Ocular Disease

Interpretation and Utilization of New and Old Technologies

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Sunday, June 12, 2022

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Disclosures- Greg Caldwell, OD, FAAO

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue, RVL, Heru
  - Disclosure: Receive speaker honorariums
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- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
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- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
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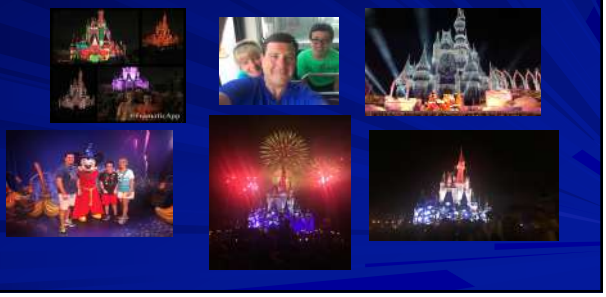
Financial Obligations



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My Goal – Today

- To be able to do something better in patient care

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Inflow versus Outflow

What is glaucoma?

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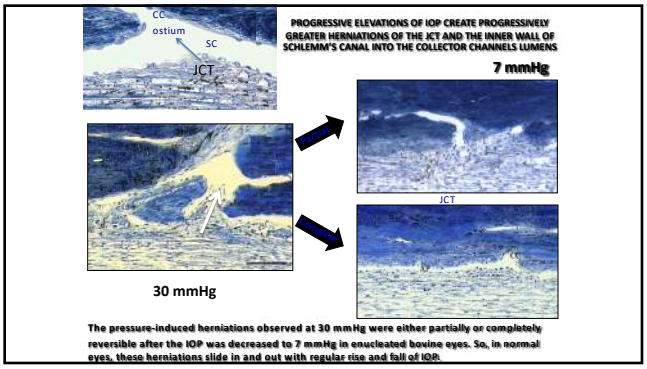

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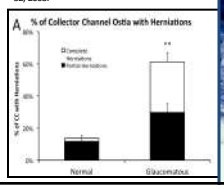
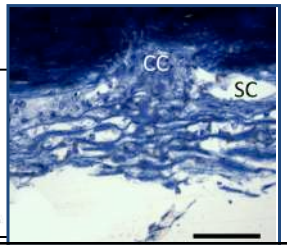
Human eyes with POAG even at 0mmHg, exhibit herniations and many more than in age-matched normal eyes

A: Significantly more herniations of the TM into CC ostia were found in POAG eyes (33 of 54), than in normal eyes (7 of 51) (61% vs. 14%, p<0.0001). In normal eyes, herniations that were present were predominantly partial (86%) rather than complete (14%). In POAG eyes, over half of the larger total number of herniations were complete (52%).

Battista SA, LuZ, Hofmann S, **Freddo TF**, Overby DR, Gong H: Acute IOP elevation reduces the available area for aqueous humor outflow and induces meshwork herniations into collector channels of bovine eyes. Invest. Ophthalmol. Vis. Sci., 49:5346-52, 2008.





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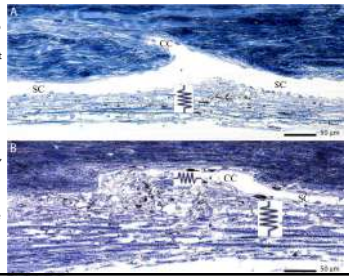
PRINCIPAL NEW FINDING

The presence of herniations, at O mm Hg, suggests they were permanent *in-vivo* obstructions in the ostia of CC, whether partial or complete. These are the only exits from Schlemm's canal. If enough of these 30 channels are fully or even partially blocked, IOP MUST go up.

This study is the first to document the existence of permanent herniations into CC ostia in POAG. Since resistances in series are additive, it could be that these previously unreported permanent herniations, which obstruct CC ostia, represent an additional source of resistance, distal to the trabecular meshwork, in POAG.



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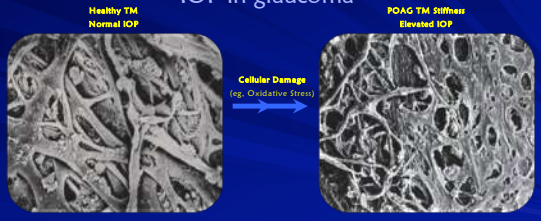
Disease at the TM is responsible for elevated IOP in glaucoma[1,2]



Scanning electron microscopy (2008v) was used to examine human TM under physiological conditions and in patients with POAG.[1]
POAG, primary open-angle glaucoma; TM, trabecular meshwork.
1. He et al. Invest Ophthalmol Vis Sci. 2008;49:1447.
2. Saeda et al. J Cell Physiol. 2015;230:810.

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The goal is to increase outflow Glaukos iStent Inject

Aqueous Angiography Before and After Stenting

Alex Huang, MD, PhD

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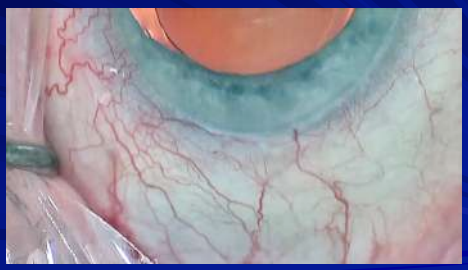
Blanching Confirms Reliable Access to Multiple Collector Channels – Hydrus Microstent



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55-Year-Old Men

500 microns CCT and 21 mm Hg with Goldmann

What is the true IOP?

1. 18 mm Hg
2. 21 mm Hg
3. 24 mm Hg
4. Don't Know

600 microns CCT and 21 mm Hg with Goldmann

What is the true IOP?

1. 18 mm Hg
2. 21 mm Hg
3. 24 mm Hg
4. Don't Know

Corneal Curvature
Corneal Thickness
Corneal Rigidity

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Pachymetry

Ultrasonic versus Optical

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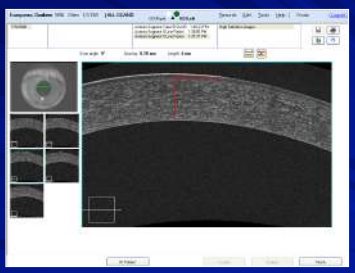
Anterior Segment Imaging
Pachymetry



CCT measurement caliper

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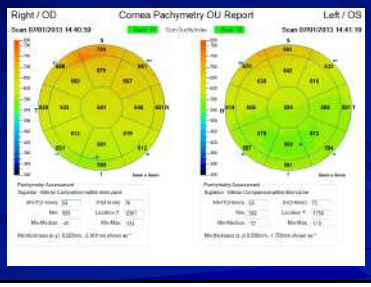
Anterior Segment Imaging with OCT Pachymetry



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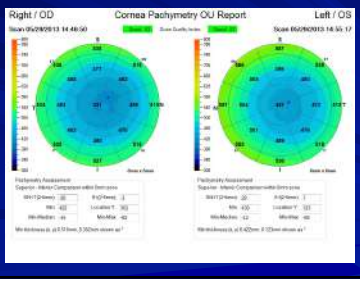
Post-LASIK



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Corneal Hysteresis

Ocular Response Analyzer G3

- Evidence - Key findings from over 800 peer-reviewed publications
- Impact of corneal biomechanics on IOP

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Key Concepts

Elasticity, Viscosity, & Damping

Good Shock Absorber

Bad Shock Absorber

Spring
JOB: Return Energy

JOB: Dissipate Energy

The Spring is not the problem here. Its the Bad Shock Absorber (*damper*) that cannot dissipate the energy and delivers a harsh ride

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Hysteresis
What it is – What it is NOT

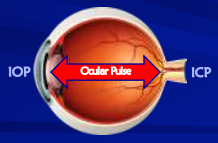
Hysteresis characterizes the response to application and removal of force in materials that ***dissipate a portion of applied energy***.

- *Not a new concept (term defined in 1890)*
- *13,000+ medical publications on hysteresis in a variety of fields*[2]

Corneal Hysteresis (CH)
Reflects cornea's ability to ***absorb and dissipate energy***

- An indication of "damping" capacity of the ocular tissue
  - **NOT an indication of "stiffness" or "rigidity"**

David Luce PhD 1935-2017
Pioneered Corneal Hysteresis



"The eye is under a constant assault"

Hysteresis tells us "How good of a shock absorber" the eye is.

1. Vincent J. Basic elasticity and viscoelasticity. In: Vincent J, ed. *Structural Biomaterials*. 3rd ed. Princeton, NJ: Princeton University Press; 2012:1-28.
2. PubMed Search for "hysteresis". on March 11, 2021 returned 13,766 results.
3. Luce DA. *J Cataract Refract Surg*. 2005;31:156-162.

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Ocular Response Analyzer G3
Measurement Values, Range, and Interpretation

- Average Normal CH is 10.5 mmHg
- Standard dev 1.5 mmHg
- Fairly stable diurnally and with age

Corneal Compensated IOP (IOPcc): Closer to the "true pressure"

Corneal Hysteresis: Normal average 10.5 Typical Range is 8-14 (low = risk)

IOPg: "Goldmann equivalent" reference

Waveform Score: signal reliability (0-10)

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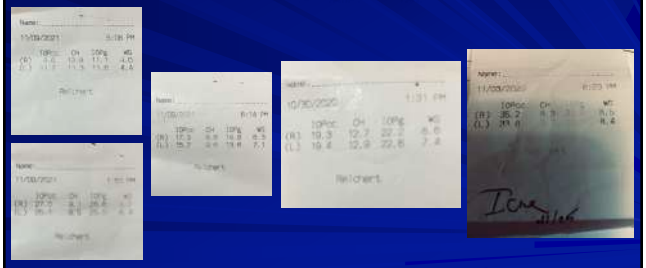
Ocular Response Analyzer G3
Measurement Values, Range, and Interpretation



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Bonus on Visual Fields

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50-year-old woman

- Recently has moved to the area and needs followed for her "ocular hypertension"
- Diagnosed 18 months ago
- Currently is using Travatan qd OU (PM)
- VA 20/15 OU
- Externals: unremarkable
- SLE: slight hyperemia OU
- IOP: 13 OD and 14 OS @ 8:30 AM

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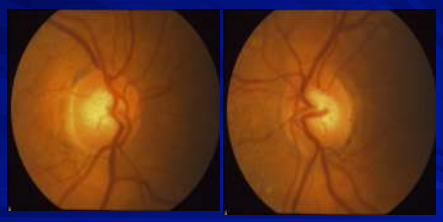
ONH Appearance



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Review of Records

- Diurnal IOP without medication
  - OD 16-19 8:00 AM thru 5:30 PM
  - OS 17-20 8:00 AM thru 5:30 PM
- Pachs
  - OD 505
  - OS 505
- VF results

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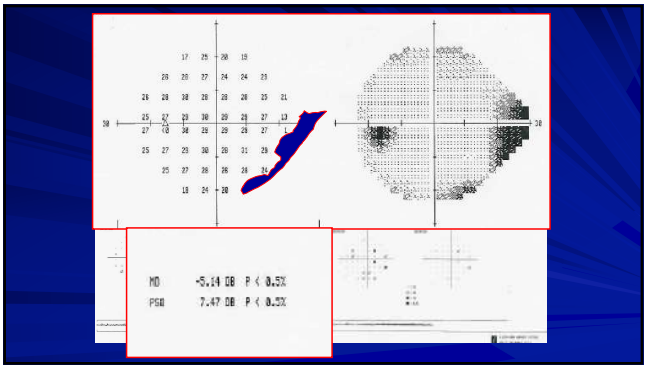

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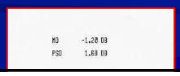
MD and PSD

MD

- 54 spots on 24-2
  - All 54 spots reduced by 1 DB (54DB)
  - MD 1DB
- 54 spots on 24-2
  - 27 spots reduced by 2 DB (54 DB)
  - MD 1 DB
- 54 spots on 24-2
  - 13.5 spots reduced by 4 DB (54DB)
  - MD 1 DB

- Moderate PSD (More localized loss)
  - 3.00 DB
- High PSD (Localized loss)
  - 5.00 DB



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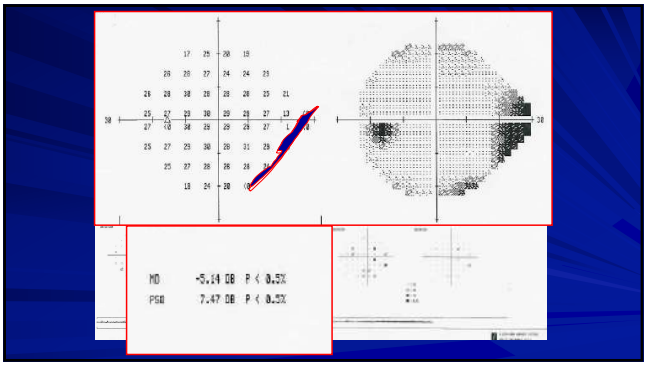

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Discussion

Why is this patient being treated?

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Treatment

- Repeat visual field
- Discontinue Travatan
- Get GDX nerve fiber analysis

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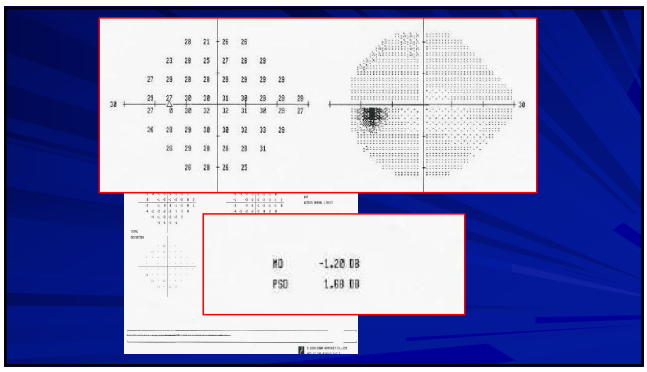

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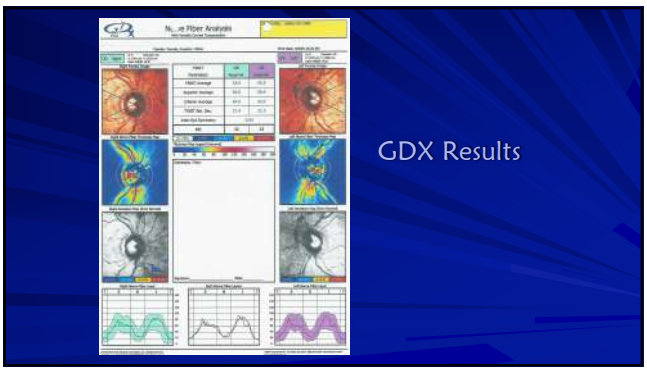

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Cranium Keeper

- Do not back door patients into the ocular hypertension treatment study
  - Via thin pach results
- A patient needs to be suffering from ocular hypertension to use the study
- Thin pachs tell us:
  - Patients with ocular hypertension are at high, medium or low risk for development
- If you have a diagnostic instrument learn how it works and make proper interpretations

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Ask Yourself

- What's the Mean Deviation (MD) of a blind eye on a 24-2 Threshold Visual Field?
  - + 5 db
  - 0
  - -5 db
  - -12 db
  - -32 db
  - -50 db

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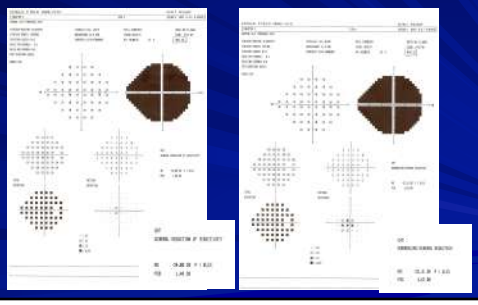
Thoughts on Mean Deviation (MD)

What is the Mean Deviation on a visual field of a blind eye?



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Thoughts on Mean Deviation (MD)

- Turn on your VF let it run
  - 30 DB (decibel)
- 0-5 (1/6) 30% reduction
- 5-10 (1/3) 40% reduction
- >10 (1/2) 50% reduction

- How many DB difference to reliable VF should cause a RAPD?
  - 3 DB for a small APD, the larger the difference the greater the APD

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Wearable Technology

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A Wearable Technology

- Born out of the University of Miami's Bascom Palmer Eye Institute
- Their goal is to provide physicians and patients access to state-of-the-art, accurate, portable technology through real-time wearable diagnostics
- **re:Vive™ by Heru™** is the modern, gamified diagnostic solution using a **lightweight, wearable headset** to aid doctors in diagnosis
- Future developments include vision augmentation applications utilizing AI algorithms to personalize vision enhancement.

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A Decade of Research, Innovation and Clinical Validation

Artificial Intelligence (AI) driven diagnostics and vision augmentation platform is backed by ten years of research and clinical validation at the University of Miami's Bascom Palmer Eye Institute where it is continuously developed.

10 Years of Clinical and Scientific Research

40 U.S. and International Patents to Date

1,000+ Patients in Clinical Trials

450 Million Patients with Visual Field Defects

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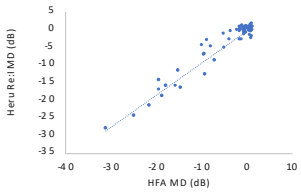
What is the Same?

re:Vive by Heru
Correlates strongly with the standard of care, throughout the dynamic range



R=0.91, P<0.001, in normal eyes and

R=0.81, P<0.001, in eyes with glaucoma and other pathologies

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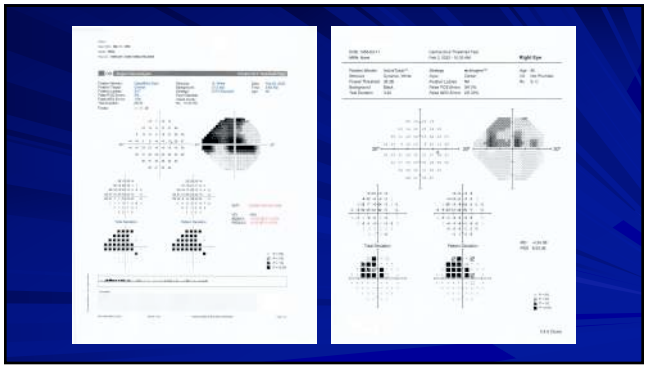

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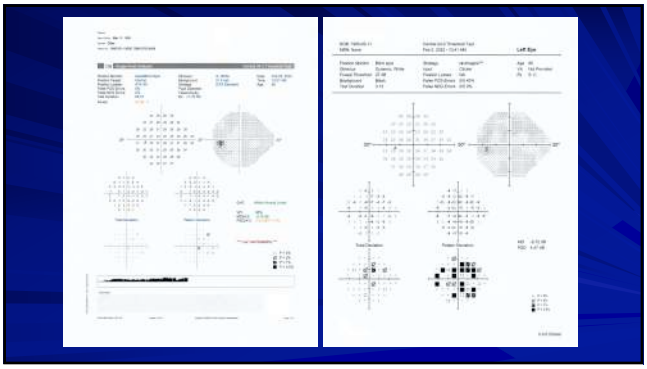

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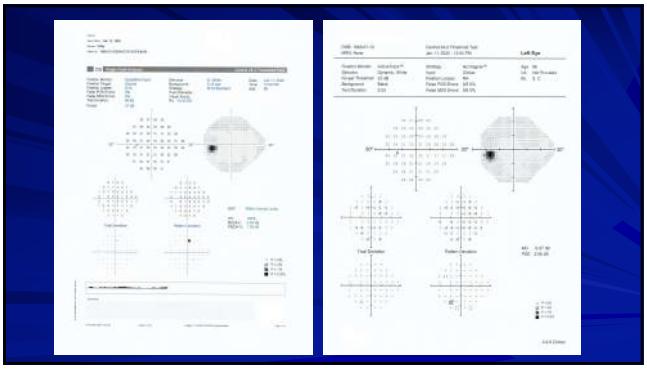

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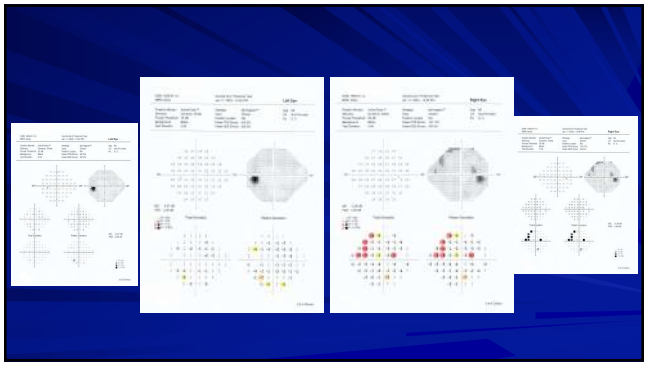

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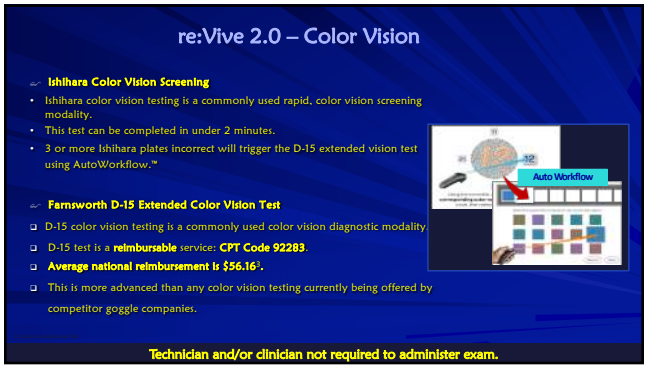

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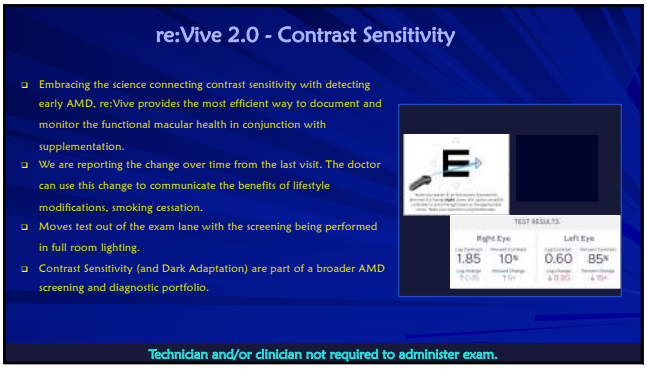

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Instruments for AMD – fragmented care

- Slit lamp/DFE
- Camera
- OCT
- OCT Angiography
- Dark adaption
- PHP
- Macula pigment eval – Scanner
- Genetic testing

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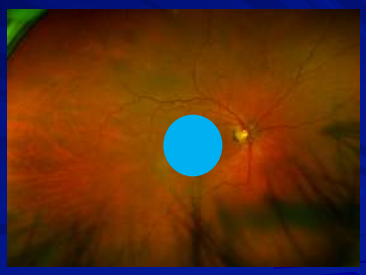
Where is the macula?



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How large is the macula?

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Early Onset Pathogenesis

- Drusen small or large are not makers for early stage AMD
  - Visible structural evidence of a pathological process
    - Underway for quite some time
- Cholesterol deposits exist beneath the surface long before drusen form
  - Cannot be seen with structure-based methods
  - Cholesterol produced by RPE and deposits into Bruch's membrane
  - Continue to layer in Bruch's membrane
- As this cholesterol accumulates the process unfolds with compromise to the outer retina
  - Inflammation
  - Oxidative stress
  - Disruption of oxygen and nutrients
  - Drusen formation
- Impaired Vitamin A across Bruch's membrane
  - Functional impairment can occur to dark adaptation

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Healthy choriocapillaris, Bruch's, RPE, and Photoreceptors

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Cholesterol barrier deposited along Bruch's and RPE

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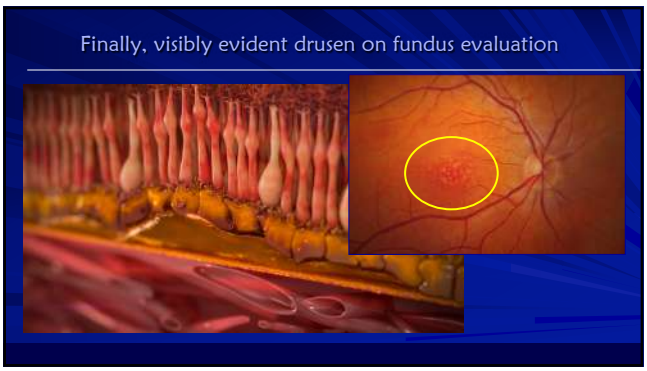

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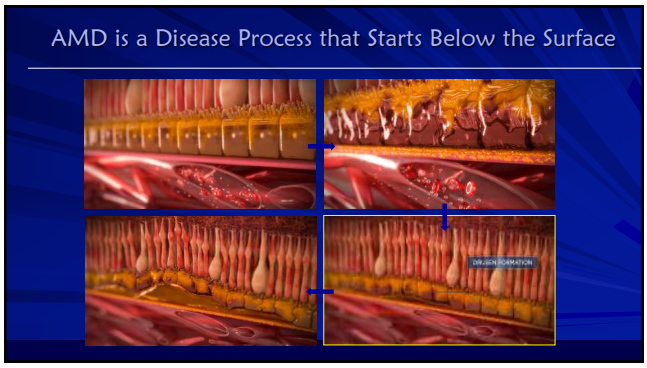

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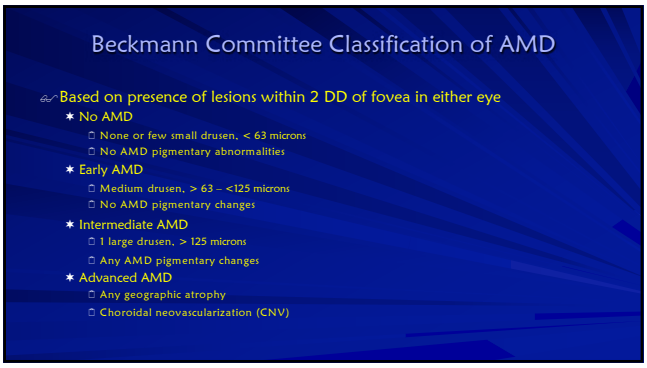

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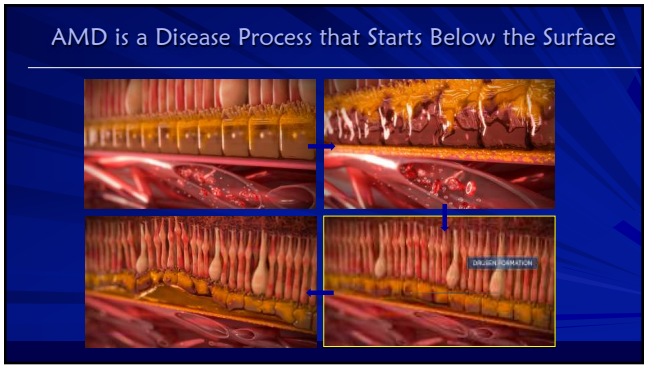

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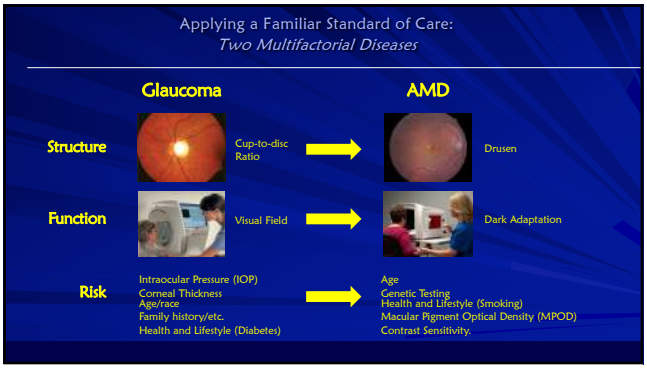

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Dark Adaptation in AMD
Function Test

- Measures how long to recover from bright light to darkness
  - ★ Rod intercept line (RI) time
- Functional test that can help overcome the challenges in diagnosing AMD
- Alabama Study on Early Are-Related Degeneration (ALSTAR)
  - ★ Able to detect subclinical 3 years before clinically visible
  - ★ 325 adults without clinically detectable AMD
- Rod deterioration happens in earliest stages of AMD
  - ★ Earlier defection before visual acuity
- AdaptDx 92284
  - ★ Sensitivity 90.6%
  - ★ Specificity 90.5%

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Dark Adaptation in AMD
Function Test
January 1st, 2020

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AdaptDx Pro Now Available for Clinical Use

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This Means We Now Have an *Early* Symptom We Can Use to Help Diagnose AMD

- Night vision impacted in early AMD: 30+ studies
- AMD patients often give up driving at night
- Night vision is impaired before day vision
- Typically ECP's chalk this complaint up to cataracts

Ask Every Patient Over 50 About Their Night Vision

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Preferential Hyperacuity Perimetry (PHP)

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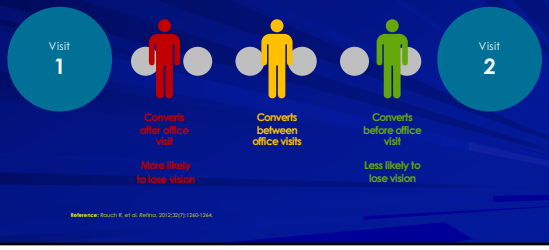
At-risk Patients May Convert to Wet AMD at Any Point Between Follow-up Visits



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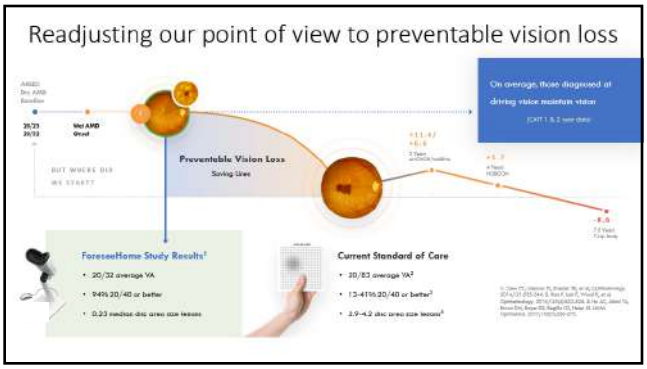

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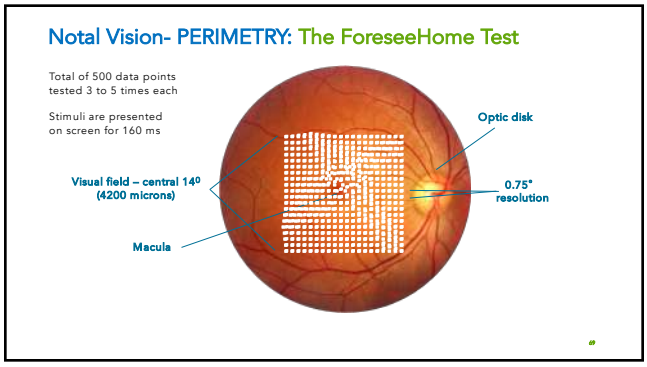

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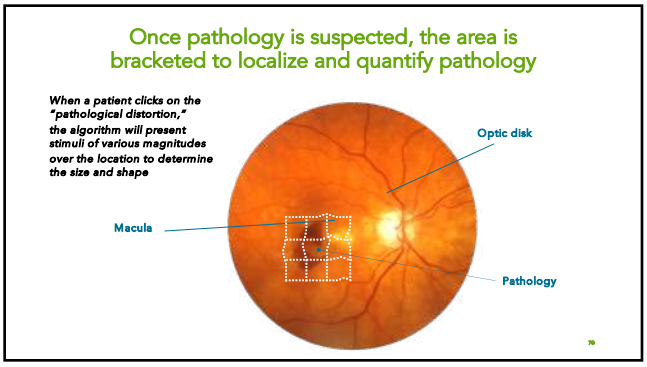

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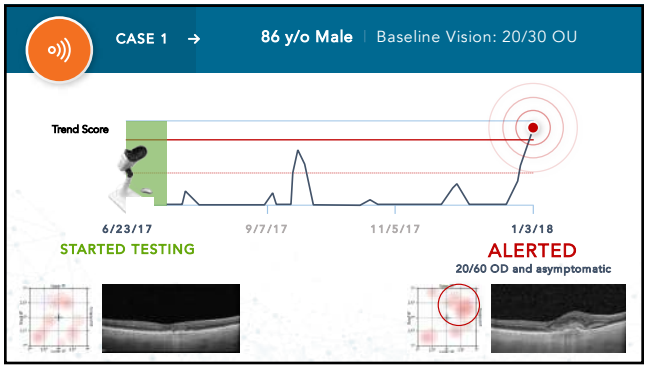

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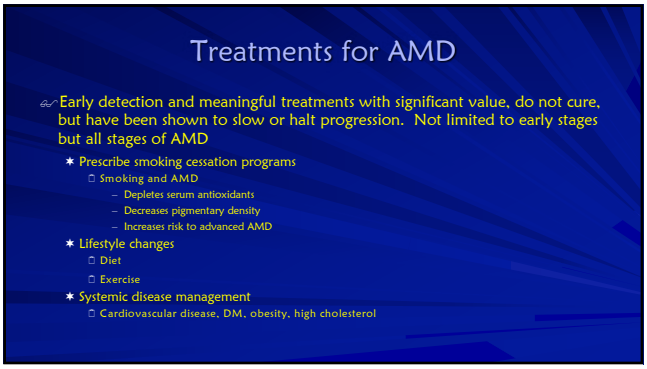


72

Treatment for AMD

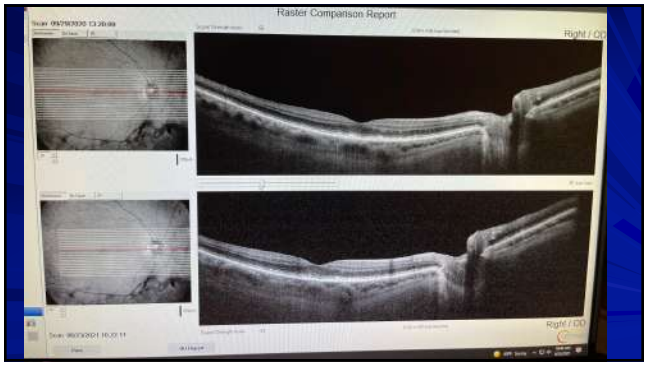
- Nutritional supplements
  - Sub-clinical/sub-structural or early disease
    - Controversy flourishes
      - No definitive guideline exists
      - Despite consensus evidence suggests using supplements
  - Intermediate – advance disease
    - No controversy on advocating for supplements
  - AREDS 1
    - Contains Beta-carotene and no lutein or zeaxanthin, no longer recommended
    - Investigated early AMD, no statistically significant benefit
  - AREDS 2
    - Recommended for intermediate and advanced AMD, study protocol
  - The Practical Guide for the Treatment of AMD - 3 primary options
    - Macular pigment supplement
      - Carotenoids: lutein, zeaxanthin, meso-zeaxanthin
    - Carotenoids, antioxidants, zinc, and vitamins C &E
      - AREDS 2
    - Carotenoid macular supplement in subclinical and early AMD. Carotenoid and antioxidant is intermediate and AMD that is progressing

73

Treatment for AMD

- Retinal light protection
  - Sun exposure
- Closer follow up
  - 12 months is currently accepted as being too long to defect progression
  - 6 months or sooner based on risk of CNV
- Low vision and rehabilitation consultation

74



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Treating Half the Retina?

Oxidative Medicine and Cellular Longevity

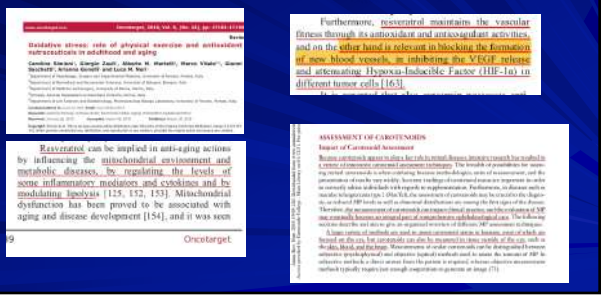
Health Benefits of Polyphenols and Carotenoids in Age-Related Eye Diseases

Abstract

Oxidative stress and inflammation play a critical role in the initiation and progression of age-related ocular abnormalities as cataract, glaucoma, diabetic retinopathy, and macular degeneration. Therefore, phytochemicals with proven antioxidant and anti-inflammatory activities, such as carotenoids and polyphenols, could be of benefit in these diseases. We searched PubMed and Web of Science databases for original studies investigating the benefits of different carotenoids and polyphenols in age-related ophthalmic diseases. Our results showed that several polyphenols (such as anthocyanins, Ginkgo biloba, quercetin, and resveratrol) and carotenoids (such as lutein, zeaxanthin, and meso-zeaxanthin) have shown significant preventive and therapeutic benefits against the aforementioned conditions. The involved mechanisms in these findings include mitigating the production of reactive oxygen species, inhibiting the tumor necrosis factor-α and vascular endothelial growth factor pathways, suppressing p53-dependent apoptosis, and suppressing the production of inflammatory markers, such as interleukin- (IL-) 1, IL-6, IL-1α, and endothelial leucocyte adhesion molecule-1. Consumption of products containing these phytochemicals may be protective against these diseases; however, adequate human data are lacking. This review discusses the role and mechanisms of polyphenols and carotenoids and their possible synergistic effects on the prevention and treatment of age-related eye diseases that are induced or augmented by oxidative stress and inflammation.

76

Carotenoids and Polyphenols



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Measuring Macular Pigment

- Retina macula biopsy
- Clinical Imaging
  - Subjective
    - ZeaVision MPSII
    - Guardion Mapcat SF
  - Clinical
    - ZeaVision MPR
    - Zeiss Visucam 200
    - Spectralis HRA+OCT
    - Spectralis MPOV

Thank you! Dr. Chris Putnam

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Measuring Macular Pigment

- Biophotonic Scanner
  - Measures carotenoids
  - Based on an optical method known as Resonant Raman Spectroscopy (RSS)
    - Used for many years in research laboratories
  - Skin RRS measurements
    - Noninvasive
    - Objective
    - Reliable methods to assess carotenoid levels
      - Ocular
      - Systemic

79

Carotenoid Levels

- Biomarker of health for diet and lifestyle
  - Yale University
- Phospholipid bi-layer
- Carotenoids, flavonoids, and polyphenols

80

Carotenoid Levels

NIH National Institutes of Health
Turning Discovery Into Health

- Quick Test (approx. 30 sec)
- Portable
- Cost Effective
- Remeasure in 60 days
- Reassurance to you and patient

81

Raman Spectroscopy

82

Resonance Raman spectroscopic evaluation of skin carotenoids as a biomarker of carotenoid status for human studies

Susan T. Mayne[a,*], Brenda Cartmel[a], Stephanie Scarmo[a,b], Lisa Jahns[c], Igor V. Ermakov[d], Werner Gellermann[d]

Yale CANCER CENTER

90 STUDIES

*Arch Biochem Biophys. PMC 2014 Nov 15.

83

ARVO STUDY

Interrelationships between Macula, Skin and Serum Carotenoids- Paul Bernstein,Werner Gellerman et al ARVO May 2016

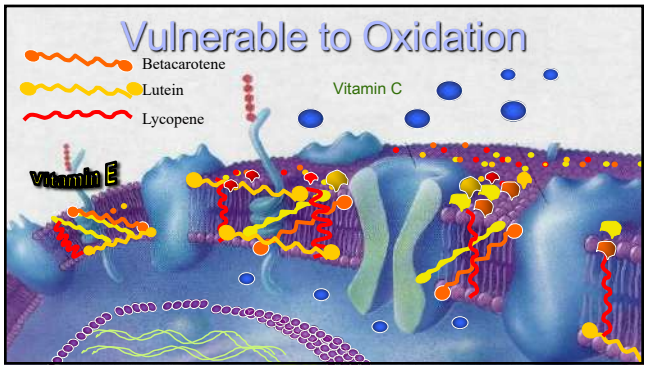
Conclusions:

"Our results emphasize the importance of measuring the total amount of carotenoids in the macula region using an objective image based modality such as AFI w Spectralis rather than subjective MPOD."

Skin resonance Raman Spectroscopy of skin carotenoids is a reasonable biomarker of macula carotenoid status, and correlates better than than subjective MPOD tests.

The objective hand scanner is better than the subjective Macuscope, QuantiEYE, and Densitometer for estimating macula pigment.

84



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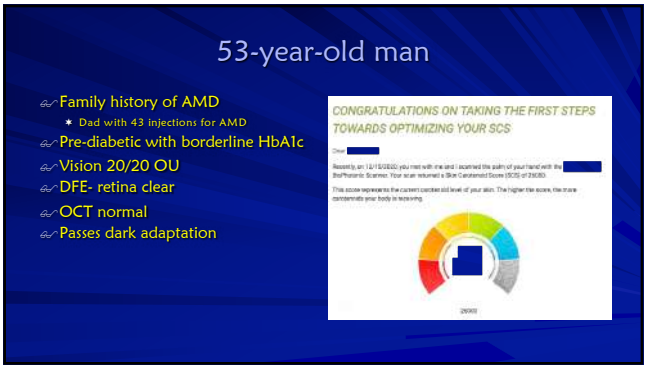

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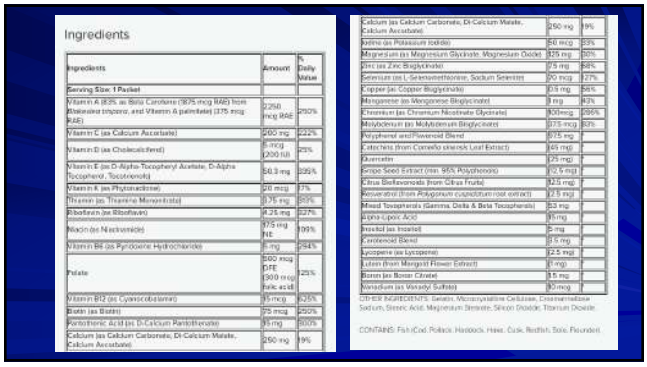

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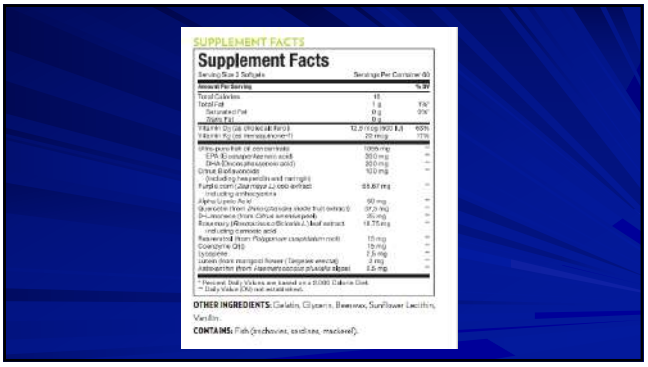

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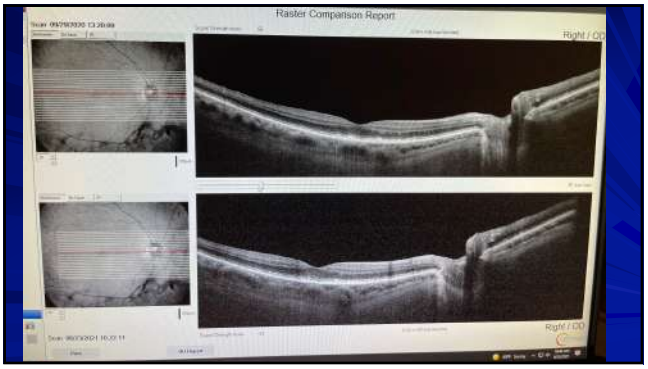

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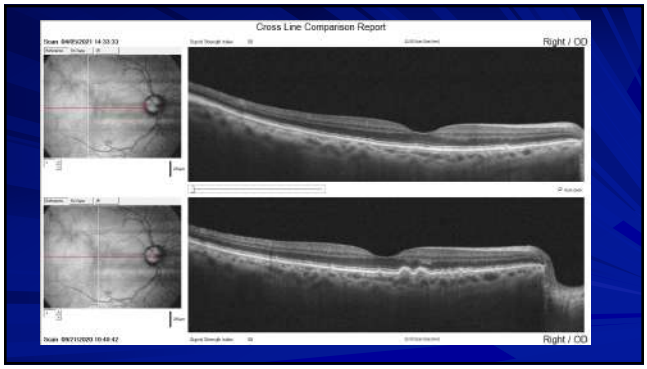

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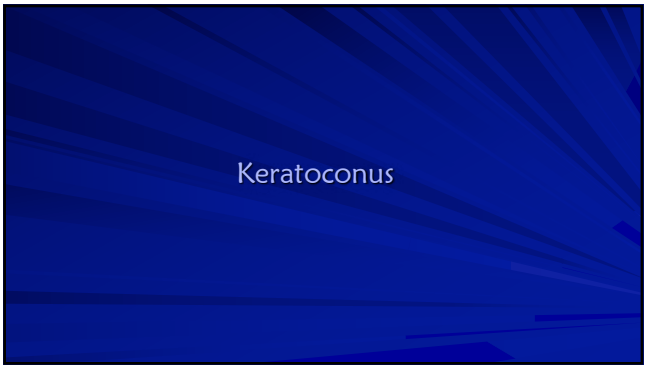

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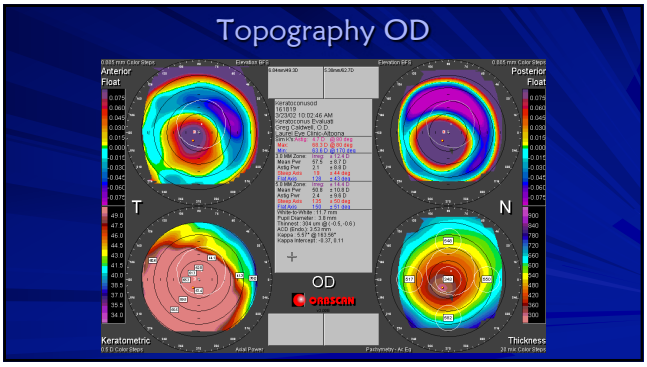

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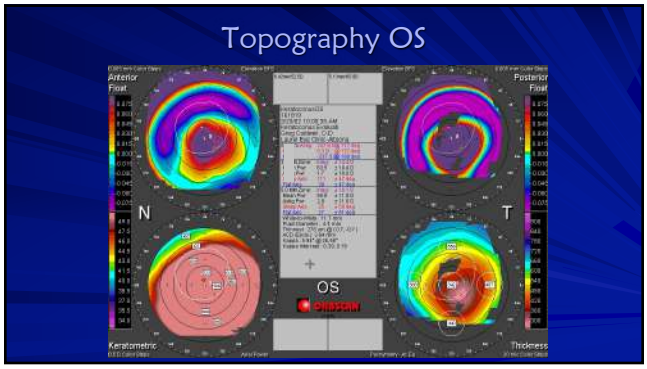

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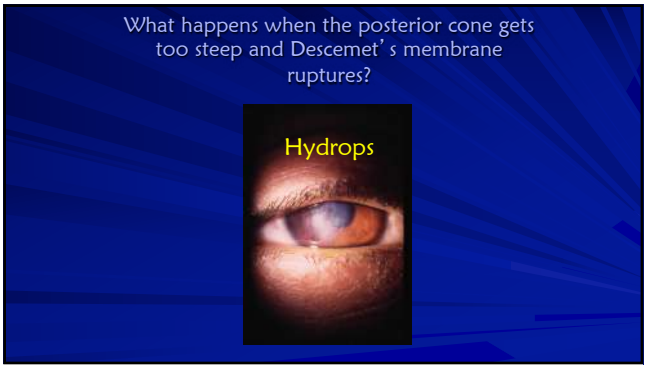

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Keratoconus

- **Progressive corneal disease**
  - Focal thinning, steepening, bulging, and irregular shape
  - Loss of biomechanical strength
  - Bilateral, asymmetric, clinically non-inflammatory
- **Caused by a combination of genetic and environmental factors**
  - Allergies and eye rubbing
- **Onset in puberty**
  - Typically progressive to 4th decade of life
  - Previously estimated 1:2000 (1986 US), more recent estimate 1:375 (2017 Netherlands)

97

Conventional Management of Keratoconus

Vision management options do not stop disease progression

98

Importance of Early Diagnosis in Keratoconus

- As keratoconus progresses, it becomes more challenging to manage
- Progressive keratoconus often results in:
  - Loss of visual acuity
  - Decreased tolerance to contact lens wear, caused by the ongoing changes in the cornea
- The earlier progressive keratoconus is diagnosed, the sooner treatment can be provided that may slow the progression of the disease.[1]
- **Important to diagnose and educate patients before visual function is lost**
- CXL is an early intervention intended to slow or halt the progression of keratoconus

1. Gelles, J. D., OD, FIAO, FCLSA. (2017, April). The Optometrist's Role in Keratoconus Management. Advanced Ocular Care.

99

Watch Out for Keratoconus!

8 Potential Signs & Symptoms

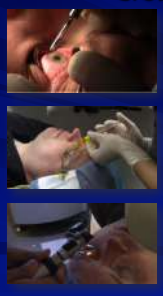
Typically onset occurs in teenage years or early twenties

LOOK OUT FOR KC!

- **Look out** for warning signs in medical history
  - History of eye rubbing
  - Family & genetic predispositions
- **Look out** for visual complaints
  - Blurred vision
  - Distortion of images
- **Look out** for refractive anomalies
  - Distortion of mires on keratometry
  - Error messages on autorefractors
  - Unsatisfactory attempts at vision correction & progressive loss of UCVA & BCVA
  - Increasing astigmatism

100

Cross-linking Procedure Summary



1. Remove epithelium
2. Soak cornea Photrexa® Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) for 30 minutes
3. Check for flare

4. Once flare is observed, measure corneal thickness

If corneal thickness is less than 400 um, instill 2 drops of Photrexa *(riboflavin 5'-phosphate in ophthalmic solution)* until the corneal thickness increases to at least 400 µm

5. Irradiate for 30 minutes

Continue applying Photrexa Viscous *(riboflavin 5'-phosphate in 20% dextran ophthalmic solution)* during irradiation.

* Refer to prescribing information for entire FDA-approved procedure

101

Amniotic Membrane History

- Amniotic membrane transplantation (AMT) in ophthalmic surgery
  - First documented in 1940
- 1995 Kim and Tseng used AMT for ocular surface reconstruction
- 1997 AmnioGraft (BioTissue), first in USA
  - Surgical AMT, sutured
- 2005 ProKera (BioTissue), single sheet, self retained, polycarbonate, in-office and sutureless
- 2012 AmbioDisk (Katena/IOP), sutureless
- 2013 BioD Optix (BioD), sutureless

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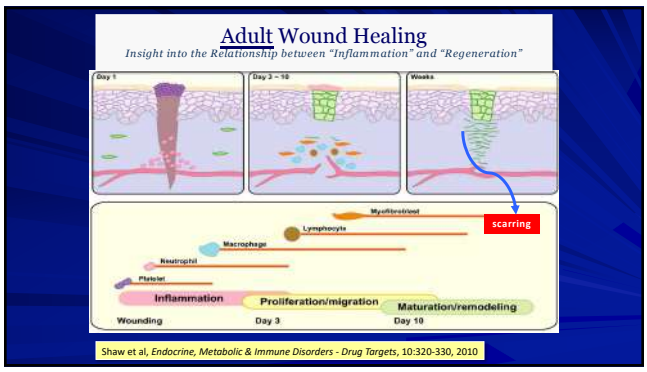

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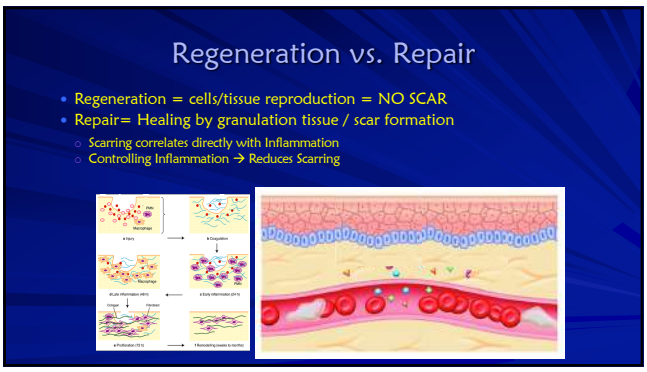

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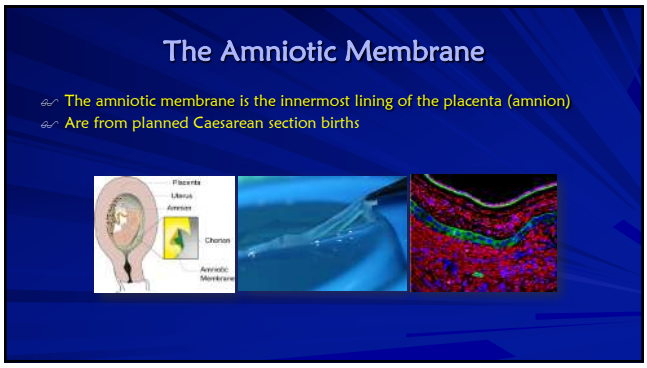

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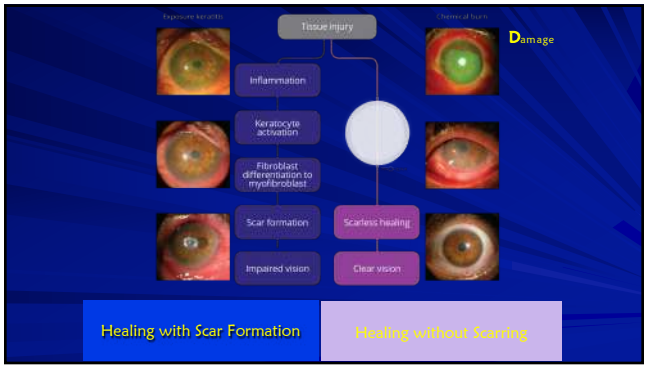

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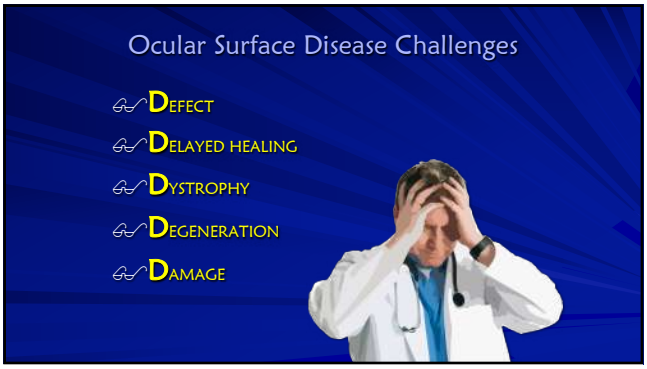

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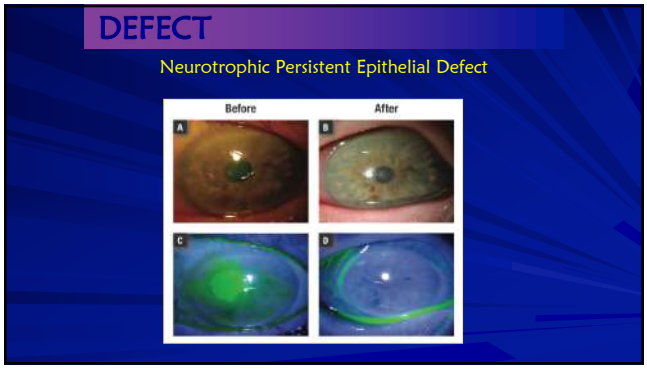

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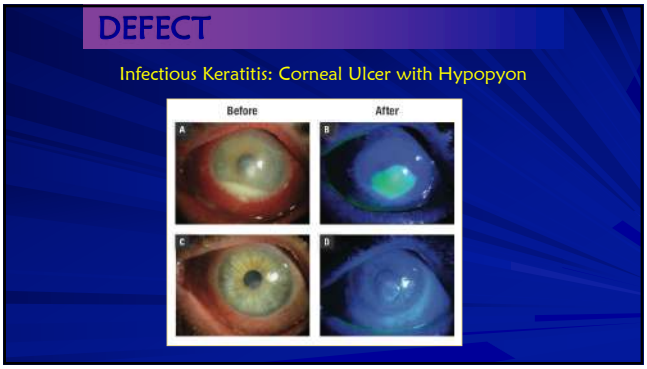

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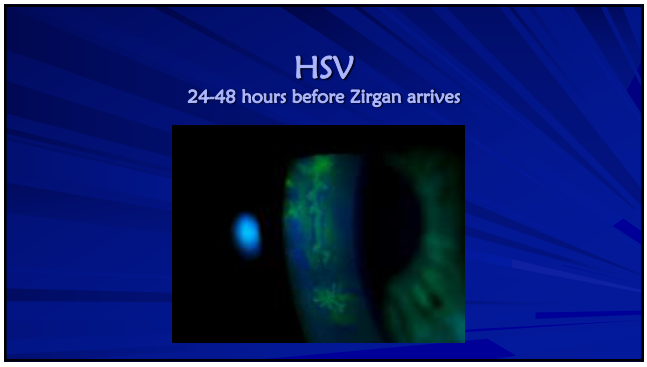

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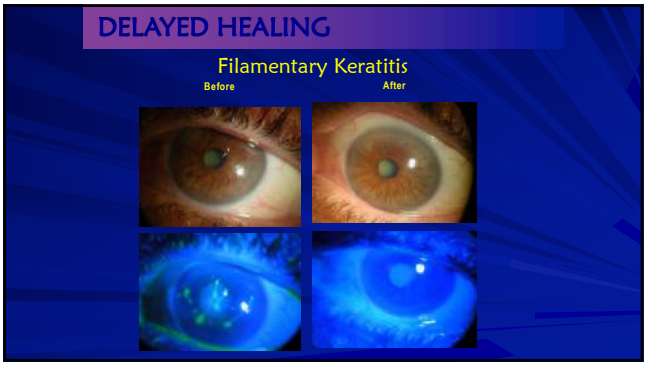

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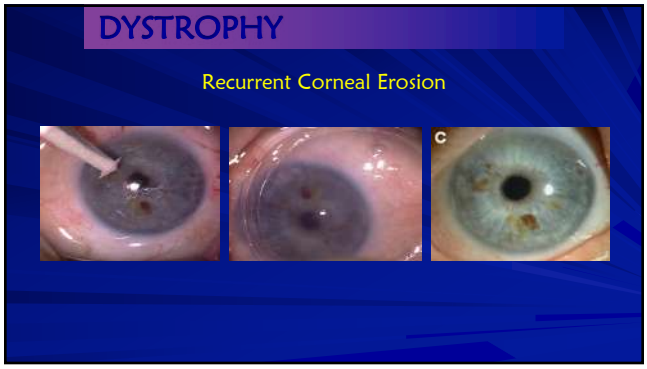

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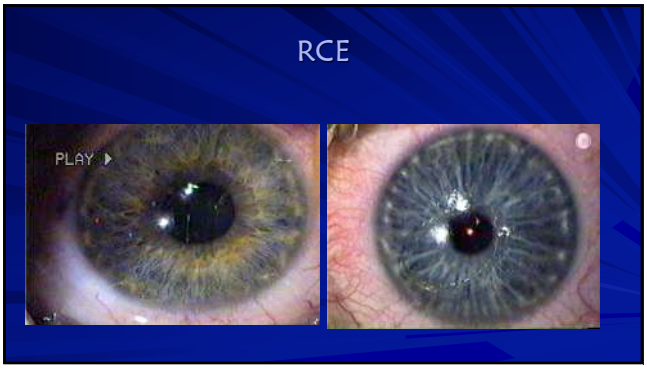

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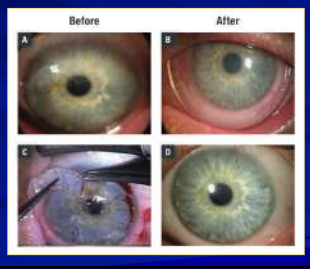
DEGENERATION

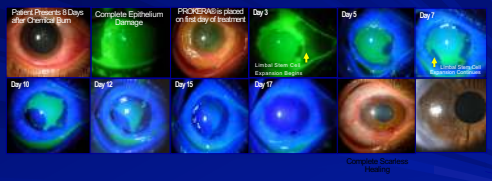
Salzmann's Nodular Degeneration



115

DAMAGE

Chemical Burn



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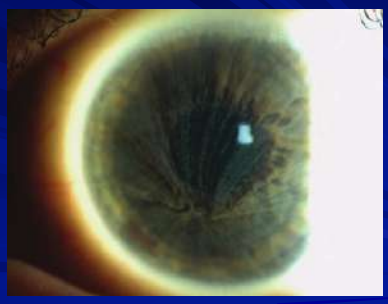
DEFECT, DELAYED WOUND HEALING, DAMAGE

Stem Cell Burnout

117

Stem Cell Burnout

118



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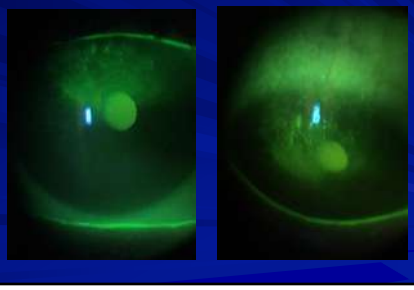
Limbal Cell Exhaustion



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Ocular Surface Disorders and Defects
including but not limited to

- Any Persistent or Non-healing Epithelial Defect
- Corneal Erosions and Ulcers
- Corneal Scars and Opacities
- Keratoconjunctivitis Sicca
- Neurotrophic or Exposure Keratoconjuntivitis
- Acute Thermal and Chemical Burns
- Keratitis (Punctate, Filamentary, Dendritic, Photo-)
- Post-infectious Keratitis (Herpetic, Vernal or Bacterial)
- Band or Bullous Keratopathy
- Adjunctive Therapy for PRK
- Foreign Body Removal
- Conjunctival Defects
- Corneal Dystrophies, including Anterior Basement Membrane Dystrophy
- Stevens-Johnson Syndrome

121

Amniotic Membrane Components

- Proteoglycans
- Growth factors
- Collagens (types I, III, IV, V and VI)
- Fibronectin
- Laminin
- Heavy chain hyaluronic acid (HC-HA)
- PTX 3 (HC-HA Complex)
  - Pentraxin 3

Direct inhibition of pro-inflammatory cells[41]
- Suppresses T-cell activation
- Inhibits giant cell formation
- Controls MMP production[7]

122

Insertion of Prokera
Minor Surgery

123

124

Prokera

Indications:
- PROKERA is intended for use in eyes in which ocular surface cells are damaged or underlying stroma is inflamed or scarred. Acting as a self-retaining biologic corneal bandage, PROKERA effectively treats superficial corneal surface diseases by suppressing inflammation and related pain, promoting epithelial healing, and avoiding haze.
- PROKERA is inserted between the eyeball and the eyelid to maintain space in the orbital cavity and to prevent closure or adhesions. Placement of the conformer also enables application of the cryopreserved amniotic membrane to the ocular surface without the need for sutures.
- PROKERA is for single-use only in one patient by an ophthalmologist or optometrist.

Contraindications:
- PROKERA should not be used in eyes with glaucoma drainage devices or filtering bleb.

Precautions:

Location & Temperature	Use After Receipt
Unopened insulated shipping container	Within the expiration date printed on outer shipping box
-80°C - 4°C (-112°F - 39.2°F) Example: ultra-low temperature freezer, standard freezer, or standard refrigerator	Within the expiration date printed on product packaging (shelf-life is 2 years from date of manufacture)

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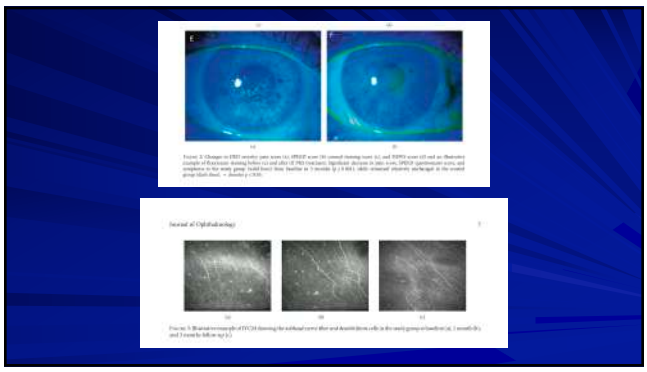


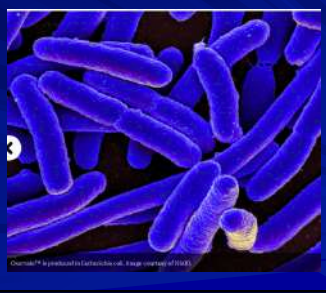
127

Oxervate™ (cenegermin-bkbj)

- Approved 2018 (August 28, 2018)
- Dompe farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
  - Used as eye drop
    - Not infused or injected
- Storage issues: in the freezer at the pharmacy
  - Patient keeps the individual vials in the fridge – once "actively ready" for use, then it is only stable for 12 hours
- Contraindications
  - None

128

Escherichia Coli



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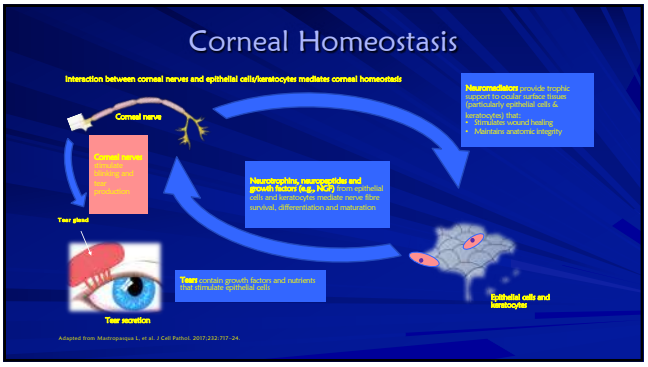
Corneal Homeostasis



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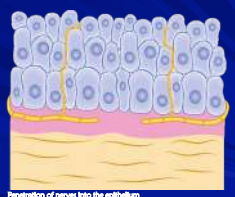
Pathophysiology of NK[1]

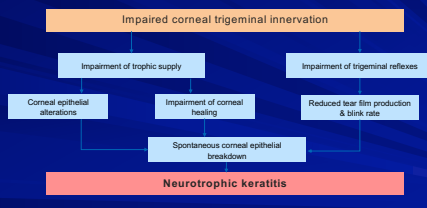
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK



1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521-42.

131

Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24.

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Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

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

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

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NK classification

Stage 1: Mild

(Epithelial changes only without epithelial defect): Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

Stage 2: Moderate

(Epithelial defect without stromal defect): Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia

Stage 3: Severe

(Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2.

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Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis[1]

Ocular symptoms
History
Clinical examination and tests

NK suspected

Test corneal sensitivity

Corneal sensitivity tests:[2]
- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Normal → NK unlikely

Reduced → Further tests required

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2.

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Corneal Sensitivity

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Endogenous NGF maintains corneal integrity by three mechanisms

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]

SHOWN IN PRECLINICAL MODELS[1]

CORNEAL INNERVATION

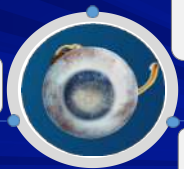
NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]

CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

TEAR SECRETION

NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]



1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017 Apr;232(6):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res*. 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-9. 4. Micera L, Colafrancesco V, Gomellini F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea*. 2002;21:1163–1168.

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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]

1. Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998;338:1174-80. 2. Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares
  - **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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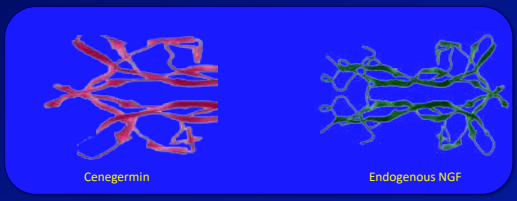
Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

Vanbar R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Dosing and Administration

Instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

- 2 — Every 2 hours
- 6 — Apply 6 times daily
- 8 — Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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Let's Hear From a Patient

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Study Conclusions

After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies OXERVATE* (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 the U.S.

Study NGF0212 (REPARO) (N=52 per group)
European patients with NK in one eye
NCT01756456

72.0% completely healed
Vehicle response rate 46.2%

Study NGF0214 (N=24 per group)
U.S 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

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[2]

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.
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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OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
  - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
  - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
  - Lenses may be reinserted 15 minutes after administration.

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Thank You!
Questions?
Ocular Disease
Interpretation and Utilization of New and Old Technologies
Greg A. Caldwell, OD, FAAO
Optometric Education Consultants
Sunday, June 12, 2022

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