the drastic improvement in BSCVA.

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REFRACTIVE SURGERY

Keratoconus: at a crossroads

by Maxine Lipner EyeWorld Senior Contributing Editor

Collagen crosslinking holds appeal for keratoconus and other diseases

When it comes to keratoconus treatment, practitioners have had very limited options—relying on use of rigid gas permeable contact lenses or, more recently on use of Intacs (Addition Technology, Des Plaines, Ill.) to help alleviate visual problems. One new potential treatment in the wings for this is use of collagen cross-linking. This holds promise not only but for keratoconus for other diseases as well, in addition to having refractive potential, according R. Doyle Stulting, M.D., Ph.D., professor of ophthalmology, Emory University, Atlanta.

To date, however, most of the work that has been done with the collagen crosslinking technique has been in conjunction with keratoconus. A. John Kanellopoulos, M.D., associate clinical professor of ophthalmology, New York University, New York, and director of laser vision, GR Institute, Athens, Greece, has been using the technique in keratoconus patients for years. The innovative method received the CE Mark in all 25 European countries as of December 2006, according to Dr. Kanellopoulos.

This patient's pre and post collagen crosslinking topography shows stabilization and some reduction in cone steepness Source: A. John Kanellopoulos, M.D.

Building new bridges

"The way the treatment works is that it forces the collagen fibers in the cornea to develop new binding bridges between them," he said. "It is as if we had a ladder and we're adding more steps to that ladder. It makes the edges of the ladder become much more stable in between them."

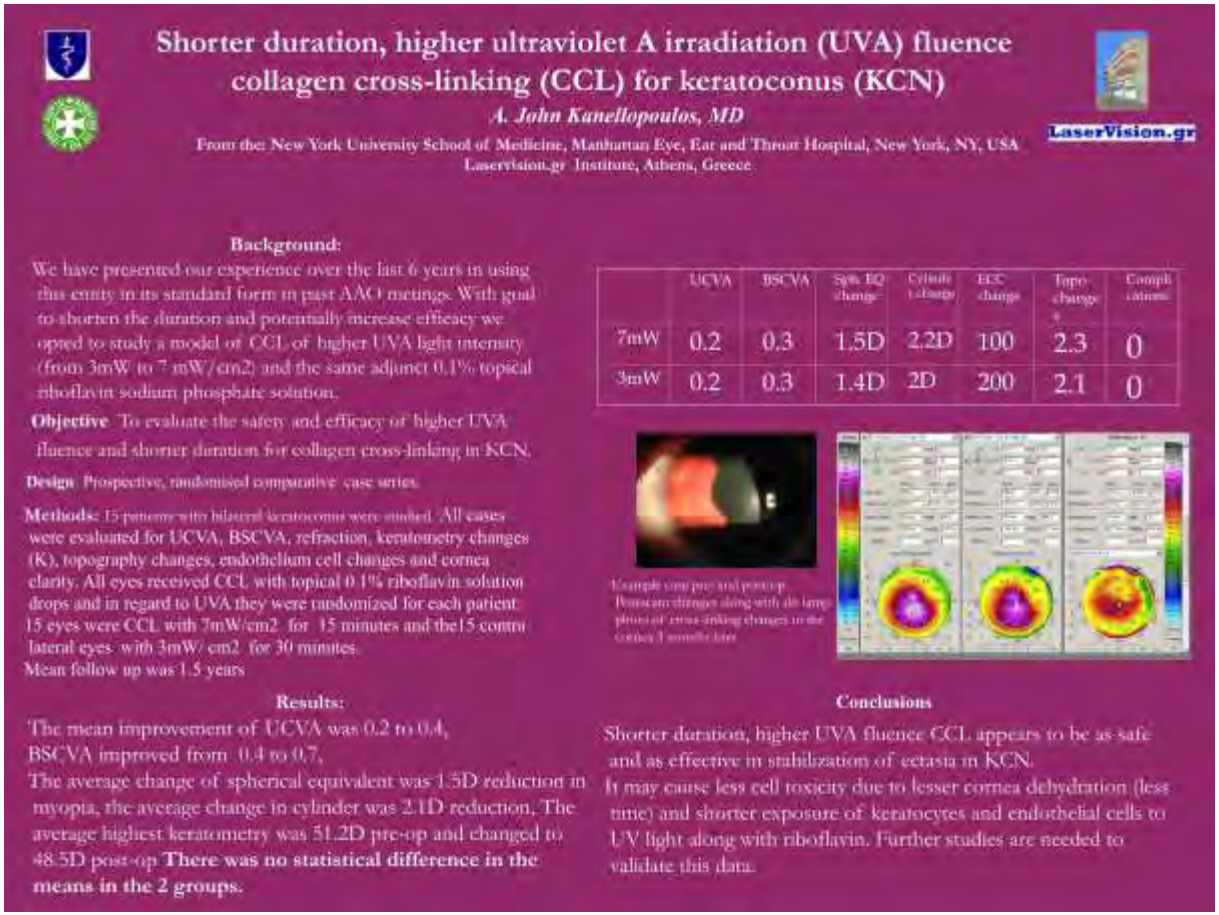
There are actually two elements involved in the cross-linking process: ultra violet radiation and vitamin B2, also known as riboflavin. The riboflavin absorbs a lot of ultraviolet A radiation. "There is a property of riboflavin that makes it absorb a lot of bad radiation and create free radicals," Dr. Kanellopoulos said. "This chemical reaction of creating free radicals forces the collagen fibers that are innocent bystanders in this chemical reaction to crosslink."

This patient had collagen crosslinking performed in the past for keratoconus; after undergoing subsequent PRK, the cornea is stable three years out and improved BSCVA from 20/50 to 20/25; here we see the patient's pre and post topo guided PRK treatment topographies and the topography showing the difference Source: A. John Kanellopoulos, M.D.

Dr. Kanellopoulos recently used the technique in the case of a patient with bilateral, progressive keratoconus. Topical 0.1% riboflavin drops

We introduced along these advanved topo-guided techniques also: Higher fluence CXL: 6, 7, 9, 10 and 12 and now 30mW/cm2

AAO 2008: CXL for 15 minutes utilizing 7mW/cm2 fluence



Shorter duration, higher ultraviolet A irradiation (UVA) fluence collagen cross-linking (CCL) for keratoconus (KCN)

A. John Kanellopoulos, MD

From the: New York University School of Medicine, Manhattan Eye, Ear and Throat Hospital, New York, NY, USA
Laservision.gr Institute, Athens, Greece

LaserVision.gr

Background:

We have presented our experience over the last 6 years in using this entity in its standard form in past AAO meetings. With goal to shorten the duration and potentially increase efficacy we opted to study a model of CCL of higher UVA light intensity (from 3mW to 7 mW/cm2) and the same adjunct 0.1% topical riboflavin sodium phosphate solution.

Objective: To evaluate the safety and efficacy of higher UVA fluence and shorter duration for collagen cross-linking in KCN.

Design: Prospective, randomized comparative case series.

Methods: 15 patients with bilateral keratoconus were studied. All cases were evaluated for UCVA, BSCVA, refraction, keratometry changes (K), topography changes, endothelium cell changes and cornea clarity. All eyes received CCL with topical 0.1% riboflavin solution drops and in regard to UVA they were randomized for each patient: 15 eyes were CCL with 7mW/cm2 for 15 minutes and the15 contra lateral eyes with 3mW/ cm2 for 30 minutes.
Mean follow up was 1.5 years

	UCVA	BSCVA	Sph. EQ change	Cylinder change	ECC change	Topo change	Complications
7mW	0.2	0.3	1.5D	2.2D	100	2.3	0
3mW	0.2	0.3	1.4D	2D	200	2.1	0

Example of one pre and post-op Pentacam changes along with the large amount of cross-linking changes in the cornea 3 months later

Results:

The mean improvement of UCVA was 0.2 to 0.4, BSCVA improved from 0.4 to 0.7,
The average change of spherical equivalent was 1.5D reduction in myopia, the average change in cylinder was 2.1D reduction, The average highest keratometry was 51.2D pre-op and changed to 48.5D post-op **There was no statistical difference in the means in the 2 groups.**

Conclusions

Shorter duration, higher UVA fluence CCL appears to be as safe and as effective in stabilization of ectasia in KCN.
It may cause less cell toxicity due to lesser cornea dehydration (less time) and shorter exposure of keratocytes and endothelial cells to UV light along with riboflavin. Further studies are needed to validate this data.

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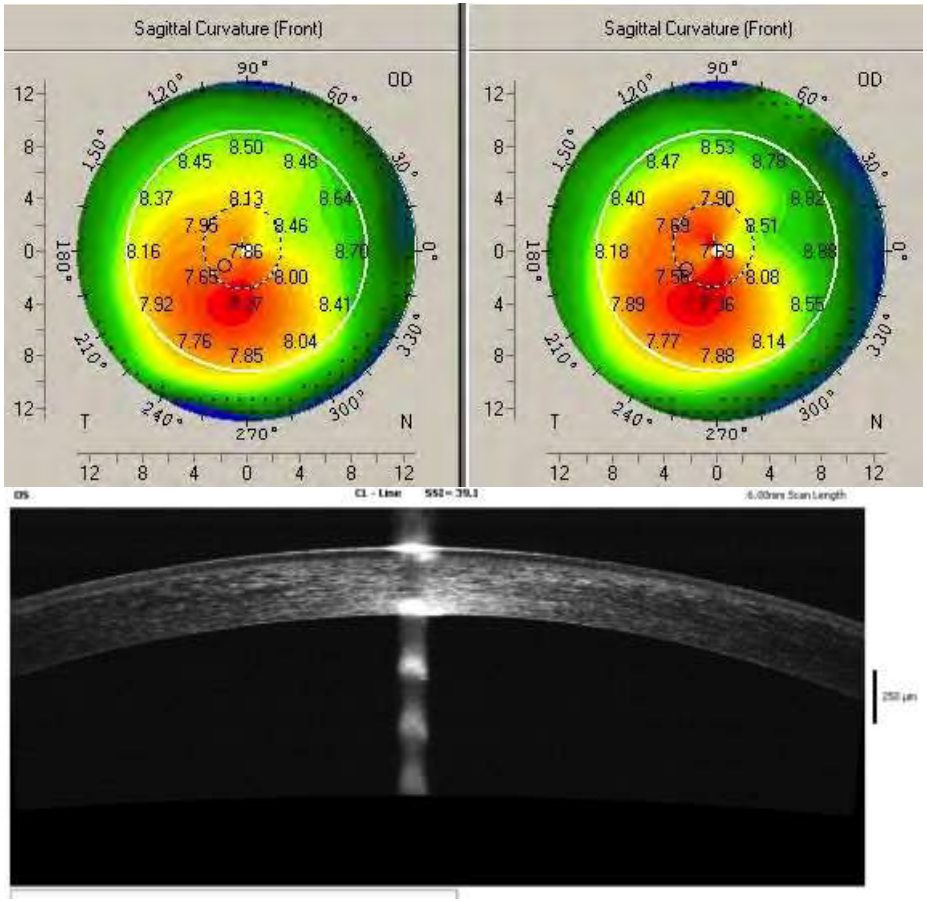
Introduction of riboflavin in a femto-pocket

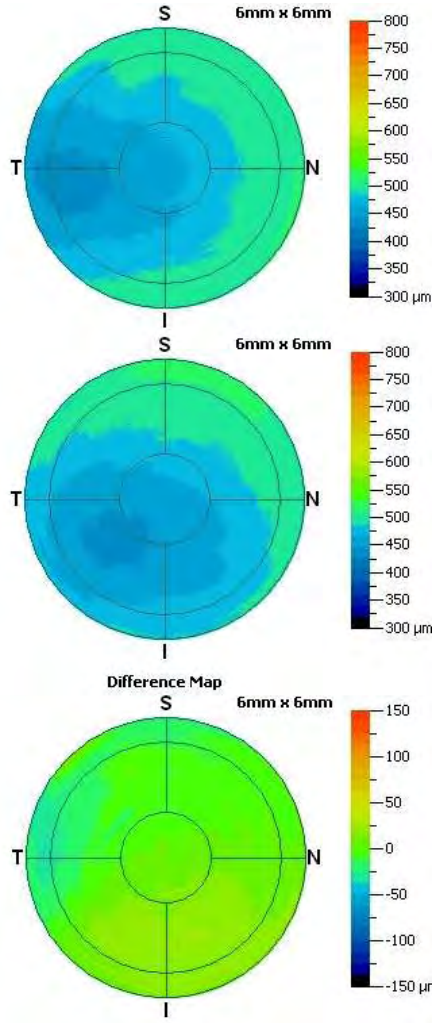
NEW TECHNIQUE

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

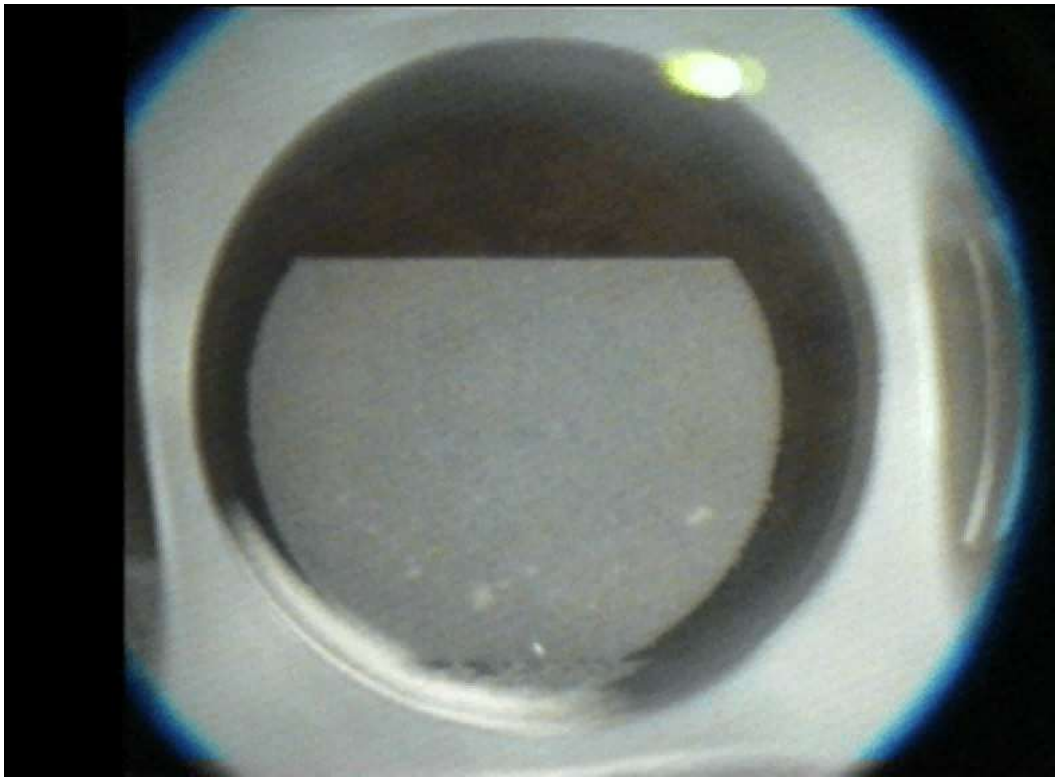
Anastasios John Kanellopoulos, MD

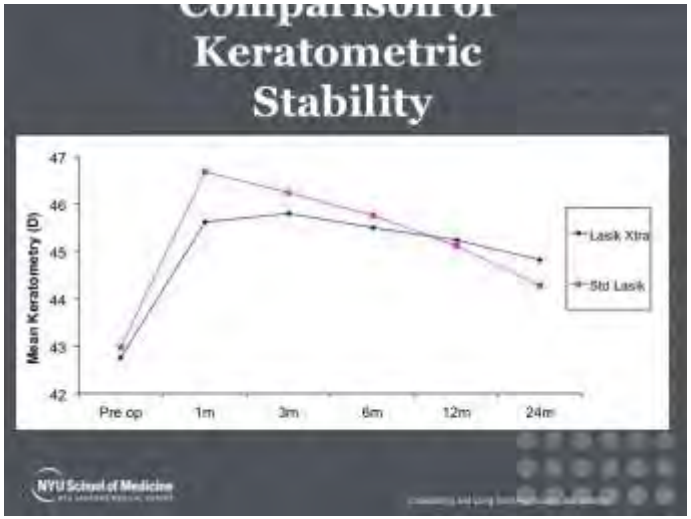
4 years after iLASIK+CXL





Introduced Prophylactic CXL in PRK and LASIK-2007





2012!

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Zurich 2007: CXL for PBK: 2 femto pockets and CXL with 10mW/cm^2

Staged Intrastromal Delivery of Riboflavin With UVA Cross-linking in Advanced Bullous Keratopathy: Laboratory Investigation and First Clinical Case

Ronald R. Krueger, MD, MSE; Jerome C. Ramos-Esteban, MD; A. John Kanellopoulos, MD

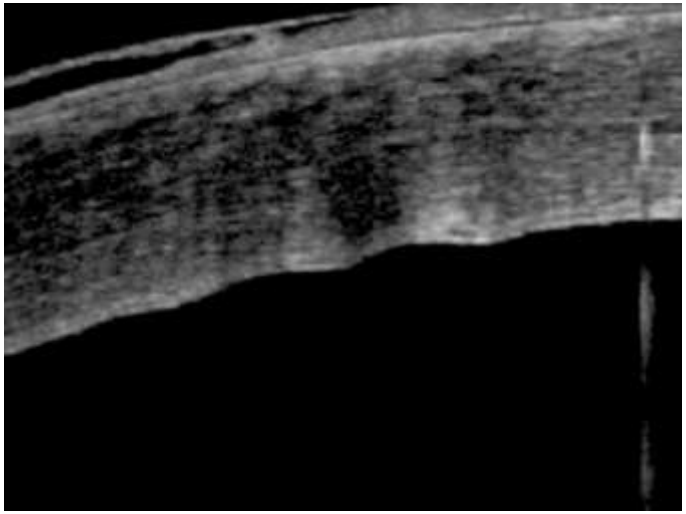

Figure 1. Schematic representation of the pockets created during staged intrastromal injection of 0.1% riboflavin and UVA cross-linking. **Figure 2.** Staged intrastromal injection of 0.1% riboflavin and UVA cross-linking.

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The Athens Protocol 7-years

ORIGINAL ARTICLE

Comparison of Sequential vs Same-day Simultaneous Collagen Cross-linking and Topography-guided PRK for Treatment of Keratoconus

Anastasios John Kanellopoulos, MD

ORIGINAL ARTICLES

Management of Corneal Ectasia After LASIK With Combined, Same-day, Topography-guided Partial Transepithelial PRK and Collagen Cross-linking: The Athens Protocol

Anastasios John Kanellopoulos, MD; Perry S. Binder, MS, MD

THE ATHENS PROTOCOL: PRK AND CXL

Meeting Visual Rehabilitation Needs

COVER STORY

Sequential Versus Simultaneous CXL and Topography-Guided PRK

Simultaneous treatment appears to superior rehabilitation of keratoconus.

BY A. JOHN KANELLOPOULOS, MD

Stability of Simultaneous Topography-guided Photorefractive Keratectomy and Riboflavin/UVA Cross-linking for Progressive Keratoconus: Case Reports

Clinical Ophthalmology — Dovepress

CASE REPORT

The management of cornea blindness from severe corneal scarring, with the Athens Protocol (transepithelial topography-guided PRK therapeutic remodeling, combined with same-day, collagen cross-linking)

Anastasios John Kanellopoulos

Stability of Simultaneous Topography-guided Photorefractive Keratectomy and Riboflavin/UVA Cross-linking for Progressive Keratoconus: Case Reports

Ronald R. Krueger, MD, MSE; A. John Kanellopoulos, MD

New York University School of Medicine

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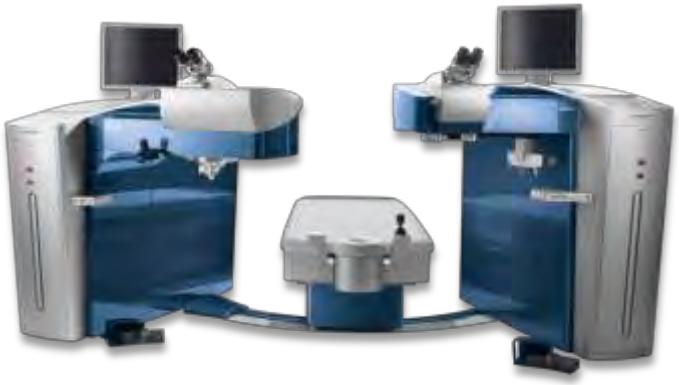
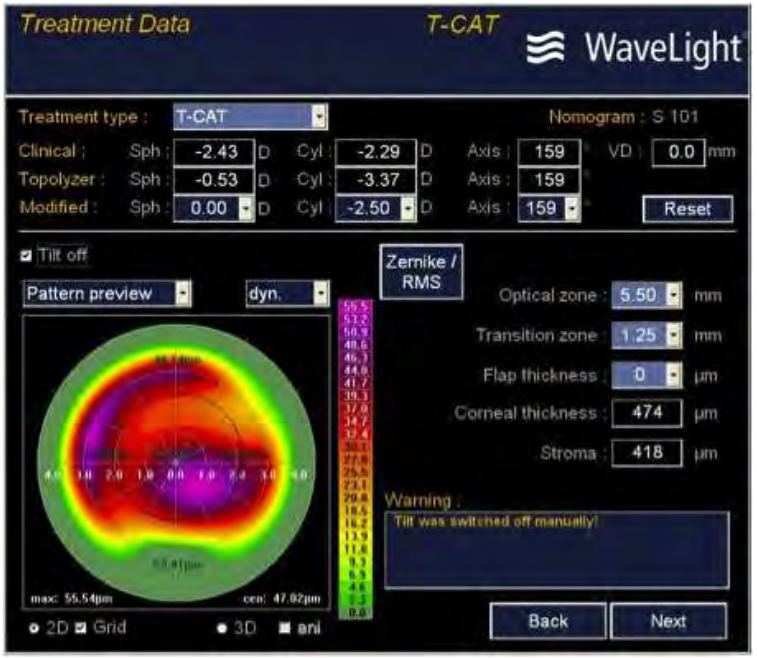
Topo-guided partial PRK

1-Topolyzer:Placido disc topography
2-Pentacam (Oculyzer)
3-Pentacam HD (oculyzer II)-Refractive suite
4-Vario (placido disc +pupil sensor+iris recognition+limbal landmarks recognition)



WaveLight® FS200
Femtosecond Laser

WaveLight® EX500
Excimer Laser



WaveLight® Refractive Suite

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The Athens Protocol 4 steps:

same day PTK > topoPRK > MMC > CXL (10mW/cm2 x 10 min)

1st PTK

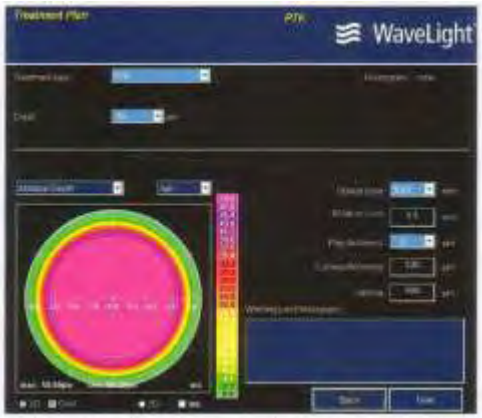

Figure 4.1: Epithelium removed with 50 micron PTK

2nd: topo -guided PRK

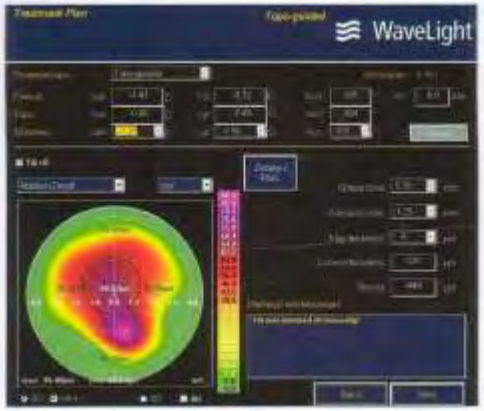

Figure 4.2: TC at treatment plan

Figure 4.3: Topography-guided PRK to correct part of the refractive error (TCAT treatment plan) maximal thickness removal 50 microns

4th: CXL

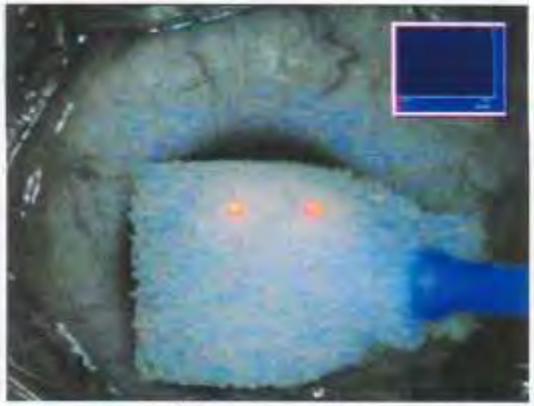

Figure 4.4: MMC solution 0.02% for 20 seconds

3rd: 30” MMC

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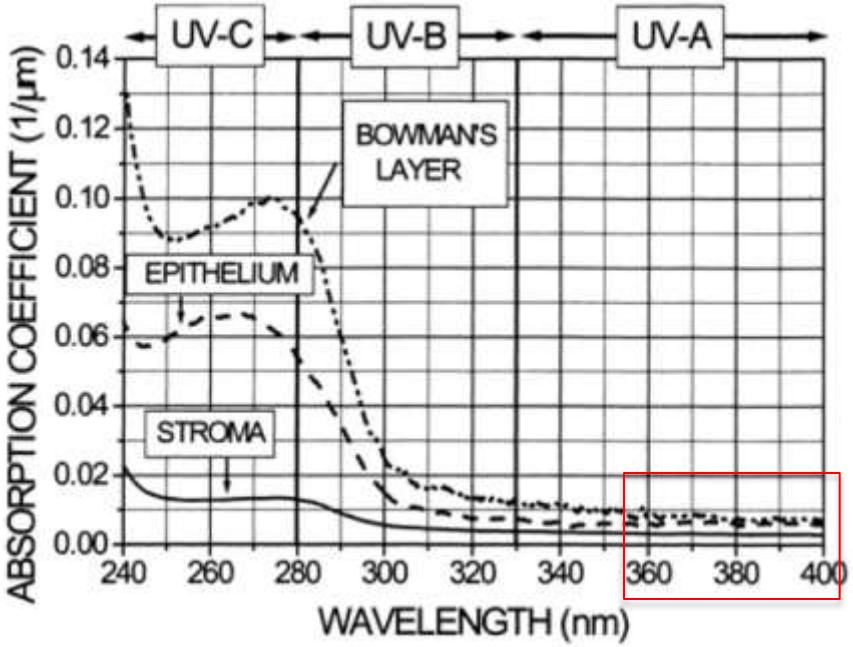

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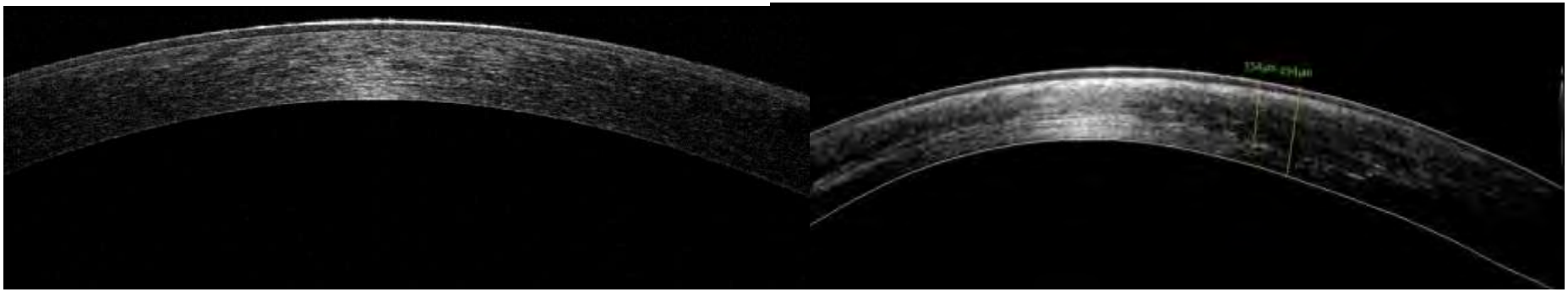
Anastasios John Kanellopoulos, MD

JRS Sept 2009

Kolozsvári et al
IOVS 2002;43:2165-2168



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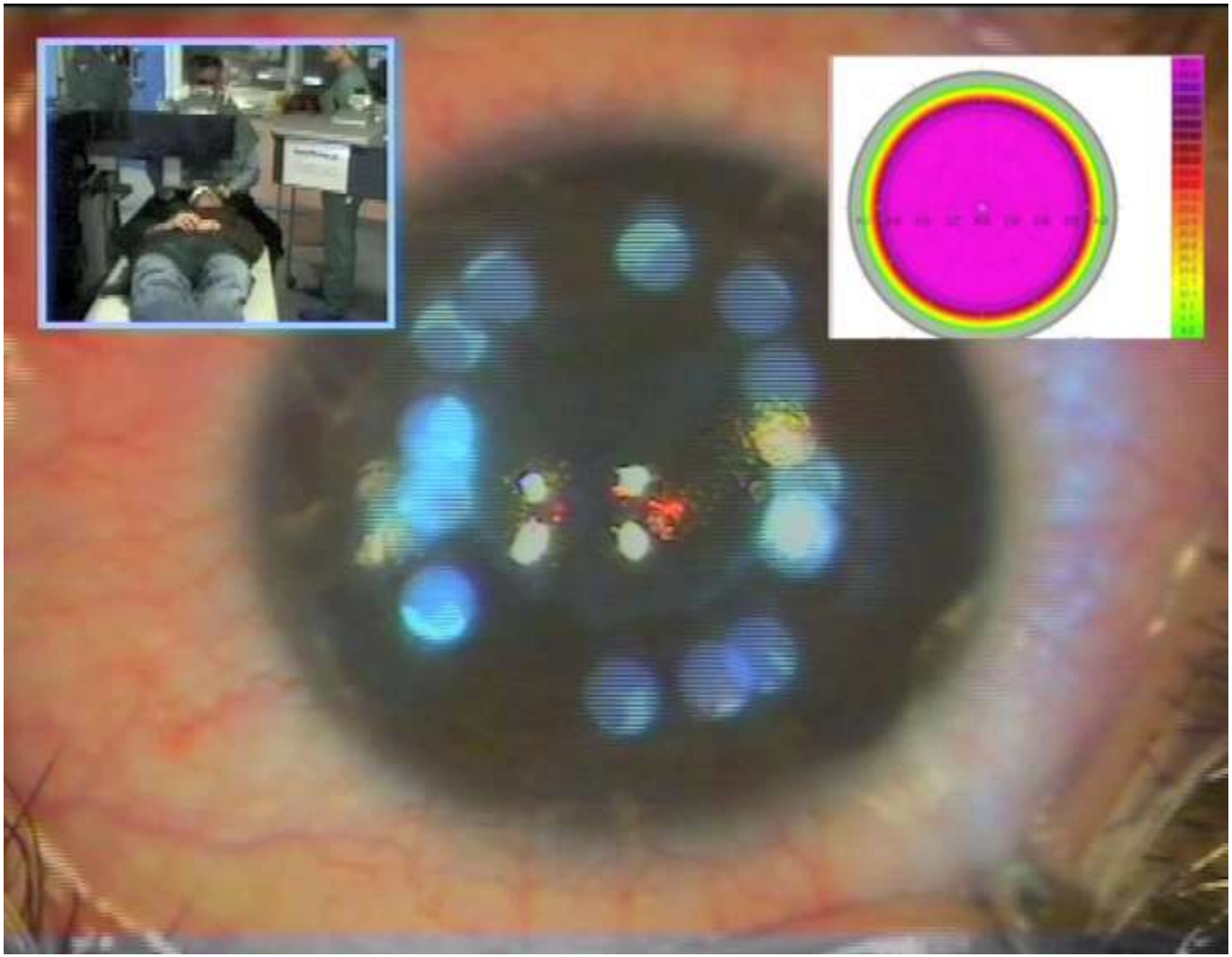
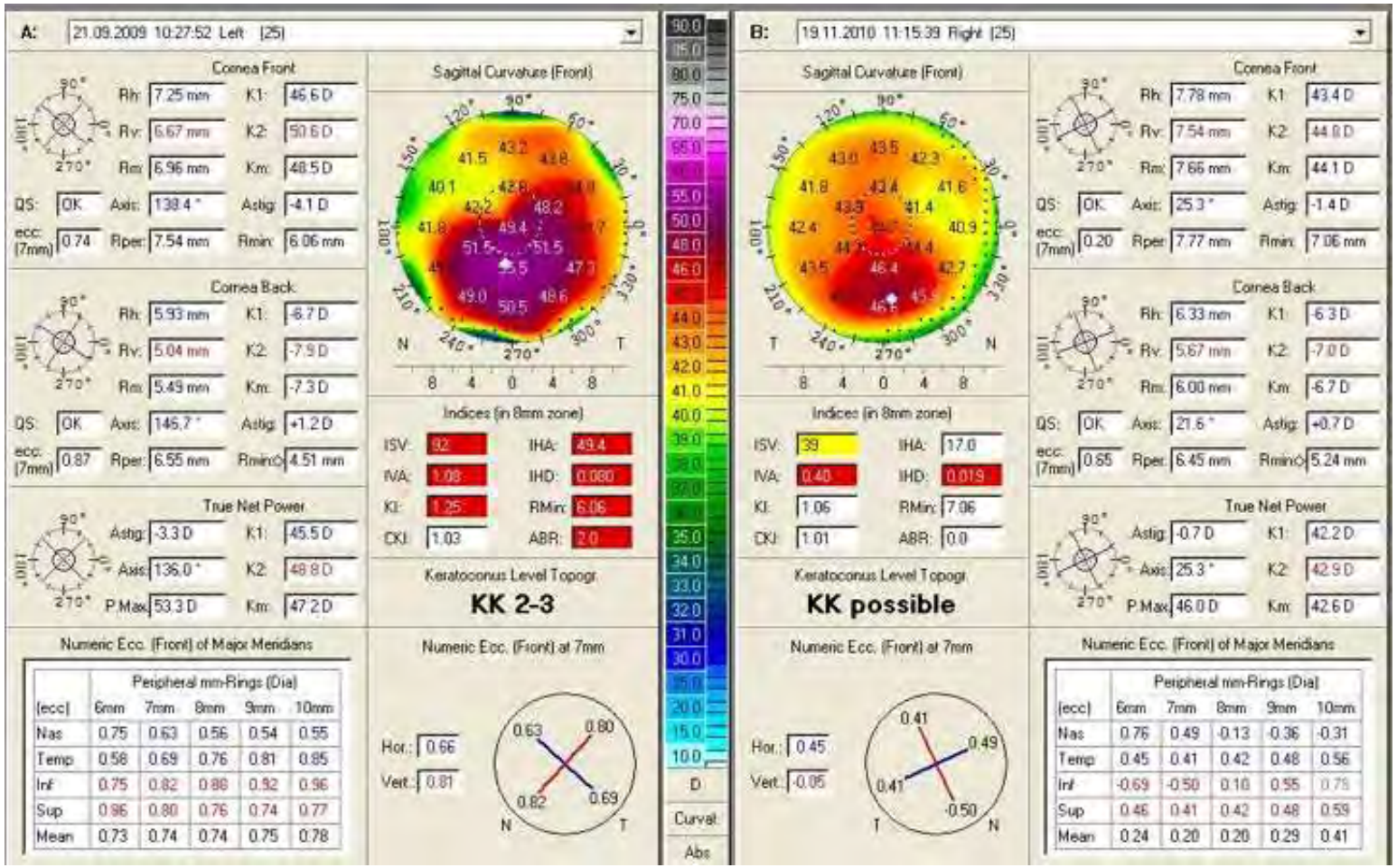
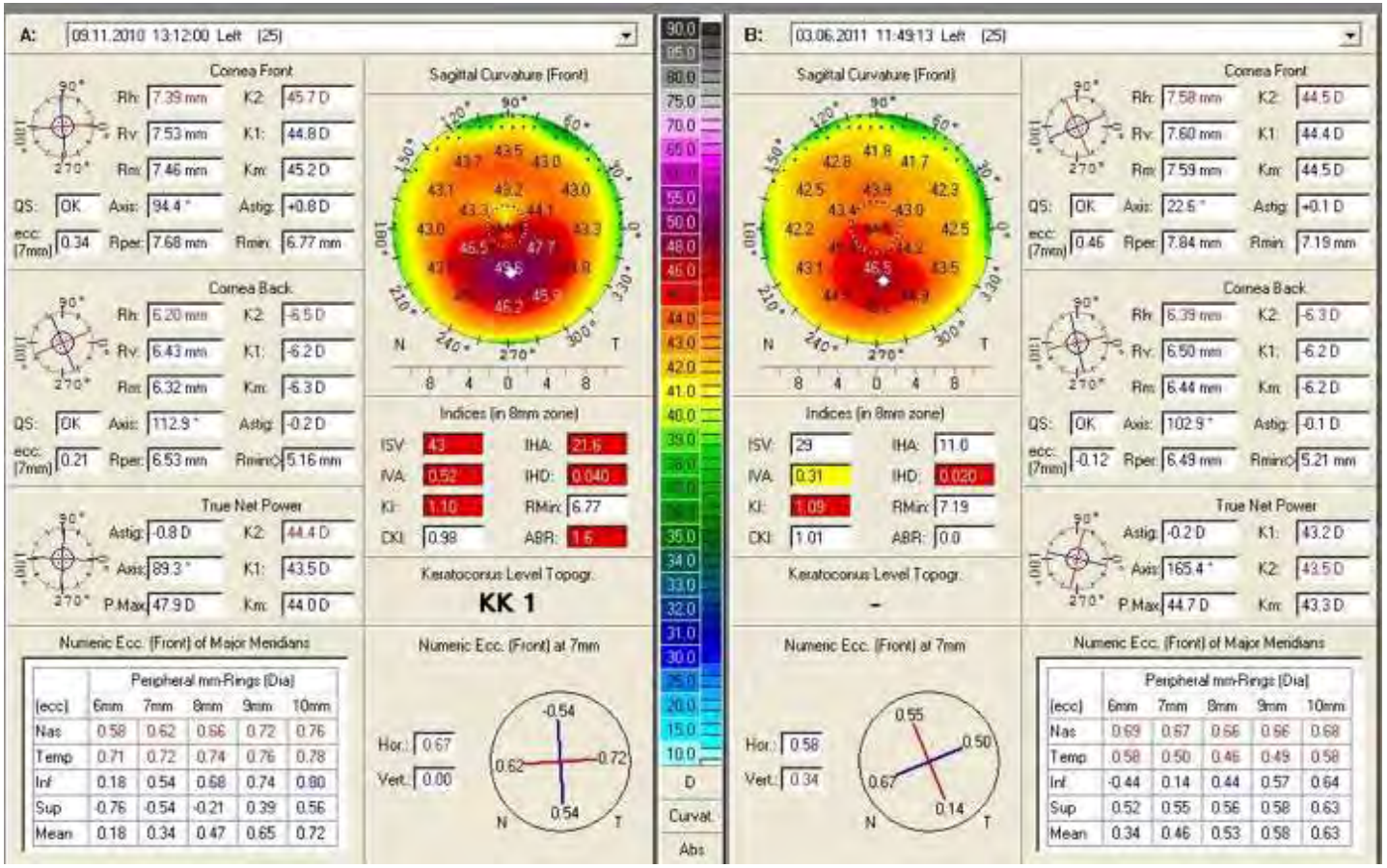
The Athens Protocol, in short video:



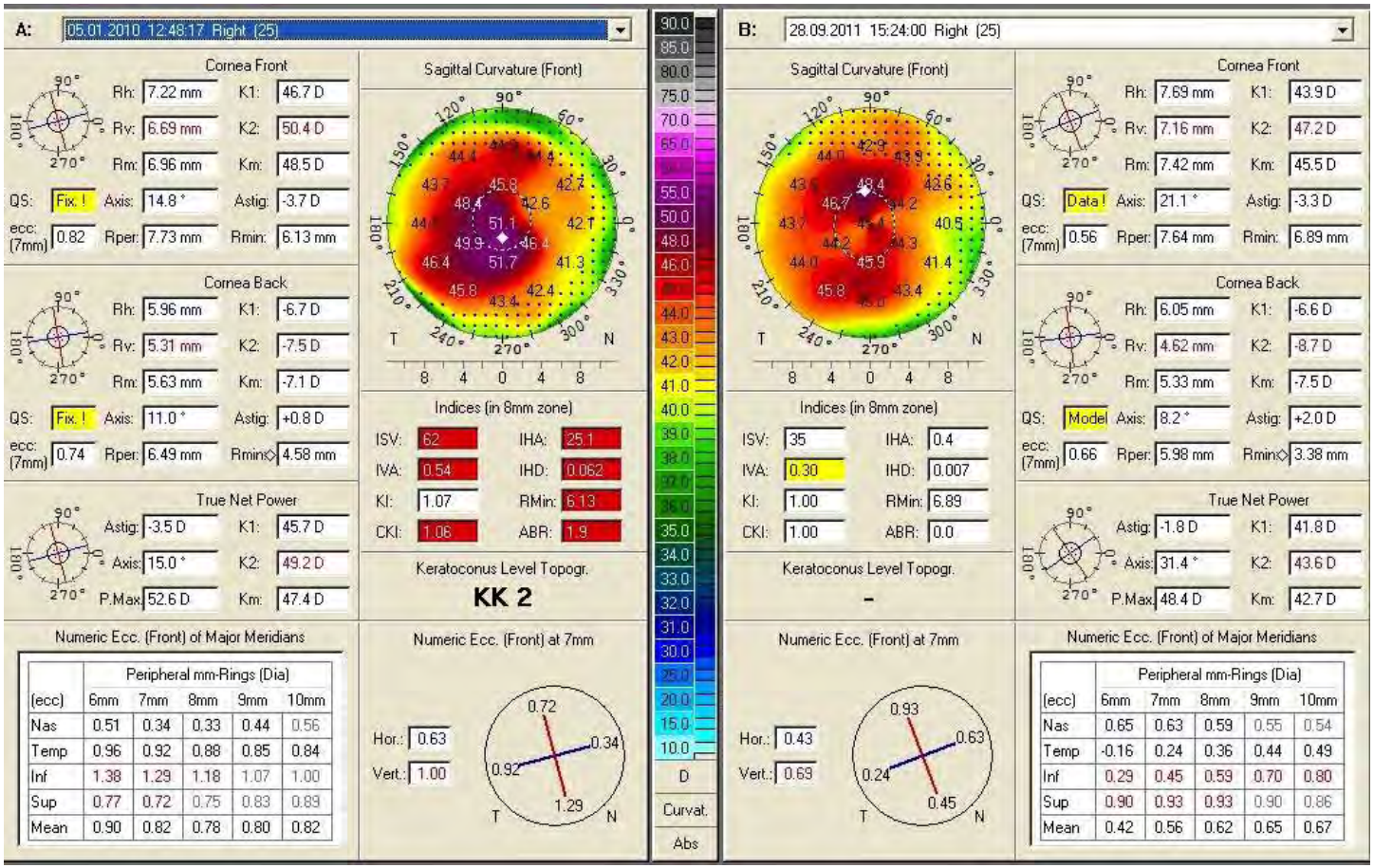
Average K from 48.5 to 44
Refraction -2.5-4.5@155 (20/70) to -1-1.5@10 (20/20)



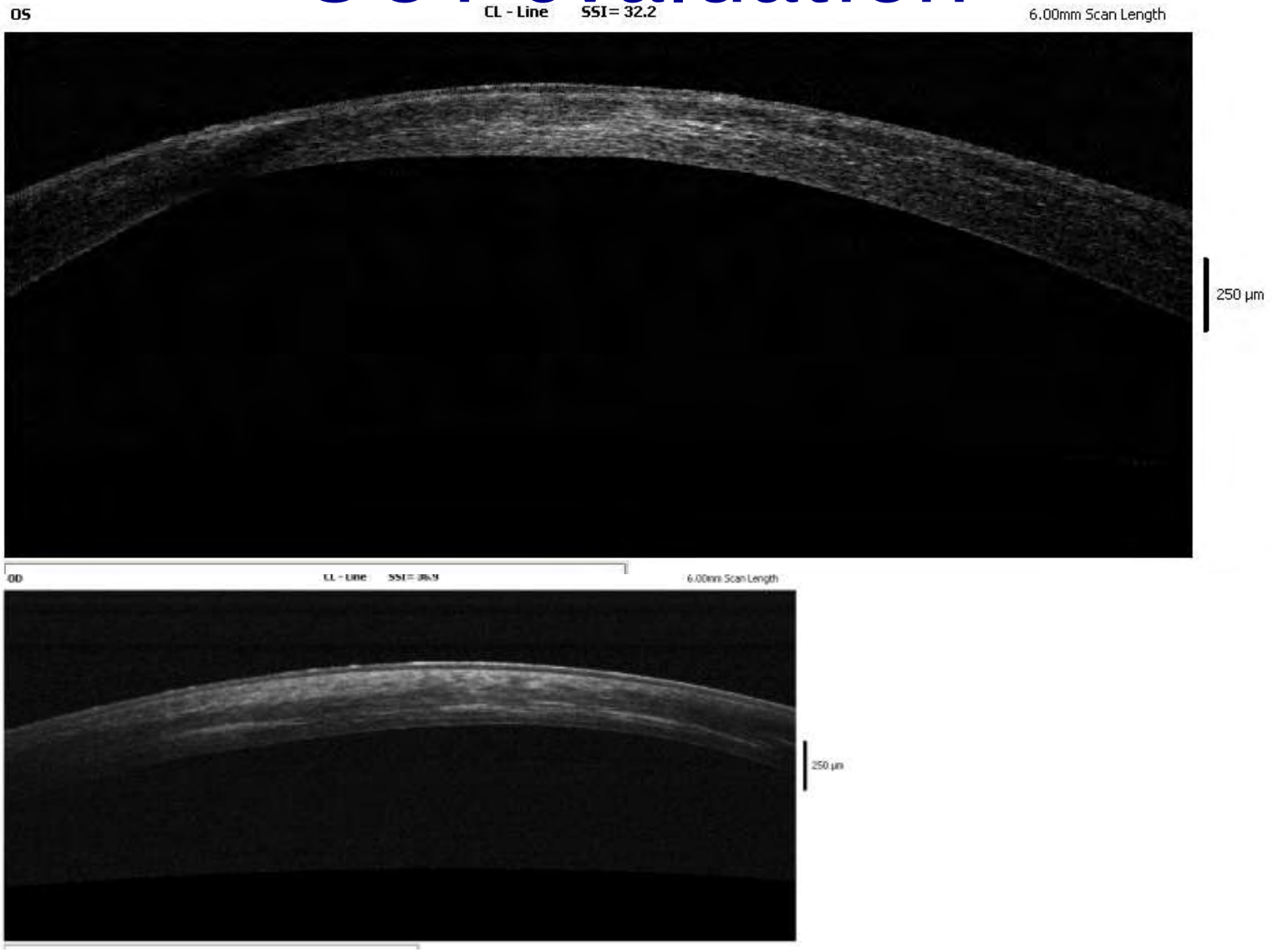
In oblique KCN: AveK from 44.6 to just 44.3!
Flattest K steeper by 1D
refraction +0.50-3.50@160(20/60) to -1.5D (20/20)



2 year follow up in a 15 y/o



OCT evaluation



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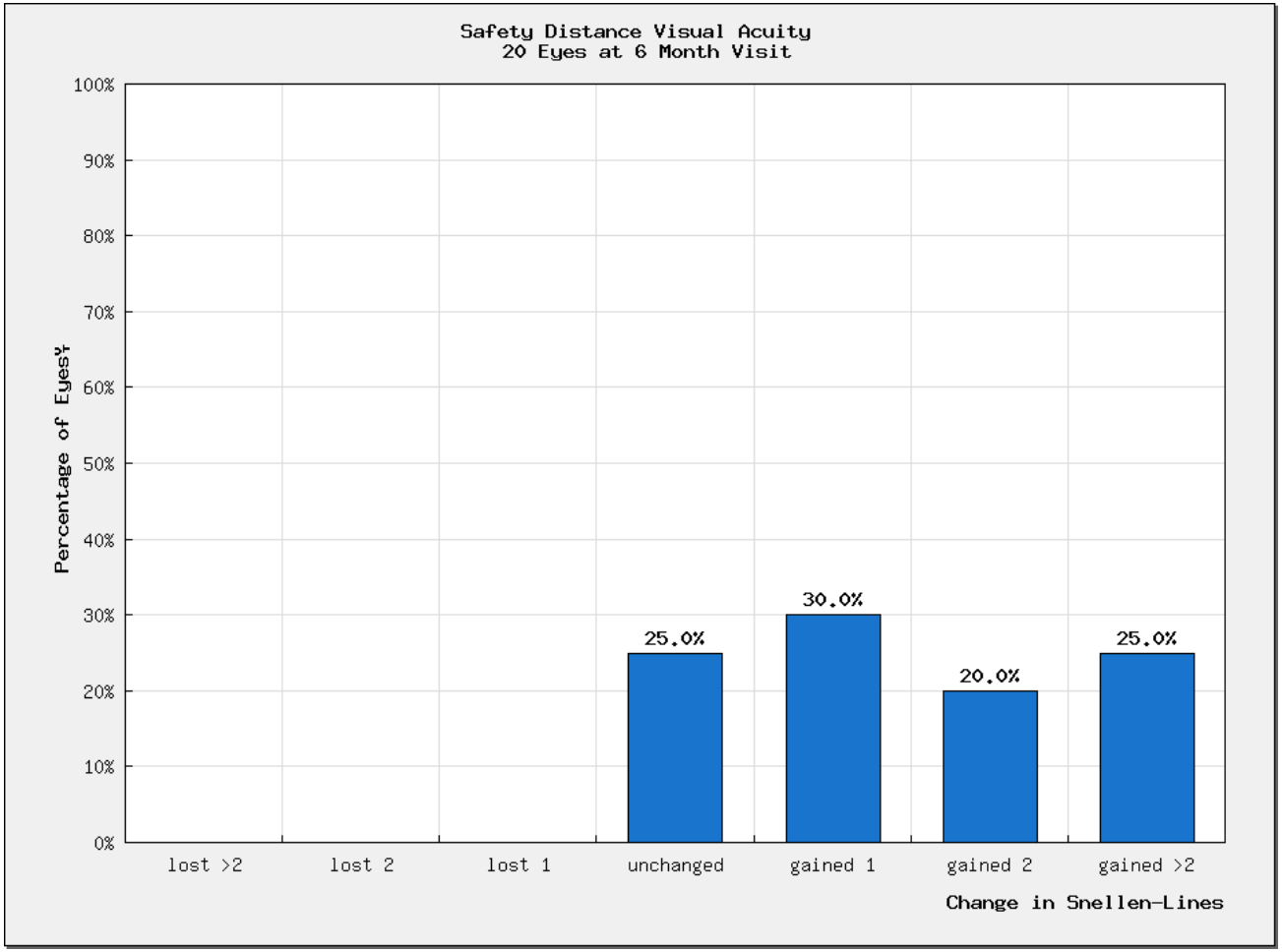
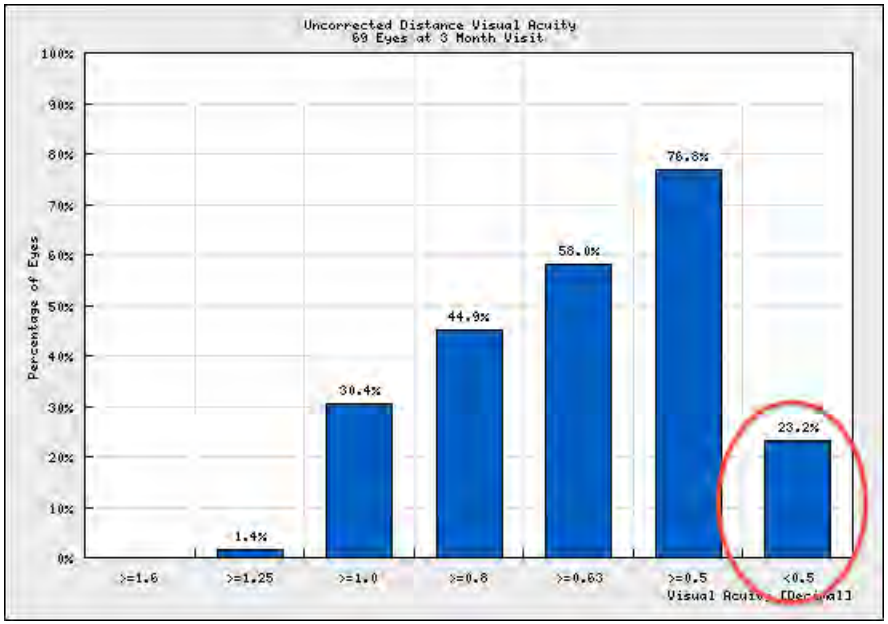
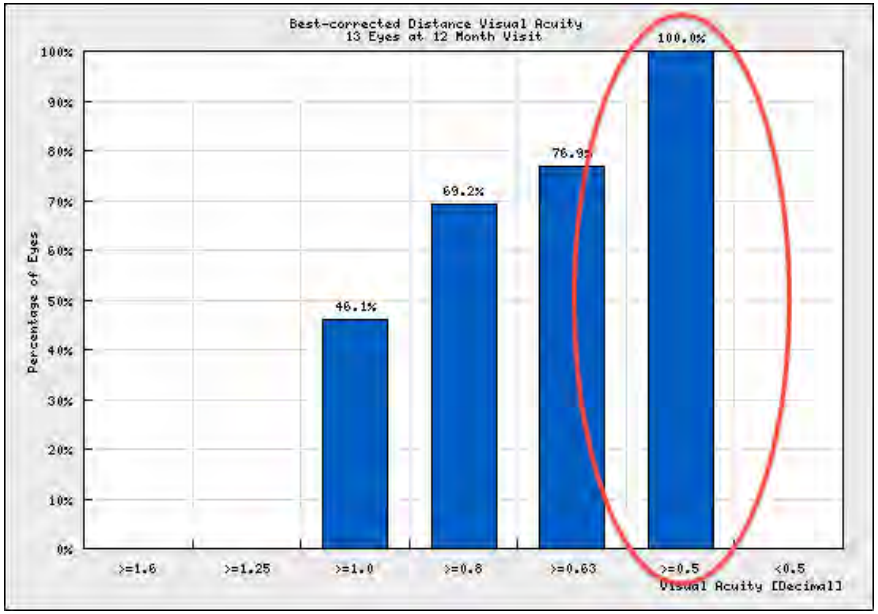
Athens Protocol: safety



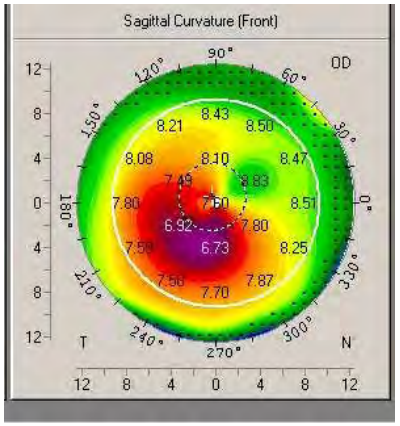
Athens Protocol:
Some improvement in UCVA, dramatic improvement in BSCVA: 98% of cases at least 20/40!)

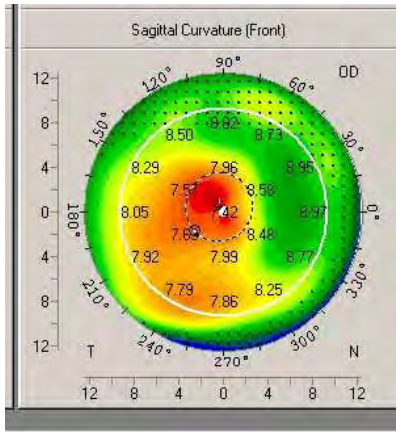




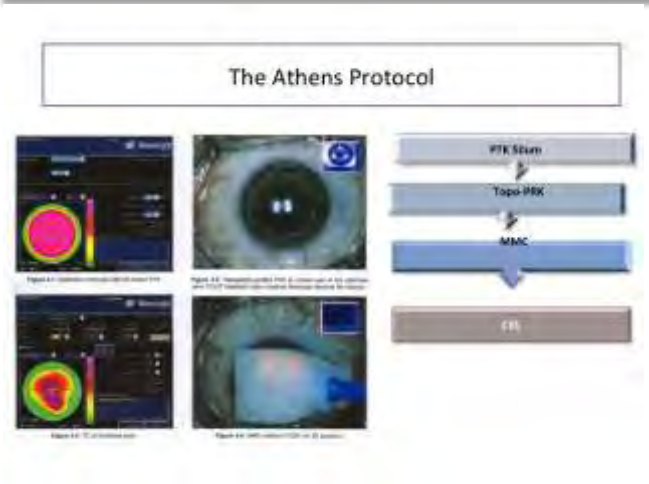
Results:

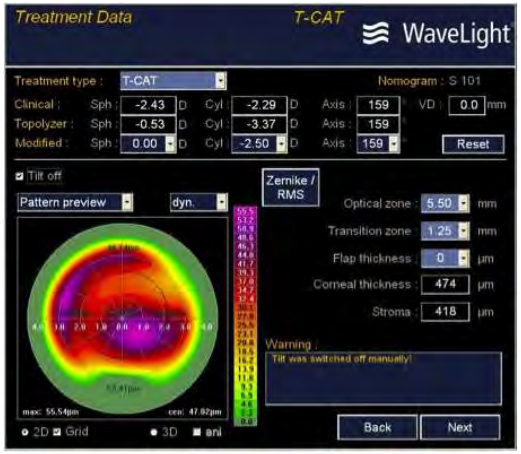
None of the cases showed further ectasia progression. UDVA improved from 0.3 to 0.5, CDVA from 0.5 to 0.8, attributed to mean improvement of the cornea index of height decentration (IHD) by 55%, SE from -3.8 to -1.6 Diopetrs, Mean K from 51.5 to 47.5. 50% of cases gained 2 lines of CDVA, 35% 3 lines respectively. Minor complications were encountered in 12% of cases.





Short and long term complications of combined topography guided PRK and CXL (the Athens Protocol) in 412 keratoconus eyes (2-7 years follow-up)





Anastasios John Kanellopoulos, MD
Director, Laservision.gr Institute, Athens, Greece
Clinical Professor NYU Medical School, NY
Financial Interests: Alcon. Wavelight

New York University School of Medicine

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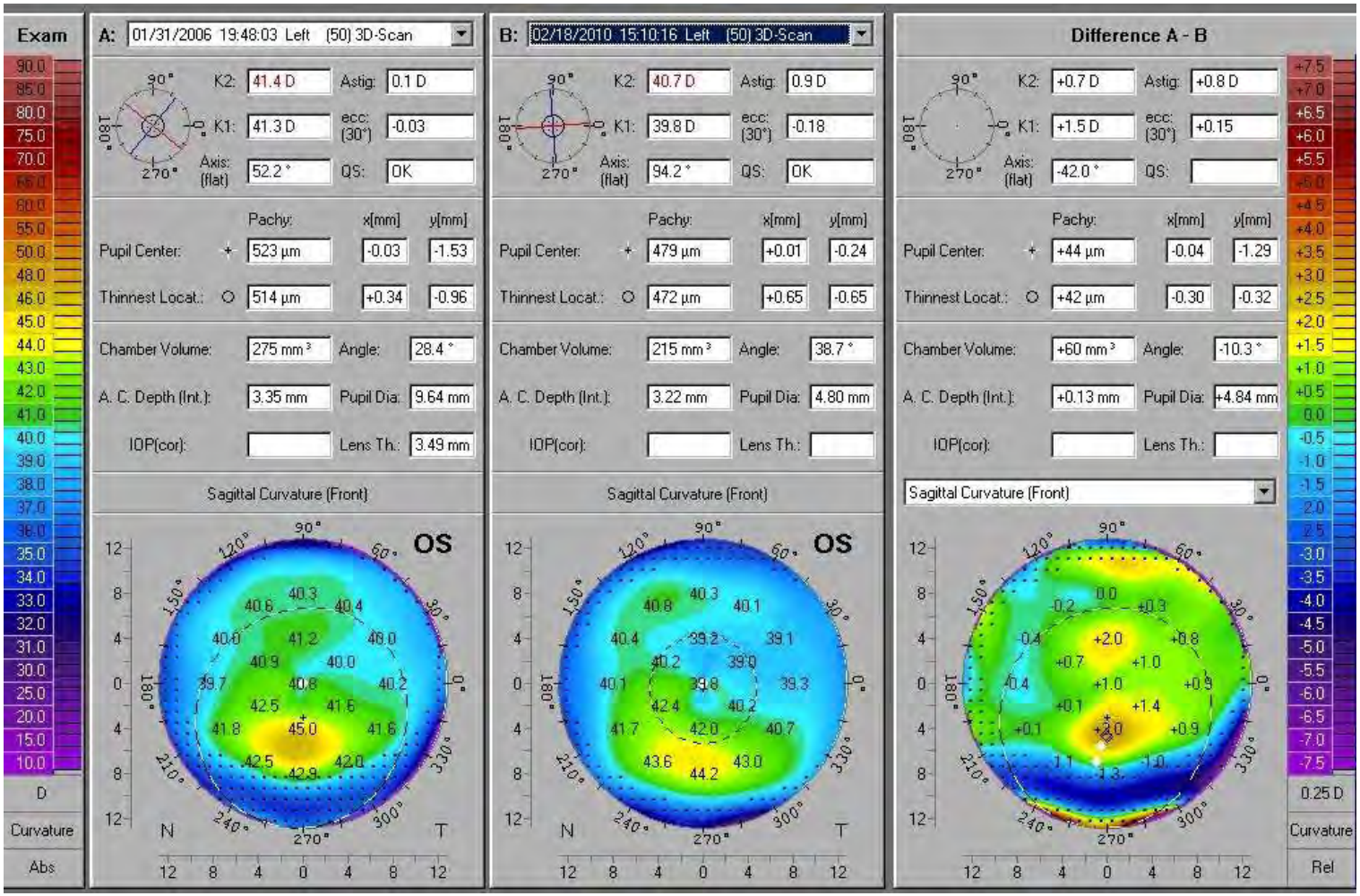
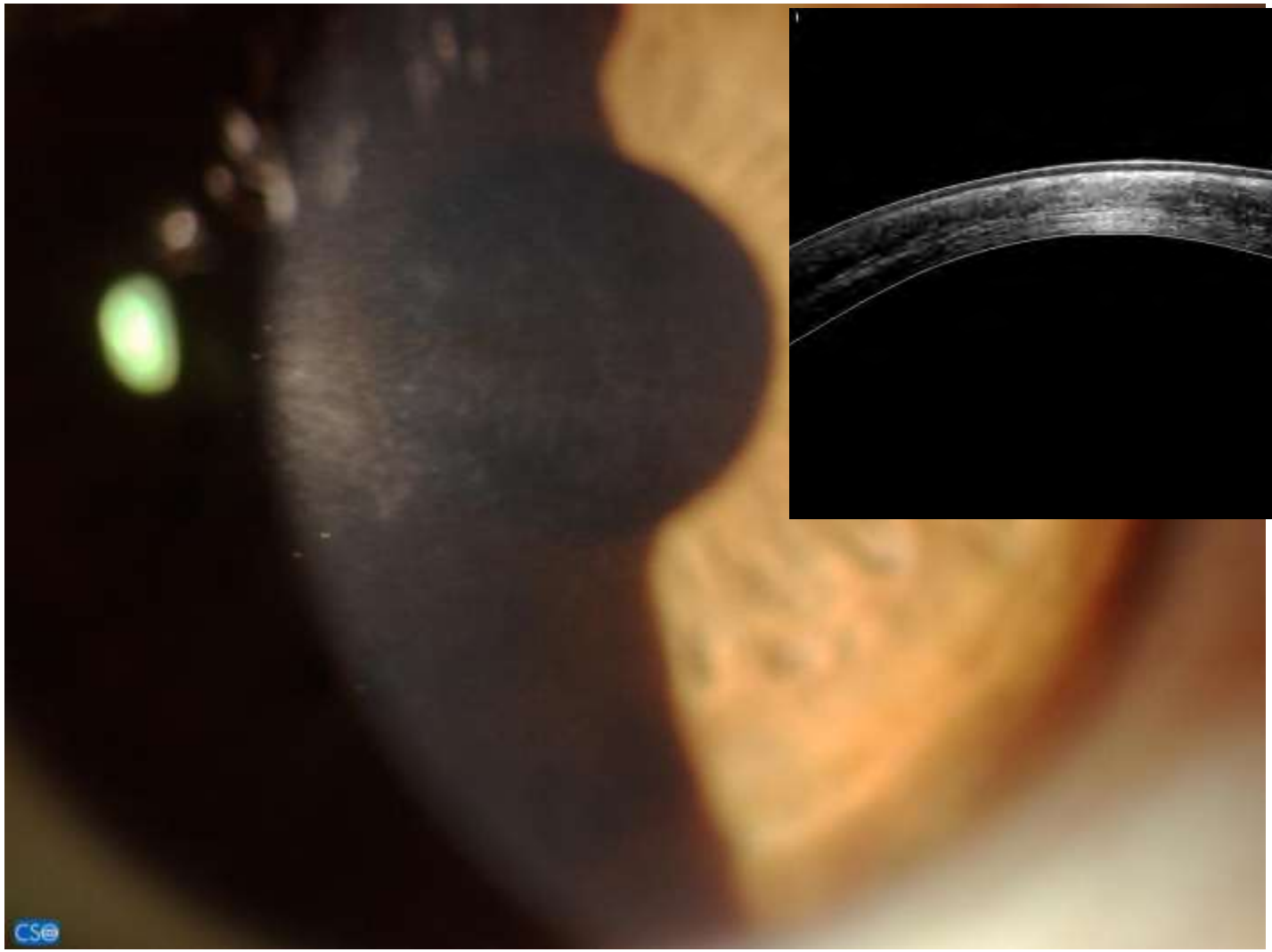
From UDVA 20/20 to 20/40 over 4 years with a 2.5D hyperopic shift



3 months later (lotemax, Autologous)



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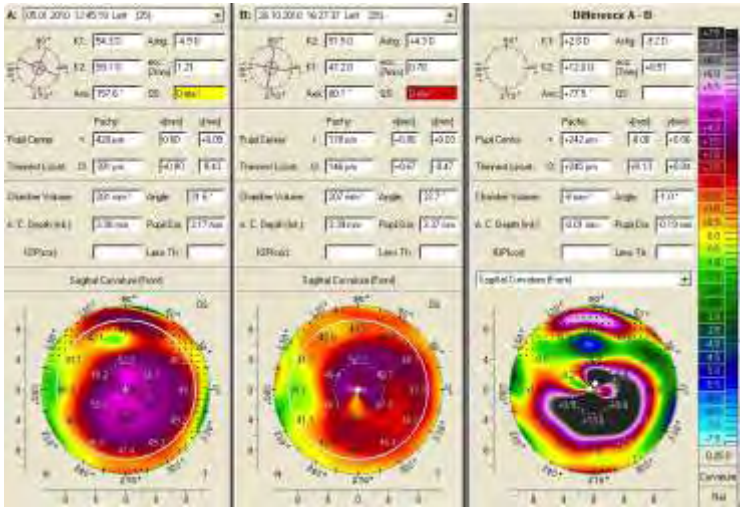
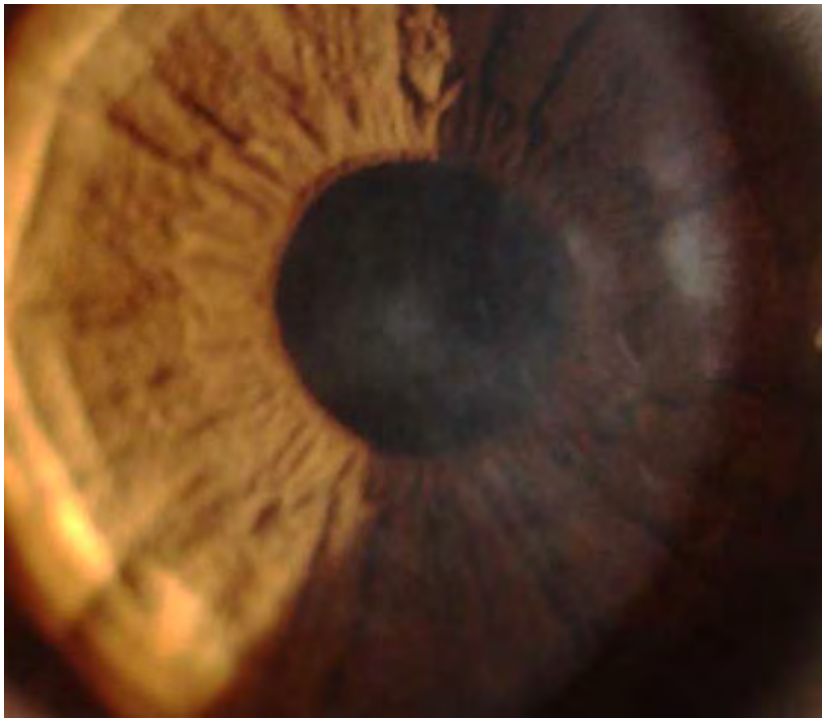
Late stromal scar





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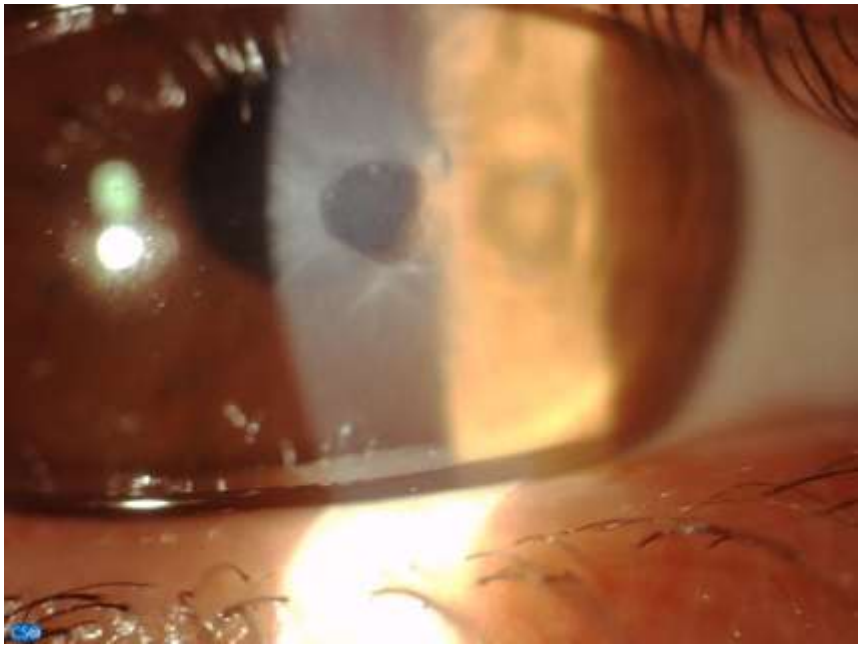
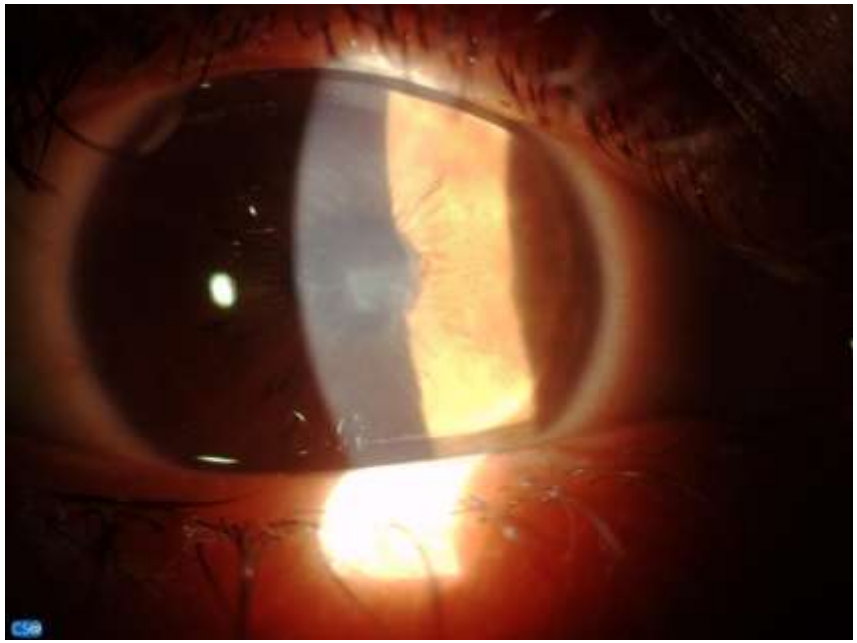
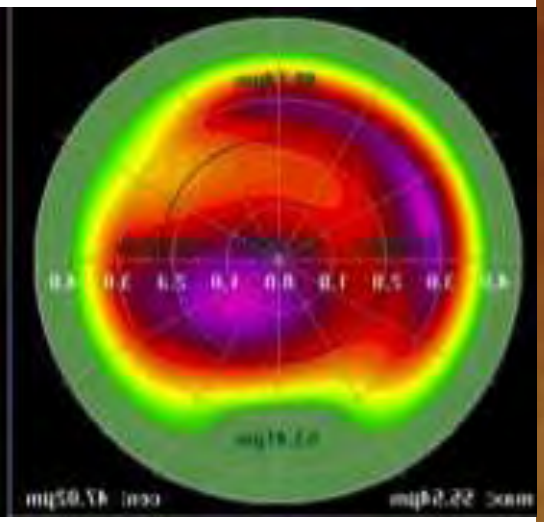
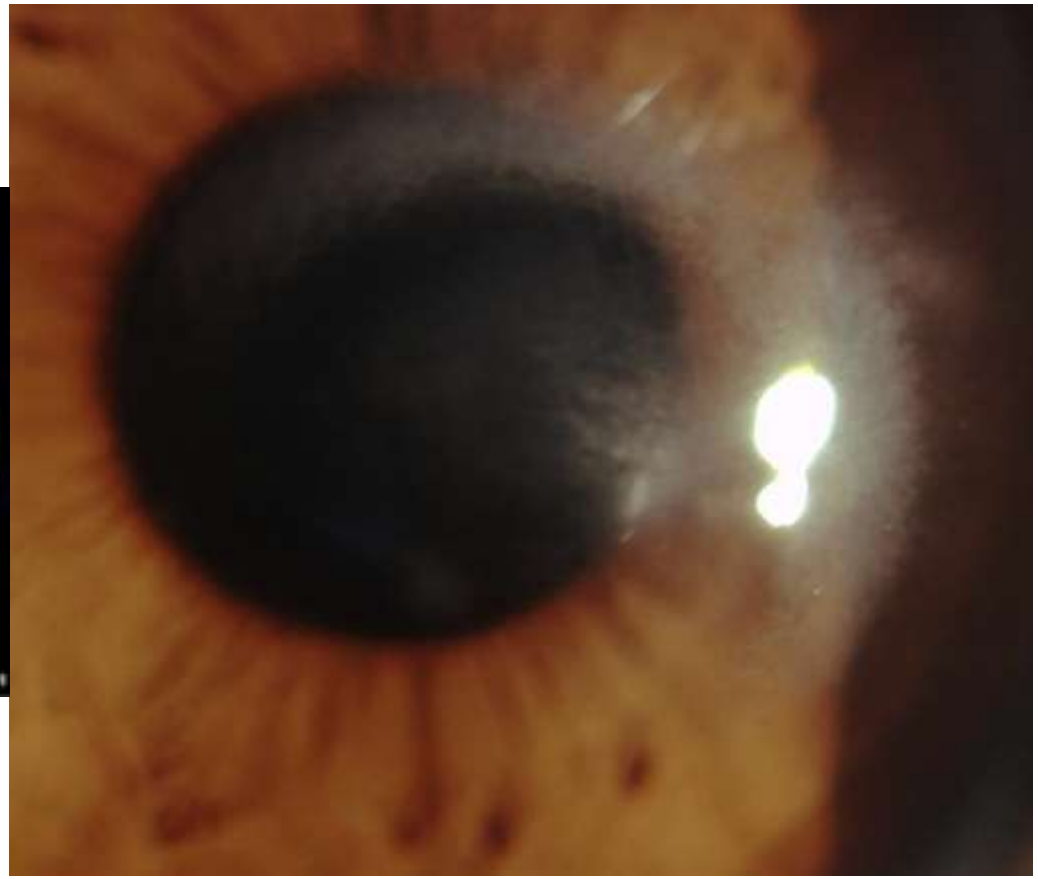
2 weeks out-delayed epitheliazation





2 months-PRK anterior stromal scar





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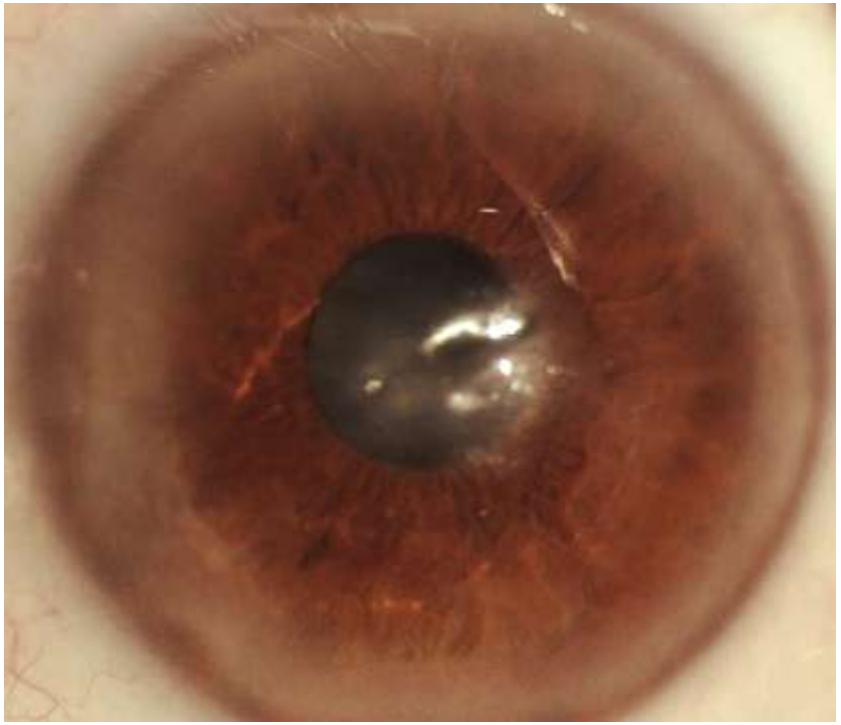
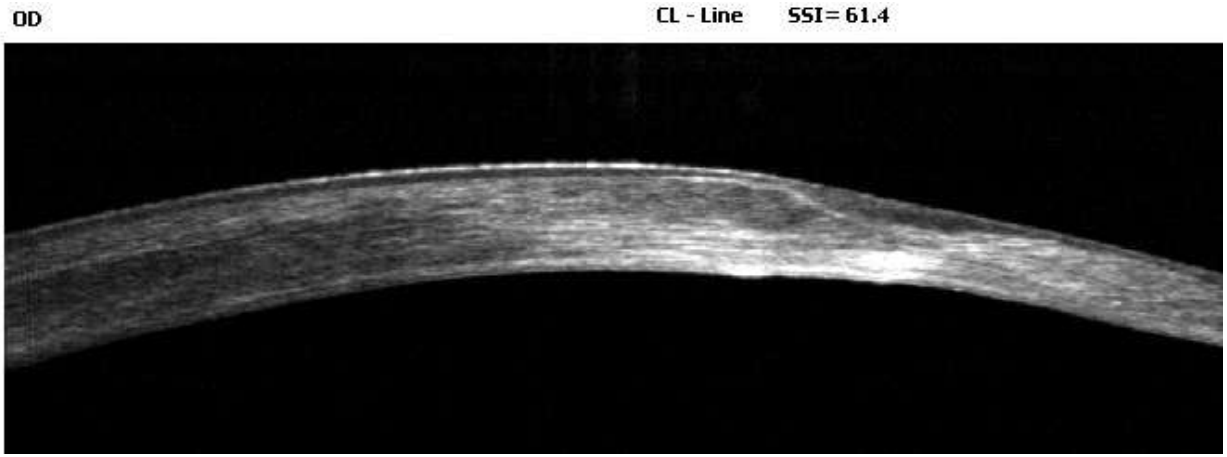
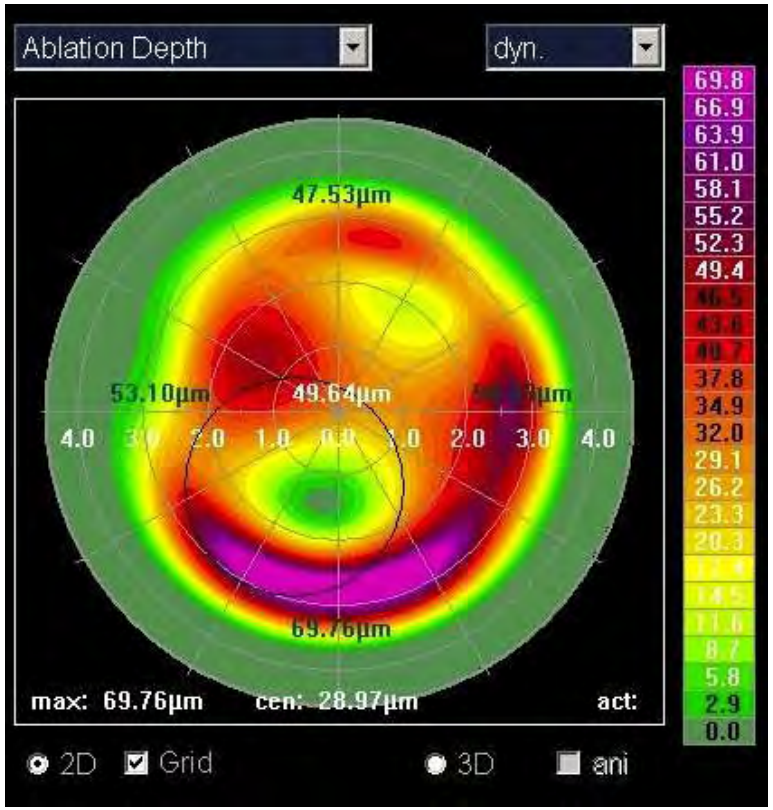
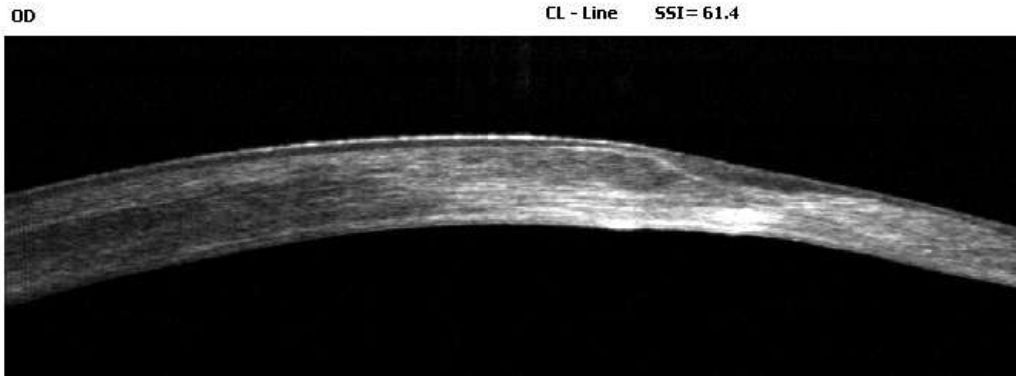
Severe scar of the cornea
BCVA 20/200,

Lamellar or PK?

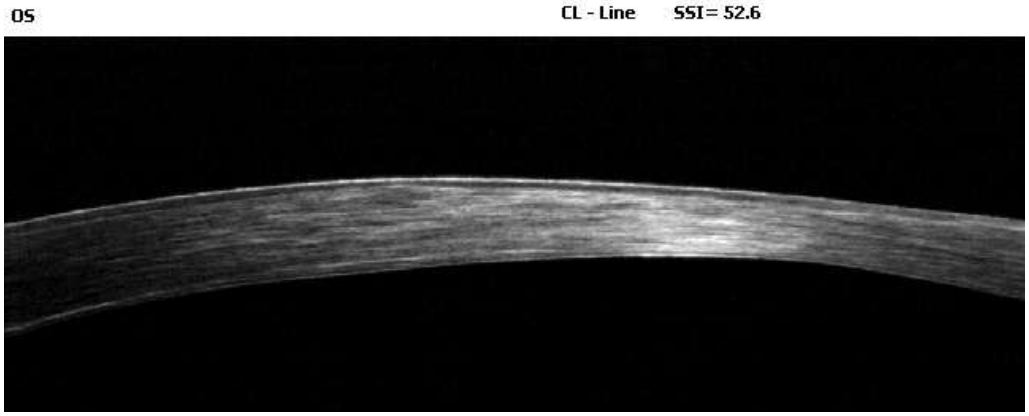








6 months s/p
Athens Protocol



New York University School of Medicine

Kanellopoulos,MD

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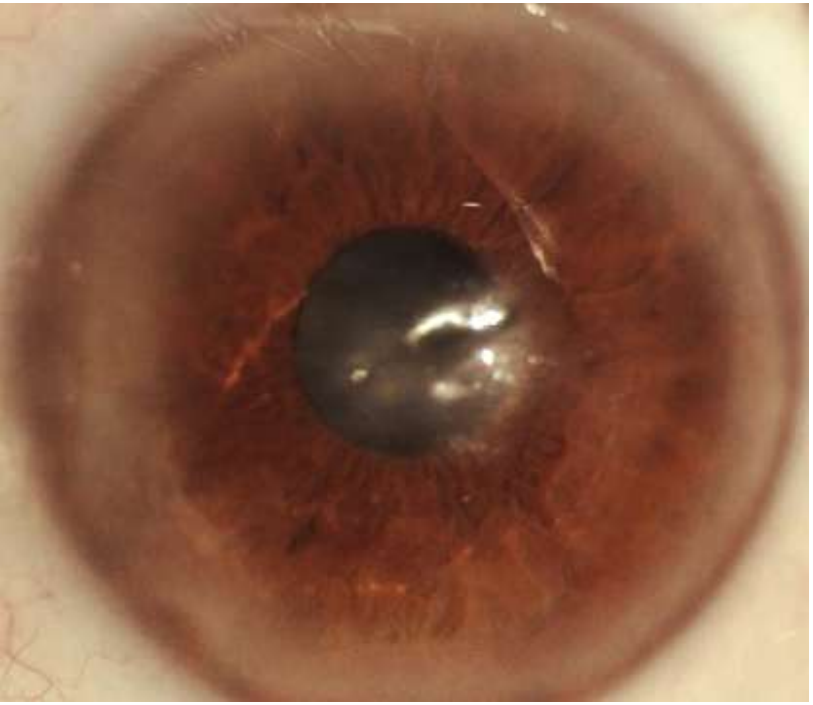
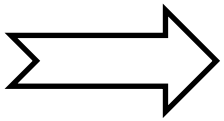
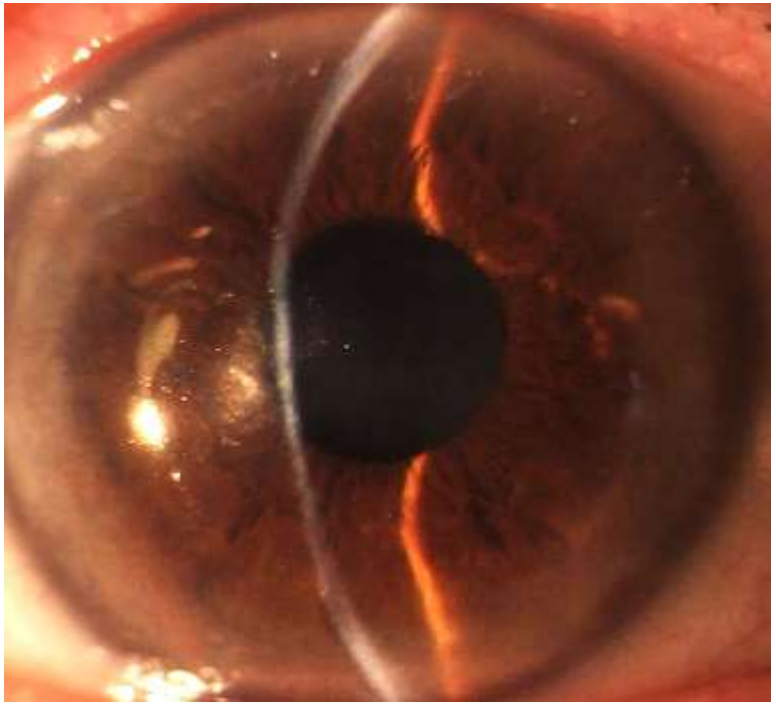
From 20/200 to 20/40!







Epithelial thickness: nl-KCN-KCNcxl'ed

Epithelial and mapping on normal and keratoconic (non-treated and treated) eyes. Kanellopoulos et al

Figure 2: Corneal report produced by the Eus software showing total corneal, epithelial, and stromal thickness pachymetry maps over 8 mm diameter. The subject's eye was normal. We observe the overall thicker epithelium over the pupil center.

Epithelial and mapping on normal and keratoconic (non-treated and treated) eyes. Kanellopoulos et al

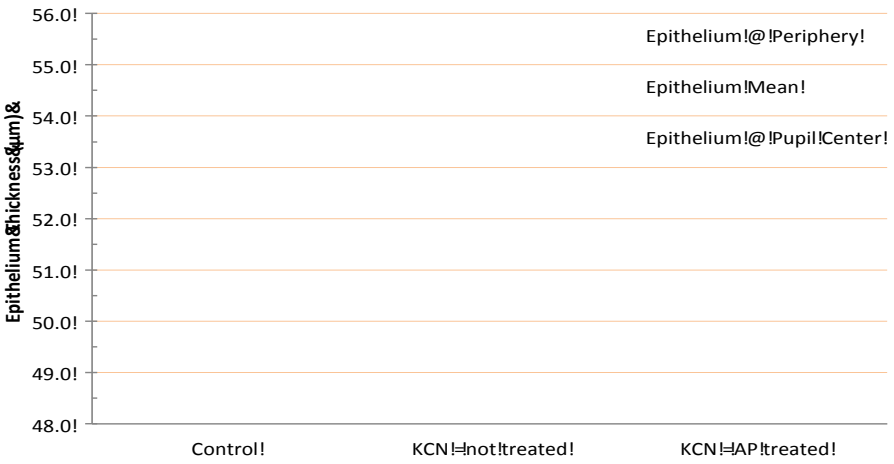


Figure 7: Epithelium thickness across the three groups of study, at the periphery, mean, and at the pupil center.

Epithelial thickness maps

- May become the earliest prognostic factor for ectasia
- We have found that in KCN there is overall INCREASE in average epithelial thickness
- Following CXL the same eyes show dramatic reduction of epithelial thickness to slightly below of normal

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LASIK flap creation using FS200 femtosecond laser (Alcon, Ft. Worth, TX)
9.5mm LASIK flap nasally decentered, adjusted for angle kappa

Treatment Parameters (Standard)

Ablation

Abl. Zone	Max. Depth	Min. Pachy	Res. Stroma
9.0 mm	104 um	597 µm	363 µm

Flap

Diameter	Thickness	Side Cut Angle	Canal Width	Canal Length Offset
9.5 mm	130 µm	70°	1.3 mm	1 mm

Hinge

Position	Length	Angle	Width
90°	3.6 mm	45°	0.4 mm

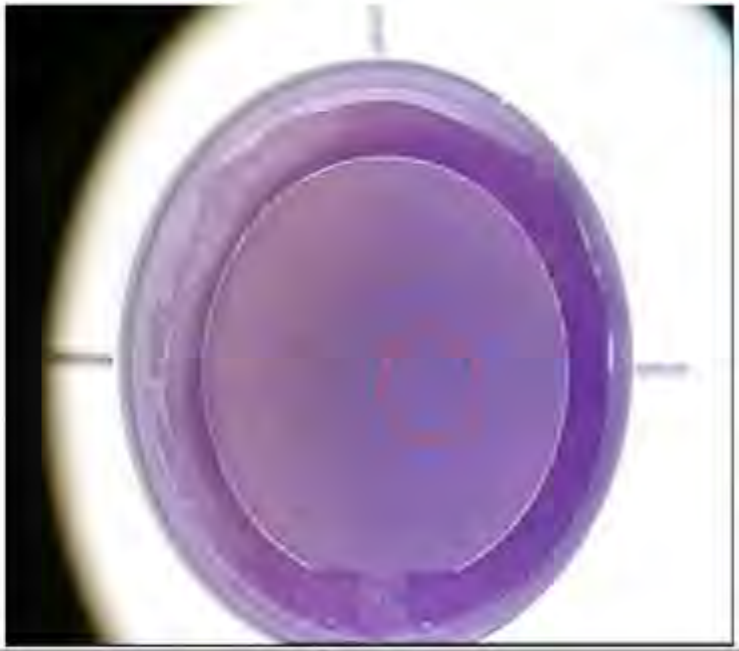
Laser pulse energy (measured)

Bed Cut	Side Cut
0.8 µJ	0.9 µJ

Laser separations

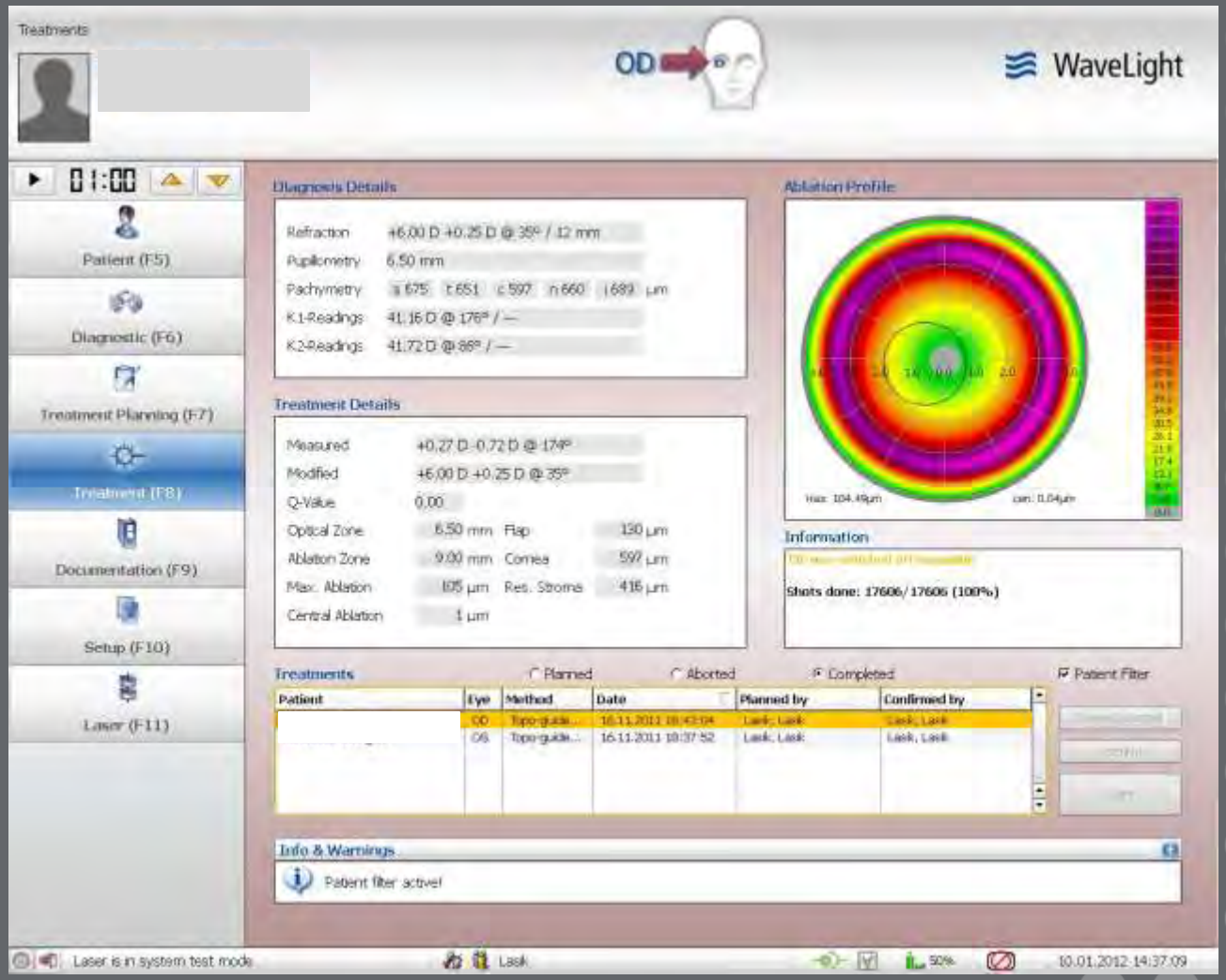
Bed Cut		Side Cut	
Spot Separations	Line Separations	Spot Separations	Line Separations
8.0 µm	8.0 µm	5.0 µm	3.0 µm

Treatment Screenshot (Standard)

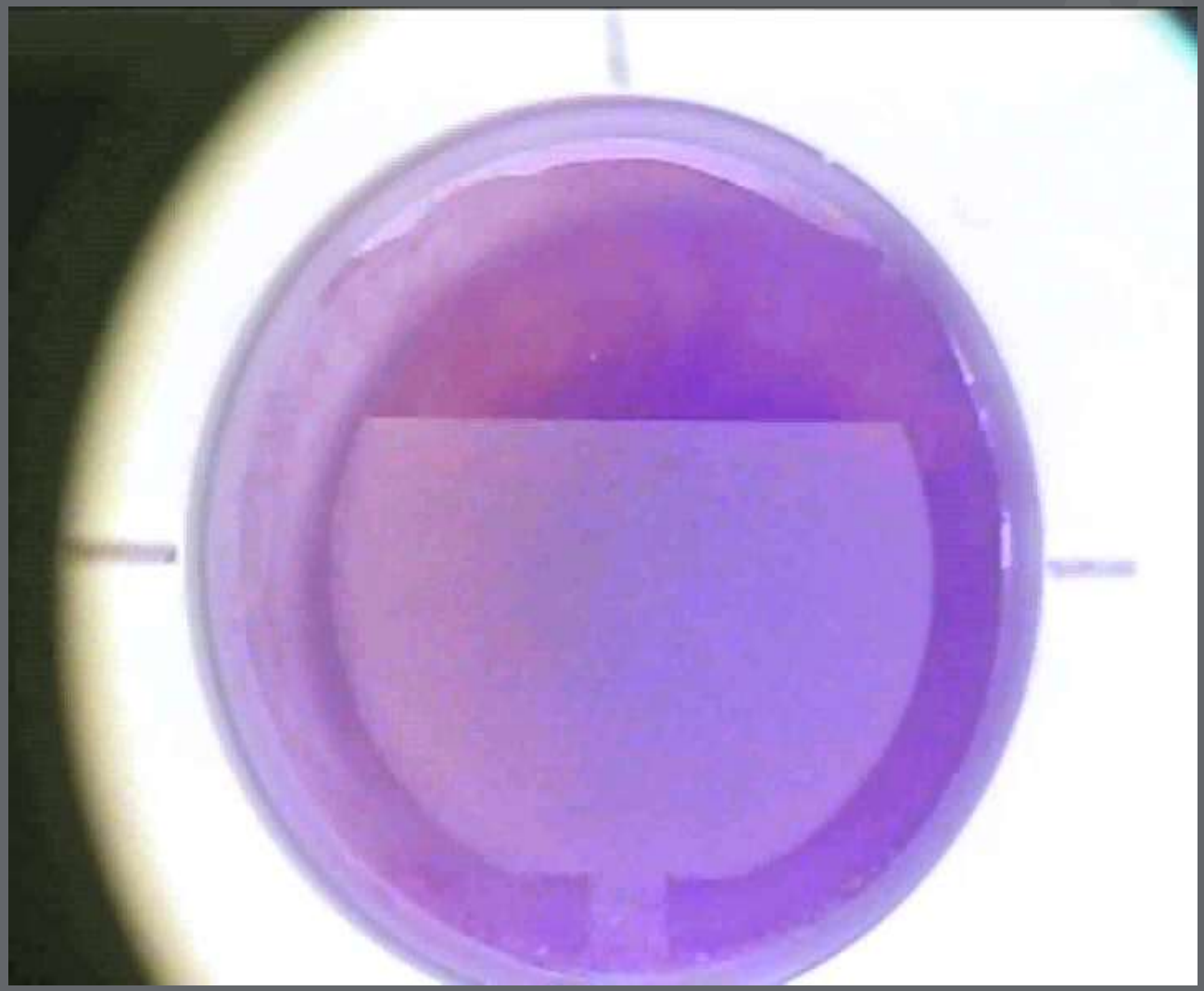


Comments

Topo-guided LASIK excimer treatment plan centered on visual axis

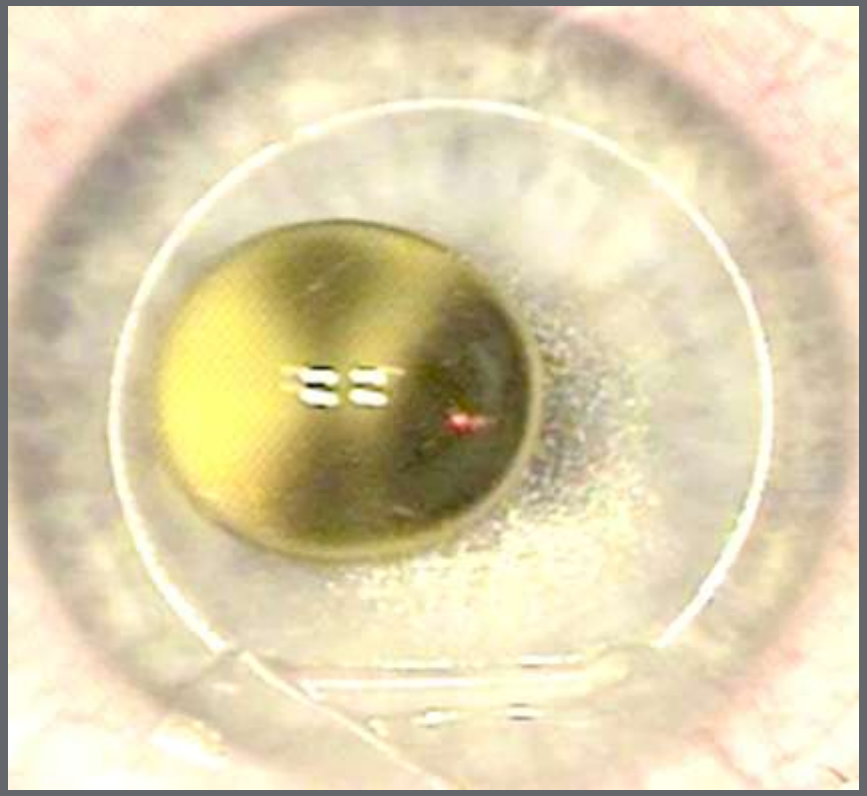


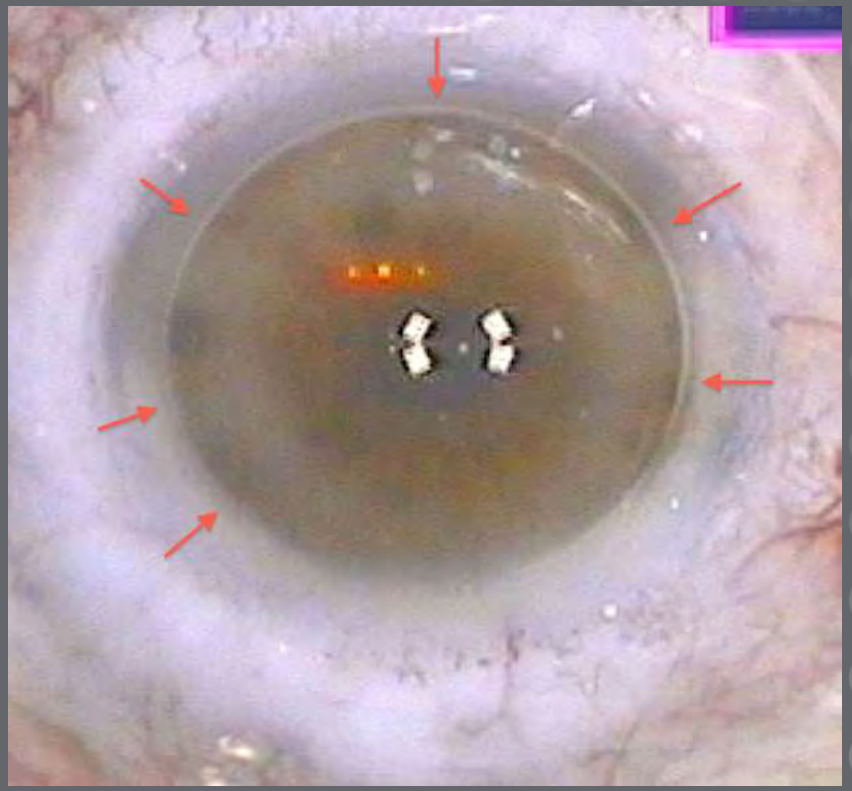
In the flap high fluence CXL: LASIK Xtra



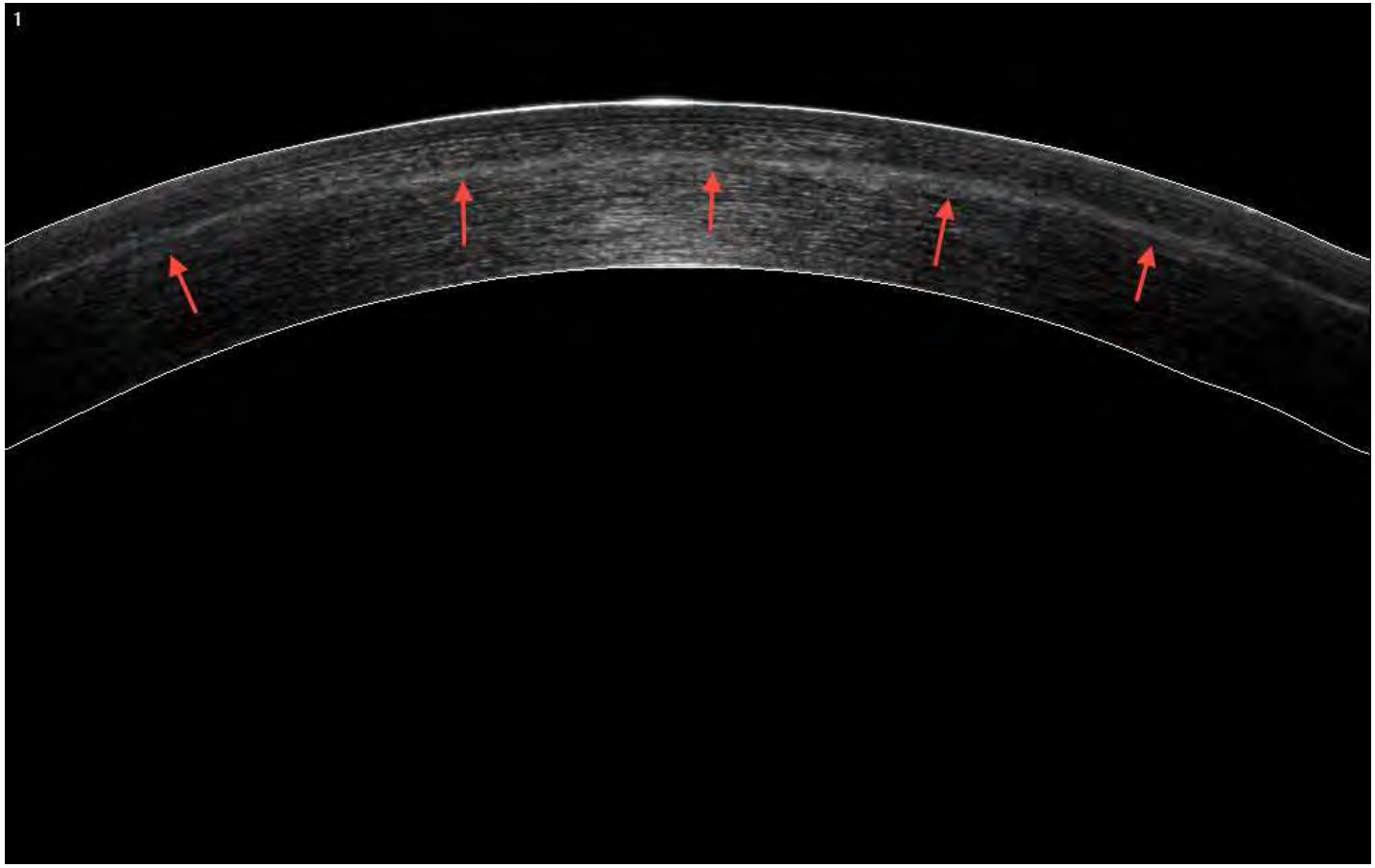
A drop of 0.1% riboflavin sodium phosphate solution

(Leiter's pharmacy, San Jose, CA)

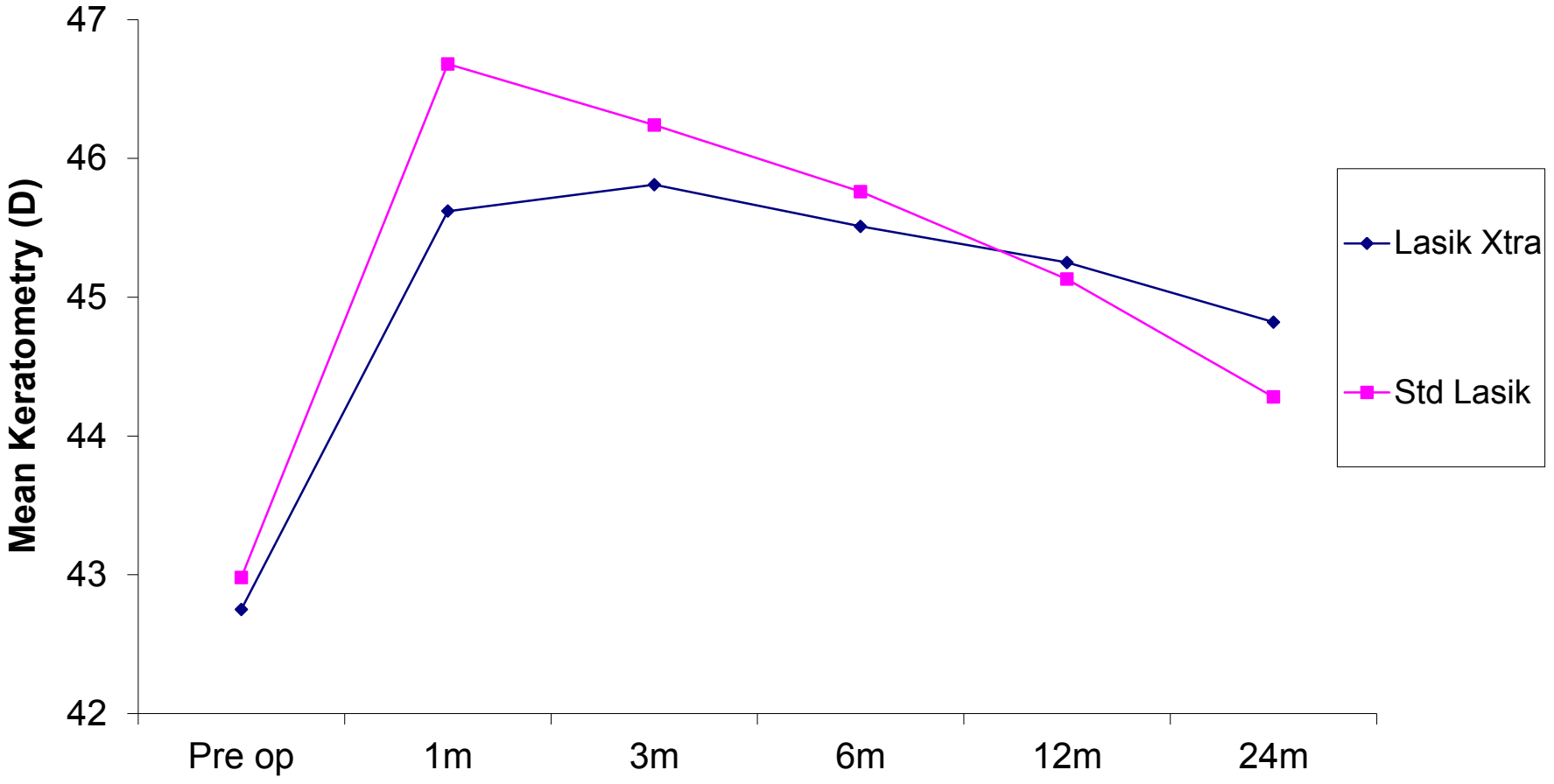




Corneal OCT (Optovue, CA, USA) in LASIK Xtra group



Comparison of Keratometric Stability



Our current protocols

- 1-Athens Protocol: topo guided PRK (Wavelight) +10'x 10mw/cm^2
- 2-LASIK Xtra with the Refractive Suite: 1' (90") 30mW/cm^2 all HYPEROPES
- 2-PRK Xtra: 1' (90") 30mW/cm^2
- 3-Transepithelial CXL: 0.25% riboflavin + 30mW/cm^2 X 3' (180")
- 3-Infection: 0.25% riboflavin + 45mW/cm^2 x 5 minutes

Thank you

Kanellopoulos MD