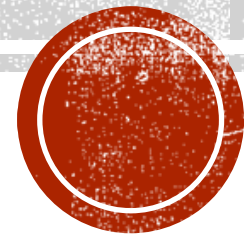# CORNEAL CROSSLINKING- WHAT SHOULD AN OPTOMETRIST KNOW

Pinakin Davey OD, PhD, FAAO, FOWNS

Professor Of Optometry

WesternU Director of Clinical Research

DISCLOSURES

Has a relevant financial relationship with

Sanofi, ZeaVision, Guardion Health and Innova systems as
a speaker or research / consultant

The content and format of this course is presented without commercial bias and
does not claim superiority and commercial product or service.

LEARNING OBJECTIVES

- Recollect basics of Keratoconus

- Know cornea signs of Keratoconus

- Understand the principles behind crosslinking

- Understand the FDA approved protocols

- Understand research behind crosslinking - epithelium off versus epithelium on

- Understand the accelerated protocol

KERATOCONUS

- Keratoconus is a
  - progressive
  - bilateral ("true unilateral keratoconus does not exist." Global consensus)
  - asymmetric
  - ectatic disease
  - progressive corneal thinning
  - protrusion of the cornea leading to irregular astigmatism
  - visual deterioration
- Incidence 1 in 2000 (probably underestimated)
- Prevalence 0.054% USA Worldwide Big range 0.0003% to 2.3%

RISK FACTORS

- Down syndrome
- relatives of affected patients especially if they are young
- ocular allergy
- ethnic factors
- mechanical factors, eg, eye rubbing

- floppy eyelid syndrome
- atopy
- connective tissue disorders (Marfan syndrome)
- Ehlers-Danlos syndrome
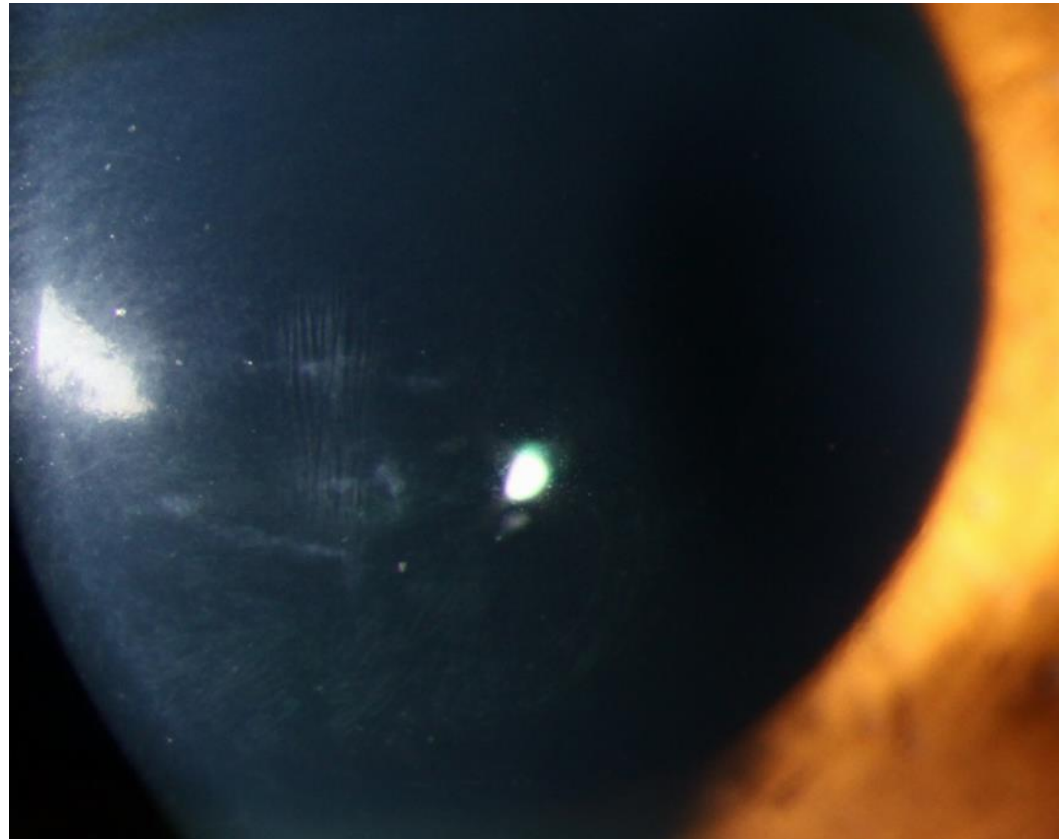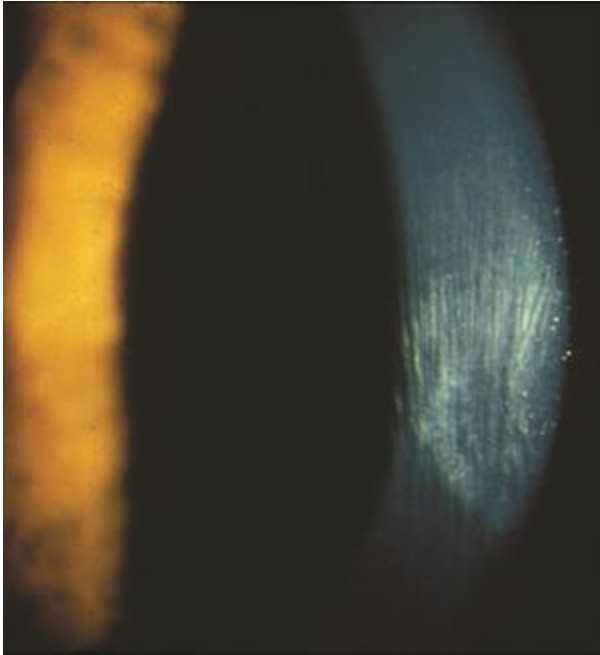- Leber congenital amaurosis
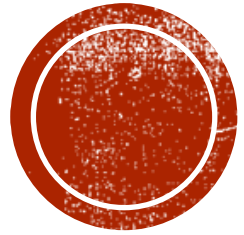
SPOT THE PATHOLOGY

NAME THE PATHOLOGY

Vogt's striae

- Stress lines in deep stroma and Descemet's membrane

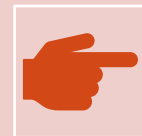- Can disappear upon application of mild pressure to lower eyelid

NAME THE SIGN
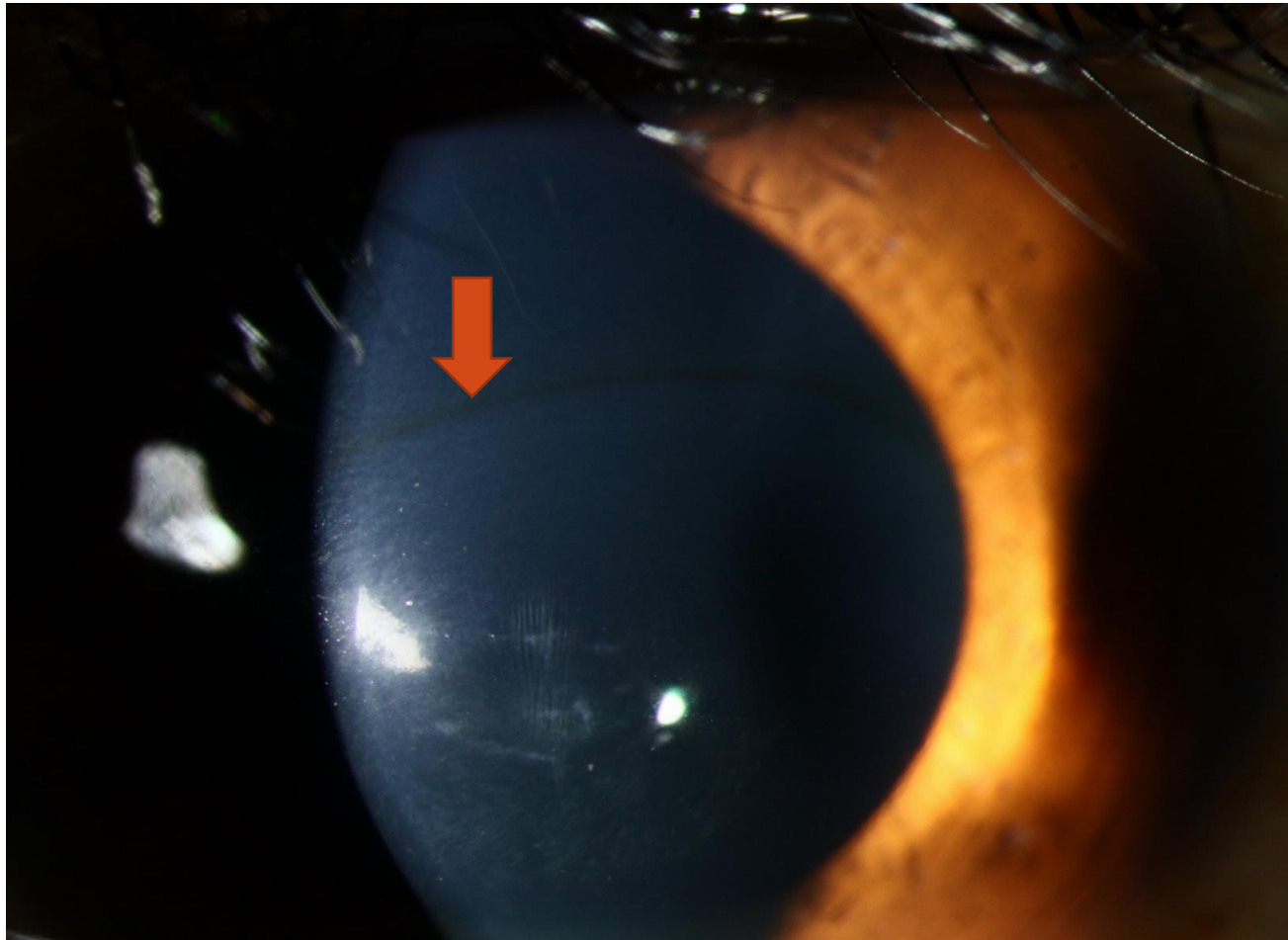

- ✔ Rizzuti's sign
- 🍂 Sharply focused bean of light near nasal limbus
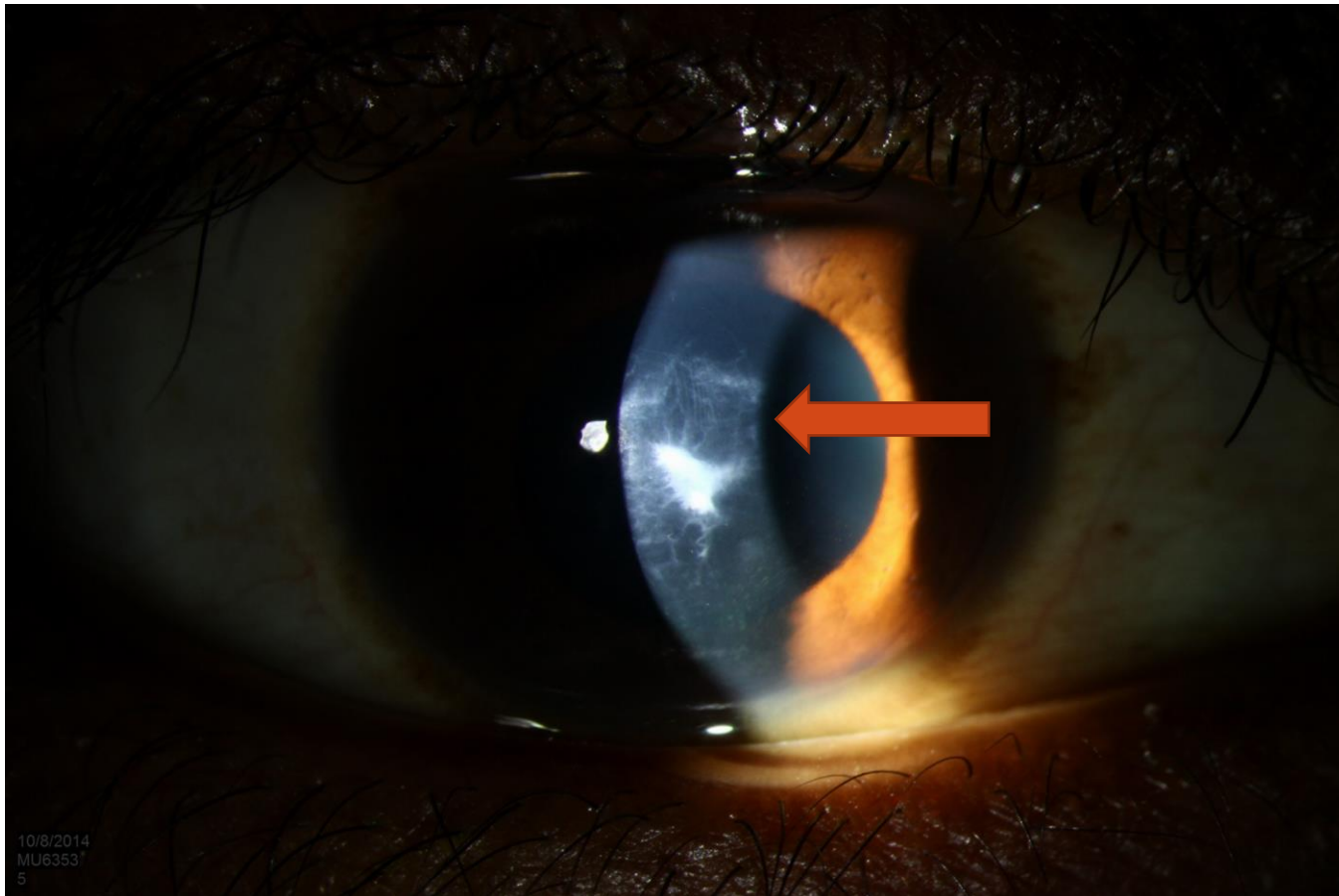- 👉 Usually, advanced keratoconus

NAME THE SIGN

Fleisher's ring

- Iron deposit on epithelium
- Cobalt blue filter might help identifying subtle lines

WHAT IS THIS?

- Opacities/scars
- Ruptures in Bowmans produces subepithelial or anterior stromal scars

NAME THE SIGN

Charlouex's oil droplet reflex

- Total internal reflection in conical cornea

- Dark shadow around mid periphery

- The dark shadow separates central bright red fundus reflex from red reflex in periphery

- Don't confuse it with galactosemia cataract-oil droplet opacity in lens

KERATOCONUS PATIENT ON SLIT LAMP

- Thin cornea at apex
- Increased endothelial reflection
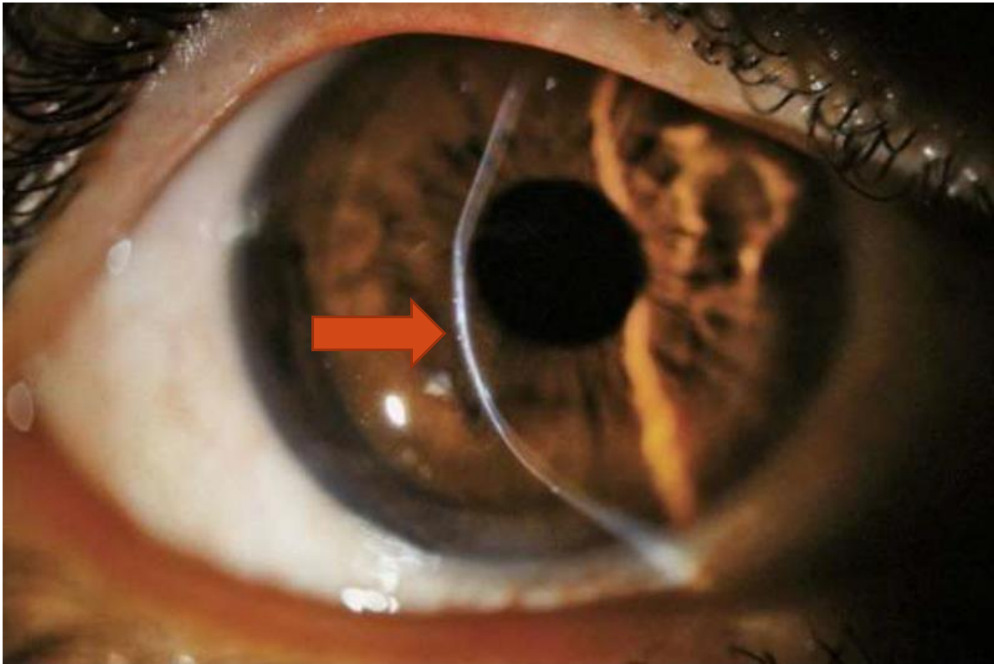
NAME THE SIGN

- Munson's sign

WHAT'S THIS?
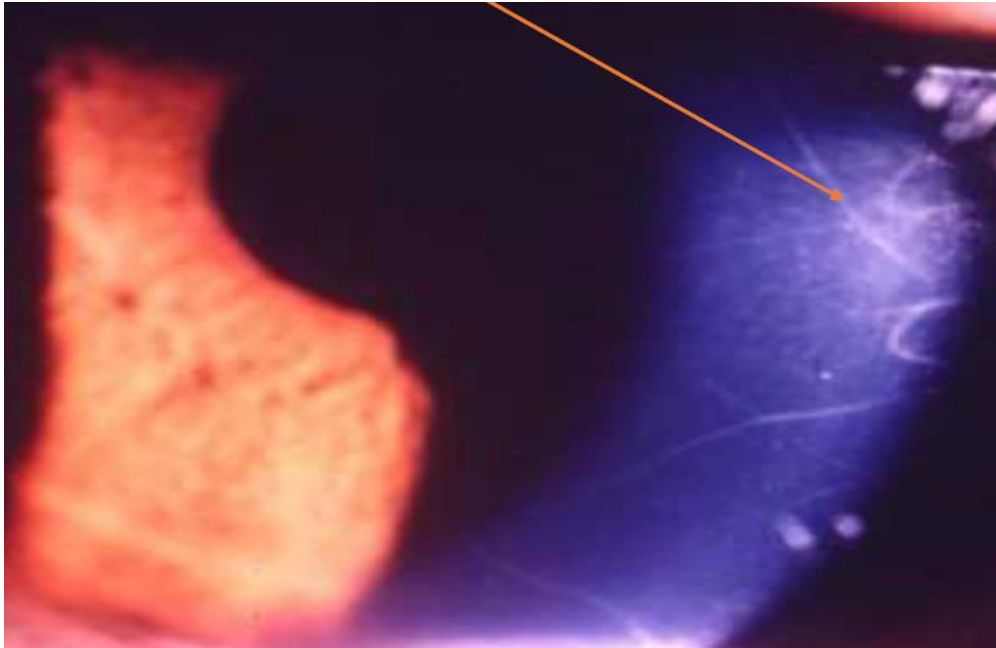
- Prominent corneal nerves

Occurred Suddenly
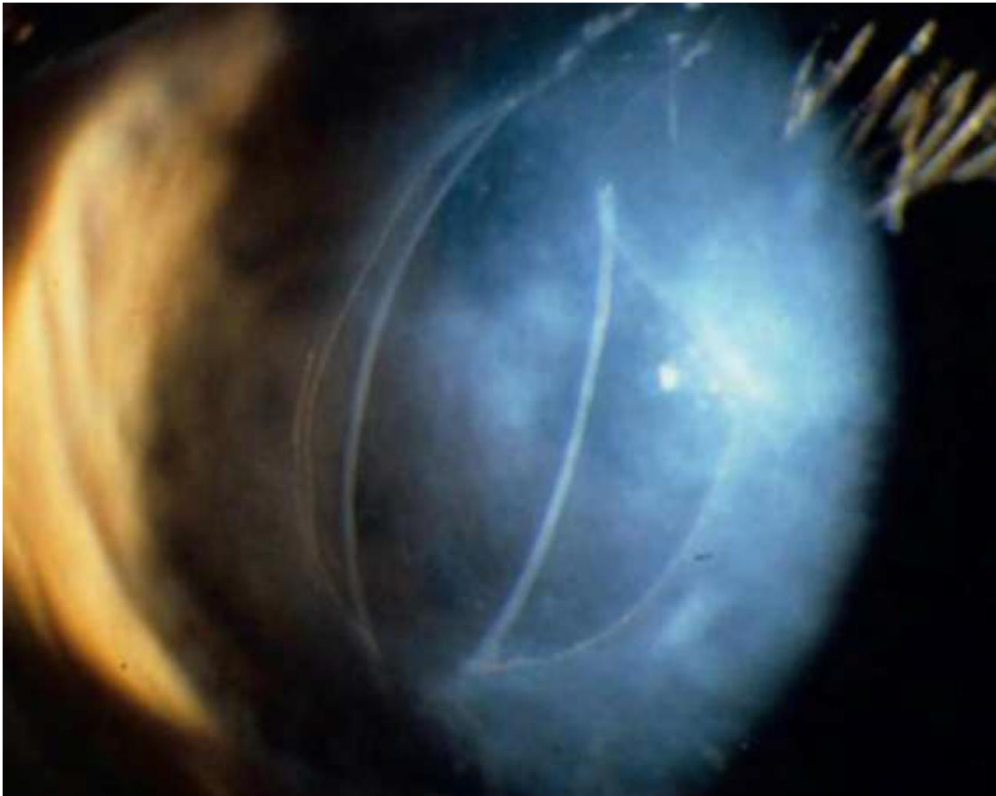
Acute hydrops

- Rupture of Descemet's membrane
- Sudden onset of redness and pain
- Sudden imbibition of aqueous humor into cornea
- Stromal edema

TYPES OF CONE

Round cone

Oval cone
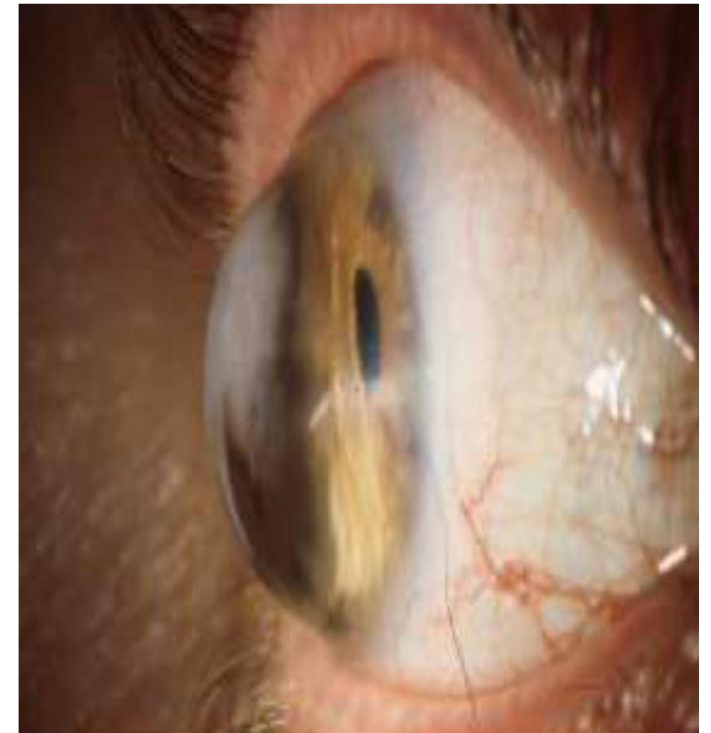
Globus cone

NATURAL HISTORY

- ## Keratoconus natural history:
  - ### Scarring
    - Overall: 14%
    - CL wear: 17%
    - CL wear & K >52D: 38%
  - ### Hydrops: 2.5%
  - ### Keratoplasty: 15-21.6%
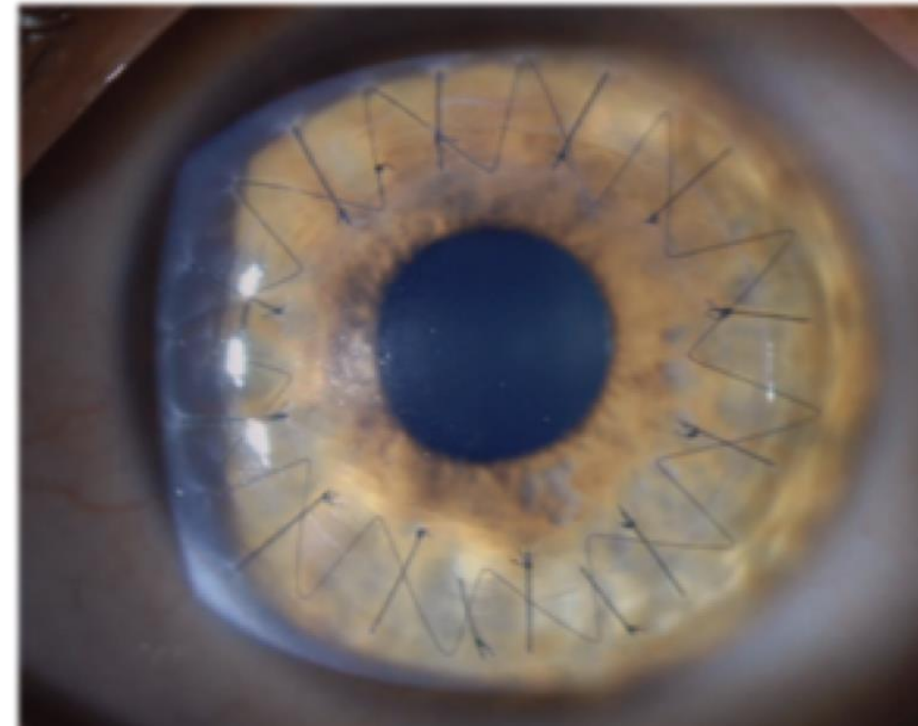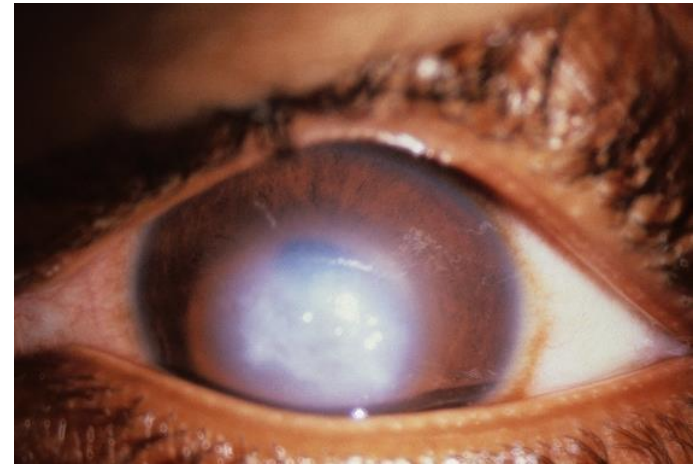
CLINICAL FINDINGS IN KERATOCONUS

Early to mid

Scissors reflex
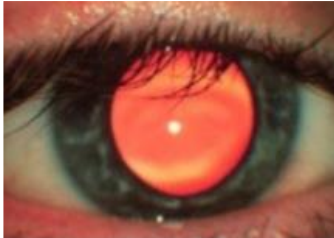
Charleux oil drop reflex
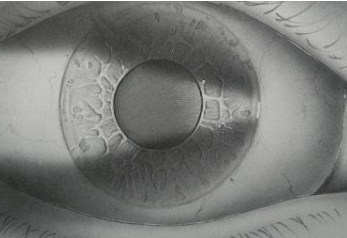
Rizzuti's reflex

Vogt's striae
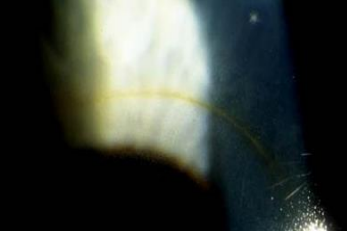
Fleischer's ring
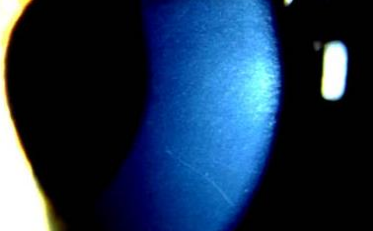
Prominent corneal nerves

Mid to late
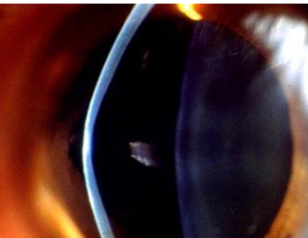
Corneal thinning
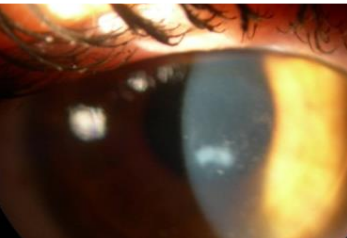
Scarring

Munson's sign
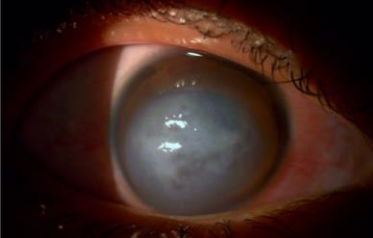
Corneal hydrops

Pictures: Courtesy of Jennifer Choo, OD, PhD

18

CLINICAL FINDINGS IN KERATOCONUS

- Example topography findings
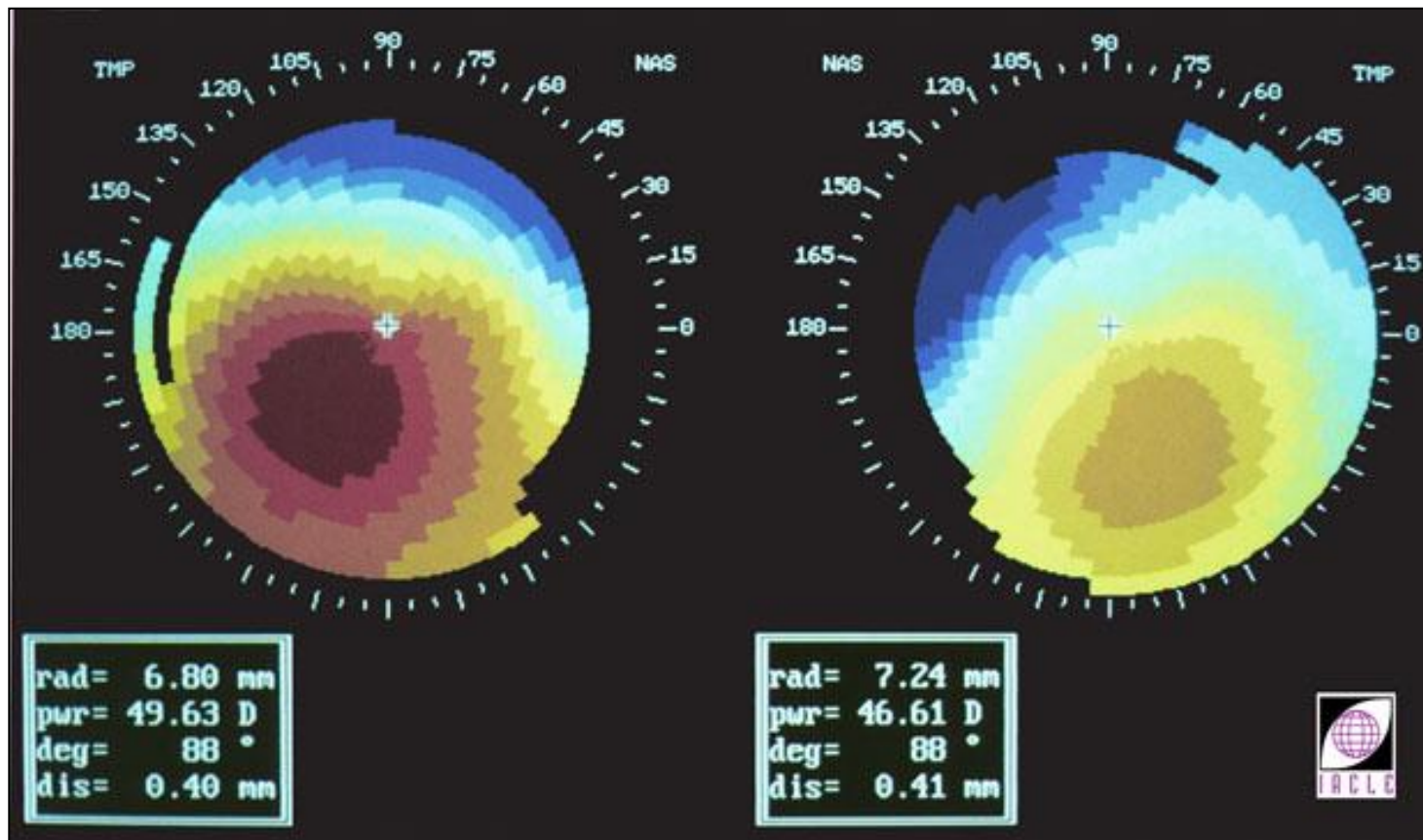
CLASSIFICATION SYSTEMS

Various systems

1. **Amsler-Krumeich** (gives stages)
    - K-readings, corneal shape (e-value), refraction, pachymetry, corneal scarring

2. **Keratometry only** (gives stages)
    - K-readings and mire quality

3. **Morphology only** (gives description)
    - Cone shape

4. **Corneal topography** (gives likelihood of having KC)
    - Kerato-refractive indices and predictive analysis

Spors

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CLASSIFICATION SYSTEMS

1. Amsler-Krumeich

CLASSIFICATION SYSTEMS

Stage	Findings
1	Eccentric steepening Myopia, induced astigmatism, or both <5.00 D K_m central <48.00 D
2	Myopia, induced astigmatism, or both from 5.00 to 8.00 D K_m central <53.00 D Absence of scarring Corneal thickness >400 microns
3	Myopia, induced astigmatism, or both from 8.00 to 10.00 D K_m central >53.00 D Absence of scarring Corneal thickness 300 – 400 microns
4	Refraction not measurable K_m central >55.00 D Central corneal scarring Corneal thickness < 200 microns

▪ Kératocõne classique et kératocône fruste; arguments unitaires. Amlser M. *Ophthalmologica*. 1946 Feb-Mar;111(2-3):96-101.

CLASSIFICATION SYSTEMS

2. **Keratometry only**

Stage	K_m central Findings
Mild	< 48.00 D
Moderate	48.00 D to 54.00 D
Severe	> 54.00 D

| Grade 0 none | Grade 1 slightly wavy mires, <1/4 of the mire | Grade 2 mod. waviness mod. doubling | Grade 3 extreme waviness extreme doubling >3/4 of the mire | Grade 4 parts missing |

Mire quality impacted

3. Morphology only

CLASSIFICATION SYSTEMS

3. **Morphology** only

Description	Morphology Findings
Nipple cone	Central location, diameter < 5 mm
Oval (sagging) cone	Diameter 5 to 6 mm
Globus cone	Diameter > 6 mm

Nipple cone   Oval cone   Globus cone
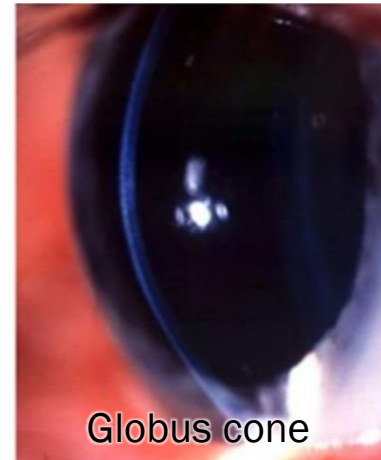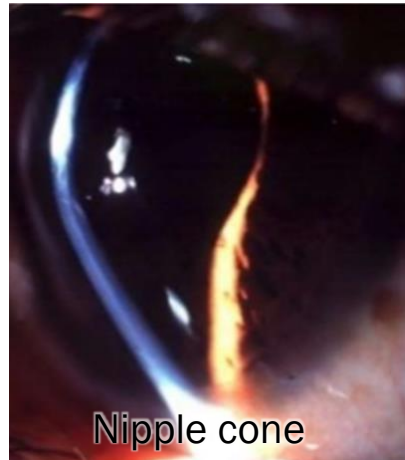
CORNEAL TOPOGRAPHY CLASSIFICATION SYSTEMS

- Rabinowitz (1999), KC screening

ROUND · OVAL · SUPERIOR STEEPENING · INFERIOR STEEPENING · IRREGULAR

SYMMETRIC BOWTIE WITH SKEWED RADIAL AXIS · ASYMMETRIC BOWTIE WITH INFERIOR STEEPENING · ASYMMETRIC BOWTIE WITH SUPERIOR STEEPENING · ASYMMETRIC BOWTIE WITH SKEWED RADIAL AXIS · SYMMETRIC BOWTIE

- K >47.20D
- I-S >1.40D
- AST >1.50D
- SRAX >21°
- KISA% >100%

Rabinowitz, Y.S. and Rasheed, K., 1999. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. Journal of Cataract & Refractive Surgery, 25(10), pp.1327-1335.

CLASSIFICATION SYSTEMS

3. **Corneal topography**

▪ Rabinowitz (1999), KC screening

$$KISA\% = \frac{(K) \times (I - S) \times (AST) \times (SRAX) \times 100}{300}$$

▪ K = central keratometry value
▪ $I - S$ = (inferior) minus (superior) diopter value
▪ $SRAX$ = skewing of the radial axes
▪ AST = keratometric astigmatism (ΔK)
▪ *all values absolute

60-100 KC suspect
> 100 highly sensitive in identifying KC

Rabinowitz, Y.S. and Rasheed, K., 1999. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. Journal of Cataract & Refractive Surgery, 25(10), pp.1327-1335.

CLASSIFICATION SYSTEMS

3. **Corneal topography**

- Medmont E-300

Medmont output	What is it?	Abnormal
Axial curvature range	Flattest to steepest curvature range	>10.00D
e value	Corneal flattening from center to periphery	>0.80
I-S Index	Difference between average inferior and superior power	>1.40D
SAI	Surface Asymmetry Index (corneal power distribution)	>0.8
SRI	Surface Regularity Index (central corneal irregularity)	>1.0

CLASSIFICATION SYSTEMS

3. **Corneal topography**

- Medmont E-300

Normalized Axial Curvature Range
> 10.00 D indicates KC

This cornea: ≈18.00D
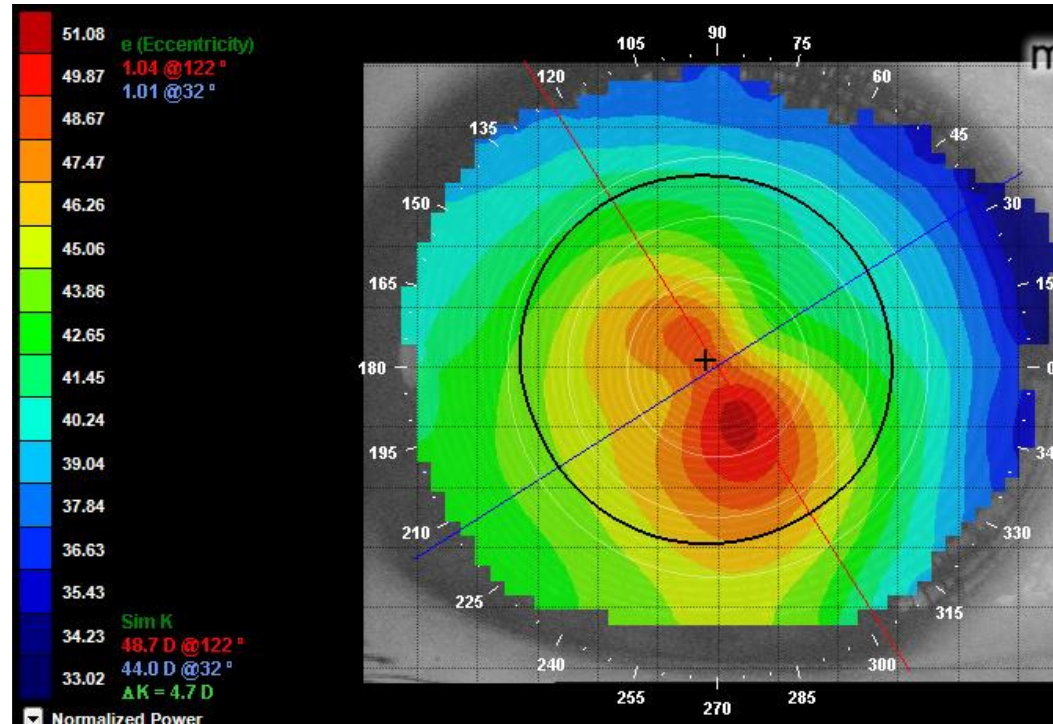
CLASSIFICATION SYSTEMS

3. **Corneal topography**

- Zeiss Atlas 9000

- PathFinder II module

- Evaluates cornea for several conditions, including KC

- Predictive analysis uses:
  - Corneal Irregularity Measurement
  - Toric Keratometric Mean
  - Shape factor (e-value square)

CROSS LINKING INDICATION

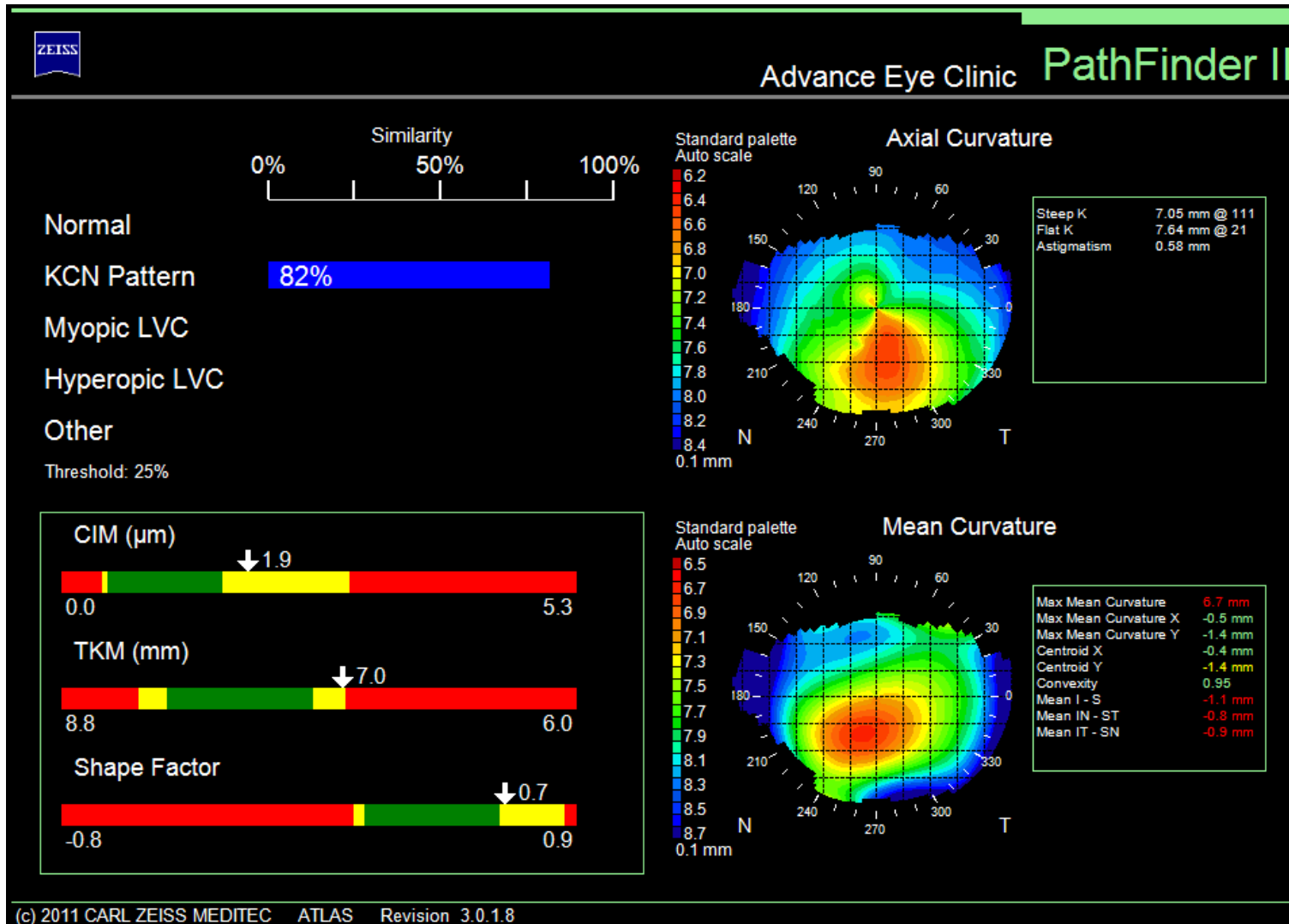- **Progressing keratoconus or post-LASIK ectasia**

- **Definition of progression is variable**

Global consensus series
  - At least 2 of these

- 1. Steepening of the anterior corneal surface
- 2. Steepening of the posterior corneal surface
- 3. Thinning and/or an increase in the rate of

  corneal thickness change

Clinical trials have used these criteria

Steepest keratometry (K_{max})	>1 D increase from baseline
Flattest keratometry (K_{min})	>1 D increase from baseline
Mean keratometry (K_{mean})	>0.75 D Increase from baseline
Corneal apex power	>1 D increase from baseline
Manifest spherical equivalent	>0.5 D difference from baseline
Central corneal thickness	>2% decrease from baseline

IDEAL CANDIDATE & WHO CAN WE RECOMMEND?

- Young patient (<30 years usually)

- Why ?

- BCVA worse than 20/20 (Spectacle or CL)

- Refraction:
  - Increase of ≥ 1 D in manifest cylinder
  - Increase of ≥ 0.5 D in manifest spherical equivalent

- Imaging:
  - Tomography: Steepening of anterior or posterior corneal surface. corneal thinning
  - OCT: evidence of progression in stromal thickness.

WHAT IS CROSSLINKING?

- The term "crosslink" derives from the assumption of creating <u>new covalent links</u> between collagen fibers in the stroma.

- Specifically, covalent chemical bonds between the amino terminals of the collagen side chains and the proteoglycans of the extracellular matrix.

- This can occur naturally in eye –glucose from aqueous humor along with exposure to sun

EFFECTS OF CROSSLINKING?
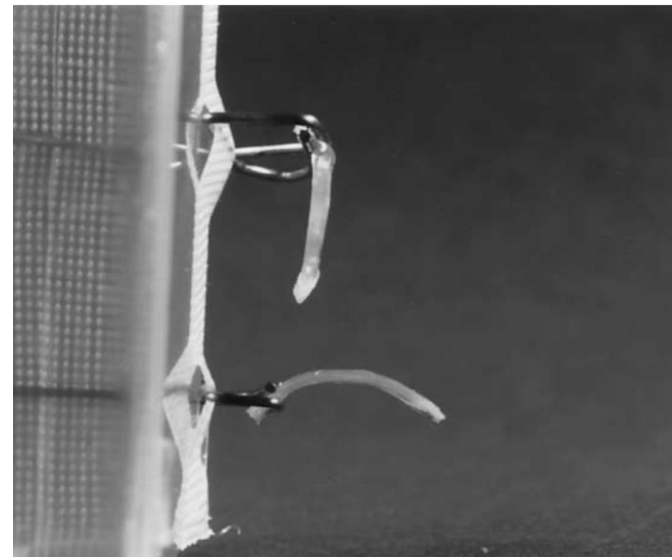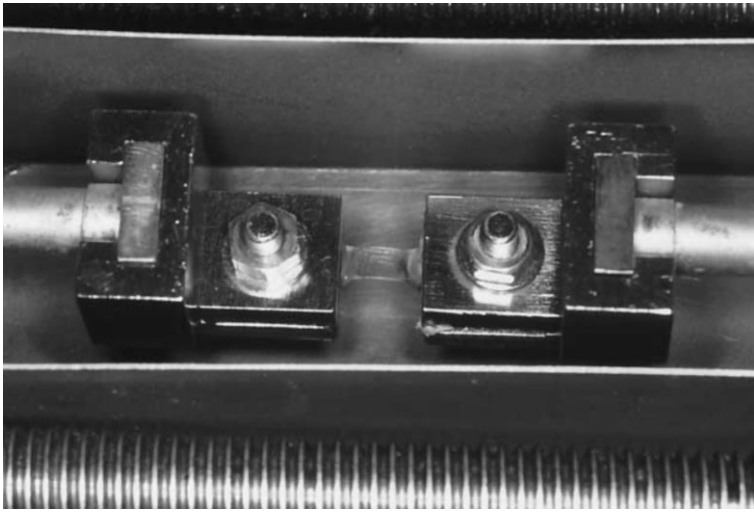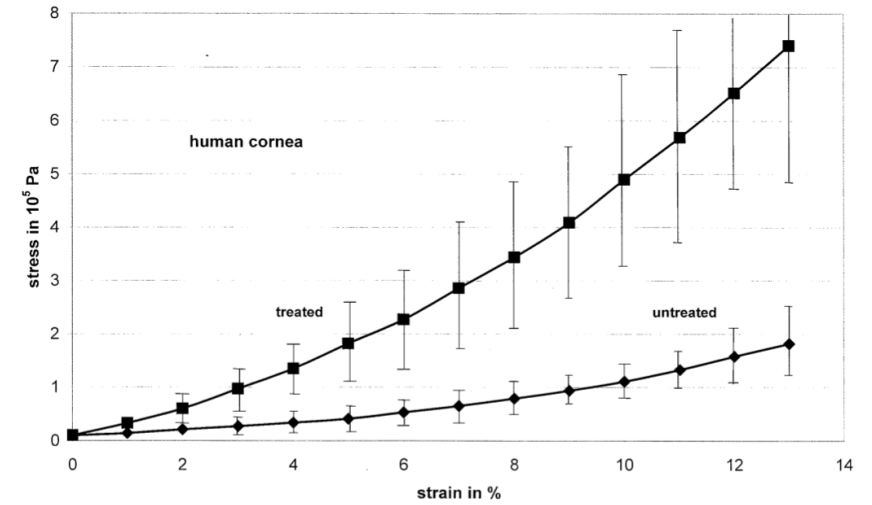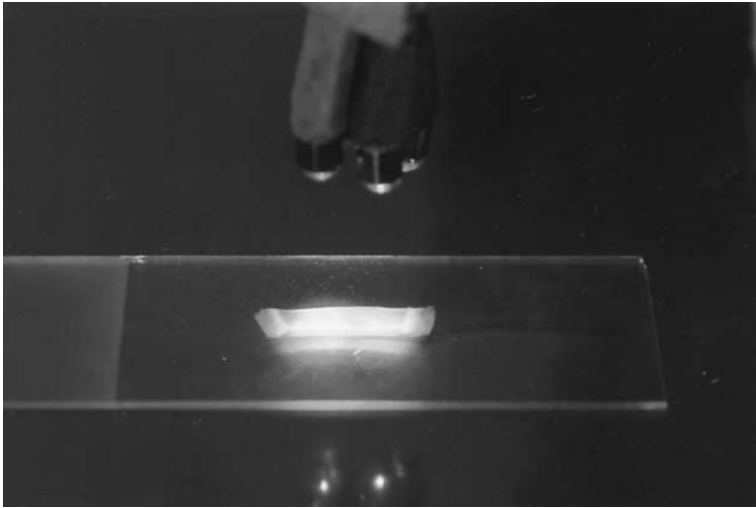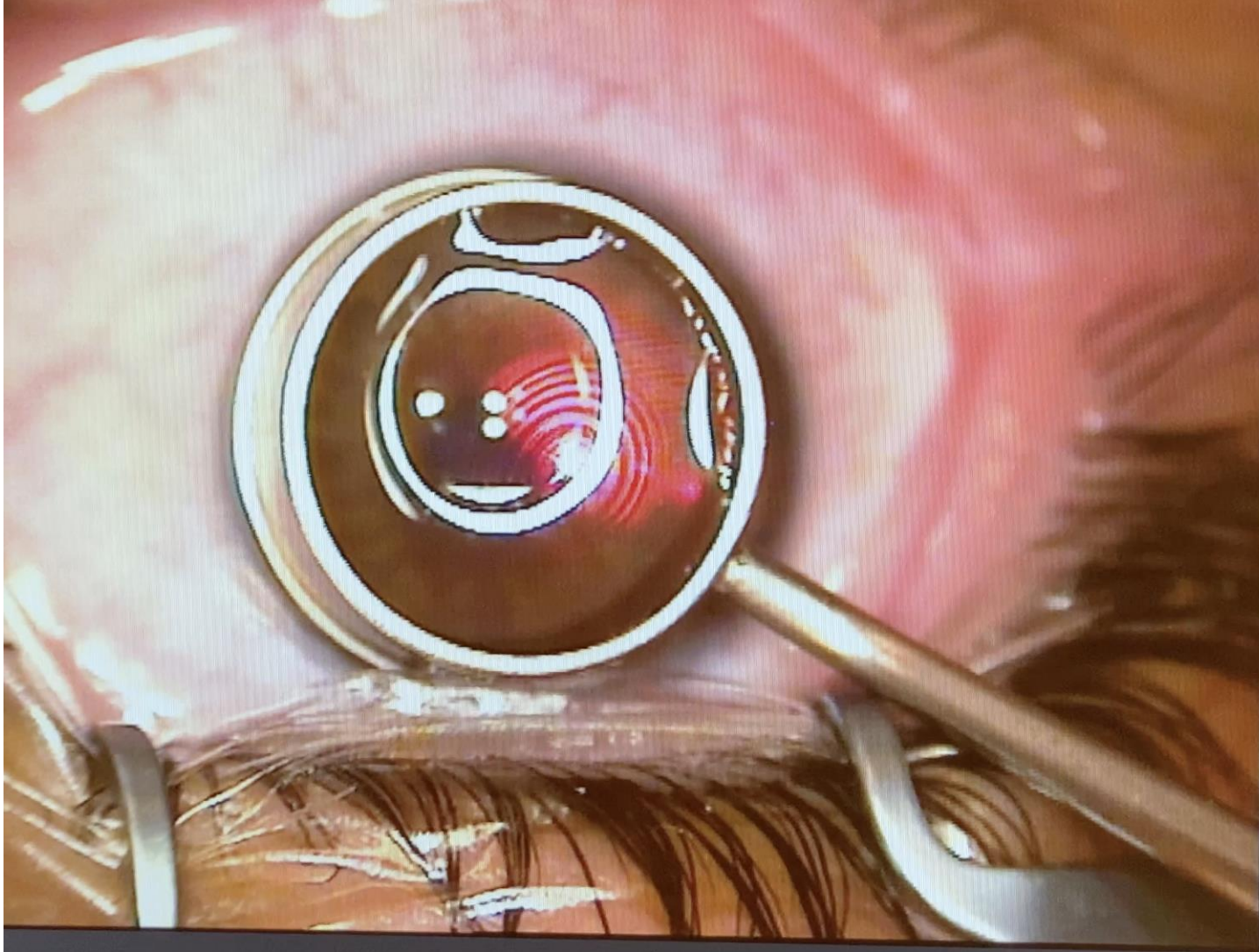
CROSSLINKING DRESDEN PROTOCOL-FDA APPROVED

- Epithelium removal
- 8-10 mm

Video courtesy Dr. Amir Marvasti Coastal Vision

CROSSLINKING DRESDEN PROTOCOL-FDA APPROVED

- Riboflavin 0.146% + 20% Dextran application before and during UVA radiation

- UVA radiation is 370 nm

- $3mW/cm^2$

- Exposure for 30 minutes

- Every 5-minutes apply (Riboflavin 0.146% + 20% Dextran)

- Total energy $5.4J/cm^2$
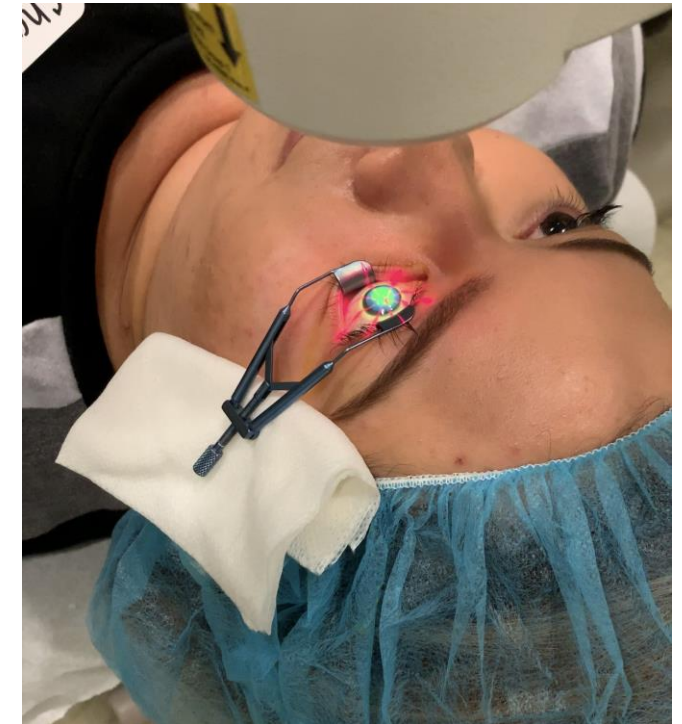
POST OPERATIVE MANAGEMENT

- Epithelial healing
  - Delayed epithelial healing
  - Infectious keratitis

- Topical steroid
  - 1-2 month tapering schedule
  - Medical management of IOP if necessary

- Corneal haze
  - Up to 90% will have some degree of it
  - Typically resolves in 6-12 months
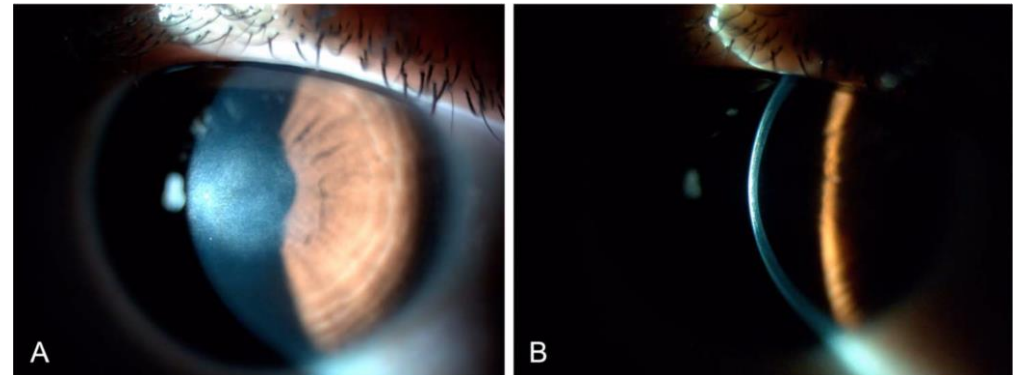
CROSSLINKING RESULTS

Post-CXL Time Course for Maximum Keratometry (K_Max)

	Baseline	1 Mth	3 Mths	6 Mths	1 year
All	58.5	59.8	58.2	57.1	56.9
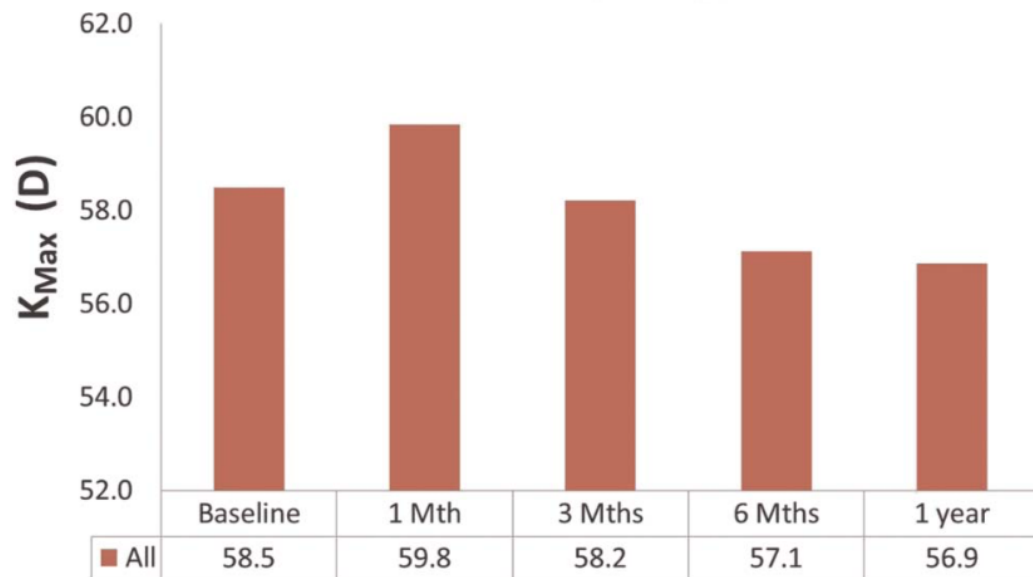
Post-CXL Time Course In UCVA and BCVA

	Baseline	1 Mth	3 Mths	6 Mths	12 Mths
UCVA	0.88	0.92	0.90	0.89	0.82
BCVA	0.34	0.38	0.30	0.26	0.24

20/137   20/117

20/45   20/34
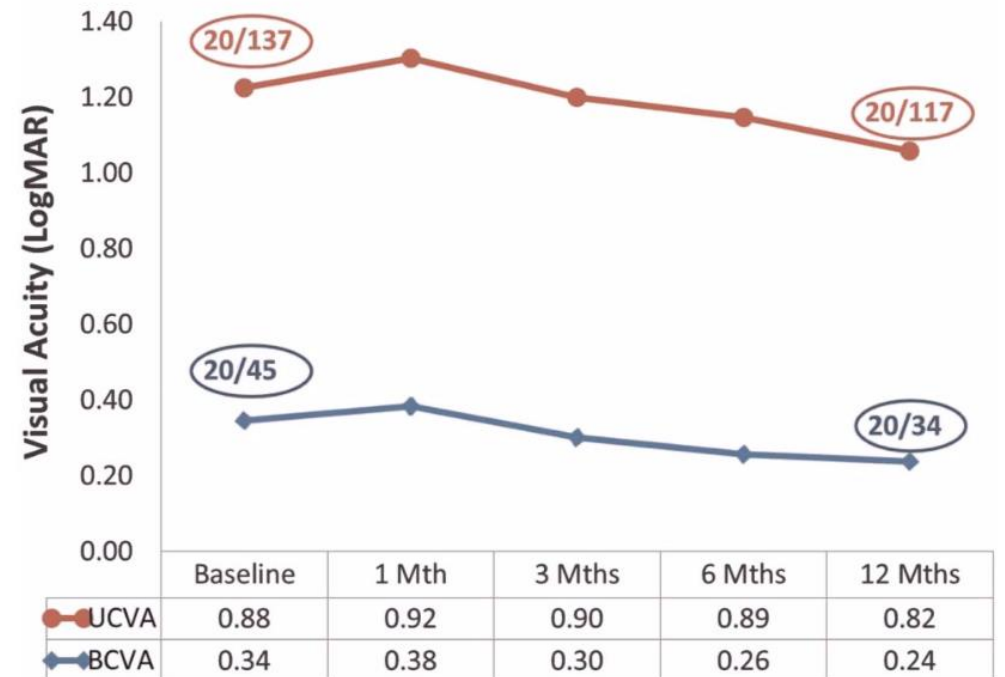
DOES IT ALL BECOME ALRIGHT?

UCVA

- No change: 51%
- Improve: 31%
- Decline: 18%

BCVA

- No change: 47%
- Improve: 45%
- Decline: 8%

Kmax

- No change: 39%
- Decrease: 51%
- Increase: 10%

CONTRAINDICATIONS

- Acute hydrops

- Total corneal thickness < 365 microns

- Relative contraindications:

- Herpetic keratitis

- Significant scarring

- Pregnancy

- Lactation

- Autoimmune disease

PATIENT EDUCATION

1. CXL will slow or stop the disease, it will not reverse it.

2. Glasses or contact lenses will still be needed after the procedure.

3. Vision might worsen before it improves.

4. Prescription might change up to 1 year after CXL.

5. You still need to be monitored after CXL for progression.

Global Consensus on Keratoconus and Ectatic Diseases

José A. P. Gomes, MD, PhD, Donald Tan, MD, PhD,† Christopher J. Rapuano, MD,‡
Michael W. Belin, MD,§ Renato Ambrósio, Jr, MD, PhD,¶ José L. Guell, MD,‖
François Malecaze, MD, PhD,** Kohji Nishida, MD,†† and Virender S. Sangwan, MD‡‡, the Group
of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases*
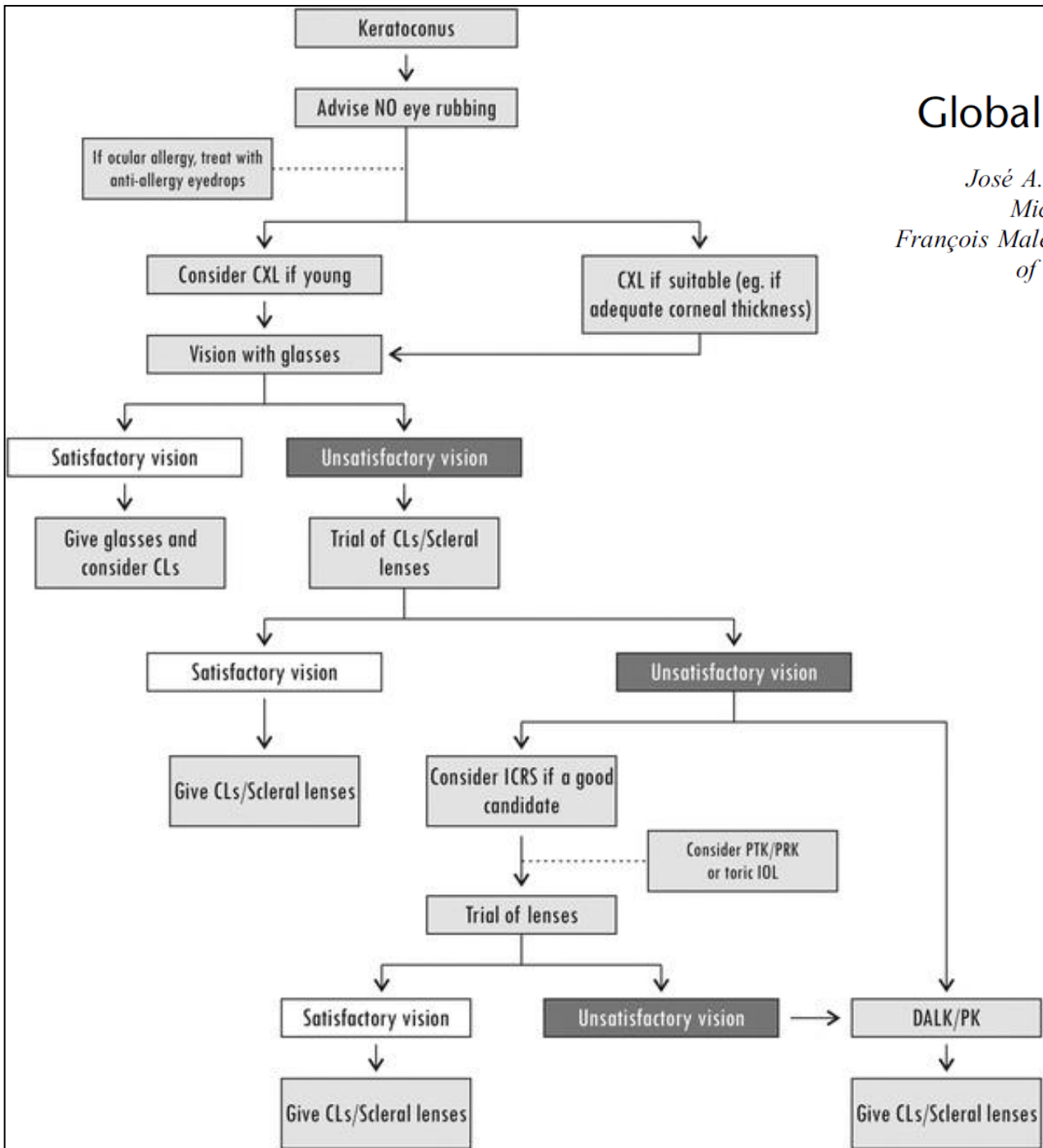
ICRS intrastromal corneal rings
DALK Deep anterior lamellar keratoplasty
PK penetrating keratoplasty
CL contact lenses
SP spectacles

KERATOCONUS TREATMENT ALGORITHM

Keratoconus Algorithm
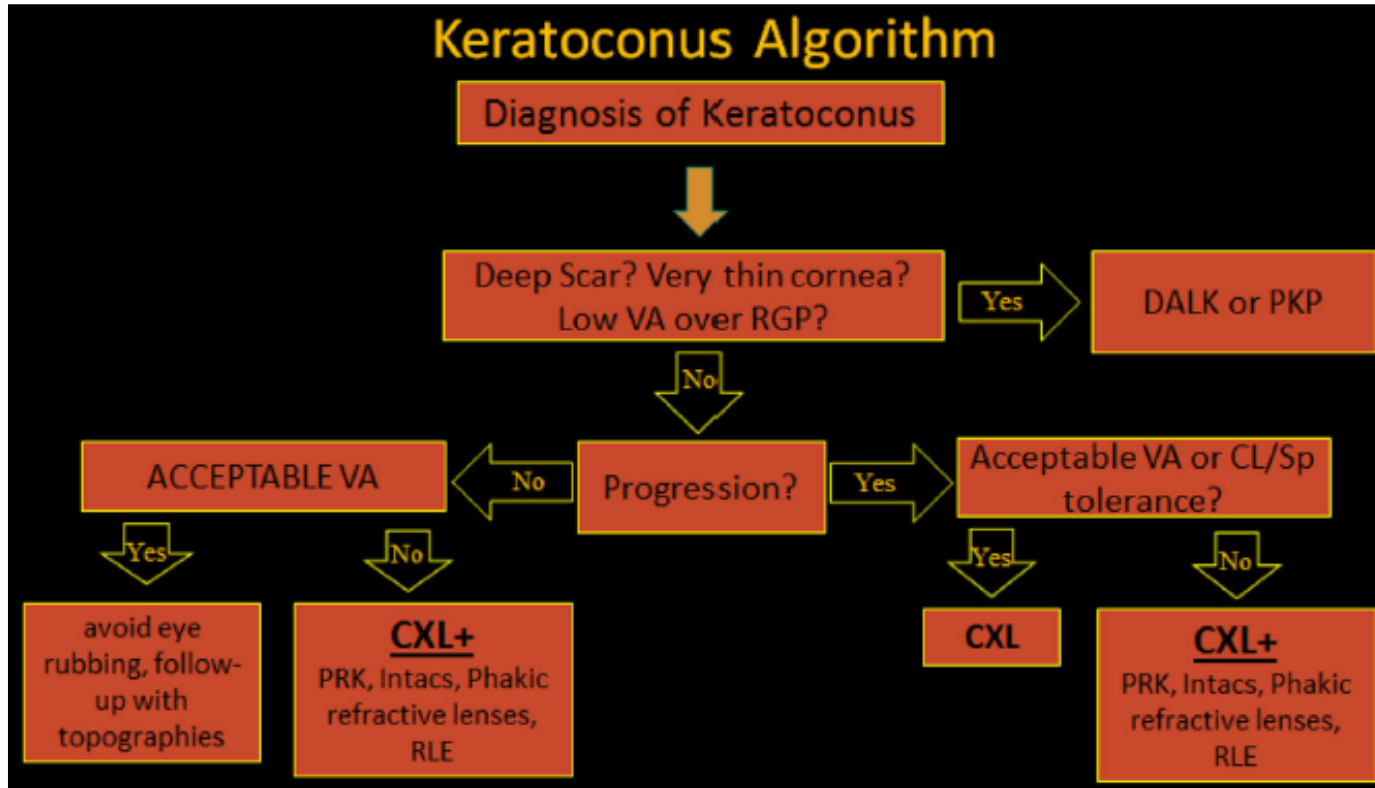
DALK Deep anterior lamellar keratoplasty
PKP penetrating keratoplasty
CL contact lenses
SP spectacles
PRK photorefractive keratectomy
RLE Refractive lens exchange

ACCELERATED CROSS LINKING (NOT FDA APPROVED)

- Bunsen-Roscoe law of photochemical reciprocity

- Same photochemical effect can be achieved by delivering a similar total energy over a shorter period of time

ORIGINAL ARTICLE

Efficacy and Safety of Accelerated Corneal Cross-linking for Progressive Keratoconus: A 5-Year Follow-up Study

Antonio Moramarco, MD; Valentina Mastrofilippo, MS; Maria Grazia Romano, COA; Danilo Iannetta, MD; Luca Braglia, MS; Luigi Fontana, MD, PhD

- Avedro KXL

- 30mW/cm^2

- 3 minute exposure

- Total energy on cornea 5.4J/cm^2

- Effective at halting keratoconus

- Did not induce changes to corneal transparency

- Endothelial cell density

- Central Foveal thickness

EPITHELIUM ON CROSSLINKING (NOT FDA APPROVED)

- Epithelium left intact, no pain

- Possibly prevents corneal crosslinking complications?

- BAK+ ethylydiaminetetraacetic acid+ tetracaine to increase riboflavin diffusion

- Iontophoresis assisted corneal crosslinking

Ophthalmology
Available online 28 December 2020
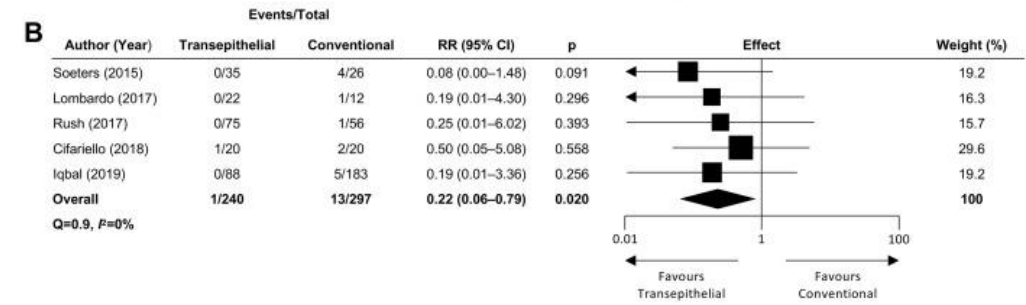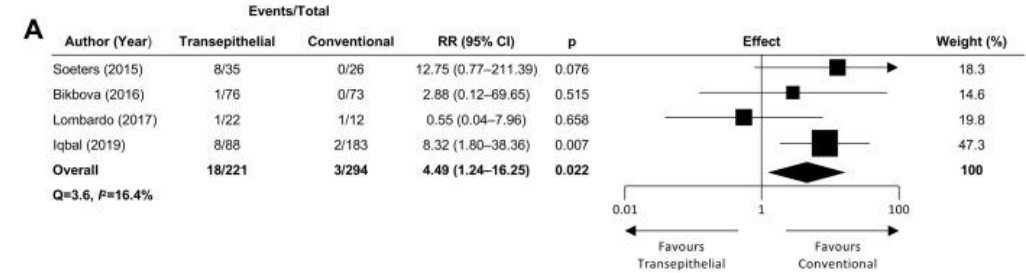In Press, Journal Pre-proof ⑦

ELSEVIER

Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia: a systematic review and meta-analysis

Siddharth Nath MD, PhD [1], Car[l] Shen MD [2], Alex Koziarz MSc [3], Laura Banfield MLIS [4], Behnam Nowrouzi-Kia MD, MPH [5], Mark A.

Show more ∨

	Events/Total					
A Author (Year)	Transepithelial	Conventional	RR (95% CI)	p	Effect	Weight (%)
Soeters (2015)	8/35	0/26	12.75 (0.77–211.39)	0.076		18.3
Bikbova (2016)	1/76	0/73	2.88 (0.12–69.65)	0.515		14.6
Lombardo (2017)	1/22	1/12	0.55 (0.04–7.96)	0.658		19.8
Iqbal (2019)	8/88	2/183	8.32 (1.80–38.36)	0.007		47.3
Overall	18/221	3/294	4.49 (1.24–16.25)	0.022		100
Q=3.6, I^2=16.4%						

Favours Transepithelial | Favours Conventional

	Events/Total					
B Author (Year)	Transepithelial	Conventional	RR (95% CI)	p	Effect	Weight (%)
Soeters (2015)	0/35	4/26	0.08 (0.00–1.48)	0.091		19.2
Lombardo (2017)	0/22	1/12	0.19 (0.01–4.30)	0.296		16.3
Rush (2017)	0/75	1/56	0.25 (0.01–6.02)	0.393		15.7
Cifariello (2018)	1/20	2/20	0.50 (0.05–5.08)	0.558		29.6
Iqbal (2019)	0/88	5/183	0.19 (0.01–3.36)	0.256		19.2
Overall	1/240	13/297	0.22 (0.06–0.79)	0.020		100
Q=0.9, I^2=0%						

Favours Transepithelial | Favours Conventional

CI = confidence interval; I^2 = heterogeneity; Q = Cochran's Q test; RR = relative risk

A- Disease progression B -Complications

Conclusions: The efficacy of transepithelial CXL remains inferior to the epithelium-off approach, although it is significantly safer.