Ocular Disease

Interpretation and Utilization of New and Old Technologies

Greg A. Caldwell, OD, FAAO

Optometric Education Consultants

Sunday, June 12, 2022

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
- Advisory Board: Allergan, Sun, Alcon, Maculogix, Dompe, Visus, Eyenovia
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- 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
- Optometric Education Consultants – Scottsdale, AZ, Orlando, FL, Mackinac Island, MI, Nashville, TN, and Quebec City, Canada - Owner

Optometric Education Consultants

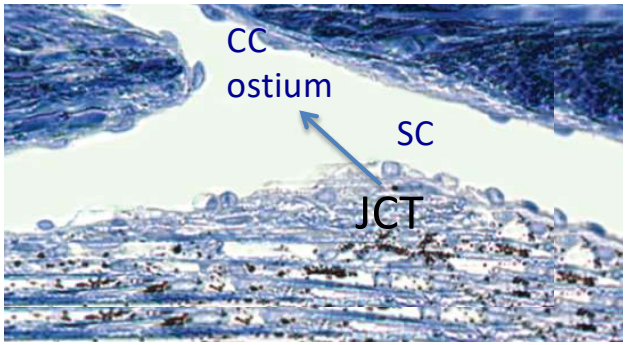
Financial Obligations

My Goal – Today

- To be able to do something better in patient care

Inflow versus Outflow

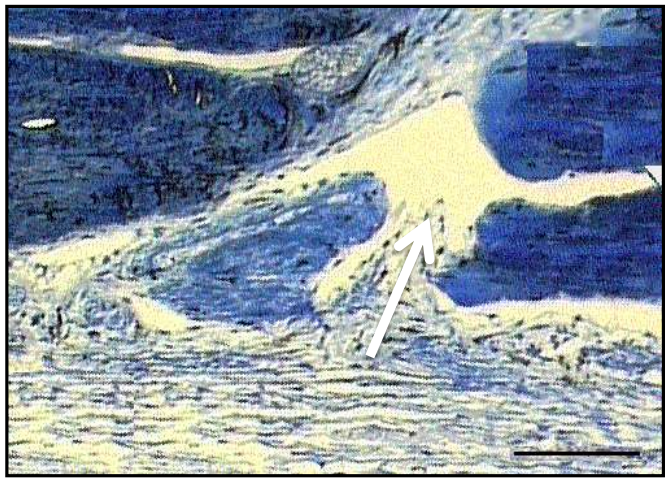
What is glaucoma?



PROGRESSIVE ELEVATIONS OF IOP CREATE PROGRESSIVELY GREATER HERNIATIONS OF THE JCT AND THE INNER WALL OF SCHLEMM'S CANAL INTO THE COLLECTOR CHANNELS LUMENS

7 mmHg

JCT



30 mmHg

Partial

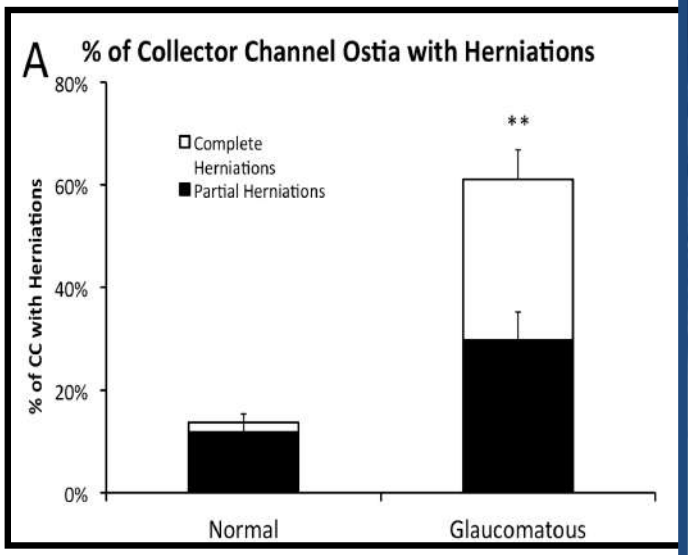
Complete

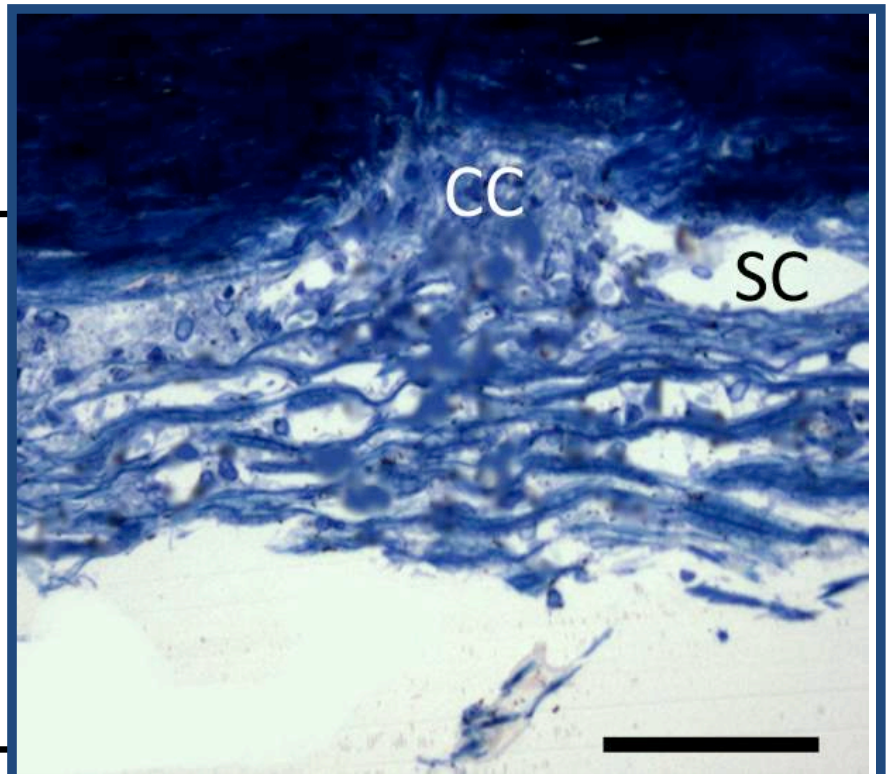
The pressure-induced herniations observed at 30 mmHg were either partially or completely reversible after the IOP was decreased to 7 mmHg in enucleated bovine eyes. So, in normal eyes, these herniations slide in and out with regular rise and fall of IOP.

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, Lu Z, 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.



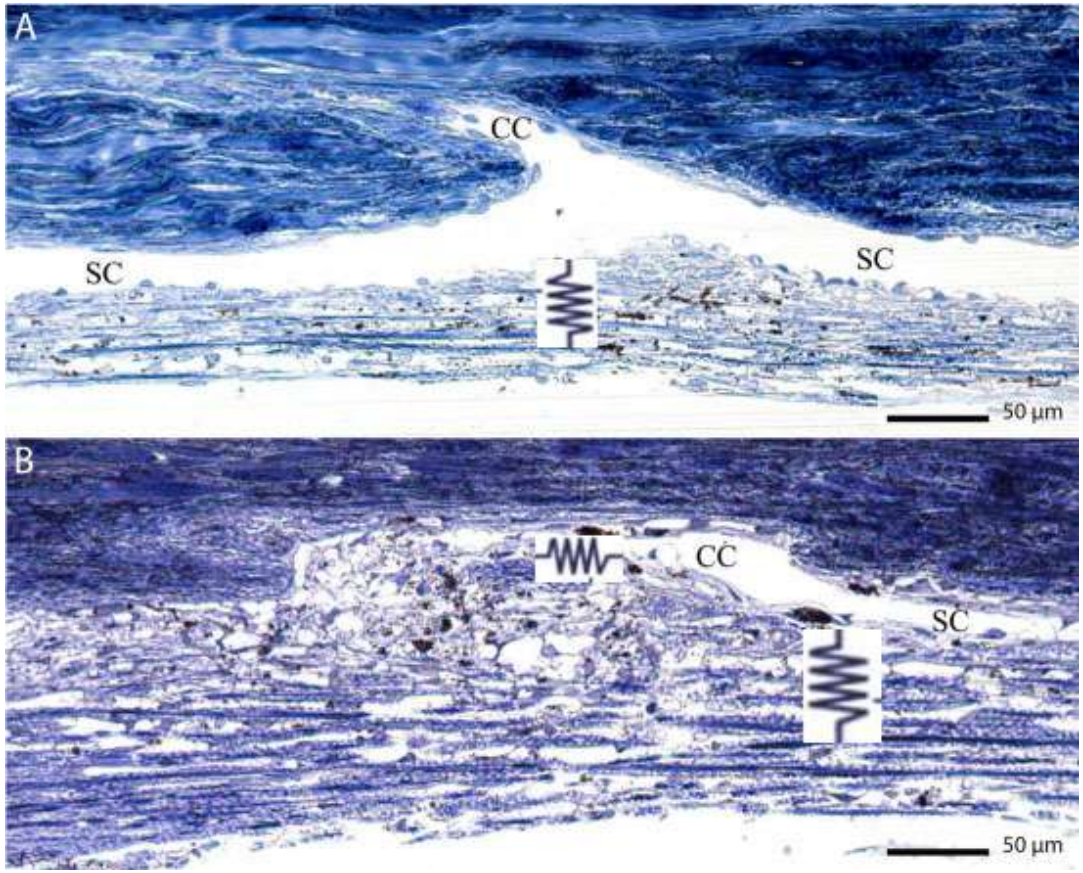


PRINCIPAL NEW FINDING

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.

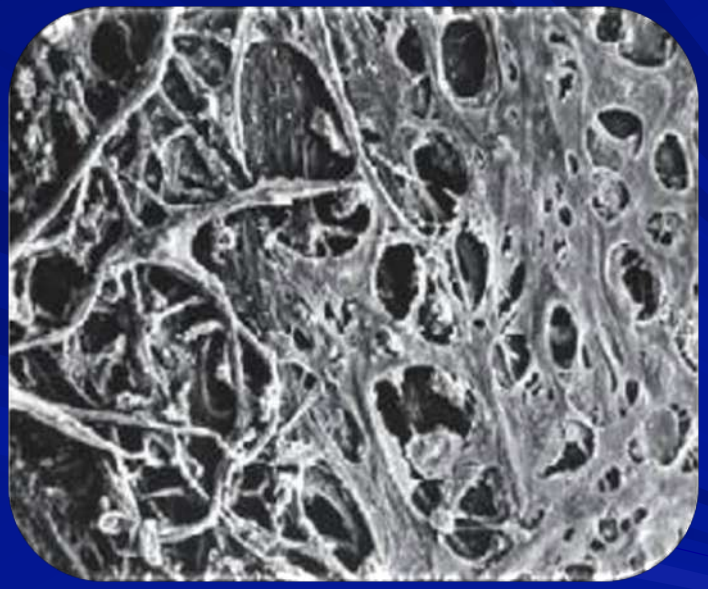


Disease at the TM is responsible for elevated IOP in glaucoma[1,2]

Healthy TM
Normal IOP

Cellular Damage
(eg, Oxidative Stress)

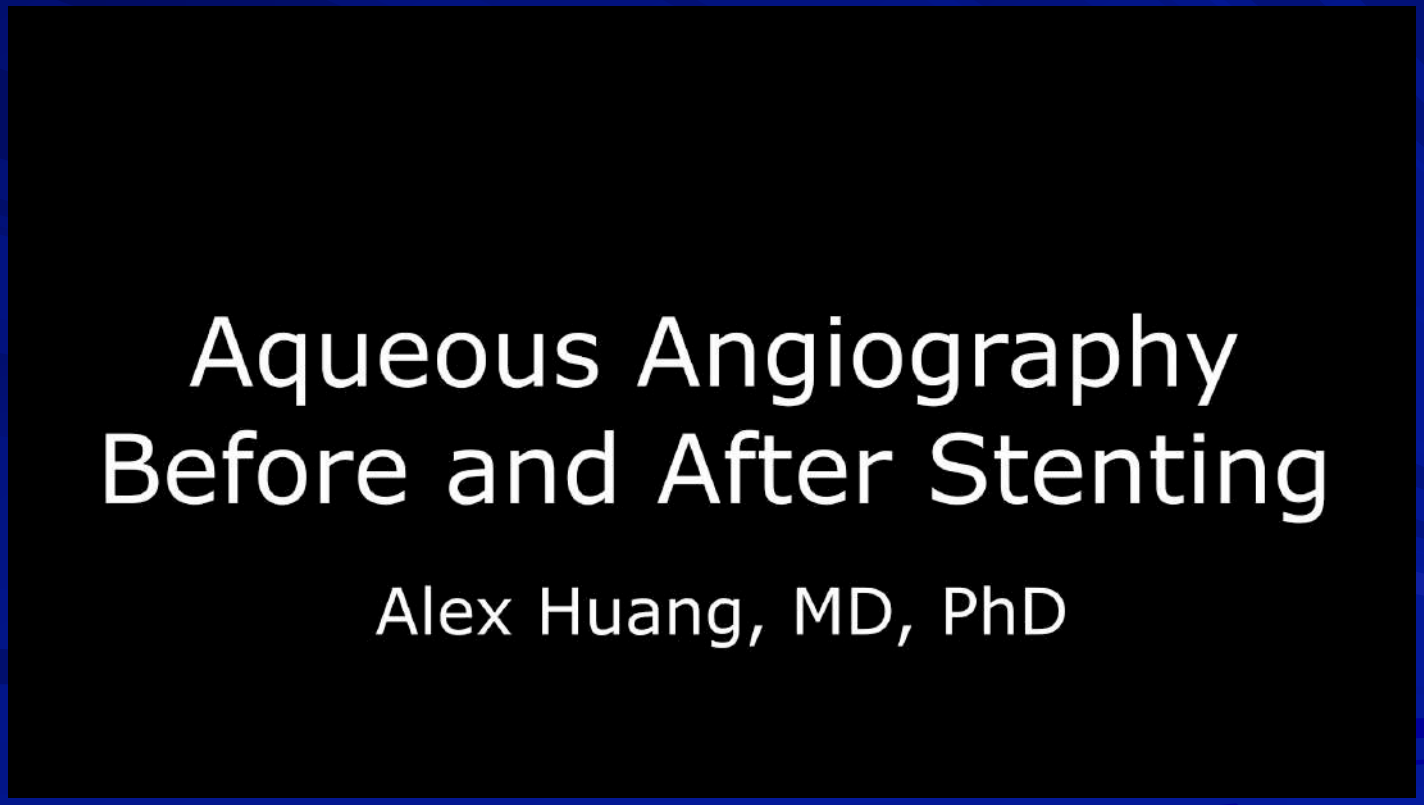
POAG TM Stiffness
Elevated IOP



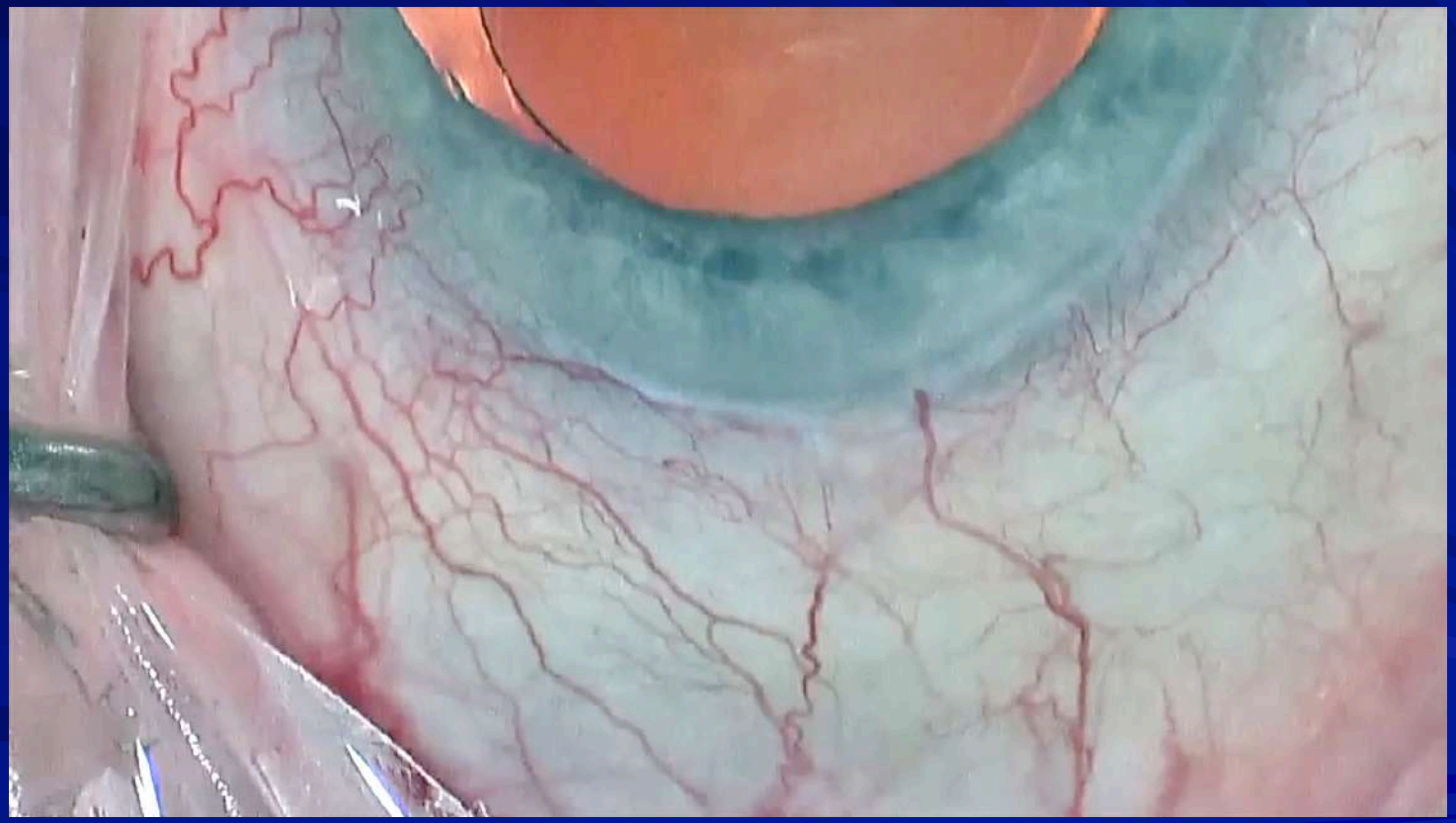
Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG.[2]
POAG, primary open-angle glaucoma; TM, trabecular meshwork.

1. He et al. *Invest Ophthalmol Vis Sci.* 2008;49:1447.
2. Saccà et al. *J Cell Physiol.* 2015;230:510.

The goal is to increase outflow
Glaukos iStent Inject



Blanching Confirms Reliable Access to Multiple Collector Channels – Hydrus Microstent



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

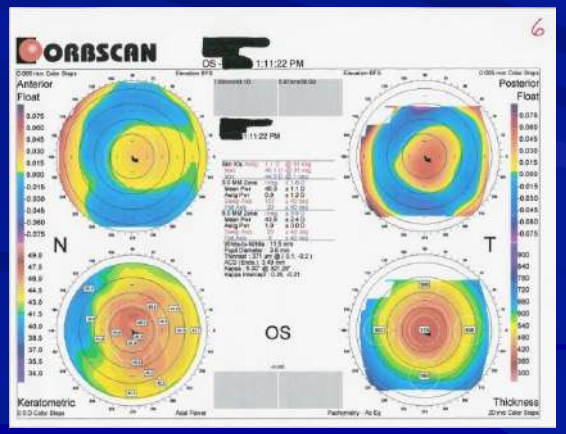
Corneal Curvature

Corneal Thickness

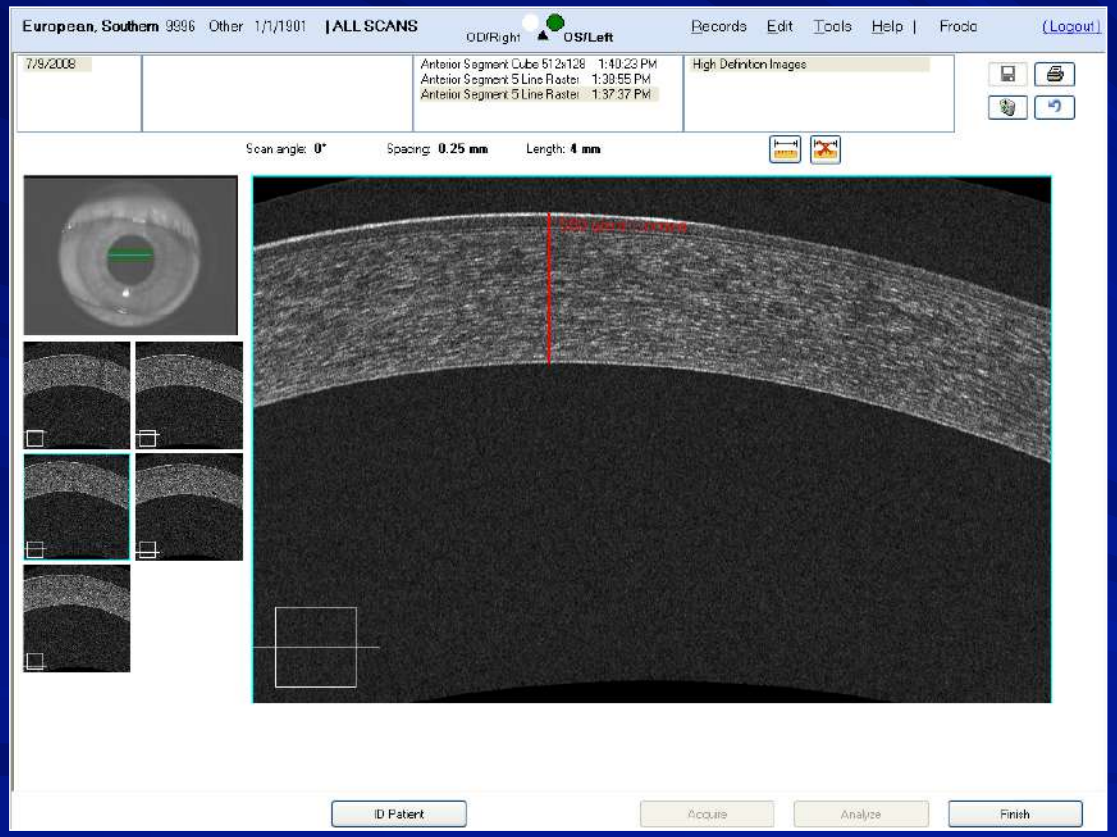
Corneal Rigidity

Pachymetry

Ultrasonic versus Optical

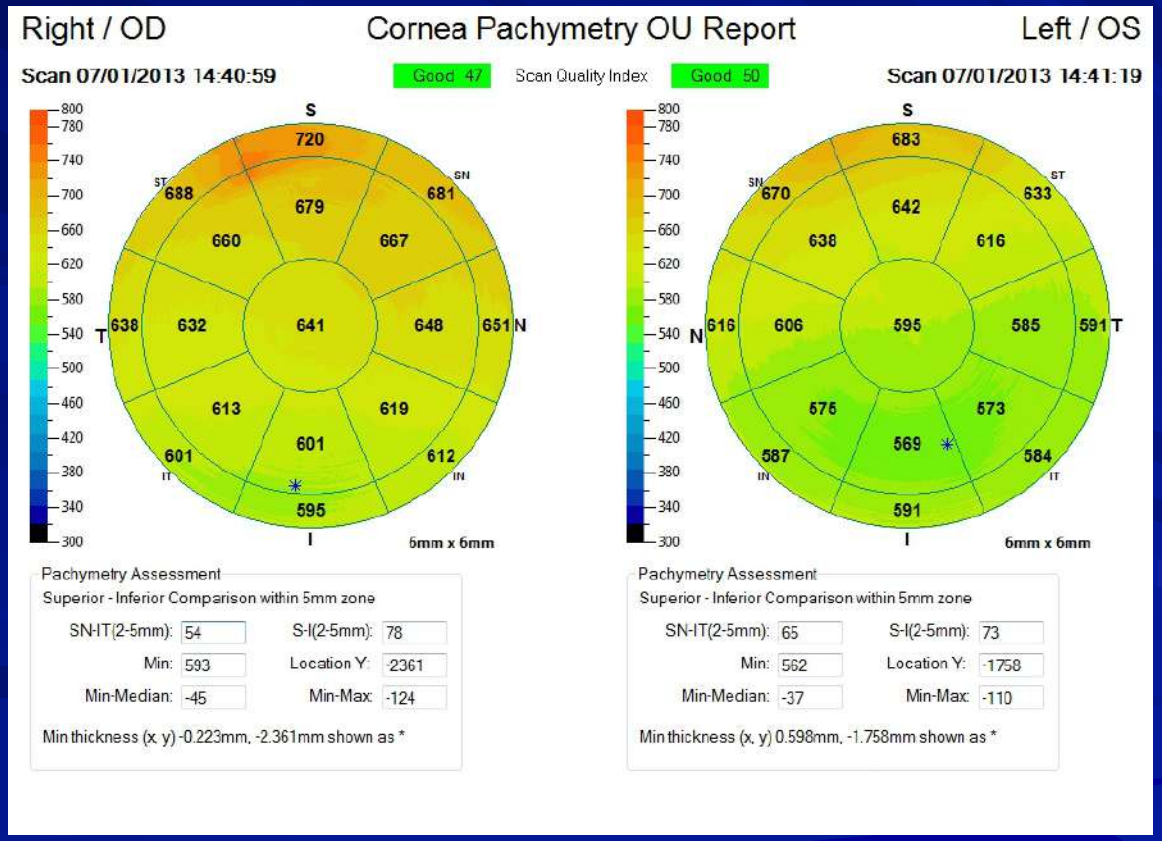


Anterior Segment Imaging
Pachymetry

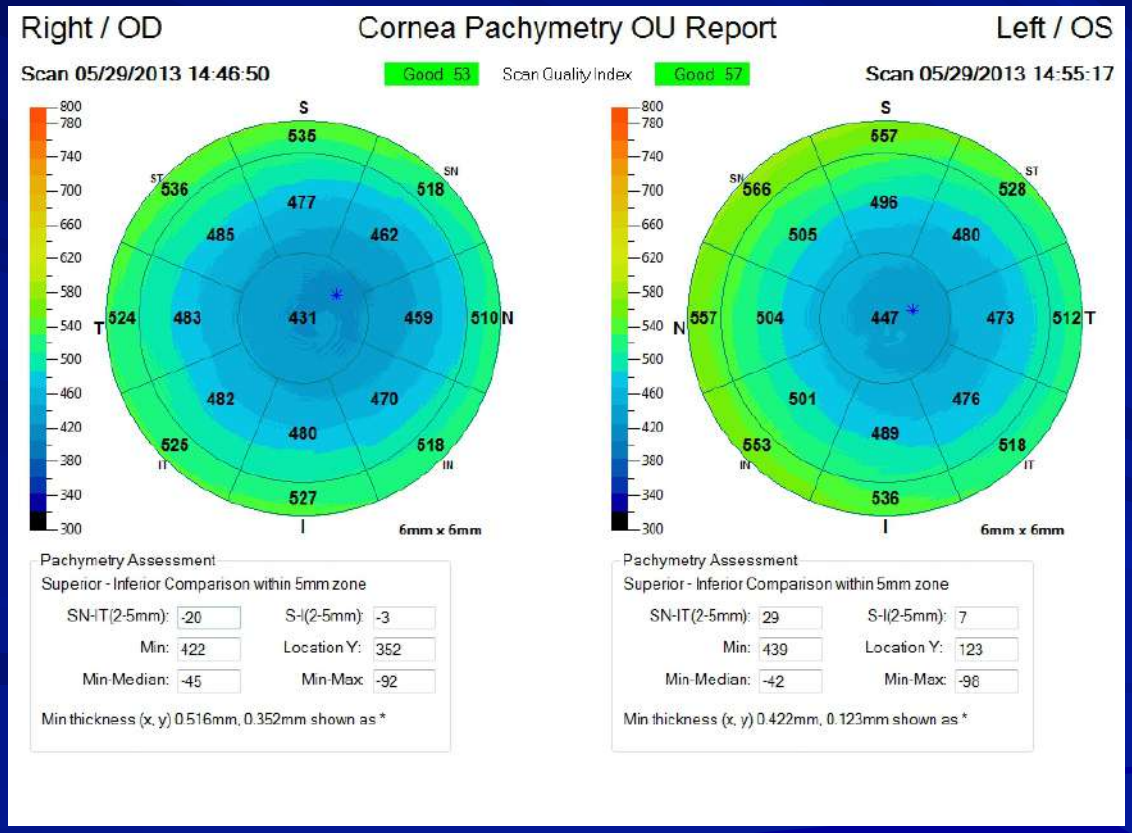


CCT measurement caliper

Anterior Segment Imaging with OCT Pachymetry



Post-LASIK


Right / OD
Cornea Pachymetry OU Report
Left / OS
Scan 05/29/2013 14:46:50
Good 53
Scan Quality Index
Good 57
Scan 05/29/2013 14:55:17
S
535
SN
518
ST
536
477
485
462
T
524
483
431
459
510 N
482
470
480
525
IT
518
IN
527
I
6mm x 6mm
Pachymetry Assessment
Superior - Inferior Comparison within 5mm zone
SN-IT(2-5mm): -20
S-I(2-5mm): -3
Min: 422
Location Y: 352
Min-Median: -45
Min-Max: -92
Min thickness (x, y) 0.516mm, 0.352mm shown as *
S
557
SN
566
ST
528
496
505
480
N
557
504
447
473
512 T
501
476
489
553
IN
518
IT
536
I
6mm x 6mm
Pachymetry Assessment
Superior - Inferior Comparison within 5mm zone
SN-IT(2-5mm): 29
S-I(2-5mm): 7
Min: 439
Location Y: 123
Min-Median: -42
Min-Max: -98
Min thickness (x, y) 0.422mm, 0.123mm shown as *

Corneal Hysteresis

Ocular Response Analyzer G3

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

Key Concepts

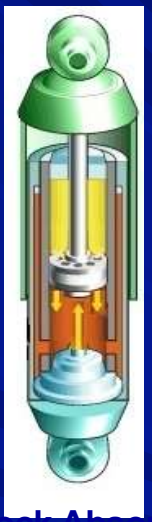
Elasticity, Viscosity, & Damping

Good Shock Absorber

Same (good) Spring Both Sides

Bad Shock Absorber

Spring
(*elastic*)
JOB: Return Energy



Shock Absorber
(aka: Damper)
(*viscous*)
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

Hysteresis

What it is – What it is NOT

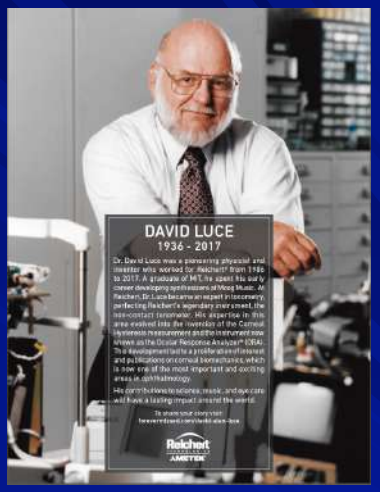
Hysteresis characterizes the response to application and removal of force in materials that ***dissipate a portion of applied energy*** [1]

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

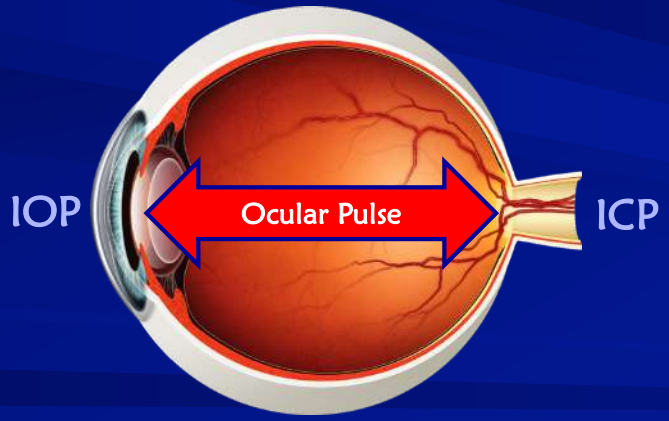
Corneal Hysteresis (CH)

Reflects cornea's ability to ***absorb and dissipate energy*** [3]

- 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 Mach 11, 2021 returned 13,766 results.
3. Luce DA. *J Cataract Refract Surg.* 2005;31:156-162.

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"

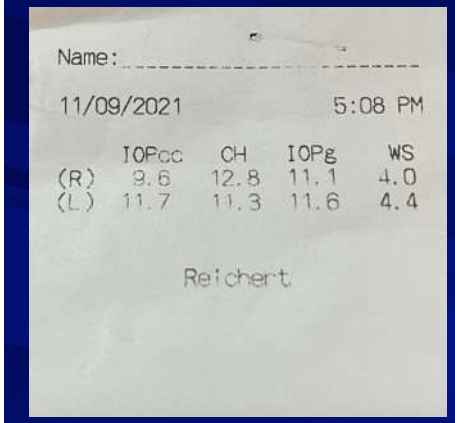
Corneal Hysteresis: Normal average 10.5 Typical Range is 8-14 (low = risk)

IOPg: "Goldmann equivalent" reference

Waveform Score: signal reliability (0-10)

Ocular Response Analyzer G3

Measurement Values, Range, and Interpretation

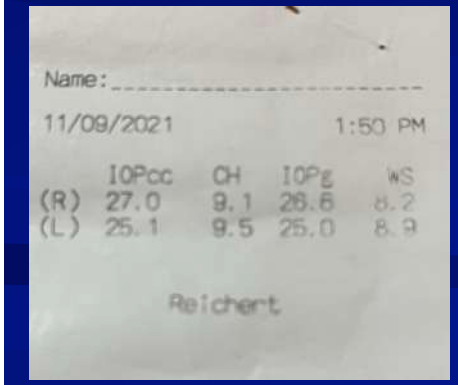


Name: _____

11/09/2021 5:08 PM

	IOPcc	CH	IOPg	WS
(R)	9.6	12.8	11.1	4.0
(L)	11.7	11.3	11.6	4.4

Reichert



Name: _____

11/09/2021 1:50 PM

	IOPcc	CH	IOPg	WS
(R)	27.0	9.1	26.6	8.2
(L)	25.1	9.5	25.0	8.9

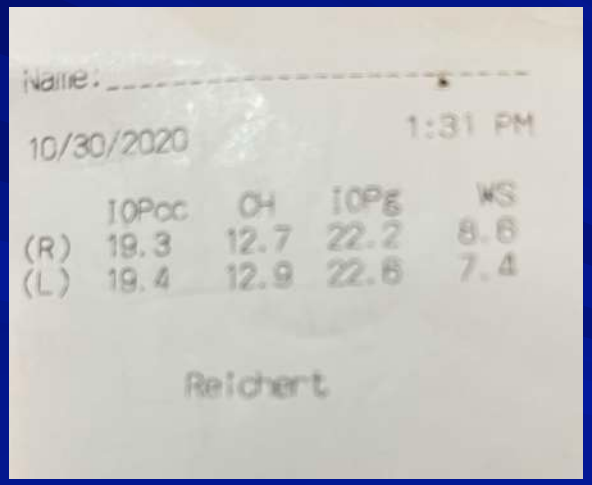
Reichert

Name: _____

11/09/2021 6:14 PM

	IOPcc	CH	IOPg	WS
(R)	17.3	8.6	14.8	6.3
(L)	15.2	9.6	13.6	7.1

Reichert

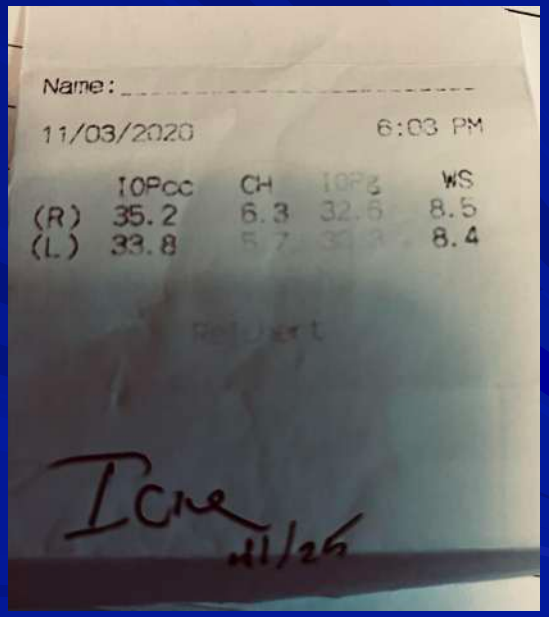


Name: _____

10/30/2020 1:31 PM

	IOPcc	CH	IOPg	WS
(R)	19.3	12.7	22.2	8.6
(L)	19.4	12.9	22.6	7.4

Reichert



Name: _____

11/03/2020 6:03 PM

	IOPcc	CH	IOPg	WS
(R)	35.2	6.3	32.6	8.5
(L)	33.8	5.7	31.3	8.4

Reichert

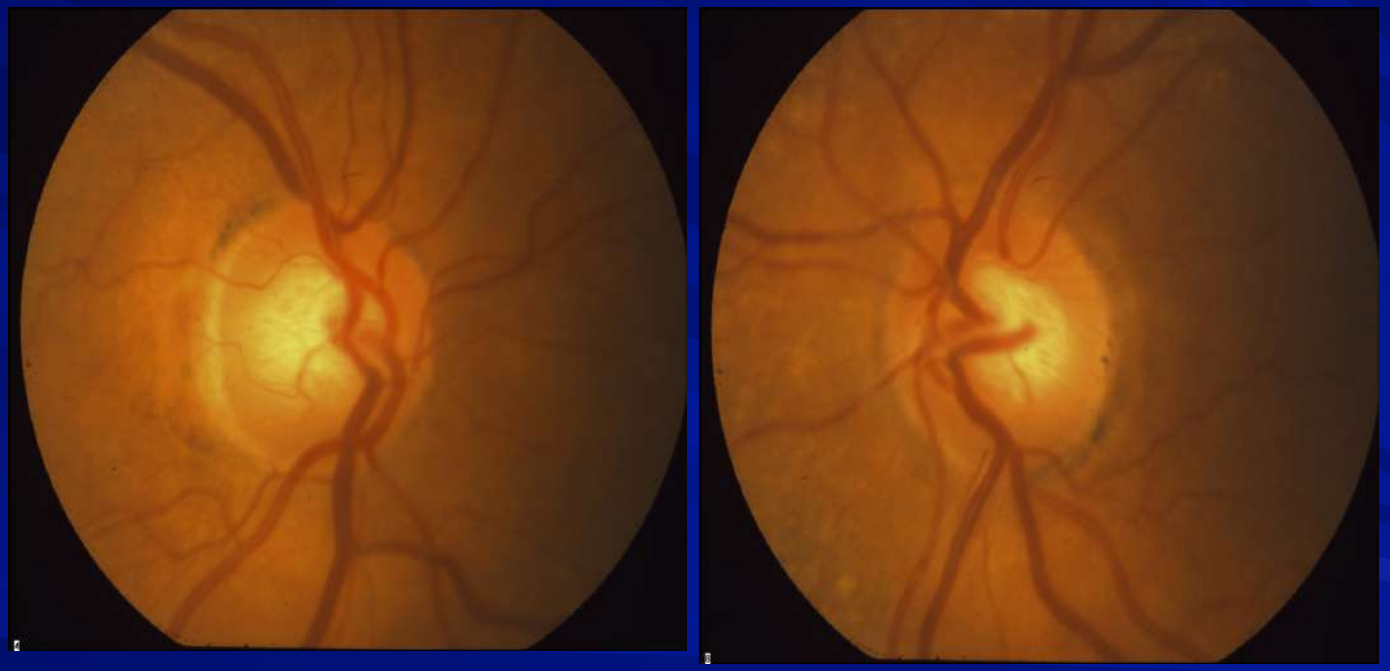
ICM 11/25

Bonus on Visual Fields

50-year-old woman

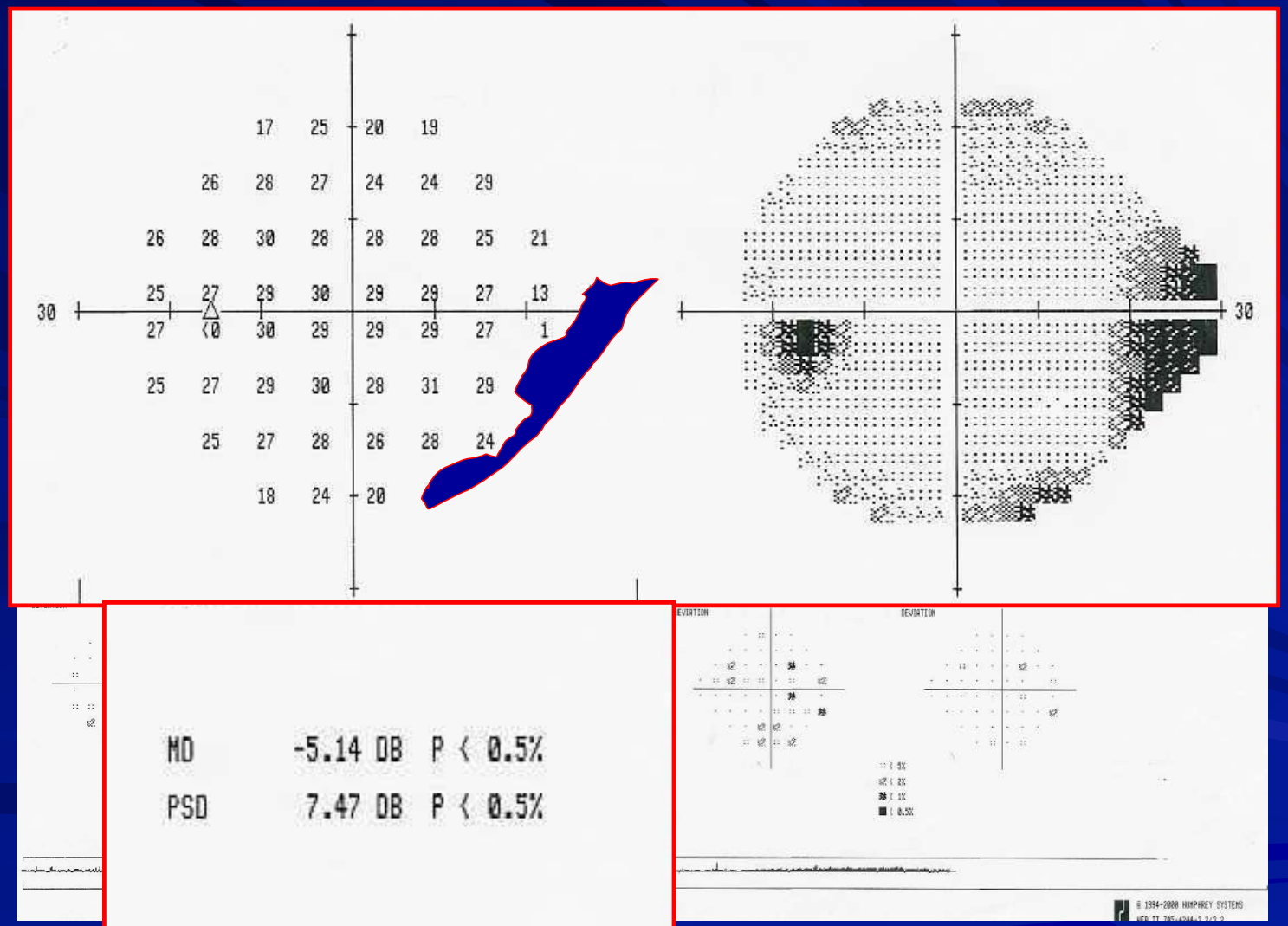
- Recently has moved to the area and needs followed for her "ocular hypertension"
- Diagnosed 18 months ago
- Currently is using Travatan qd OU (PM)
- VA 20/15 OU
- Externals: unremarkable
- SLE: slight hyperemia OU
- IOP: 13 OD and 14 OS @ 8:30 AM

ONH Appearance



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

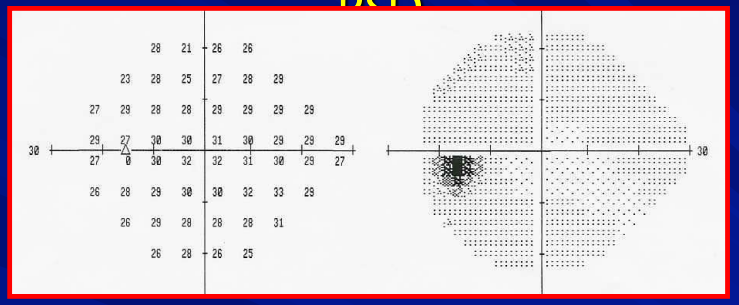

17 25 20 19
26 28 27 24 24 29
26 28 30 28 28 28 25 21
25 27 29 30 29 29 27 13
30
27 (0 30 29 29 29 27 1
25 27 29 30 28 31 29
25 27 28 26 28 24
18 24 20
30
MD -5.14 DB P < 0.5%
PSD 7.47 DB P < 0.5%
DEVIATION
DEVIATION
© 1994-2000 HUMPHREY SYSTEMS

MD and PSD

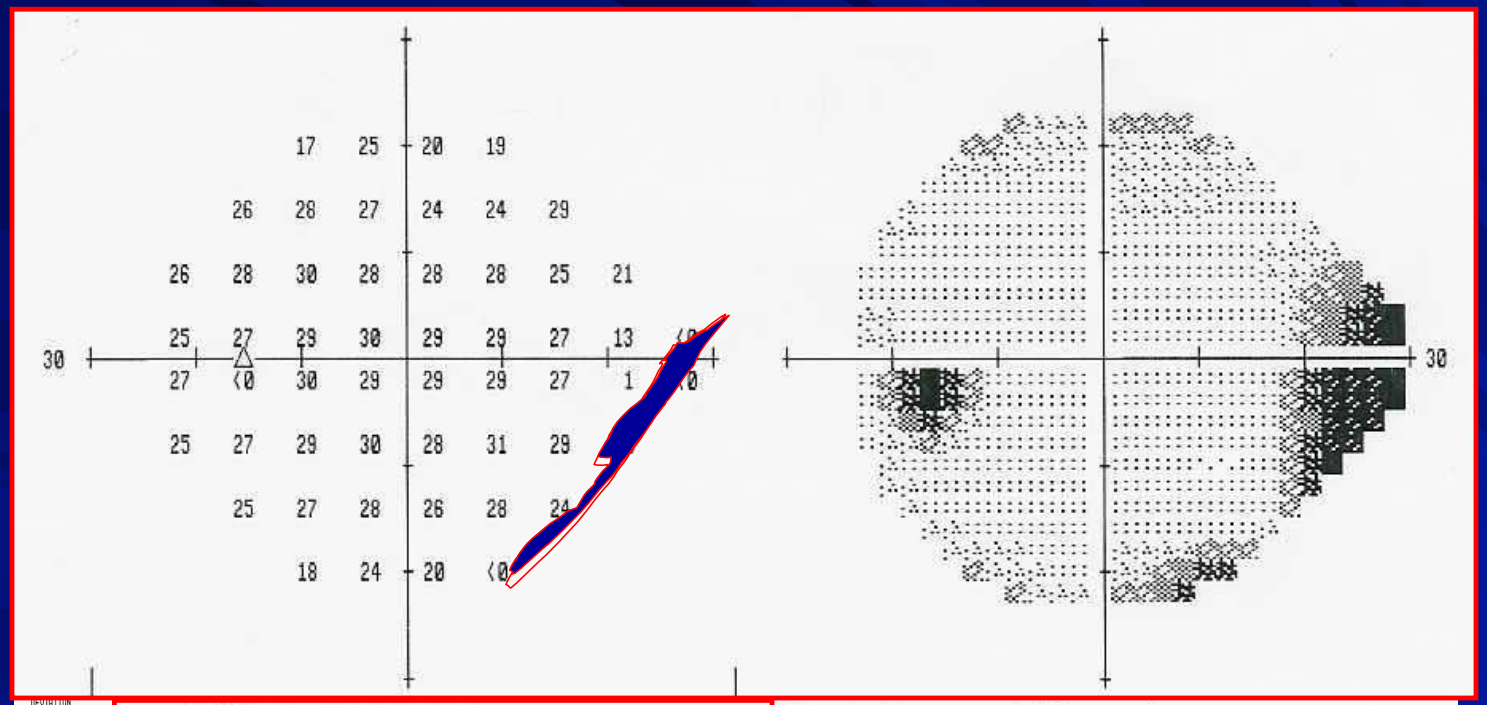
MD

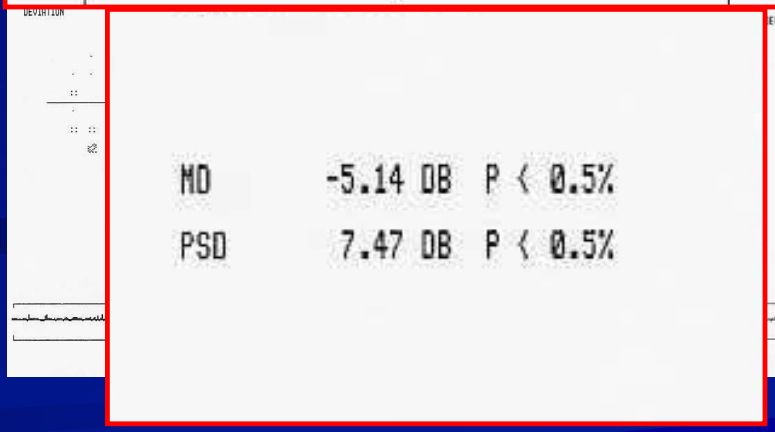
- 54 spots on 24-2
  - All 54 spots reduced by 1 DB (54DB)
  - MD 1DB
- 54 spots on 24-2
  - 27 spots reduced by 2 DB (54 DB)
  - MD 1 DB
- 54 spots on 24-2
  - 13.5 spots reduced by 4 DB (54DB)
  - MD 1 DB

PSD



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


17 25 20 19
26 28 27 24 24 29
26 28 30 28 28 28 25 21
25 27 29 30 29 29 27 13
27 30 29 29 29 27 1
25 27 29 30 28 31 29
25 27 28 26 28
18 24 20
30
30

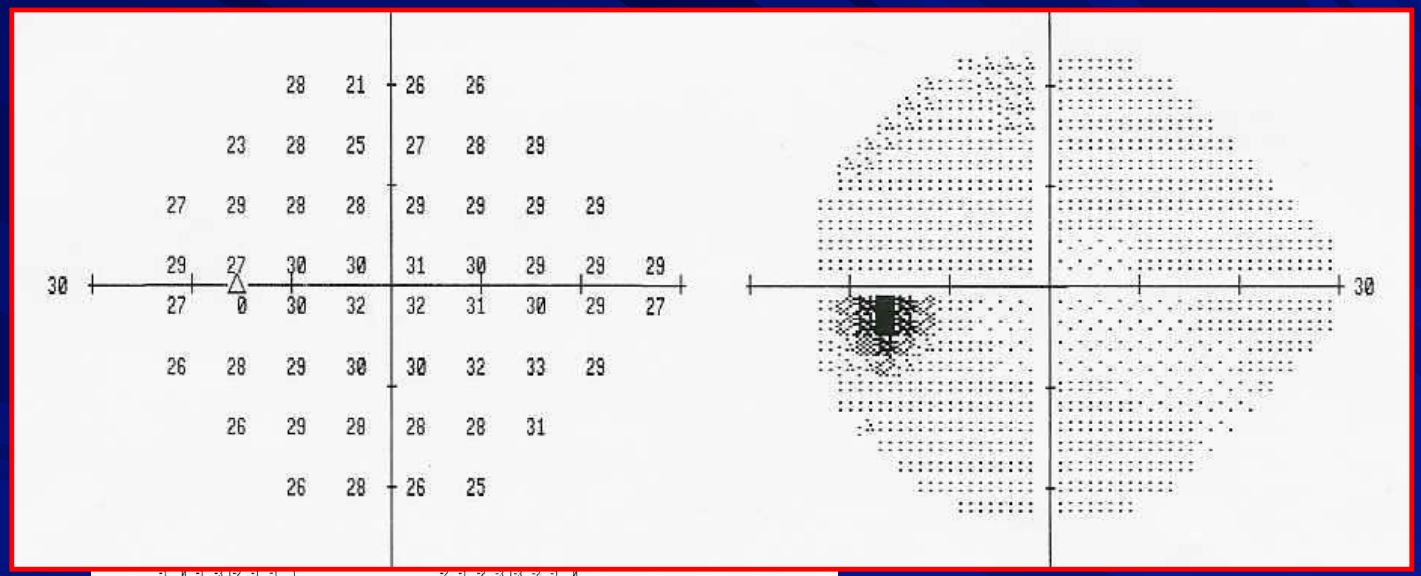

MD -5.14 DB P < 0.5%
PSD 7.47 DB P < 0.5%

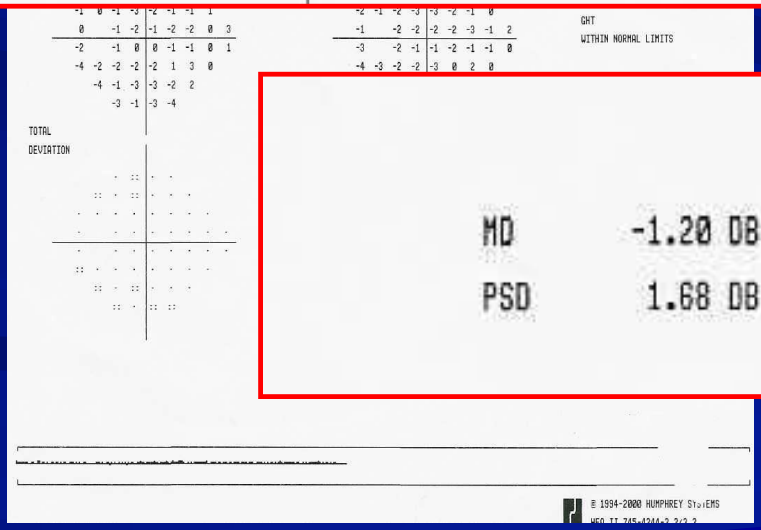

DEVIATION
DEVIATION
© 1994-2000 HUMPHREY SYSTEMS

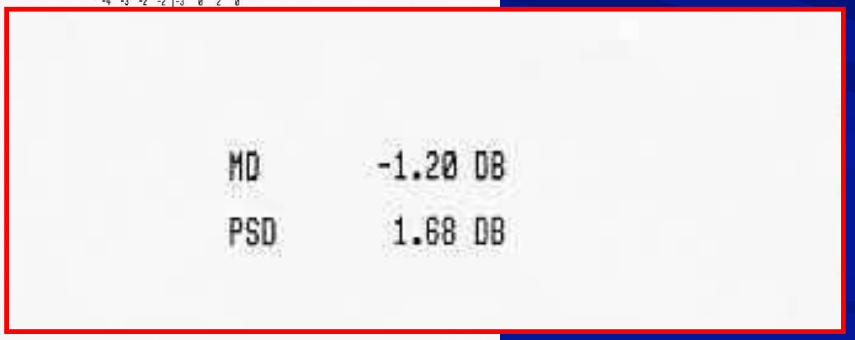
Discussion
Why is this patient being treated?

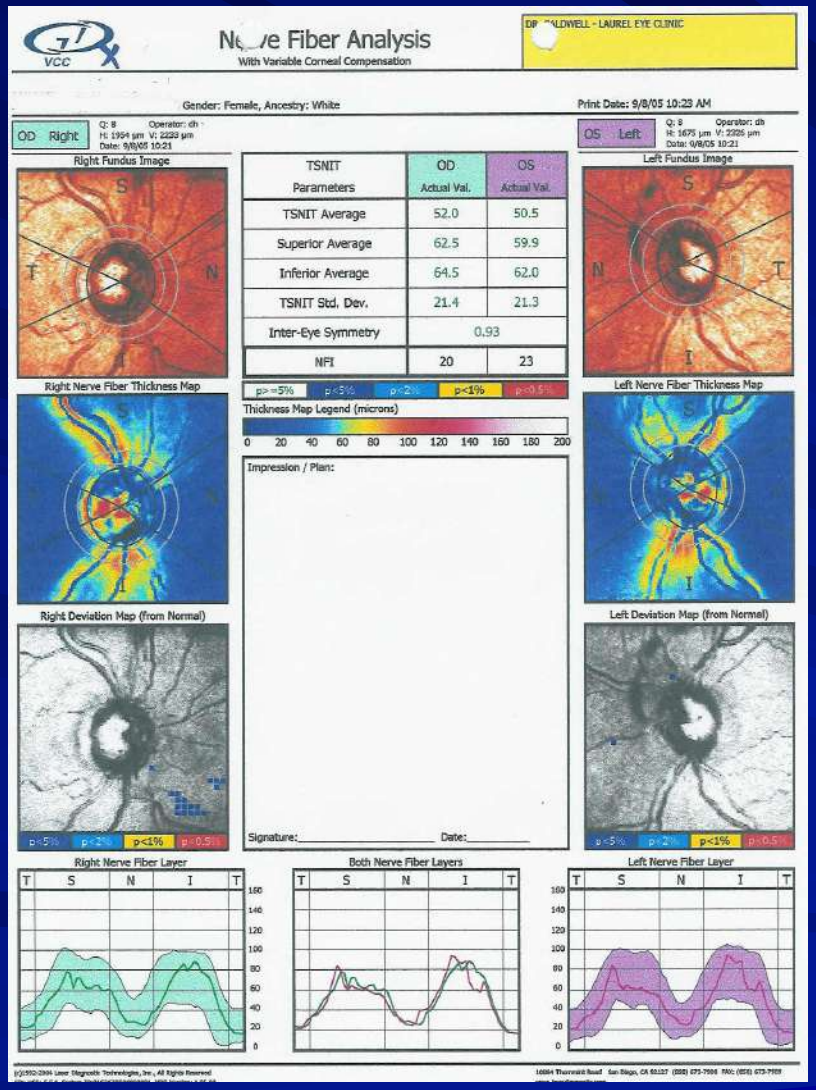
Treatment

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


28 21 26 26
23 28 25 27 28 29
27 29 28 28 29 29 29 29
29 27 30 30 31 30 29 29 29
30 27 0 30 32 32 31 30 29 27 30
26 28 29 30 30 32 33 29
26 29 28 28 28 31
26 28 26 25


TOTAL
DEVIATION
GHT
WITHIN NORMAL LIMITS
© 1994-2000 HUMPHREY SYSTEMS


MD -1.20 DB
PSD 1.68 DB


Nerve Fiber Analysis
With Variable Corneal Compensation
Gender: Female, Ancestry: White
Print Date: 9/8/05 10:23 AM
OD Right
OS Left
Right Fundus Image
Left Fundus Image
TSNIT Parameters
OD Actual Val.
OS Actual Val.
TSNIT Average 52.0 50.5
Superior Average 62.5 59.9
Inferior Average 64.5 62.0
TSNIT Std. Dev. 21.4 21.3
Inter-Eye Symmetry 0.93
NFI 20 23
Right Nerve Fiber Thickness Map
Left Nerve Fiber Thickness Map
Thickness Map Legend (microns)
0 20 40 60 80 100 120 140 160 180 200
Impression / Plan:
Signature: Date:
Right Deviation Map (from Normal)
Left Deviation Map (from Normal)
Right Nerve Fiber Layer
Both Nerve Fiber Layers
Left Nerve Fiber Layer
T S N I T

GDX Results

Cranium Keeper

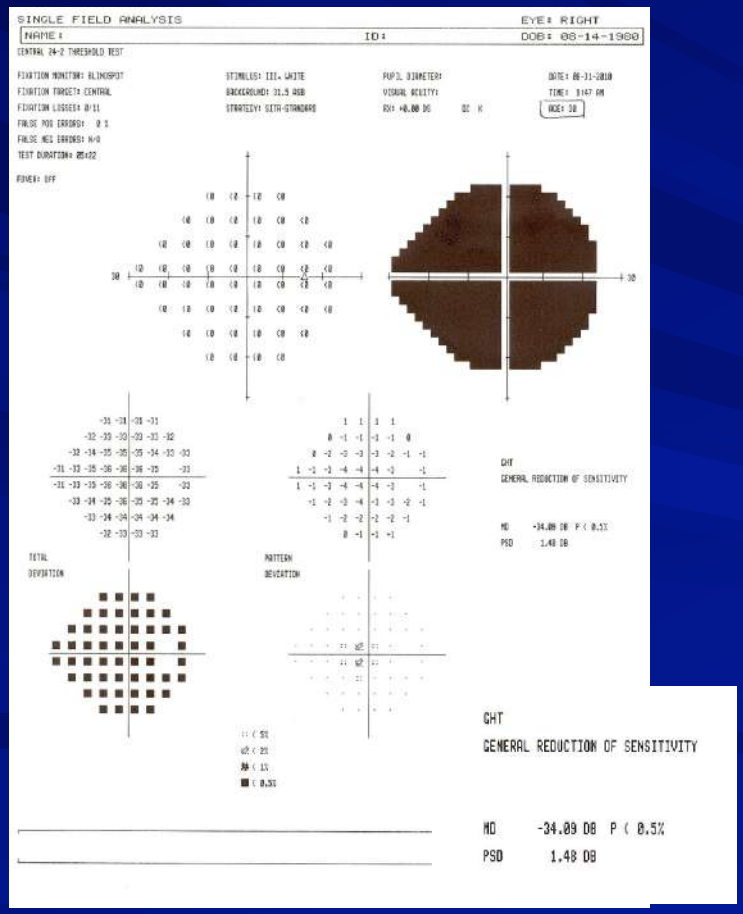
- Do not back door patients into the ocular hypertension treatment study
  - Via thin pach results
- A patient needs to be suffering from ocular hypertension to use the study
- Thin pachs tell us:
  - Patients with ocular hypertension are at high, medium or low risk for development
- If you have a diagnostic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

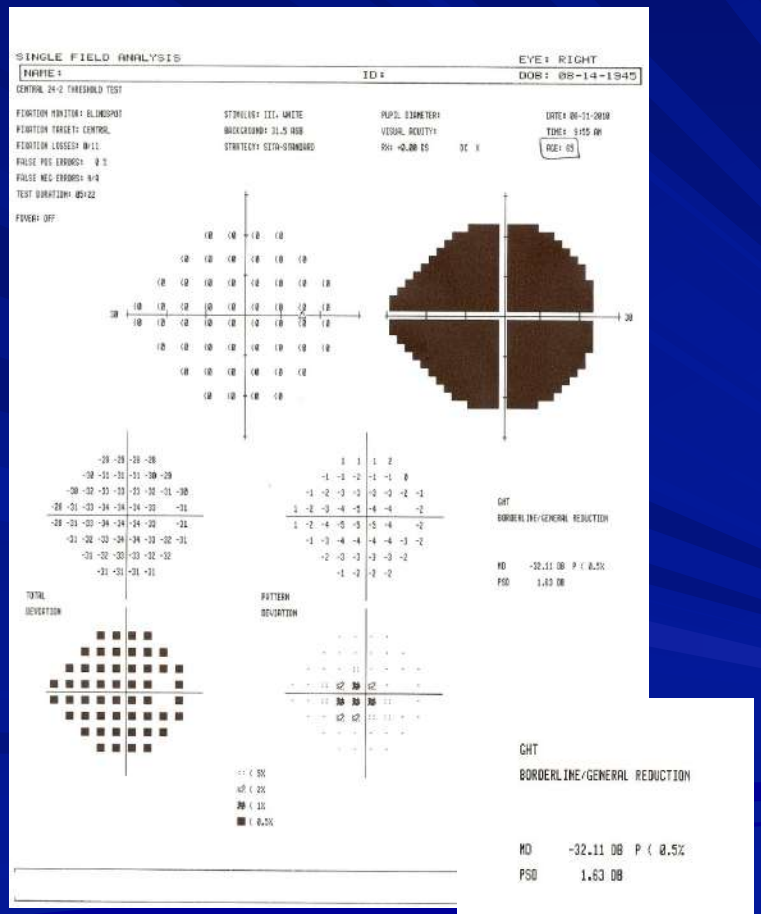
Ask Yourself

- 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

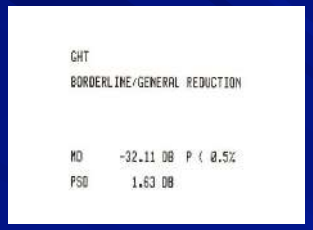
Thoughts on Mean Deviation (MD)

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





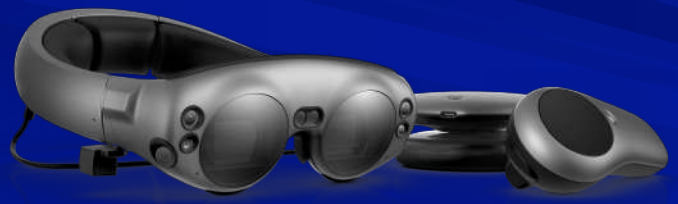
Thoughts on Mean Deviation (MD)



- 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

Wearable Technology



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.

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

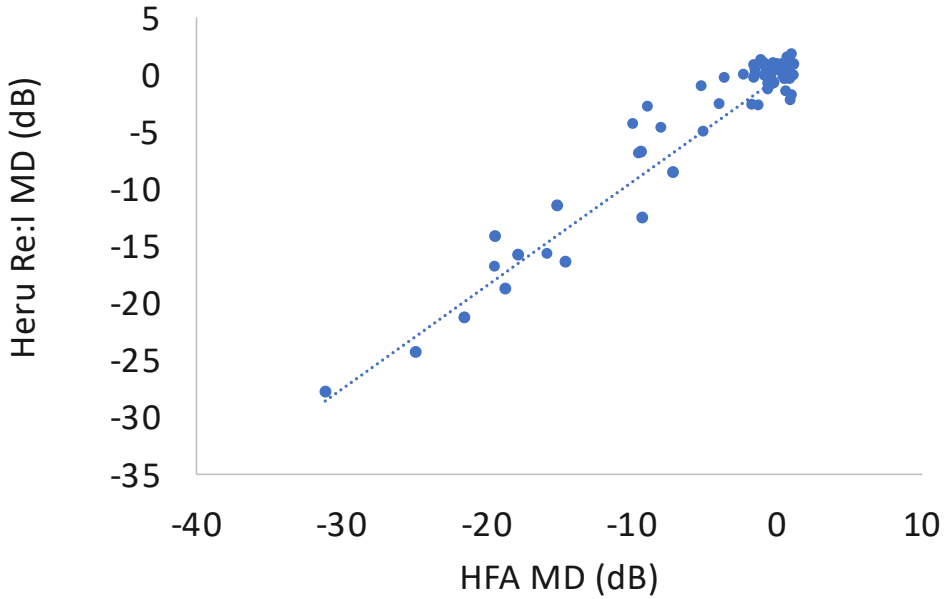
40 U.S. and International Patents to Date

1,000+ Patients in Clinical Trials

450 Million Patients with Visual Field Defects

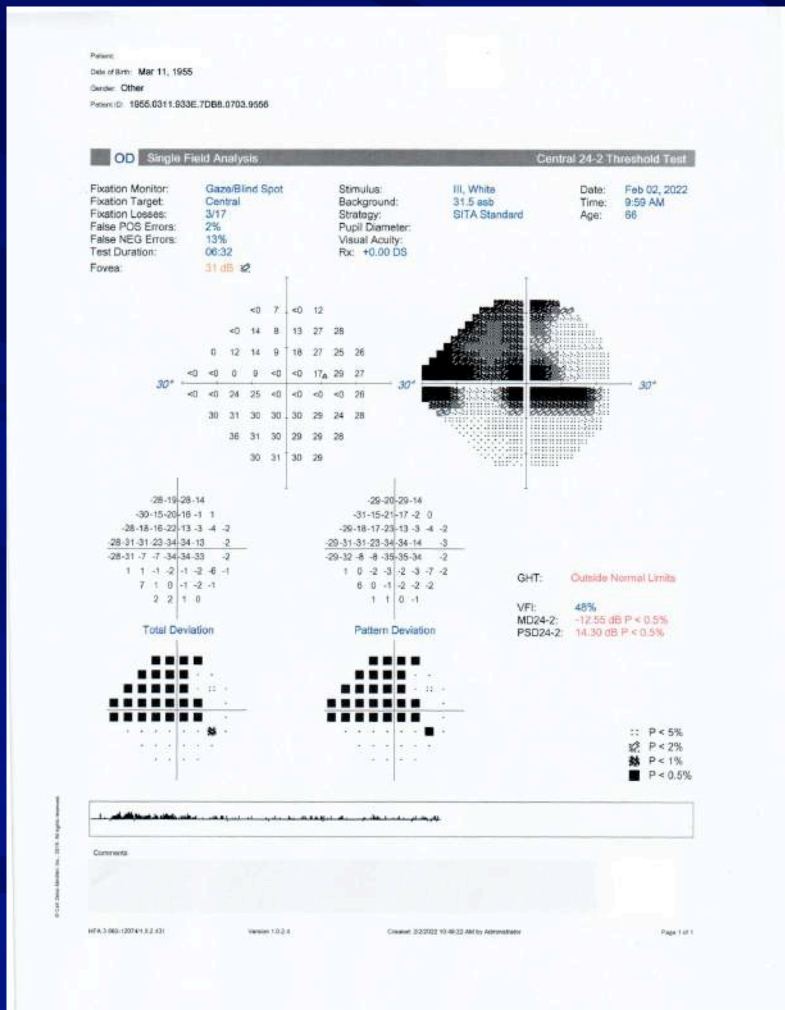
What is the Same?

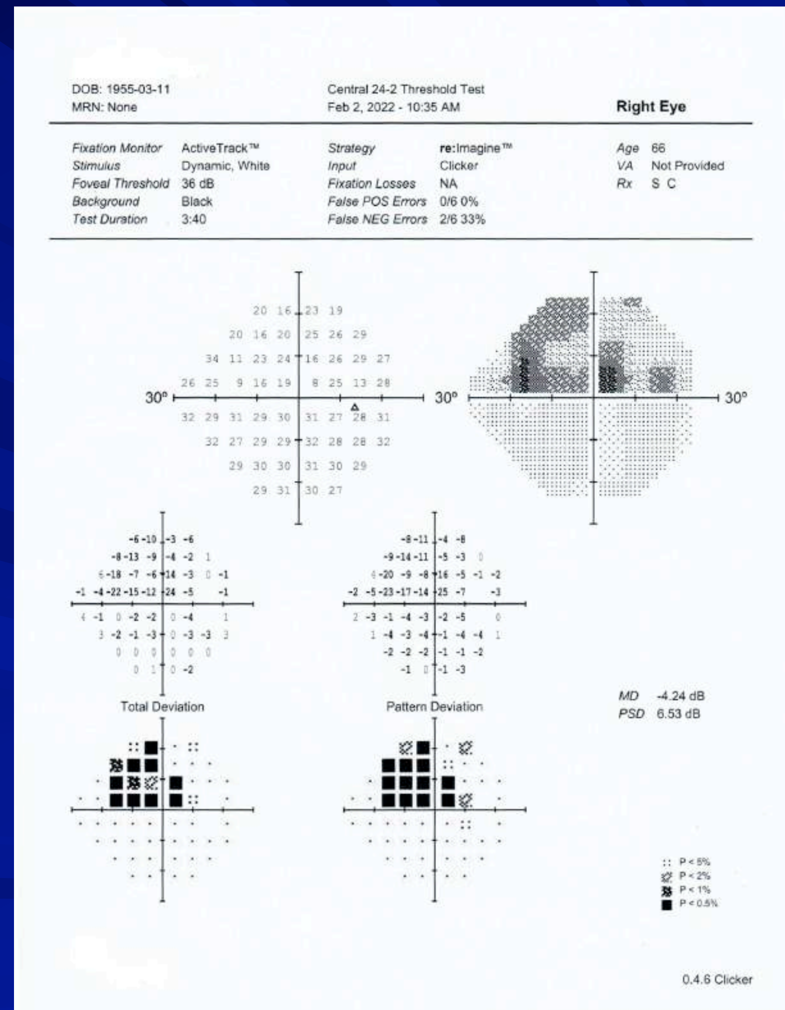
re:Vive by Heru
Correlates strongly with the standard of care, throughout the dynamic range



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

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

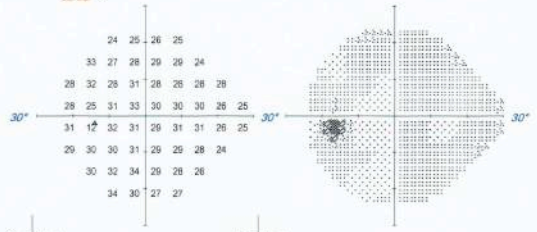

Patient:
Date of Birth: Mar 11, 1955
Gender: Other
Patient ID: 1955.0311.933E.7DB8.0703.9556
OD Single Field Analysis
Central 24-2 Threshold Test
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 3/17
False POS Errors: 2%
False NEG Errors: 13%
Test Duration: 06:32
Fovea: 31 dB
Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +0.00 DS
Date: Feb 02, 2022
Time: 9:59 AM
Age: 66
30°
Total Deviation
Pattern Deviation
GHT: Outside Normal Limits
VFI: 48%
MD24-2: -12.55 dB P < 0.5%
PSD24-2: 14.30 dB P < 0.5%
P < 5%
P < 2%
P < 1%
P < 0.5%
Comments


DOB: 1955-03-11
MRN: None
Central 24-2 Threshold Test
Feb 2, 2022 - 10:35 AM
Right Eye
Fixation Monitor ActiveTrack™
Stimulus Dynamic, White
Foveal Threshold 36 dB
Background Black
Test Duration 3:40
Strategy re:Imagine™
Input Clicker
Fixation Losses NA
False POS Errors 0/6 0%
False NEG Errors 2/6 33%
Age 66
VA Not Provided
Rx S C
30°
Total Deviation
Pattern Deviation
MD -4.24 dB
PSD 6.53 dB
P < 5%
P < 2%
P < 1%
P < 0.5%
0.4.6 Clicker

Patient:
Date of Birth: Mar 11, 1955
Gender: Other
Patient ID: 1955.0311.933E.7DB8.0703.9556

OS Single Field Analysis — Central 24-2 Threshold Test

Fixation Monitor:	Gaze/Blind Spot	Stimulus:	III, White	Date:	Feb 02, 2022
Fixation Target:	Central	Background:	31.5 asb	Time:	10:07 AM
Fixation Losses:	4/14 XX	Strategy:	SITA Standard	Age:	66
False POS Errors:	5%	Pupil Diameter:			
False NEG Errors:	2%	Visual Acuity:			
Test Duration:	05:07	Rx:	+1.75 DS		
Fovea:	32 dB ::				



GHT: Within Normal Limits

VFI: 96%
MD24-2: -0.78 dB
PSD24-2: 2.00 dB P < 5%

*** Low Test Reliability ***

:: P < 5%
P < 2%
P < 1%
P < 0.5%

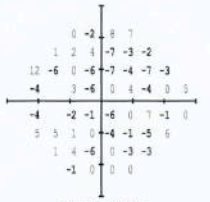
Comments

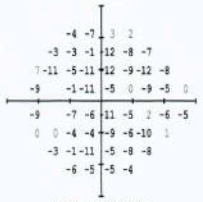
DOB: 1955-03-11
MRN: None

Central 24-2 Threshold Test
Feb 2, 2022 - 10:41 AM

Left Eye

Fixation Monitor	Blind spot	*Strategy*	re:Imagine™	*Age*	66
Stimulus	Dynamic, White	*Input*	Clicker	*VA*	Not Provided
Foveal Threshold	27 dB	*Fixation Losses*	NA	*Rx*	S C
Background	Black	*False POS Errors*	2/5 40%		
Test Duration	3:13	*False NEG Errors*	0/5 0%		





MD -0.72 dB
PSD 4.47 dB

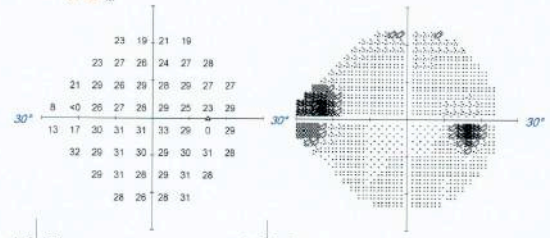
:: P < 5%
P < 2%
P < 1%
P < 0.5%

0.4.6 Clicker

Patient:
Date of Birth: Jan 12, 1955
Gender: Other
Patient ID: 1955.0112.B204.E70C.5CF8.B435

OD Single Field Analysis — Central 24-2 Threshold Test

Fixation Monitor:	Gaze/Blind Spot	Stimulus:	III, White	Date:	Jan 11, 2022
Fixation Target:	Central	Background:	31.5 asb	Time:	12:02 PM
Fixation Losses:	0/15	Strategy:	SITA Standard	Age:	66
False POS Errors:	3%	Pupil Diameter:			
False NEG Errors:	0%	Visual Acuity:			
Test Duration:	05:14	Rx:	+2.25 DS		
Fovea:	31 dB				



GHT: Outside Normal Limits

VFI: 94%
MD24-2: -2.83 dB P < 2%
PSD24-2: 5.23 dB P < 0.5%

:: P < 5%
P < 2%
P < 1%
P < 0.5%

Comments

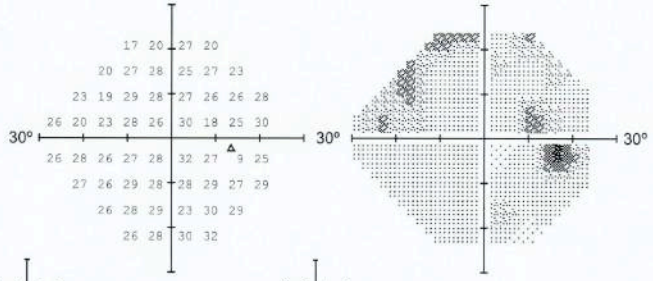
HFA 3 900-1007/01.5.2.451 Version 1.0.2.4 Created: 1/11/2022 2:39:32 PM by Administrator Page 1 of 1

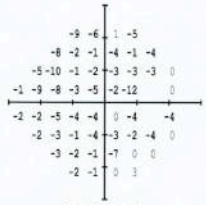
DOB: 1955-01-12
MRN: None

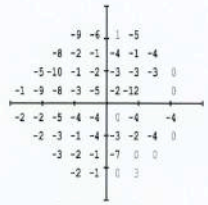
Central 24-2 Threshold Test
Jan 11, 2022 - 12:48 PM

Right Eye

Fixation Monitor	ActiveTrack™	*Strategy*	re:Imagine™	*Age*	66
Stimulus	Dynamic, White	*Input*	Clicker	*VA*	Not Provided
Foveal Threshold	30 dB	*Fixation Losses*	NA	*Rx*	S C
Background	Black	*False POS Errors*	1/6 17%		
Test Duration	3:44	*False NEG Errors*	0/6 0%		



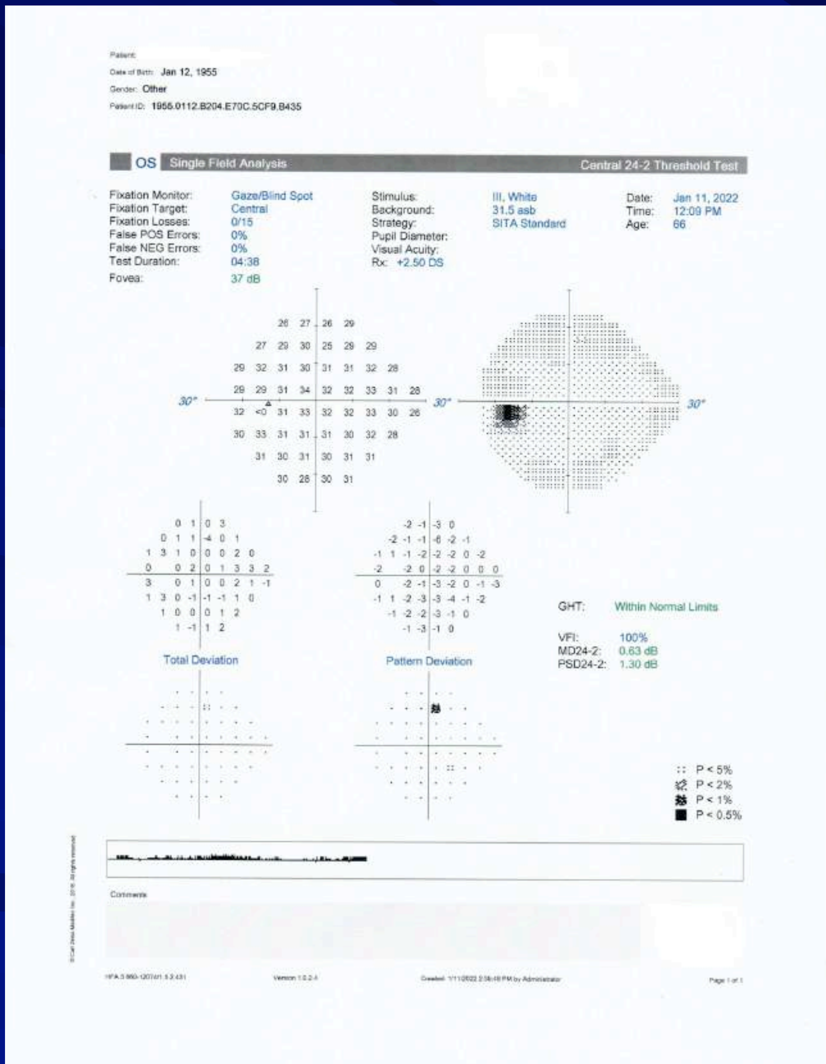


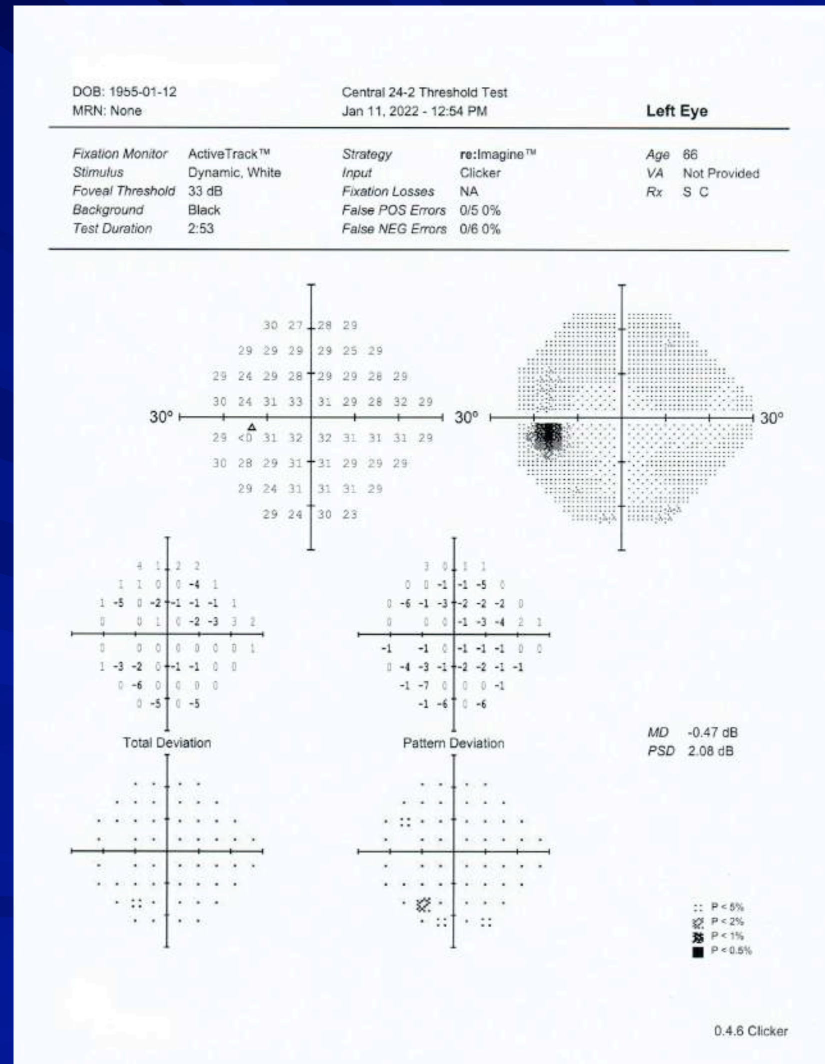


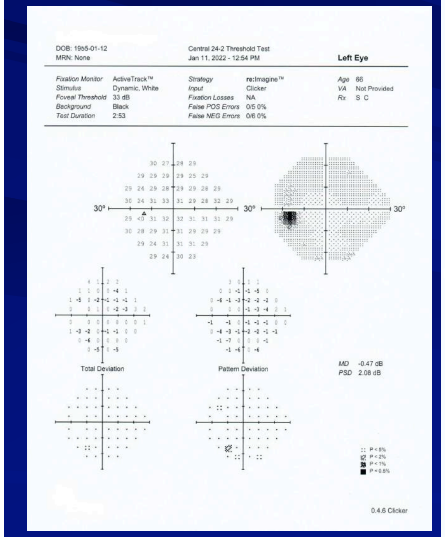
MD -3.38 dB
PSD 3.06 dB

:: P < 5%
P < 2%
P < 1%
P < 0.5%

0.4.6 Clicker


Patient:
Date of Birth: Jan 12, 1955
Gender: Other
Patient ID: 1955.0112.B204.E70C.5CF9.B435
OS Single Field Analysis
Central 24-2 Threshold Test
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/15
False POS Errors: 0%
False NEG Errors: 0%
Test Duration: 04:38
Fovea: 37 dB
Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +2.50 DS
Date: Jan 11, 2022
Time: 12:09 PM
Age: 66
30°
Total Deviation
Pattern Deviation
GHT: Within Normal Limits
VFI: 100%
MD24-2: 0.63 dB
PSD24-2: 1.30 dB
P < 5%
P < 2%
P < 1%
P < 0.5%
Comments


DOB: 1955-01-12
MRN: None
Central 24-2 Threshold Test
Jan 11, 2022 - 12:54 PM
Left Eye
Fixation Monitor ActiveTrack™
Stimulus Dynamic, White
Foveal Threshold 33 dB
Background Black
Test Duration 2:53
Strategy re:Imagine™
Input Clicker
Fixation Losses NA
False POS Errors 0/5 0%
False NEG Errors 0/6 0%
Age 66
VA Not Provided
Rx S C
30°
Total Deviation
Pattern Deviation
MD -0.47 dB
PSD 2.08 dB
P < 5%
P < 2%
P < 1%
P < 0.5%
0.4.6 Clicker



DOB: 1955-01-12
MRN: None

Central 24-2 Threshold Test
Jan 11, 2022 - 12:54 PM

Left Eye

Fixation Monitor	ActiveTrack™	*Strategy*	re:Imagine™	*Age*	66
Stimulus	Dynamic, White	*Input*	Clicker	*VA*	Not Provided
Foveal Threshold	33 dB	*Fixation Losses*	NA	*Rx*	S C
Background	Black	*False POS Errors*	0/5 0%		
Test Duration	2:53	*False NEG Errors*	0/6 0%		

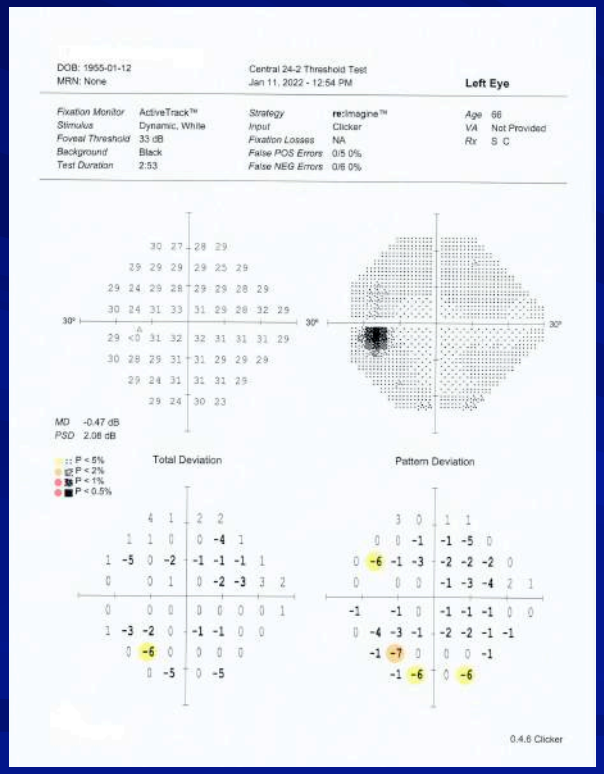
30° 30° 30°

Total Deviation Pattern Deviation

MD -0.47 dB
PSD 2.08 dB

:: P < 5%
P < 2%
P < 1%
P < 0.5%

0.4.6 Clicker



DOB: 1955-01-12
MRN: None

Central 24-2 Threshold Test
Jan 11, 2022 - 12:54 PM

Left Eye

Fixation Monitor	ActiveTrack™	*Strategy*	re:Imagine™	*Age*	66
Stimulus	Dynamic, White	*Input*	Clicker	*VA*	Not Provided
Foveal Threshold	33 dB	*Fixation Losses*	NA	*Rx*	S C
Background	Black	*False POS Errors*	0/5 0%		
Test Duration	2:53	*False NEG Errors*	0/6 0%		

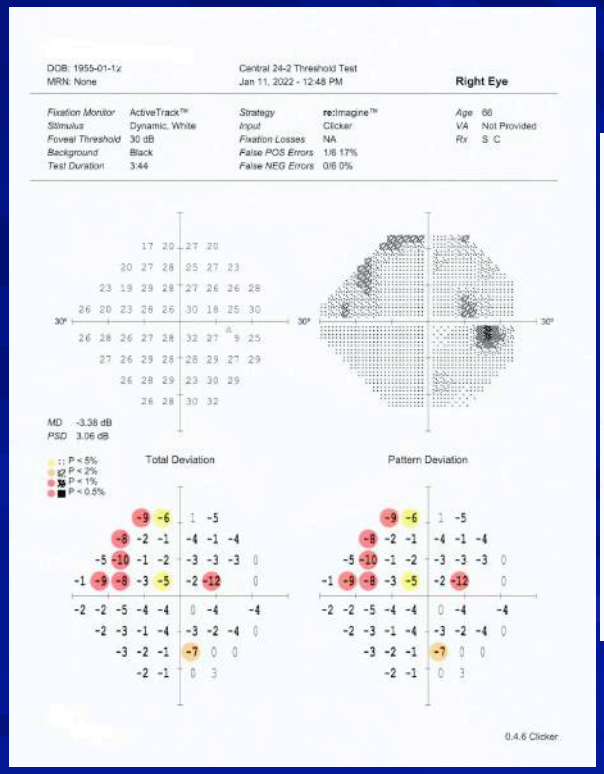
30° 30° 30°

MD -0.47 dB
PSD 2.08 dB

Total Deviation Pattern Deviation

:: P < 5%
P < 2%
P < 1%
P < 0.5%

0.4.6 Clicker



DOB: 1955-01-1x
MRN: None

Central 24-2 Threshold Test
Jan 11, 2022 - 12:48 PM

Right Eye

Fixation Monitor	ActiveTrack™	*Strategy*	re:Imagine™	*Age*	66
Stimulus	Dynamic, White	*Input*	Clicker	*VA*	Not Provided
Foveal Threshold	30 dB	*Fixation Losses*	NA	*Rx*	S C
Background	Black	*False POS Errors*	1/6 17%		
Test Duration	3:44	*False NEG Errors*	0/6 0%		

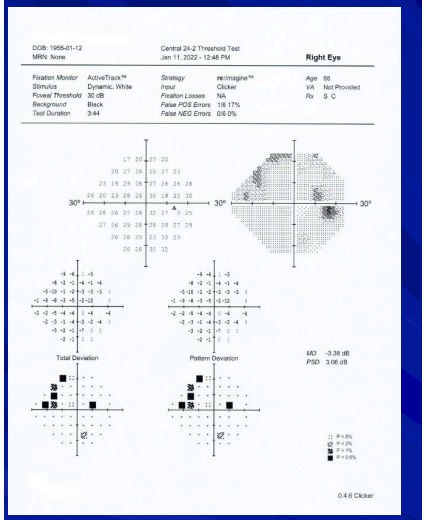
30° 30° 30°

MD -3.38 dB
PSD 3.06 dB

Total Deviation Pattern Deviation

:: P < 5%
P < 2%
P < 1%
P < 0.5%

0.4.6 Clicker



DOB: 1955-01-12
MRN: None

Central 24-2 Threshold Test
Jan 11, 2022 - 12:48 PM

Right Eye

Fixation Monitor	ActiveTrack™	*Strategy*	re:Imagine™	*Age*	66
Stimulus	Dynamic, White	*Input*	Clicker	*VA*	Not Provided
Foveal Threshold	30 dB	*Fixation Losses*	NA	*Rx*	S C
Background	Black	*False POS Errors*	1/6 17%		
Test Duration	3:44	*False NEG Errors*	0/6 0%		

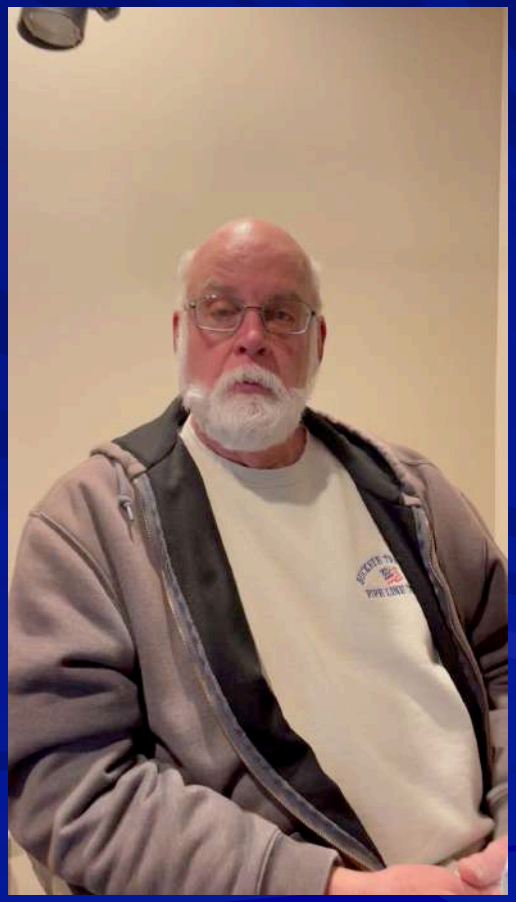
30° 30° 30°

Total Deviation Pattern Deviation

MD -3.38 dB
PSD 3.06 dB

0.4.6 Clicker

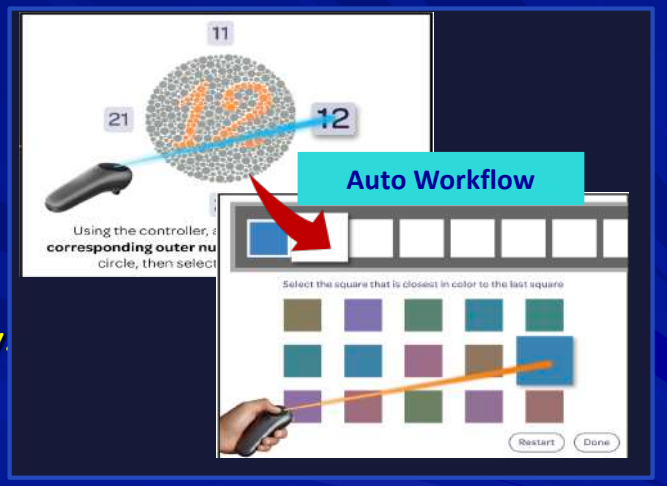
Patients' Thoughts



re:Vive 2.0 – Color Vision

Ishihara Color Vision Screening

- Ishihara color vision testing is a commonly used rapid, color vision screening modality.
- This test can be completed in under 2 minutes.
- 3 or more Ishihara plates incorrect will trigger the D-15 extended vision test using AutoWorkflow.™



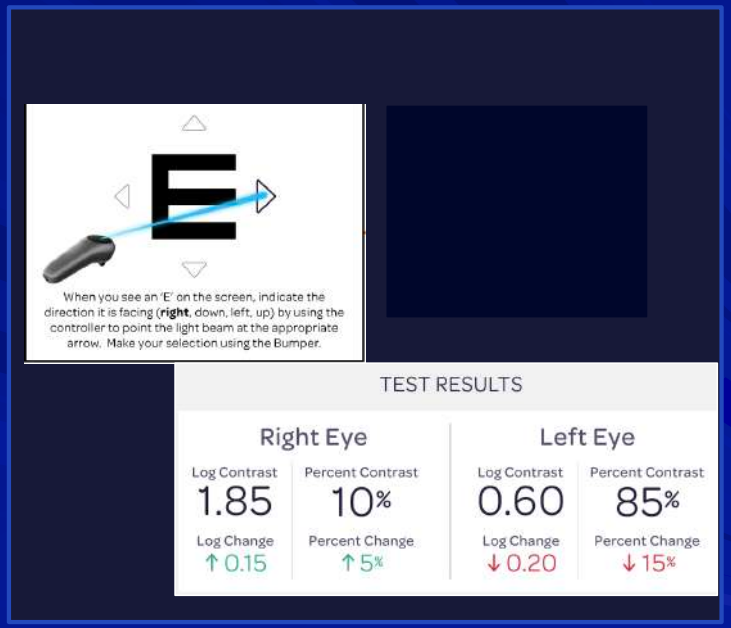
Farnsworth D-15 Extended Color Vision Test

- D-15 color vision testing is a commonly used color vision diagnostic modality.
- D-15 test is a **reimbursable** service: **CPT Code 92283**.
- **Average national reimbursement is $56.16[3].**
- This is more advanced than any color vision testing currently being offered by competitor goggle companies.

Technician and/or clinician not required to administer exam.

re:Vive 2.0 - Contrast Sensitivity

- Embracing the science connecting contrast sensitivity with detecting early AMD, re:Vive provides the most efficient way to document and monitor the functional macular health in conjunction with supplementation.
- We are reporting the change over time from the last visit. The doctor can use this change to communicate the benefits of lifestyle modifications, smoking cessation.
- Moves test out of the exam lane with the screening being performed in full room lighting.
- Contrast Sensitivity (and Dark Adaptation) are part of a broader AMD screening and diagnostic portfolio.

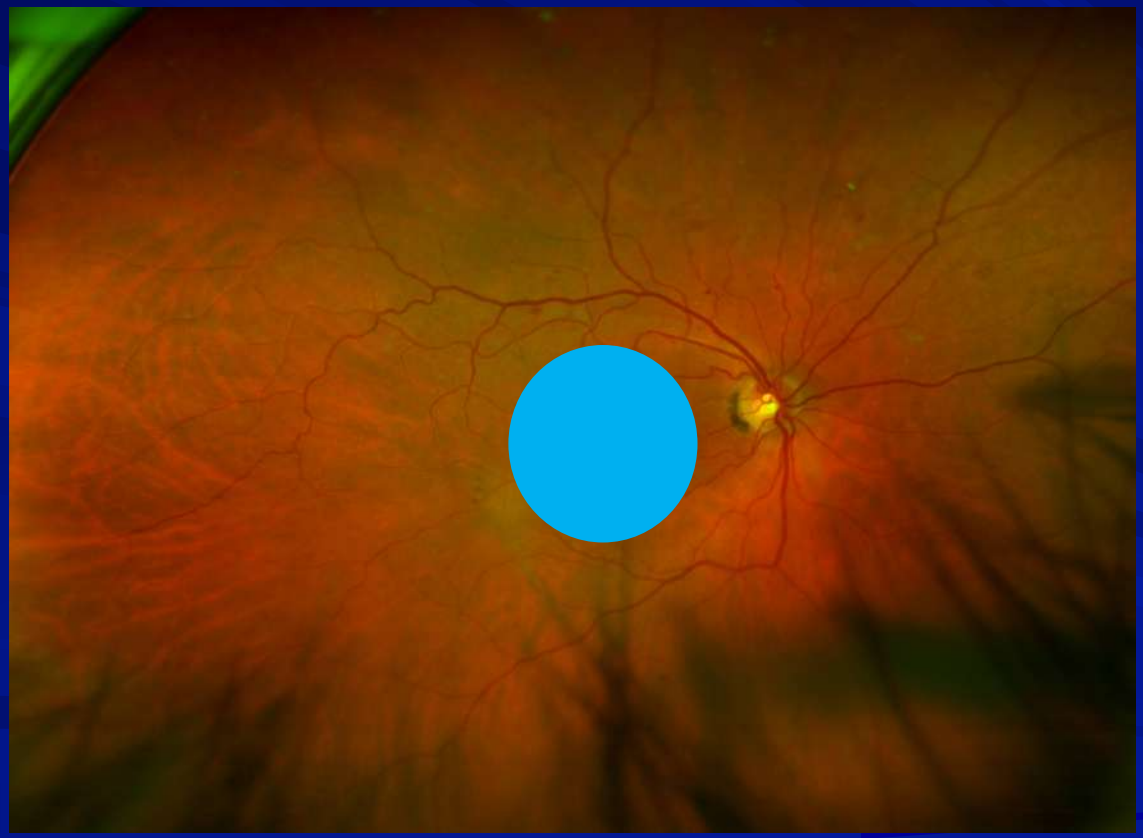


Technician and/or clinician not required to administer exam.

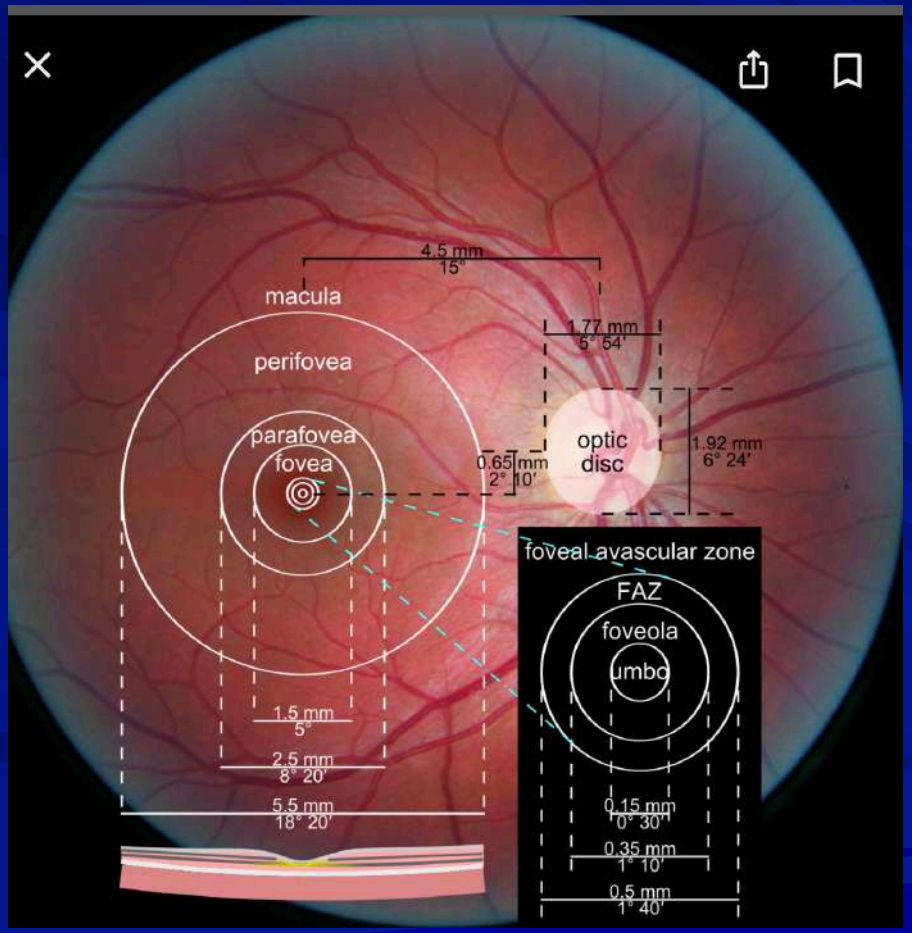
Instruments for AMD – fragmented care

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

Where is the macula?



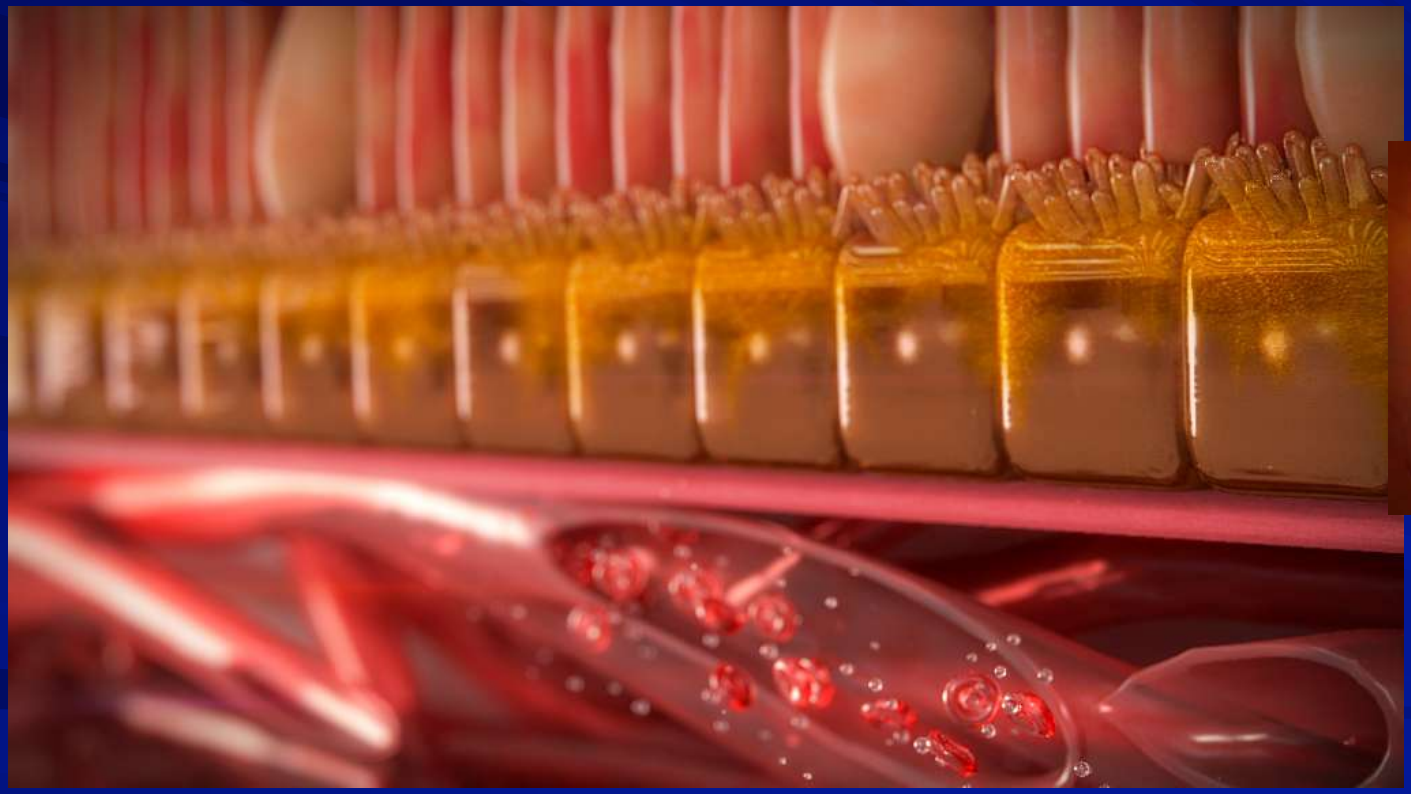
How large is the macula?



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

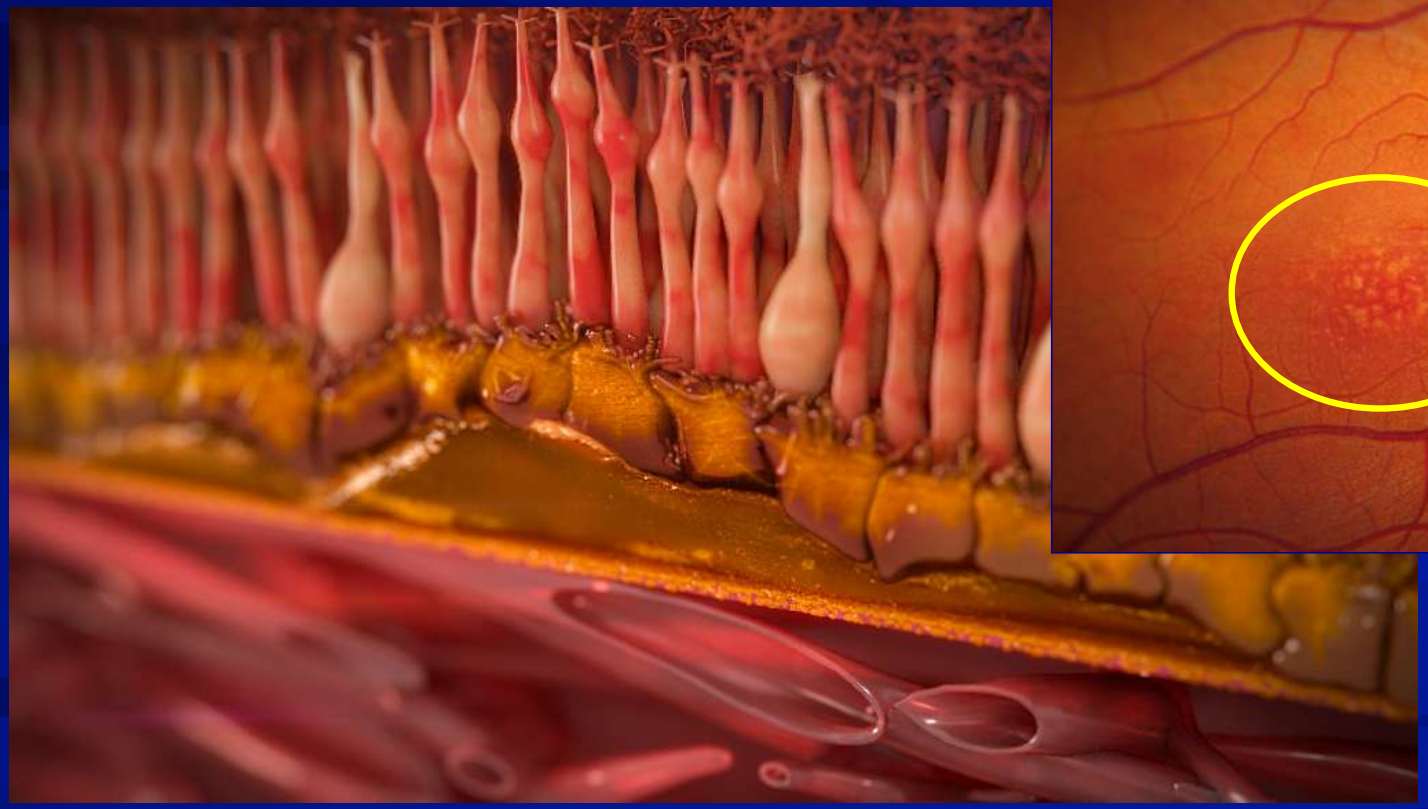
Healthy choriocapillaris, Bruch's, RPE, and Photoreceptors

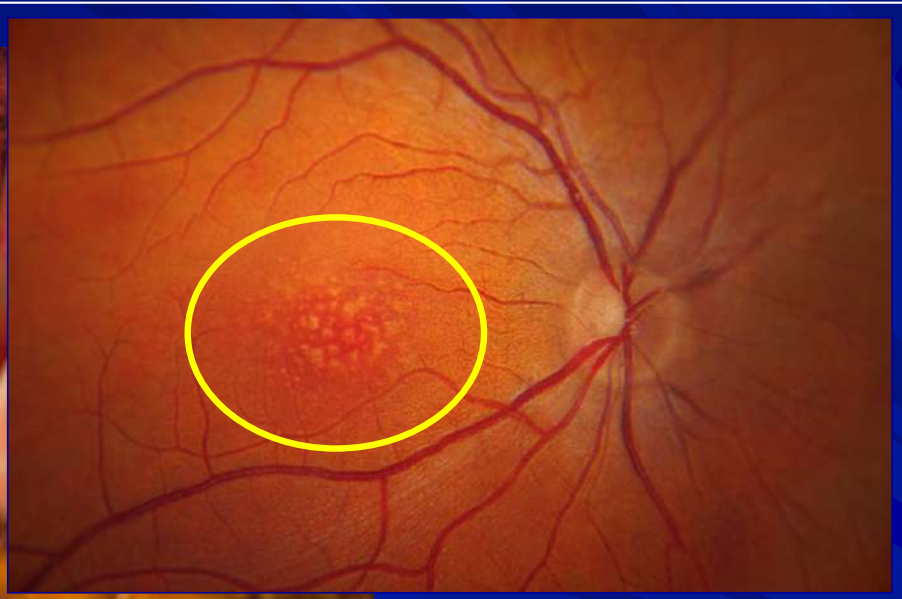


Cholesterol barrier deposited along Bruch's and RPE

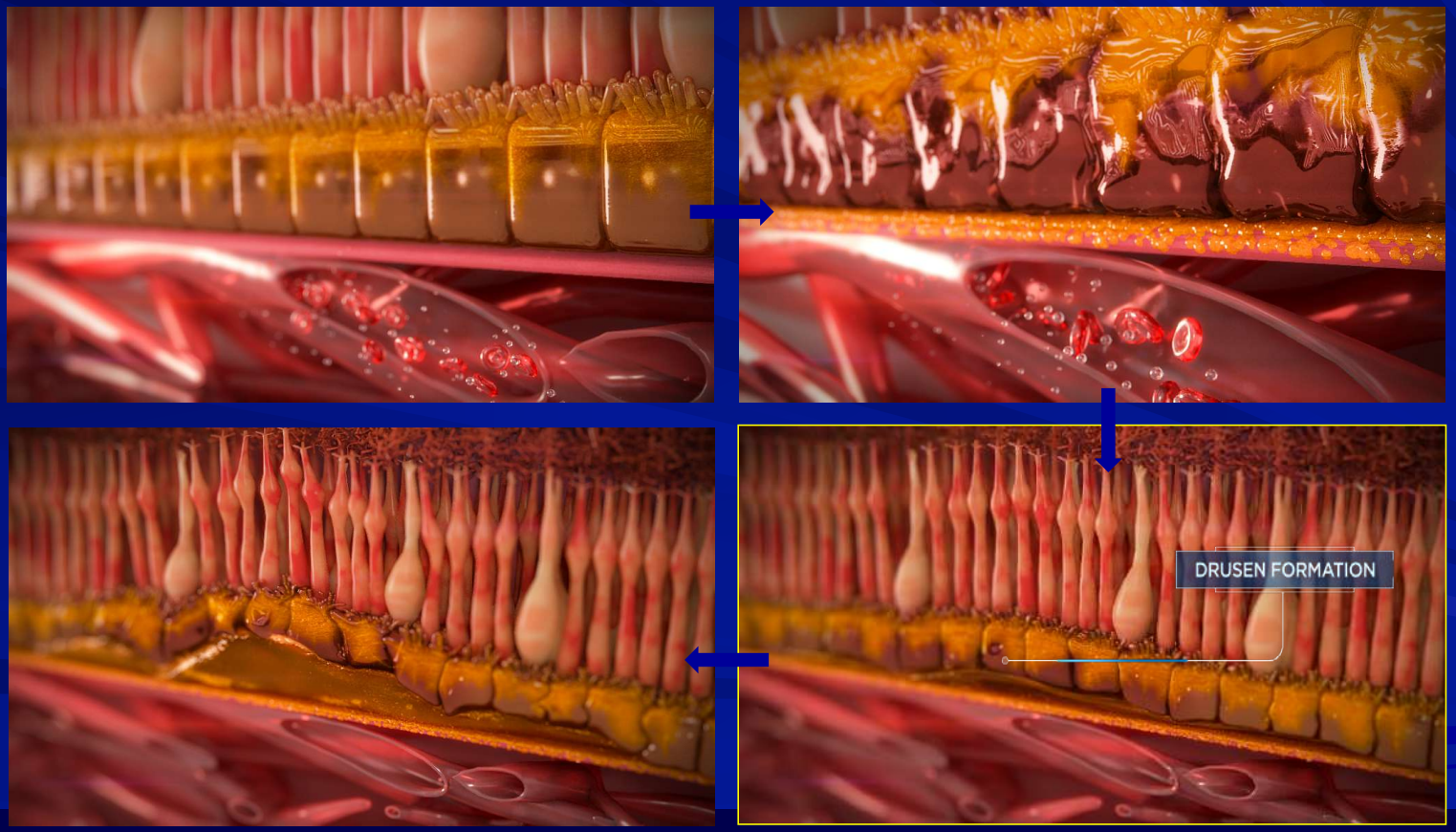
RPE Secretes even more cholesterol and degenerates

Finally, visibly evident drusen on fundus evaluation





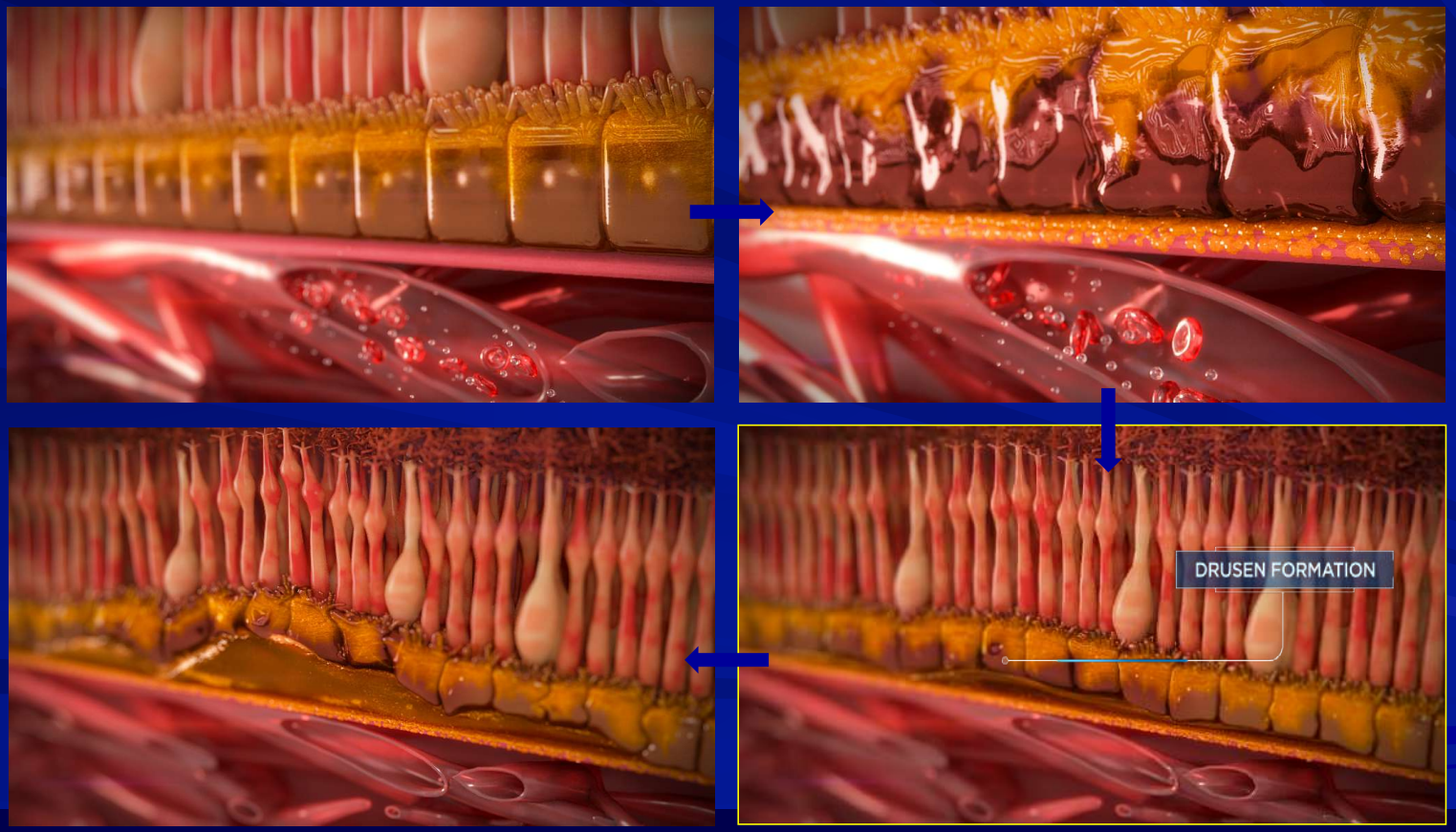
AMD is a Disease Process that Starts Below the Surface



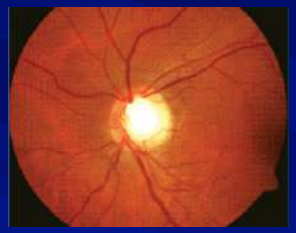
Beckmann Committee Classification of AMD

- Based on presence of lesions within 2 DD of fovea in either eye
  - No AMD
    - None or few small drusen, < 63 microns
    - No AMD pigmentary abnormalities
  - Early AMD
    - Medium drusen, > 63 – <125 microns
    - No AMD pigmentary changes
  - Intermediate AMD
    - 1 large drusen, > 125 microns
    - Any AMD pigmentary changes
  - Advanced AMD
    - Any geographic atrophy
    - Choroidal neovascularization (CNV)

AMD is a Disease Process that Starts Below the Surface



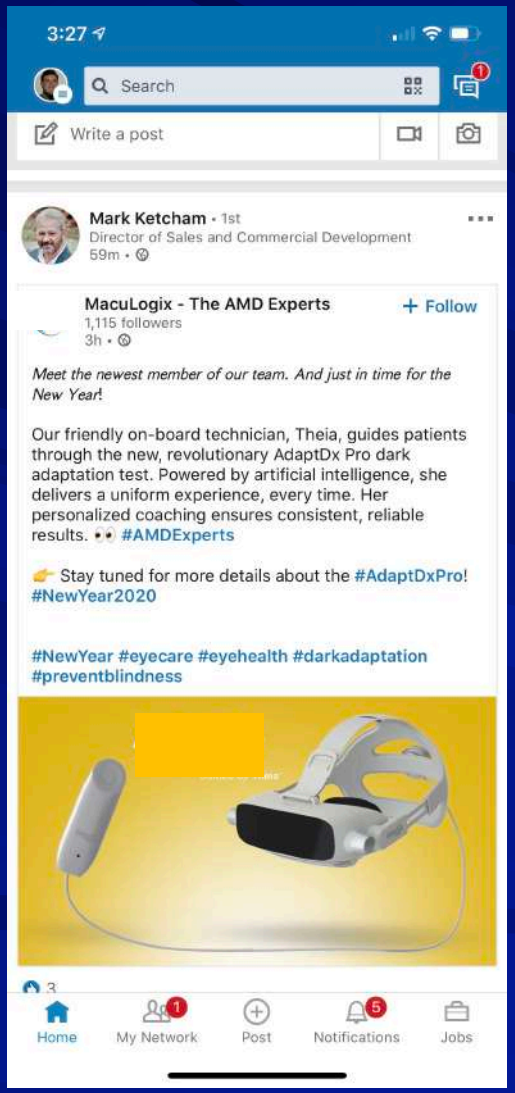
Applying a Familiar Standard of Care:
Two Multifactorial Diseases

	Glaucoma		AMD
Structure	 Cup-to-disc Ratio	→	 Drusen
Function	 Visual Field	→	 Dark Adaptation
Risk	Intraocular Pressure (IOP) Corneal Thickness Age/race Family history/etc. Health and Lifestyle (Diabetes)	→	Age Genetic Testing Health and Lifestyle (Smoking) Macular Pigment Optical Density (MPOD) Contrast Sensitivity.

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%



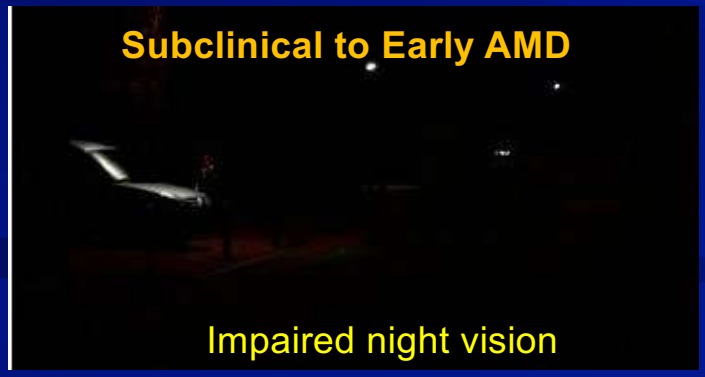
Dark Adaptation in AMD

Function Test

January 1st, 2020

AdaptDx Pro Now Available for Clinical Use

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

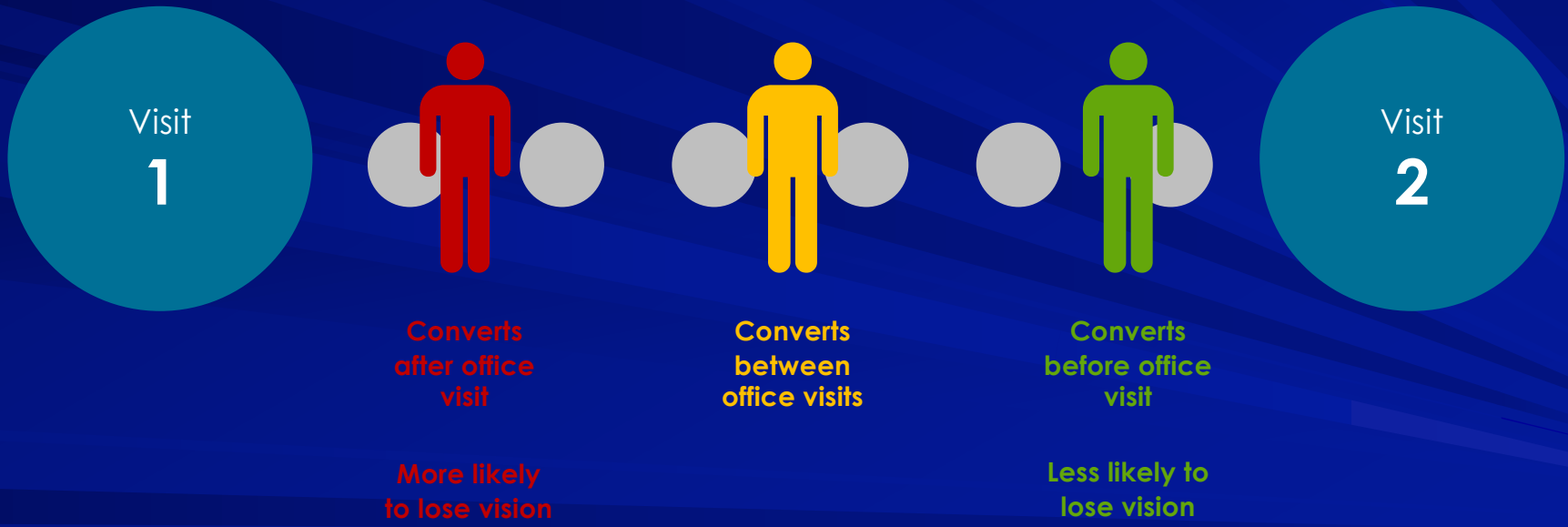


- Night vision impacted in early AMD: 30+ studies
- AMD patients often give up driving at night
- Night vision is impaired before day vision
- Typically ECP's chalk this complaint up to cataracts

Ask Every Patient Over 50 About Their Night Vision

Preferential Hyperacuity Perimetry (PHP)

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



Reference: Rauch R, et al. *Retina*. 2012;32(7):1260-1264.

Notal Vision - ForeseeHome® product overview

Uses Preferential Hyperacuity Perimetry (PHP)

Medicare covered

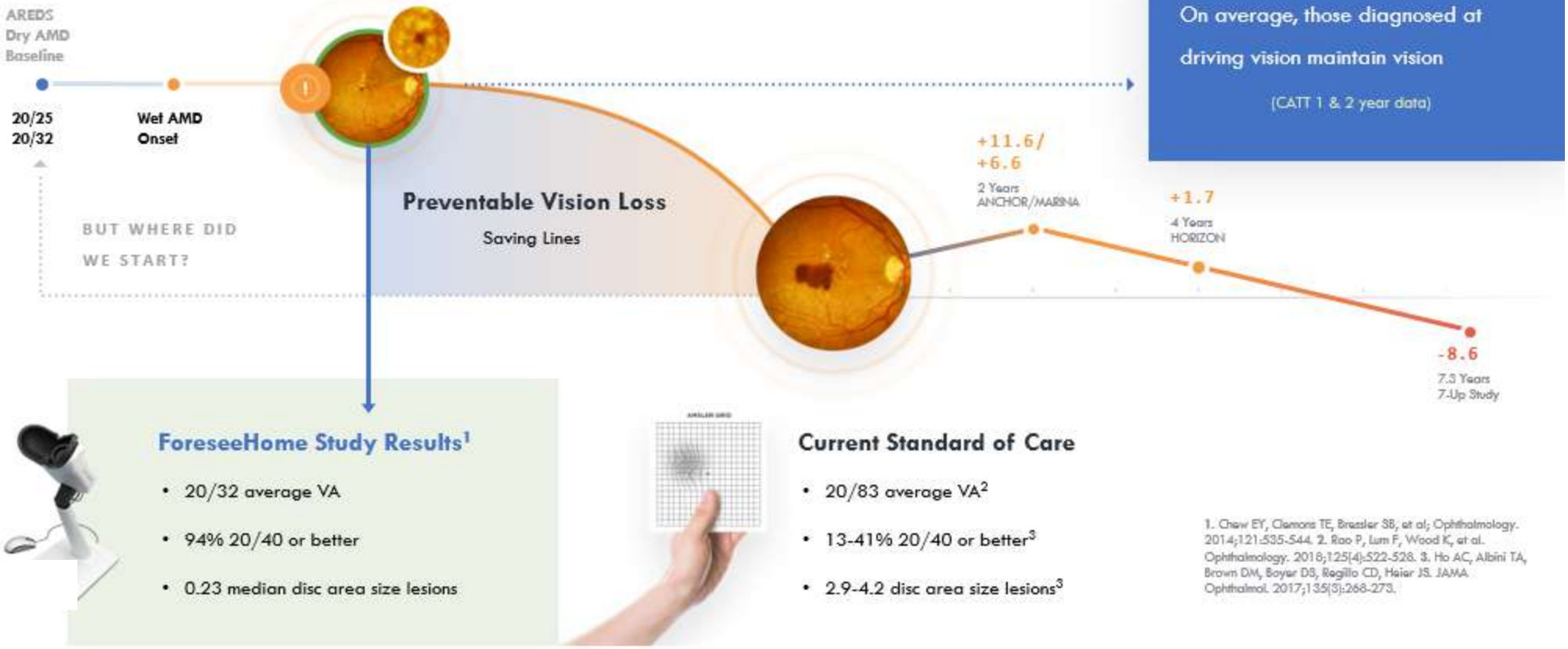
600+ active prescribers

6,000+ actively testing patients

Proven efficacy with level 1 evidence

Reference: Data on File.

Readjusting our point of view to preventable vision loss



ForeseeHome Study Results[1]

- 20/32 average VA
- 94% 20/40 or better
- 0.23 median disc area size lesions

Current Standard of Care

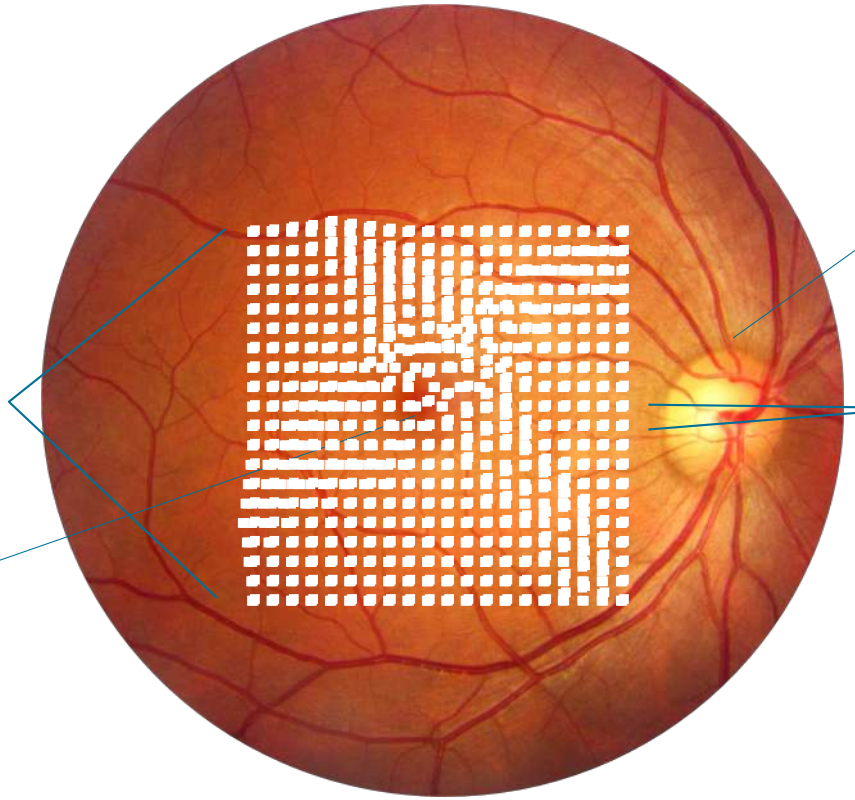
- 20/83 average VA[2]
- 13-41% 20/40 or better[3]
- 2.9-4.2 disc area size lesions[3]

1. Chew EY, Clemons TE, Bressler SB, et al; Ophthalmology. 2014;121:535-544. 2. Rao P, Lum F, Wood K, et al. Ophthalmology. 2018;125(4):522-528. 3. Ho AC, Albini TA, Brown DM, Boyer DS, Regillo CD, Heier JS. JAMA Ophthalmol. 2017;135(3):268-273.

Notal Vision- PERIMETRY: The ForeseeHome Test

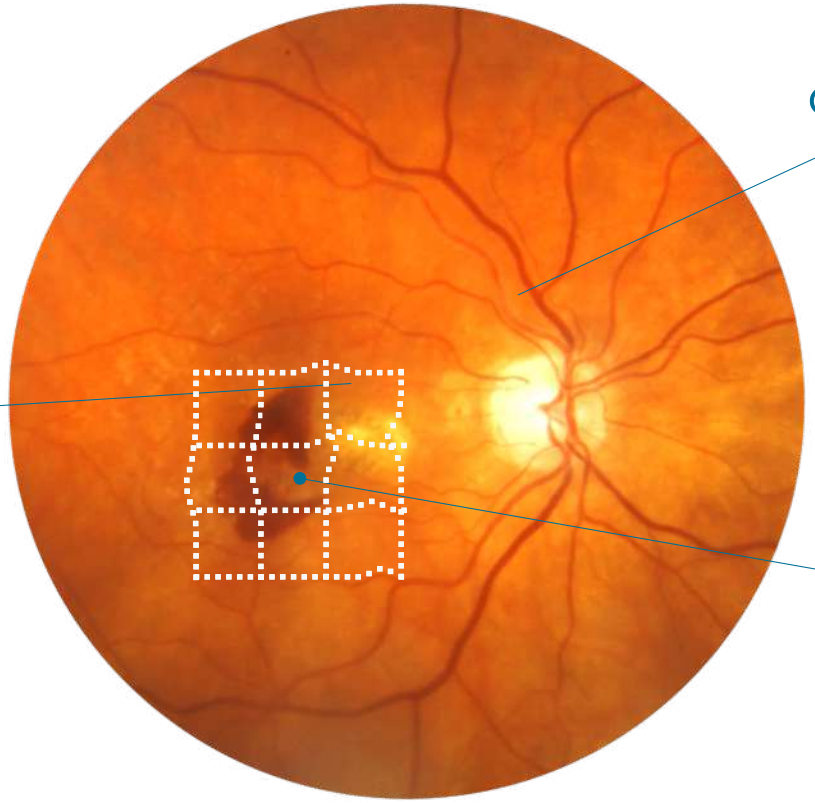
Total of 500 data points tested 3 to 5 times each

Stimuli are presented on screen for 160 ms



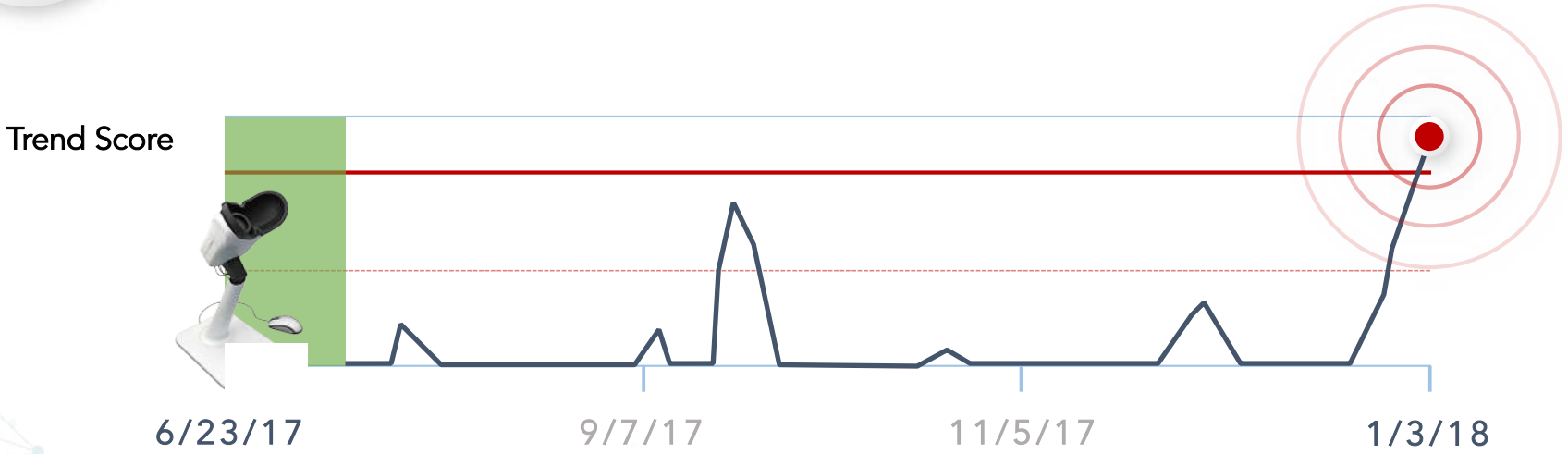
Once pathology is suspected, the area is bracketed to localize and quantify pathology

When a patient clicks on the "pathological distortion," the algorithm will present stimuli of various magnitudes over the location to determine the size and shape

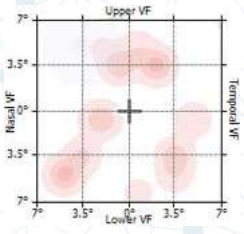


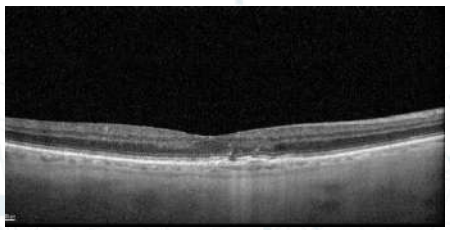
CASE 1 →

86 y/o Male | Baseline Vision: 20/30 OU



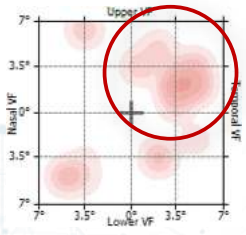
STARTED TESTING

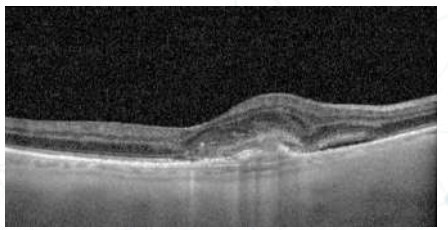




ALERTED

20/60 OD and asymptomatic





Treatments for AMD

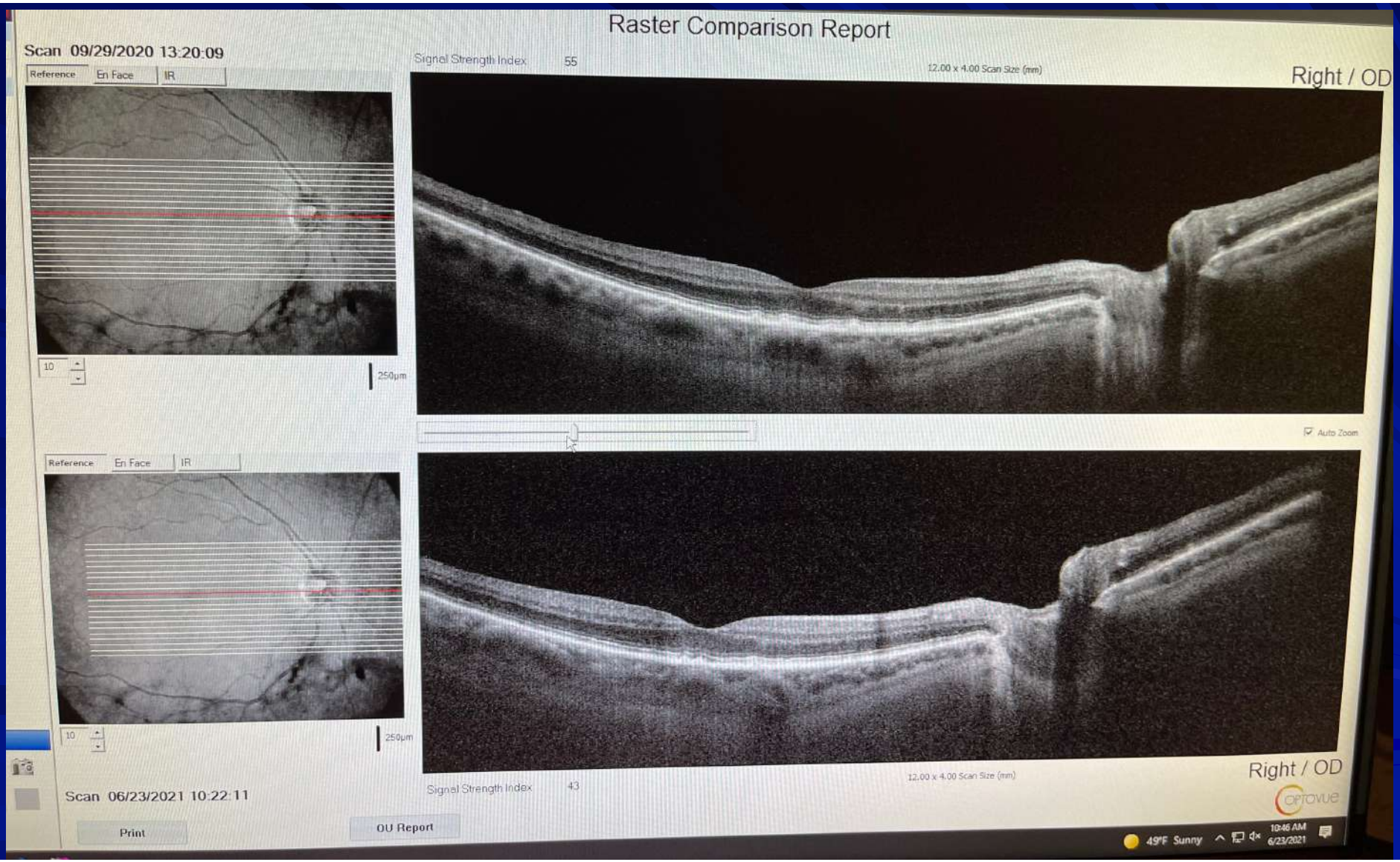
- Early detection and meaningful treatments with significant value, do not cure, but have been shown to slow or halt progression. Not limited to early stages but all stages of AMD
  - Prescribe smoking cessation programs
    - Smoking and AMD
      - Depletes serum antioxidants
      - Decreases pigmentary density
      - Increases risk to advanced AMD
  - Lifestyle changes
    - Diet
    - Exercise
  - Systemic disease management
    - Cardiovascular disease, DM, obesity, high cholesterol

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

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


Raster Comparison Report
Scan 09/29/2020 13:20:09
Reference
En Face
IR
Signal Strength Index 55
12.00 x 4.00 Scan Size (mm)
Right / OD
10
250µm
Auto Zoom
Reference
En Face
IR
10
250µm
Scan 06/23/2021 10:22:11
Signal Strength Index 43
12.00 x 4.00 Scan Size (mm)
Right / OD
Print
OU Report
49°F Sunny
10:46 AM
6/23/2021

Treating Half the Retina?

Oxid Med Cell Longev. 2019; 2019: 9783429.
Published online 2019 Feb 12. doi: 10.1155/2019/9783429
PMCID: PMC6390265
PMID: 30891116

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

Simona Bungau, [1] Mohamed M. Abdel-Daim, [2,3] Delia Mirela Tit, [1] Esraa Ghanem, [4] Shimpei Sato, [3] Maiko Maruyama-Inoue, [3] Shin Yamane, [3] and Kazuaki Kadonosono [3]

Abstract

Go to:

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 mezoxanthin) 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-) 8, IL-6, IL-1a, 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.

Carotenoids and Polyphenols

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 24), pp: 17181-17198

Revie

Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging

Carolina Simioni[1], Giorgio Zauli[1], Alberto M. Martelli[2], Marco Vitale[3,4], Gianni Sacchetti[5], Arianna Gonelli[1] and Luca M. Neri[1]

[1]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy
[2]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[3]Department of Medicine and Surgery, University of Parma, Parma, Italy
[4]CoreLab, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy
[5]Department of Life Sciences and Biotechnology, Pharmaceutical Biology Laboratory, University of Ferrara, Ferrara, Italy

Correspondence to: *Luca M. Neri,* ***email:*** *luca.neri@unife.it*

Keywords: *exercise training; nutraceuticals; flavonoids intake; aging; antioxidant supplementation*

Received: *January 26, 2018* ***Accepted:*** *March 08, 2018* ***Published:*** *March 30, 2018*

Furthermore, resveratrol maintains the vascular fitness through its antioxidant and anticoagulant activities, and on the other hand is relevant in blocking the formation of new blood vessels, in inhibiting the VEGF release and attenuating Hypoxia-Inducible Factor (HIF-1α) in different tumor cells [163].

Resveratrol can be implied in anti-aging actions by influencing the mitochondrial environment and metabolic diseases, by regulating the levels of some inflammatory mediators and cytokines and by modulating lipolysis [125, 152, 153]. Mitochondrial dysfunction has been proved to be associated with aging and disease development [154], and it was seen

ASSESSMENT OF CAROTENOIDS

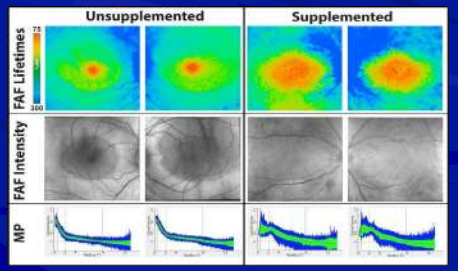
Impact of Carotenoid Assessment

Because carotenoids appear to play a key role in retinal diseases, intensive research has resulted in a variety of innovative carotenoid assessment techniques. The breadth of possibilities for assessing retinal carotenoids is often confusing because methodologies, units of measurement, and the presentation of results vary widely. Accurate readings of carotenoid status are important in order to correctly advise individuals with regards to supplementation. Furthermore, in diseases such as macular telangiectasia type 2 (MacTel), the assessment of carotenoids may be crucial to the diagnosis, as reduced MP levels as well as abnormal distributions are among the first signs of the disease. Therefore, the measurement of carotenoids can impact clinical practice, and the evaluation of MP may eventually become an integral part of comprehensive ophthalmological care. The following sections describe and aim to give an organized overview of different MP assessment techniques.

A large variety of methods are used to assess carotenoid status in humans, most of which are focused on the eye, but carotenoids can also be measured in tissue outside of the eye, such as the skin, blood, and the brain. Measurements of ocular carotenoids can be distinguished between subjective (psychophysical) and objective (optical) methods used to assess the amount of MP. In subjective methods, a direct answer from the patient is required, whereas objective measurement methods typically require just enough cooperation to generate an image (73).

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



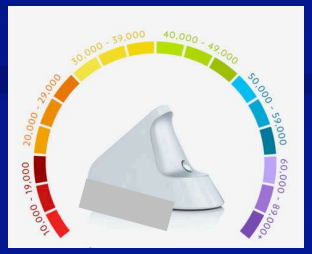
Thank you! Dr. Chris Putnam

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

Carotenoid Levels

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



ARVO
The Association for Research in Vision and Ophthalmology

Scanner correlates to blood and macular pigment

read study

Clinical and Epidemiologic Research

Correlations Between Macular, Skin, and Serum Carotenoids

Christopher D. Conrady,[1] James P. Bell,[1] Brian M. Besch,[1] Aruna Gorusupudi,[1] Kelliann Farnsworth,[1] Igor Ermakov,[2] Mohsen Sharifzadeh,[2] Maia Ermakova,[2] Werner Gellermann,[1,2] and Paul S. Bernstein[1]

[1]Department of Ophthalmology and Visual Sciences, Moran Eye Center, Salt Lake City, Utah, United States
[2]Image Technologies Corporation, Salt Lake City, Utah, United States

Correspondence: Paul S. Bernstein, Moran Eye Center, University of Utah School of Medicine, 65 Mario Capecchi Drive, Salt Lake City, UT 84132, USA; paul.bernstein@hsc.utah.edu.

Submitted: March 7, 2017
Accepted: June 18, 2017

Citation: Conrady CD, Bell JP, Besch BM, et al. Correlations between macular, skin, and serum carotenoids. *Invest Ophthalmol Vis Sci*. 2017;58:5616–5627. DOI:10.1167/iovs.17-21818

Purpose. Ocular and systemic measurement and imaging of the macular carotenoids lutein and zeaxanthin have been employed extensively as potential biomarkers of AMD risk. In this study, we systematically compare dual wavelength retinal autofluorescence imaging (AFI) of macular pigment with skin resonance Raman spectroscopy (RRS) and serum carotenoid levels in a clinic-based population.

Methods. Eighty-eight patients were recruited from retina and general ophthalmology practices from a tertiary referral center and excluded only if they did not have all three modalities tested, had a diagnosis of macular telangiectasia (MacTel) or Stargardt disease, or had poor AFI image quality. Skin, macular, and serum carotenoid levels were measured by RRS, AFI, and HPLC, respectively.

Results. Skin RRS measurements and serum zeaxanthin concentrations correlated most strongly with AFI macular pigment volume under the curve (MPVUC) measurements up to 9° eccentricity relative to MPVUC or rotationally averaged macular pigment optical density (MPOD) measurements at smaller eccentricities. These measurements were reproducible and not significantly affected by cataracts. We also found that these techniques could readily identify subjects taking oral carotenoid-containing supplements.

Conclusions. Larger macular pigment volume AFI and skin RRS measurements are noninvasive, objective, and reliable methods to assess ocular and systemic carotenoid levels. They are an attractive alternative to psychophysical and optical methods that measure MPOD at a limited number of eccentricities. Consequently, skin RRS and MPVUC at 9° are both reasonable biomarkers of macular carotenoid status that could be readily adapted to research and clinical settings.

Keywords: macular pigment, carotenoids, macula

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

Raman Spectroscopy

478nm PHOTONS ARE EMITTED FROM THE SCANNER

AS 478nm PHOTONS STRIKE CAROTENOIDS IN THE SKIN, THEY ARE REFLECTED BACK AS 518nm PHOTONS

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]

[a] Yale School of Public Health and Yale Cancer Center, 60 ... 8034, Ne... USA
[b] Center for Science in the Public Interest, 1220 L Street ... ite 300, ...ton, D... USA
[c] USDA/ARS Grand Forks Human Nutrition Research Ce... 0 2nd Ave... h, G... s, ND 58...
[d] Department of Physics and Astronomy, University of ... t Lake City ... 12,

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Carotenoids
Skin
Resonance Raman spectroscopy
Beta-carotene
Biomarker

ABSTRA...

...spectrosc... ...nvasive method that has been developed to assess carot-... human tissues ... ...an skin *in vivo*. Skin carotenoid status has been suggested as a promising biomarker for human studies. This ...nu...ript describes research done relevant to the devel-opment of this biomarker, including its rep...od...ibility, ...lidity, feasibility for use in field settings, and factors that affect the biomark... s...ch a... t, ...mok..., and adiposity. Recent studies have evaluated the response of the bi...mar...r to ...ntroll... c...otenoid interventions, both supplement-based and dietary [e.g., provision... of a hi...h-ca...ter...id ...uit and vegetable (F/V)-enriched diet], demonstrating consistent response to interv...tio... The totality of evidence supports the use of skin carotenoid status as an objec-tive biomarker ...f ...V intake, although in the cross-sectional setting, diet explains only some of the var-iation in this biomarker. However, this limitation is also a strength in that skin carotenoids may effectively serve as an integrated biomarker of health, with higher status reflecting greater F/V intake, lack of smoking, and lack of adiposity. Thus, this biomarker holds promise as both a health biomarker and an objective indicator of F/V intake, supporting its further development and utilization for medical and public health purposes.

90 STUDIES

*Arch Biochem Biophys. PMC 2014 Nov 15.

ARVO STUDY

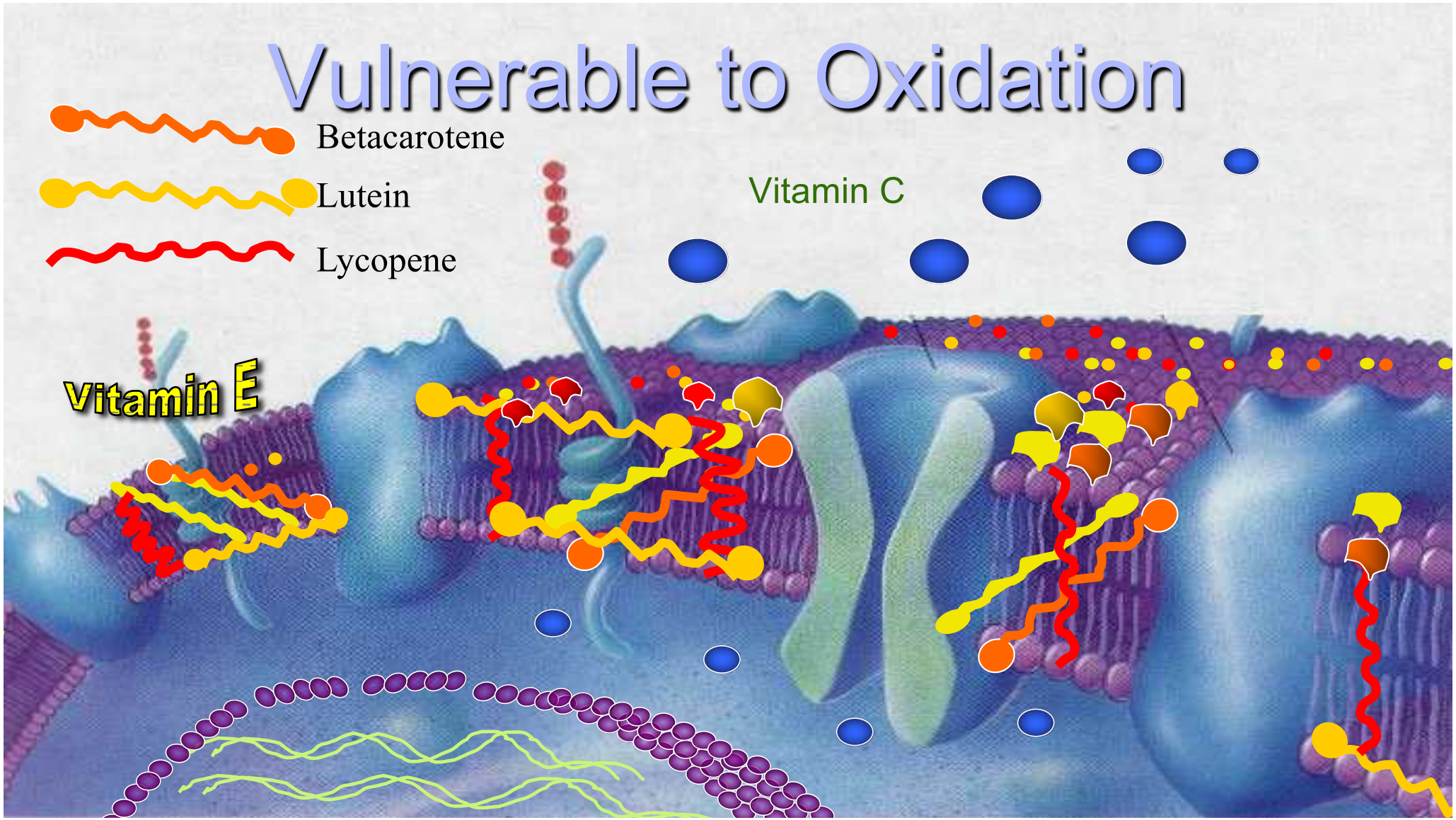
Interrelationships between Macula, Skin and Serum Carotenoids- Paul Bernstein,Werner Gellerman et al ARVO May 2016

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."

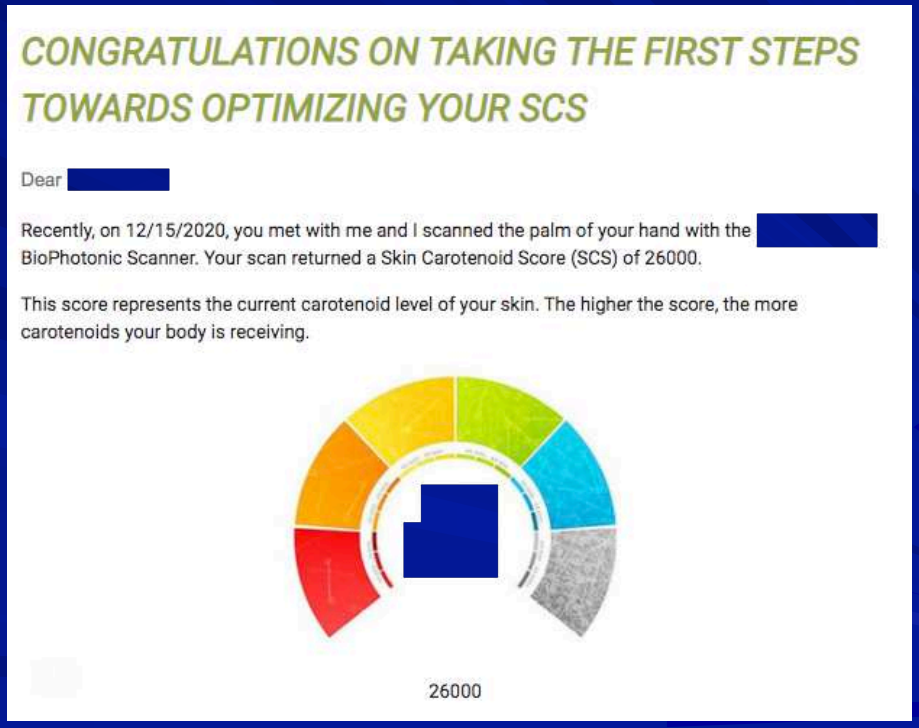
Skin resonance Raman Spectroscopy of skin carotenoids is a reasonable biomarker of macula carotenoid status. and correlates better than than subjective MPOD tests.

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


Vulnerable to Oxidation
Betacarotene
Lutein
Lycopene
Vitamin C
Vitamin E

53-year-old man

- Family history of AMD
  - ★ Dad with 43 injections for AMD
- Pre-diabetic with borderline HbA1c
- Vision 20/20 OU
- DFE- retina clear
- OCT normal
- Passes dark adaptation



CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

Dear [redacted]

Recently, on 12/15/2020, you met with me and I scanned the palm of your hand with the [redacted] BioPhotonic Scanner. Your scan returned a Skin Carotenoid Score (SCS) of 26000.

This score represents the current carotenoid level of your skin. The higher the score, the more carotenoids your body is receiving.

Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	7.5 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	*
Catechins (from *Camellia sinensis* Leaf Extract)	(45 mg)	*
Quercetin	(25 mg)	*
Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	*
Resveratrol (from *Polygonum cuspidatum* root extract)	(2.5 mg)	*
Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	3.5 mg	*
Lycopene (as Lycopene)	(2.5 mg)	*
Lutein (from Marigold Flower Extract)	(1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	10 mcg	*

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

SUPPLEMENT FACTS

Supplement Facts

Serving Size 2 Softgels — Servings Per Container 60

Amount Per Serving		% DV
Total Calories	15	
Total Fat	1 g	1%*
Saturated Fat	0 g	0%*
Trans Fat	0 g	
Vitamin D_3 (as cholecalciferol)	12.5 mcg (500 IU)	63%
Vitamin K_2 (as menaquinone-7)	20 mcg	17%
Ultra-pure fish oil concentrate:	1055 mg	**
EPA (Eicosapentaenoic acid)	300 mg	**
DHA (Docosahexaenoic acid)	200 mg	**
Citrus Bioflavonoids (including hesperidin and naringin)	100 mg	**
Purple corn (*Zea mays L.*) cob extract including anthocyanins	66.67 mg	**
Alpha Lipoic Acid	50 mg	**
Quercetin (from *Dimorphandra mollis* fruit extract)	37.5 mg	**
D-Limonene (from *Citrus sinensis* peel)	25 mg	**
Rosemary (*Rosmarinus officinalis L.*) leaf extract including carnosic acid	18.75 mg	**
Resveratrol (from *Polygonum cuspidatum* root)	15 mg	**
Coenzyme Q10	15 mg	**
Lycopene	2.5 mg	**
Lutein (from marigold flower (*Targetes erecta*))	2 mg	**
Astaxanthin (from *Haematococcus pluvialis* algae)	0.5 mg	**

* Percent Daily Values are based on a 2,000 Calorie Diet.
** Daily Value (DV) not established.

OTHER INGREDIENTS: Gelatin, Glycerin, Beeswax, Sunflower Lecithin, Vanillin.

CONTAINS: Fish (anchovies, sardines, mackerel).

53-year-old man

CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

Dear [redacted]

Recently, on 12/27/2020, you met with me and I scanned the palm of your hand with the [redacted] BioPhotonic Scanner. Your scan returned a Skin Carotenoid Score (SCS) of 33000.

This score represents the current carotenoid level of your skin. The higher the score, the more carotenoids your body is receiving.

33000

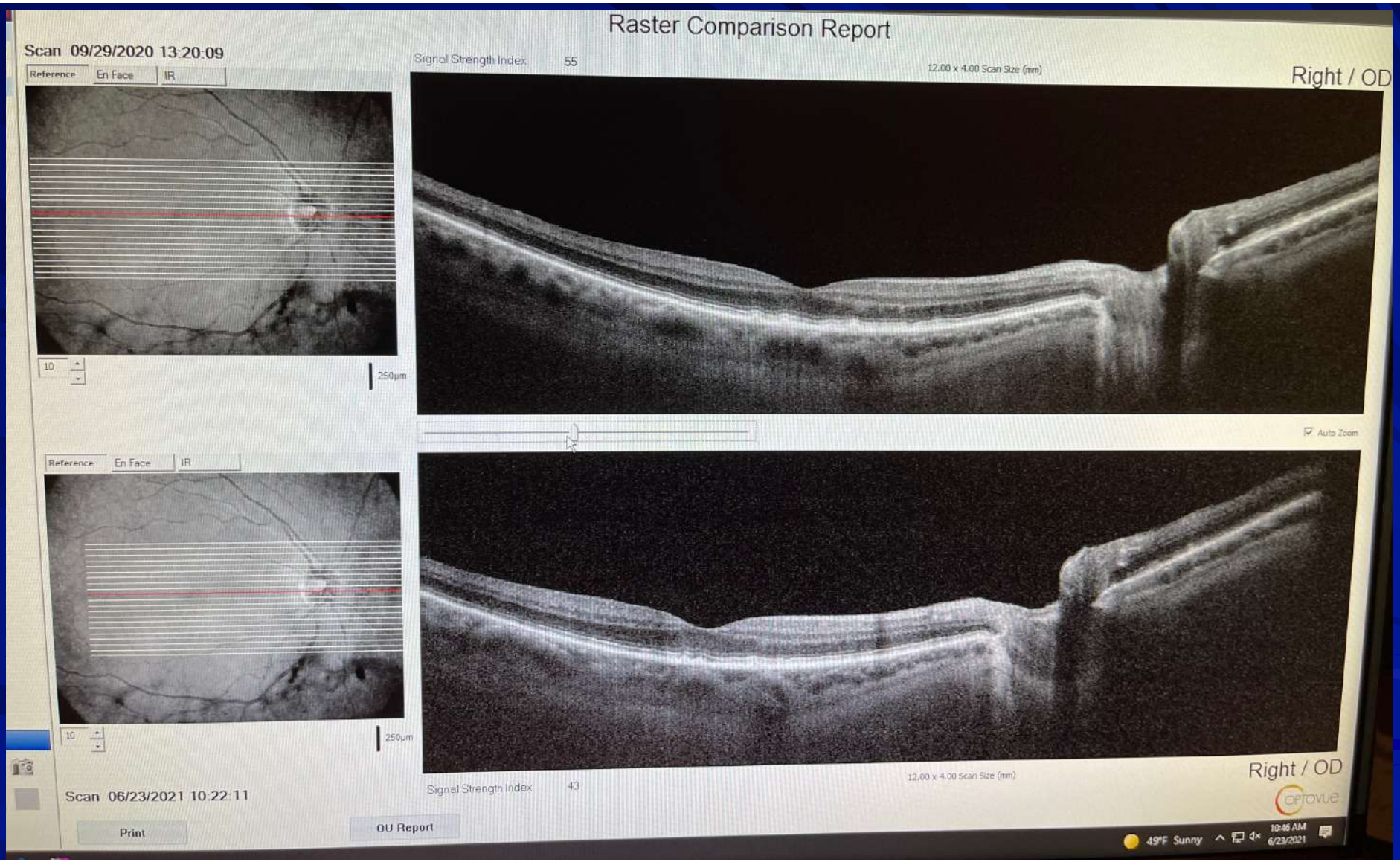
CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

Dear [redacted]

Recently, on 01/23/2021, you met with me and I scanned the palm of your hand with the [redacted] BioPhotonic Scanner. Your scan returned a Skin Carotenoid Score (SCS) of 47000.

This score represents the current carotenoid level of your skin. The higher the score, the more carotenoids your body is receiving.

47000


Raster Comparison Report
Scan 09/29/2020 13:20:09
Reference
En Face
IR
Signal Strength Index 55
12.00 x 4.00 Scan Size (mm)
Right / OD
10
250µm
Auto Zoom
Reference
En Face
IR
10
250µm
Scan 06/23/2021 10:22:11
Signal Strength Index 43
12.00 x 4.00 Scan Size (mm)
Right / OD
Print
OU Report
49°F Sunny
10:46 AM
6/23/2021

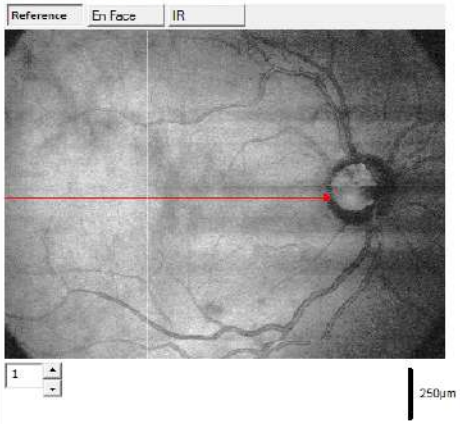
Cross Line Comparison Report

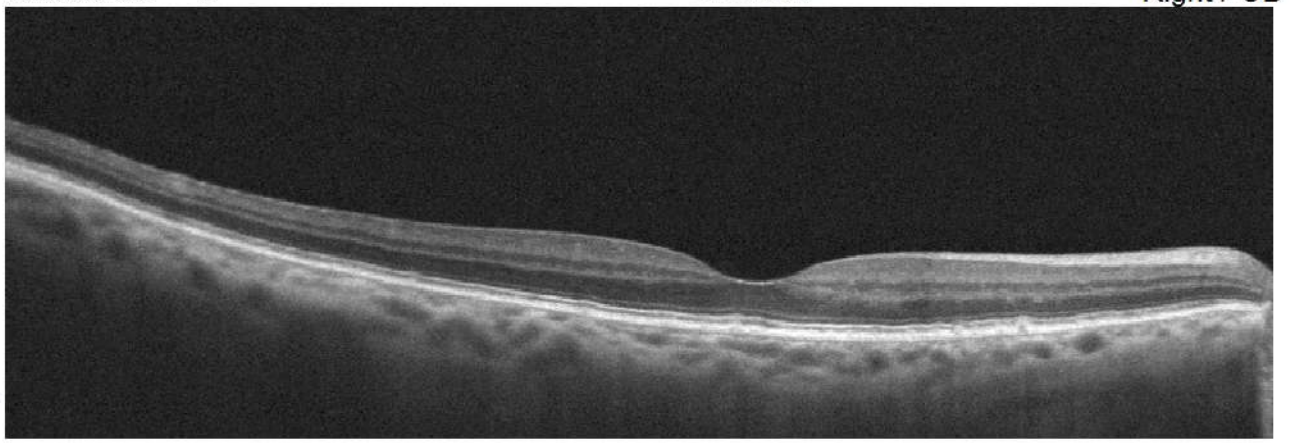
Scan 04/05/2021 14:33:33

Signal Strength Index 58

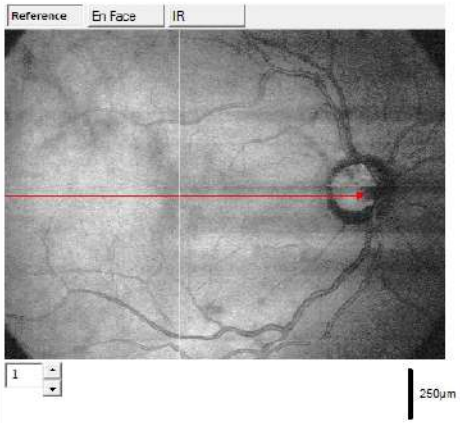
10.00 Scan Size (mm)

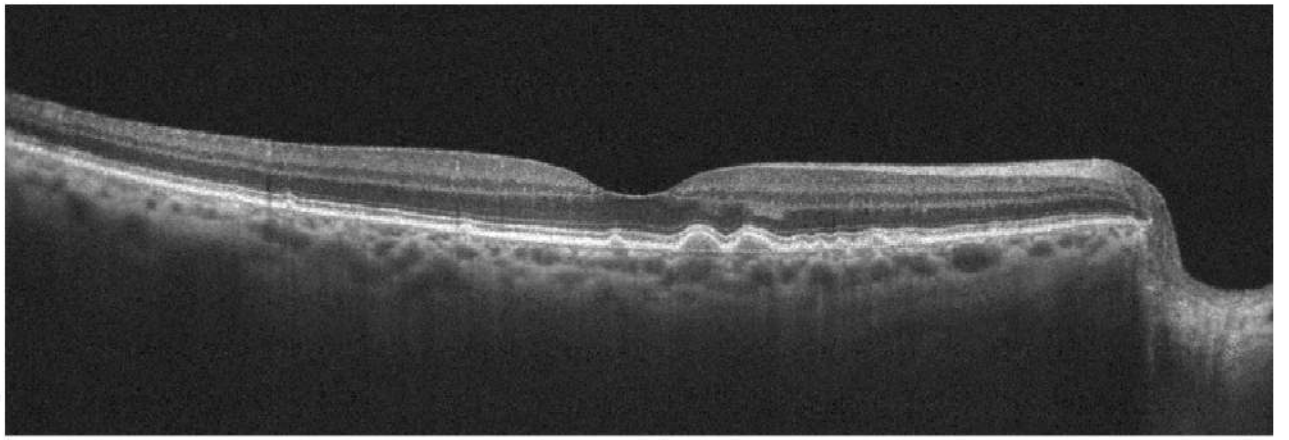
Right / OD





Auto Zoom





Scan 09/21/2020 10:40:42

Signal Strength Index 59

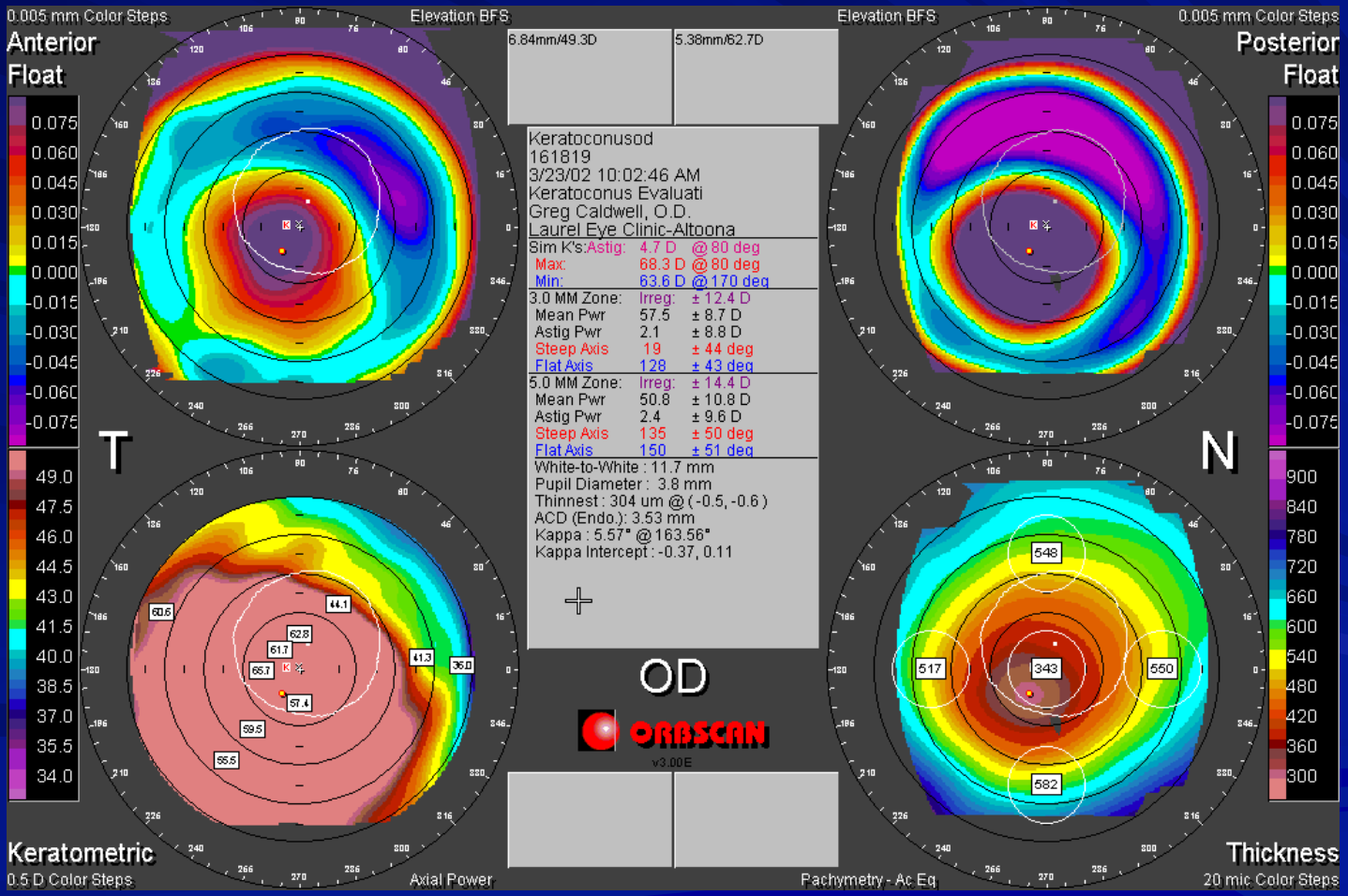
10.00 Scan Size (mm)

Right / OD

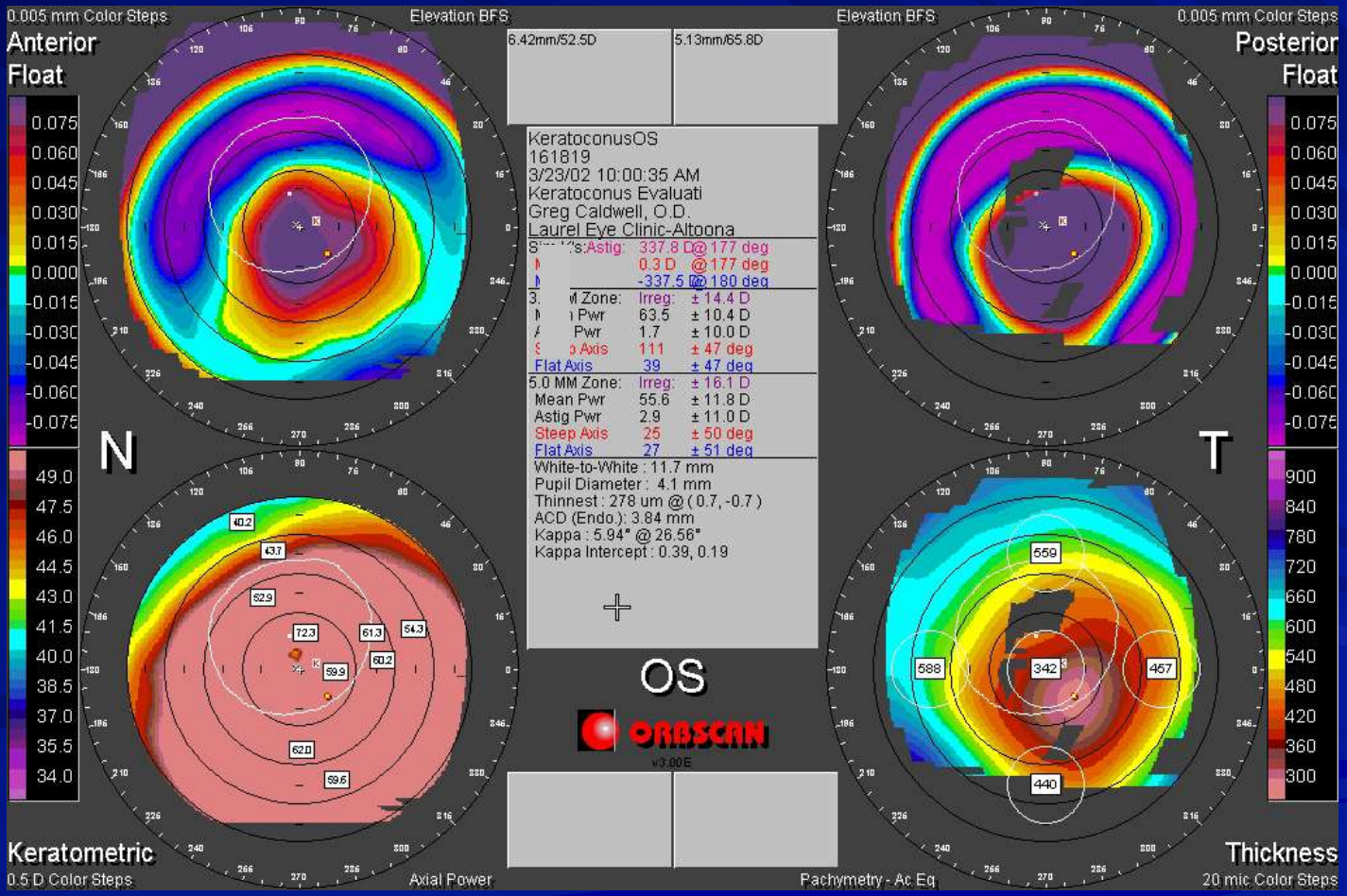
Keratoconus

Advanced Keratoconus

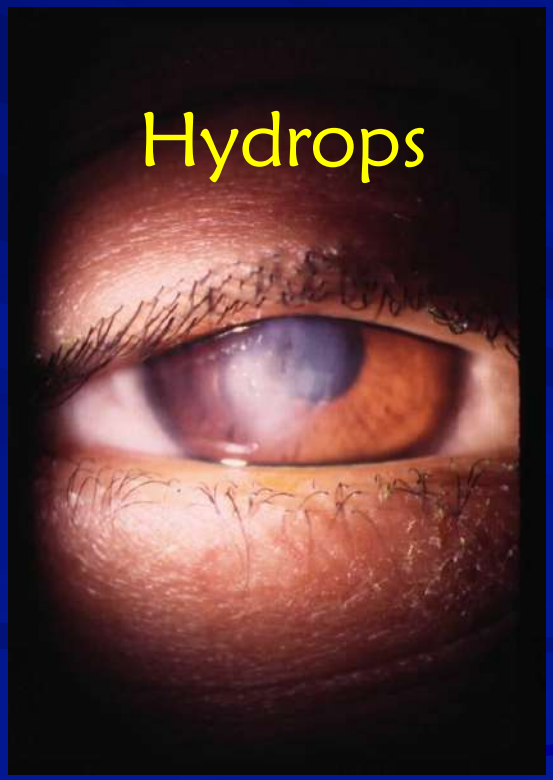
Topography OD



Topography OS



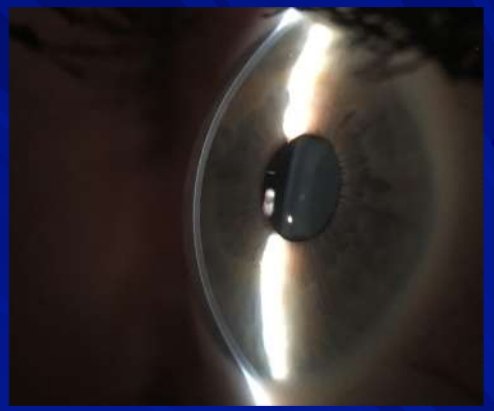
What happens when the posterior cone gets too steep and Descemet's membrane ruptures?



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)

Normal



KC

Photos courtesy of Dr. John Gelles, O.D. of CLEI

Conventional Management of Keratoconus

Disease Severity

Increasing complexity of interventions and loss of best corrected visual acuity with disease progression

Corneal Transplant

Intrastromal Ring Segments

Specialty and Scleral Lenses

Rigid Contact Lenses

Eyeglasses

Vision management options do not stop disease progression

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.

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

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.

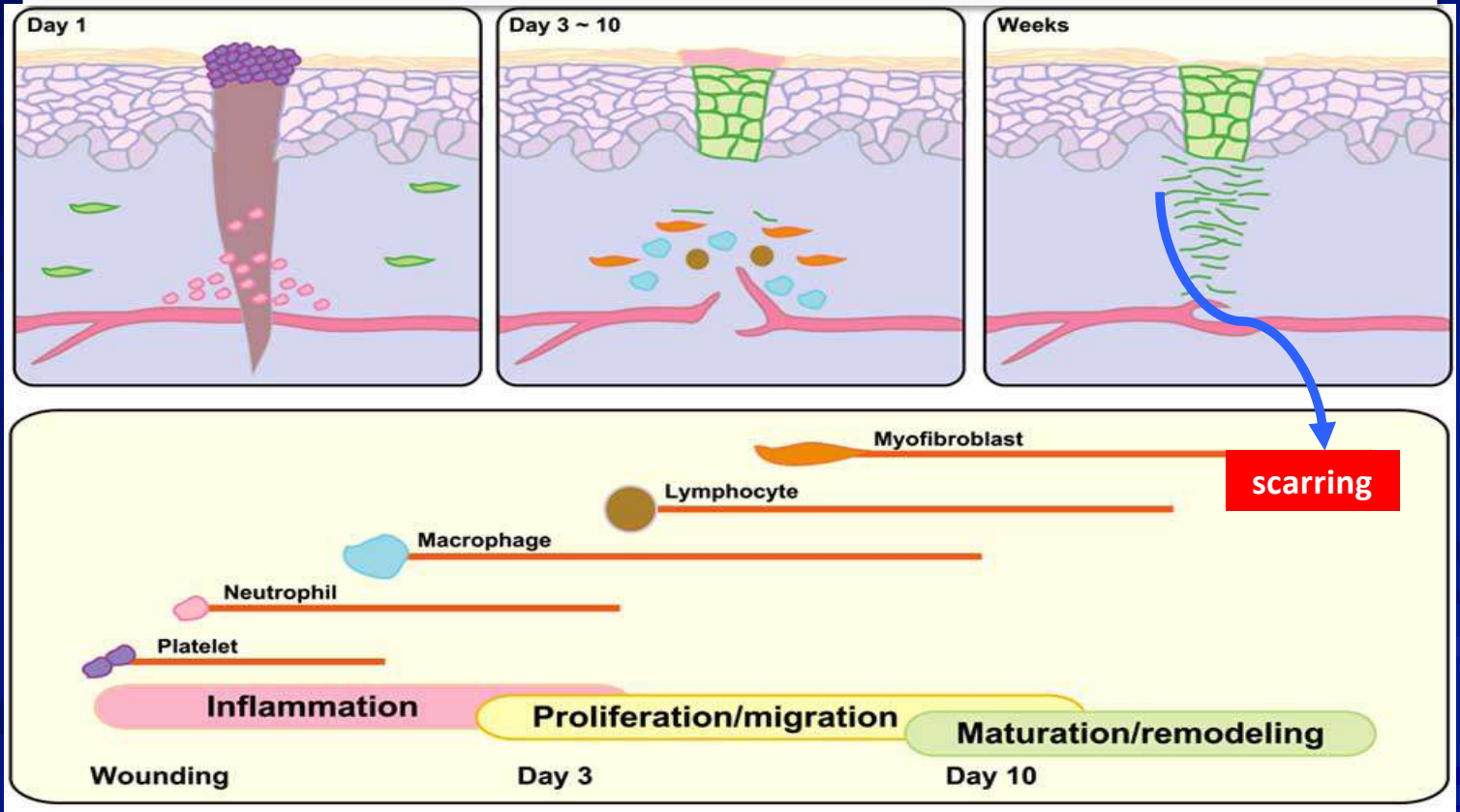
* Refer to prescribing information for entire FDA-approved procedure

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

Adult Wound Healing

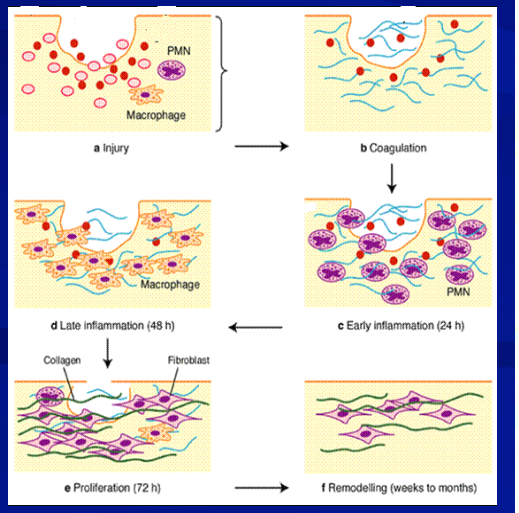
Insight into the Relationship between "Inflammation" and "Regeneration"

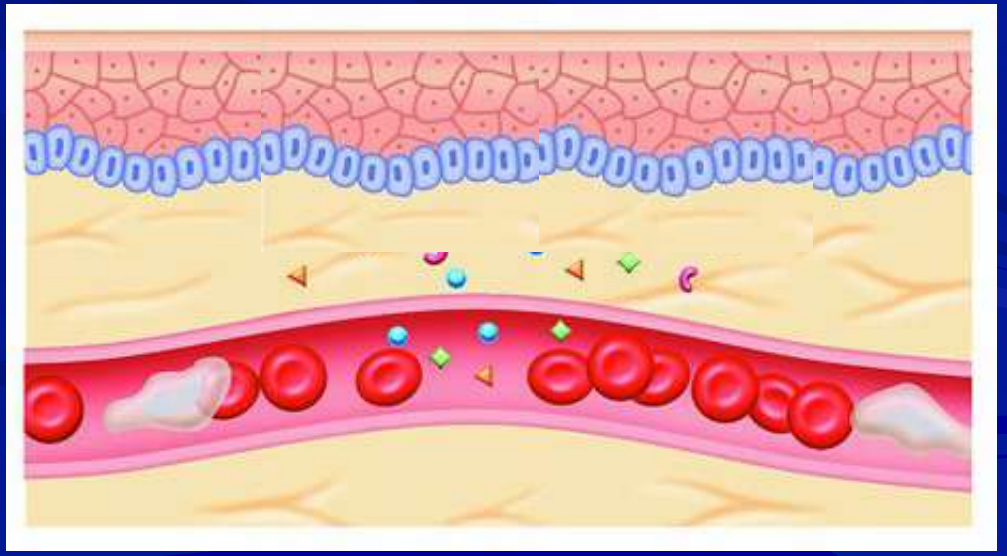


Shaw et al, *Endocrine, Metabolic & Immune Disorders - Drug Targets*, 10:320-330, 2010

Regeneration vs. Repair

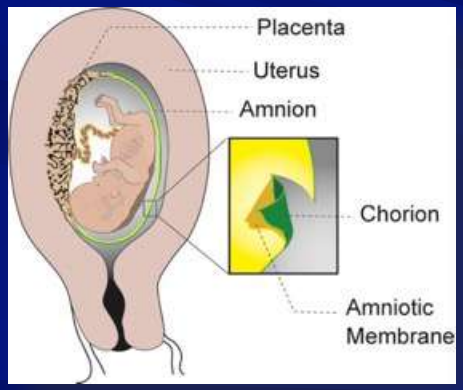
- Regeneration = cells/tissue reproduction = NO SCAR
- Repair= Healing by granulation tissue / scar formation
  - Scarring correlates directly with Inflammation
  - Controlling Inflammation → Reduces Scarring

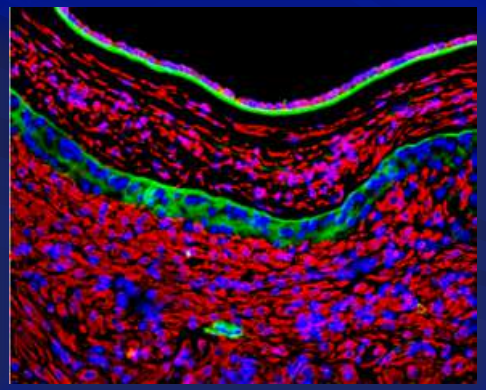




The Amniotic Membrane

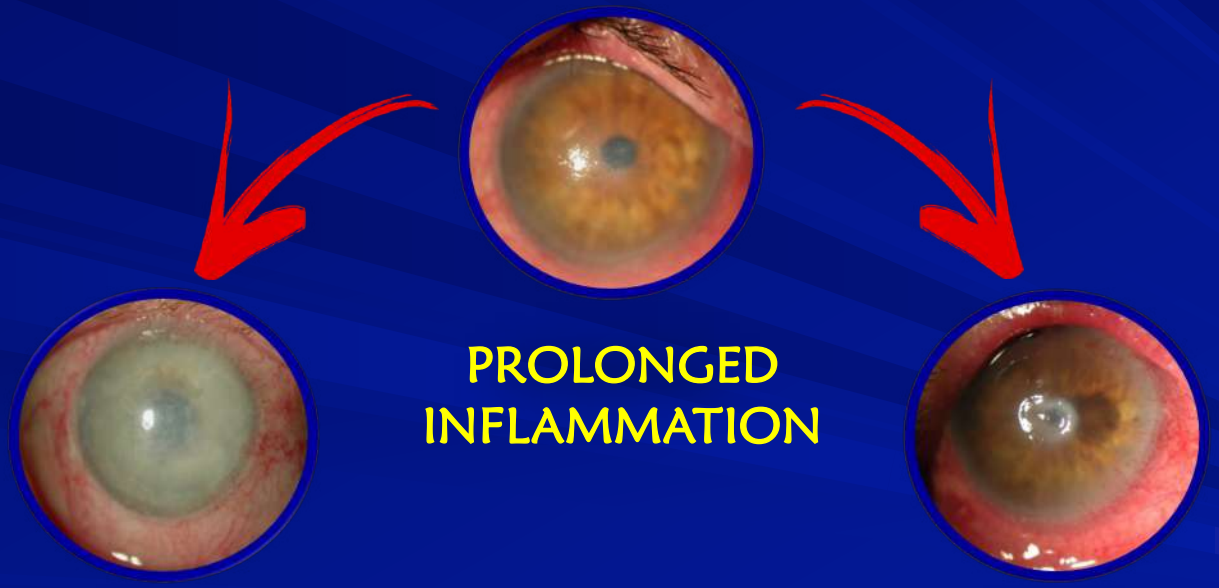
- The amniotic membrane is the innermost lining of the placenta (amnion)
- Are from planned Caesarean section births





Normal Adult Wound Healing

Our body does not achieve state-of-the-art healing on its own…



PROLONGED INFLAMMATION

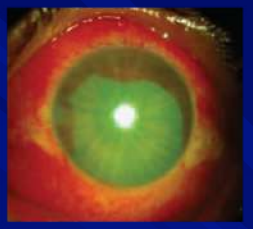
RESIDUAL HAZE

SCAR FORMATION

Exposure keratitis

Chemical burn

Damage



Tissue injury

Inflammation

Keratocyte activation

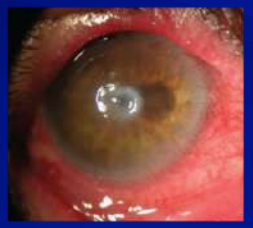
Fibroblast differentiation to myofibroblast

Scar formation

Impaired vision

Scarless healing

Clear vision



Healing with Scar Formation

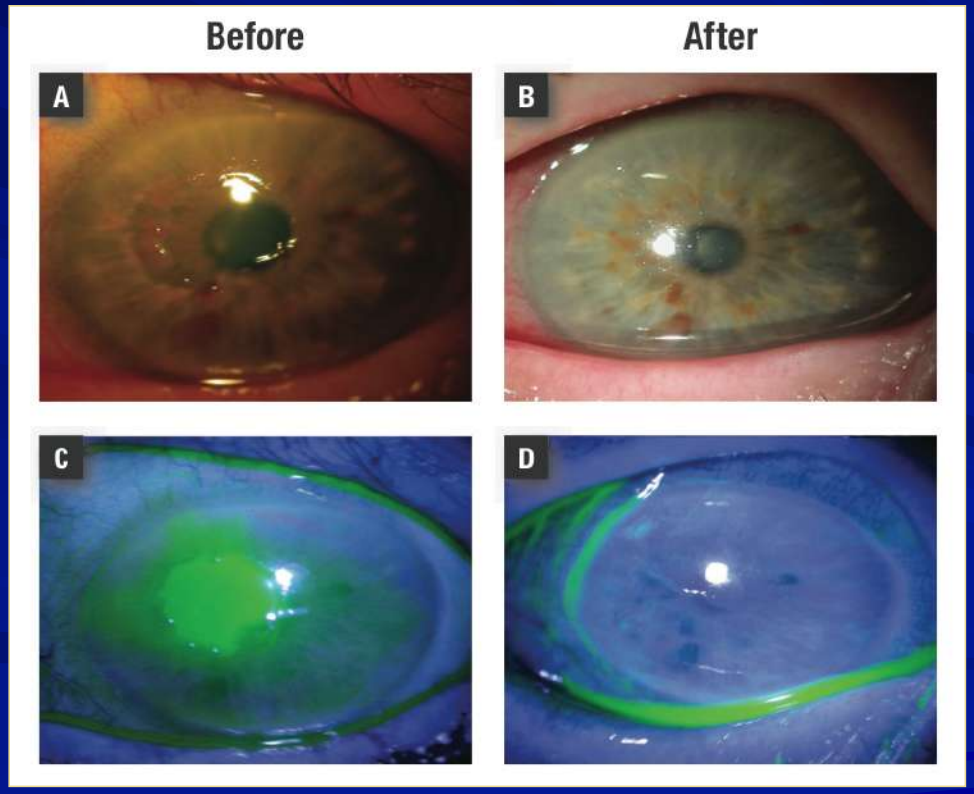
Healing without Scarring

Ocular Surface Disease Challenges

- **D**EFECT
- **D**ELAYED HEALING
- **D**YSTROPHY
- **D**EGENERATION
- **D**AMAGE

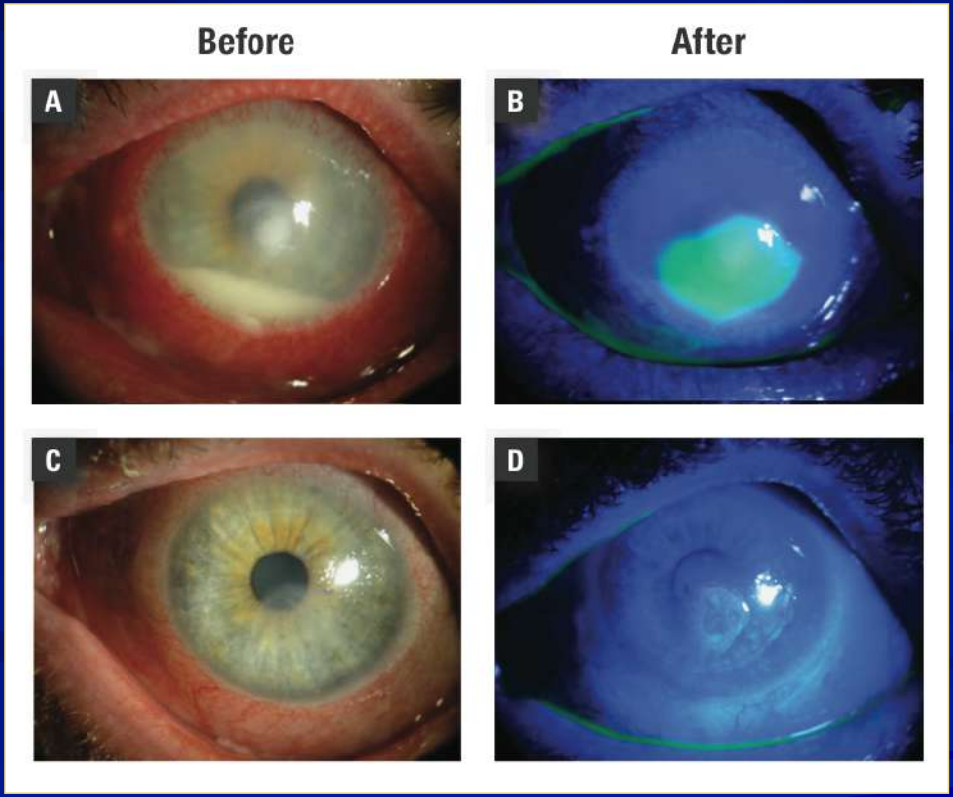
DEFECT

Neurotrophic Persistent Epithelial Defect



DEFECT

Infectious Keratitis: Corneal Ulcer with Hypopyon



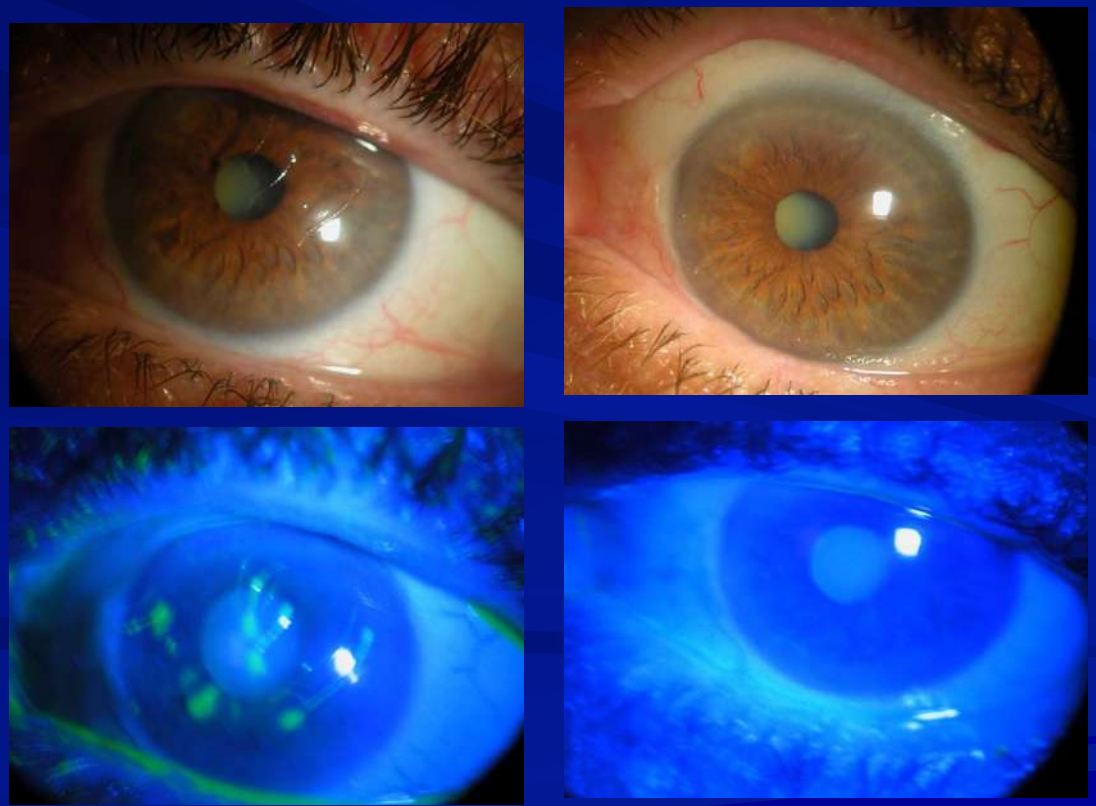
HSV

24-48 hours before Zirgan arrives

DELAYED HEALING

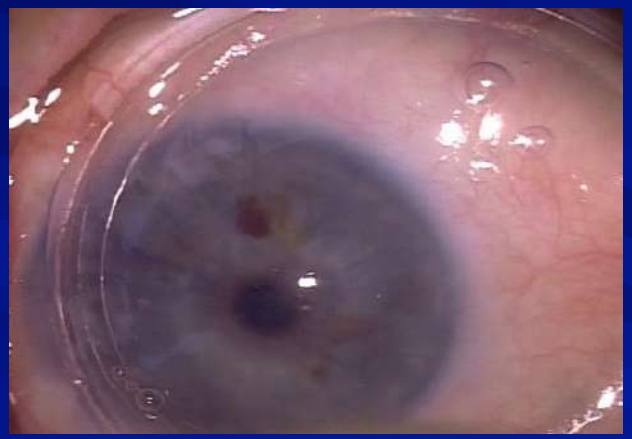
Filamentary Keratitis

Before **After**

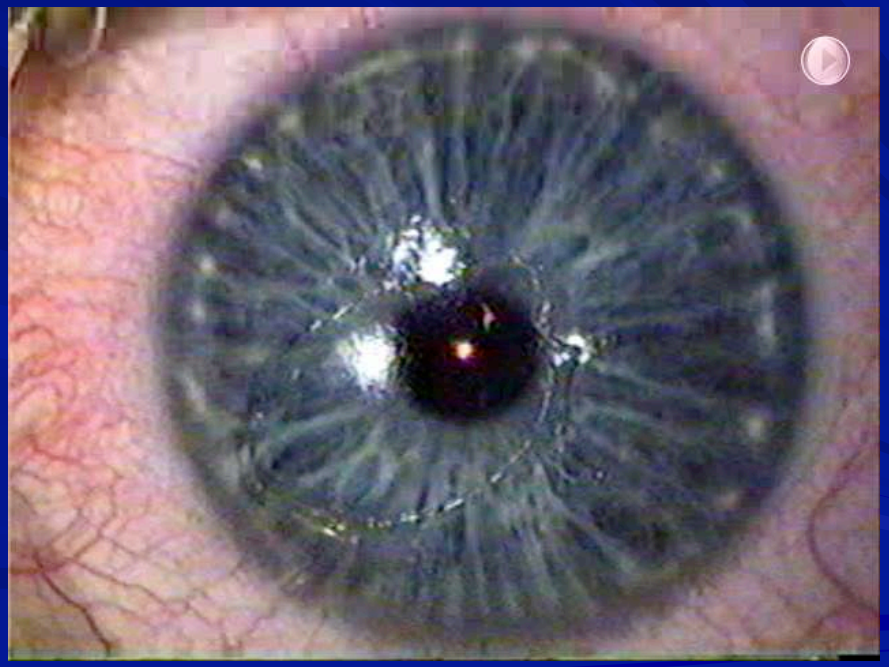


DYSTROPHY

Recurrent Corneal Erosion

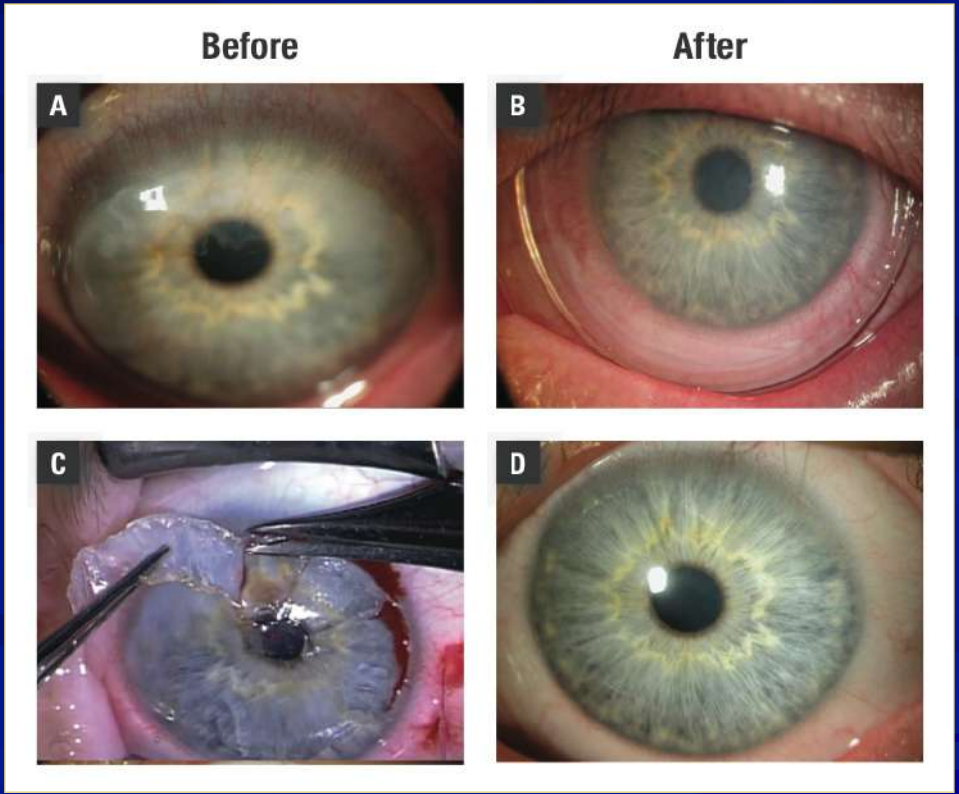


RCE



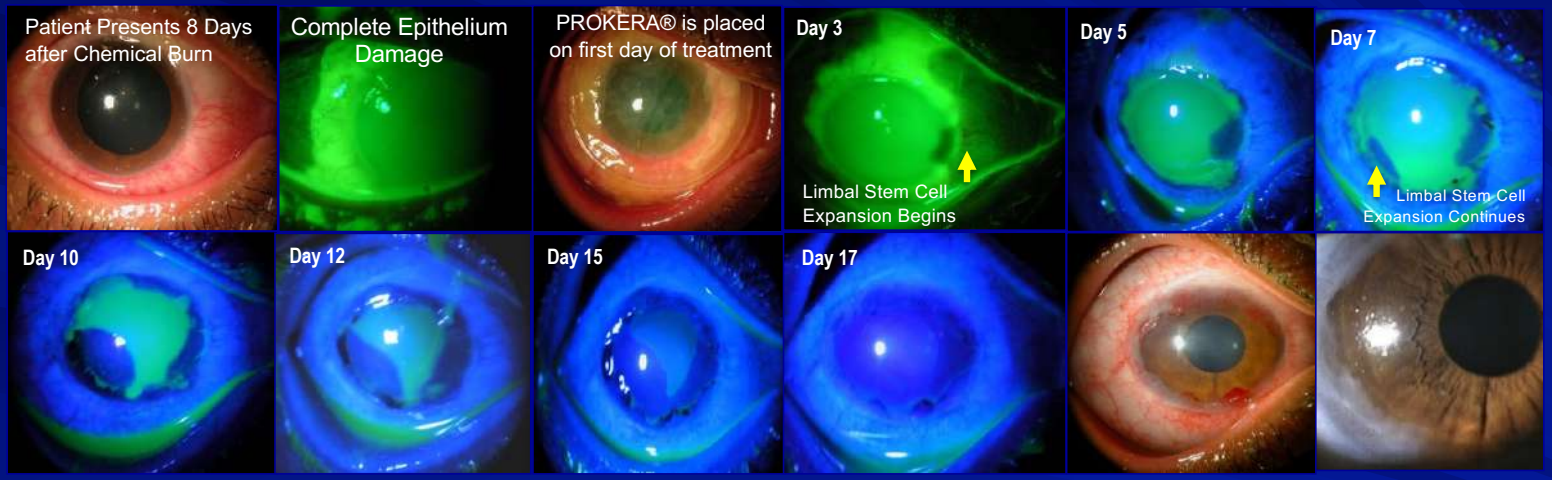
DEGENERATION

Salzmann's Nodular Degeneration



DAMAGE

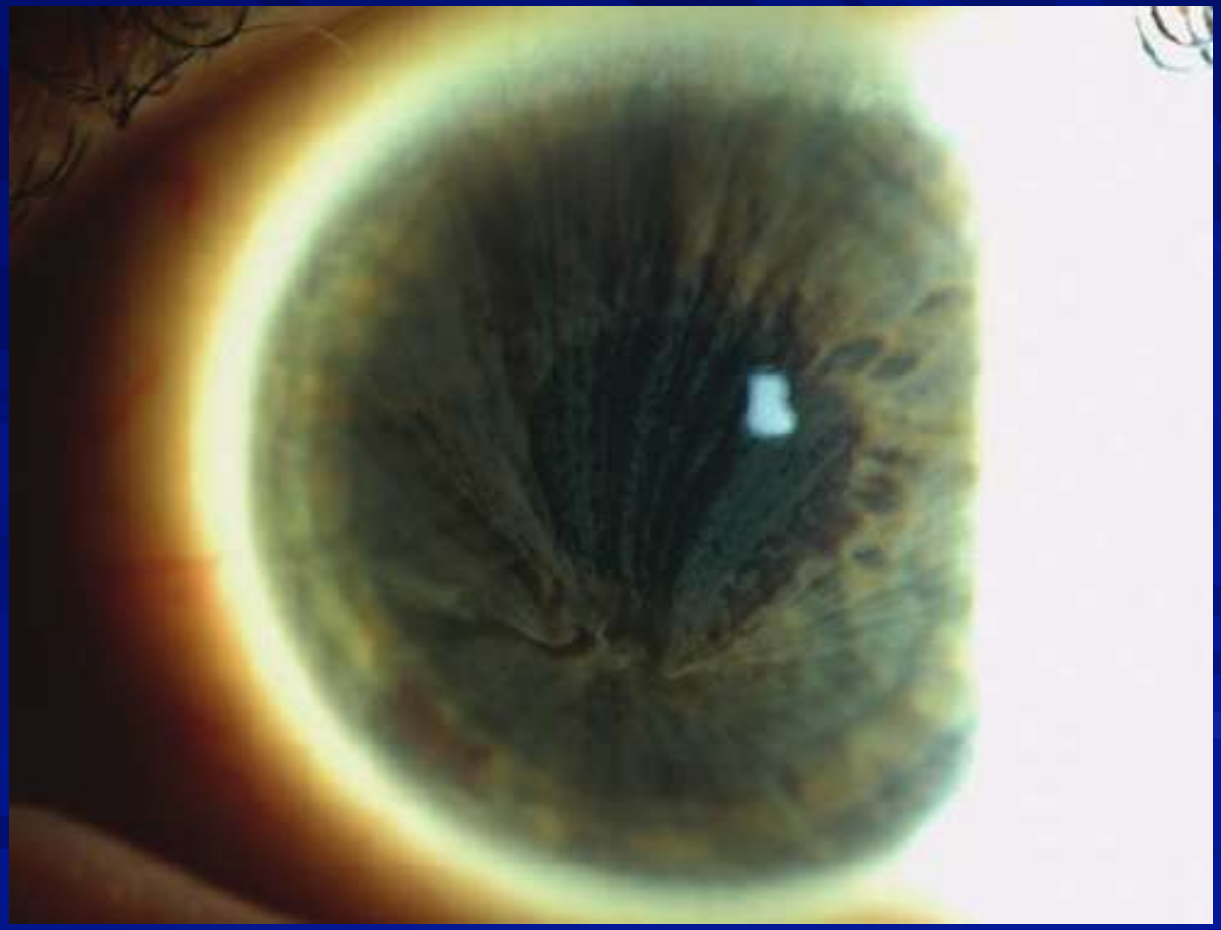
Chemical Burn



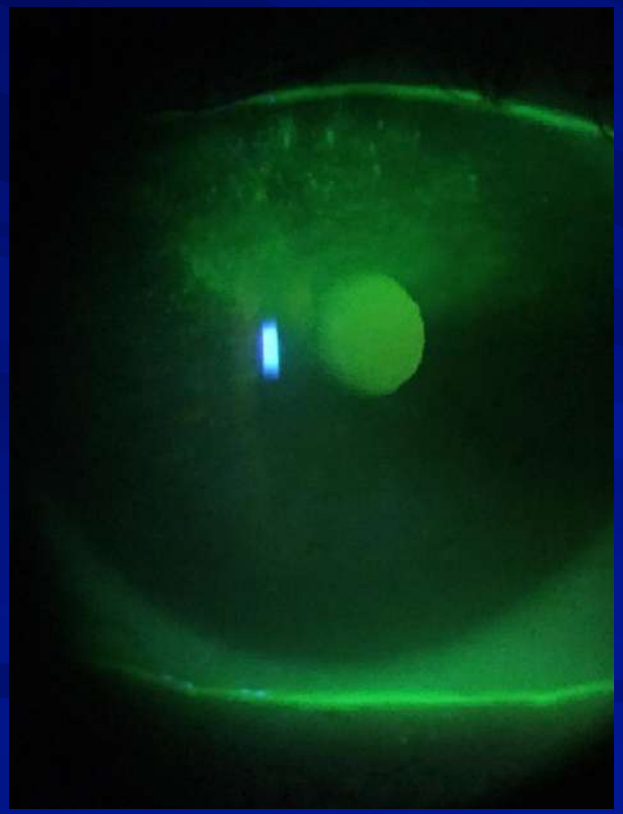
DEFECT, DELAYED WOUND HEALING, DAMAGE

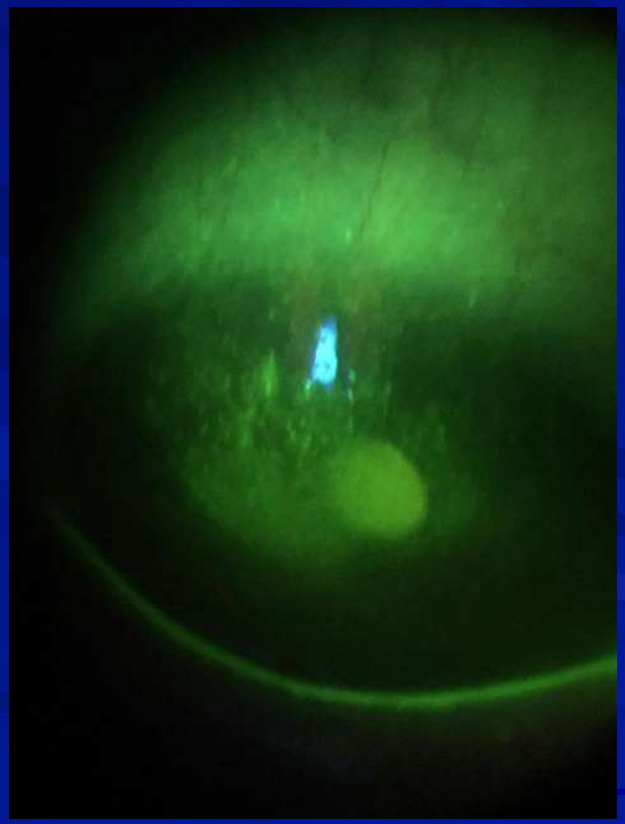
Stem Cell
Burnout

Stem Cell Burnout



Limbal Cell Exhaustion





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

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[4,5]

- Suppresses T-cell activation
- Inhibits giant cell formation
- Controls MMP production[7]

Insertion of Prokera
Minor Surgery

Bio Optix®

Amniotic Extracellular Matrix

BioD
Enhancing Life Through Birth®

Allograft Tissue Information and Product Preparation Insert

Contents / How Supplied

This package contains Human Cellular and Tissue Based Products (HCT/P) as defined by US FDA 21 CFR Part 1271.

CAUTION:

Federal (USA) law restricts this product to sale by or on the order of a licensed physician.

The **Donated Human Tissue** has been determined eligible for transplantation by a licensed Medical Director according to the criteria listed in the Donor Selection section below.

Product Description

BioDOptix™ is a human amnion membrane allograft provided in prescribed geometric configurations. BioDOptix is dehydrated during processing and should be dry when the package is opened. The inner peel pouch and tissue product are terminally sterilized via E-beam irradiation and may be placed directly into the sterile field. Included in the packaging along with this insert are a Tracing Record and a set of patient labels.

- BioDOptix is sterilely packaged for single patient, one time use only.
- Once opened, BioDOptix must be used immediately or discarded.

Introduction

BioDlogics, LLC, is registered with the Food and Drug Administration (FDA) as a manufacturer and distributor of human cells, tissue, and cellular and tissue-based products (HCT/P). All donor recoveries are performed by BioRecovery, LLC, an affiliate of BioDlogics, LLC. BioRecovery, LLC is also registered with the FDA and adheres to the regulations regarding HCT/P recovery and the screening and testing of the tissue donor as verified through supplier audits.

Donor Selection

The Medical Director of the registered recovery agency has determined that the donor of the tissue contained in this product is eligible to donate tissue for transplantation based on meeting the following criteria:

1. **The results of donor screening indicated that the donor was free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases, and**
2. The results of donor testing for the following relevant communicable disease agents are negative or non reactive:
   - Antibodies to the human immunodeficiency virus type 1and type 2 (anti-HIV-1 and anti-HIV-2)
   - HIV-1/Hepatitis B/Hepatitis C by Transcription Mediated Amplification
   - Hepatitis B surface antigen (HBsAg)
   - Hepatitis B total core antibody
   - antibodies to the hepatitis C virus (anti-HCV)
   - Antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II)
   - Syphilis using FDA-licensed tests. If the blood sample to be used for syphilis screening is determined and documented to be unacceptable for the screening assay (e.g. hemolysis, sample testing time restriction) then an FDA-licensed treponemal-specific confirmatory assay may be performed instead (e.g. FTA-Abs).

All laboratories performing these tests are certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493 or have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS).

At the time of recovery, cultures of the tissue are taken and grown out for evaluation. Additionally, a donor's medical history and behavior risk assessment, incorporating U.S. Public Health Service guidelines, are obtained prior to donation. Discussions with physicians and/or the donor mother are conducted to identify circumstances that may lead to the exclusion of the donor or donated tissue. The blood sample test results, donor medical history, behavior risk assessment, physical assessment, and information from other sources or records, which may pertain to donor suitability, have been evaluated by a Medical Director. The Medical Director is a licensed physician who completes a comprehensive review of every donor record. The results are used to determine that the donor suitability **criteria** at the time of tissue recovery have **been met, and that the tissue is acceptable for transplantation.**

The names and addresses of the testing laboratories, the interpretation of all required infectious disease tests, a listing of the documents reviewed as part of the relevant medical records and all pertinent donor medical information can be quickly retrieved upon request for any allograft tissue recovered on the behalf of BioDlogics, LLC.

Recovery

Tissue recovery is aseptically performed by BioRecovery, LLC, an FDA-registered tissue bank. At the time of recovery, medical records are collected and reviewed as part of donor eligibility.

Processing

BioDOptix is processed by BioDlogics, LLC, in a controlled environment using methods designed to prevent contamination and cross-contamination of the products. Technical quality assurance standards are rigorously maintained. Ethanol is used during processing and trace residuals remain on the product.

Tissue Distribution

BioDOptix is distributed by BioDlogics, LLC.

Tissue Storage

It is the responsibility of the Tissue Dispensing Service and/or end user to maintain BioDOptix in its original packaging and at room temperature until ready for use.

HCT/P Tracking

Important notice to end-user: Recipient records must be maintained for the purpose of tracing tissue post-transplant per The Joint Commission and FDA requirements. The allograft ID number must be recorded in the operative record. The Tracing Record must be completed and returned to BioDlogics, LLC. Patient labels which include tissue numbers are contained in this package to aid in the tracking process.

General Usage

BioDOptix is intended for use as a wound covering. This product is an allograft tissue intended for homologous use at the direction of a physician.

Precautions

1. BioDOptix contains trace amounts of ethanol. It should not be used in patients with known sensitivity to ethanol.
2. In order to reduce the risk of complications, BioDOptix should not be in used the presence of active infection.
3. Although donor tissue is evaluated and processed following strict FDA guidelines, the donor screening methods are limited and may not detect all diseases. As with any allograft, complications at the graft site may occur post operatively that are not readily apparent. These include, but are not limited to:
   - transmission of communicable diseases, including those of unknown etiology
   - transmission of infectious agents such as viruses, bacteria and fungi
   - immune rejection of, or allergic reaction to, implanted HCT/P.

Adverse Reactions

Adverse reactions or outcomes that potentially involve the use of BioDOptix should be reported immediately to the BioDlogics, LLC Customer Service Department

Recommended Instructions for use of BioDOptix

These recommendations are designed only to serve as a general guideline. They are not intended to supersede institutional protocols or professional clinical judgment concerning patient care.

Preparation Instructions

1. Open carton or box containing BioDOptix and remove the peel-pack.
2. Peel open the outer package and remove the inner foil pouch using aseptic technique.

Note:

-The inner tray and its contents are sterile and may be placed directly into the sterile field.

3. Peel the inner pouch open and place the implant with the accompanying mesh into the sterile field.

Note:

-Care must be taken in transferring/removing the graft from the package as it is lightweight and may be easily displaced.

-The BioDOptix graft is translucent and will look off-white or yellowish on the mesh that is still in contact with allograft.

-It is important to note that the drier the surface to be covered with the graft, the easier the application.

4. Remove the graft from the mesh piece of sterile mesh to facilitate placement of the graft if the surgeon wants to hydrate the graft before application. The mesh reflects the epithelial side of the tissue (surface closest to the fetus).

If the allograft has been hydrated prior to application, leave the graft on the mesh to aid in placement.Once the graft is positioned in the desired location, grasp a corner of the allograft with forceps to hold it in place while gently pealing off the mesh.

DO NOT LEAVE ANY MESH IN WOUND

5. It is sometimes necessary to gently "brush" or "massage" the thin membrane at the edges to smooth out wrinkles and folds that can occur during graft placement.
6. If removal and replacement are needed, re-apply the mesh for ease of manipulation.
7. After final placement, discard the mesh.

Return Policy

All return orders of BioDOptix require a Return Authorization (RA) number before product may be returned for credit. Please contact the BioDlogics Customer Service Team for more information.

Note: BioDlogics LLC makes no claims concerning the biological properties of allograft tissue. All tissue has been collected, processed, stored, and distributed in compliance with the FDA regulations governing HCT/Ps. Although every effort has been made to ensure the safety of allograft material, current technologies may not preclude the transmission of disease.

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)

Journal of Ophthalmology
Volume 2017, Article ID 6404918, 10 pages
https://doi.org/10.1155/2017/6404918

Hindawi

Clinical Study

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

Thomas John,[1,2] Sean Tighe,[3,4] Hosam Sheha,[3,4,5] Pedram Hamrah,[6,7] Zeina M. Salem,[6,7] Anny M. S. Cheng,[3,4] Ming X. Wang,[8] and Nathan D. Rock[8]

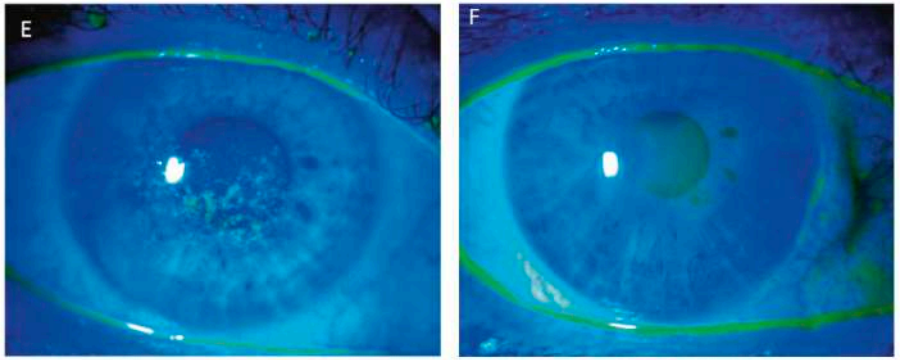
[1]*Thomas John Vision Institute, Tinley Park, Cook County, IL, USA*
[2]*Loyola University at Chicago, Maywood, Chicago, IL, USA*
[3]*Ocular Surface Center and TissueTech, Inc., Miami, FL, USA*
[4]*Florida International University Herbert Wertheim College of Medicine, Miami, FL, USA*
[5]*Research Institute of Ophthalmology, Cairo, Egypt*
[6]*Boston Image Reading Center, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[7]*Center for Translational Ocular Immunology, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[8]*Wang Vision Institute, Nashville, TN, USA*

Correspondence should be addressed to Hosam Sheha; hoss88@gmail.com

Received 12 May 2017; Accepted 28 June 2017; Published 15 August 2017

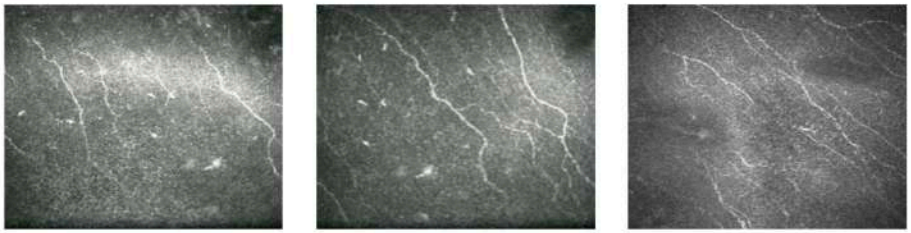
Academic Editor: Suphi Taneri

(c) (d)



(e) (f)

Figure 2: Changes in DED severity: pain score (a), SPEED score (b) corneal staining score (c), and DEWS score (d) and an illustrative example of fluorescein staining before (e) and after (f) PKS treatment. Significant decrease in pain score, SPEED questionnaire score, and symptoms in the study group (solid lines) from baseline to 3 months ($p \leq 0.001$), while remained relatively unchanged in the control group (dash lines). $*$ denotes $p \leq 0.05$.



(a) (b) (c)

Figure 5: Illustrative example of IVCM showing the subbasal nerve fiber and dendritiform cells in the study group at baseline (a), 1 month (b), and 3 months follow-up (c).

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

Escherichia Coli

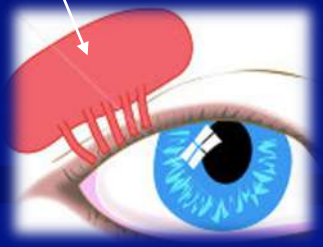
Oxervate™ is produced in Escherichia coli. Image courtesy of NIAID.

Corneal Homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis

Corneal nerves stimulate blinking and tear production

Tear gland



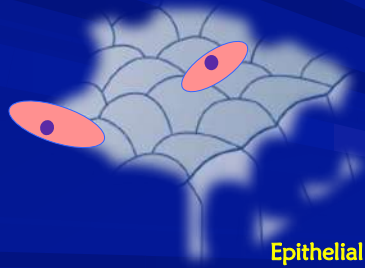
Tear secretion

Tears contain growth factors and nutrients that stimulate epithelial cells

Neurotrophins, neuropeptides and growth factors (e.g., NGF) from epithelial cells and keratocytes mediate nerve fibre survival, differentiation and maturation

Neuromediators provide trophic support to ocular surface tissues (particularly epithelial cells & keratocytes) that:

- Stimulates wound healing
- Maintains anatomic integrity

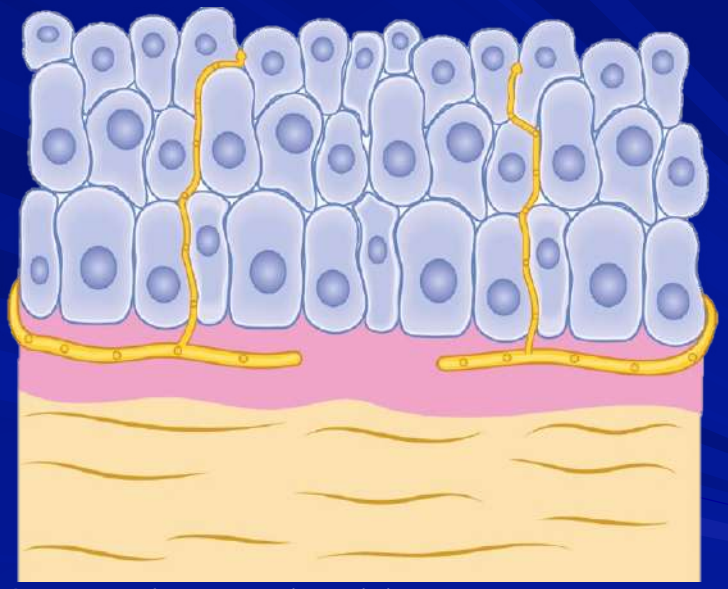


Epithelial cells and keratocytes

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

Pathophysiology of NK[1]

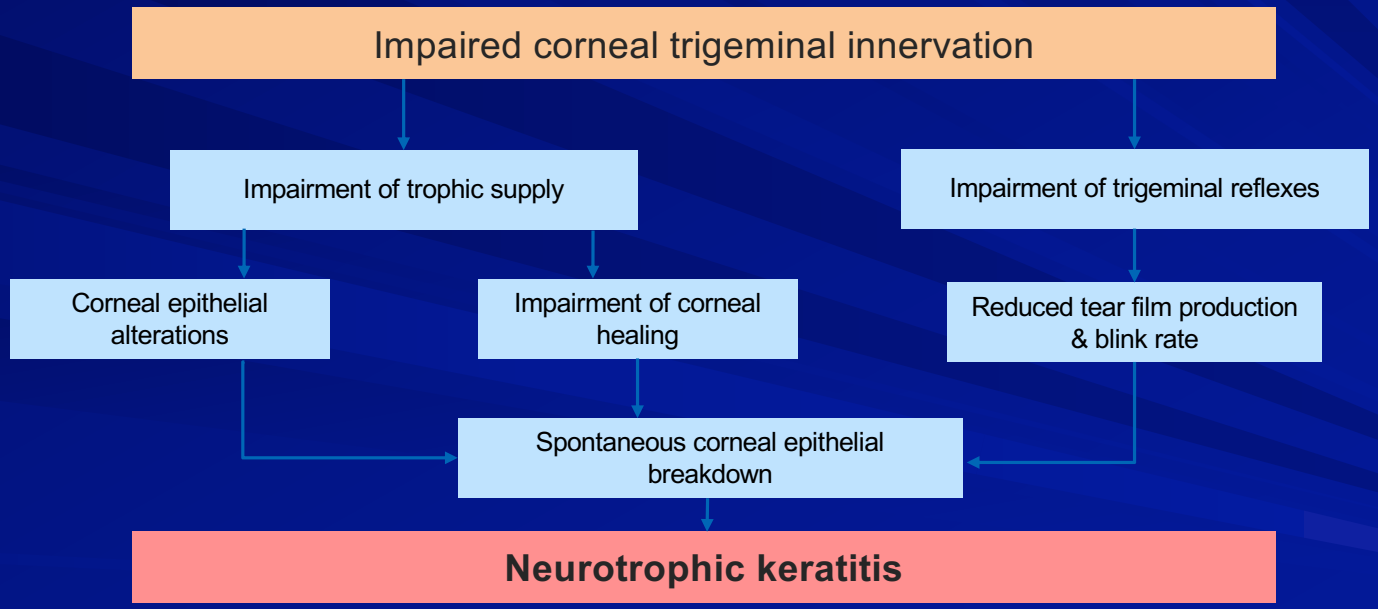
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production 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



Penetration of nerves into the epithelium

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

Trigeminal nerve damage leading to NK[1]



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

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

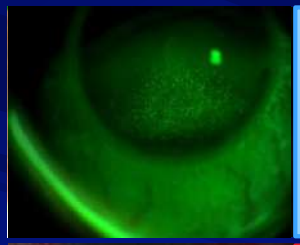
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

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

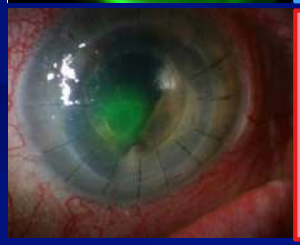
1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

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

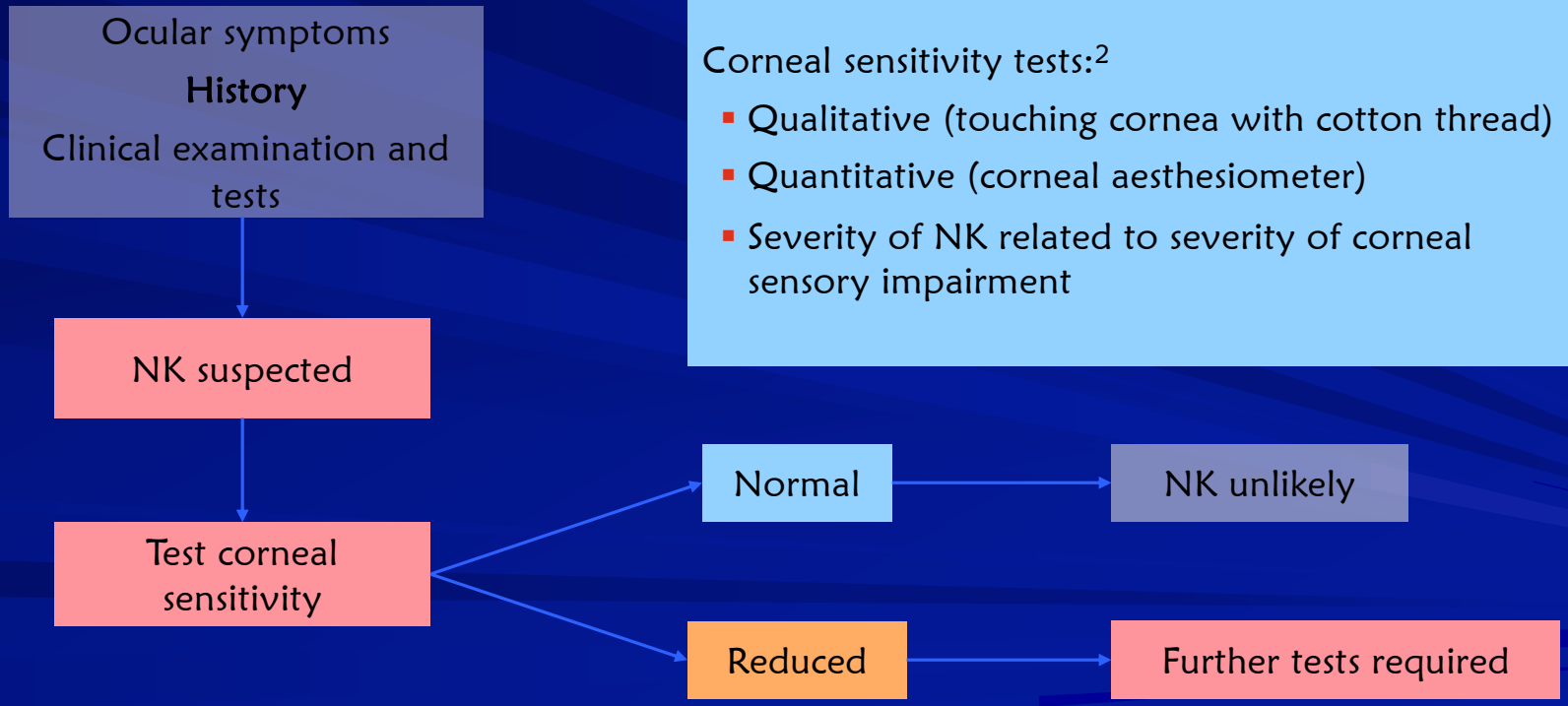
Stage 3: Severe

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

Images by kind consent of Prof. Messmer and Prof. Dua

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semarero F, et al. Ophthalmologica 2014;231:191–7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

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



Corneal sensitivity tests:[2]

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

Corneal Sensitivity

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]

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

TEAR SECRETION

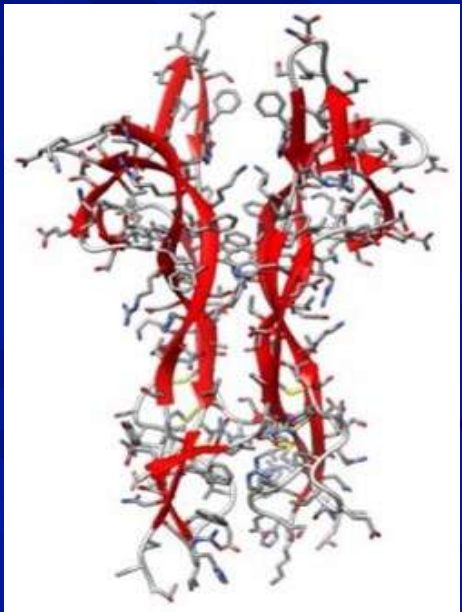
CELL PROLIFERATION AND DIFFERENTIATION

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

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(4):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. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2010;29:1163–1168

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.

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

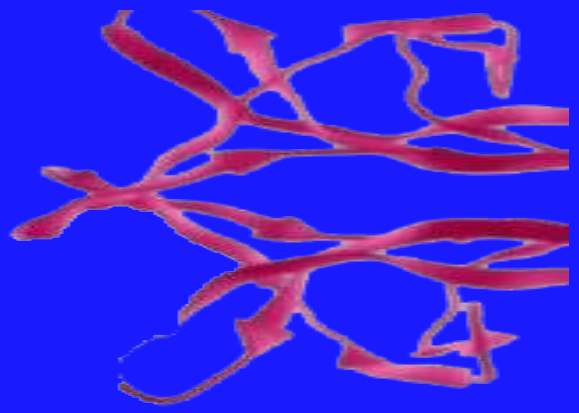
The Delivery System Kit Contains:

- 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

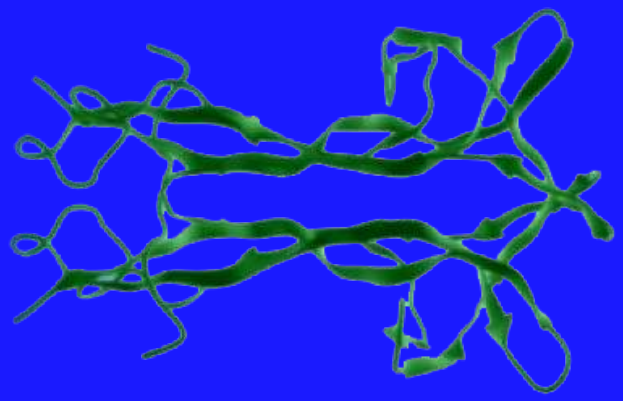
- **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

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

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin



Endogenous NGF

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

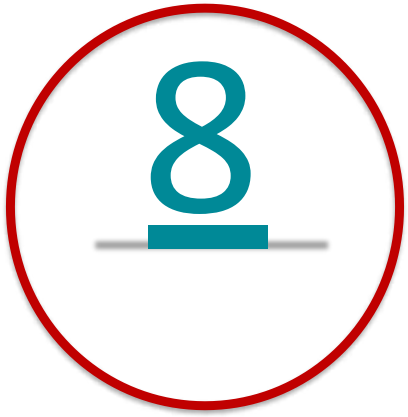
Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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)

Every 2 hours

Apply 6 times daily

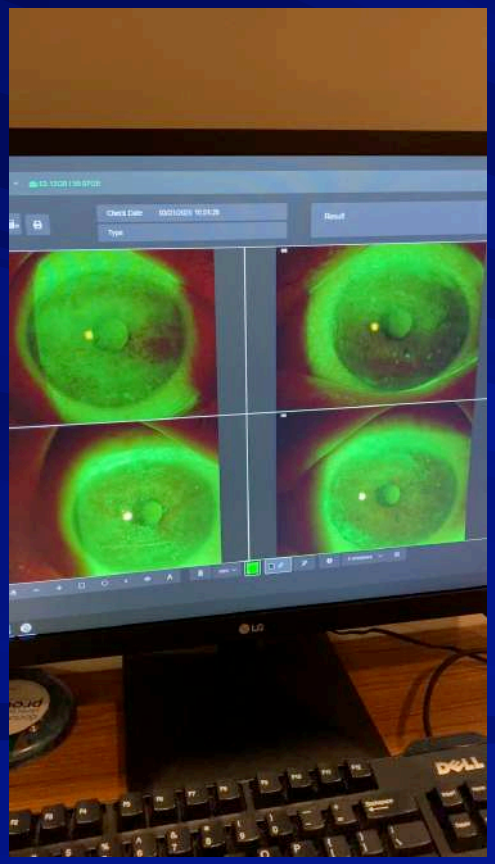


Continue for 8 weeks

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

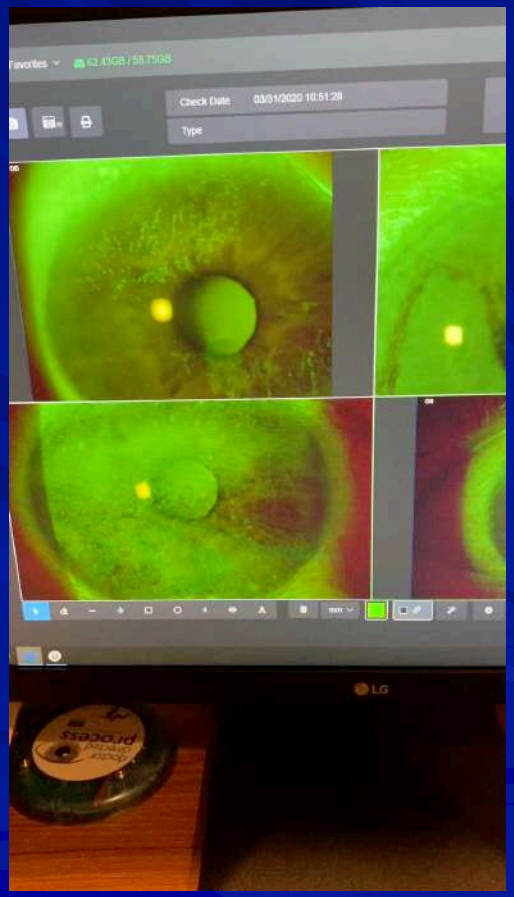
Let's Hear From a Patient

April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks

May 12, 2020 - After 6 weeks



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.

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

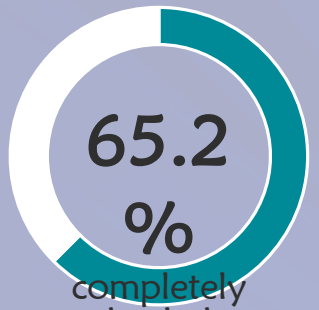
NCT01756456

Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



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[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. Chao W, J. BOC, R. D et al. Data on file. Healing of persistent epithelial defects of 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.

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.

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