A Review of Corneal Dystrophies and Degenerations

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Financial Disclosures For Marc r Bloomenstein, OD, FAAO

- Allergan-Speaker/Consultant
- Avellino-Consultant
- Azura-Consultant
- Bausch & Lomb-Speaker/Consultant
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All financial relationships have been mitigated.

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Corneal Dystrophies

- Group of corneal diseases that are genetically determined and have been traditionally classified with respect to the corneal layer affected
- Defined as a corneal opacity or alteration, which is most often bilateral and progressive and centrally located
- Tend to be avascular and involve all the areas of the cornea
- New Classification system describes old name, new name, defective gene, inheritance pattern, phenotype of disorder and typical complications.

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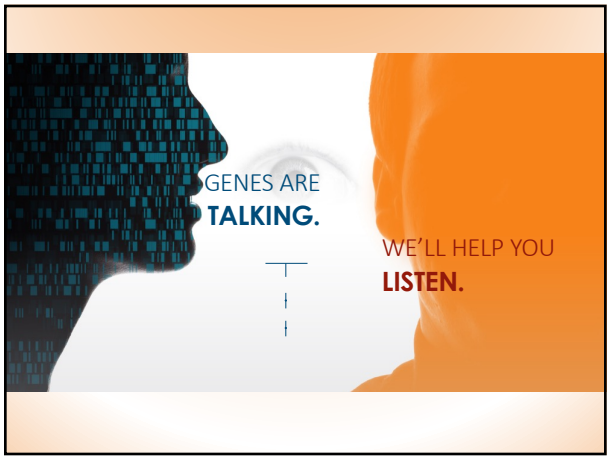
GENETICS IN **REFRACTIVE SURGERY** WHAT TO KNOW BEFORE YOU CUT THE CORNEA

5

GENETIC DATA **CAN HELP US...**

PERFORM THE RIGHT REFRACTIVE SURGERY PROCEDURE ON THE RIGHT PATIENT.

6


GENES ARE
TALKING.
WE'LL HELP YOU
LISTEN.

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EYE GENETICS 101
THE GOAL: REDUCE SURGICAL RISK
By Personalizing The Refractive Procedure Decision
Diagnostics
Observation & Measurement
Environment
Patient Variables
Genetic Data
Personalized Keratoconus Risk & CD Diagnosis

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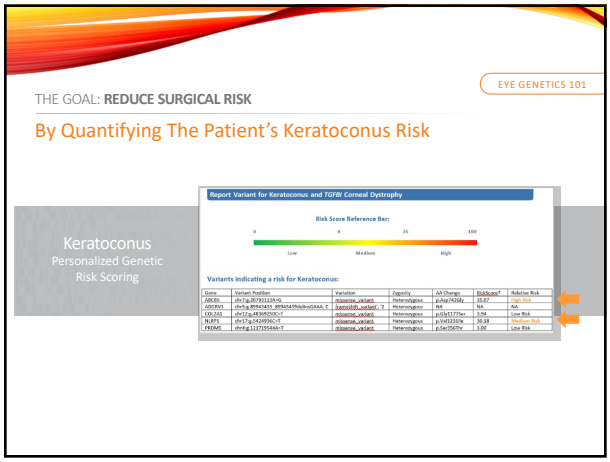
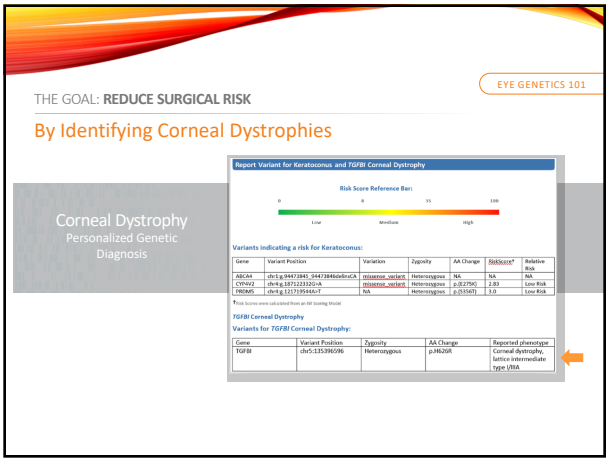

EYE GENETICS 101
THE GOAL: REDUCE SURGICAL RISK
By Quantifying The Patient's Keratoconus Risk
Keratoconus
Personalized Genetic Risk Scoring
Report Variant for Keratoconus and TGFBI Corneal Dystrophy
Risk Score Reference Bar:
Variants indicating a risk for Keratoconus:

10


EYE GENETICS 101
THE GOAL: REDUCE SURGICAL RISK
By Identifying Corneal Dystrophies
Corneal Dystrophy
Personalized Genetic Diagnosis
Report Variant for Keratoconus and TGFBI Corneal Dystrophy
Risk Score Reference Bar:
Variants indicating a risk for Keratoconus:
TGFBI Corneal Dystrophy
Variants for TGFBI Corneal Dystrophy:

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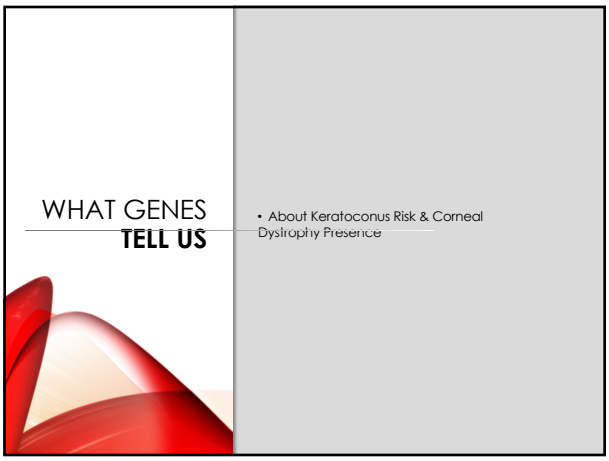
EYE GENETICS 101
THE GOAL: REDUCE SURGICAL RISK
With An Easy Testing Method
With Nurse Or Tech
Overnight Shipping
Digital Report
Evaluation Support On Request

12


WHAT GENES
TELL US
• About Keratoconus Risk & Corneal Dystrophy Presence

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HOW **GENES TELL US**

Next Generation Sequencing Technology

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NGS TECHNOLOGY

NEXT GENERATION **SEQUENCING**

Variants indicating a risk for Keratoconus:

Gene	Variant Position	Variation	Zygosity	AA Change	RiskScore†	Relative Risk
ABCB5	chr7:g.20795113A>G	missense_variant	Heterozygous	p.Asp742Gly	35.07	High Risk
ADGRV1	chr5:g.89943433_89943439delinsGAAA, C	frameshift_variant ~2	Heterozygous	NA	NA	NA
COL2A1	chr12:g.48369250C>T	missense_variant	Heterozygous	p.G9r11775er	3.54	Low Risk
NLRP1	chr17:g.5424936C>T	missense_variant	Heterozygous	p.Val1231Ile	30.18	Medium Risk
PRDM5	chr6:g.121719544A>T	missense_variant	Heterozygous	p.Ser356Thr	3.00	Low Risk

†Risk Scores were calculated from an IW Scoring Model

Other Variants:

Gene	Variant Position	Variation	Zygosity	AA Change
LRRN1	chr3:g.38873307>G	missense_variant	Heterozygous	p.Ser335Arg

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ANTERIOR DYSTROPHIES

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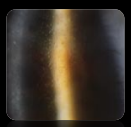
Meesmann's Dystrophy

- **Autosomal dominantly**
- **Symptoms**
  - **Foreign body sensation due to epithelial erosion**
  - **Decreased visual acuity is usually minimal**
- **Signs:**
  - **Myriads of tiny intraepithelial cysts that are most prominently seen in the interpalpebral zone**
  - **Slowly progressive**
  - **Bilateral, symmetric**
  - **Develops in the first 1 or 2 years of life**
- **Treatment:**
  - **Superficial corneal debridement**
  - **PTK**



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Meesmann's Dystrophy

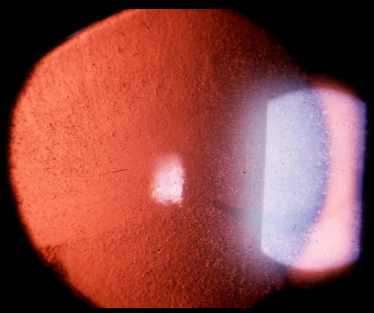

Photo Courtesy Tracy Swartz OD, FAAO

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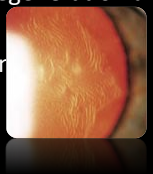
Epithelial Basement Dystrophy (EBMD)

- Abnormal corneal epithelial regeneration and maturation
- Abnormal basement membran
- Very common dystrophy
- Considered age related
  - Prevalence increases with age
    - Onset is around 40-70 y.o.
  - Late onset supports degeneration vs. dystrophy



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EBMD

- 10-69% of patients are symptomatic
- Symptoms
  - Foreign body sensation
    - Worse in dry weather
    - Wind
    - Air conditioning
  - Blurred vision
  - Dry eye
    - Increased TBUT
  - Discomfort
    - 10% experience RCE's

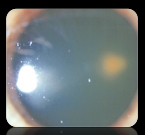

Photo Courtesy Tracy Swartz OD, FAAO

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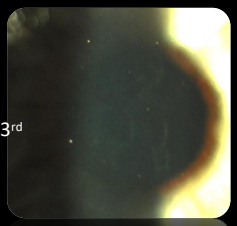
EBMD

- Appears as a map, dot or fingerprint
  - Chalky patches
  - Intraepithelial microcysts
  - Fine lines within central 2/3rd of cornea
- Bilateral and asymmetric
- Females> Males
- Negative staining is a good indicator



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EBMD

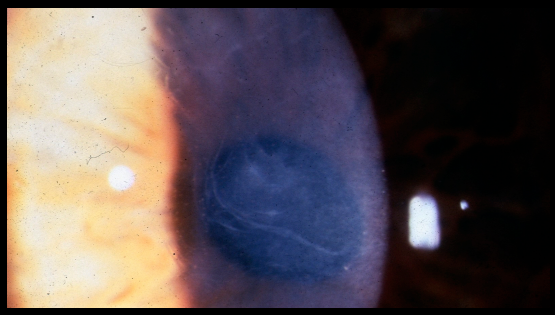

Photo Courtesy Tracy Swartz OD, FAAO

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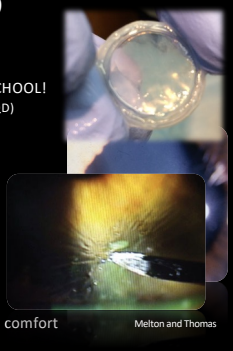
EBMD

- Treatment of EBMD
  - Monitoring cornea for any RCE-OLD SCHOOL!
    - Azasite qhs or oral doxycycline (50 mg/QD)
    - Lotepredrnol etabonate
    - Copious Artificial tears
    - Fresh Kote
    - Cyclosporine bid
    - Bandage contact lens while active (1M)
    - Punctal plugs
    - Consider humidifier
  - Amniotic Membrane
  - Surgery may be needed
    - PTK
    - Puncture
  - Monitor for changes in visual acuity or comfort



Melton and Thomas

Photo Courtesy Tracy Swartz OD, FAAO

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EBMD POST-PTK

Photo Courtesy Tracy Swartz OD, FAAO

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THE "PREVENTED" CORNEAL EROSION

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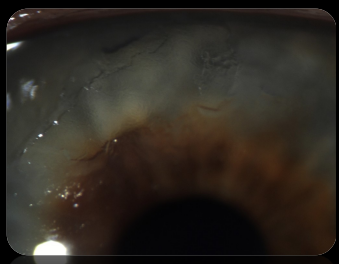
43 yo female

- "I felt like something was stabbing my eye"
- "This happened another time and the doctor told me to use ointment at night"
- Type II Diabetes
- NKMA



"IT REALLY HURTS"

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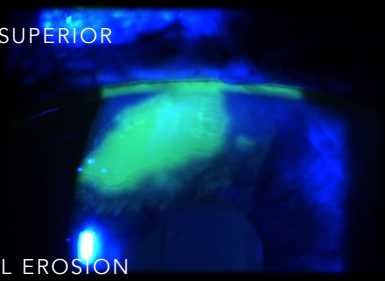
THE RECURRENT EROSION

VA: 20/100 PH 20/30
SLIT-LAMP:
SUPERFICIAL SUPERIOR ABRASION
+ STAINING



DX: CORNEAL EROSION

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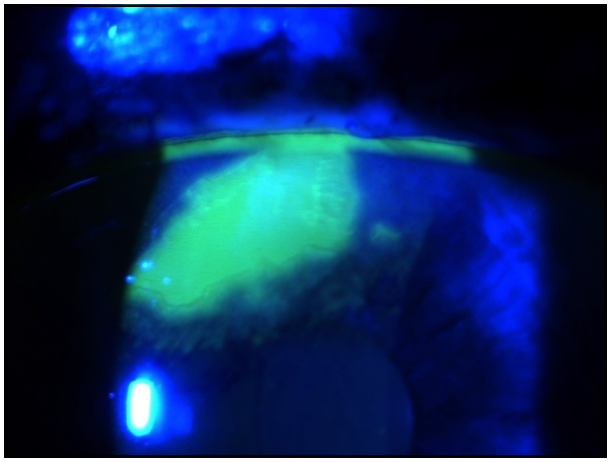

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EBMD

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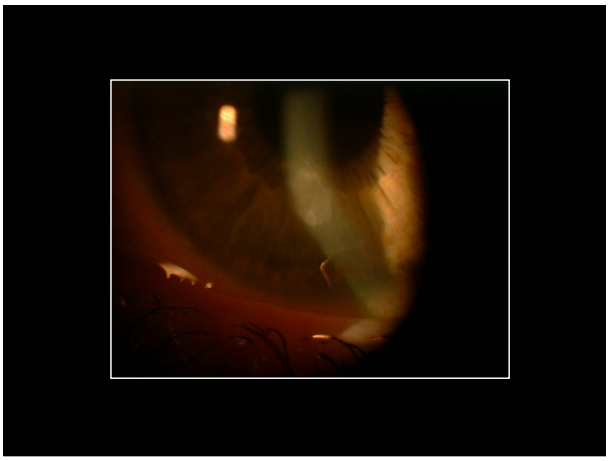

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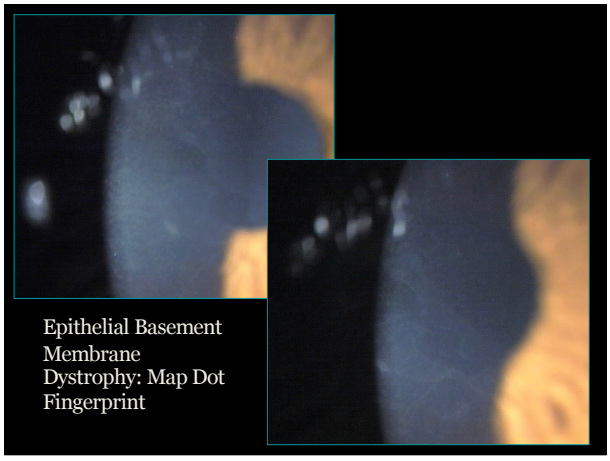

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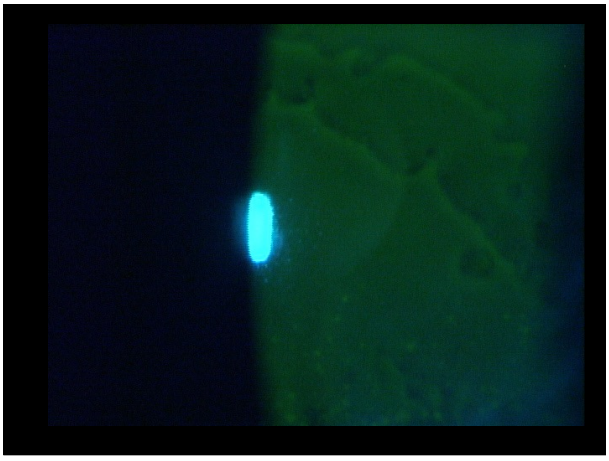

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87% of all RCE occurs in what part of the cornea?

Inferior Cornea

Reidy JJ, Pauli MP et al. *Cornea* 2000 Nov.

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46% of all patients in this study had EBMD

- James Reidy et al. Recurrent erosions of the cornea: epidemiology and treatment. *Cornea* 2000 Nov; 19(6):767-71
- The remainder had trauma induced causes
  - *Fingernail*
  - *Paper cut, etc.*

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Diagnosis:

- **Recurrent Corneal Erosion**
- **EBMD**

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Treatment:

- **What medications should be avoided?**
- **Bland Artificial Tear Ointments**

Eke T, et al. Recurrent symptoms following traumatic corneal abrasion. *Eye* 1999 June.

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Prokera

NON-HEALING ABRASION

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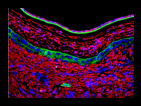
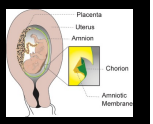
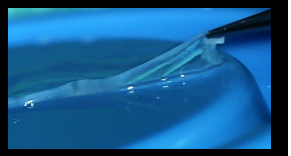
The Amniotic Membrane

- The amniotic membrane is the innermost lining of the placenta (amnion)
- Amniotic membrane shares the same cell origin as the fetus
  - –Stem cell behavior
- Structural similarity to all human tissue







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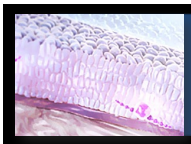

Inflammation's Effect on Healing

- **Inflammation:** the first sign of wound healing & is also the hallmark symptom of all ocular surface diseases
- Uncontrolled inflammation leads to:
  - Chronic pain and discomfort/irritation
  - Delayed healing, more tissue damage
  - Vision-threatening complication, e.g., scar/haze
- Effective control of inflammation is an important strategy to promote healing and minimize the risk of scar/haze

Non-Resolved Inflammation ⇄ Tissue Damage

Controlling Inflammation is Key to Preventing Tissue Damage!

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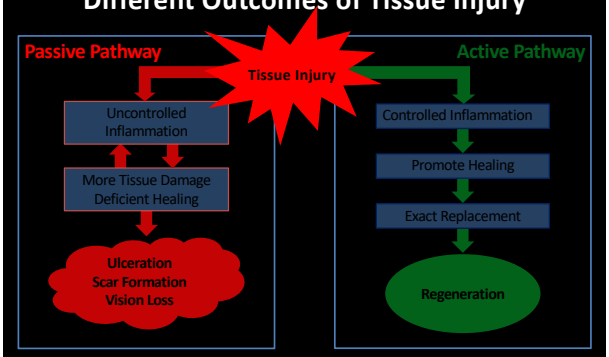
Different Outcomes of Tissue Injury



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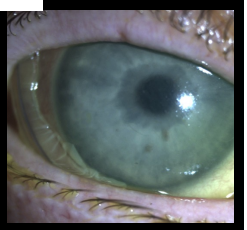
Clinical Study

Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

CAM vs. conventional DE Tx	
Reduction in VAS	•7.1 to 2.2
Reduction in SPEED	•21.8 to 5.9
Increase in CND/CNL	•Baseline: 12,241 +/- 5083 um/mm² •3 mo: 18,827 +/- 5453 um/mm²
Improvement in TBUT	•8.3 +/- 2.5 to 13.9 +/- 2.2
Control group showed no change in all parameters	



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The CRYOTEK™ Method

- Patented and proprietary cryopreservation
- Ensures key active components of the Extracellular Matrix (ECM) are retained
- The **only** method that retains both:
  - The integrity of the tissue structure
  - The key active (ECM) components
- Safe and effective
  - Supported by over **300** peer-reviewed articles
  - Over **100,000** implanted
- Bio-Tissue Cryopreserved Amniotic Membrane is the **ONLY** AM granted wound healing indication by the FDA.

biotissue

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PROKERA®: BIOLOGIC CORNEAL BANDAGE

PROKERA® utilizes the proprietary CryoTek™ cryopreservation process that maintains the active extracellular matrix of the amniotic membrane which uniquely allows for regenerative healing.

PROKERA® is the only FDA-cleared therapeutic device that both reduces inflammation and promotes scar less healing

PROKERA® can be used for a wide number of ocular surface diseases with severity ranging from mild, moderate, to severe

Photo Courtesy Tracy Swartz OD, FAAO

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Acellular Amniotic Membrane

ACELLFX

- HCT/P (human cells, tissue, and cellular-based product)
- Nutrient rich
  - Collagen III, IV, and V
  - Fibronectin
  - Lamin
  - Proteoglycans
- Thea Pharmaceuticals

Human amniotic membrane sourced from Cesarean donors

Processed without chemicals, cross-linking agents, germicides or antibiotics

Air dried

Sterilized

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Acellular Amniotic Membrane

- Ready to use immediately
  - No thawing
  - No rinsing
- No up/Down orientation
- Flexible membrane with no ring
- Allows for multiple applications
- Convenient storage at room temperature for 5 eyars
- WOO-WOO

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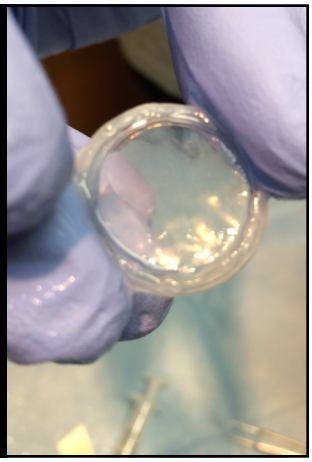
TREATMENT

STANDARD PROTOCOL:

- BCL
- ANTI-BIOTIC
- ANTI-INFLAMMATORY
- RTC
- NEW REGIMENT
- PROKERA
  - LATERAL TAPE TARSORAPHY
  - PATIENT EDUCATION
- RTC 5 DAYS



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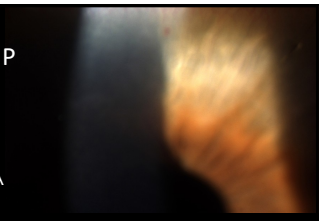
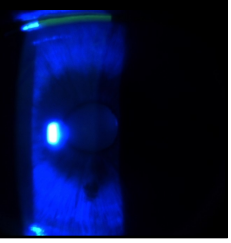
5 DAY FOLLOW-UP



"THE PAIN IS GONE"
- REMOVED PROKERA
- VASC: 20/15

SLIT-LAMP:
CORNEAL CLEAR



TX: RESTASIS BID
RTC 4-6 WEEKS

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3 MONTH FOLLOW-UP

- "MY EYE FEELS GREAT"
- VASC: 20/15
- SLIT-LAMP: CLEAR CORNEA
- DX:

PCE (PREVENTED CORNEAL EROSION)
TX: CPM(RESTASIS)

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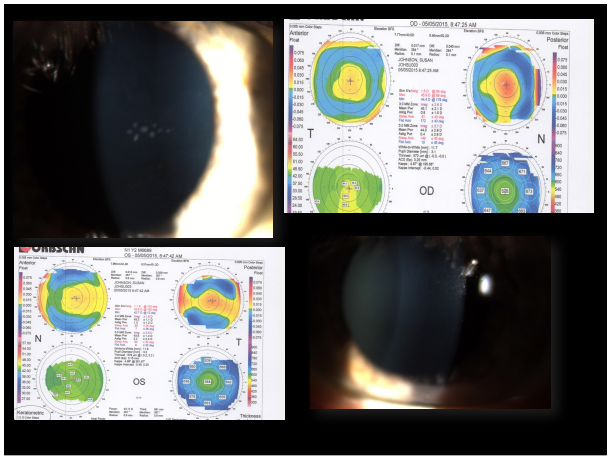

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Hx of RCE

- Plan: RTC in 3 days/Debride Cornea/Insert Prokera Slim
- Plan:
  - Tape tarsoraphy
  - Zymaxid qid/Prolensa qd/Pred Forte qid
    - RTC:
      - 6 days

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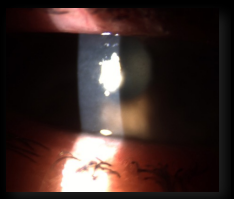
CPAM Removed

- Vasc 20/100
- "My eye feels great"
- Follow-up in 2 weeks
  - Cyclosporine BID
  - Retaine MGD q1h



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My Vision is blurry…like a lot.

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"Can I do my other eye first?"

- 72 yo Male
  - Cataracts in both eyes
    - Scheduled for surgery in left eye
    - Starting using drops pre-op
      - "I may have hit my eye with the tip of the drop?"
      - "My vision is way worse now"
    - VaSC
      - 20/200 ph 20/70 OD
      - 20/CF ph 20/200 OS
    - Slex:
      - OD-Corneal Clear, NSC/ASC
      - OS-

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Testing corneal sensitivity IS IMPORTANT TO DIAGNOSING NK

QUALITATIVE

COTTON THREAD
- When the cotton thread gently touches the cornea, normal subjects show a blink reaction and can describe the sensation of touch
- Patients with a loss of corneal sensitivity DO NOT react

QUANTITATIVE

COCHET-BONNET AESTHESIOMETER
- Commonly used
- Quantifies corneal sensitivity by a nylon filament of different lengths touching the cornea to elicit a blink or patient response
- Each quadrant of the cornea can be tested separately

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579.

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"It is still blurry…"

- Used a BCL, AB
  - RTC 1wk
  - NO IMPROVEMENT
  - BCL-missing…however the patient stated "It feels fine!"
  - "Can I do surgery on the other eye?"
    - Cotton-tip sensation:
      - OD-5/10
      - OS- 0/10
- Prokera Slim inserted
- Rx'd Oxervate

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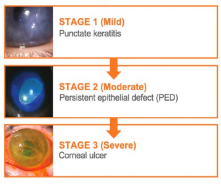
Mackie Classification

NK Is a Degenerative Disease[1]

The Mackie Classification Represents One Way to Assess NK Progression[2,3]



- Some vision loss can potentially be seen **in all stages of NK**[3]
- If untreated, **moderate NK progresses to severe disease** with associated risks of **profound vision loss** resulting from scarring and corneal perforation[3]

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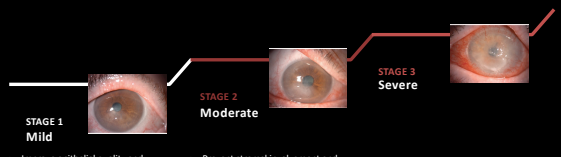
Mackie Classification



- Improve epithelial quality and transparency
- Avoid epithelial breakdown
- Prevent stromal involvement and corneal ulcer formation
- Stop stromal melting
- Prevent perforation that could lead to essential vision loss

1. Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain*. 2018;10:37-45. **2.** Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

66

NK Study Group 7 Step Staging

Stage	Clinical Features	Imaging
0	Altered sensation without keratopathy	
1 (mild)	Epitheliopathy without stromal haze	
2 (moderate)	Epitheliopathy with stromal haze	
Stage 3 (severe)	Persistent or recurrent epithelial defects	
Stage 4 (severe)	Persistent or recurrent epithelial defect and stromal scarring without corneal ulceration	
Stage 5 (severe)	Persistent or recurrent epithelial defect with corneal ulceration	
Stage 6 (severe)	Corneal perforation	

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Systemic

- Diabetes
- Multiple sclerosis
- Vitamin A deficiency
- Leprosy
- Amyloidosis

Photo Courtesy Tracy Swartz OD, FAAO

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Central nervous system

- Aneurysms
- Stroke
- Degenerative disorders of the CNS
- Post-neurosurgical procedures

Photo Courtesy Tracy Swartz OD, FAAO

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Genetic

- Riley-Day syndrome
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoesthesia

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Ocular Conditions for NK

- Post-herpes keratitis
- Chemical and physical burns
- Abuse of topical anesthetics
- Drug toxicity (eg, BAK)
- Chronic ocular surface injury
- Ocular surgery (eg, LASIK, cataract surgery)
- Contact lens wear
- Orbital neoplasia
- Corneal dystrophies
- Chronic DED

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Only FDA Approved for NK

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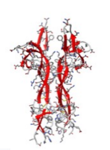
Active ingredient structurally identical to human nerve growth factor produced in ocular tissues



- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons[1]
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s[1]
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein[2]

biotissue

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FDA APPROVAL WAS BASED ON COMPLETE CORNEAL HEALING DEFINED AS ABSENCE OF STAINING OF THE CORNEAL LESION AND NO PERSISTENT STAINING IN THE REST OF THE CORNEA AFTER 8 WEEKS OF TREATMENT.

CENEGERMIN CLINICAL TRIALS: STUDY OVERVIEW

	NGF0212 (REPARO) (n=156)	**NGF0214** (n=48)
Geography	Europe 6 Countries (Italy, Germany, UK, France, Spain, Poland) 32 Clinical Centers	USA 11 Clinical Centers
Design	3 treatment arms: (vehicle, cenegermin 10 mcg/mL, cenegermin 20 mcg/mL)	2 treatment arms: (vehicle, cenegermin 20 mcg/mL)
Vehicle & cenegermin composition	Without antioxidant	With antioxidant (methionine)
Duration of follow up	48 weeks	24 weeks
Uni/bilateral disease	Unilateral	Unilateral and bilateral
Endpoints	Week 8 (based on a post-hoc analysis) Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area) *Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4	Week 8 Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area)

1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology* 2018;125:1332-1343. 2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial. *Ophthalmology*. 2020;127(1):14-26.

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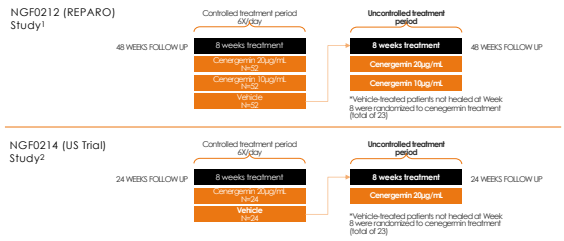
CENEGERMIN CLINICAL TRIALS: STUDY DESIGN



1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332-1343. 2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve

75

CENEGERMIN CLINICAL TRIALS: INCLUSION AND EXCLUSION CRITERIA

MAIN INCLUSION CRITERIA

- Adult NK patients with stage 2 or 3 NK
  - Unilateral NK only in NGF0212/REPARO
  - Unilateral or bilateral NK permitted in NGF0214
- Evidence of decreased corneal sensitivity (<40mm by Cochet-Bonnet aesthesiometer) within the area of the PED or corneal ulcer and outside of the area of the defect, in at least 1 corneal quadrant
- Refractory to ≥1 nonsurgical treatment
- No improvement in in 2 weeks prior to enrollment

MAIN EXCLUSION CRITERIA

- Infection, inflammation, other ocular disease requiring topical treatment
  - Glaucoma patients were switched to systemic meds during the study
- Severe blepharitis or MGD
- Prior surgical treatment for NK
  - Exception for AMT performed >6 weeks prior or membrane disappeared >2 weeks prior
- Stromal involvement in posterior third, corneal melting, or perforation in study eye

1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332-1343. 2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal

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CENEGERMIN CLINICAL TRIALS: BASELINE DEMOGRAPHICS

	NGF0212/REPARO Study1,3		NGF0214 (US Trial) Study 2,3	
	OXERVATE® (N=52)	VEHICLE (N=52)	OXERVATE® (N=24)	VEHICLE (N=24)
PRIMARY NK DIAGNOSIS, NO. (%)				
Stage 2 (moderate)	27 (51.9)	28 (53.8)	15 (62.5)	18 (75.0)
Stage 3 (severe)	25 (48.1)	24 (46.2)	9 (37.5)	6 (25.0)
Underlying cause, no. (%)				
Herpetic eye disease	11 (21.2)	18 (34.6)	9 (37.5)	8 (33.3)
Neurosurgical procedure	8 (15.3)	7 (13.4)	1 (4.2)	5 (20.8)
Ocular surgery or procedure	5 (9.6)	7 (13.4)	3 (12.5)	4 (16.7)
Dry eye disease	6 (11.5)	5 (9.6)	3 (12.5)	3 (12.5)
Ocular surface injury/inflammation	5 (9.6)	5 (9.6)	2 (8.3)	1 (4.2)
Other	5 (9.6)	3 (5.8)	2 (8.3)	1 (4.2)
Topical medication (glaucoma)	1 (1.9)	1 (1.9)	1 (4.2)	1 (4.2)
Stroke	2 (3.8)	0	0	1 (4.2)
Unknown origin	1 (1.9)	0	2 (8.3)	0
Systemic medication	0	0	1 (4.2)	0

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE®. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332-1343. 2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial. Ophthalmology. 2020;127(1):14-26.
3. Accessdata.fda.gov. Drug approval package: OXERVATE (Cenegermin-bkbj). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000SumR.pdf. Published 2018. Accessed November 13, 2018

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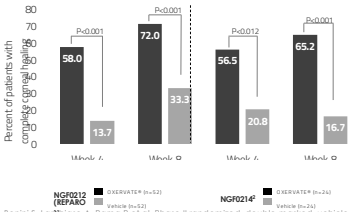
CENEGERMIN CLINICAL TRIALS: RESULTS



Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE® patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.3

Complete corneal healing defined as 0-mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment(last post-baseline observation carried forward; chi-squared test).

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE®. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

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3. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2019

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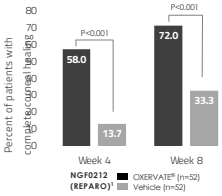
80% of patients who achieved Complete corneal healing* in Study NGF0212 (REPARO) were still healed 48 weeks after completing one 8-week OXERVATE® treatment cycle1,2

CENEGERMIN CLINICAL TRIALS: NGF0212 1-YEAR FOLLOW-UP DATA



*Complete corneal healing defined as 0-mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE®. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE® patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing3

1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332-1343. 2. Data on file. Clinical study report. Study NGF0212. Boston, MA: Dompé U.S. Inc.; 2016.. 3. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2019.

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- No serious adverse reaction related to the treatment occurred in any clinical trials1,2
- The majority of adverse reactions were mild and transient ocular reactions that did not require treatment discontinuation or corrective treatment2

CENEGERMIN CLINICAL TRIALS: SAFETY RESULTS

The most common adverse reaction was eye pain (16%) following instillation, which was reported in approximately 16% of patients.3

12/75 = 16%
7/21 = 30.4% (US trial)
5/52 = 9.6% (REPARO)

Other adverse reactions occurring in 1%-10% of patients taking OXERVATE® and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and tearing.3

1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332-1343. 2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial. Ophthalmology. 2020;127(1):14-26 3. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2019.

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Study Conclusions

After 8 weeks of treatment, 6 times daily

In most patients across two clinical studies, cenegermin ophthalmic solution 0.002% was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

50 clinical trial sites in Europe and US

Study NGF0214 (N=24 per group)

US patients with NK in one or both eyes

NCT02227147

65.2% completely healed

Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment… **80%** Remained healed for one year*

*Based on REPARO, the study with longer follow-up

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June,2017, Barcelona, Spain. 2017. 3. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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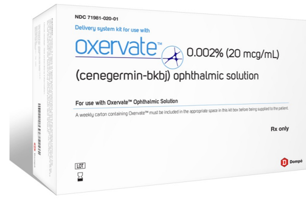
RECOMBINANT NGF

- Multiple studies support use of NGF to repair damaged nerves
- Oxcervate (Dompe, Italy)
  - FDA approval December 2018 for neurotrophic keratitis
  - 85,000 x 6 weeks
- NGF also important for epithelial cell turnover & migration[1], LSCN maintenance[2]
- Could it be used to mitigate pain response?



1) Blanco-Mezquita T, et al. IOVS, 2013 Jun 4;54(6):3880-90.
2) Kolli S, et al. Stem Cells. 2019 Jan;37(1):139-149.

82

NK Treatment Options[1-3]

Treatments are typically used according to NK stage/severity but are not mutually exclusive of one another. The table is not an exhaustive list of all available treatment options.

Topicals	In-Office Procedures	Surgical Intervention
Artificial tears	Therapeutic contact lenses	Tarsorrhaphy
Corticosteroids	Punctal occlusion	Conjunctival flap
Autologous serum eye drops	Non-surgical eyelid closure	Corneal transplant
Antibiotics	Multilayer amniotic membrane transplantation (AMT)	Direct neurotization
Cenegermin-bkbj ophthalmic solution 0.002% [20 mcg/ml]	Tissue adhesives	Sutured AMT

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131;
2. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232:717-724.
3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579;

26

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Treatment Algorithms

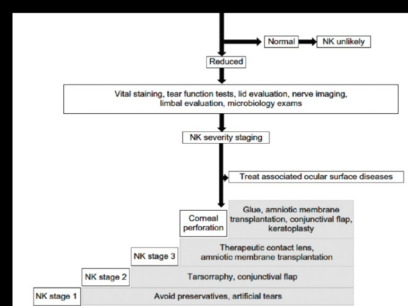

Photo Courtesy Tracy Swartz OD, FAAO

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Bowman's Layer Dystrophies

- Reis-Buckler
  - Autosomal Dominant
  - Early marked visual loss
  - Corneal Surface is smooth

- Thiel-Behnke
  - Autosomal Dominant
  - Corneal sensation normal
  - May present with RCE's

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Reis-Buckler

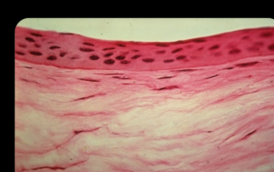

Photo Courtesy Tracy Swartz OD, FAAO

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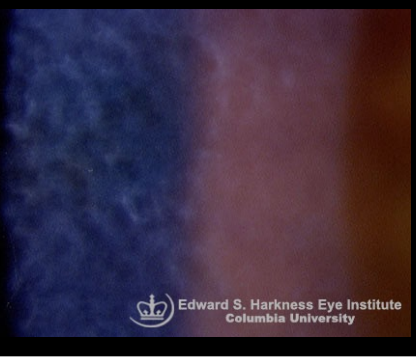
Thiel-Behnke Dystrophy



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STROMAL DYSTROPHIES

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Granular Dystrophy (Groenouw Type I)

- Discrete white granular opacities in central anterior corneal stroma
- Increasing number, density, size and depth as age
- RCE's are commonly associated with pain
- Sub-epithelial scarring/dense stomal deposits reduce visual acuity
- PKP if disease progresses

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GRANULAR DYSTROPHY

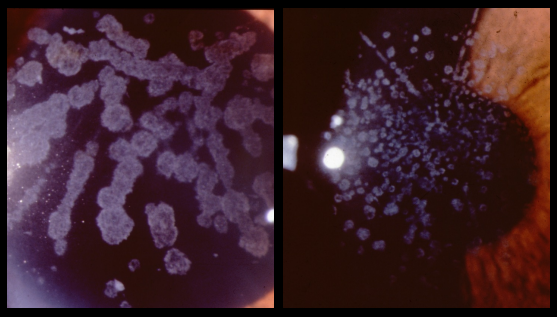

Photo Courtesy Tracy Swartz OD, FAAO

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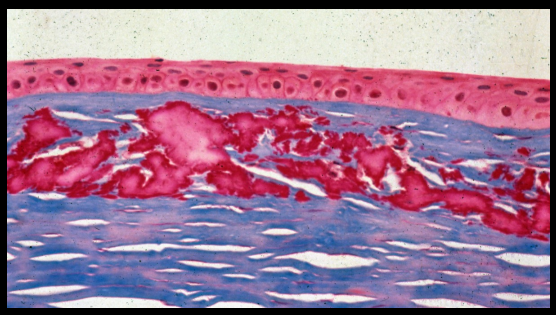
GRANULAR DYSTROPHY



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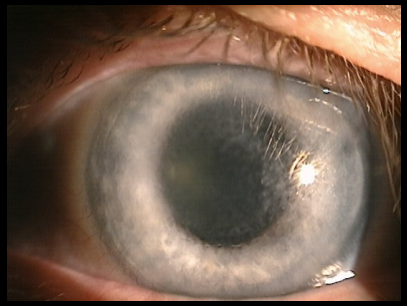
Granular Dystrophy



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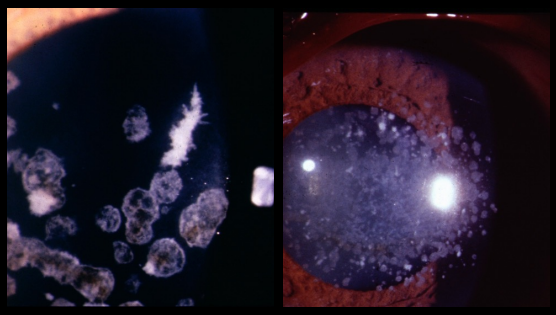
GRANULAR DYSTOPHY



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GRANULAR DYSTROPHY

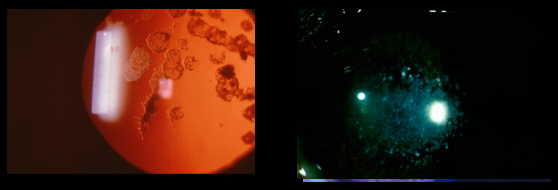

Photo Courtesy Tracy Swartz OD, FAAO

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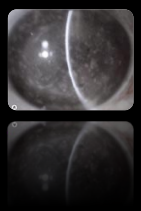
Macular Dystrophy (Groenouw Type II)

- Grayish opacities with indistinct edges in superficial stroma
- Over time
  - Extends into deeper stromal layers
  - Intervening stroma becomes hazy
  - CORNEA THINS
  - Visual acuity is decreased
  - Light sensitivity and pain
- Surgery is expected by 20-30 years old



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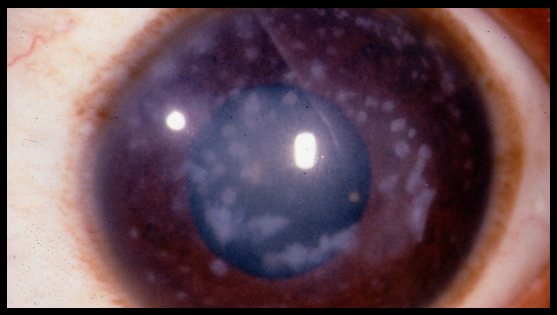
Macular Dystrophy



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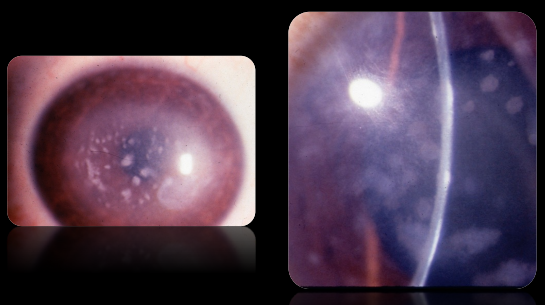
96

Macular Dystrophy



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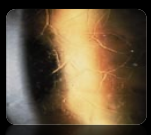
Lattice Dystrophy (Type I)

- Clinically appears
  - Linear, refractive branching deposits within the anterior stroma
- Central cornea becomes opaque and scars decreasing the visual acuity
- Autosomal Dominant
- 1st Decade
  - > 4th decade decrease VA
- RCE's are associated with Lattice
- Surgical intervention recommended with decreased acuity



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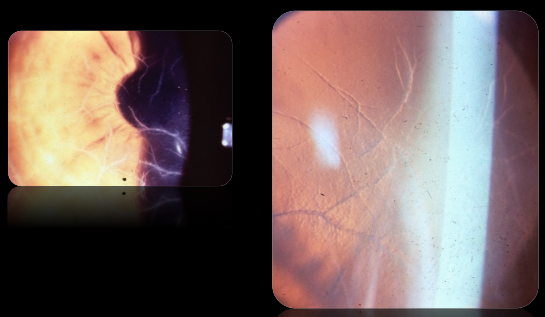
Lattice Dystrophy



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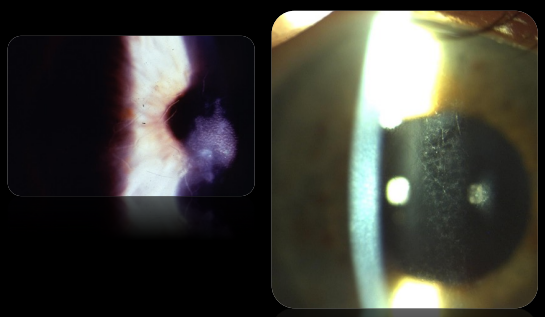
Lattice Dystrophy



100

Schnyder Corneal Dystrophy (SCD)

- Central discoid opacification posterior to Bowman's membrane in anterior stroma
- Formerly thought crystals were in all opacities
  - 50-54% present
- Opacities can consist of:
  - Small needle shaped refractileals crystals
    - White
    - Polychromatic
  - May extend into deeper stroma-avoiding epithelium
- Vision is relatively unaffected
- Associated with familial hypercholesterolemia

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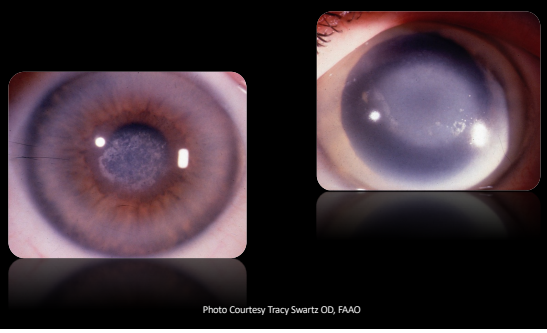
Schnyder's Corneal Dystrophy



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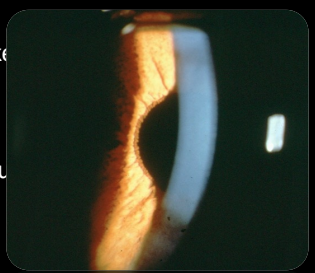
Other Stromal Dystrophies

- Avellino
- Gelatinous Drop Like
- Fleck
- Central Cloudy
- Posterior Amorphou



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POSTERIOR MEMBRANE DYSTROPHIES

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Posterior Polymorphous

- Autosomal dominant
- Teens to 20's
- Vesicles at Descemet's/Endothelium
- Signs
  - Vesicle bands
  - Diffuse opacities
  - Edema
  - Corneal steepening
  - Increase IOP

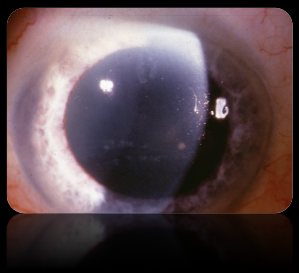

Photo Courtesy Tracy Swartz OD, FAAO

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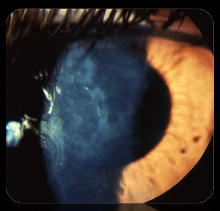
Posterior Polymorphous (PPMD)

- Vesicles are hallmark of PPMD
- Bilateral
- Trabecular meshwork can become covered with epithelial cells and basement membrane
- Synechiae can be present



106

Fuch's Dystrophy

- Autosomal dominant inheritance
- Bilateral / Asymetry
- Late onset > 50 y.o.
- Females affected 3 times more than males
  - 5.7 % develop edema
- Characterized
  - Corneal guttata
    - Excessive accumulation of abnormal endothelial secretions
    - Appears in 30-40th year of life

Photo Courtesy Tracy Swartz OD, FAAO

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Fuch's Dystrophy

- Characterized
  - Corneal Guttata
    - Small refractile "drops" on corneal endothelium
    - Affects the "pump" action of the endothelium
  - Edema
    - Greater in the AM
    - Desiccates as day goes on
    - Long standing edema may lead to corneal scarring
    - RCE's common

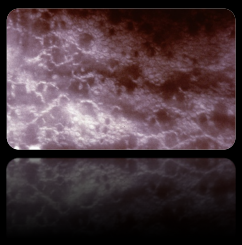

Photo Courtesy Tracy Swartz OD, FAAO

108

Fuch's Dystrophy

- Symptoms vary with degree of guttata and compromise of the endothelial tissue
- Moderate guttata
  - May affect visual function
  - May induce mild-moderate edema
    - Halos around lights
    - Hazy vision > a.m.
- Severe guttata
  - Vision decreases
  - Possible bullous develops

109

FUCH'S DYSTROPHY

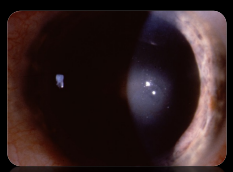

Photo Courtesy Tracy Swartz OD, FAAO

110

Fuch's Dystrophy

- Treatment
  - Early stages of disease
    - Increase artificial tears
    - Hyperosmotics qhs
    - BCL used if Bullous is present
    - EDUCATION!
  - Visual function is significantly compromised
    - Penetrating keratoplasty
    - Deep Lamellar endothelial keratoplasty (DLEK)
    - Descemet stripping automated endothelial keratoplasty (DSAEK)

111

Fuch's Dystrophy

Photo Courtesy Tracy Swartz OD, FAAO

112

Fuch's Dystrophy

- DLEK
  - Recipient cornea is stripped of Descemet's membrane and endothelium
  - Transplantation of donor cornea through small incision
  - Results in
    - Improves endothelial function, corneal clarity and restores vision
  - Minimally affects refraction
  - Can provide rapid visual recovery
  - Maintains structural integrity of the cornea

113

Congenital Hereditary Endothelium Dystrophy (CHED)

- Rare congenital dystrophy
  - First weeks-6 months old
- Bilateral-symmetric
- Non-inflammatory clouding
- Signs
  - Opacification extending to limbus with clear zones
  - Thickening
  - No neo/No extra tissue
  - No increase in IOP

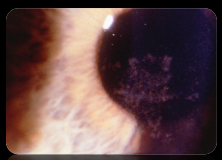

Photo Courtesy Tracy Swartz OD, FAAO

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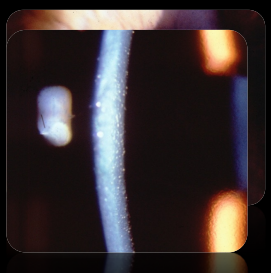
Congenital Hereditary Endothelium Dystrophy



- Nystagmus is present
- VA can be as low as 20/100
- No neo/No extra tissue
- No increase in IOP
- Diagnosis of exclusion

Photo Courtesy Tracy Swartz OD, FAAO

115

Congenital Hereditary Endothelium Dystrophy

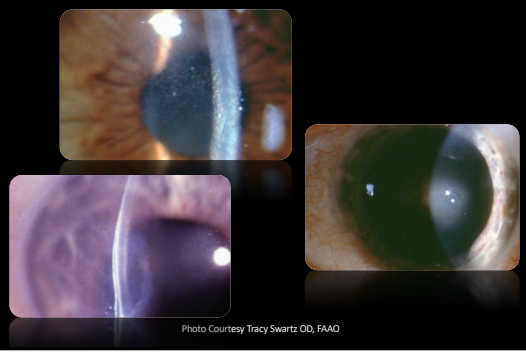


Photo Courtesy Tracy Swartz OD, FAAO

116

Iridocorneal Endothelial Syndrome

ICE

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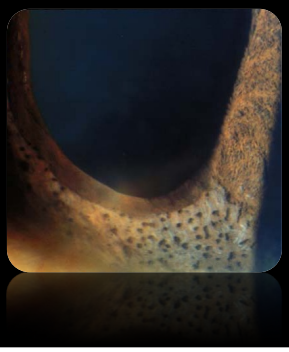
ICE

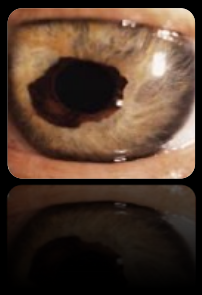
- F>M
- Diagnosed 3rd to 5th Decade
- 3 Main features
  - Iris changes
  - Corneal swelling
  - Glaucoma
- Unknown etiology



118

ICE

- Abnormal endothelium
- Irido-corneal adhesions
- 80-100% develop glaucoma
  - Increase IOP
  - Edema
- Iris
  - Mild to severe atrophy
  - Nodules may be present
  - Glassy membrane on iris
- Condition can be relentless and difficult to treat



119

CORNEAL DEGENERATIONS

120

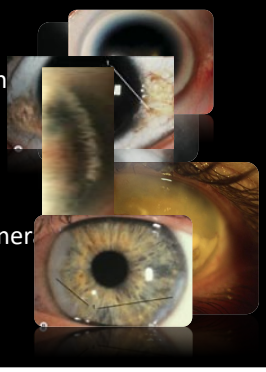
Corneal Degenerations

- Defined as a deterioration or change from a higher to a lower form, especially change of tissue to a lower or less functionally active
- Non-inherited
- Unilateral or bilateral
- Asymmetric
- Develop in later years
- Variable progression
- Systemic disease can be associated

121

Degenerations

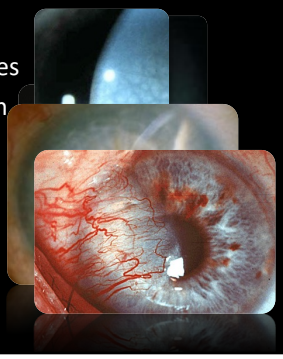
- Arcus
- Spheroidal degeneration
- Amyloid
- Limbal girdle of Vogt
- Band keratopathy
- Salzman's nodular degener



122

Degenerations

- Coats white Ring
- Hassal-Henle bodies
- Crocodile shagreen
- Senile furrow
- Dellen
- Pingueculae
- Pterygium



123

ECTATIC DISORDERS

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Keratoconus

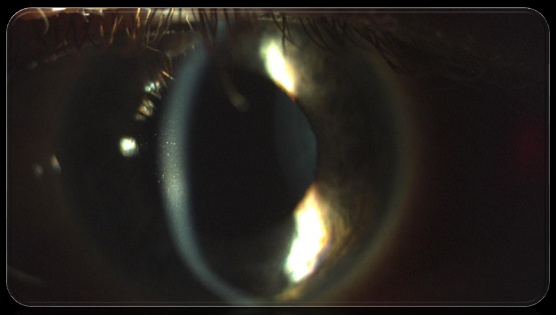


Photo Courtesy Tracy Swartz OD, FAAO

125

Keratoconus

- Ectatic corneal dystrophy
- Bilateral with asymmetry
- Manifests in 20-30'ss
- Most likely a multigenic disease
  - Complex mode of inheritance
  - Environmental factors influence manifestation
- Etiology
  - Increased enzyme activities /decreased levels of enzyme inhibitors= toxicity
  - Destruction of normal corneal matrix results in thinning and scarring

126

Keratoconus

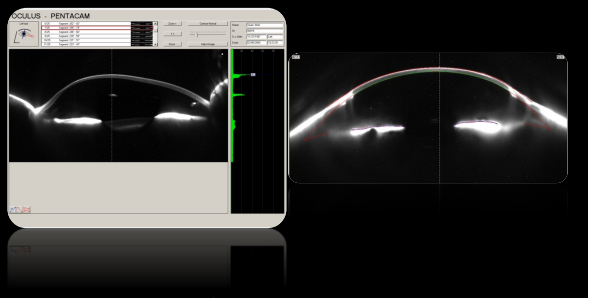
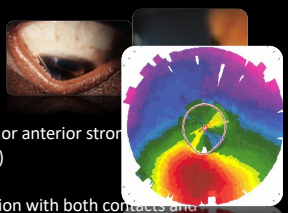


Photo Courtesy Tracy Swartz OD, FAAO

127

Keratoconus

- Diagnosis
  - Slit lamp findings
    - Munson's Sign
    - Central corneal thinning
    - Fleischer's ring
    - Scarring at Bowman's layer or anterior stron
    - Vogt's striae (vertical striae)
  - Irregular astigmatism
    - Resulting in difficult refraction with both contacts and glasses
  - Topographically
    - Inferior steepening



128

Keratoconus

- Gestates for approximately 10-20 years and then stabilizes
- Severity is variable between patients
- Often asymmetric appearance
- Thinning can be extensive:
  - Resulting in rupture in Descemet's m
    - This results in aqueous infusion into str
      - Hydrops

129

KERATOCONUS DESCEMET'S BREAK

Photo Courtesy Tracy Swartz OD, FAAO

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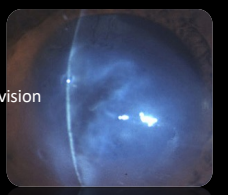
Keratoconus

- Hydrops
  - Symptoms
    - Sudden decrease in best corrected vision
    - Foreign body sensation
    - Pain
  - Signs
    - Conjunctival hyperemia/redness
    - Prominent central or inferior corneal edema
    - Clouding
  - Self-limited in 8-10 weeks as endothelial cells regenerate at ruptured Descemet's membrane



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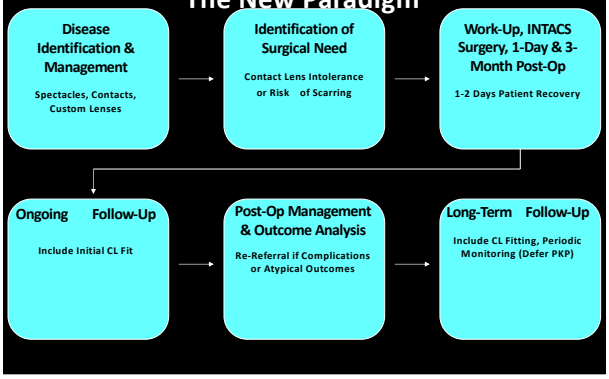
Keratoconus

- Treatment
  - Hydrops
    - Hyperosmotics
    - Antibiotics to avoid secondary infection
    - PKP
  - RGP's
    - Bi-Aspheric I-Kone Design Valley Contax
    - Hyrokone
    - SynergEyes High Dk Hybrid

132

Keratoconus Treatment Flow The New Paradigm



133

TREATMENT IS ON THE WAY

LINKING UP..

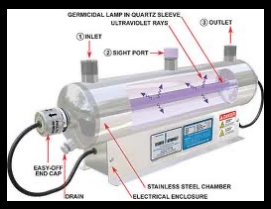
134

CXL Is Everywhere

We see
Collagen Cross Linking
EVERYWHERE
in our world but
NEVER
pay attention to it

135

Our Water Supply is UV Treated



136

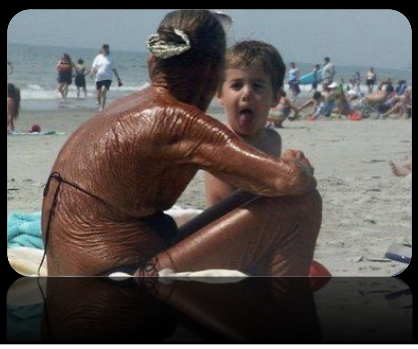
Camelback Water Bottle

137

Tanning (cross-linking) leather has been around for over 6000 years.

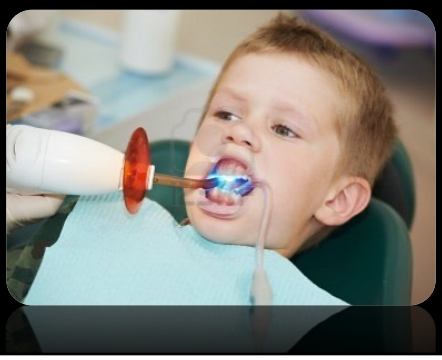
138

This woman is 6000 years old.
CXL Works!



139

Safe enough for a child



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Ever Get A Manicure?

141

WHAT' S THE TECHNIQUE?

How do you do it?

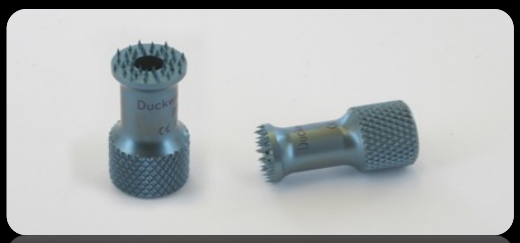
142

"Dresden" Technique

- Anesthetic drops
- Prepare cornea
- Riboflavin drops for 30 mins
- UV light for 30 mins
- Bandage contact lens
- Postop Course: Similar to PRK

143

Daya Epithelial Disrupter

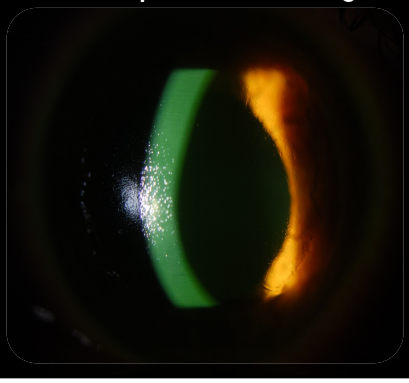


144

Riboflavin 0.1% Drops

145

Epi Off Loading



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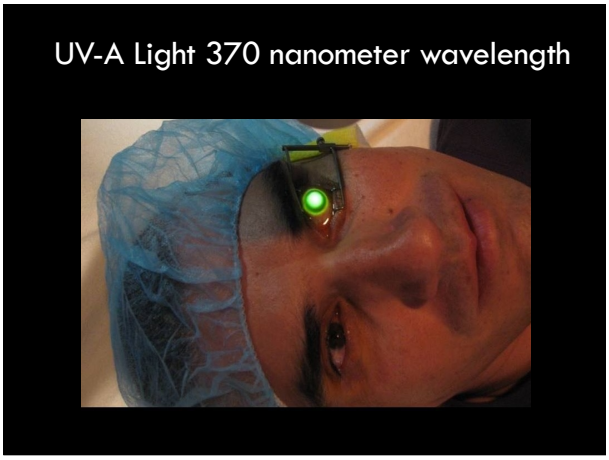
147



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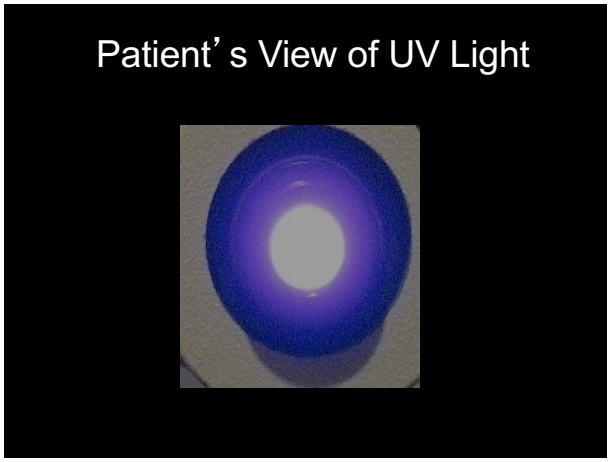

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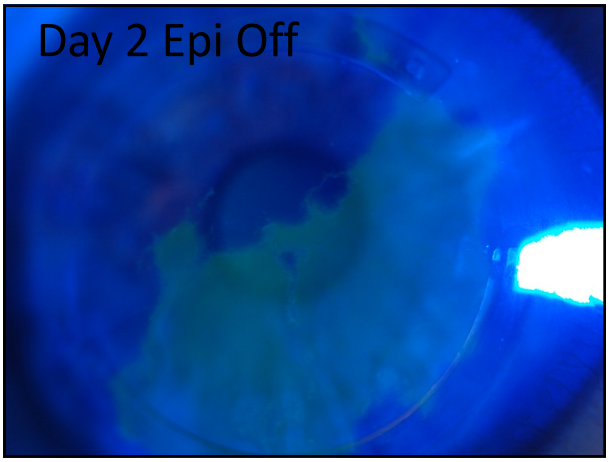

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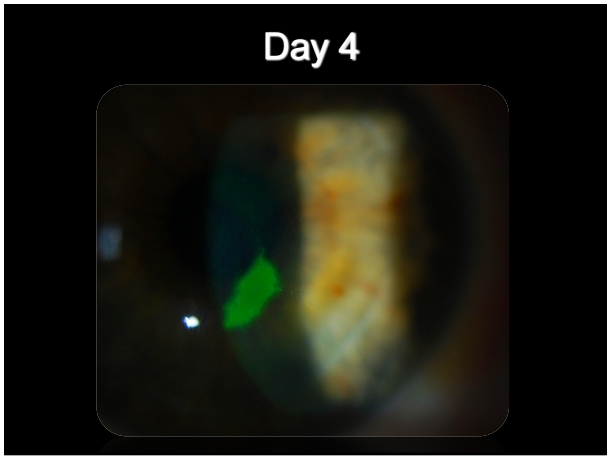

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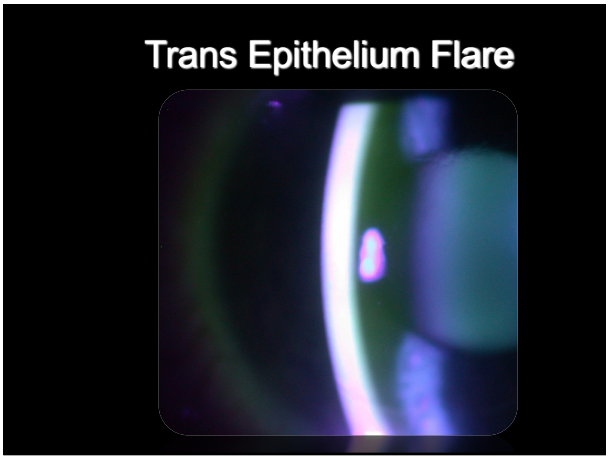
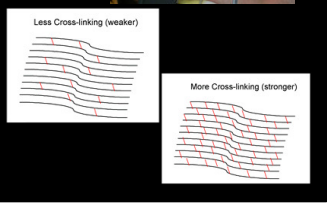


152

Corneal Collagen Cross-Linking with Riboflavin (CXL)

- Increase in cross links
- Strengthens Cornea
- Riboflavin eye drops are applied to the cornea
- The riboflavin is activated by a UV-light

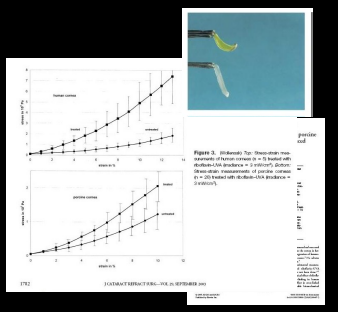


153

Corneal Crosslinking

Riboflavin & UVA

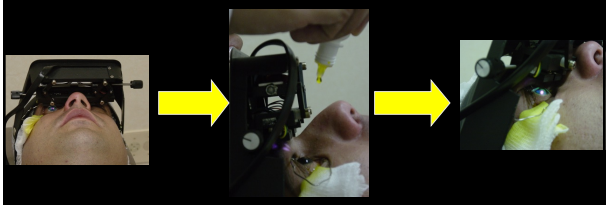
- Increase in corneal rigidity
  - 329% human corneas
- Young's modulus
  - Increased 4.5X in human corneas



Wollensack G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin–ultraviolet-A-induced cross-linking. J Cataract Refract Surg 2003; 29:1780–1785

154

Corneal Crosslinking with Riboflavin: CXL



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Corneal Crosslinking Clinical Applications

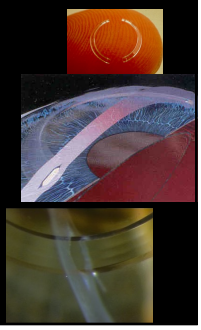
- Keratoconus/Iatrogenic keratectasia
- Corneal stabilization
  - Intacs
  - CK, LTK
  - RK, HK
  - Extended PRK/LASEK
  - CRT/Orthokeratology
- Corneal ulcers
- Myopia control

157

Corneal Crosslinking Clinical Applications

Treatment: Corneal Ectasia/Iatrogenic KC

- Intracorneal ring segments
  - FDA approved for nearsightedness 1998
  - FDA approved under HDE 2004
- Provide structural support to thinned peripheral cornea
- Flattens cone
- Pulls cone toward center of cornea
  - Decreases irregular astigmatism



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Epithelium off-Corneal collagen Crosslinking

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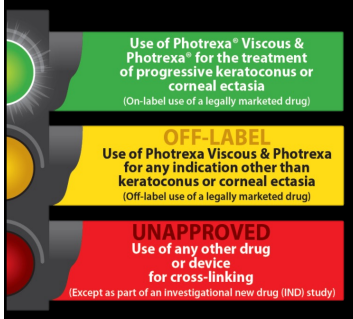


Use of CXL in the US

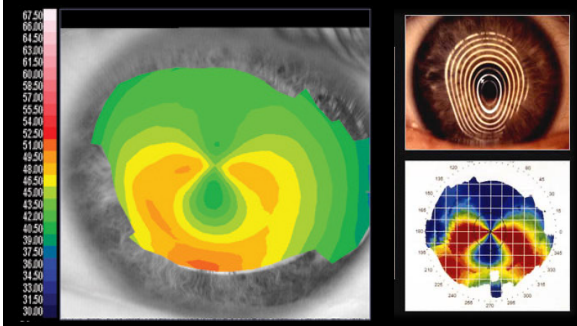
160

Pellucid Marginal Degeneration (PMD)

- Bilateral thinning of the inferior peripheral cornea
- Thinning occurs 1-2 mm above inferior limbus
  - Separated by an area of uninvolved cornea between limbus and thin zone
- Hydrops may present in the thinner area
- Commonly seen in 2nd to 3rd decade
- Non-hereditary
- M=F

161

Pellucid Marginal Degeneration



162

PMD

- Subjective symptoms
  - Increase in against-the-rule astigmatism
  - Unexplained decrease in visual acuity
- Affected area is clear of lipids or vascularization
- Corneal topography has distinct inferior steepening
  - Crab claw
  - Kissing doves
  - Beard and mustache

163

PMD

- Treatment
  - Glasses
    - Traditionally may be sufficient with PMD
    - Matching astigmatism
  - Contact lens
    - Challenging fits with increase astigmatism (ATR)
    - Asymmetrical astigmatism
  - Surgical intervention
    - PK
    - Inferior lamellar patch graft

164

Terrien's Marginal Degeneration

- Rare bilateral asymmetric disease
- Unknown etiology
- Superior peripheral cornea thins/Ectatic

Photo Courtesy Tracy Swartz OD, FAAO

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Terrien's Marginal Degeneration

- Occurs at any age or sex
  - Although more typical in middle aged males
- No signs of inflammation
  - No injection of conjunctiva
  - No A/C chamber reaction
- Increase in regular and irregular astigmatism
  - Asymptomatic
  - Change in vision may be a prompt

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Terrien's Degeneration

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Terrien's Marginal Degeneration

- Circumferential yellow demarcation
  - Lipid and fine pannus
  - Often resembles a pterygium
- Perforation is rare, without trauma
- Hydrops may occur
- Topography
  - Corneal flattening at juncture of furrow
  - Steepening 90 degrees from flat area
  - Spherical and regular central area

168

Terrien's Marginal Degeneration

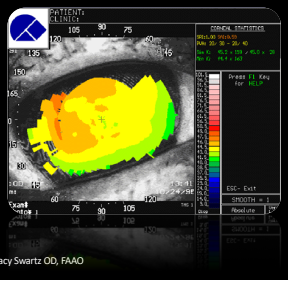


Photo Courtesy Tracy Swartz OD, FAAO

169

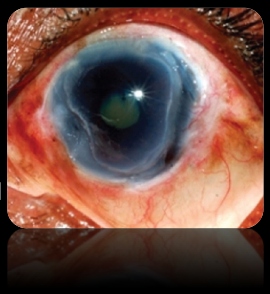
Terrien's Marginal Degeneration

- Management
  - Asymptomatic thus education and supportive
  - Irritated red eyes on occasion
    - Lotemax qid
  - Early refractive treatments
    - Spectacles
    - Contact lenses
      - RGP
      - Piggyback lenses
  - Surgical intervention includes PK

170

Mooren's Ulcer

- Painful relentless chronic ulcerative keratitis
- Initially starts peripherally and progresses circumferentially and centrally
- Idiopathic



171

Mooren's Ulcer

- Divided into 3 distinct variations
  - Unilateral Mooren's
    - Progressive ulceration in elderly
  - Bilateral Aggressive Mooren's
    - Younger patients
    - Circumferentially progresses towards central ulceration
  - Bilateral indolent Mooren's
    - Middle aged patients
    - Progressive peripheral guttering
      - Bilaterally
      - Little inflammation

172

Mooren's Ulcer

- Pathophysiological mechanism unknown
  - Possibly autoimmune
- Presents
  - Redness
  - Tearing
  - Photophobia
  - PAIN
    - Often worse than inflammation indicates
  - Visual disruption-irregular astigmatism
  - Iritis

173

Mooren's Ulcer

- Treatment
  - Steroids
    - Pred Forte q1h
  - Cycloplegia
  - Topical antibiotic
    - 4th generation floroquinolone
  - Oral steroids
  - Conjunctival resection
  - Immunosuppressive therapy

174

Let's Put It All Together

"POP QUIZ"

175

Case 1

- 68 y.o. male
- Presents to office for general eye exam
  - Painless
  - Asymptomatic
- Last eye exam was NEVER
- "I hate Dr's you are all crazy-I am here because I need my drivers license"

176

Case 1

- Ocular Marshmallowitis
- Arcus Senilis
- Limbal girdle of Voigt
- Terrien's Marginal Degeneration

177

Case 2

- 53 y.o. nursery school teacher
- "I noticed a white spot in my eye "
  - The kids have been sneezing a lot
  - We play with glue a lot
- + NIDDM; HTN;
- UCVA 20/25 -OU

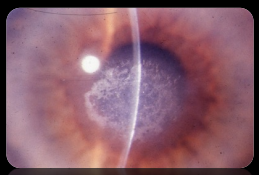


Photo Courtesy Tracy Swartz OD, FAAO

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Case 2

- Reiss-Buckler's
- Keratoconjunctivitis Sicca
- Schnyder's Corneal Dystrophy
- Avellino Degeneration
- Snot
  - Hardened and gelled over time!

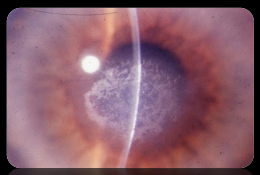

Photo Courtesy Tracy Swartz OD, FAAO

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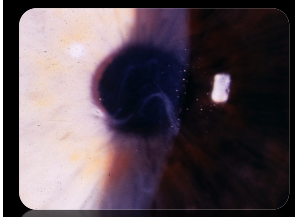
Case 3



- 63 y.o. Wal-Mart greeter
- "I want LASIK surgery"
- UCVA
  - OD-20/30
    - PL -1.25 X 053
  - OS-20/25
    - .25 -1.00 X 068
- No corneal staining
- Hx of pain eye from time to time in AM

Photo Courtesy Tracy Swartz OD, FAAO

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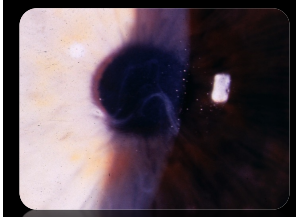
Case 3



- Keratoconus
- EBMD
- Plumitis
- Who cares! Can't we just be done with this lecture already- seriously enough of these ridiculous questions. "Bored with this!"

Photo Courtesy Tracy Swartz OD, FAAO

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Case 4

- 37 y.o. professional roller- blader
- "My eye is irritated, red and I don't see as well as I used to"
- My girlfriend is a pre-school teacher
- I use Visine!

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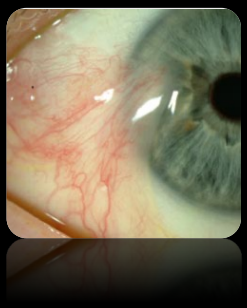
Case 4



- Crocodile Shagreen
- Pterygium
- Macular Dystrophy
- Phlegm
  - More snot!

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Case 5

- 29 y.o. male
  - Roadie/stylist/agent for an **ABBA** cover band
  - In town for the county fair
  - Noticed some blurred vision when applying hair spray in the male leads hair
  - "I just wanted to recreate the awesomeness that was and is ABBA"
  - 'My eye hurts"

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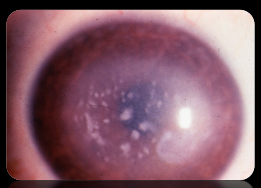
Case 5



- BCVA
  - OD 20/60
  - OS 20/50
- Pachymetry
  - OD 445µ
  - OS 438µ
- Mild staining noted on the cornea
- Deep scarring more centrally located
- Strong aerosol smell

Photo Courtesy Tracy Swartz OD, FAAO

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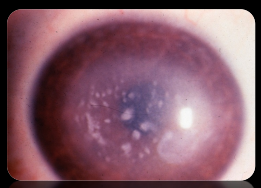
Case 5



- Arcus Inversus
- Lattice Degeneration
- Hair Net Dystrophy
- Macular Dystrophy
- Punishment for bringing ABBA back!

Photo Courtesy Tracy Swartz OD, FAAO

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Case 6

- 58 y.o. feline exerciser
- "I have not had an exam in a few years"
- Hx of taking drop with "yellow" top
- Wants a new Rx
  - VA CC 20/400
  - IOP 33 mm Hg

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Case 6

- PPMD
- WB
- SUV
- CHED
- LOST
- OAT
- GDx
- ICE
  - Too cold, Too cold

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Thank you

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