

# Higher Fluence CXL



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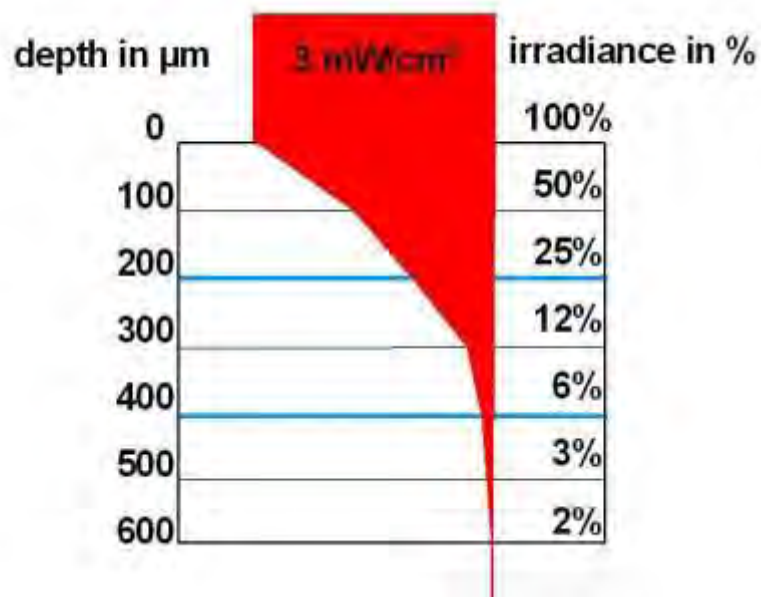
# Financial Disclosures:

- Alcon/Wavelight (MAB)
- Bausch & Lomb (Crystalens)
- Ocular Therapeutix
- Seros Medical( MAB)
- Avedro (MAB)



# Decrease of UV-intensity

courtesy E. Spoel MD



3.00  $\text{mW}/\text{cm}^2$

1.49  $\text{mW}/\text{cm}^2$

0.74  $\text{mW}/\text{cm}^2$

0.36  $\text{mW}/\text{cm}^2$

0.18  $\text{mW}/\text{cm}^2$

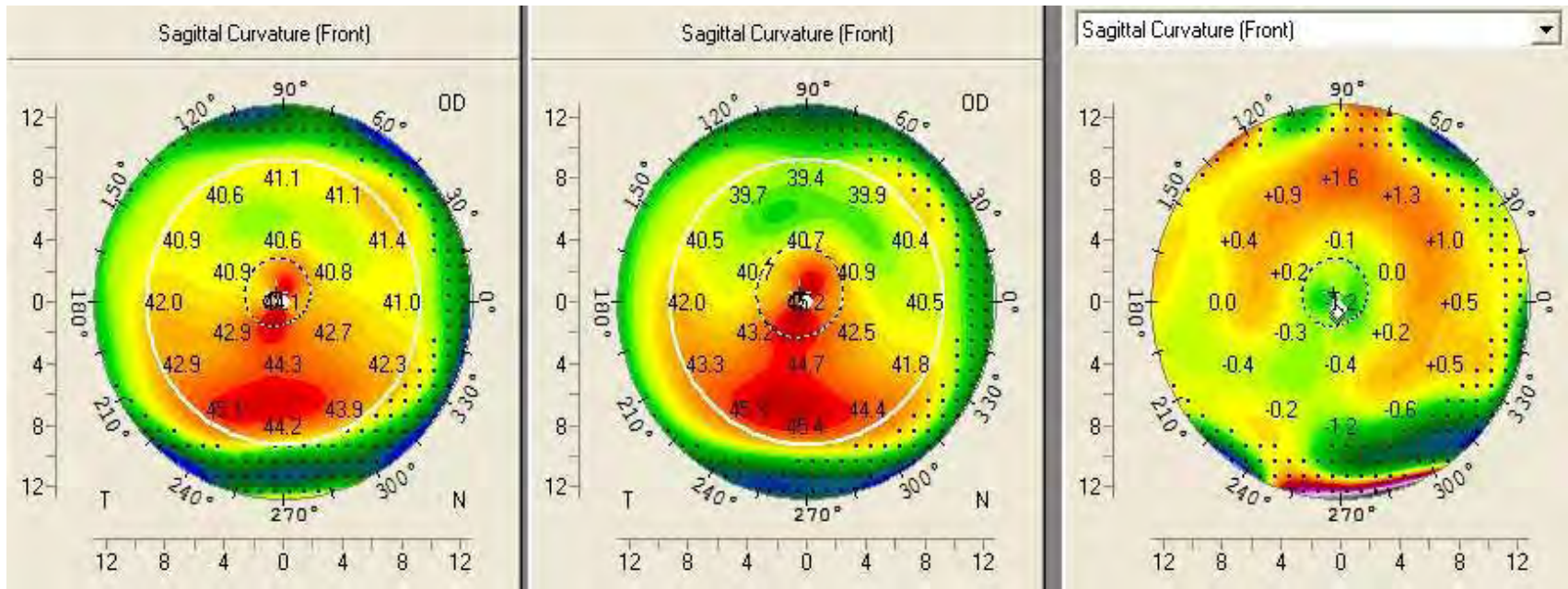
0.09  $\text{mW}/\text{cm}^2$



Dresden protocol 3mw/cm<sup>2</sup>

Post-LASIK ectasia: -1 -1.75@ 75. Pach 445, Treated with epi-on CXL ( C3R) 3mW/cm<sup>2</sup> for 30'.



Same case seen 3 years later with ectasia progression



# We introduced: Higher fluence CXL: 6 mW/cm<sup>2</sup>

AAO 2008:  
CXL for 15  
minutes  
utilizing  
7mW/cm<sup>2</sup>  
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

**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/cm<sup>2</sup>) 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, randomised comparative case series.

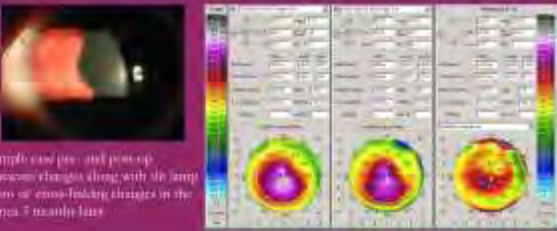
**Methods:** 15 patients with bilateral keratoconus were studied. All cases were evaluated for UCVA, BSCVA, refraction, keratometry changes (K), topography changes, endothelium cell changes and cornea clarity. All eyes received CCL with topical 0.1% riboflavin solution drops and in regard to UVA they were randomized for each patient; 15 eyes were CCL with 7mW/cm<sup>2</sup> for 15 minutes and the 15 contra lateral eyes with 3mW/cm<sup>2</sup> for 30 minutes. Mean follow up was 1.5 years.

	UCVA	BSCVA	Sph. DQ change	Cylinder (D)pre	ECC change	Time change	Comp. contacts
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

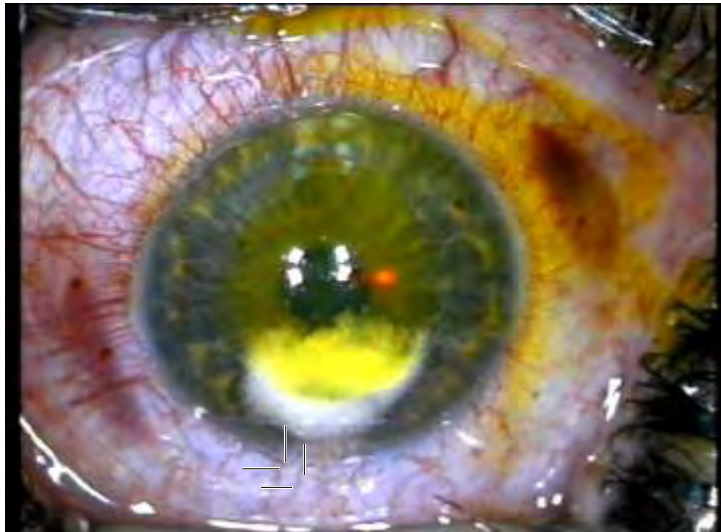
**Results:**  
The mean improvement of UCVA was 0.2 to 0.4, BSCVA improved from 0.4 to 0.7, The average change of spherical equivalent was 1.5D reduction in myopia, the average change in cylinder was 2.1D reduction, The average highest keratometry was 51.2D pre-op and changed to 48.5D post-op. **There 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.

**Example case pre- and post-op:**  
Retrospective changes along with the lamp photo of cross-linking changes in the cornea 7 months later.




# Introduction of riboflavin in a femto-pocket CXL with 10mW/cm<sup>2</sup> for 10 minutes



NEW TECHNIQUE



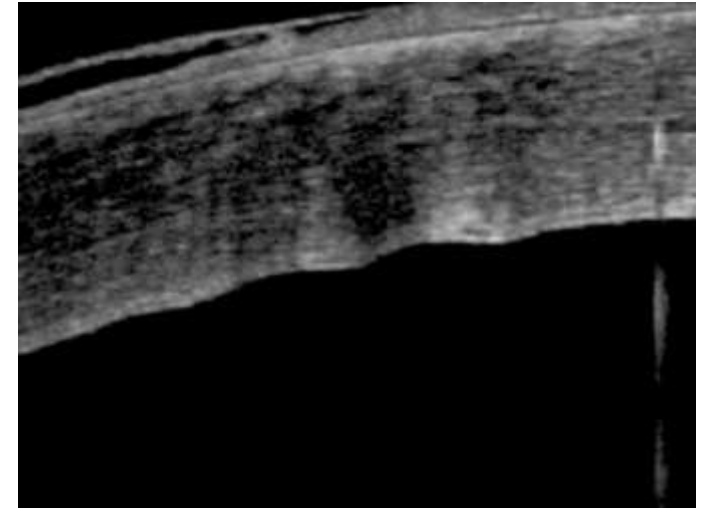
## **Collagen Cross-linking in Early Keratoconus With Riboflavin in a Femtosecond Laser-created Pocket: Initial Clinical Results**

Anastasios John Kanellopoulos, MD

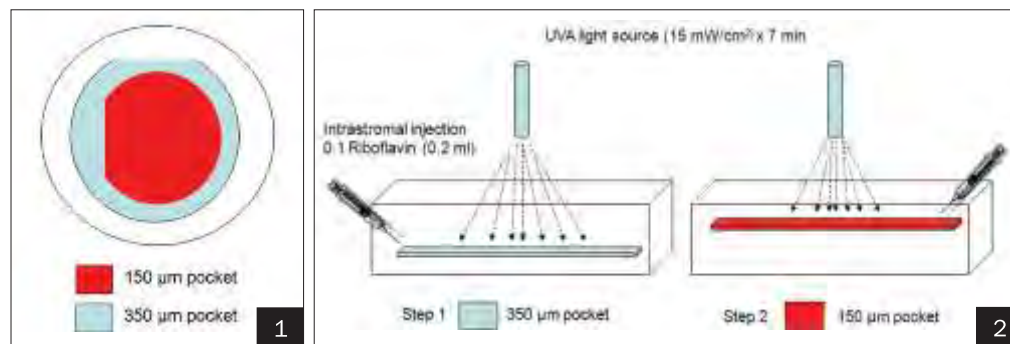
# Zurich 2007: CXL for PBK: 2 femto pockets and CXL with 10mW/cm<sup>2</sup>

## 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



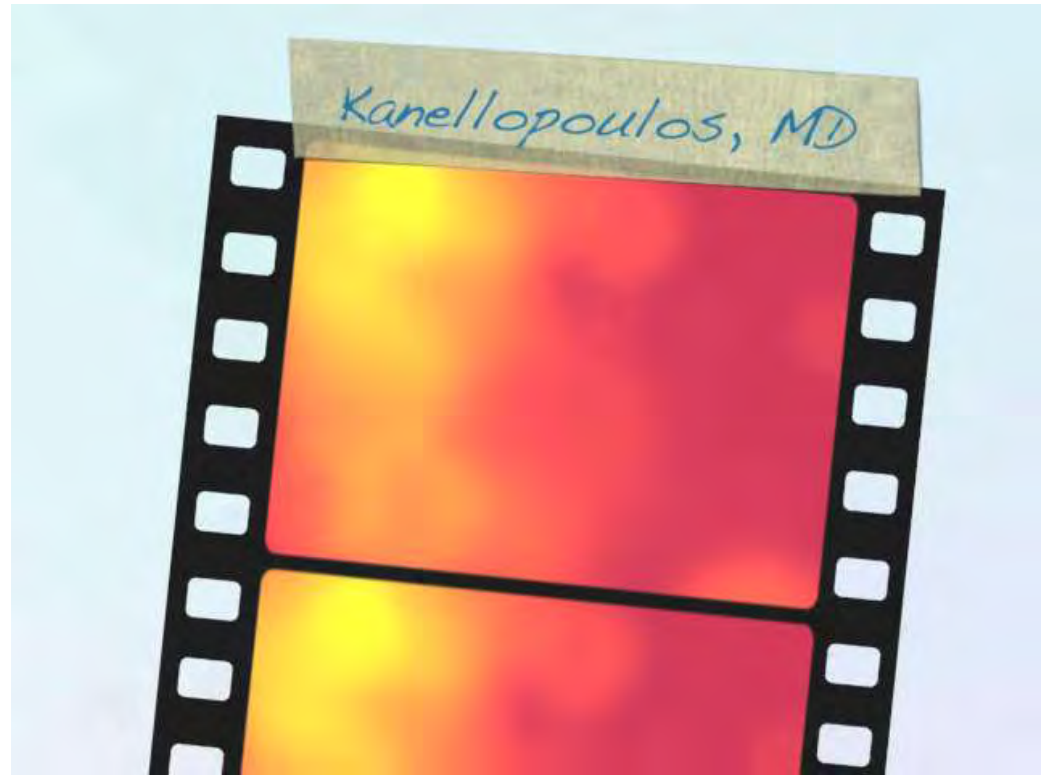
UVA Cross-linking in Advanced Bullous Keratopathy/Krueger et al



**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.

# Cornea remodeling without tissue removal shrinkage + CXL (10mW/cm<sup>2</sup> x 10')

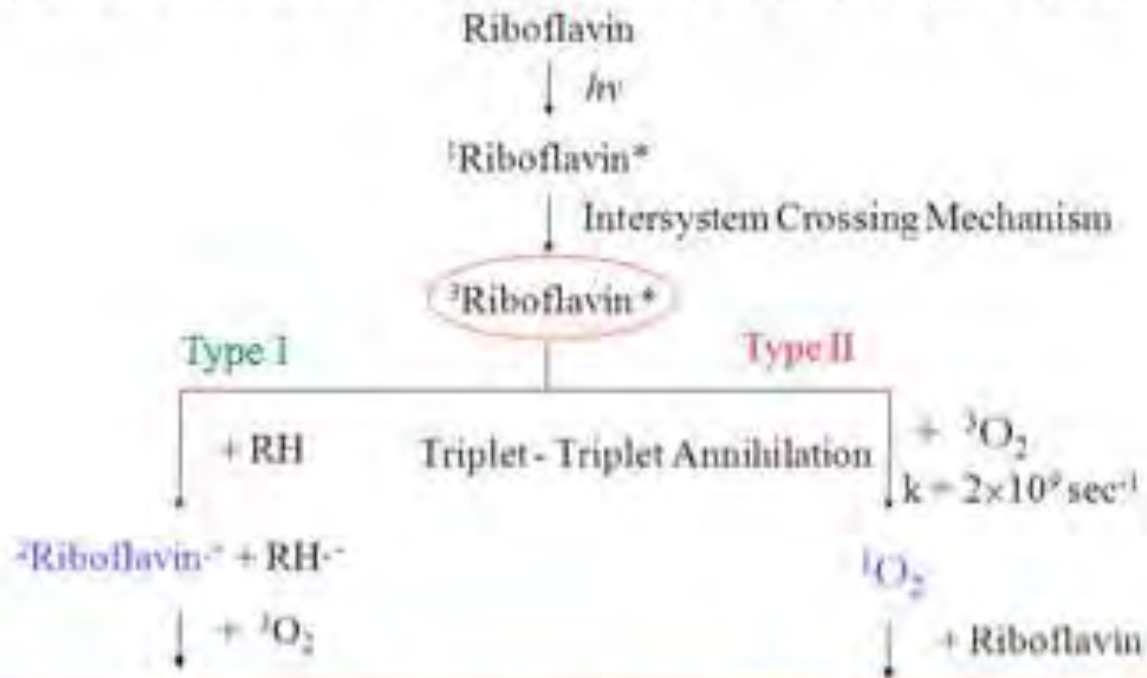
- Avedro,  
Keraflex first reports
- Kanellopoulos,  
Herakar:TRXL





# Theoretical Model for Cross-linking

## 2 General Paths For Riboflavin And Oxygen Reactions



**90%    Crosslinking    10%**

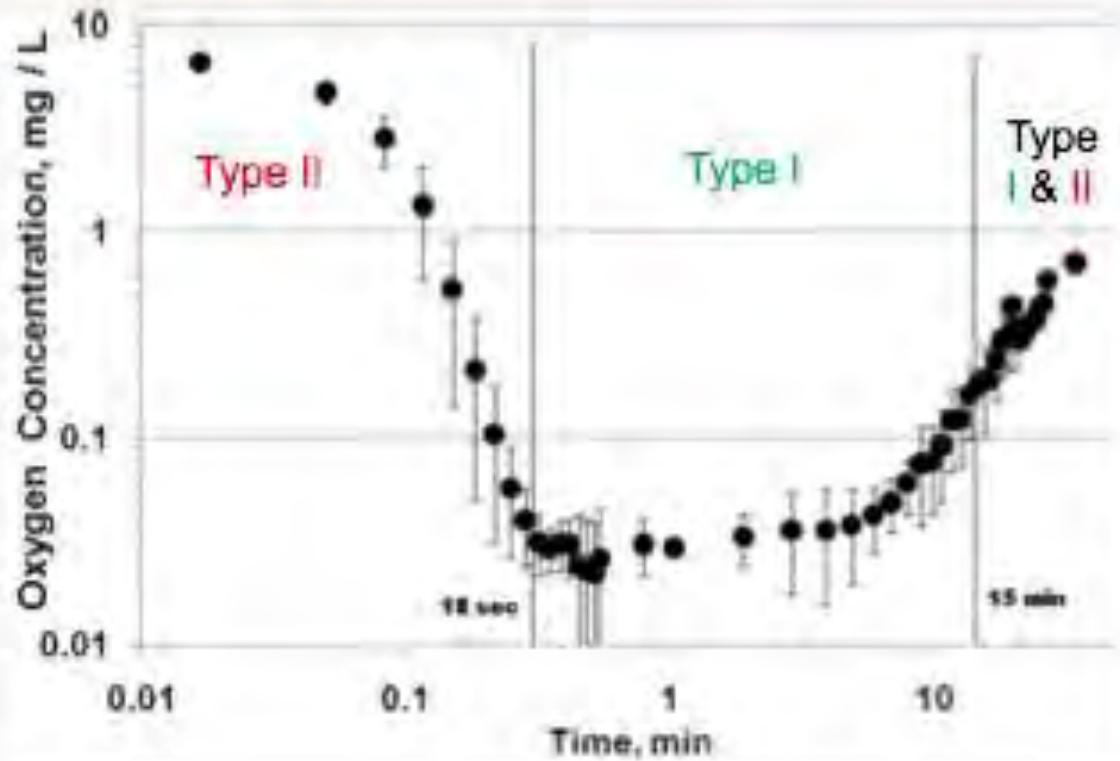
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# Oxygen Depletion Over 30 Minutes

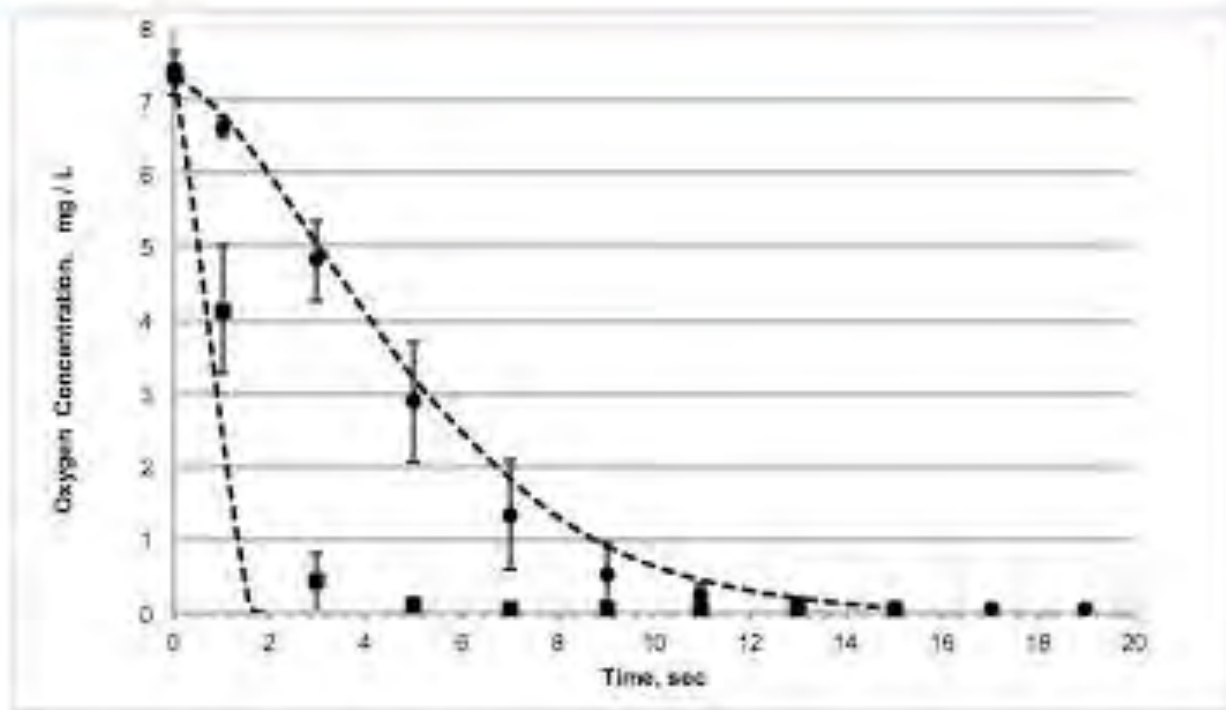


Depletion and gradual replenishment of dissolved oxygen below a 100  $\mu\text{m}$  thick corneal flap, saturated with 0.1% RF during 3  $\text{mW}/\text{cm}^2$  UVA irradiation at 25  $^{\circ}\text{C}$ .

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# Theoretical Model vs Experimental Data



Depletion of dissolved oxygen below a 100  $\mu\text{m}$  thick corneal flap, saturated with 0.1% RF during 3  $\text{mW}/\text{cm}^2$  (\*) and 30  $\text{mW}/\text{cm}^2$  (■) UVA irradiation at 25  $^\circ\text{C}$ . Dashed lines are the modeled results.

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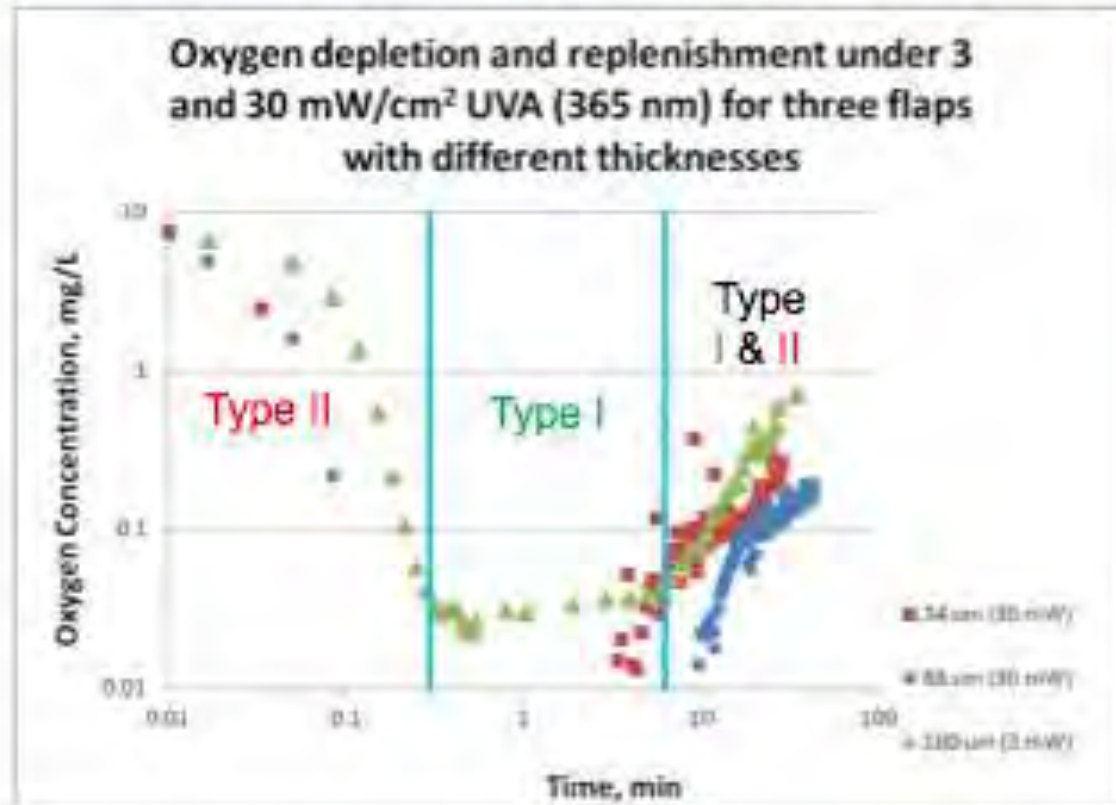
New York University  
School of Medicine

Kanellopoulos, MD

LaserVision.gr  
Institute for laser



# Oxygen Depletion Over 30 Minutes



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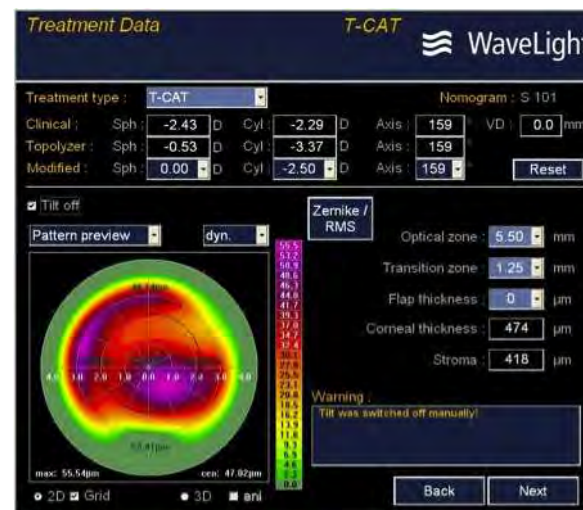
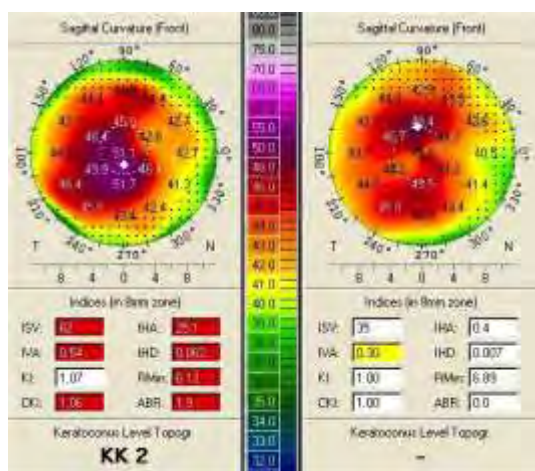
New York University  
School of Medicine

Kanellopoulos, MD

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# The Athens Protocol: Simultaneous surface ablation and CXL for correction of Refractive error in eyes with early keratoconus



ISRS/AAO keynote



# The Athens Protocol: topo-guided PRK+6mW/cm<sup>2</sup> CXL x15'

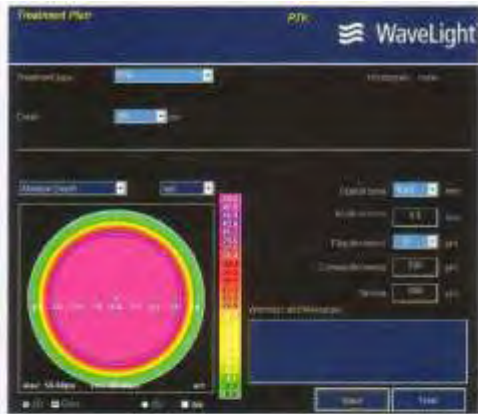


Figure 4.1: Epithelium removed with 50 micron PTK

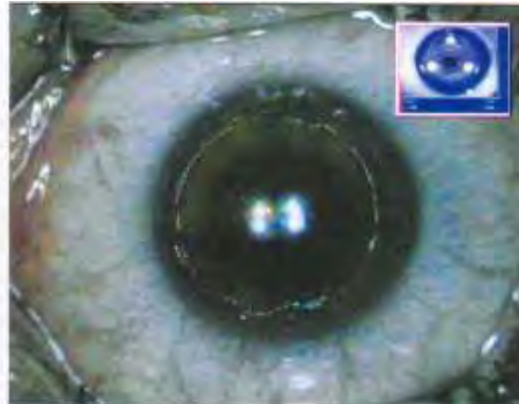


Figure 4.3: Topography-guided PRK to correct part of the refractive error (TCAT treatment plan) maximal thickness removal 50 microns

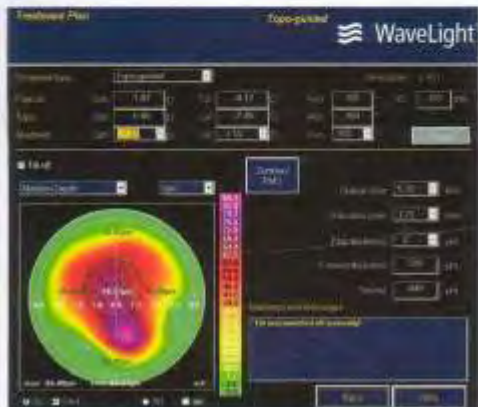


Figure 4.2: TC at treatment plan

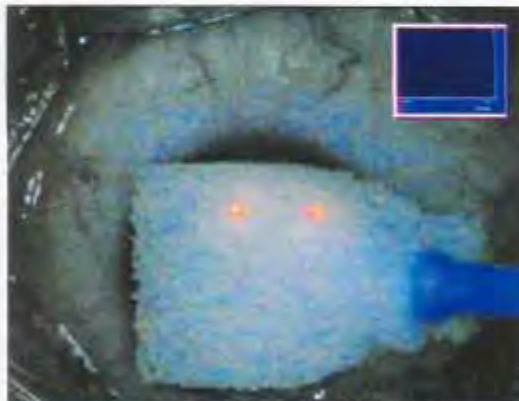
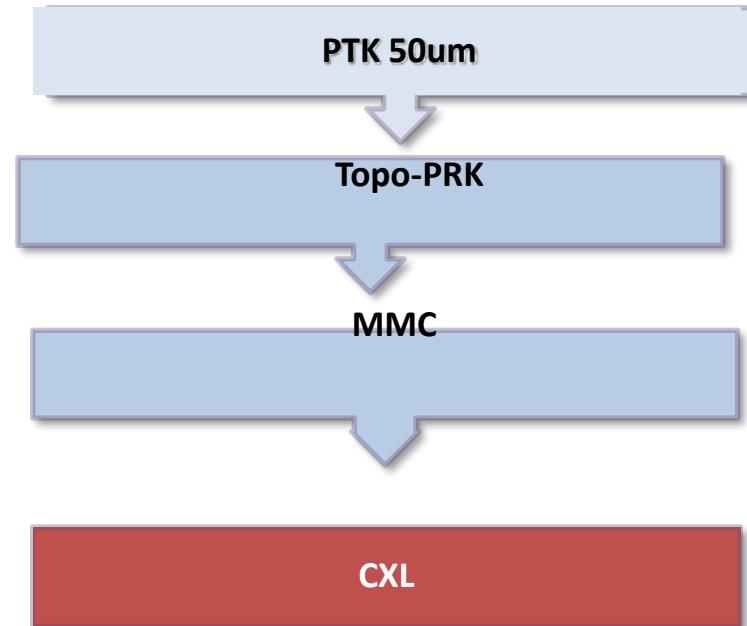
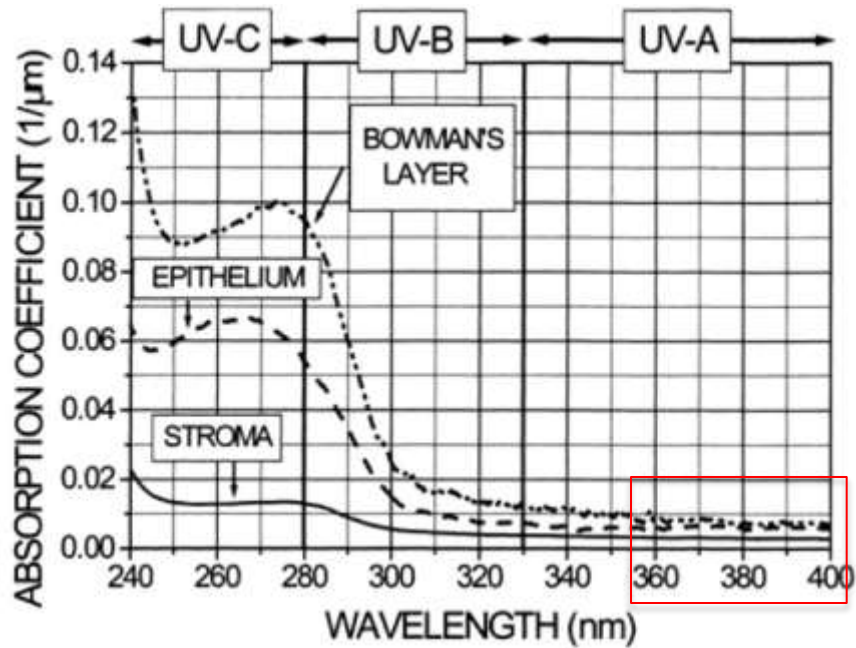


Figure 4.4: MMC solution 0.02% for 20 seconds



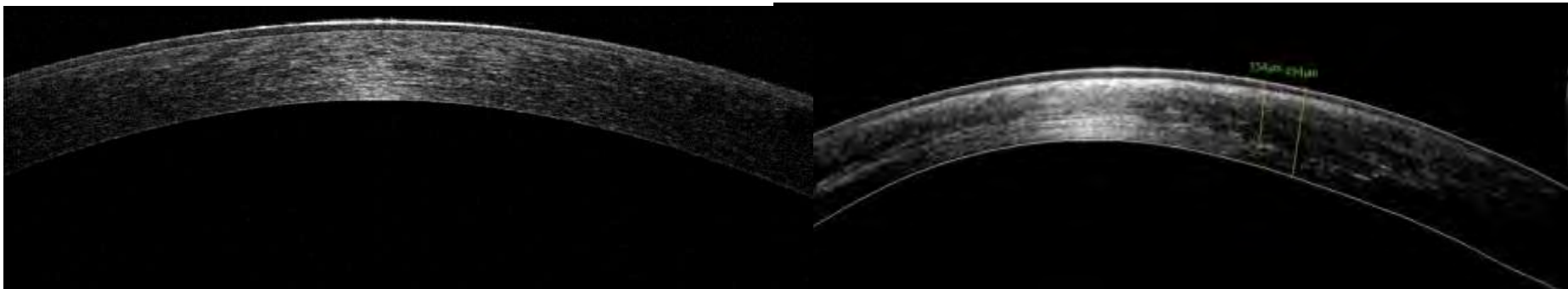


## Comparison of Sequential vs Same-day Simultaneous Collagen Cross-linking and Topography-guided PRK for Treatment of Keratoconus

Anastasios John Kanellopoulos, MD

JRS Sept 2009

**Kolozsvári et al**  
IOVS 2002;43:2165-2168



New York University  
School of Medicine

Kanellopoulos, MD

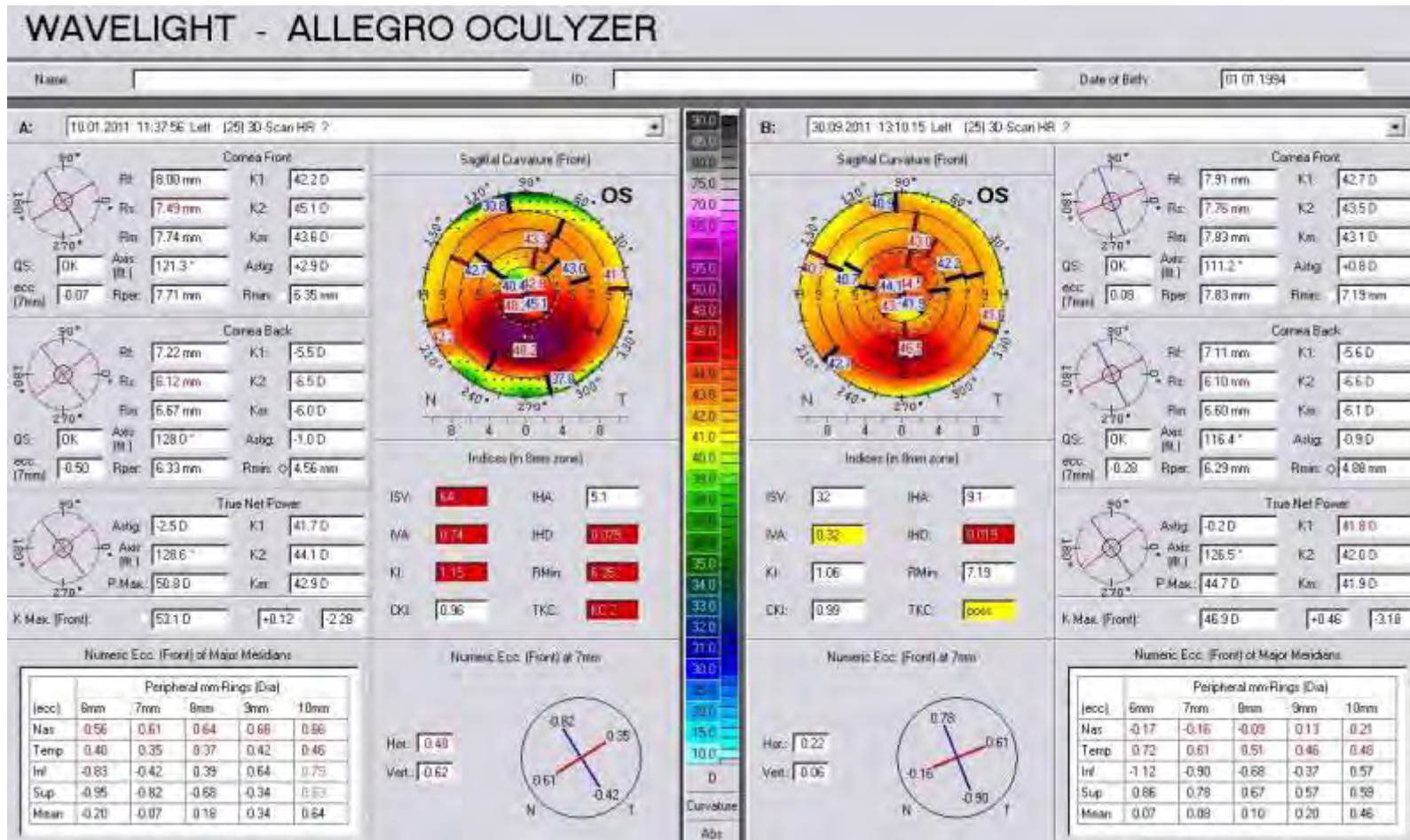
**LaserVision.gr**  
Institute for laser



# Topometric improvement: Significant reduction in IHD

Myopia induction!

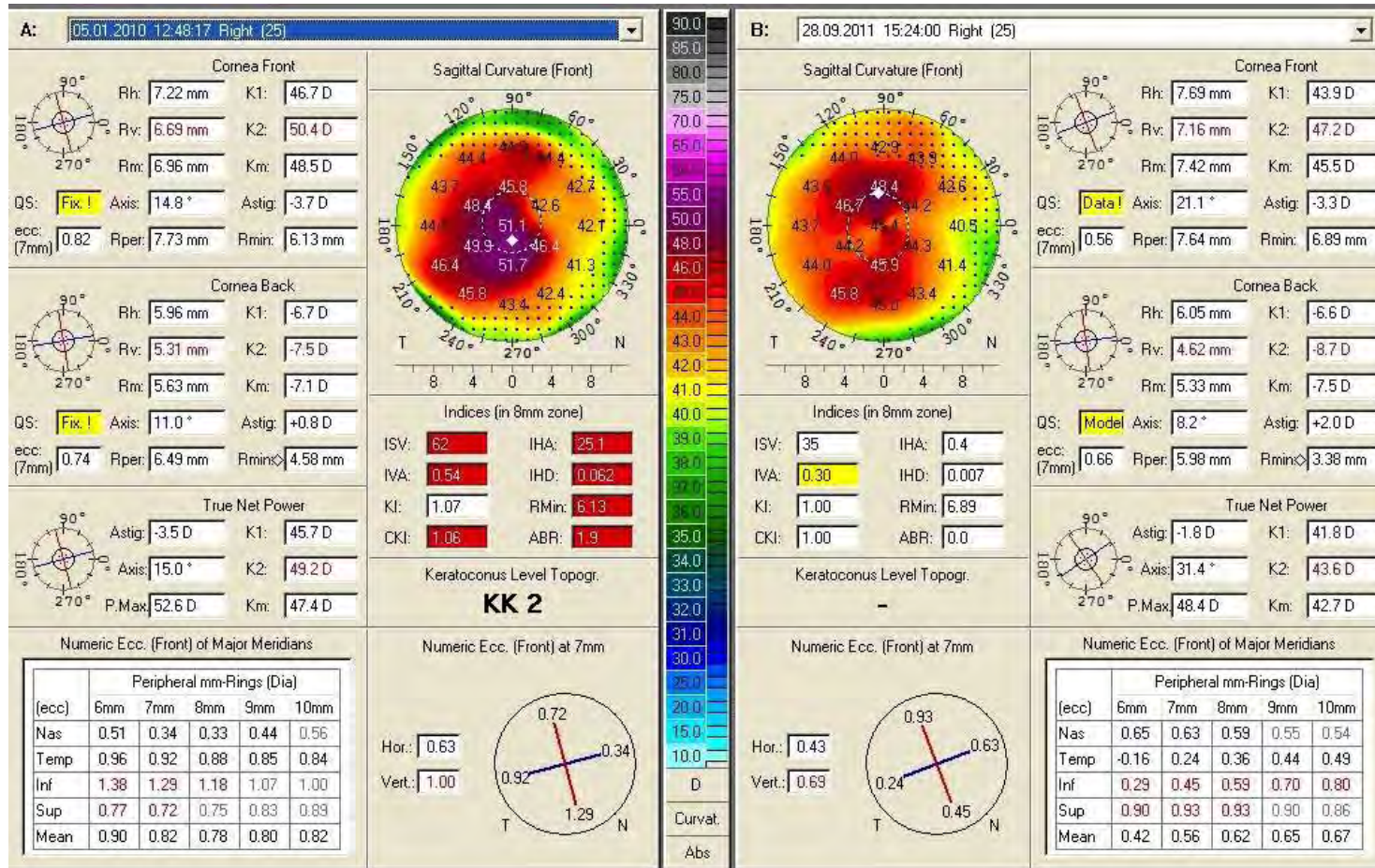
Refraction from +0.75-3.50@10 (20/60) to -0.75-0.75@170 (20/20) due to improvement of the topometric parameters



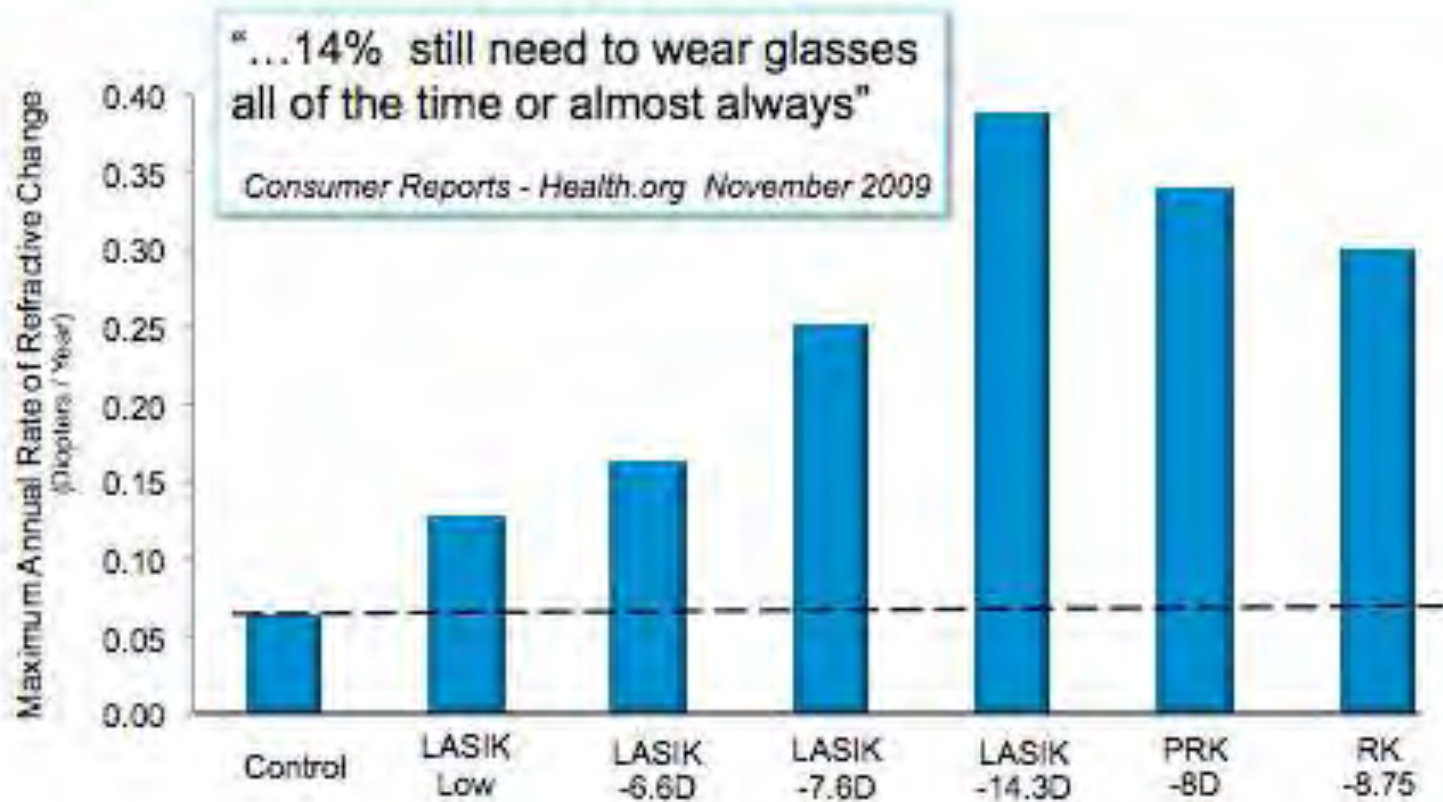
# 2 year follow up in a 15 y/o

## Topometric improvement:

### Significant reduction in IHD (Index of Height Decentration)



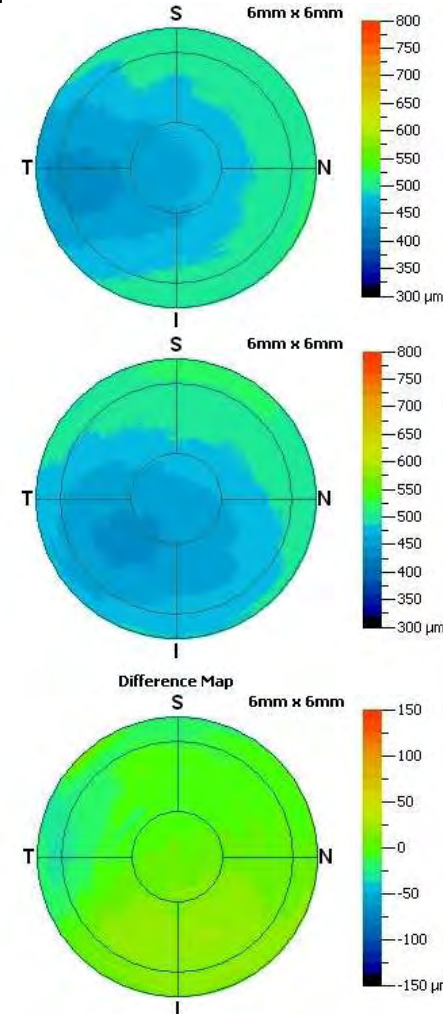
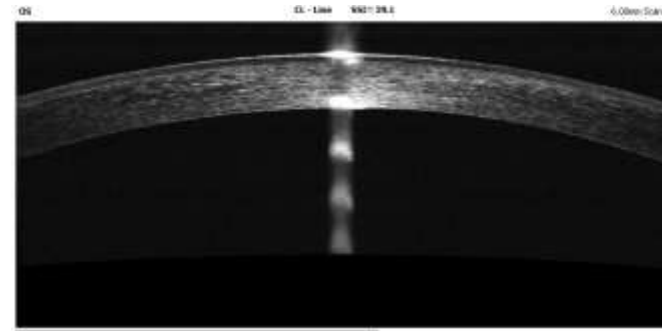
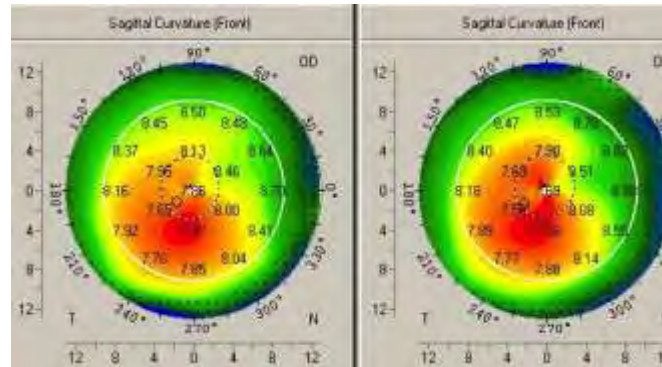
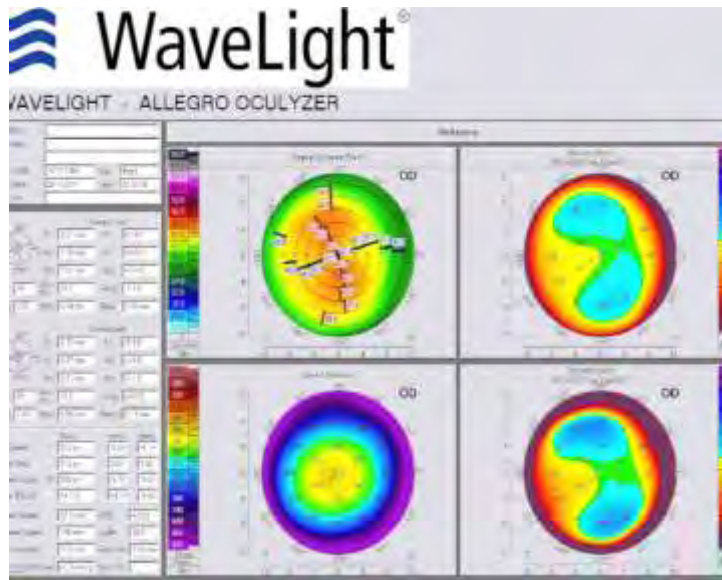
# Long term LASIK regressions:



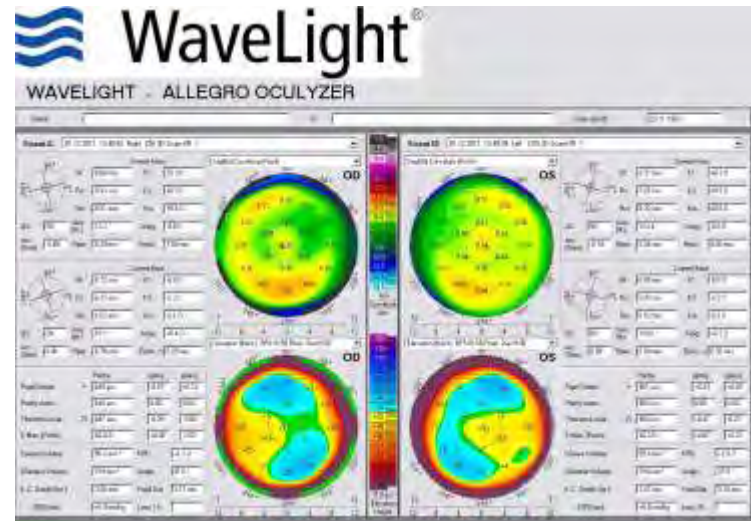
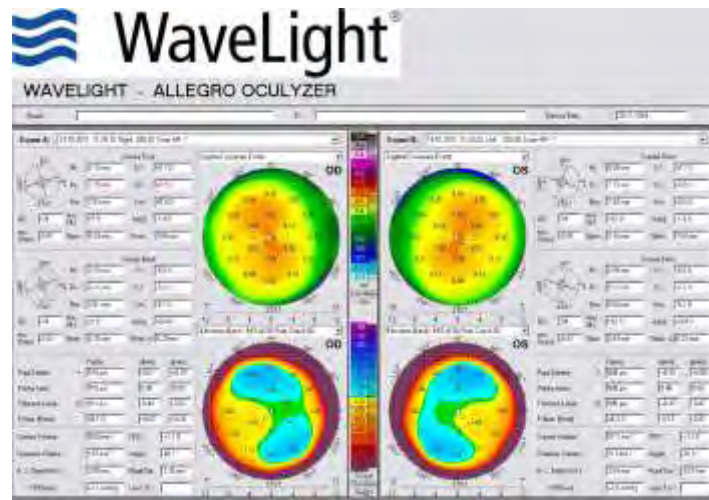
# 2008 Prophylactic CXL in LASIK



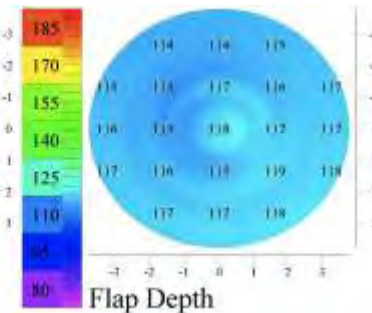
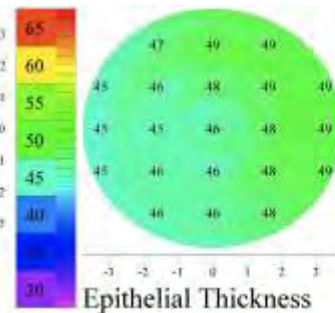
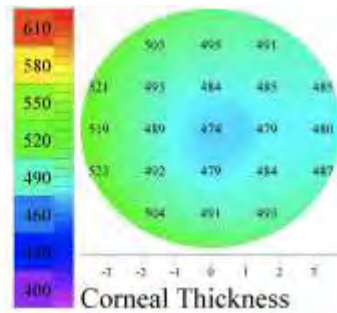
# 5 years LASIK Xtra



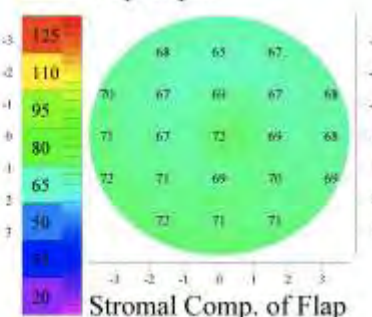
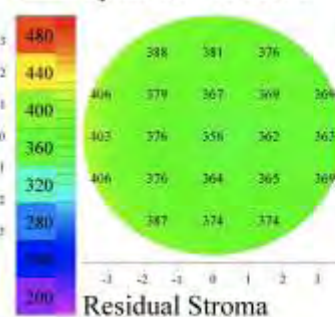
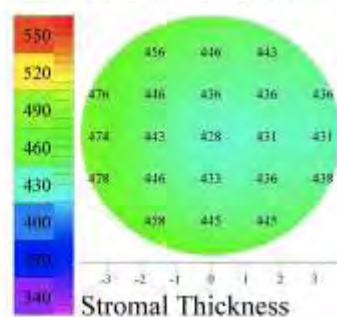
# Every day practice LASIK Xtra



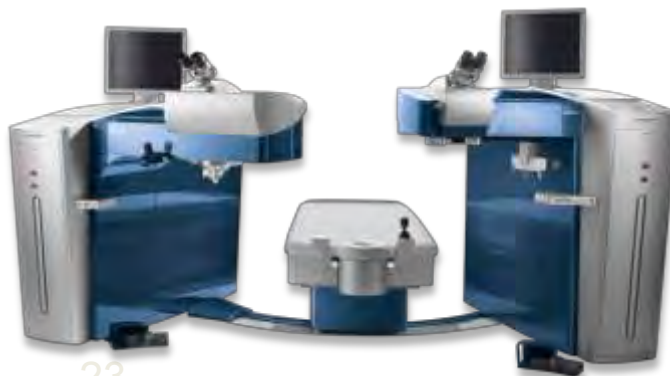
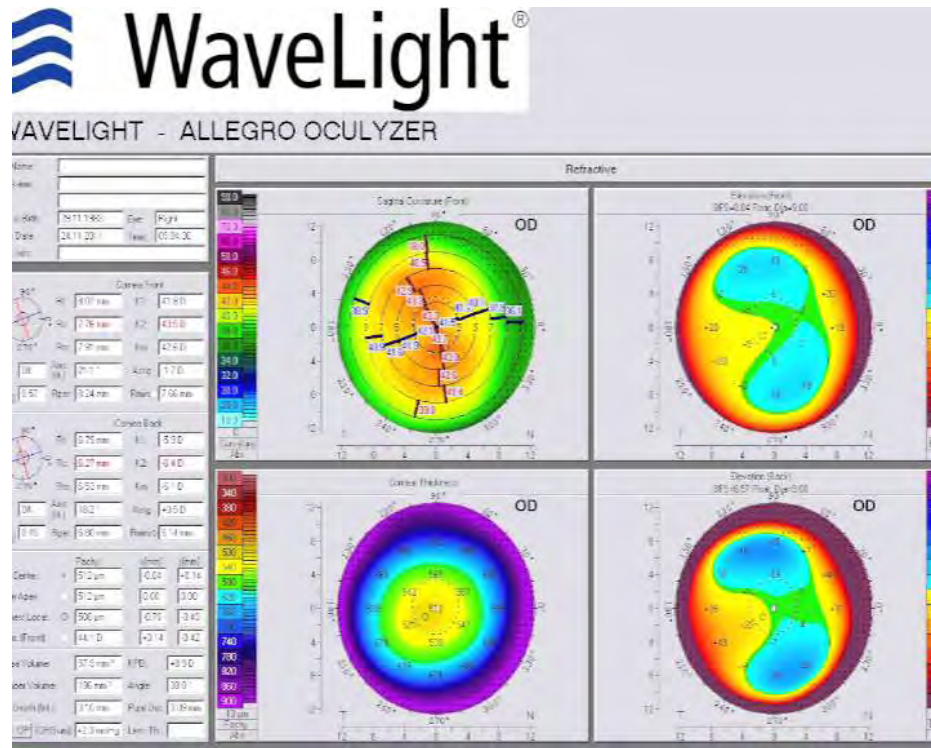
Mean Epithelial Thickness Overall	47µm
Minimum Stromal Thickness	427µm
Minimum Corneal Thickness	473µm
Mean Corneal Thickness @ 0-3 mm	478µm
Mean Corneal Thickness @ 3-6 mm	489µm

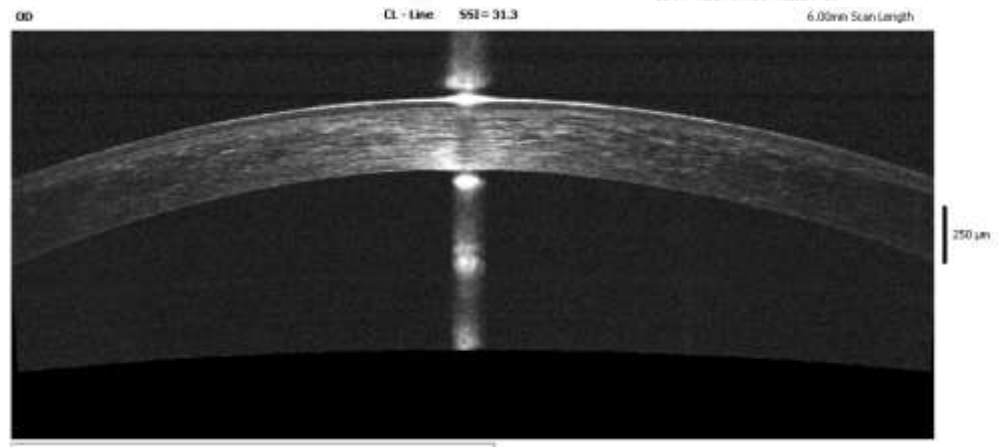
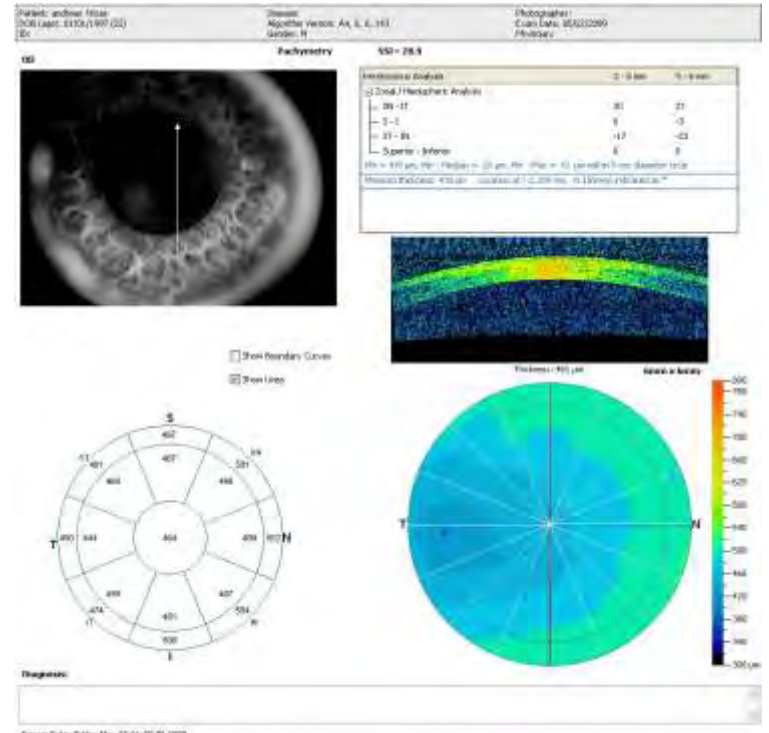
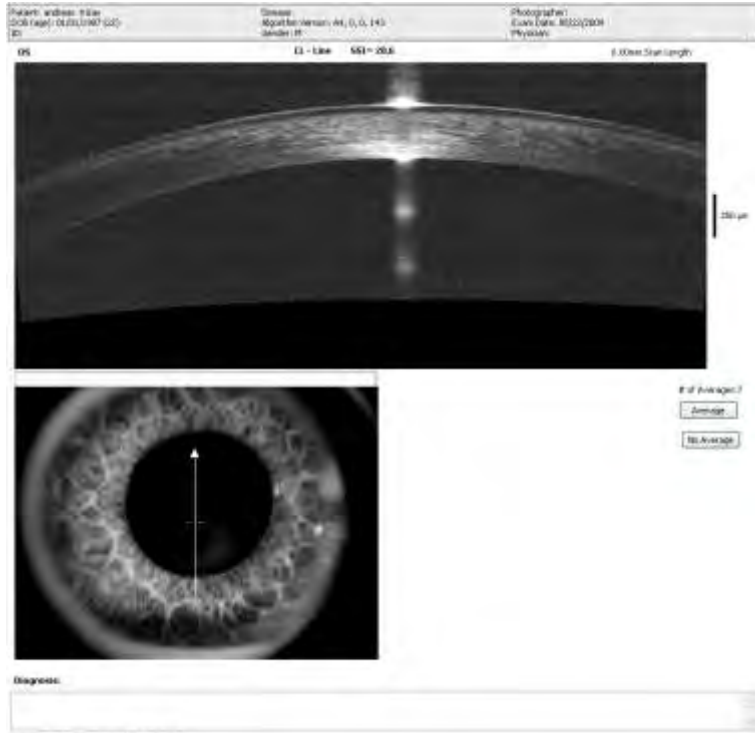


Minimum Residual Stroma	354µm
Mean Stromal Component of Flap	69µm
Mean Flap Depth Overall	116µm
Mean Flap Depth @ 0-3 mm	117µm
Mean Flap Depth @ 3-6 mm	116µm



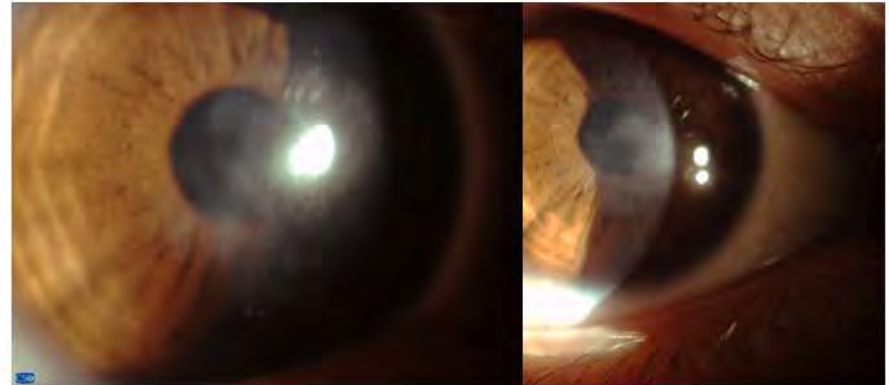
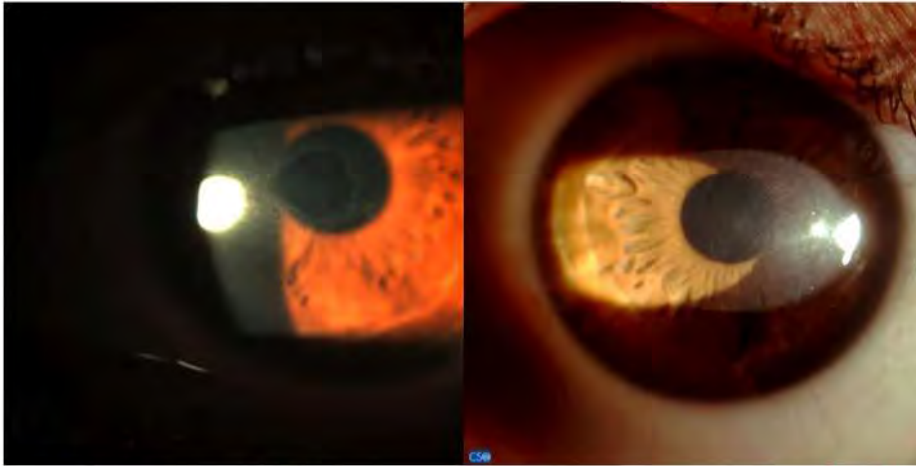
# LASIK Xtra within the Alcon Refractive Suite



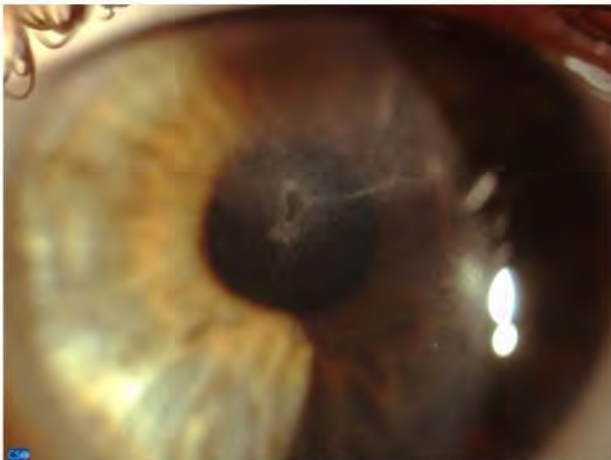


Healing delay-day4-ok on 1 month

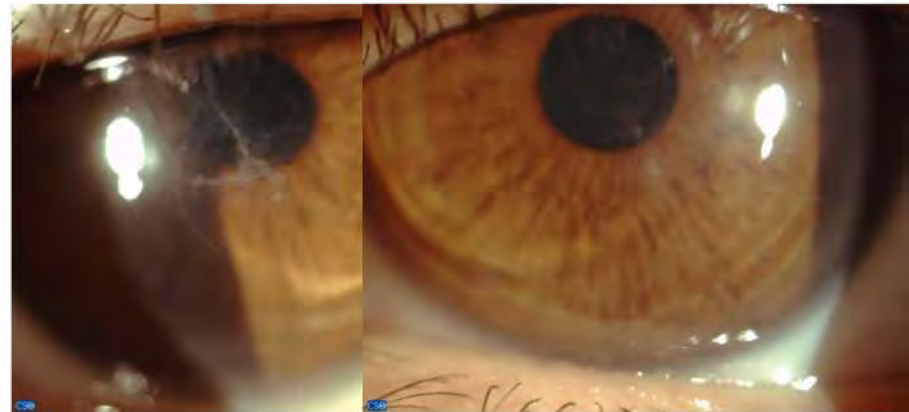
PRK-like haze 1 year after, in heavy sunbathing improved with steroids



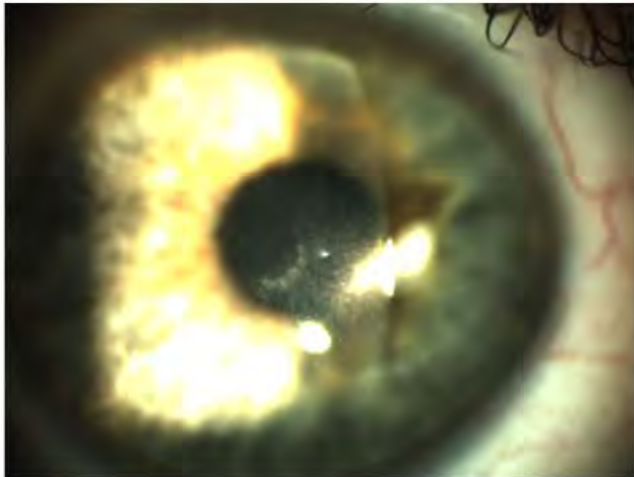
Week 2



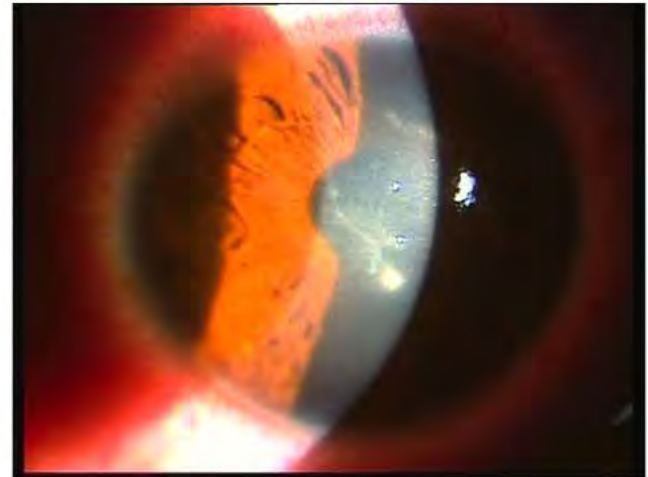
Week 2



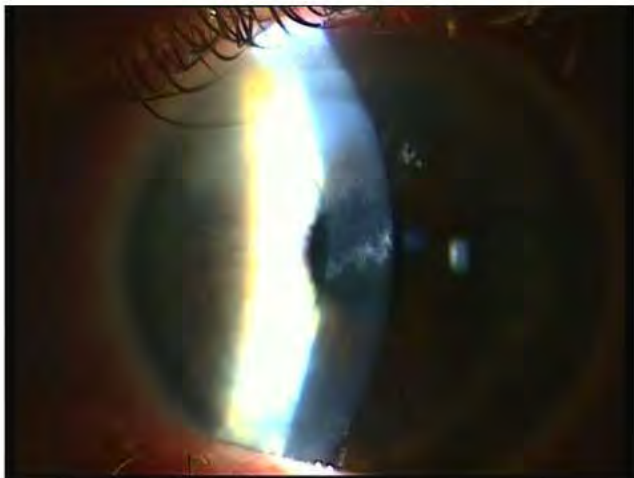
Salzman's-like nodule(s) can persist to 3 months postop



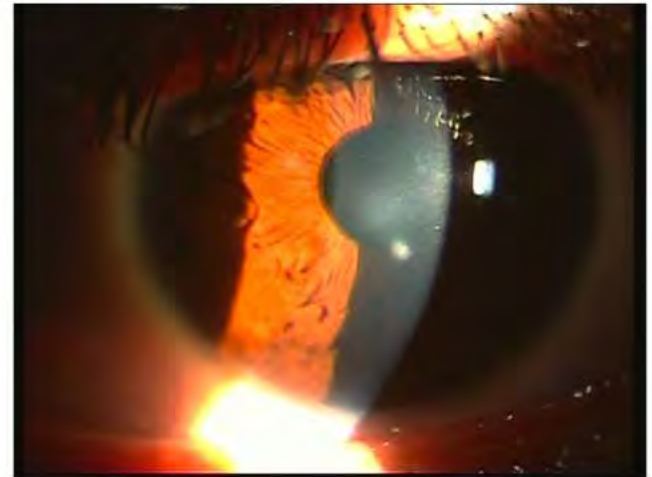
Delayed epithelial healing with white spots



Haze



Faint Scar and white spot



# High Fluence Transpethelial CXL early findings

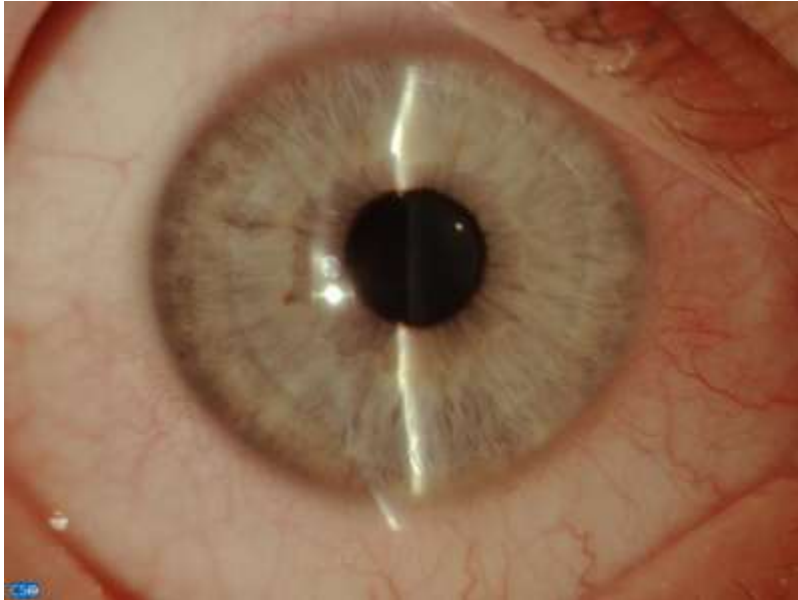
There is significant CXL effect

The epithelium does not seem to absorb significant riboflavin

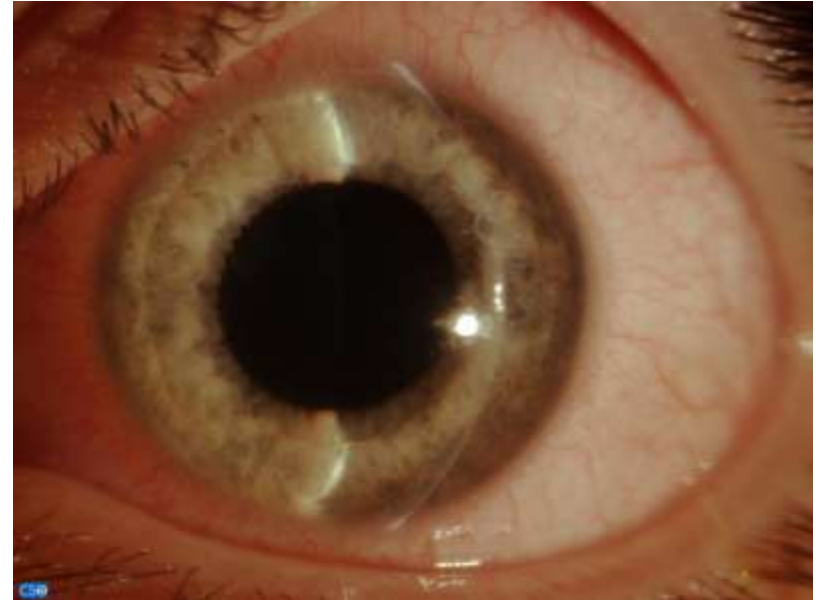
Extremely comfortable, no recoup time

Long term data necessary

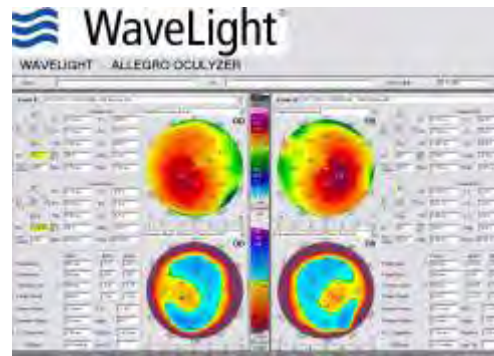
Trans epi 0.25% Ribo + 30mW X 3 min



Untreated



Treated



# Hyperopic LASIK xtra



**LaserVision.gr**

PATIENT NAME: V.R. COULOUSSIS (60668003) DOB: 11/08/1967

REFL. SIZE: 4.5-5.5 DOMINANT EYE: OS FACIOMETRY: 33.6-33.8 LN:

RESTACAM:  HUPH:  VISA:  HL:  ECC:  WF:

RECOMMENDED SURGERY: LASIK  PRK  LK  FSK  AK  (transverse)

CONTACT LENS USE:  CL  IM

Right eye			Left eye		
K	Sphere	Cylinder	K	Sphere	Cylinder
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17
41.75	-0.25	1.17	41.2	-0.25	1.17

Procedure: DATE: 11/2/2011  Sun  Mon  Tue  Wed  Thu  Fri  Sat

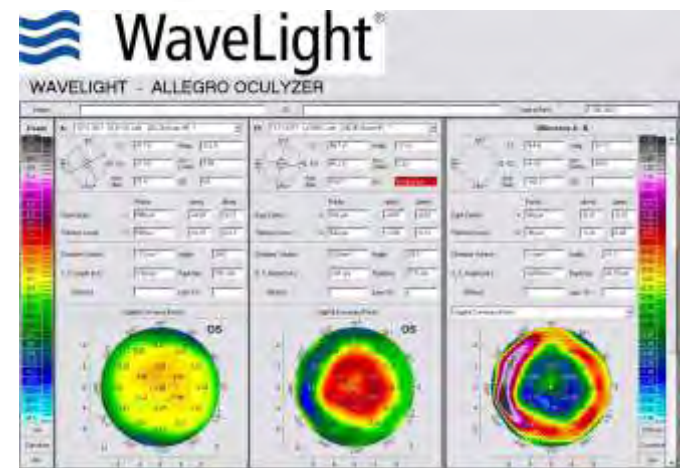
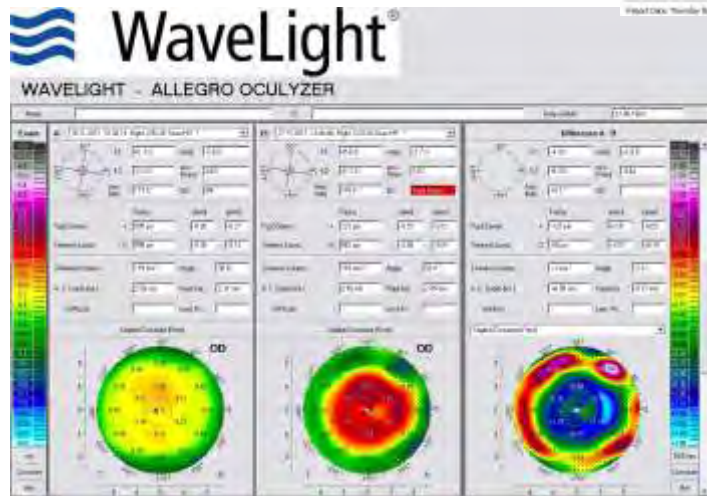
Time: 10:00 AM

Procedure:  LASIK  PRK  LK  FSK  AK

Right eye: Sphere: +1.00, Cylinder: -0.25, Axis: 135, Total: +0.75

Left eye: Sphere: +1.00, Cylinder: -0.25, Axis: 135, Total: +0.75

Handwritten notes: "D7 G10" and "10:00 AM".



- **CXL and long term Hyperopic LASIK stability. Initial clinical findings in a contralateral eye study**

**Purpose:** The evaluation of the safety and efficacy of the application of intrastromal CXL in a contralateral eye study in routine hyperopic LASIK

**Methods:** 27 consecutive hyperopic and hyperopic astigmatic bilateral topography-guided LASIK patients were randomized to receive 5 minutes of 10mW/cm<sup>2</sup> CXL after in-the-flap administration of a single drop of 0.1% sodium phosphate riboflavin solution. All cases were treated with the Allegretto 400Hz Eye-Q excimer laser and femtosecond laser flap creation. Peri-operative refractive error, keratometric, topographic and topometric measurements were evaluated with a mean follow-up of 23 months (22-35).

**Results:** Mean sphere was +3.25D, Cyl: -1.75D. The CXL cases demonstrated a mean regression from treatment of +0.22D (diopters), the non-CXL cases: + 0.72 D, showing a very strong statistically significant difference even in the first 6 patients despite the expected flattening effect of CXL.

**Conclusions:** These preliminary data suggest that the combination of CXL in hyperopic LASIK may offer a very significant synergy in efficacy, suggesting that hyperopic LASIK long term regression may be more related to cornea biomechanical changes, than just residual accommodation.

# Conclusions higher fluence CXL

Our current protocols

1-**Athens Protocol: topoPRK +10'x 10mw/cm<sup>2</sup>**

2-**LASIK Xtra: 1' (60") 30mW/cm<sup>2</sup>**

2-**PRK Xtra: 1' (60") 30mW/cm<sup>2</sup>**

3-**Transepithelial CXL: 0.25% riboflavin +  
30mW/cm<sup>2</sup> X 3' (180")**

3-**Infection: 0.25% riboflavin + 45mW/cm<sup>2</sup> x 5  
minutes**



## Conclusions higher fluence CXL

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)



## 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<sup>+</sup> interaction

CXL may prove to be the standard collagen stabilizer and adjunct disinfectant in LASIK, PRK and even cataract surgery



Thank you

