STATE BOARD OF OPTOMETRY
2450 DEL PASO ROAD, SUITE 105, SACRAMENTO, CA 95834
P (916) 575-7170 F (916) 575-7292 www.optometry .ca.gov

Continuing Education Course Approval Checklist

Title: Corneal Ectasias and Corneal Crosslinking

Provider Name: Kaiser c/o Dr. Jeong-Ah Kim

☑Completed Application
Open to all Optometrists? ☑Yes ☐No
Maintain Record Agreement? ☑Yes ☐No

☑Correct Application Fee

☐Detailed Course Summary

☑Detailed Course Outline

☑PowerPoint and/or other Presentation Materials

☐Advertising (optional)

☑CV for EACH Course Instructor

☑License Verification for Each Course Instructor
Disciplinary History? ☐Yes ☑No

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CONTINUING EDUCATION COURSE APPROVAL APPLICATION

$50 Mandatory Fee

Cashiering and Board Use Only			
Receipt #	Payor ID	Beneficiary ID	Amount
1-2769	3815685	890747	50

Pursuant to California Code of Regulations (CCR) § 1536, the Board will approve continuing education (CE) courses after receiving the applicable fee, the requested information below and it has been determined that the course meets criteria specified in CCR § 1536(g).

In addition to the information requested below, please attach a copy of the course schedule, a detailed course outline and presentation materials (e.g., PowerPoint presentation). Applications must be submitted 45 days prior to the course presentation date.

Please type or print clearly.

Course Title	**Course Presentation Date**
CORNEAL ECTASIAS AND CORNEAL CROSSLINKING	03/14/2017

Course Provider Contact Information

Provider Name

JEONG-AH (First) KIM (Last) JENNIFER (Middle)

Provider Mailing Address

27107 TOURNEY RD
Street **City** SANTA CLARITA **State** CA **Zip** 91355

Provider Email Address jenniferkim100@hotmail.com 1-661-222-2171

Will the proposed course be open to all California licensed optometrists?	☒ YES ☐ NO
Do you agree to maintain and furnish to the Board and/or attending licensee such records of course content and attendance as the Board requires, for a period of at least three years from the date of course presentation?	☒ YES ☐ NO

Course Instructor Information

Please provide the information below and attach the curriculum vitae for each instructor or lecturer involved in the course. If there are more instructors in the course, please provide the requested information on a separate sheet of paper.

Instructor Name

GARY (First) GROESBECK (Last) (Middle)

License Number G52329	**License Type** MD
Phone Number (760) 599-2409	**Email Address** gary.d.groesbeck@gmail.com

I declare under penalty of perjury under the laws of the State of California that all the information submitted on this form and on any accompanying attachments submitted is true and correct.

Signature of Course Provider *Date* 2-1-17

Gary Groesbeck, MD
Corneal Ectasias and Corneal Crosslinking

1. Corneal Stucture
    A. Anatomy
    B. Biomechanics
    C. Testing of Corneal Structure
    D. Clinical applications for Evaluation and Treatment of Corneal disease

2. Corneal Ectasias
    A. Keratoconus
    B. Pellucid Marginal Degeneration
    C. Terrien's Marginal Degeneration
    D. Post-refractive surgery Ectasias

3. Corneal Collagen Crosslinking - Patient Selection
    A. Indications
    B. Contraindications
    C. Safety Factors

4. General Surgical Principles
    A. Riboflavin Loading
    B. UVA light application
    C. Postop Care

5. Complications
    A. Short term changes
    B. Long term effects

5. Outcomes:
    A. Germany Study
    B. Italina Study
    C. Australian Study
    D. US FDA Phase III Trials

6. Variations in Surgical Technique
    A. Epithelium-Off
    B. Epithelium-On
    C. Variable Duration treatments
    D. Adaptive techniques for Thin Corneas
    D. Corneal Crosslinking + Intacs

7. Clinical Application
    A. Current Status of Corneal CXL in SCPMG/Kaiser Permanente
    B. Future Trends

Corneal Collagen Crosslinking

Gary Groesbeck MD
Vista Ophthalmology

Kaiser Ocular Symposium XXIV

Financial Disclosure

I have no financial or non-financial relationships to disclose as to any devices or products mentioned in this presentation.

Keratoconus

- Most common corneal dystrophy
- 1:2000 incidence
- no gender predilection
- Some studies show 4-7x greater incidence in Asians compared to caucasians.
- bilateral but usually asymmetric
- Inferocentral anterior protrusion lead to steeped curvature and scarring and striae at Descemet’s level.

Keratoconus

- KC results in myopia, irregular astigmatism which may require rigid contact lens to achieve best correction

- 10-20% of patients require PKP

Keratoconus - Etiology

- Genetic, biochemical, and physical factors
- Can be sporadic or associated w vernal disease or connective tissue disorders
- Ocular trauma associated w eye rubbing, CL wear, allergic eye disease
- Inflammatory mediators may lead to tissue degradation and corneal thinning

Pellucid marginal degeneration

- Less common than KC
- Usually affects inferior peripheral cornea rather than paracentral
- Band of thinning from 4:00 to 8:00
- ill-disposed for conventional PKP due to location
- 9 mm treatment zone for CXL usually covers this area adequately.

Corneal anatomy

- 5 layers:
  - Epithelium
  - Bowman’s layer
  - Stroma proper
  - Descemet membrane
  - Endothelium
- Each layer has different structural and functional characteristics

Corneal anatomy

- Corneal stroma
  - Bowmans layer and stroma proper
    - 90% of thickness
    - Greatest contributor to corneal biomechanics
    - 15% collagen, 7% other constituents, 78% water

Corneal anatomy

- Corneal stroma
  - Fibrillar collagen is organized into bundles of unidirectional fibrils termed lamellae
  - In Bowman’s layer, collagen fibers are arranged randomly in a mat-like fashion, with proteoglycans mixed into
  - Type VI collagen fibrils interconnect the neighboring Type I collagen fibrils
  - Fibrils are 10” extensible with high elasticity

Corneal anatomy

- Bowman layer is acellular 10 um thick superficial layer
  - highly interwoven Type I collagen fibrils
- Stroma
  - organized into bundles called lamellae
  - anterior third - highly interwoven, thin, obliquely oriented lamellae
  - Posterior two thirds - minimally interwoven, wider, mostly parallel lamellae

Corneal anatomy

- Endothelium
  - 4 um thick
  - no direct biomechanical function, but thru it’s dehydration of storm has an effect on the cornea’s properties
  - Secretes a 12 um basement membrane = Descemet membrane
- Descemet membrane Type IV and Type VIII collagen and glycoproteins fibronectin, laminin, and thrombospondin

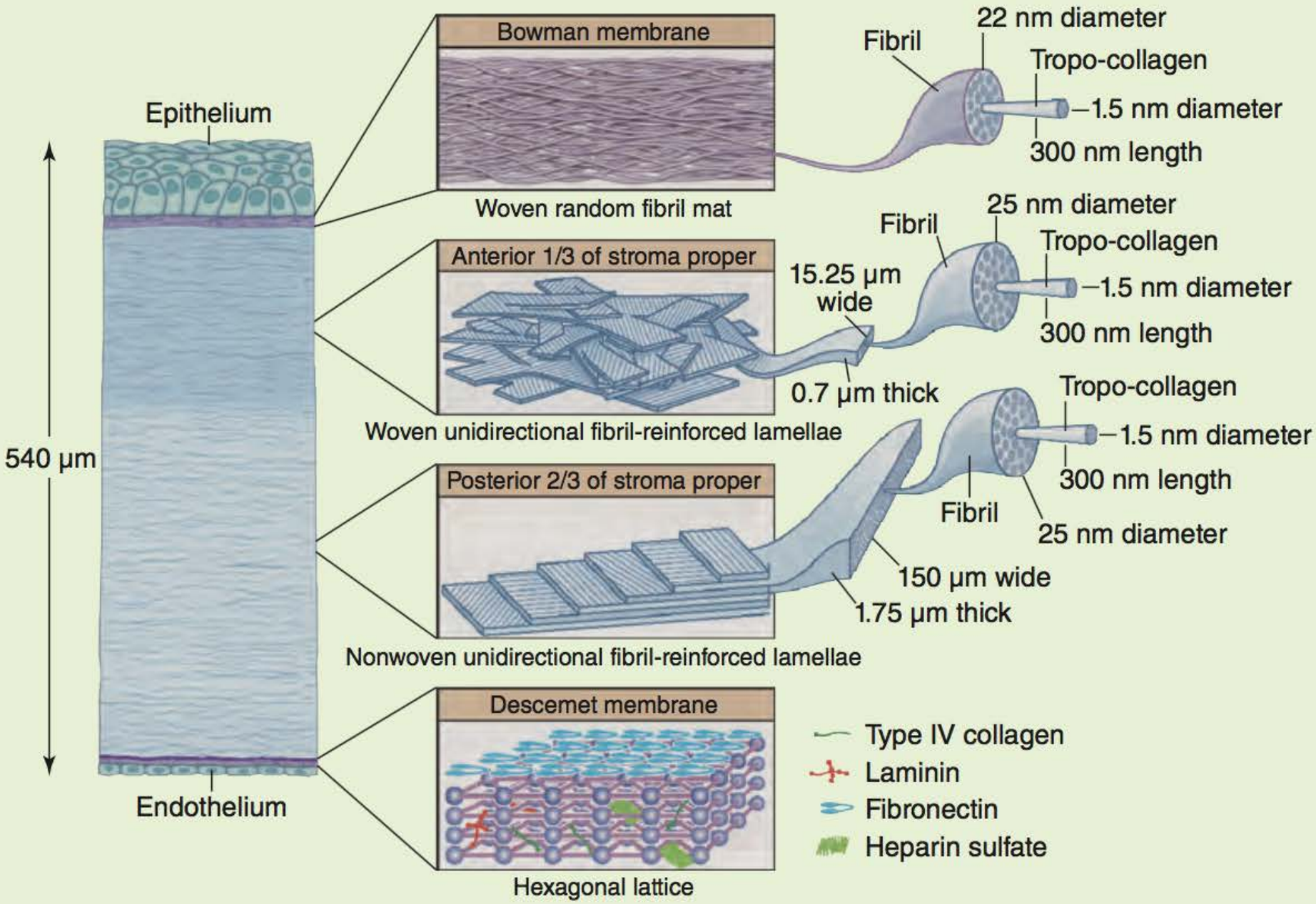

Figure 1 A schematic image of the normal cornea with a magnified view of the various anatomic layers. (Kaufman PL, et al, eds. Adapted from Dawson DG, Ubels JL, Edelahauser HF. Cornea and sclera. In: Levin LA et al, eds. A*dler's Physiology of the Eye*. 11th ed. New York: Elsevier/Mosby; 2011:107.)

Corneal anatomy

- Average central thickness = 545 um
  - Standard deviation 35 um
  - Range 440-650 um
- Peripheral thickness = 700 um

Corneal anatomy

- Strongest in parallel direction of corneal fibrils
- Anterior 40% is strongest, stiffest, most interwoven
    - 2-5 x stiffer than posterior stromal layer
- Posterior 60% is 50% weaker due to non-interwoven structure
    - easier to dissect, but more prone to sheer in trauma

Corneal anatomy

Stressor	increase in mm Hg
Arterial pulsations	1-2 mm
Accommodation	4 mm
Diurnal changes	5 mm
Respiration	5 mm
Valsalva Maneuver	8 mm
Recumbent or inverted position	10 mm
Normal blink	5-10 mm
Hard squeeze blink	50-110 mm
Light rubbing	5-20 mm
Hard knuckle rubbing	23-135 mm
Accidental eye impact	variable

Corneal anatomy

- Variable strength of superficial and deep layers has relevance for LASIK flap depth
- Anterior stroma = 40% x 545 um = 218 um.
  - thin sub-Bowmans flap 90-120 um
  - Average flap 140-160 um microkeratome
  - Femto flap = 100-120 um

Introduction

- Cornea - naturally crosslinks with age
  - oxidation of ends of collagen fibrils
    - explains why Keratoconus stabilizes with age
  - Crosslinking stiffens to a more rigid state

Keratoconus

- Conventional management - contacts, glasses
  - improve vision, but don’t alter course of the disease
- Crosslinking -
  - effective to stiffen cornea and slow or stop progression
  - long term results are lacking

Corneal Crosslinking

- Stiffens and strengthens cornea
- > 97% success rate in stopping primary keratectasia
- <1% complication rate

Corneal Collagen Crosslinking

- Chemical technique using UV-A and Vitamin B12 (riboflavin) to strengthen chemical bonds within the cornea
- Goal of treatment is to stop progressive and irregular changes of cornea leading to high astigmatism

History of Crosslinking

- Developed late 1990’s at University of Dresden
  - Theo Seiler
    - UV-A and Riboflavin as absorption limiter
- experimented in pork and rabbit eyes
  - induced oxidation of ends of collagen fibrils

How it works

- Spoerl & Seiler - riboflavin + UVA = stiffer porcine and rabbit corneas more resistant to enzymatic degradation
- Wollensak - 320% gain in corneal biomechanical strength
- Effect most pronounced in anterior 200 um of cornea
- Changes in structure from CXL may prevent collagenases from accessing inter-fibrillar connections
- Could etiology of Keratoconus involve imbalance of proteolytic enzymes and endogenous inhibitors in KC corneas?

How it works

- Riboflavin is activated by UVA light which enhances crosslinking between stromal collagen fibers
- Photosensitive Riboflavin is activated to an excited state
- Excited Riboflavin reacts w oxygen creating free radicals and reactive oxygen species
- These reactive species induce covalent bonding between protein molecules in the storm including collagen and proteoglycans.

Corneal Crosslinking

- Riboflavin loading = 1 gtt q 1-2 min x 30 min
- SLE determines endpoint = flare in AC from B2 solution
- UVA 3-18 mW/cm2 for ectasia

- Exact mechanism is uncertain, but speculation is that singlet oxygen production leads to enhanced cross linking by binding endogenous free carbonyl groups to collagen fibrils
- CXL can be combined w surface ablations or intrastromal rings

History of Crosslinking

- Safety studies showed endothelium was not damaged if sufficient riboflavin was used to limit the penetration of the UV-A light
- Human studies began in 2003 at Univ. of Dresden
  - 16 subjects
  - 70% had flattening of anterior corneal curvature
  - 65% had improvement in uncorrected visual acuity

Corneal Crosslinking

- Epithelium off technique
  - debridement of epithelium followed by application of riboflavin and then UV-A light
- Epithelium on technique
  - Epithelium intact - special riboflavin solution followed by UVA

History of Crosslinking

- FDA approval of Avedro granted April 18, 2016
- Orphan drug status was previously given to Avedro in 2011
  - Avedro has 7 years exclusive marketing rights for corneal cross linking in US using riboflavin and UV-A system

FDA LASIK risk factors

- < 25 yrs old
- > 250 um flap thickness
- > -8.00 D correction attempt
- > 40% depth flap
- Abnormal corneal topography
- Central corneal thickness < 500 um
- ATR or Oblique astigmatisme > 2.00 D
- Mean keratometry > 47 D

Patient Selection

- Indications: to stop progression of ectasia
- Best candidates are those with progressive ectasia of cornea
- Keratoconus
- Post refractive surgery ecstasy
- Pellucid marginal degeneration
- Terrien’s marginal degeneration

Patient Selection

- What is progression?
  - No definitive criteria
  - Change in refraction
  - Change in uncorrected acuity
  - Change in best corrected acuity
  - Change in topography or keratometry

Patient Selection

- Need to know more than just anterior surface contour provided by Zeiss Atlas topographer
- Pentacam and other instruments measure and and posterior surface and contours

Safety considerations

- Negative effects on ocular structures?
- UVA is cytotoxic to endothelium, iris, retina
- Isolated reports of endothelial or iris damage from CXL

Safety considerations

- UVA penetration is calibrated based on corneal thickness
- Not less than 400 um
- with 3 mW/cm2, UVA at endothelium is less than 1/2 the cytotoxic level
- Wavelength 367-370 nm is outside the photokeratitis range (270-315 nm) and cataractogenic range = 270-315 nm)
- Total treatment time of 30 minutes delivers 5.4 J/cm2

Safety considerations

- Investigators are studying different irradiance, duration of UVA exposure, and riboflavin concentration in hopes of finding treatment algorithm for treating thinner corneas

What is progression?

- 1 D steepening by topography
- KC manifests at puberty, progresses until 30-40, then stabilizes.
- Rapidly progressing KC in young person is best candidate for CXL.
- Rx not indicated for 40 yr old w no evidence of progression.

Contraindications

- Corneal thickness of less than 400 microns is a contraindication to the standard treatment protocol
- Prior herpetic infection -may result in viral reactivation
- Concurrent infection
- Severe corneal scarring or opacification
- History of poor epithelial wound healing
- Severe ocular surface disease (ex. dry eye)
- Autoimmune disorders

Contraindications

- Patients w advanced disease - thin corneas and steep maximal corneal curvatures
- >58 D prep K’s = greater risk of Rx failure and postop haze formation
- >35 yrs old w 20/25 BVA preop may be worse postop due to scarring

Eligibility per Focal Points

- < 35 yrs old
- > 400 um CCT after debridement
- < 58 D on maximal K’s preop

Contraindications

- Severe dry eye
- vernal/atopic inflammatory disease
- ? Pregnancy
- Central preop scarring won’t improve postop

How do you do it?

- Dresden method: Wollensak et al
- 0.1% riboflavin
- UVA irradiation 370 nm @ 3 mW/cm2 providing 5.4 J/cm2 of energy to cornea

How do you do it?

- 1. Corneal anesthesia via topical proparacaine or 0.5% tetracaine solution drops x 3.
- 2. Orbital and eyelid area prepped w betadine, lid speculum positioned.
- 3. Central 7-9 mm epithelium derided
- 4. Baseline CCT measured to confirm > 400 um
- 5. 0.1% iso-osmolar riboflavin in 20% dextran is instilled onto corneal surface q 2-3 min for 30 minutes

How do you do it?

- 6. SLE exam to confirm riboflavin has fully infused the cornea by detecting yellow coloration and flare in the anterior chamber
- 7. Corneal pachymetry is reconfirmed before proceeding w light
- 8. Sponge ring is placed around limbus to protect limbal stem cells
- 9. UVA light focused onto area of absent epithelium to photo-activate riboflavin. UVA source is about 2-5 cm away from eye.
- 10. Irradiation is applied for 30 minutes w riboflavin gtts q 3 minutes

How do you do it?

- 11. BSS and topical anesthetic drops alternated to prevent desiccation and to maintain anesthesia.
- 12. Corneal pachymetry is checked at 10, 20, and 30 minutes. If pachymetry falls below 400 um, hypotonic riboflavin drops are used instead of routine isotonic drops
- 13. After irradiation rx, a broad-spectrum antibiotic such as moxifloxicin is instilled and a bandage SCL is positioned on the eye and left until reepithelialization occurs, usually 4-7 days.
- 14. Patients went home with “artificial” tears along with a course of topical antibiotic and steroid.

Postop care

- similar to PRK
- Very symptomatic early on: pain, tearing, FB sensation, photophobia
- Bandage scl placed
- Epithelium heals in 4-7 days - at which time SCL is removed and only steroid gets are continued
- Prednisolone 1% vs dexamethasone

Postop care

- similar to PRK
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Postop care

- Slow taper of steroid drops over 4 weeks
- followup appts on POD 1, 1 week, 1 month
- Then 3 months, 6 months, and 1 year.
- Thereafter pt’s may followup q 6-12 months.

Trial results

- Nearly all studies report stabilizing and reducing K’s
- regression of corneal steepness averaged about 2.00 diopters across all studies
- Studies show stability to 5 years, but beyond that is unknown
- Significant inconsistencies in literature.
- Variable definitions of progression, variable measurements, etc.

Table 1. Results of Major Clinical Studies for Standard CXL

AUTHOR[a]	MAXIMUM FOLLOW-UP	NO. OF EYES START/END	% HALTED OR IMPROVED	IMPROVEMENT
Wollensak, et al (2003)	[illegible]	23/2	95.5 (70)	K[illegible]ax 2.01 D, B[illegible]CVA 1.2[illegible] lines S[illegible] 14 D
Caporossi, et al (2006)	3 months	10/10	—	Kmax 1.90 D BCVA 1.66 lines, UCVA 3.6 lines
Raiskup-Wolf, et al (2008)	6 years	241/5	81 (57)	Kmax 2.44 D BCVA –0.18 LogMAR
Jankov, et al (2008)	6 months	25/25	100 (52)	Kmax 2.14 D UVCA –0.11 LogMAR
Wittig-Silva, et al (2008)	12 months	33/9	(>50)	Kmax 1.45 D BCVA–0.12 LogMAR
Vinciguerra, et al (2009)	2 years	28/28	—	Kmax 1.35 D BCVA –0.15 LogMAR, UCVA –0.24 LogMAR
Agrawal (2009)	1 year	37/37	92 (54)	Kmax 2.47D BCVA improved >1 line
Coskunseven, et al (2009)	1 year	19/19	—	Kmax 1.57D BCVA –0.10 LogMAR, UCVA –0.06 LogMAR
Koller, et al (2009)	1 year	192/155	98 (37.7)	Kmax 0.89D BCVA –0.55 LogMAR
Derakhshan, et al (2011)	6 months	31/31	90.3 (77)	Kmax 0.65 D BCVA 1.7 lines, UCVA 2 lines
Hersh, et al (2011)	1 year	49/49	89.8 (51.0)	Kmax 2.00 D BCVA –0.14 LogMAR, UCVA –0.05 LogMAR
Viswanathan, et al (2013)	4 years	51/?	—	Kmax 0.96 D BCVA –0.05 LogMAR
Goldich, et al (2012)	2 years	14/14	92.8	Kmax 2.40 D BCVA –0.07 LogMAR
Vinciguerra, et al (2012) (<18-year-olds studied)	2 years	40/40	—	Kmax 1.27 D BCVA –0.19 LogMAR, UCVA –0.21 logMAR SE –1.57 D
Vinciguerra, et al (2013)	4 years	400/?	—	BCVA: –0.11 LogMAR (<18 years old @ 12 months) –0.31 LogMAR (18–29 years old @ 36 months) –0.33 LogMAR (30–39 years old @ 36 months) –0.25 LogMAR (>40 years old @ 36 months)

Table 2. Results of Clinical Studies for Epi-On CXL

AUTHOR[a]	FOLLOW-UP	NO. OF EYES START/END	IMPROVEMENT
Filippello, et al (2012)	18 months	20/20	Kmax: 2.97D UCVA –0.66 LogMAR, BCVA: –0.11 LogMAR
Koppen, et al (2012)	Up to 18 months	53/18	Sphere, Cyl, Kmax and refractive power remained stable from baseline without statistically significant improvements at 18 months.
Lessicotti, et al (2012)	12 months	63/51	BCVA: –0.036 LogMAR SE: 0.35D (overall favorable but limited effect)

Complications

- Risks: improper UVA delivery -
  - excess energy
  - incorrect wavelength
  - insufficient riboflavin
- Iritis, keratin precipitates, corneal edema and haze can develop with inadequate riboflavin

Risks

- Haze
- Scarring
- Delayed wound healing
- corneal melt
- Infectious keratitis

Risks

- Haze is common, but respond well to topical steroids within a year.
- Minimal effect on tear film stability or basic tear secretion

Trial results

- Nearly all studies report stabilizing and reducing K’s
- regression of corneal steepness averaged about 2.00 diopters across all studies
- Studies show stability to 5 years, but beyond that is unknown
- Significant inconsistencies in literature.
- Variable definitions of progression, variable measurements, etc.

Variations in technique

- Epi off
  - greater penetration of riboflavin
  - “gold standard” technique
- Epi-on procedures
  - less infection risks
  - Reduced haze, reduced pain

Future Improvements

- Shorter treatments using more intense irradiation would be desirable.

- Avedro has a device capable of doing in 3 minutes what now takes 30 minutes to do.

- More intense UVA means potentially more toxicity - Must follow corneal thicken

Future directions

- Keratoconus rx w intrastromal ring segments.
- Intacs
- CXL in combination with PRK.
  - post LASIK patients are already thin

Future directions

- Treatment of corneas thinner than 400 um
  - Hypo-osmolar Riboflavin solution
    - to hydrate and thicken cornea enough to treat
- CXL in combination with PRK.
  - post LASIK patients are already thin

- The End

CURRICULUM VITAE

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Spouse: Diane Groesbeck

Professional Activities:

Full-time clinical comprehensive ophthalmology practice, Southern California Permanente Medical Group:

- ~12,000 cataract surgeries performed since 1985
- Chief of Ophthalmology Dept, San Diego area (22 MD's) 2005-2011
- Lead ophthalmologist, Vista Eye Center, 1992-present
- Kaiser-Bellflower, 1986-1988, San Diego, 1988-present

Clinical Instructor, UCSD Dept. of Ophthalmology, 1992-2006
Fellow, American Academy of Ophthalmology 1988-present
Board-certified, American Board of Ophthalmology, 1988

Education:

Pasadena High School, Pasadena, California

Brigham Young University, Provo, Utah

- B. S., Zoology, 1978 summa cum laude
- Phi Kappa Phi
- Varsity Water Polo team

University of California, San Diego, School of Medicine

- M.D., 1982
- Research:
  "Current Concepts on Endophthalmitis" (senior thesis)
- Ranking: No rankings, honors, or honor societies were permitted during the years of my attendance at UCSD School of Medicine

L.D.S. Hospital, Salt Lake City, Utah

- Rotating internship, 1982-1983

University of California, San Diego, Dept. of Ophthalmology

- Ophthalmology residency, 1983-1986
- OKAP Scores: 1984: 83% 1985: 79% 1986: 85%

Community Activities:

Church youth leader

References:

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