I. Objectives
A. Discuss the Corneal Pathology & Genetic Basis for Keratoconus
B. Review the Causes of Corneal Ectasia
C. Overview the New Technologies, including Corneal Crosslinking Procedure and Treatment Process
D. Outline Risks & Benefits of Corneal Crosslinking

II. Diagnosing Corneal Pathology
A. There are various corneal pathologies where topography can be useful in diagnosis:
   1. Pellucid Marginal Degeneration
   2. Keratoconus
   3. Forme Fruste Keratoconus
   4. Keratectasia
B. Keratoconus – Genetic Basis
   1. Keratoconus is thought to be a genetic condition
   2. Results in abnormal collagen produced.
   3. Identification of a gene responsible for KC cases will eventually improve diagnosis.
   4. Will assist in identifying those patients who are at risk for developing clinical KC.
C. Forme Fruste Keratoconus
   1. Subset of Keratoconus
   2. No clinical sign are visible on examination of the cornea but an abnormal topography is present.
   3. Thought to be "Early Keratoconus"
   4. Represents 40% of total cases diagnosed.
D. Keratoconus - Defined
   1. Definition: Degeneration of the structure of the cornea which slowly changes the shape of the cornea from a normal round to a cone shape.
   2. First discovered in 1748 by German Oculist: Burchard Mauchart
   3. Demographics:
      a) Often discovered during adolescence or early 20's & is often hereditary.
      b) Found in all parts of the United States and the rest of the world and has c) No known significant geographic, cultural or social pattern.
E. Keratoconus - Symptoms
   1. Earliest symptom is:
      a) Subtle blurring of vision that may not be fully corrected with glasses
      b) Often corrected to within 20/20 with RGPs if the patient is CL tolerant (Fleischer ring)
   2. Moderate to severe symptoms:
      a) Increase in myopia & regular astigmatism
      b) The astigmatism eventually becomes irregular
      c) Results in loss of BCVA. (Vogt striae)
   3. Progression:
      a) Over a 10-20 year time period
      b) Eventually slows down or even stabilizes
F. Keratoconus – Signs & Tests
   1. Early Onset Diagnosis:
      a) Usually difficult to discover on slit-lamp exam
      b) Corneal topography (Humphrey Atlas) creates map of the shape of the front of the cornea
   2. Moderate & Advanced Onset Diagnosis:
      a) Usually can be observed on Slit-lamp examination
      b) Corneal Tomography (Orbscan or Pentacam) can be very helpful creating a map of the front and back surface of the cornea.
3. **Advanced Onset Diagnosis:**
   a) Cornea will be thinner at the point of the cone.
   b) Can be measured using pachymetry (Visante) or specialized tomography’s (Orbscan & Pentacam) measures cornea thickness optically.

G. **Corneal Ectasia - Defined**

1. **Iatrogenic Keratectasia :**
   a) Surgically induced ectasia: “dilation or distention of a hollow organ”
   b) May represent an accelerated version of the naturally occurring disease Keratoconus in many patients.

2. **Post-surgical ectasia:**
   a) Usually associated with LASIK
      1. LASIK penetrates the cornea much more deeply than other procedures.
      2. Post-surgical ectasia is less commonly reported with surface ablation or PRK.

3. **Corneal Ectasia - Symptoms**
   a) Post-LASIK Ectasia: Presents on average 18 months after surgery.
   b) In some cases it may present in as little as 2 weeks or many years after surgery.
   c) May experience progressive myopia
   d) Irregular astigmatism resulting in visual symptoms: shadows, ghosting and other visual distortions fluctuating vision.
   e) Progressive condition
   f) Dependent on each patient.
   g) May progress rapidly or slowly, and is unpredictable.

4. **Corneal Ectasia – Signs & Tests**
   a) Ectasia is diagnosed earliest with corneal topography and tomography and later with a slit lamp examination.
   b) Pachs: Pt. ex: NJ, 39 y.o. S/P LASIK OS 2004

5. **Risks of Ectasia**
   a) Flap Thickness / Diameter
   b) Microkeratome
   c) Femtosecond Laser
   d) Ablation Depth
      1. High Myope
      2. High Cyl
      3. Risks of Ectasia
      4. Irregular topography
         (a) Look at BOTH Anterior & Posterior Surface

H. **Current Treatment Options**

1. **Mild Cases:** Specs or SCLs may help with vision.
2. **Moderate Cases:** cornea becomes thinner & more irregular in shape with progression.
   a) Gas Permeable – GP, preferred starting lenses
   b) “Piggybacking” – RGP/GP over a Soft CL, helps if comfort is an issue
   c) Hybrid – Rigid center with a soft “skirt”, ex. SynergEyes

3. **Advanced Cases:**
   a) Semi-Scleral / Scleral – GP rests on sclera
   b) Other specialized lenses may offer visual recovery as long as the patient is contact lens tolerant.
   c) Corneal transplantation – PKP Penetrating Keratoplasty.
      1. Corneal transplantation or Corneal grafting
      2. Surgical procedure where a damaged or diseased cornea is replaced by donated corneal tissue
      3. The graft has been removed from a recently deceased individual
      4. Donor has no known diseases or other factors that may affect the viability of the donated tissue or the health of the recipient.
   d) Penetrating Keratoplasty – PKP:
      1. First performed in 1905 by Eduard Zirm, MD from the former Czech Republic
      2. complete removal of all layers of the cornea
e) Lamellar Keratoplasty – partial removal, depending on part of cornea that is damaged.

I. Newer Treatments: may DELAY or PREVENT need for corneal transplantation.
1. Conductive Keratoplasty (CK)
   a) Using high-frequency radio energy
2. Intracorneal Ring Segments (Intacs)
   a) Corneal implants
   b) Shape of the cornea is “normalized” so that vision with contact lenses
      and/or spectacles improves
   c) No tissue is removed,
   d) Natural optics of the eye are enhanced and the structural integrity of the cornea
      is maintained.
   e) Initially designed for treatment of low myopia
   f) Seldom used for myopia compared to current Laser Vision Correction options

J. Newer Treatment: Cross-Linking
1. Uses Riboflavin (Vitamin B2) drops combined with Ultraviolet Light
2. Causes the cornea to become more rigid and stop the thinning condition from getting worse.
3. Can provide better spectacle and contact lens correction

K. Purpose of Cross-Linking (CXL)
1. Adds cross-links or “cross beams” to the corneal collagen fibers
2. Made more stable
3. Holds its shape and focusing power better.
4. Used to treat corneas:
   a) Still progressing or worsening
   b) To slow, or stop and sometimes reverse the effects of Keratoconus or Ectasia
   c) NOT for corneas that are no longer progressing, has no current benefits

L. History of Cross-Linking
III. Studied since 1994
1. University of Dresden Seiler, Spoer, Wollensak
2. 23 eyes treated (K-values Max 48-72D)
   a) In ALL treated eyes, the progression of KC stopped
   b) 70% reduction of K-readings by 2.01 D
   c) 1.14D reduction of refractive error
   d) 65% improvement in VA (3.6 lines Caprorossi et al)

B. Collagen CXL: How It Works
1. Strengthens the weak corneal structure.
   a) The cornea is made up of many layers of collagen fibers arranged in a very
      regular pattern.
   b) These layers of collagen are called the Stromal Lamellae.
   c) The collagen fibers of neighboring layers are linked together to provide strength
      to the cornea.
      (1) In conditions where the cornea is abnormally weak, such as Keratoconus
          and Post-Surgical Ectasia, there are fewer of these links and therefore the
          cornea will bulge.
      (2) CXL works by increasing these collagen cross-links.
   2. The Riboflavin:
      a) Acts as a photosensitizer such that when exposed to ultraviolet-A (UV-A) light at
         370nm
      b) Causes the generation of reactive oxygen species
      c) Can react further with various other molecules, which induce chemical bonds that
         bridge the groups of collagen fibers

C. Collagen CXL: Pre-Op Findings
1. Documentation of corneal progression:
   a) Increased ametropia (Spectacle Rx)
   b) Progression on:
      (1) Keratometry manual or simulated
      (2) Topography & Tomography
      (3) Corneal Pachymetry – Thinnest
(4) Provide CL type & Refraction & VAs
   c) A dilated exam completed within the last 12 months

2. Setting expectations will determine candidacy

D. Collagen CXL: Pt. Expectations
1. Patients are hopeful, wanting “Cure for Keratoconus”.
2. Expectations are communicated and reinforced.
   a) Cross-Linking WILL NOT work like laser vision correction to improve vision without glasses.
   b) Cross-Linking WILL NOT work like Intacs to improve irregular corneal shape.
   c) Cross-Linking WILL NOT prevent the need for vision correction in the form of glasses or contacts.

E. Collagen CXL: Procedure
1. Epi-On vs. Epi-Off?
   a) Removal of Epithelium: used for most techniques
2. Conventional methods of epithelial removal:
   a) Mechanical device
   b) Femto-laser
   c) ETOH

F. Riboflavin 0.1% Drops: Photrex Viscous (Avedro)
1. Average 30 minutes duration with a drop every 2 minutes until Riboflavin is present throughout the cornea and in the anterior chamber
2. If corneal thickness is too thin for treatment, additional hypotonic solution (Photrex) may be used to temporarily thicken the cornea until it 400 microns

G. Collagen CXL: Slit Lamp Exam
1. Riboflavin must be present in the entire cornea including the anterior chamber before the next phase of the treatment can proceed – UV Light Exposure
2. Looks orange throughout the cornea and A/C
3. Once full saturation is confirmed by slit lamp observation, central pachymetry is checked to ensure greater than 400 microns

H. Collagen CXL: UV Light
1. UV Light + Riboflavin at nJoy under IRB
2. Eye is exposed to UV Light at 5 cm depth from pt.’s eye with approx. 8mm spot size, so not to hit limbal stem cells.
3. Exposure of UV-A light is done for 5 minutes at 18mW/cm²
4. FDA Approved: Avedro KXL is done for 30 min at 3mW/cm²
5. Bandage Contact Lens
   a) For comfort and removed similar to surface ablation (PRK) with laser vision correction

I. Collagen CXL: Recovery
1. Very similar to PRK
   a) Days 1-3 vision is okay but comfort is poor
   b) Days 4-5 vision is poor but comfort is better
   c) Days 5-14+ vision is fluctuating
   d) Contact lens wear
      (1) Patients can begin wearing CLs - usually 2-3 weeks after the procedure
   e) Rx and lens type will need to be adjusted weeks & months and potentially years after the procedure
2. Corneal CrossLinking occurs slowly
   a) First 4-8 weeks Cross-Linking begins
   b) Studies indicate corneal structure continues to strengthen beyond 5+ years

J. Collagen CXL: Post-Op Findings
1. Very similar to PRK
2. After treatment, antibiotic drops are applied
3. Bandage CL is placed
4. Clear eye shield is worn overnight until the next day when the surface of the eye has healed.
5. Oral analgesics are required for the first 1-2 days.
6. Monitor 1 week until cornea is Re-epithelialized
7. Once contact lens removed…1 month, 3 month, 6 month, Annual exam just as important !!!

K. Collagen CXL: Inclusion Criteria
1. Diagnosis of Keratoconus or Forme Fruste or corneal ectasia with progression over last 6 months or longer.
2. 12 years or older
3. Pachymetry of 425 microns or more prior to epithelial debridement at the thinnest point in the eye to be treated.
4. Willingness to complete all study visits.

L. Collagen CXL: Exclusion Criteria
1. Allergy to Riboflavin.
2. Pregnant or planning to be, or breastfeeding
3. End-stage keratoconus: Kmax 58, per Dresden Protocol.
4. Cornea pachymetry: less than 425 microns
5. Prior to epithelial debridement at the thinnest point in the eye to be treated.
6. History of corneal disease, not including dry eyes.
7. HSV or HZO,
8. RCE: Recurrent erosion,
9. Corneal melt or dystrophy
10. Collagen CXL: Exclusion Criteria
   a) Clinically significant corneal scarring treatment zone that is not related to keratoconus or corneal ectasia
   b) A history of delayed epithelial healing in the eye(s) to be treated.
   c) Patients with significant nystagmus or any other condition that would prevent a steady gaze during the treatment or other diagnostic tests.
   d) Taking Vitamin C (ascorbic acid) supplements within 1 week of the cross-linking treatment.

M. Collagen CXL: Treatment Options
1. Bilateral CXL allowed if indicated for both eyes or
2. Patient preference if performed unilaterally
3. Can be combined with INTACS resulting in a “Combo Procedure”
4. Can be combined with Laser Vision Correction for suspected of thinner/weaker corneas
   a) PRK Xtra / LASIK Xtra

N. CXL: Pros & Cons
1. Advantages:
2. No injection, no stitches & no incisions as in Keratoplasty
3. Simple ONE time treatment
4. Halts the progress and causes some regression
5. Increase in corneal stiffness of the anterior 200-250 μm

O. Possible Side Effects: only if correct measures are not implemented
1. Endothelial cell loss
2. Crystalline lens opacity
3. Pain or Infection
4. Stromal Haze
5. Delayed Epithelial healing
6. Retinal Damage

P. Collagen CXL: Conclusions
1. Slows / Halts progression of: Keratoconus and Corneal Ectasia
2. Decreases corneal curvature
3. Regularizes cornea surface
4. Improves UCVA and BCVA
5. Effects seem to last indefinitely, as bonds continue to get stronger and stronger with time
6. Offers safe and effective treatment for conditions with no currently available treatment and may help avoid…..
7. Corneal transplant by 15%
8. Disability, cost, loss of productivity, etc..