CORNEAL CROSS-LINKING (CXL)

J. Bradley Randleman, M.D.

CXL Experts Meeting
Zurich Switzerland
December 2, 2016

Presenter Introduction

- **J. Bradley Randleman, MD**
- Professor of Ophthalmology,
  Keck School of Medicine of USC

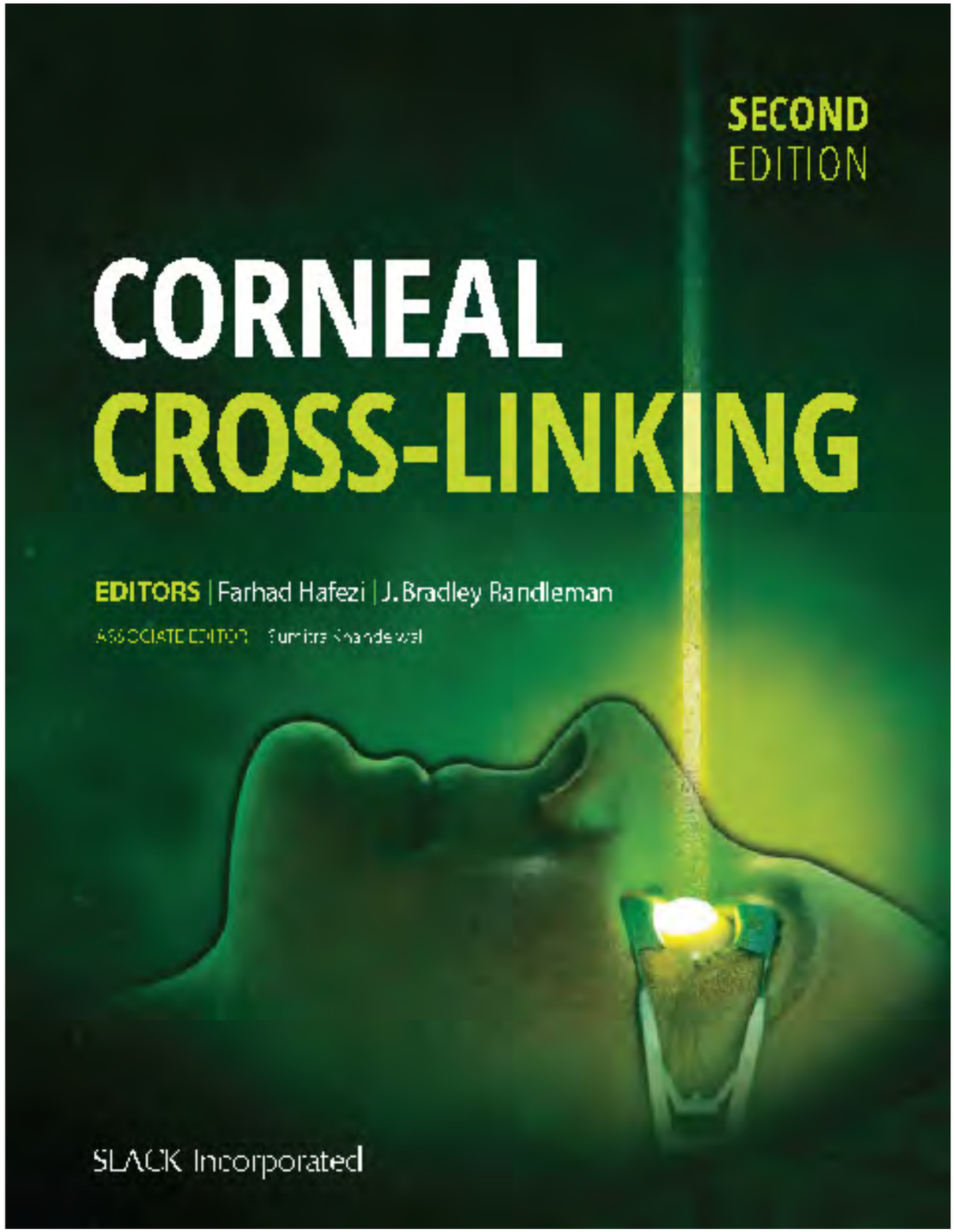
- Director, Cornea & Refractive Surgery
  USC Roski Eye Institute

- Editor-in-Chief, *Journal of Refractive Surgery*

randlema@usc.edu

USC Roski Eye Institute
Keck Medicine of USC

No Financial Disclosures



USC Roski Eye Institute
Keck Medicine of USC

Major review

SURVEY OF OPHTHALMOLOGY 60 (2015) 509–525

Corneal cross-linking

J. Bradley Randleman, MD[a,b,*], *Sumitra S. Khandelwal, MD*[c], *Farhad Hafezi, MD, PhD*[d,e,f,g]

[a] *Department of Ophthalmology, Emory University, Atlanta, Georgia, USA*
[b] *Emory Vision, Emory Eye Center, Atlanta, Georgia, USA*
[c] *Baylor College of Medicine, Cullen Eye Institute, Houston, Texas, USA*
[d] *ELZA Institute, Zurich, Switzerland*
[e] *Laboratory for Ocular Cell Biology, University of Geneva, Geneva, Switzerland*
[f] *Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA*
[g] *Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zurich, Zurich, Switzerland*

OVERVIEW

- CXL Basic principles
- Primary Indications: Ectatic corneal disorders
- CXL Protocols
- Complications & Controversies
- Patient Selection: Beginning & Advanced

Major review

Corneal cross-linking

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[a] Department of Ophthalmology, Emory University, Atlanta, Georgia, USA
[b] Emory Vision, Emory Eye Center, Atlanta, Georgia, USA
[c] Baylor College of Medicine, Cullen Eye Institute, Houston, Texas, USA
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[e] Laboratory for Ocular Cell Biology, University of Geneva, Geneva, Switzerland
[f] Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA
[g] Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zurich, Zurich, Switzerland

ARTICLE INFO

Article history:
Received 29 November 2014
Received in revised form 28 April 2015
Accepted 30 April 2015
Available online 14 May 2015

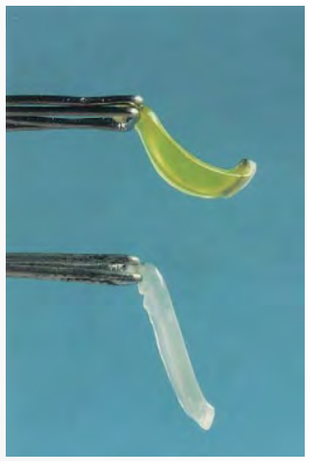
Keywords:
cornea
CXL
cross-linking
keratoconus
ectasia
infectious keratitis
cross-linking plus
accelerated cross-linking

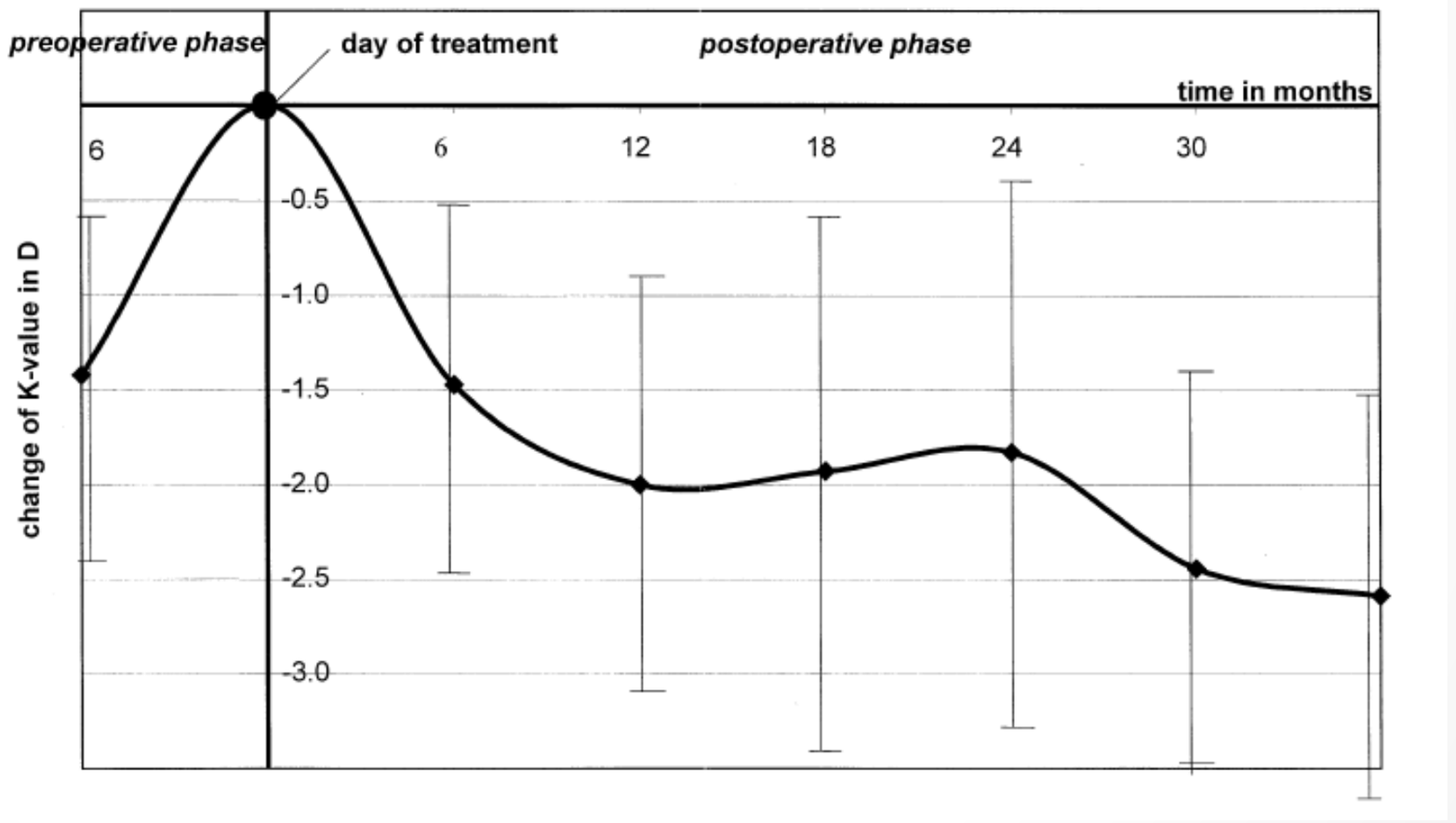
ABSTRACT

Since its inception in the late 1990s, corneal cross-linking has grown from an interesting concept to a primary treatment for corneal ectatic disease worldwide. Using a combination of ultraviolet-A light and a chromophore (vitamin B2, riboflavin), the cornea can be stiffened, usually with a single application, and progressive thinning diseases such as keratoconus arrested. Despite being in clinical use for many years, some of the underlying processes, such as the role of oxygen and the optimal treatment times, are still being worked out. More than a treatment technique, corneal cross-links represent a physiological principle of connective tissue, which may explain the enormous versatility of the method. We highlight the history of corneal cross-linking, the scientific underpinnings of current techniques, evolving clinical treatment parameters, and the use of cross-linking in combination with refractive surgery and for the treatment of infectious keratitis.

Crosslinking for keratoconus (KC)

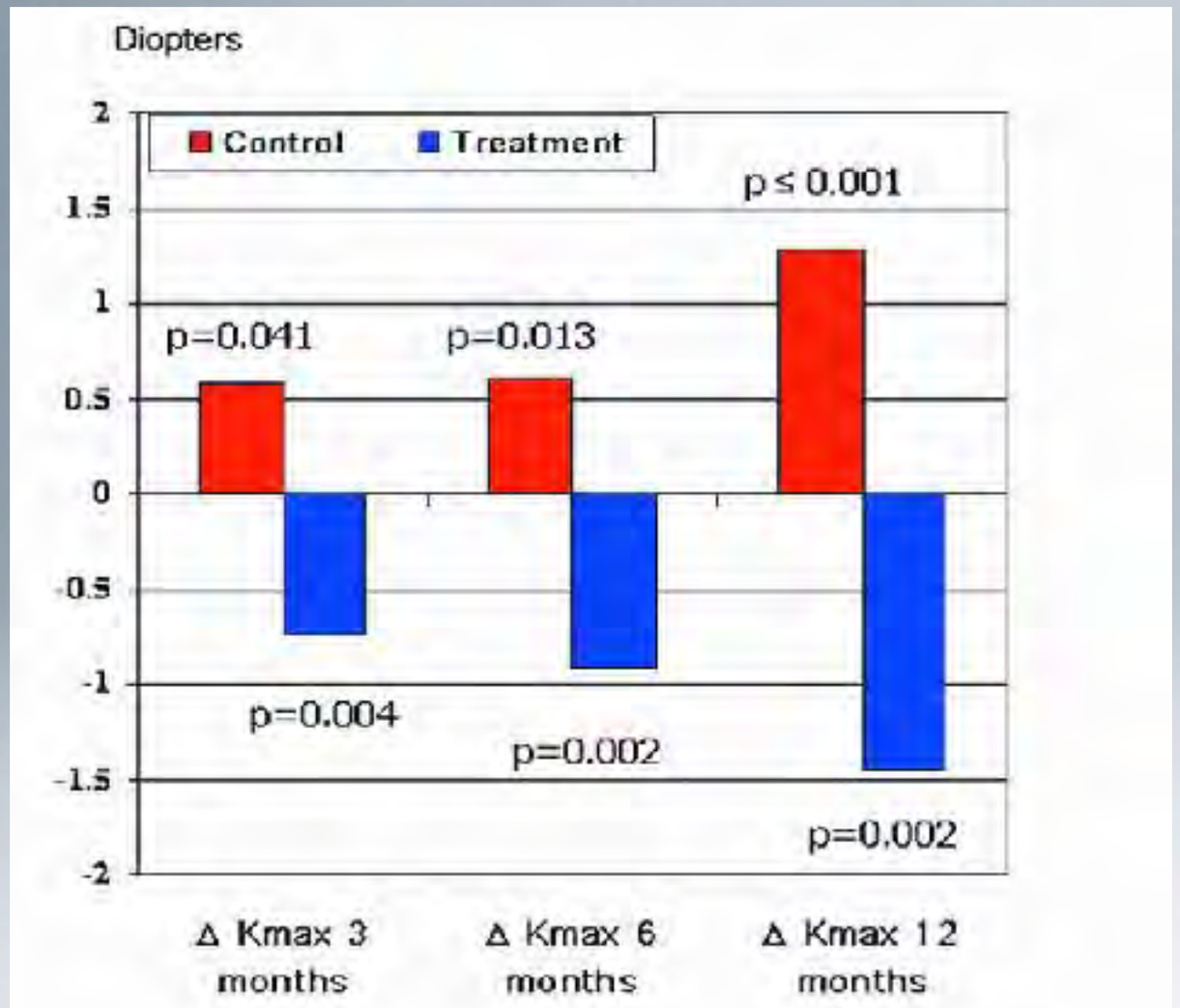
- Non-enzymatic collagen stiffening with riboflavin and UVA light

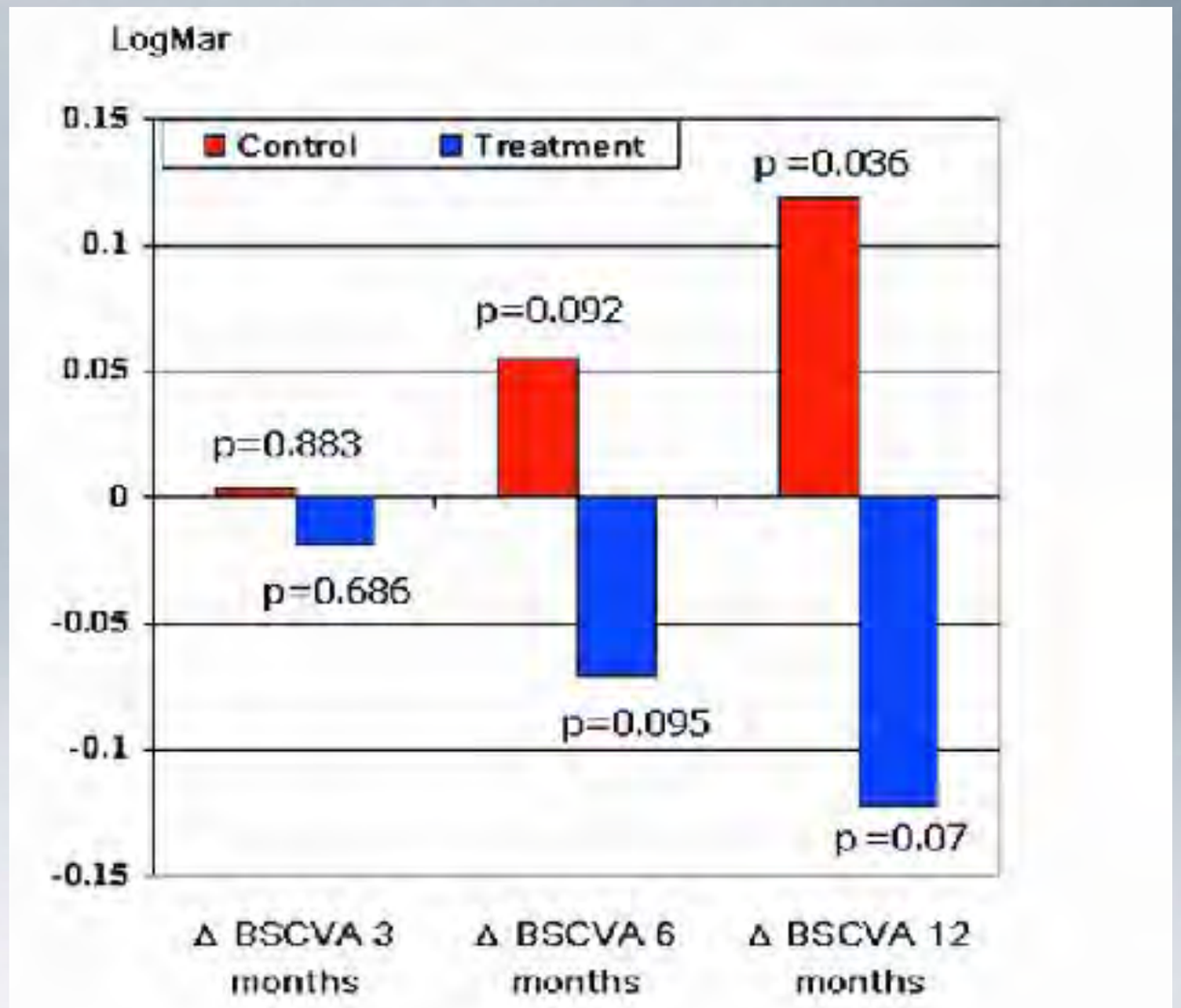




Wollensak, Spoerl, Seiler Am J Ophthalmol 2003

CX: CLINICAL RESULTS





Wittig-Silva JRS 2008

Goals for CXL in Ectasias

- Stabilize ectatic process
- Reduce corneal steepening
- Improve CTL fitting
- Provide alternatives for visual rehabilitation
  - Intracorneal ring segments
  - PRK

Avoid corneal transplantation!

avedro

Avedro Receives FDA Approval for Photrexa® Viscous, Photrexa® and the KXL® System for Corneal Cross-Linking

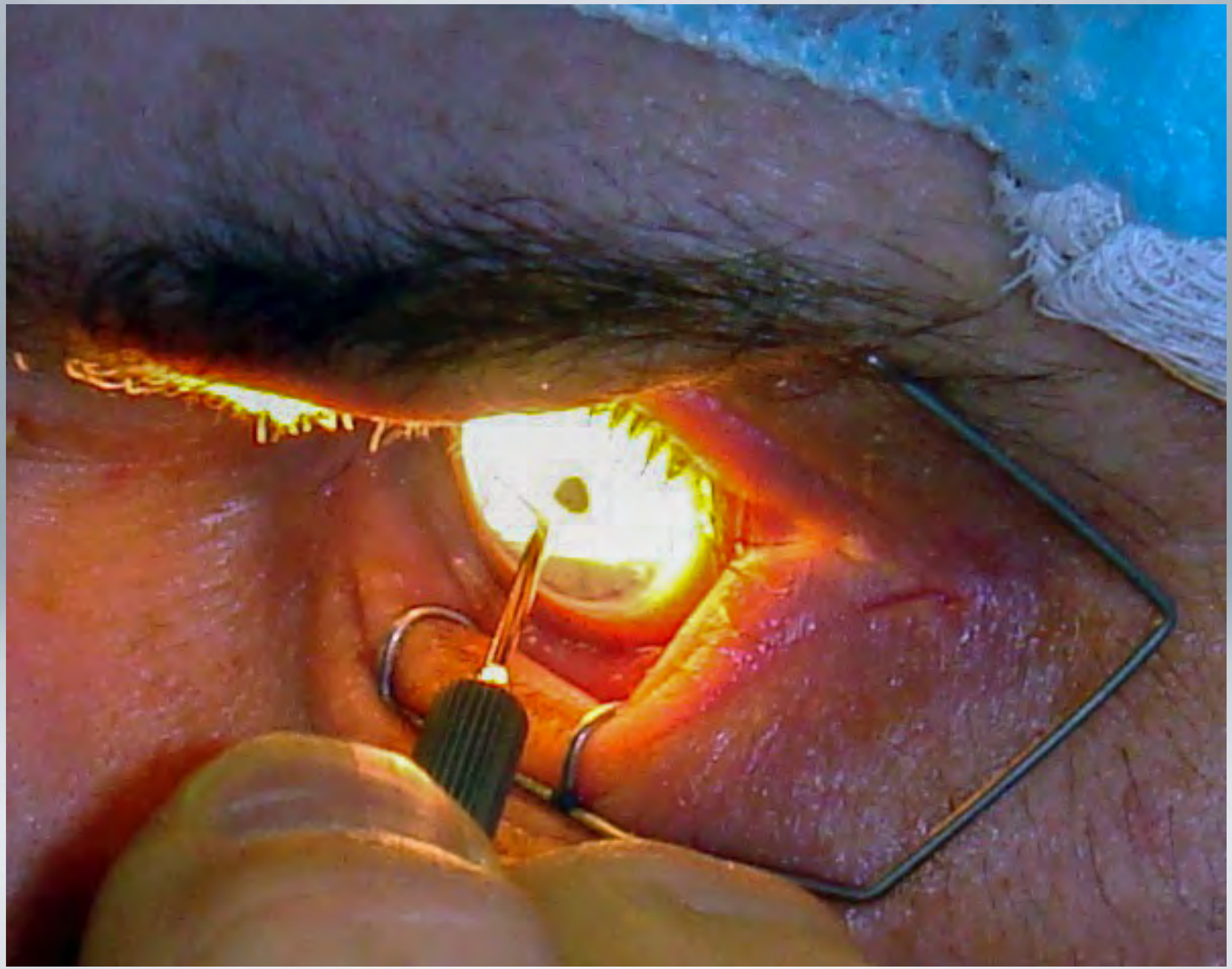
Photrexa Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution) 0.146%, Photrexa (riboflavin 5′-phosphate ophthalmic solution) 0.146%, and the KXL system are the first and only FDA-approved therapeutic treatment for progressive keratoconus

Waltham, Massachusetts, USA, Apr 18, 2016

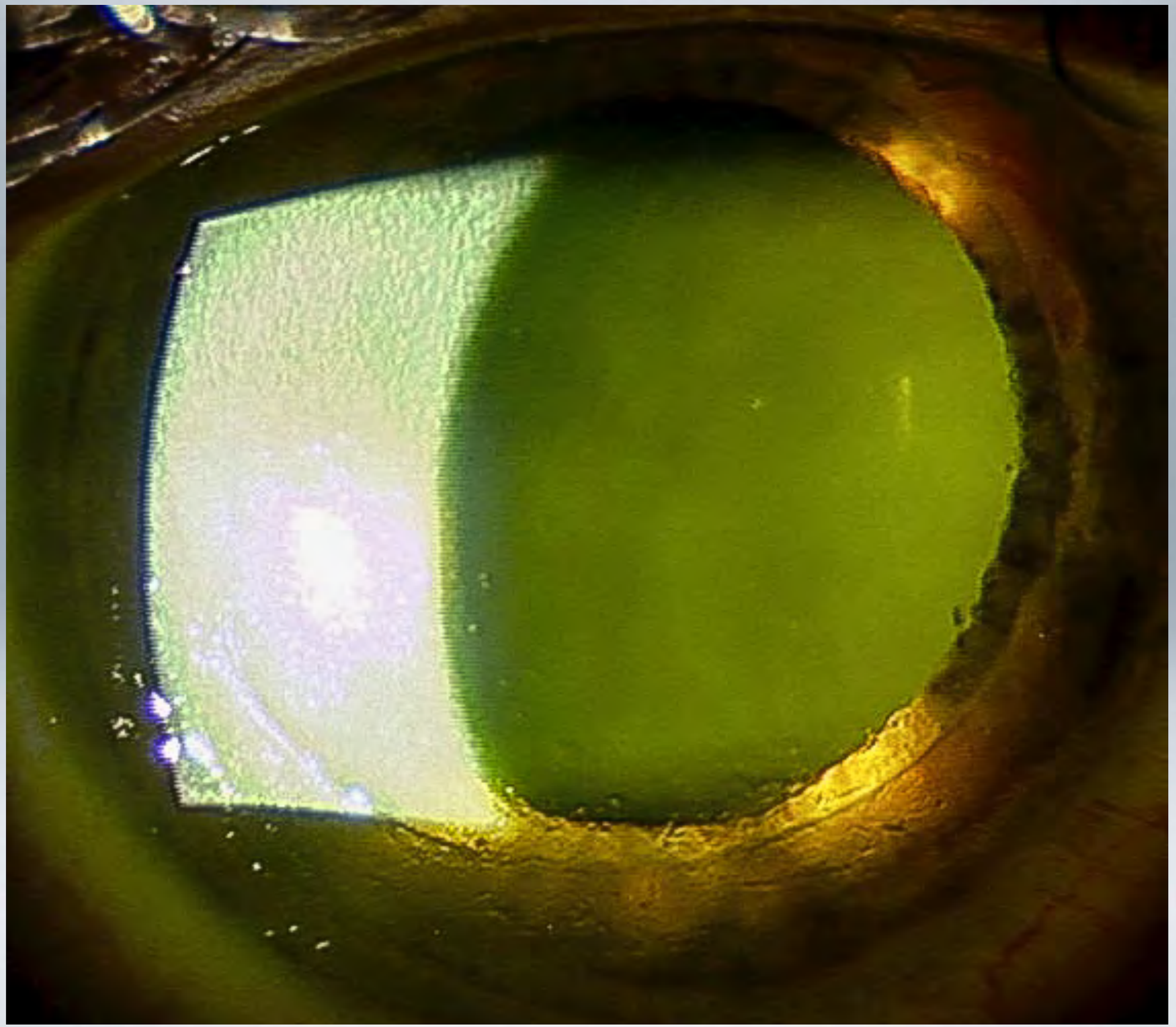
CXL:
STEP BY STEP

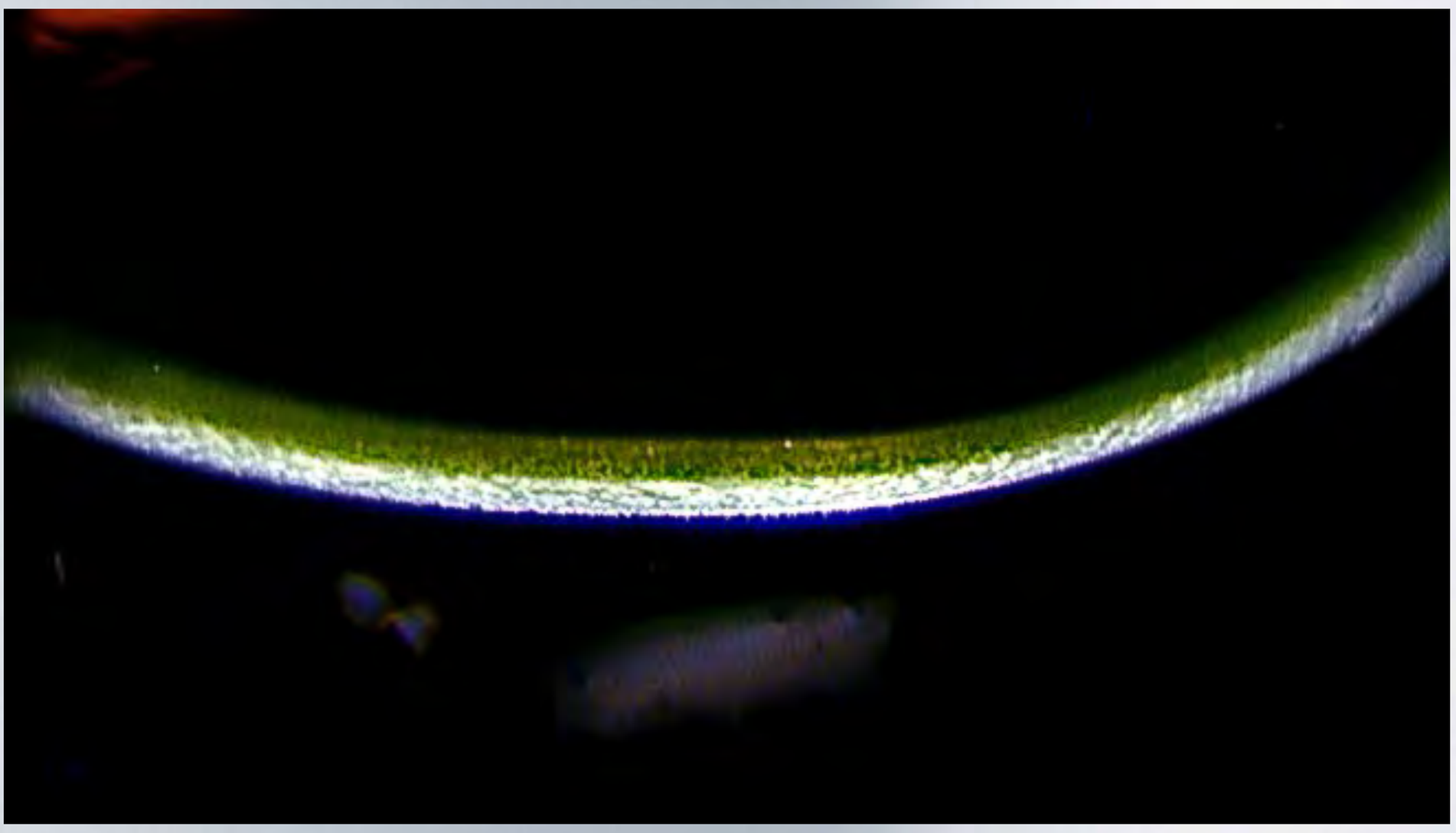
Procedure: Standard Dresden Technique

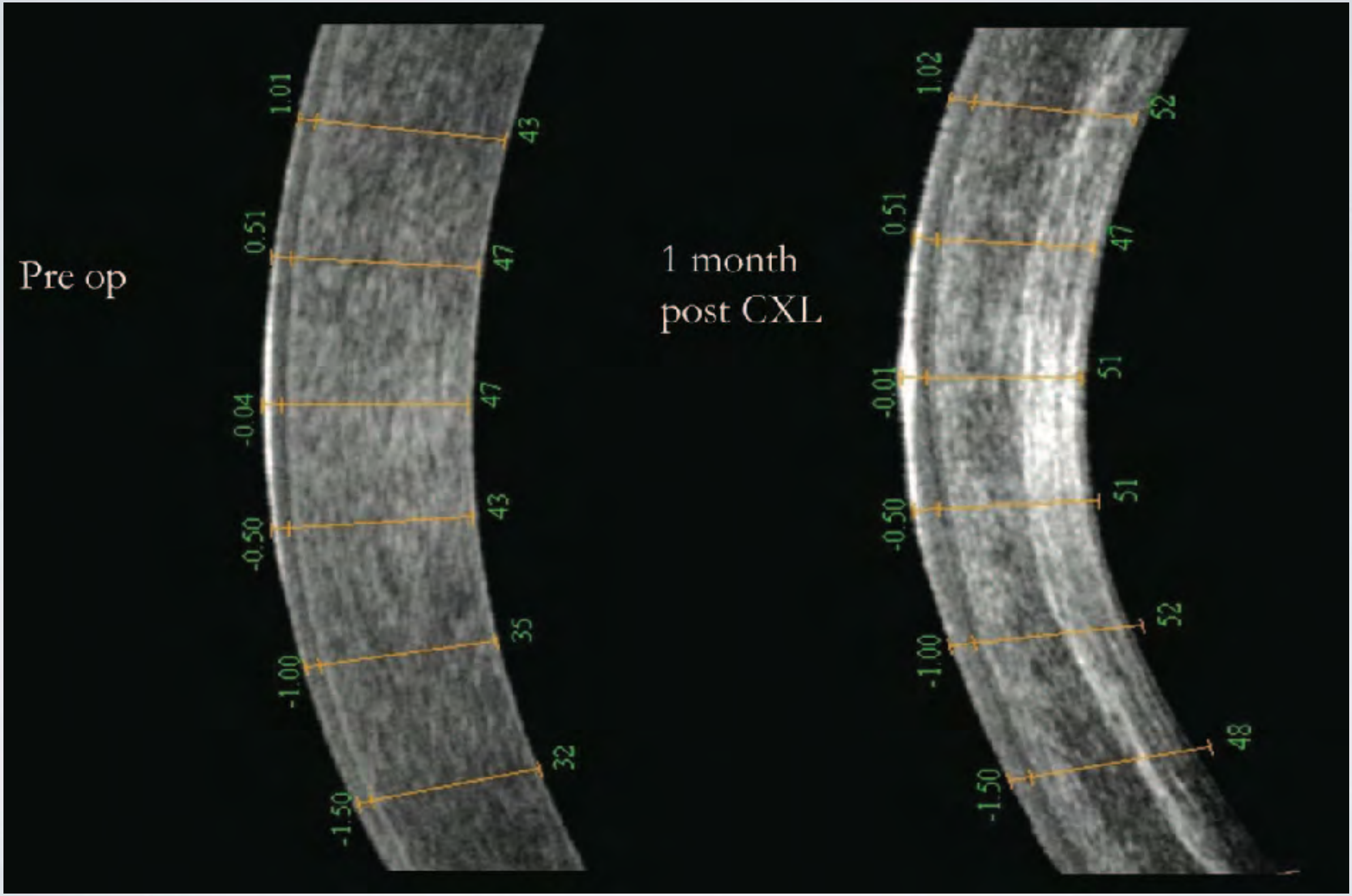
- 9 mm epithelial removal
- Riboflavin 0.1% drops x 30 min
- Riboflavin 0.1% drops x 30 min with
  30 minutes 365 nm UVA (3mW/cm^2)
- UV-X , Peschke Meditrade, Zurich




UV-X™
Beam Aperture






Pre op
1.01
43
0.51
47
-0.04
47
-0.50
43
-1.00
35
-1.50
32
1 month
post CXL
1.02
52
0.51
47
-0.01
51
-0.50
51
-1.00
52
-1.50
48

CXL IN THE US

KXL System

Avedro's KXL System, the only FDA approved cross-linking device, offers:

- UVA Irradiation: 30 minutes at 3 mW/cm2
- Laser alignment for patient positioning
- Wireless control for beam alignment in the X, Y and Z axes
- Fully-integrated stable delivery platform
- Touch screen operation
- Self-calibration of UVA irradiation intensity

CXL IN THE US

Photrexa Formulations

Photrexa Viscous

(riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%

Technical information:

Formulation: 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical ophthalmic use

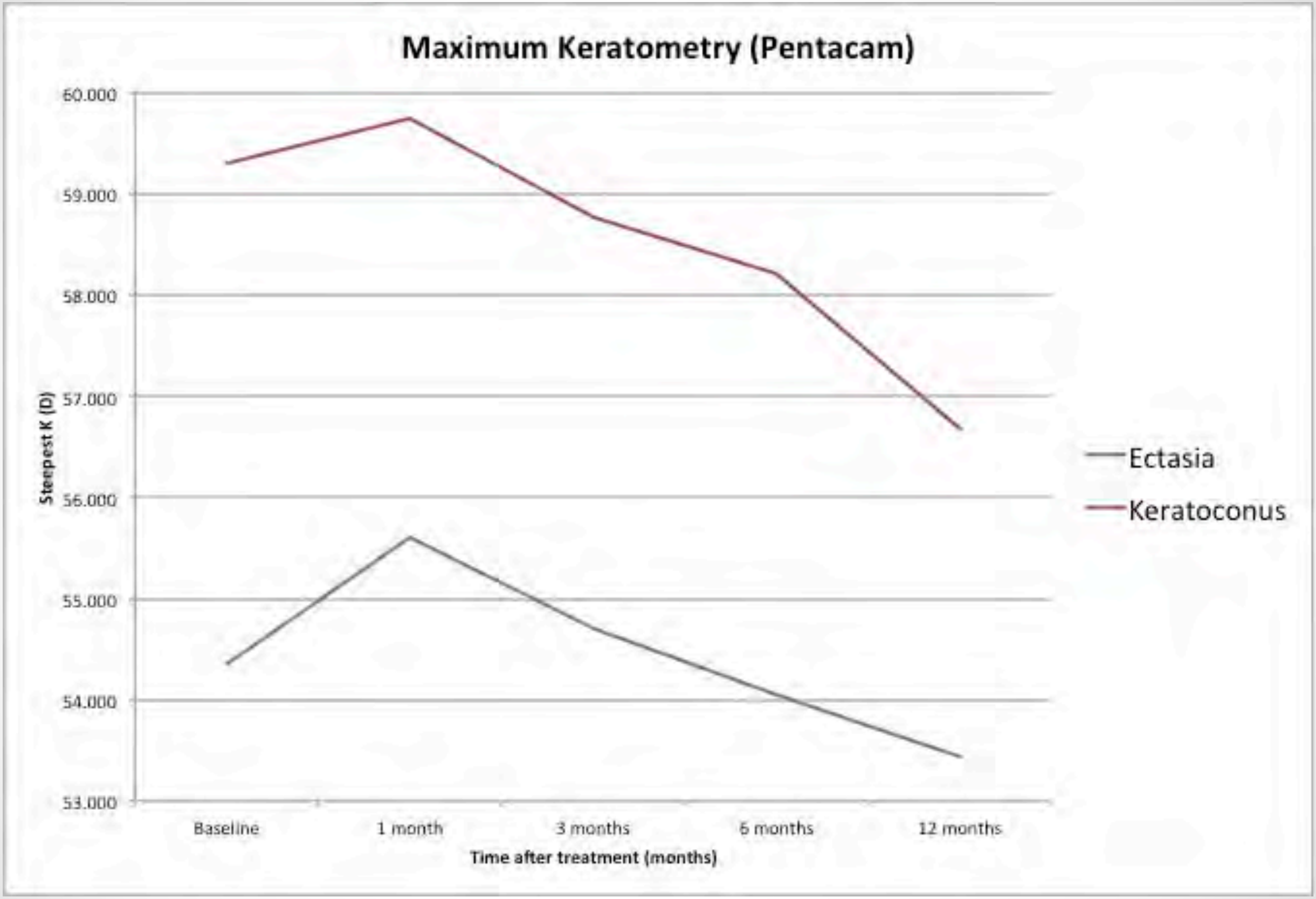
Photrexa

(riboflavin 5'-phosphate ophthalmic solution) 0.146%

Technical information:

Formulation: 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution for topical ophthalmic use

CXL FOR CORNEAL ECTASIAS



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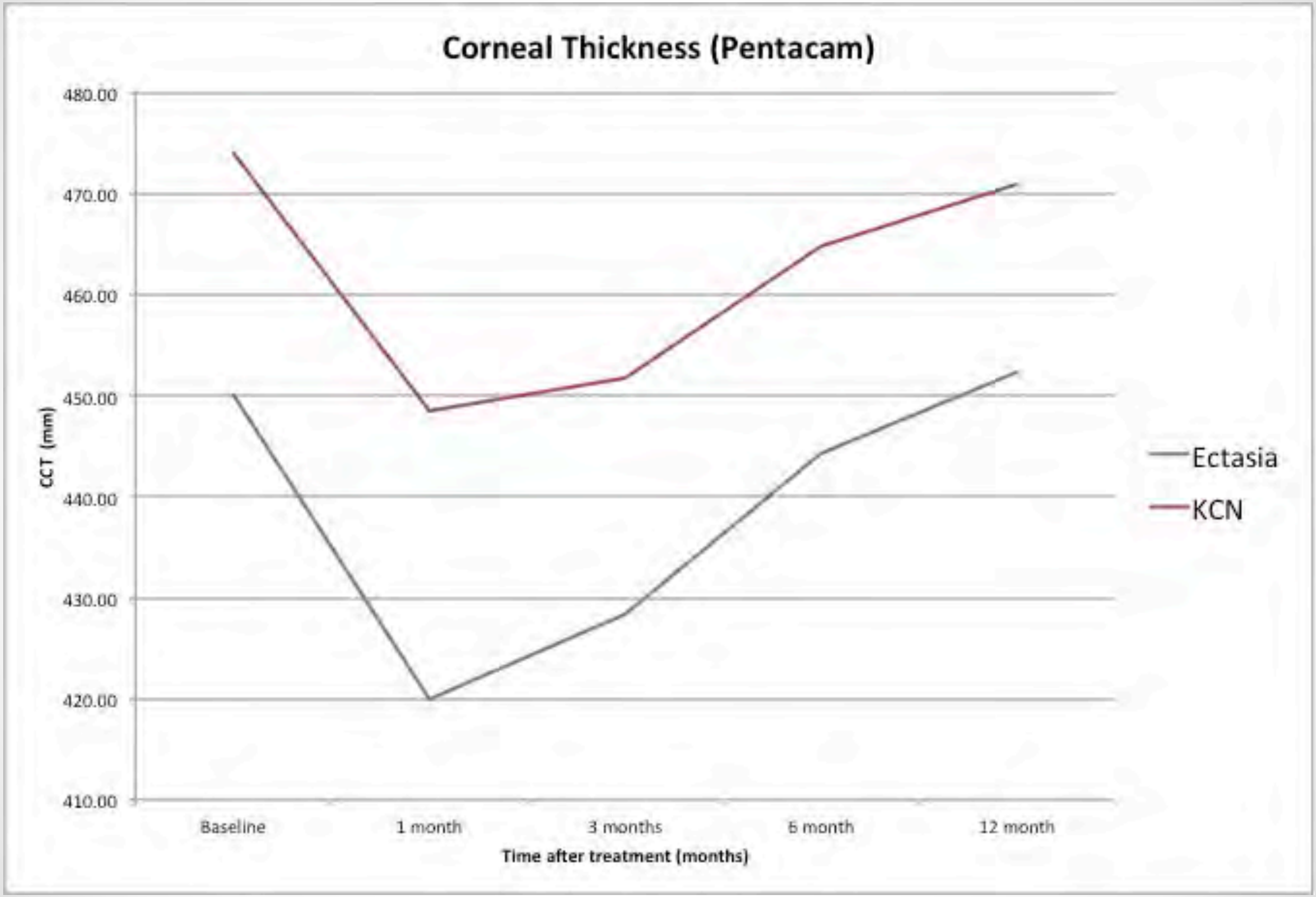

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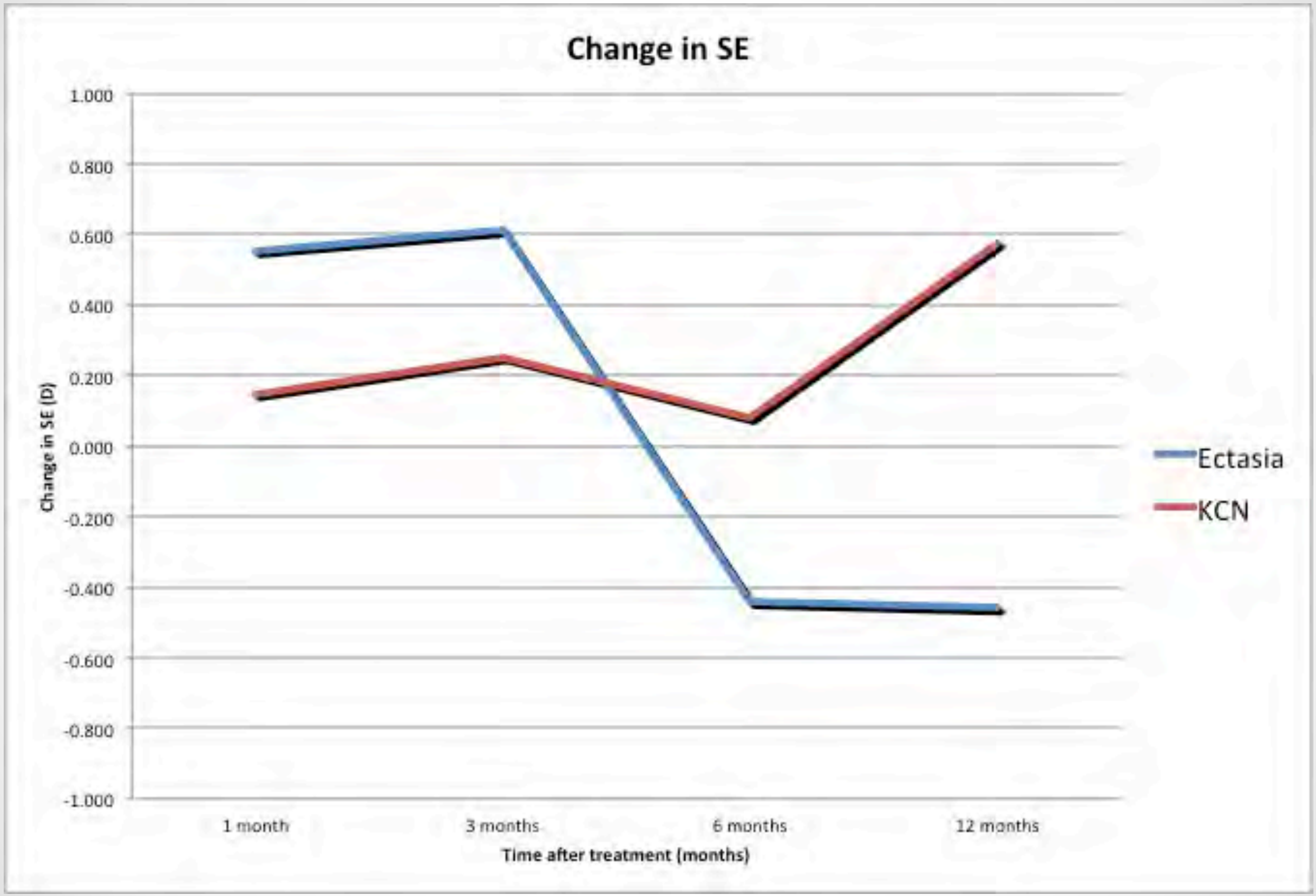

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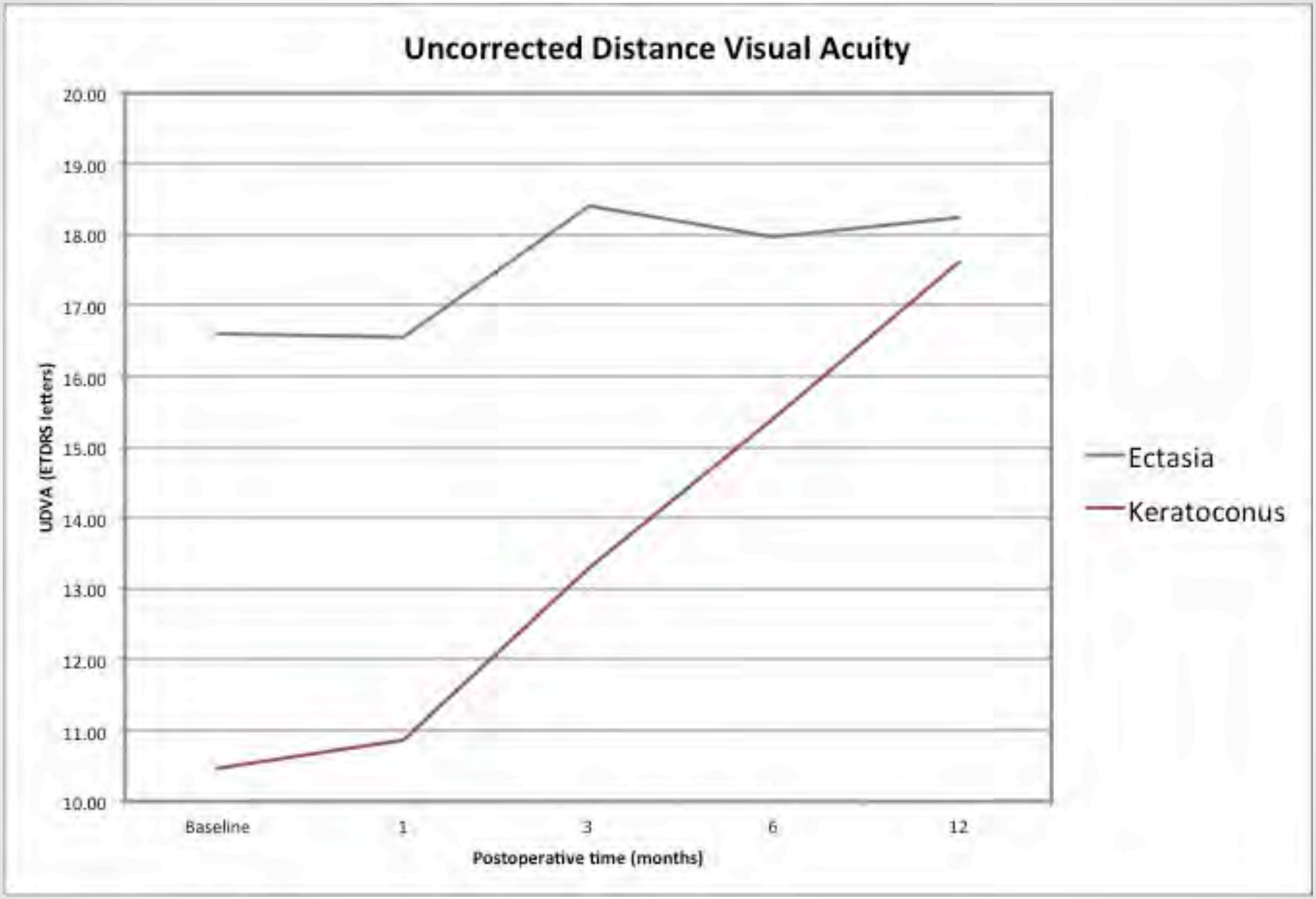

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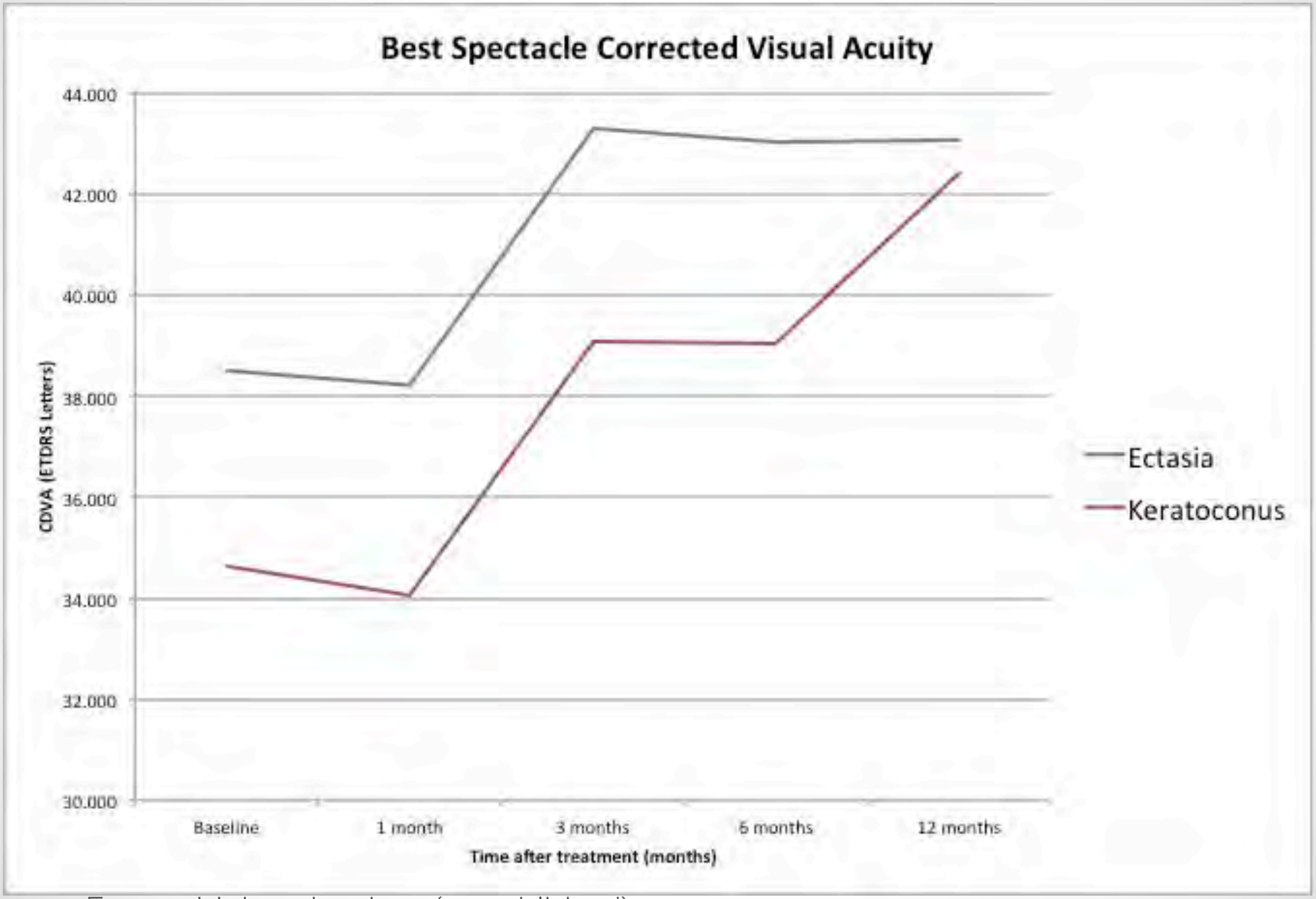

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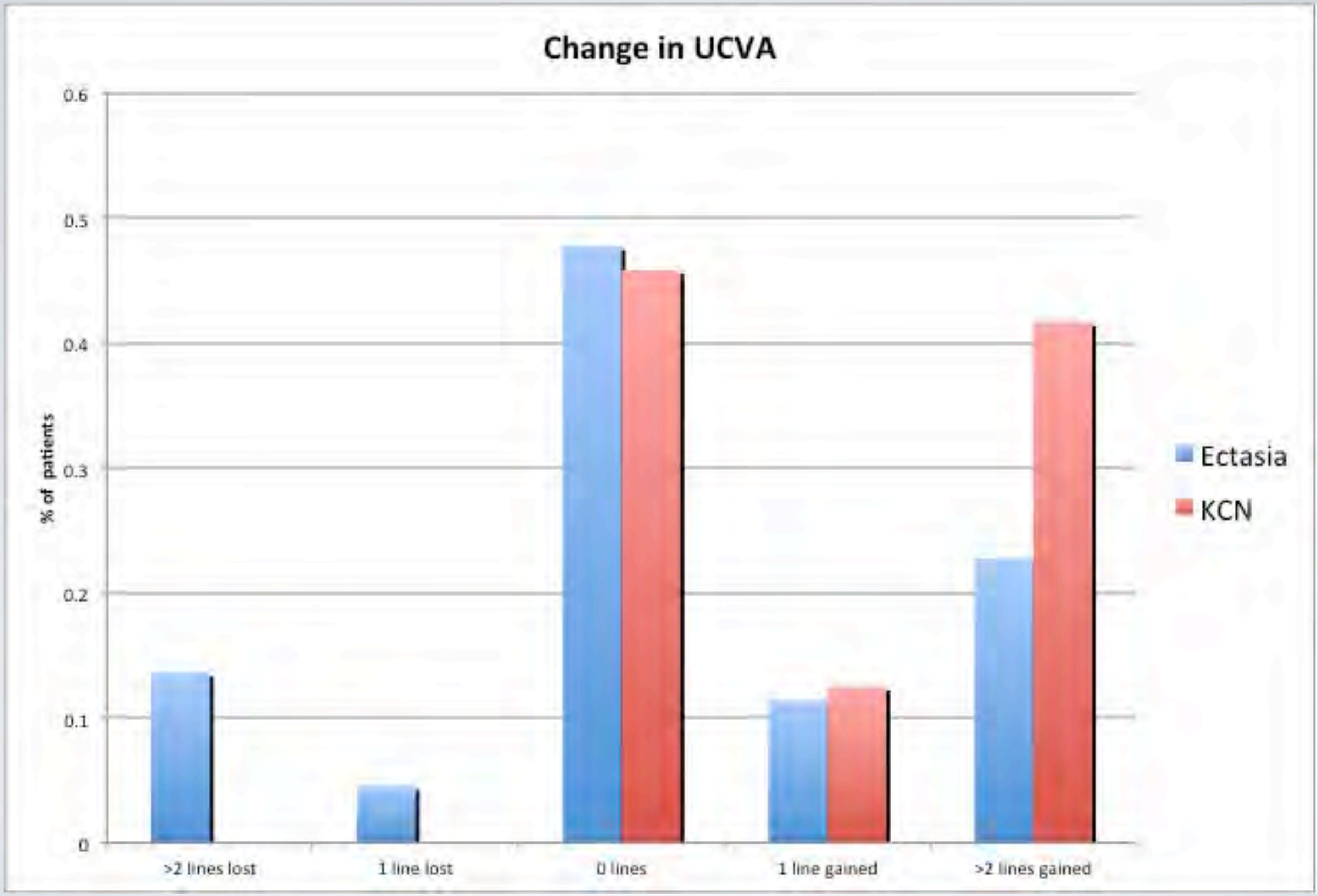
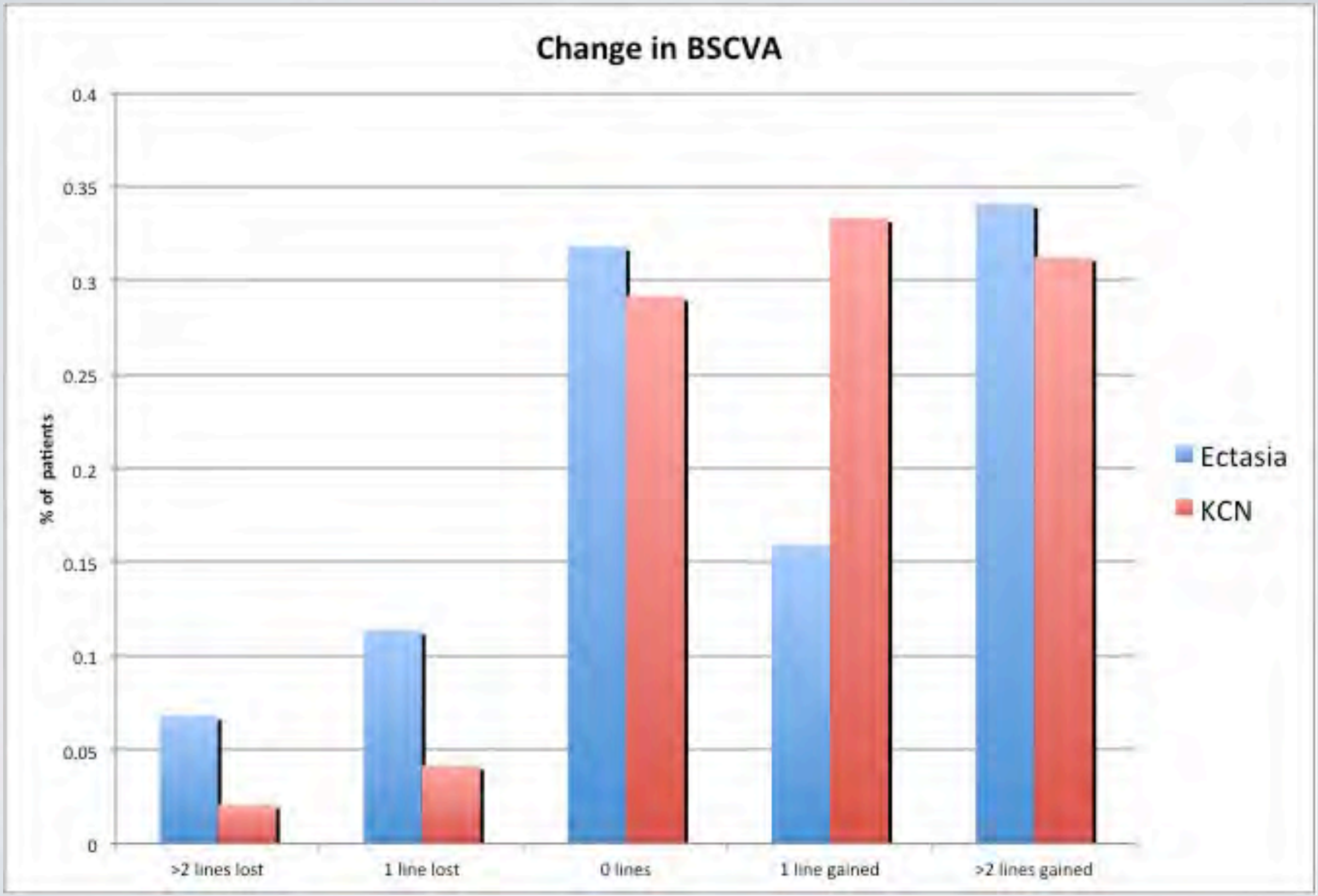
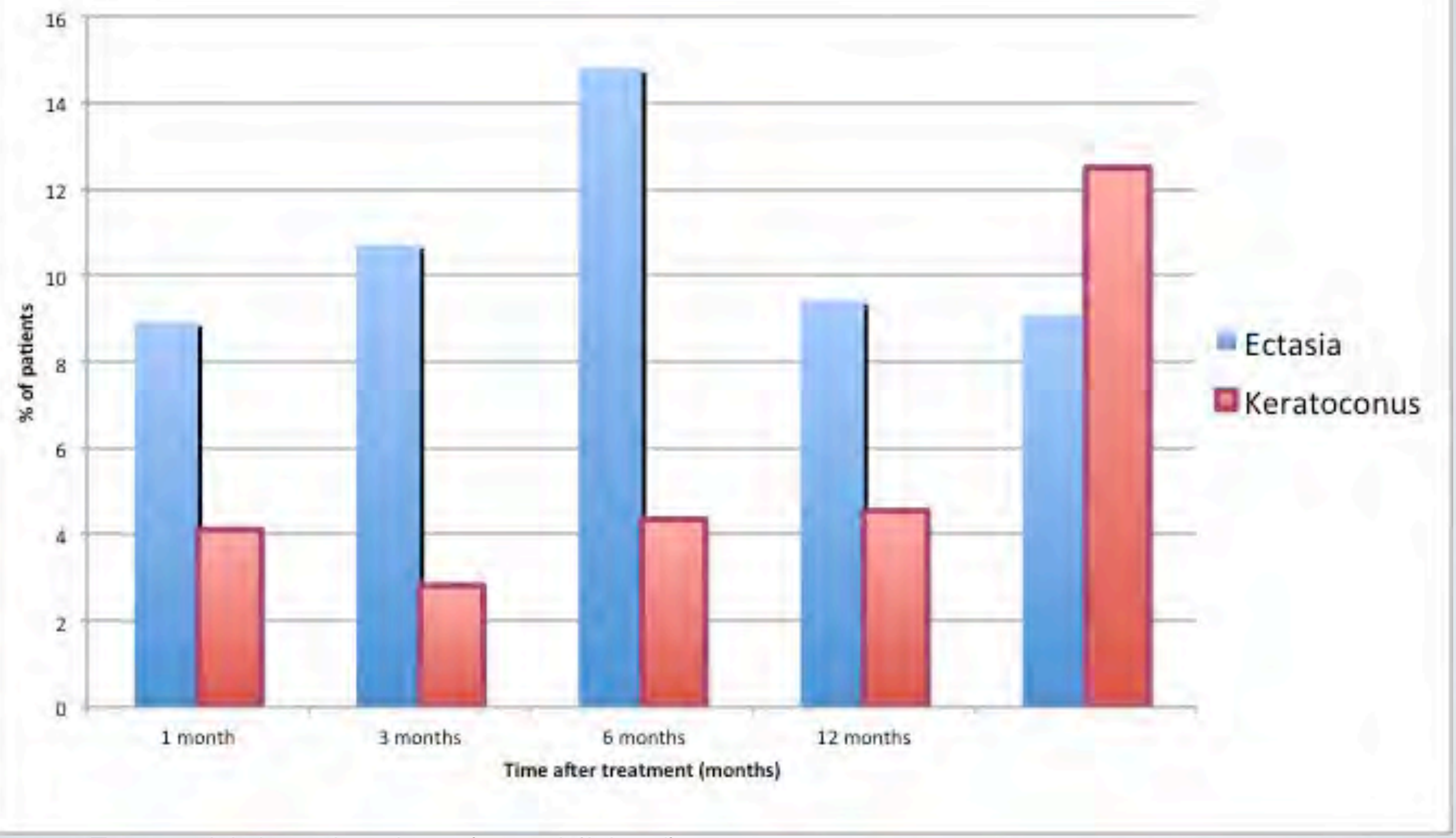

Change in UCVA
0.6
0.5
0.4
0.3
0.2
0.1
0
% of patients
>2 lines lost
1 line lost
0 lines
1 line gained
>2 lines gained
Ectasia
KCN

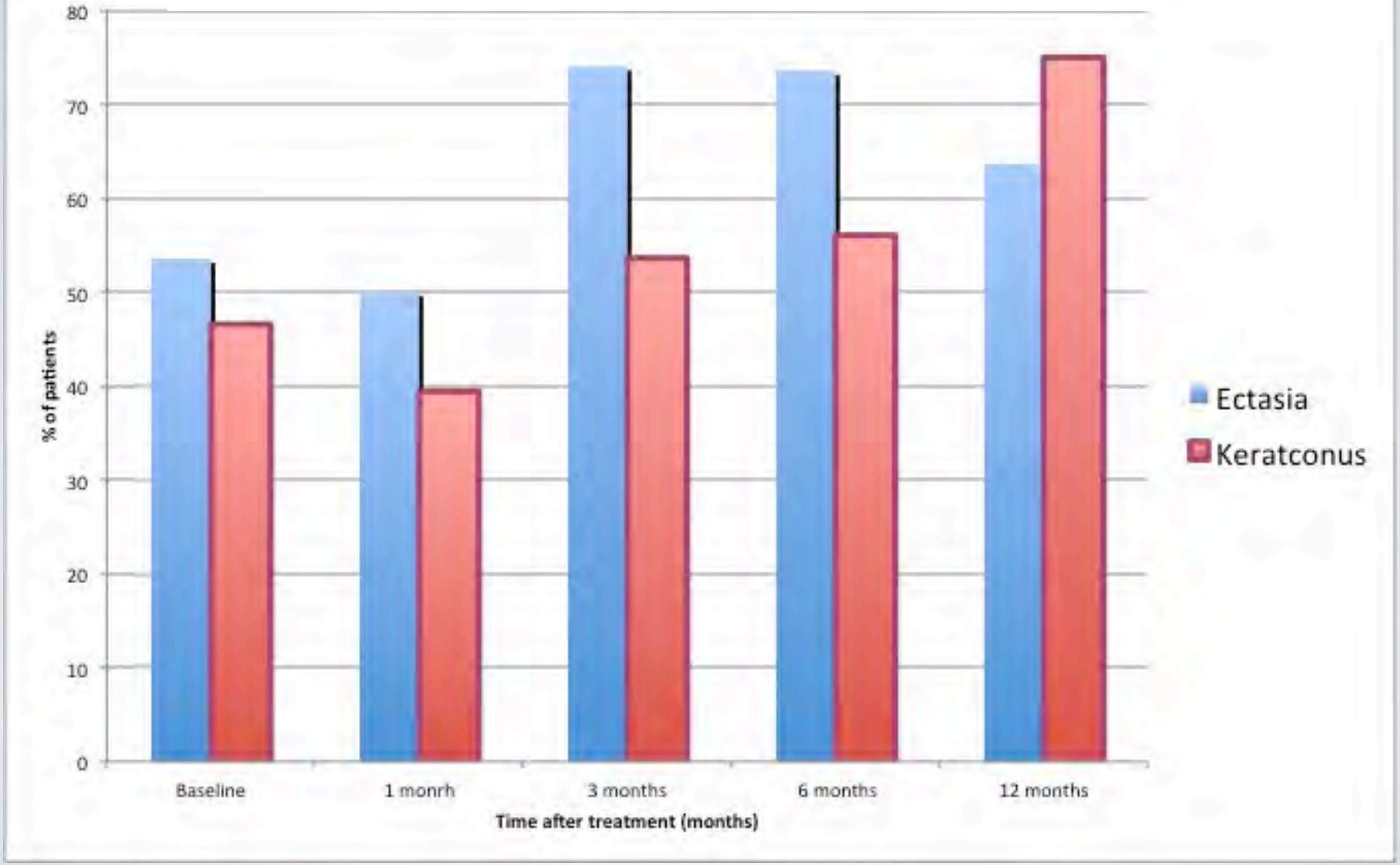

Change in BSCVA
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
% of patients
>2 lines lost
1 line lost
0 lines
1 line gained
>2 lines gained
Ectasia
KCN

Eyes Achieving UDVA 20/40 or Better



Emory University data (unpublished)

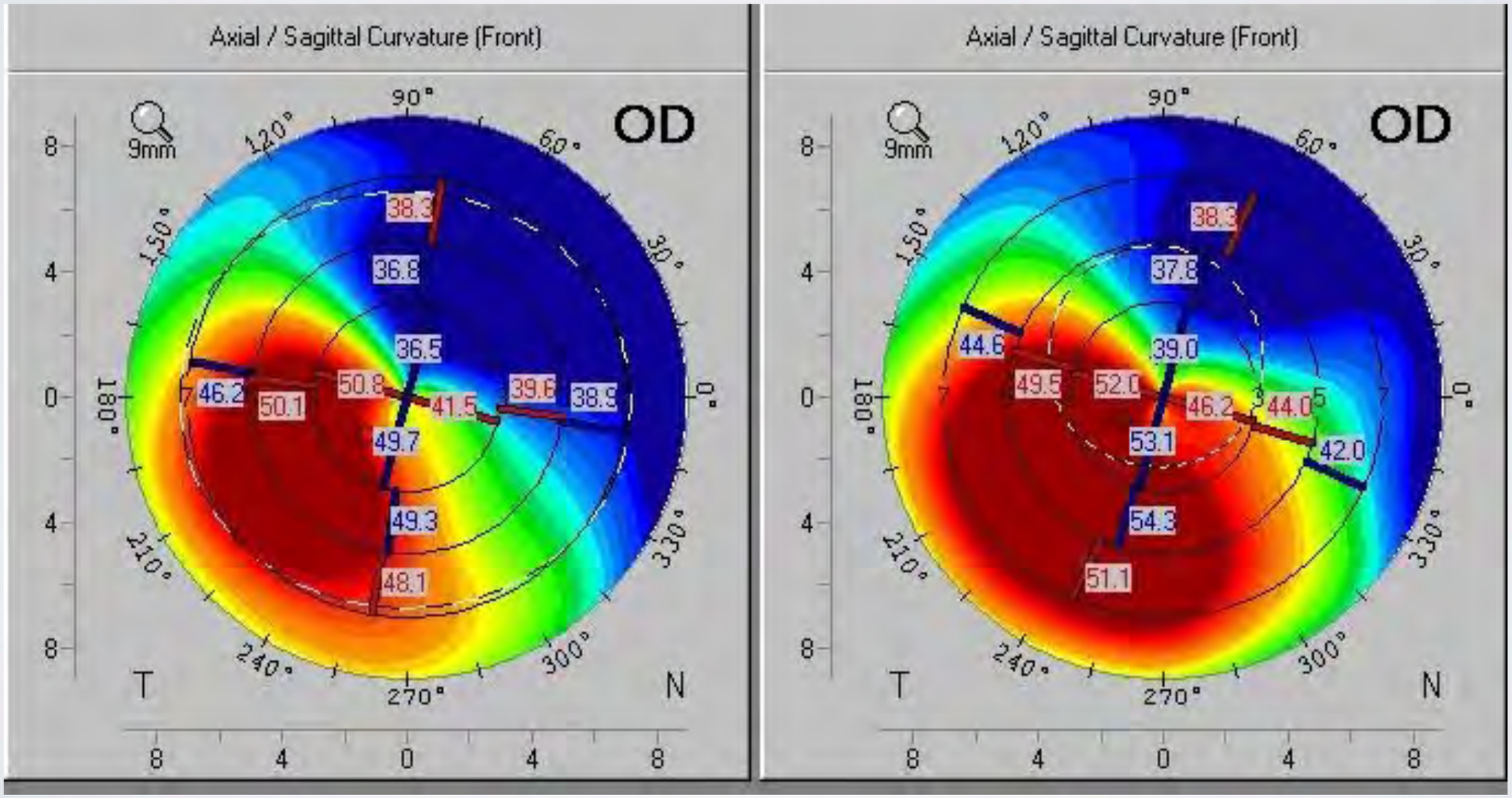
Eyes Achieving BSCVA 20/40 or Better



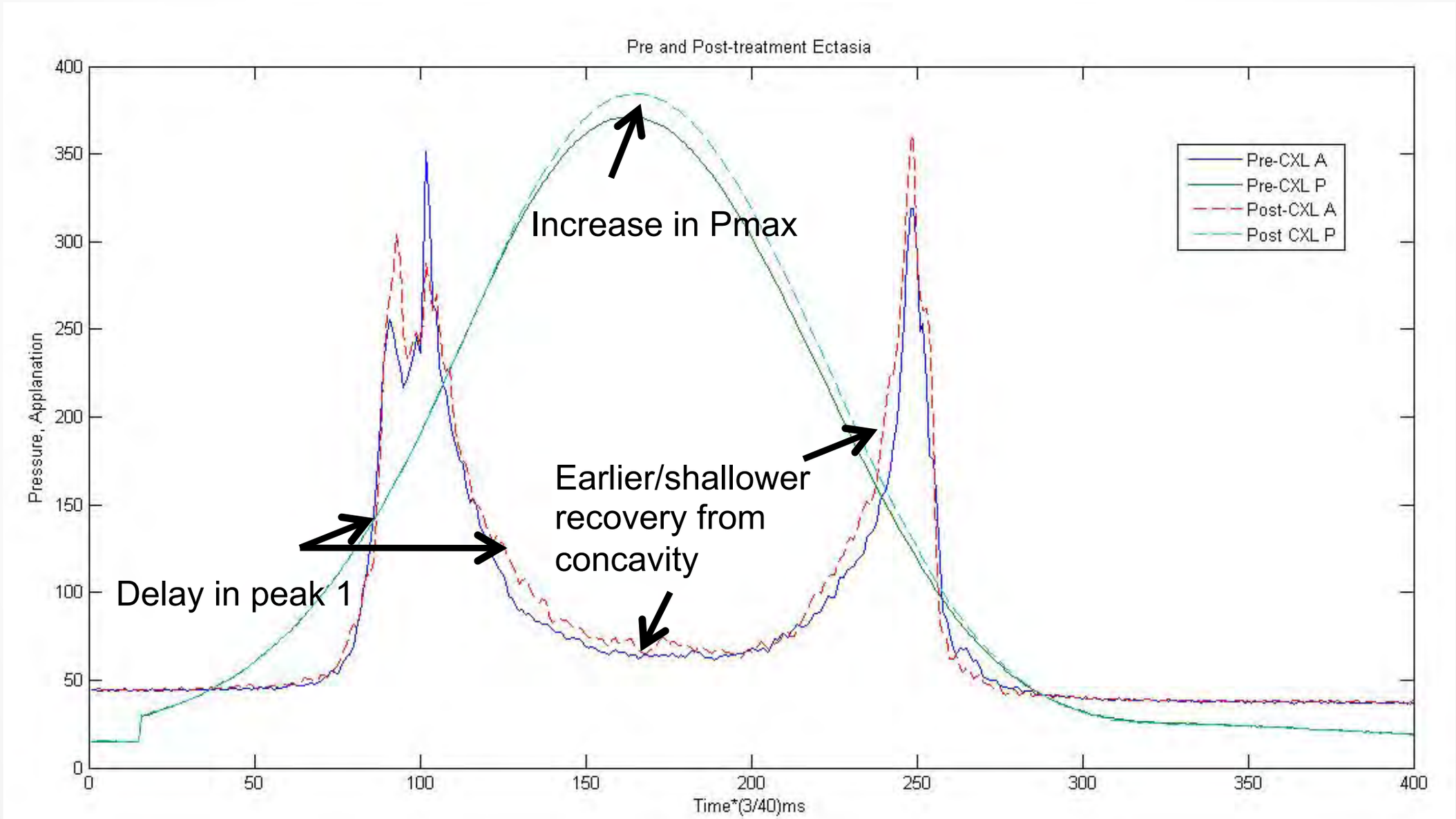
Emory University data (unpublished)

MEASURING CXL CHANGES: CHALLENGES

Difference Maps



ORA changes with crosslinking in post-LASIK ectasia



Hallahan KM, Rocha KM, Roy AS, Randleman JB, Stulting RD, Dupps WJ. Effects of corneal crosslinking on ocular response analyzer waveform-derived variables in keratoconus and post-refractive surgery ectasia. *Eye Contact Lens* 2014 Nov;40:339-44

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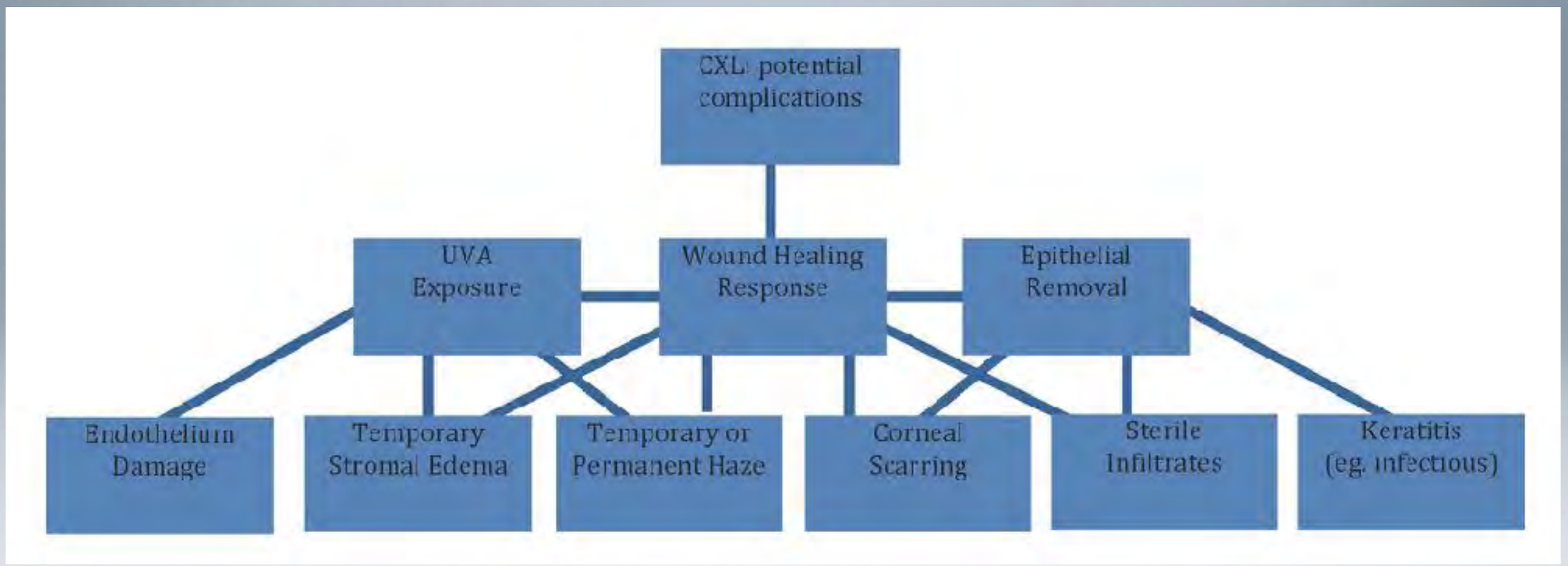
Corneal Collagen Cross-Linking Complications and Their Management

J. Bradley Randleman, MD and Karolinne Maia Rocha, MD, PhD

CXL COMPLICATIONS

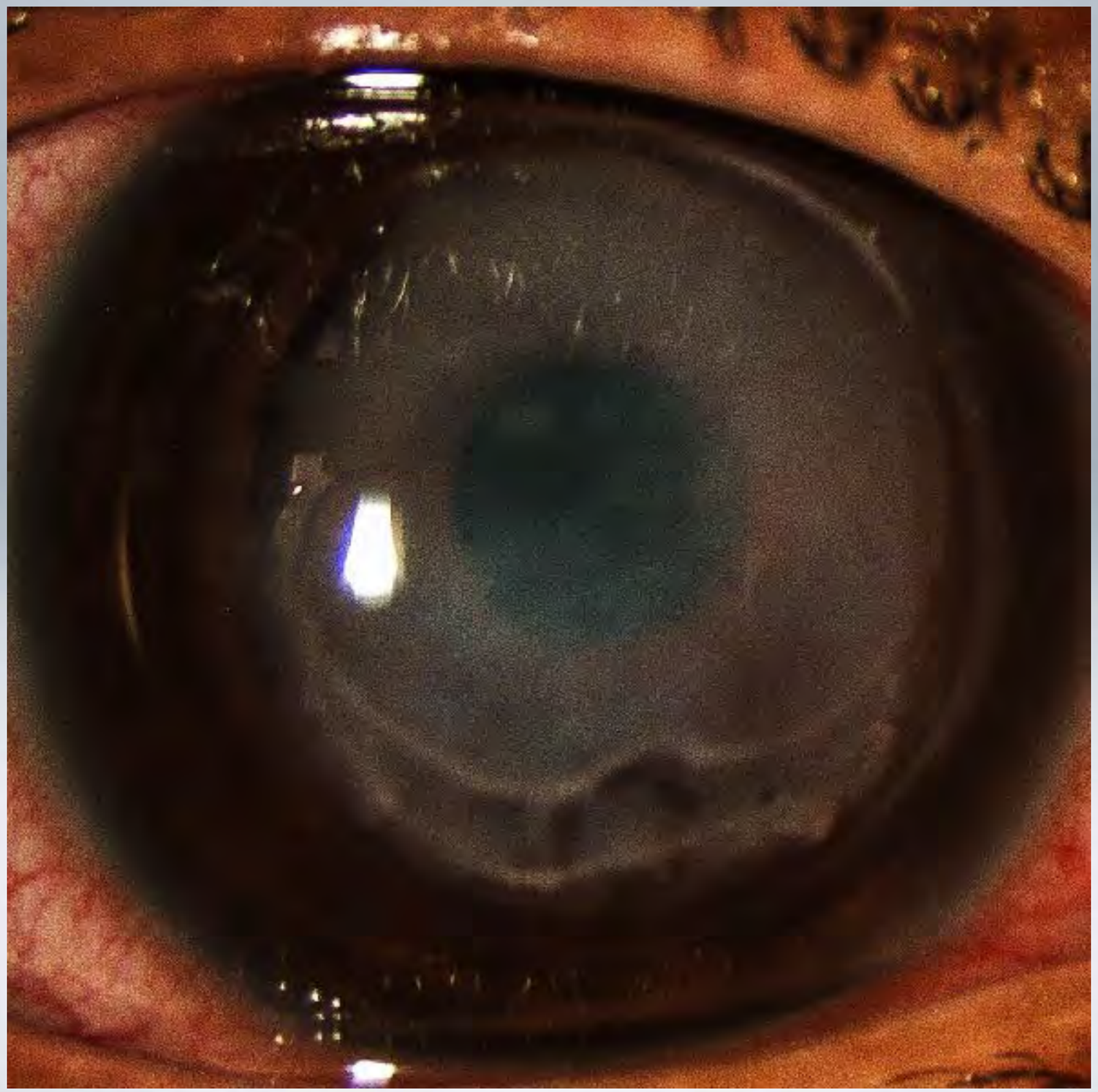
- Corneal Damage
- Infectious Keratitis
- Lack of efficacy
- Failed remodeling

COMPLICATIONS

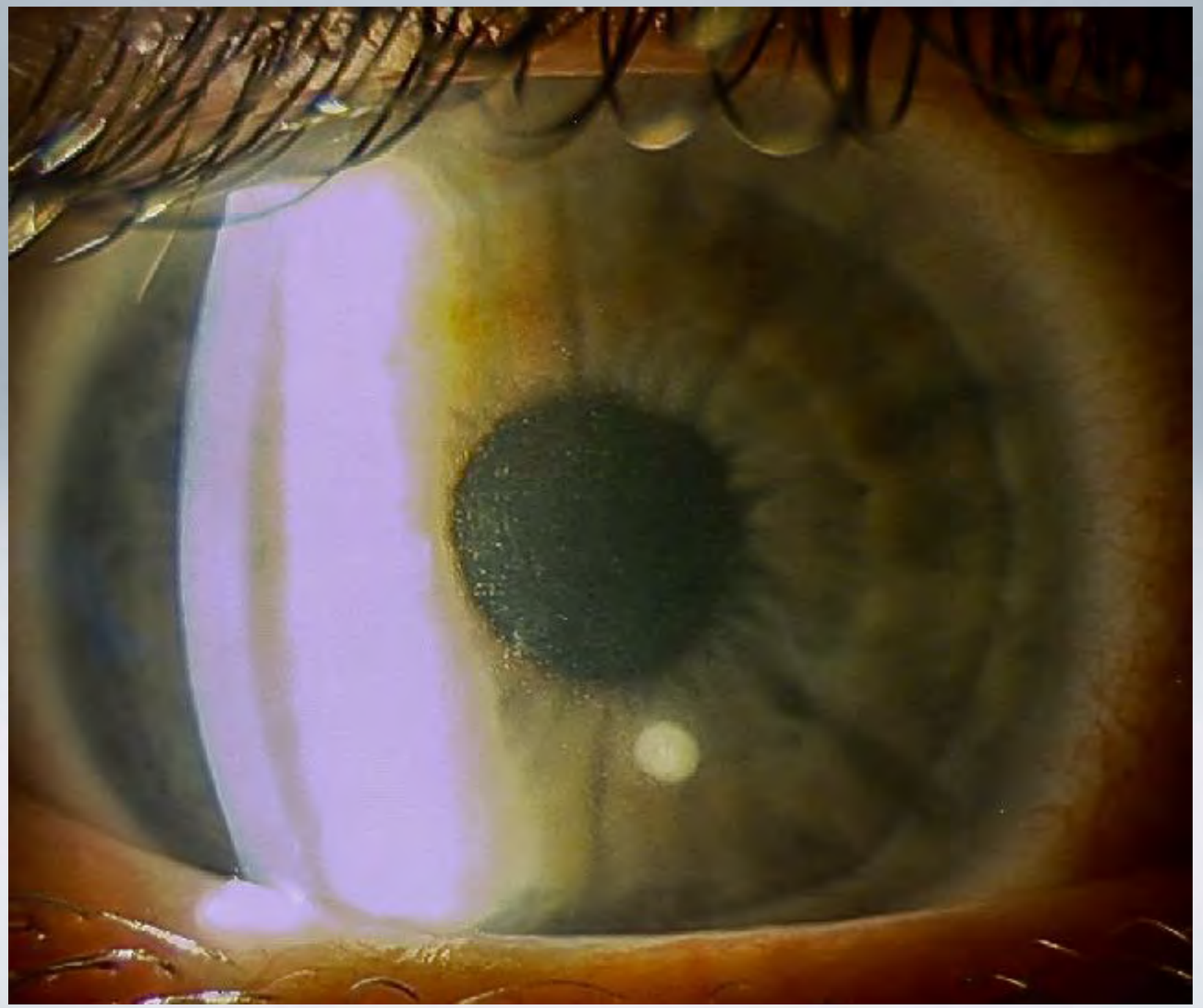


DELAYED HEALING

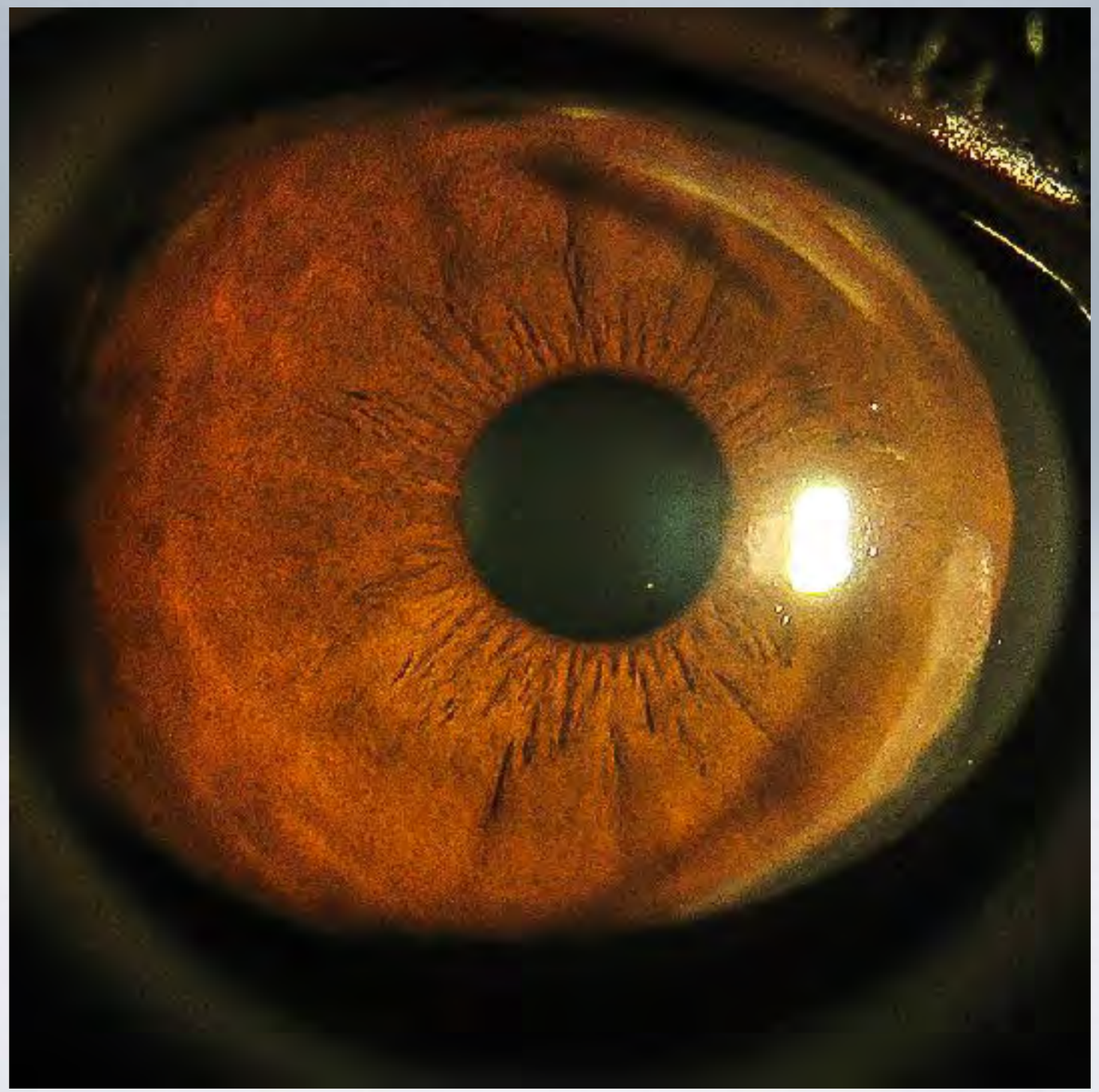
CORNEAL MELT



PERIPHERAL INFILTRATES

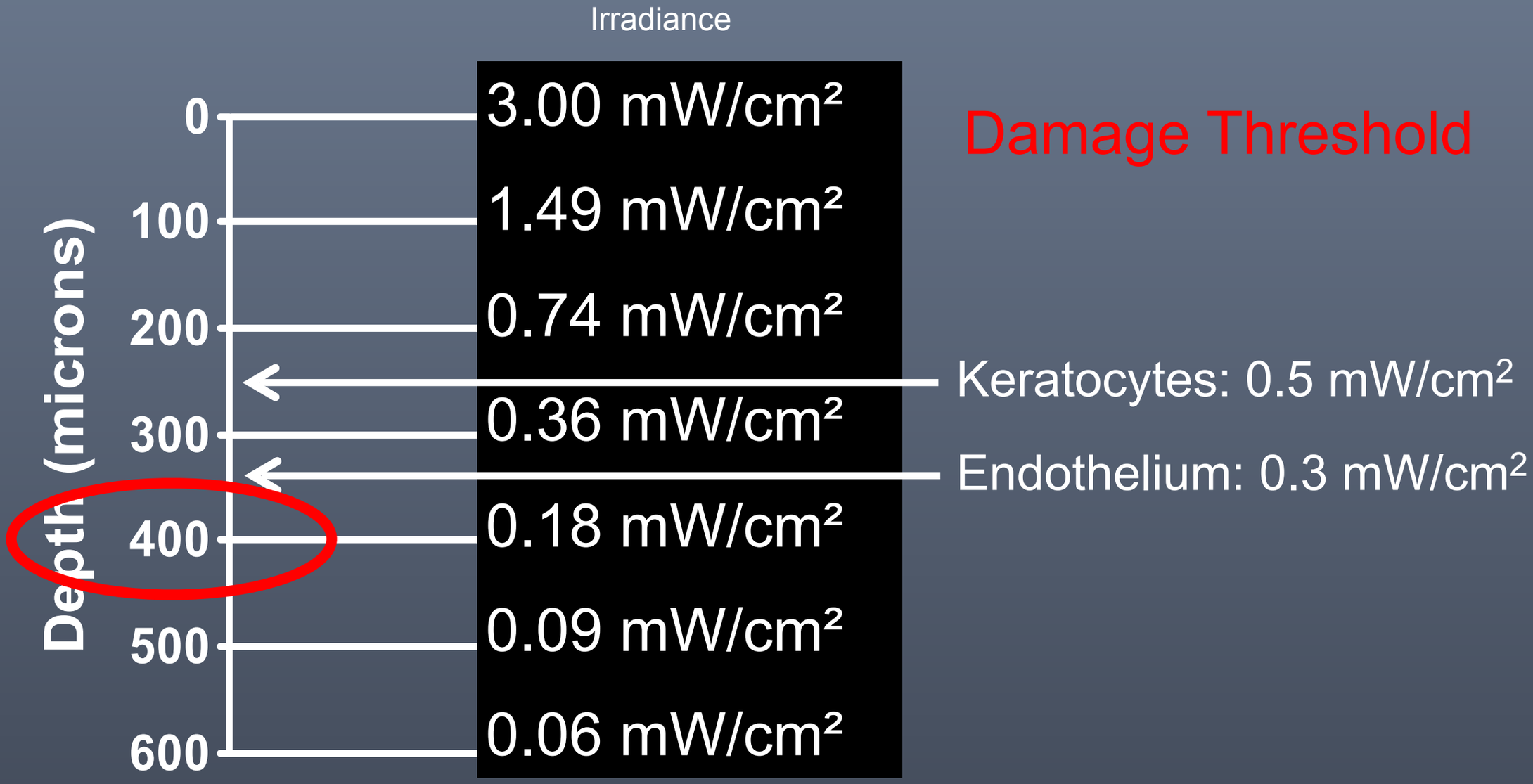


PERIPHERAL INFILTRATES



ENDOTHELIAL DAMAGE

UVA Corneal Absorption in Presence of Riboflavin



ORIGINAL ARTICLE

Contact Lens-Assisted Collagen Cross-Linking (CACXL): A New Technique for Cross-Linking Thin Corneas

Soosan Jacob MS, FRCS, DNB; Dhivya Ashok Kumar, MD; Amar Agarwal, MS, FRCS, FRCOpth; Sushanth Basu, DO; Pratheek Sinha, BOptom; Ashvin Agarwal, MS

[*J Refract Surg.* 2014;30(6):366-372.]

Figure 2. Intraoperative anterior segment optical coherence tomography image showing the soft contact lens on the cornea. Note: The contact lens and riboflavin film contributed the additional 108 µm of treatment zone.

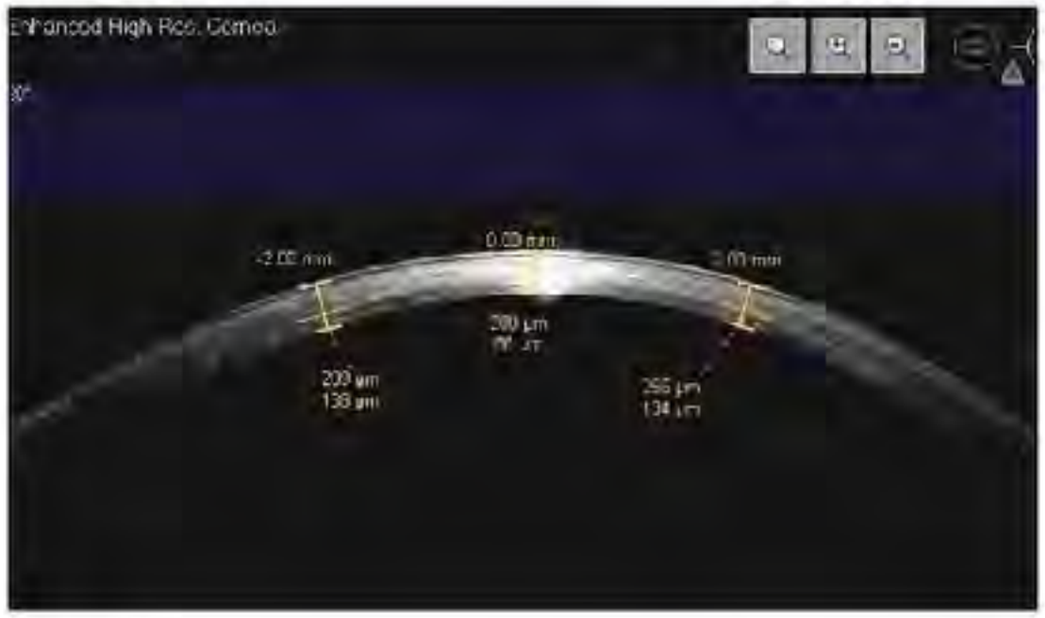


Figure 3. The postoperative stromal demarcation line seen at 1 month after contact lens-assisted corneal cross-linking as seen with anterior segment optical coherence tomography.

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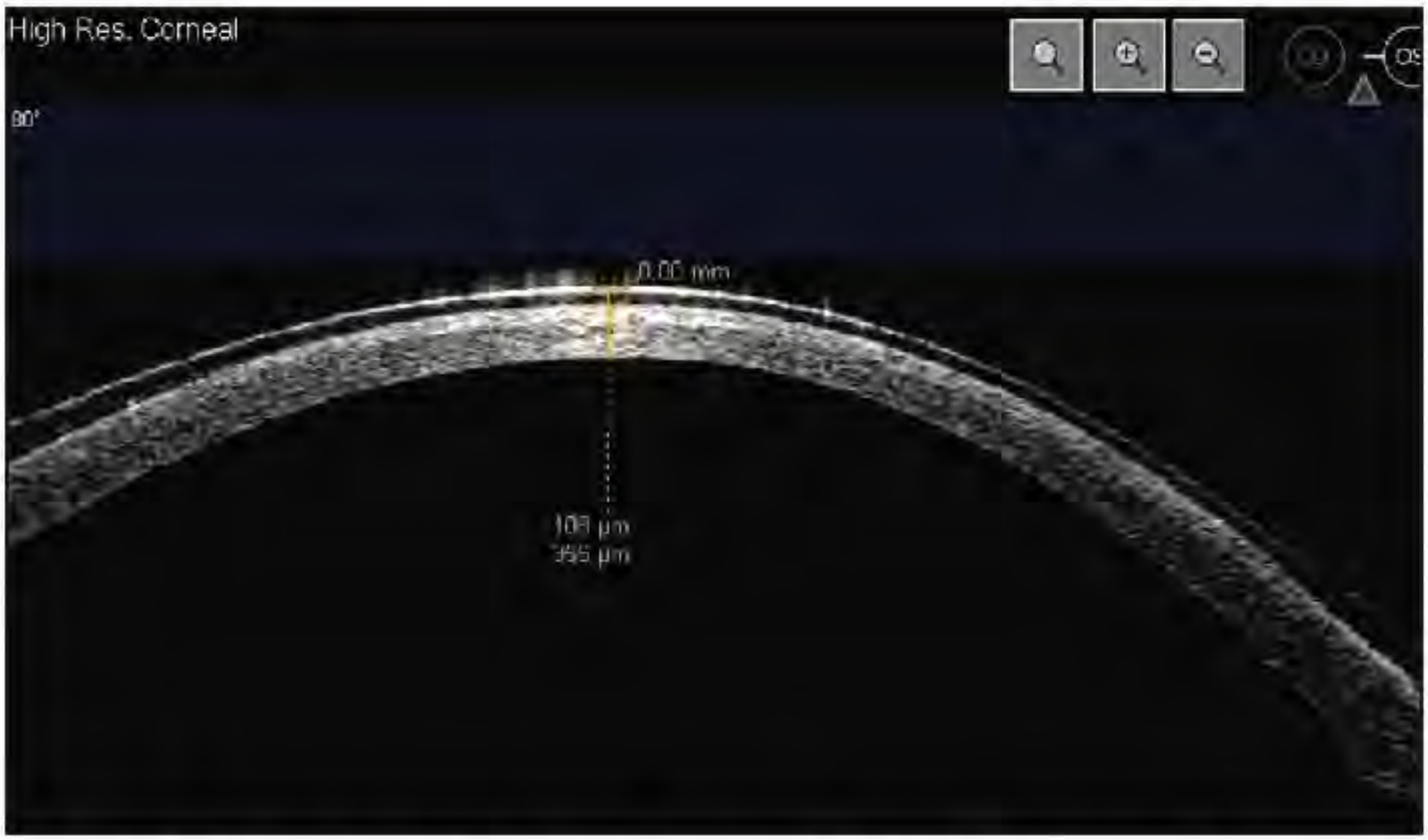


Figure 2. Intraoperative anterior segment optical coherence tomography image showing the soft contact lens on the cornea. Note: The contact lens and riboflavin film contributed the additional 108 µm of treatment zone.

ORIGINAL ARTICLE

In Vivo Confocal Microscopy After Contact Lens-Assisted Corneal Collagen Cross-linking for Thin Keratoconic Corneas

Cosimo Mazzotta, MD, PhD; Soosan Jacob, MS, FRCS, DNB; Amar Agarwal, MS, FRCS, FRCOphth; Dhivya Ashok Kumar, MD

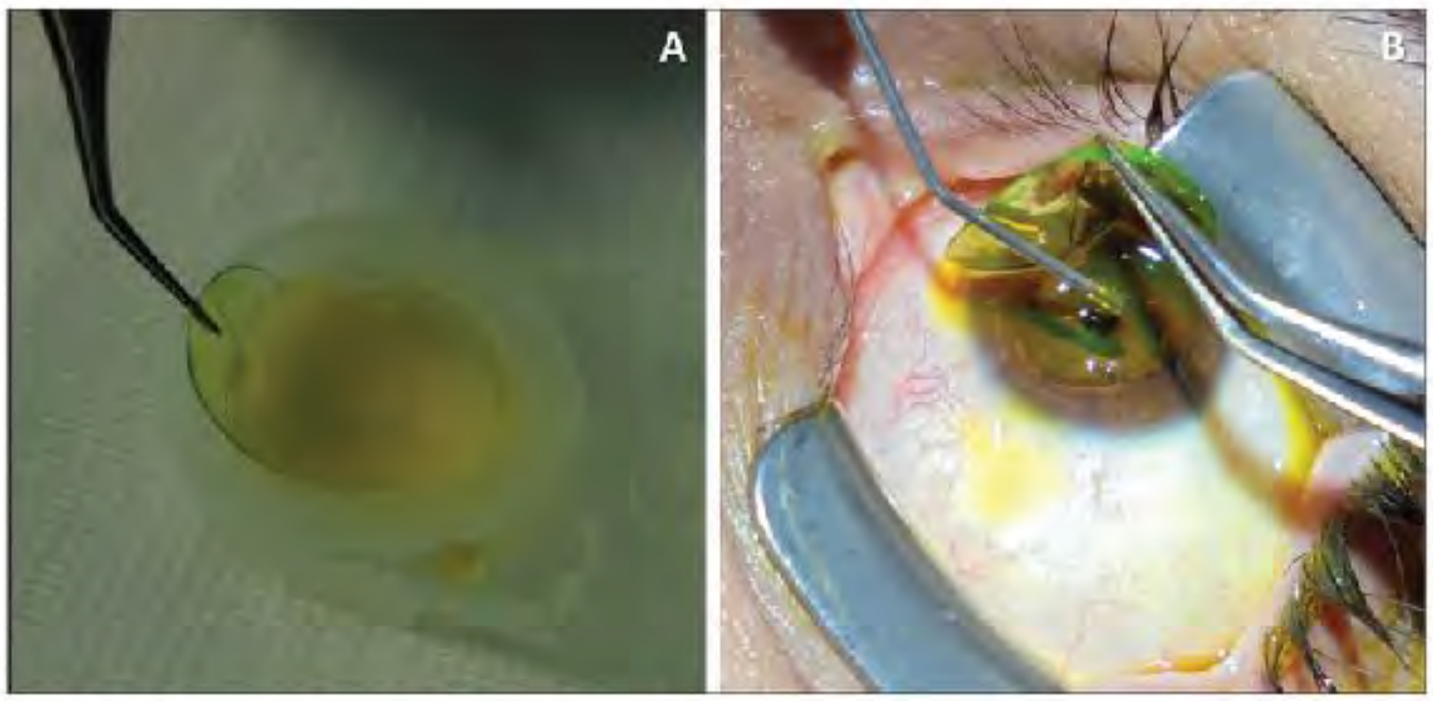


Figure 1. (A) Contact lens immersed in riboflavin 0.1% during contact lens-assisted corneal collagen cross-linking. (B) Riboflavin 0.1% solution application under and above the contact lens during contact lens-assisted cornea collagen cross-linking treatment.

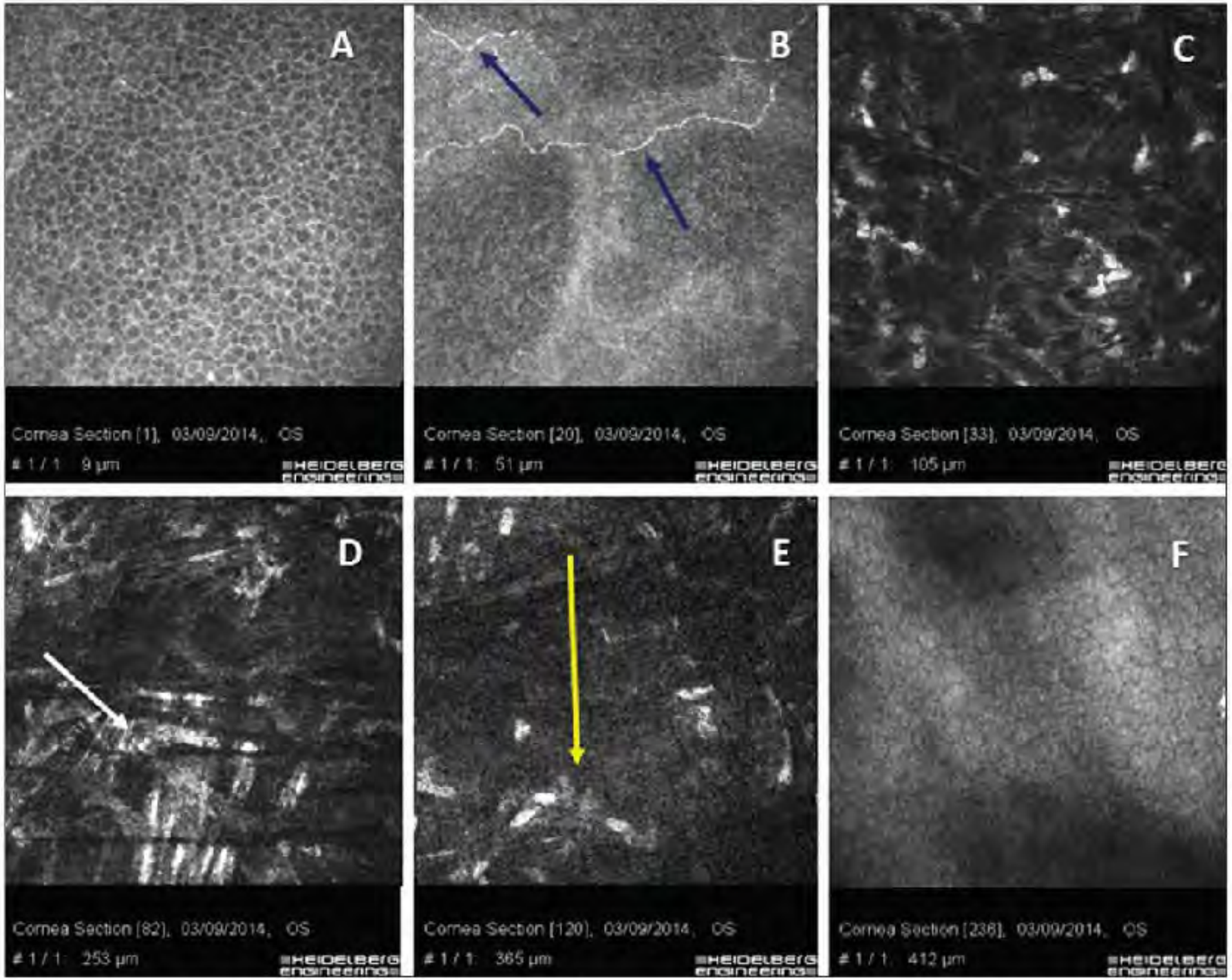
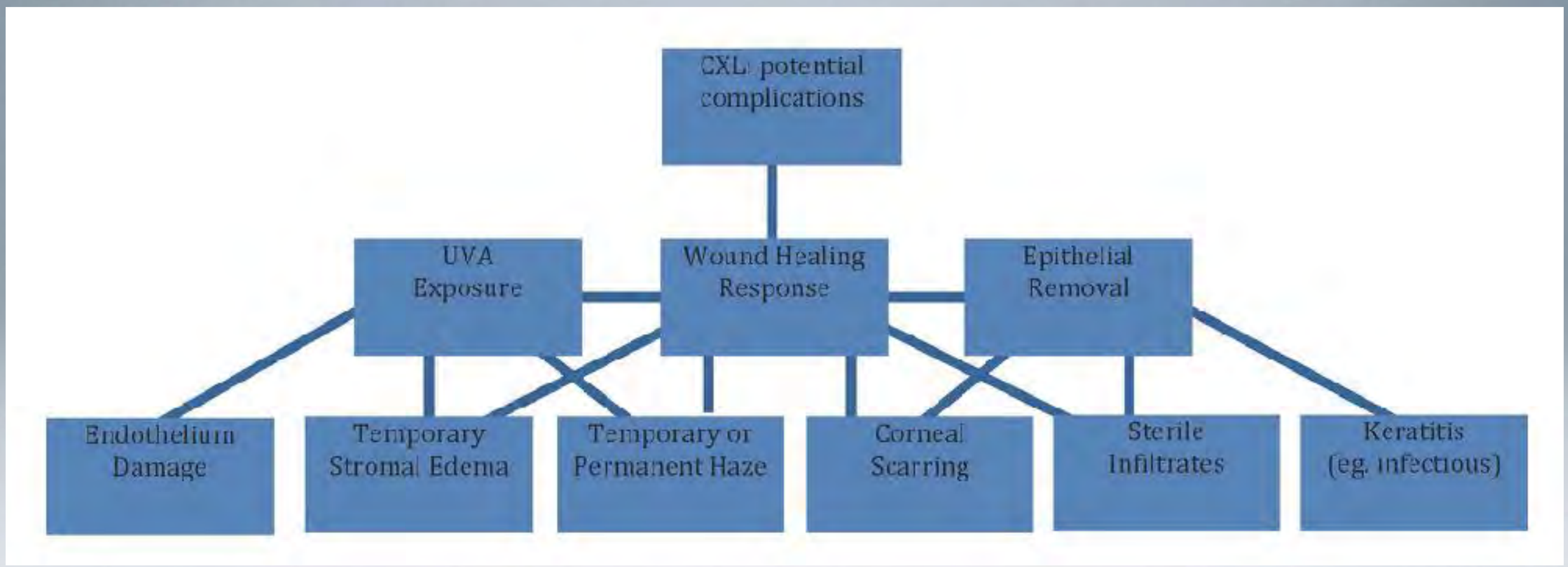


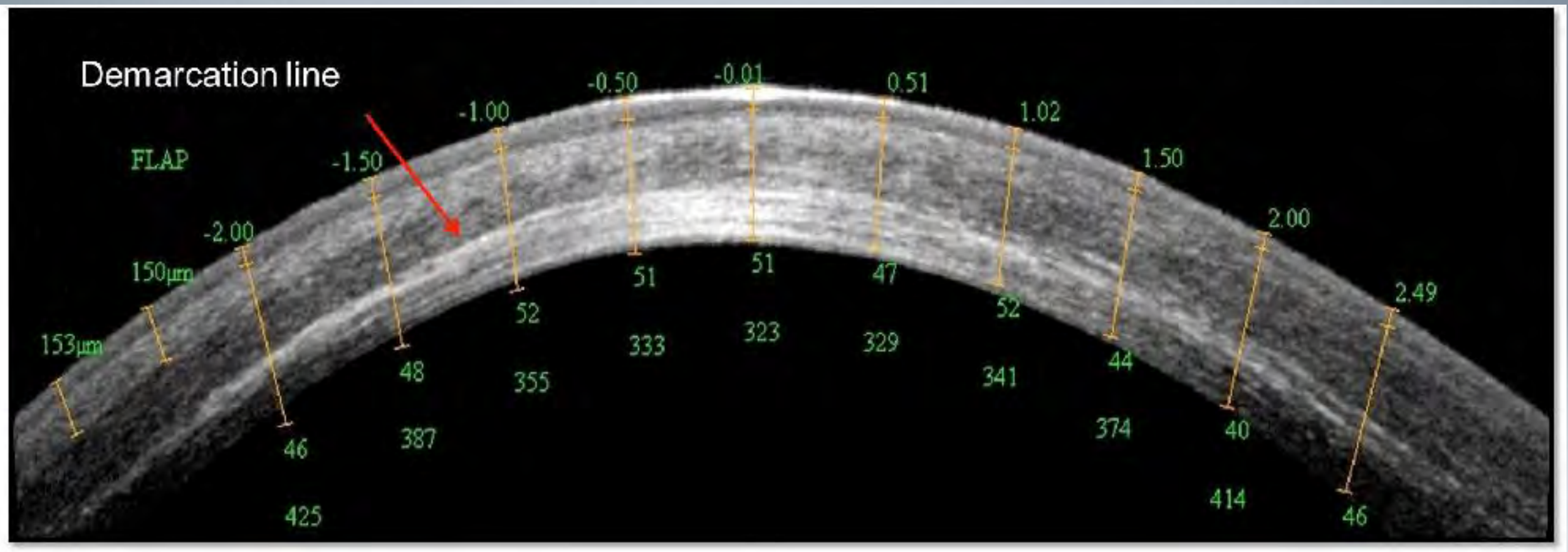
Figure 3. In vivo confocal microscopy analysis performed 3 months after treatment. Scan A shows regular basal epithelium mosaic and cell borders. Scan B shows corneal reinnervation with the presence of subepithelial plexus fibers (blue arrows). Scan C shows initial keratocyte nuclei repopulation of the anterior stroma at 100 µm with progressive edema reduction. Scan D shows edema reduction of the deep stroma followed by gradual keratocyte repopulation and hyperreflective microbands of high molecular weight collagen (white arrow). Scan E shows demarcation line with the presence of activated repopulating keratocytes. Scan F shows regular endothelium mosaic.

COMPLICATIONS



Failed Remodeling

EPI-OFF CXL


Demarcation line
FLAP
-2.00
-1.50
-1.00
-0.50
-0.01
0.51
1.02
1.50
2.00
2.49
150µm
153µm
46
48
52
51
51
47
52
44
40
46
425
387
355
333
323
329
341
374
414

ORIGINAL ARTICLE

In Vivo Imaging of Riboflavin Penetration During Collagen Cross-linking With Hand-held Spectral Domain Optical Coherence Tomography

Chintan Malhotra, MS; Rohit Shetty, DNB, FRCS (Glasgow); Rajesh S. Kumar, MS; Himabindu Veluri, MS; Harsha Nagaraj, MS; K. Bhujang Shetty, MS

ORIGINAL ARTICLE

Corneal Confocal Microscopy Following Conventional, Transepithelial, and Accelerated Corneal Collagen Cross-linking Procedures for Keratoconus

David Touboul, MD; Nathan Efron, PhD, DSc; David Smadja, MD; Caroline Garra; Delphine Praud; Florence Malet, MD; Joseph Colin, MD

Epithelium MUST be removed for efficacy

ORIGINAL ARTICLE

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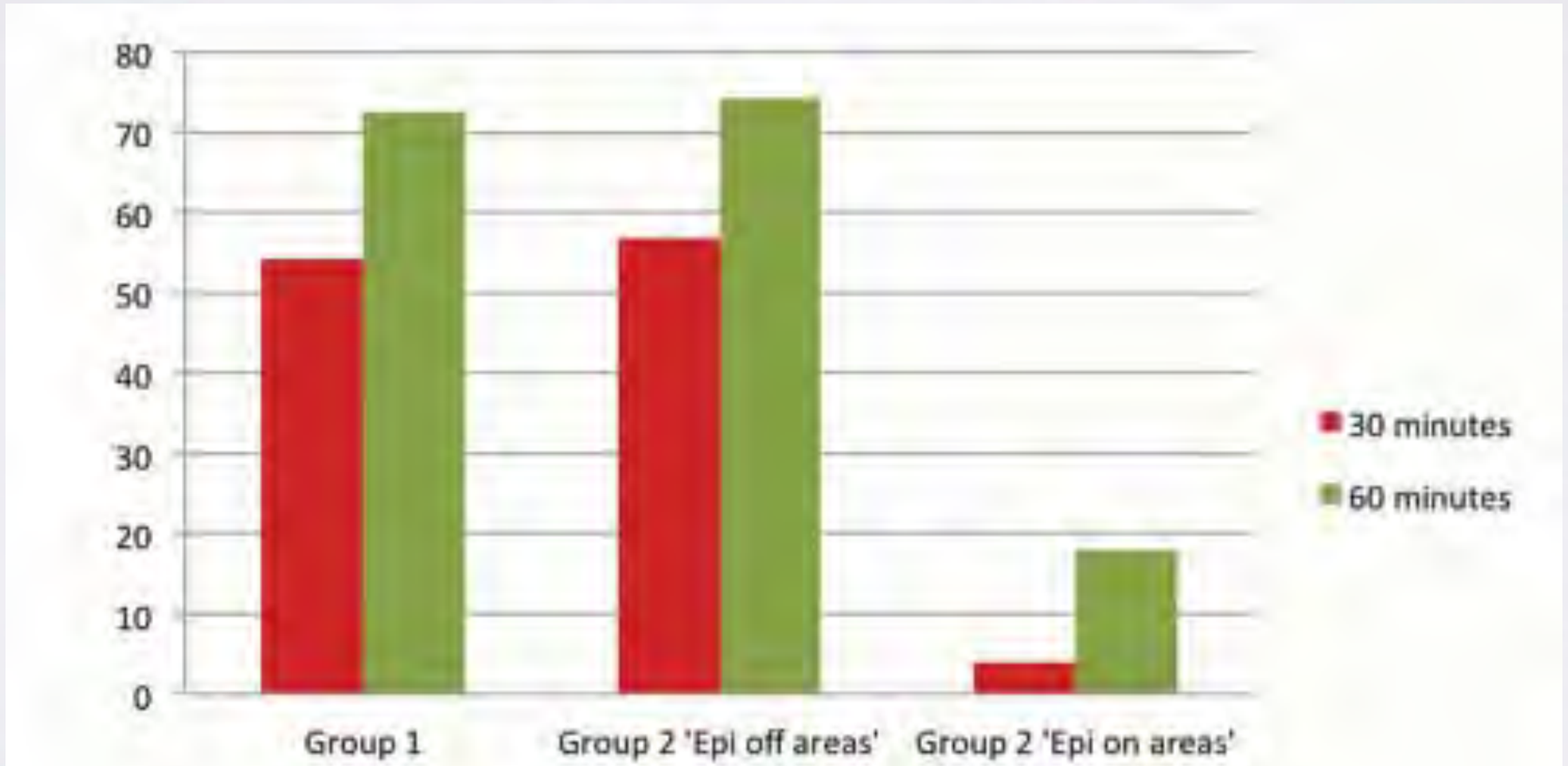

Group 1: Epithelium removed completely
Group 2: Epithelium removed in grid pattern

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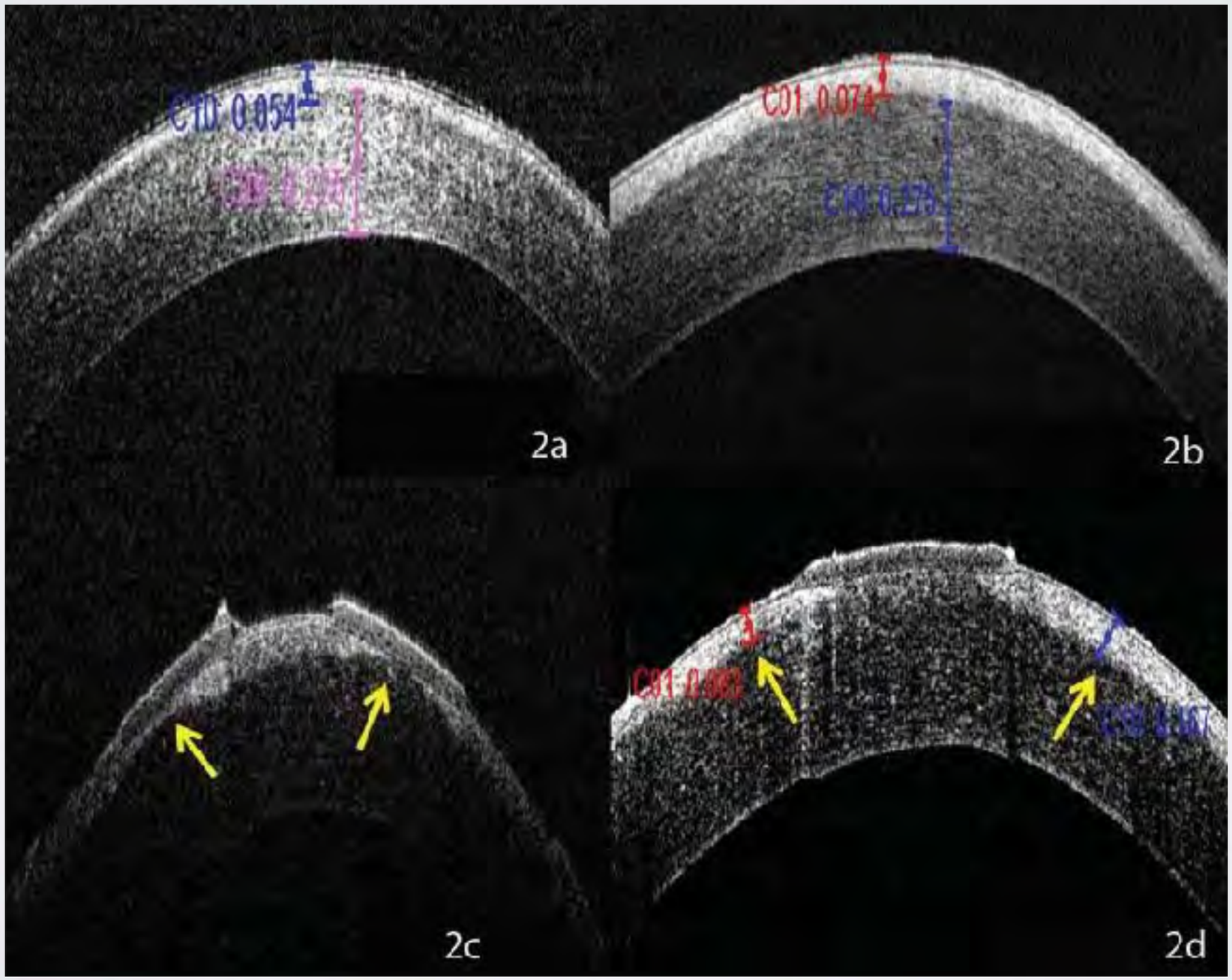
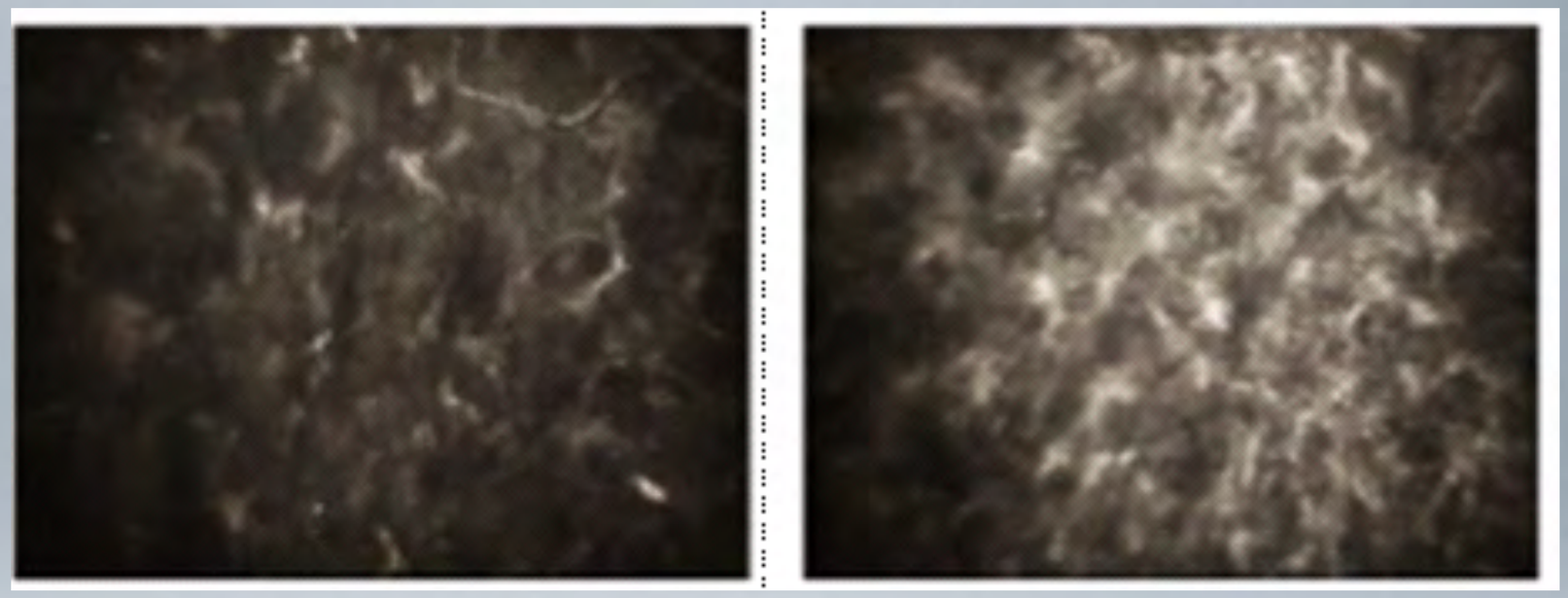


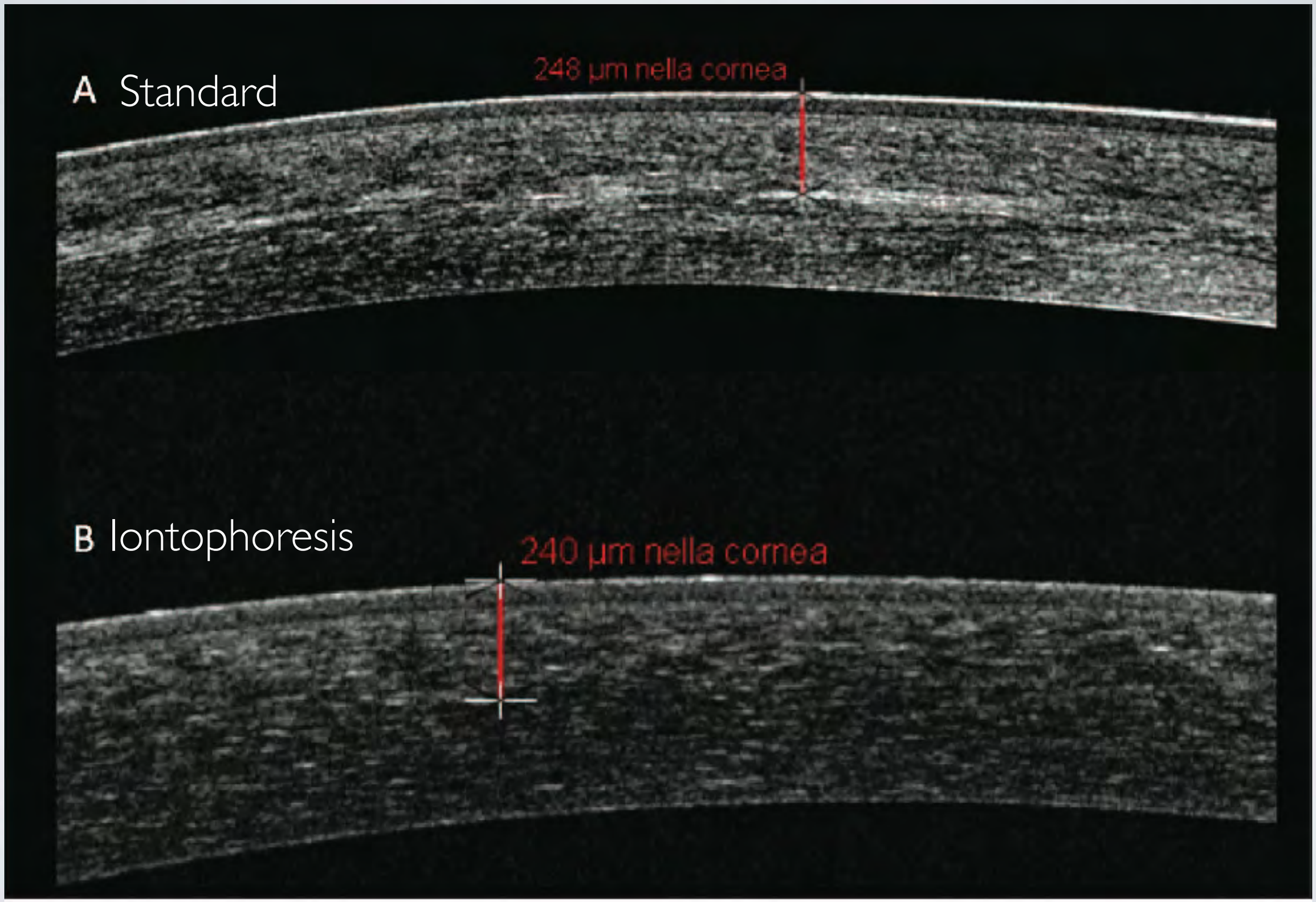
EPITHELIUM ON OR OFF?

- **Epithelium must be removed for efficacy**

Epi Off



Epi On

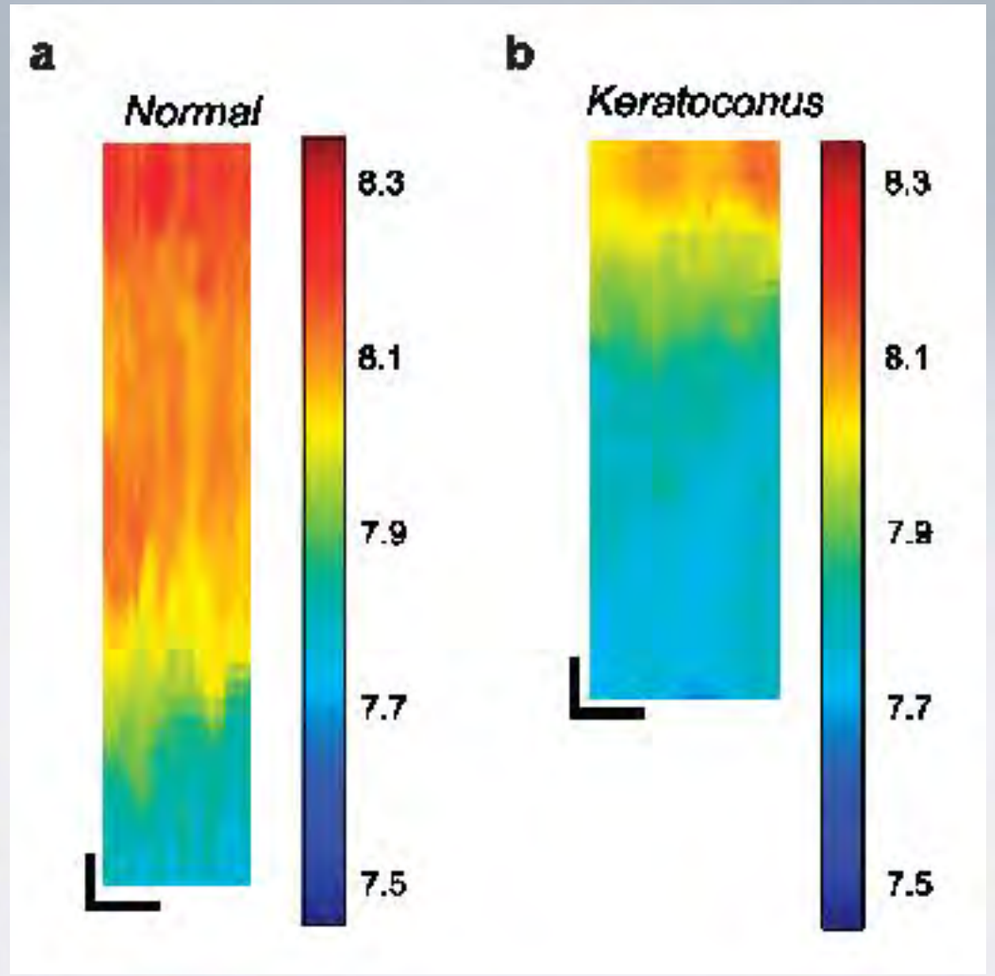

A Standard
248 µm nella cornea
B Iontophoresis
240 µm nella cornea

Cornea

Biomechanical Characterization of Keratoconus Corneas Ex Vivo With Brillouin Microscopy

Giuliano Scarcelli,[1,2] Sebastien Besner,[1,2] Roberto Pineda,[3] and Seok Hyun Yun[1,2,4]

[1]Wellman Center for Photomedicine, Massachusetts General Hospital, Cambridge, Massachusetts, United States
[2]Department of Dermatology, Harvard Medical School, Boston, Massachusetts, United States
[3]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, United States
[4]Harvard-MIT Health Sciences and Technology, Cambridge, Massachusetts, United States

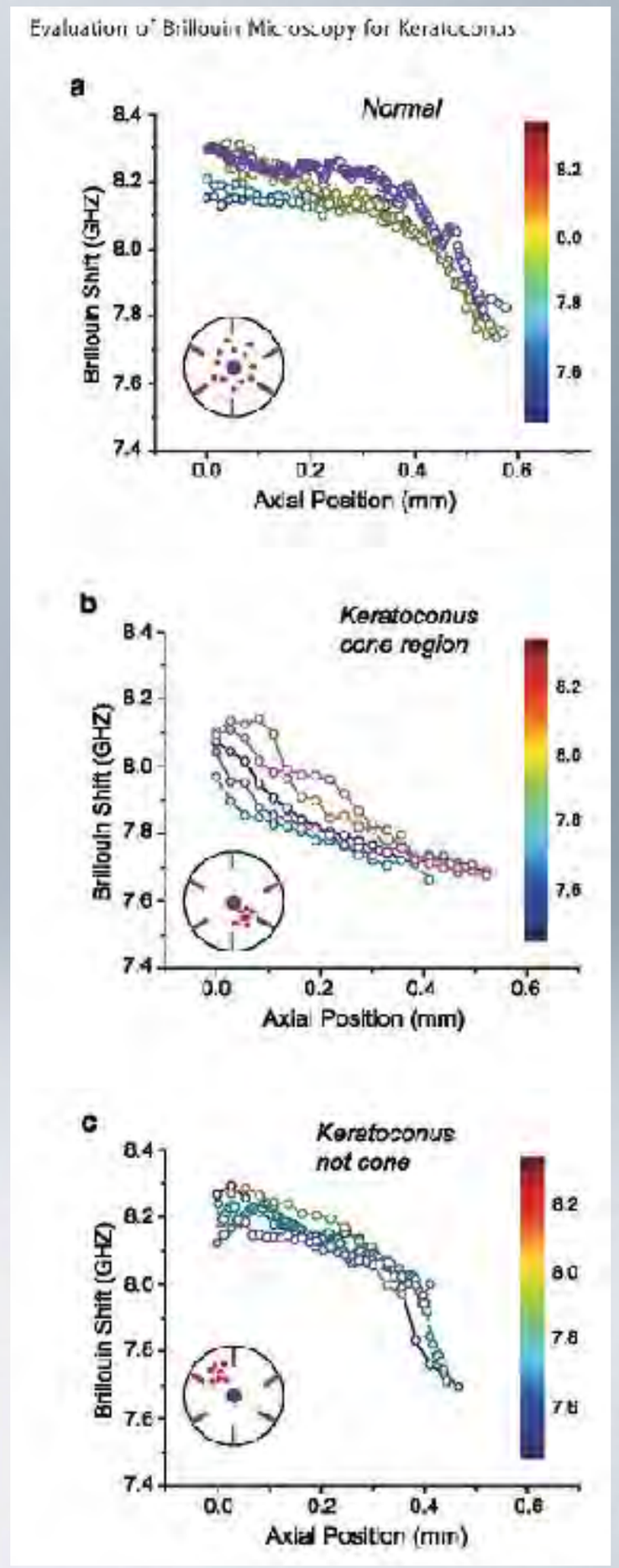


Cornea

Biomechanical Characterization of Keratoconus Corneas Ex Vivo With Brillouin Microscopy

Giuliano Scarcelli,[1,2] Sebastien Besner,[1,2] Roberto Pineda,[3] and Seok Hyun Yun[1,2,4]

[1]Wellman Center for Photomedicine, Massachusetts General Hospital, Cambridge, Massachusetts, United States
[2]Department of Dermatology, Harvard Medical School, Boston, Massachusetts, United States
[3]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, United States
[4]Harvard-MIT Health Sciences and Technology, Cambridge, Massachusetts, United States

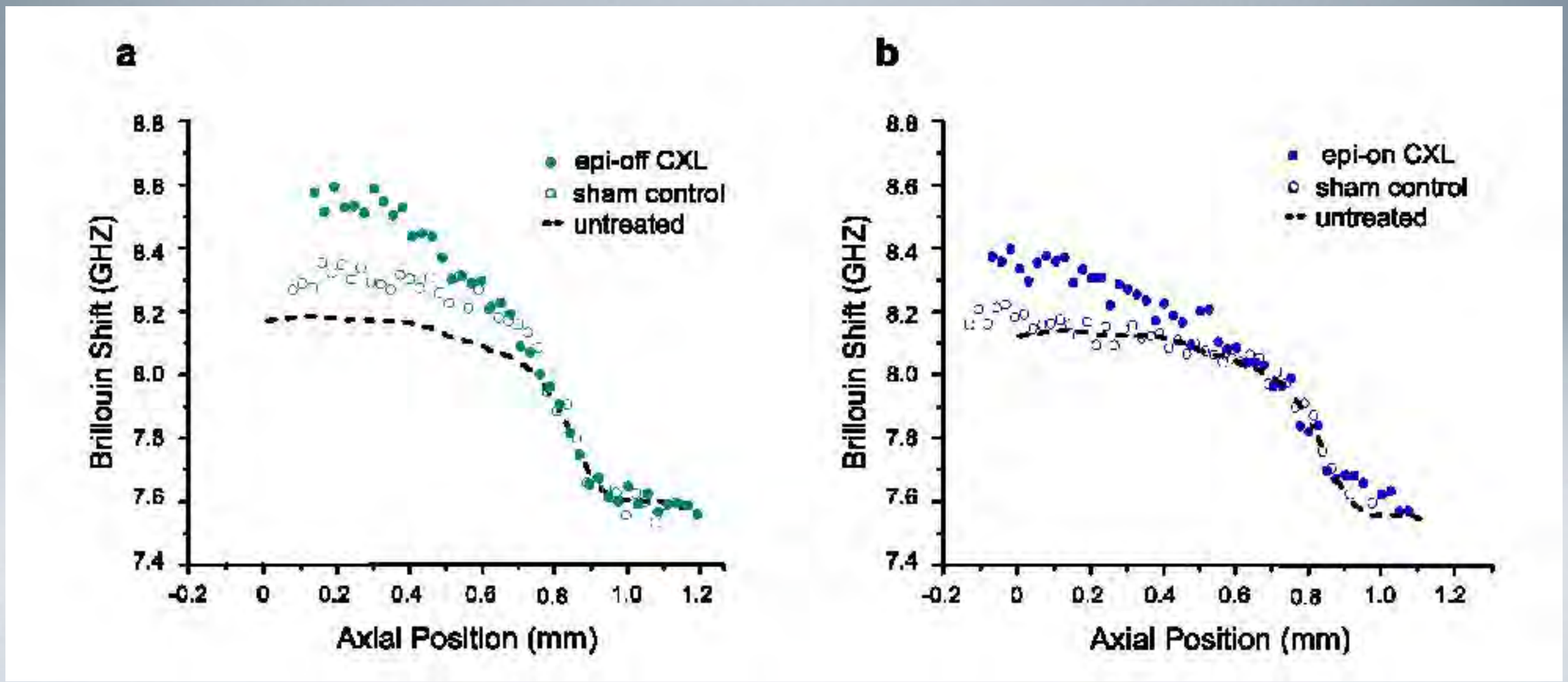


Cornea

Brillouin Microscopy of Collagen Crosslinking: Noncontact Depth-Dependent Analysis of Corneal Elastic Modulus

Giuliano Scarcelli,[1,2] Sabine Kling,[3] Elena Quijano,[1] Roberto Pineda,[4] Susana Marcos,[3] and Seok Hyun Yun[1,5]

Invest Ophthalmol Vis Sci. 2013;54:1418–1425)



Cornea

The Efficacy of Corneal Cross-Linking Shows a Sudden Decrease with Very High Intensity UV Light and Short Treatment Time

Jeremy Wernli,[1] *Silvia Schumacher,*[1] *Eberhard Spoerl,*[2] *and Michael Mrochen*[1]

(Invest Ophthalmol Vis Sci. 2013;54:1176–1180)

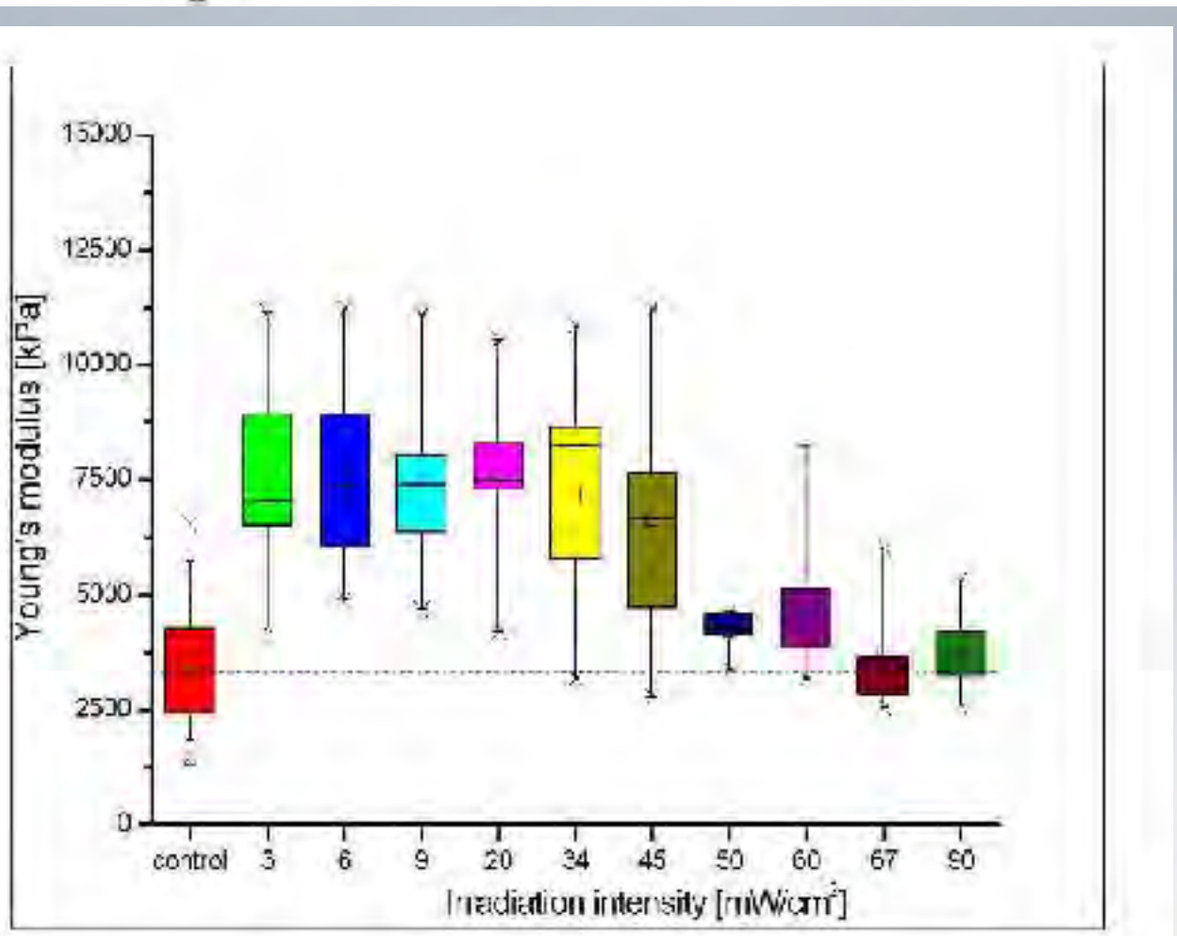


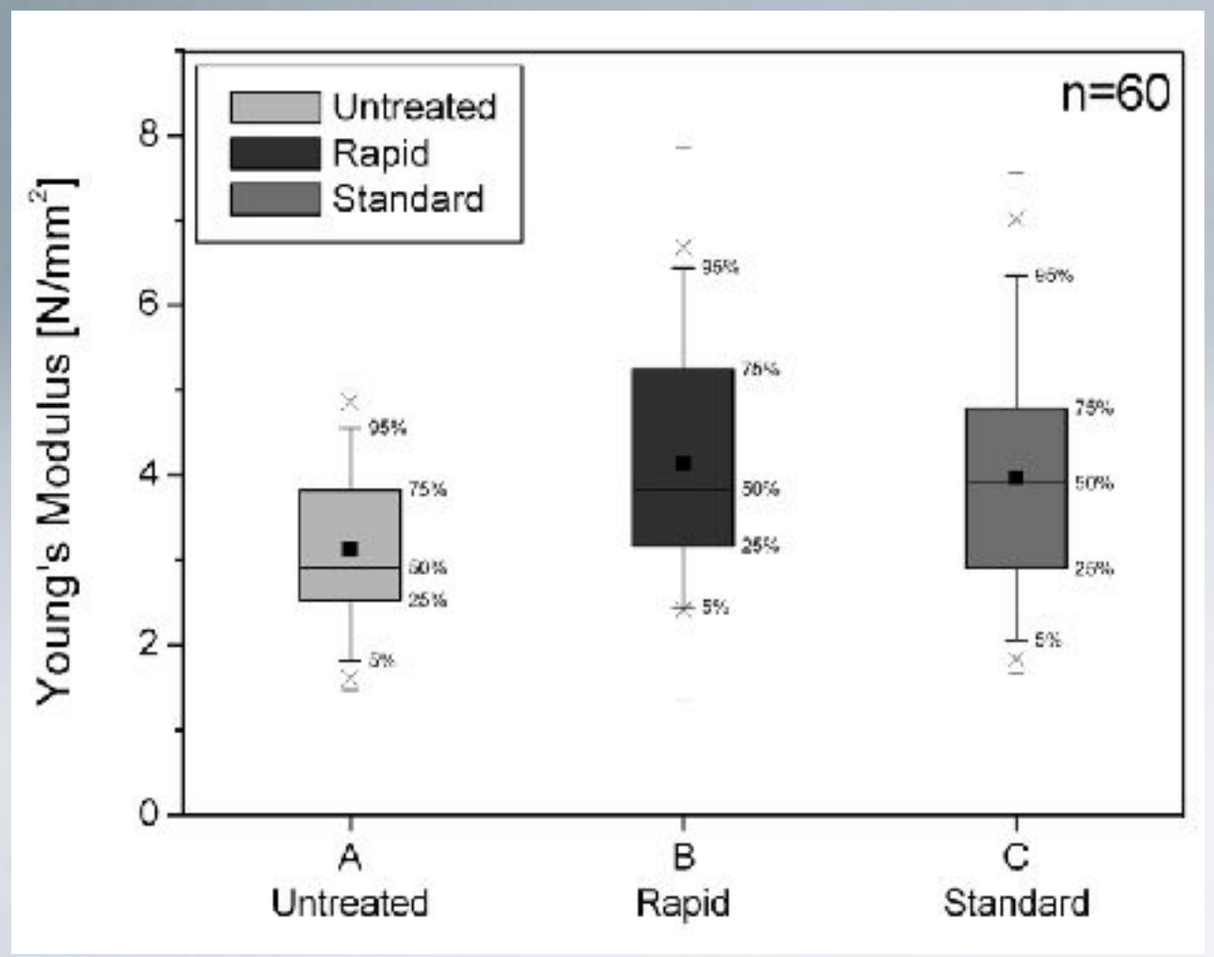
Figure 3. Young's moduli at 10% strain for the control and different treatment groups. Box plot whiskers indicate the fifth and the 95th percentiles, *crosses* (x) indicate the first and the 99th percentiles and *dashes* (-) indicate the minimum and maximum values within the groups.

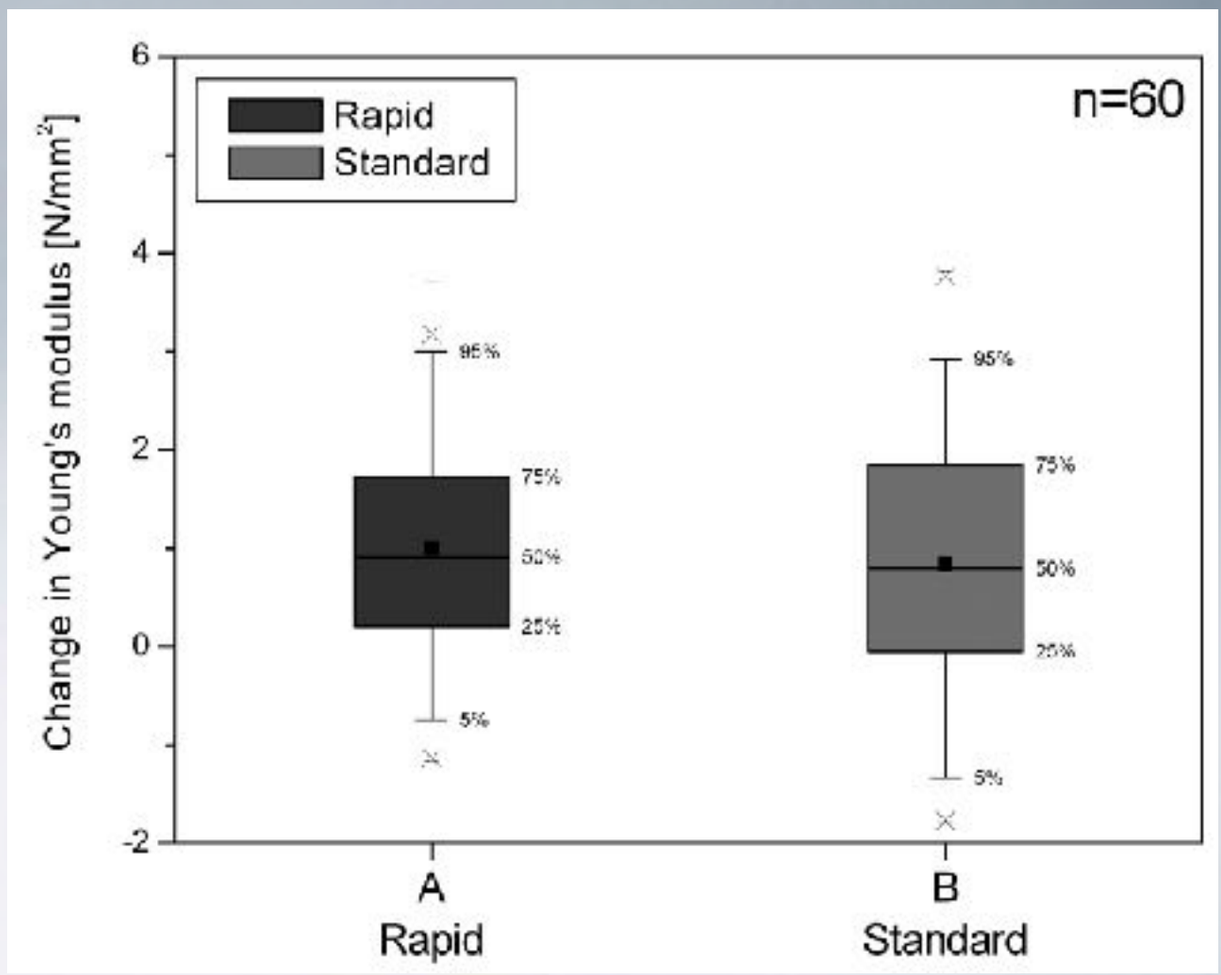
Cornea

Equivalence of Biomechanical Changes Induced by Rapid and Standard Corneal Cross-linking, Using Riboflavin and Ultraviolet Radiation

Silvia Schumacher, Lydia Oefliger, and Michael Mrochen

(*Invest Ophthalmol Vis Sci.* 2011;52:9048-9052)





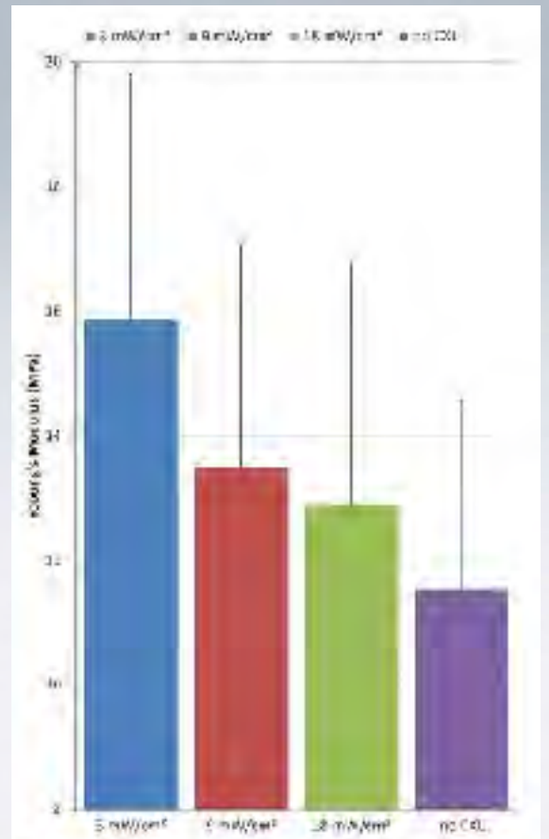
Cornea

Corneal Biomechanical Properties at Different Corneal Cross-Linking (CXL) Irradiances

Arthur Hammer,[1] Olivier Richoz,[1] Samuel Arba Mosquera,[2] David Tabibian,[1] Florence Hoogewoud,[1] and Farhad Hafezi[1,3]

[1]Department of Ophthalmology, Geneva University Hospitals, Geneva, Switzerland
[2]SCHWIND eye-tech-solutions, Kleinostheim, Germany
[3]Doheny Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, California, United States

Invest Ophthalmol Vis Sci. 2014;55:2881–2884.



CXL PROTOCOLS

- Epi-Off
  - Standard (30 min x 3mW/cm2)
  - Accelerated
    - 10 min x 5mW/cm2
    - 5 min x 18 mW/cm2
    - 3-4 min x 30mW/cm2
- Epi-on
  - “regular”
  - iontophoresis

PATIENT SELECTION

- Progressive keratoconus/ectasia
    - high risk for progression
        - adolescents
        - signs of progression
        - history of changing vision
- Issues with current visual correction

PROTOCOL

- Follow the evidence:
    - Epithelium-off
    - Standard protocol

CONCLUSIONS

- Complications can arise after CXL
- Requires diligence early postoperative
- Affects screening for CXL
- Affects patient and surgeon acceptance of protocols

CONCLUSIONS

- Variations in clinical protocols occurring faster than research into these protocol variations
- Variability in comparative results depending on the metric followed
- Best metrics to follow still undetermined

Thank You

USC Roski Eye Institute
Keck Medicine of USC

randlema@usc.edu