The Role of Phenotype in Selectively Enriching Patients for Clinical Studies

Developing Treatments for Dry Age-Related Macular Degeneration (AMD) Workshop
November 15, 2014
National Academy of Sciences Building, Lecture Room
2101 Constitution Ave., N.W., Washington, DC

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Genentech: Research grant/Study advisory board

GlaxoSmithKline: Research grant/Consultant

Healios K.K.: Consultant

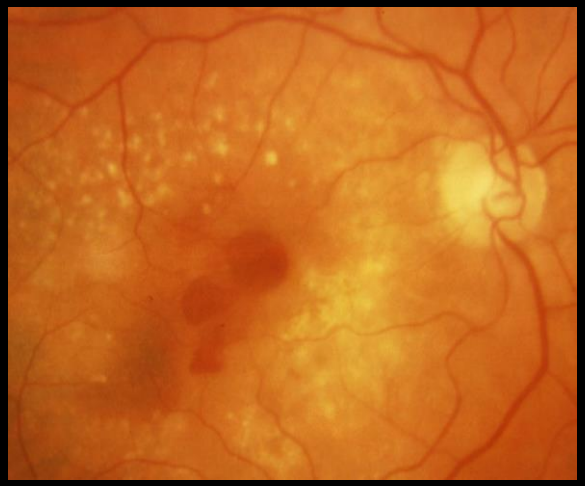
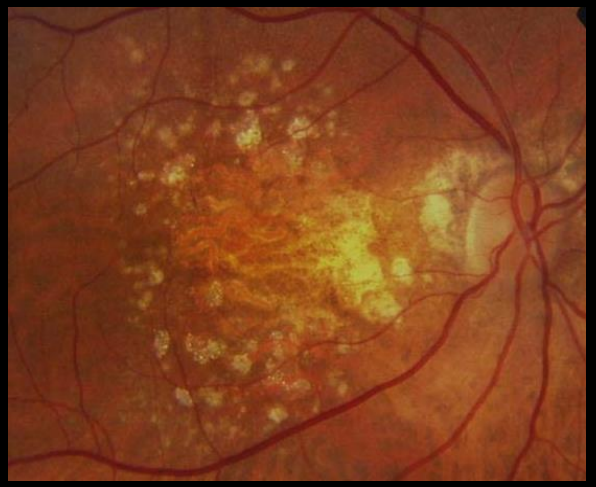
Oraya: Consultant

Hoffman-La Roche: Study advisory board

Vision Medicines: Consultant

Xcovery Vision: Study advisory board

Dry AMD Treatments: Therapeutic Goals

- Prevent vision loss
- Slow the loss of vision
- Restore lost vision

Dry AMD Treatments: Visual Acuity as an Endpoint?

- Visual acuity
  - Vision loss takes years
  - Unrealistic short-term clinical trial endpoint
  - Vision loss may not correlate with disease progression
  - Surrogate outcome/endpoint needed for clinical trials

Baseline
20/25

6 Months
20/25

Growth of GA with no loss of vision

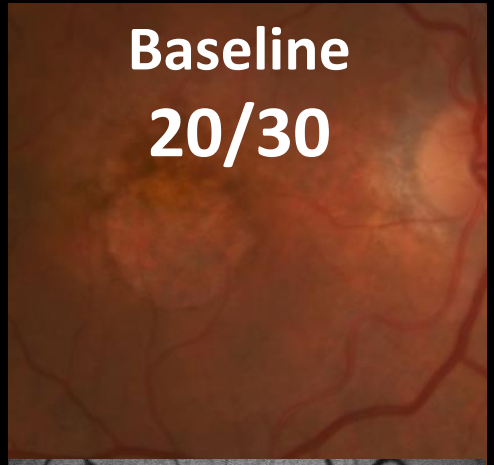
+2.4 mm^2

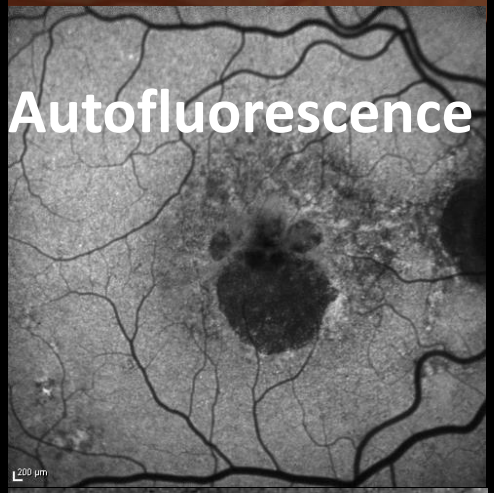
Autofluorescence

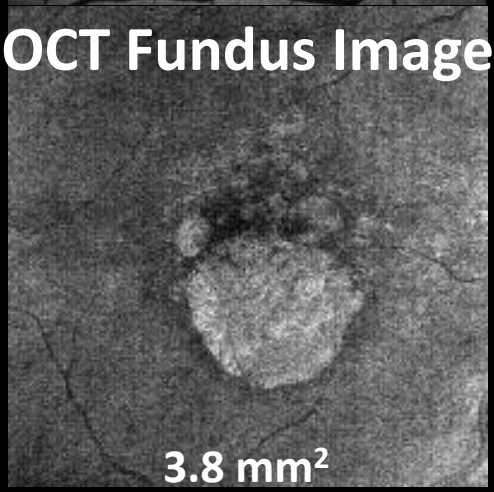
OCT Fundus Image

3.0 mm^2

5.4 mm^2

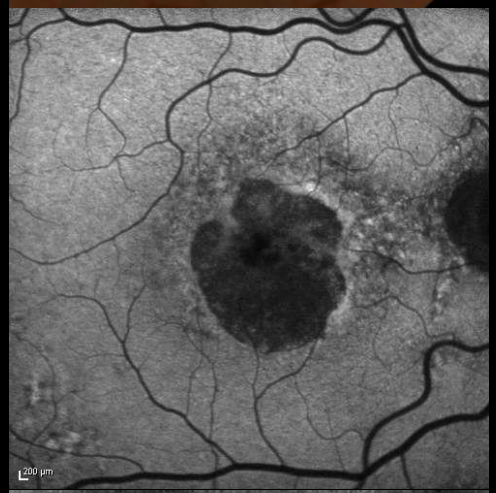


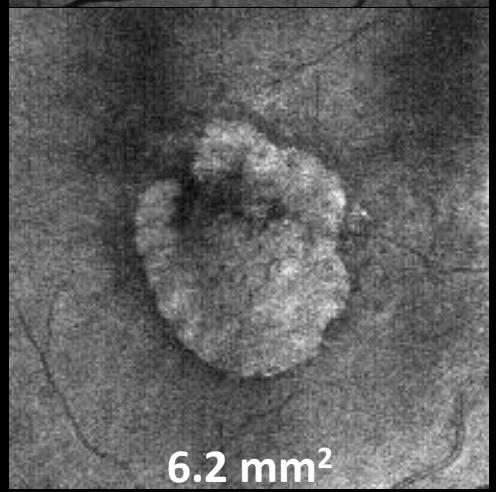




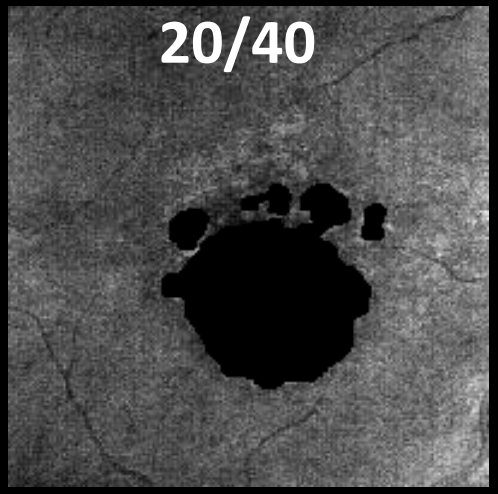
Growth of GA with loss of vision

+2.4 mm²



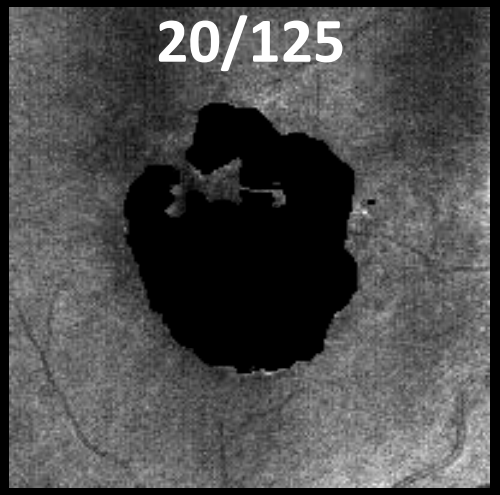


Baseline
20/40

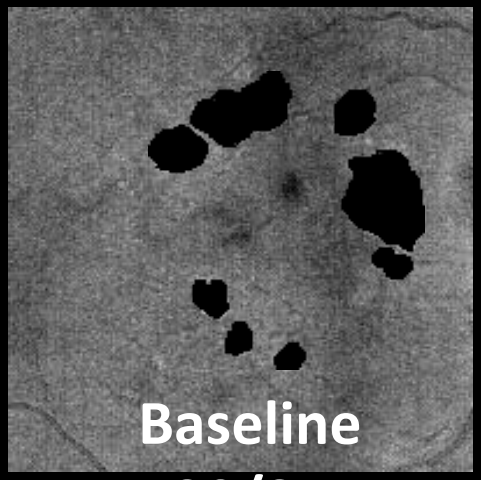


+2.4 mm^2

Week 26
20/125



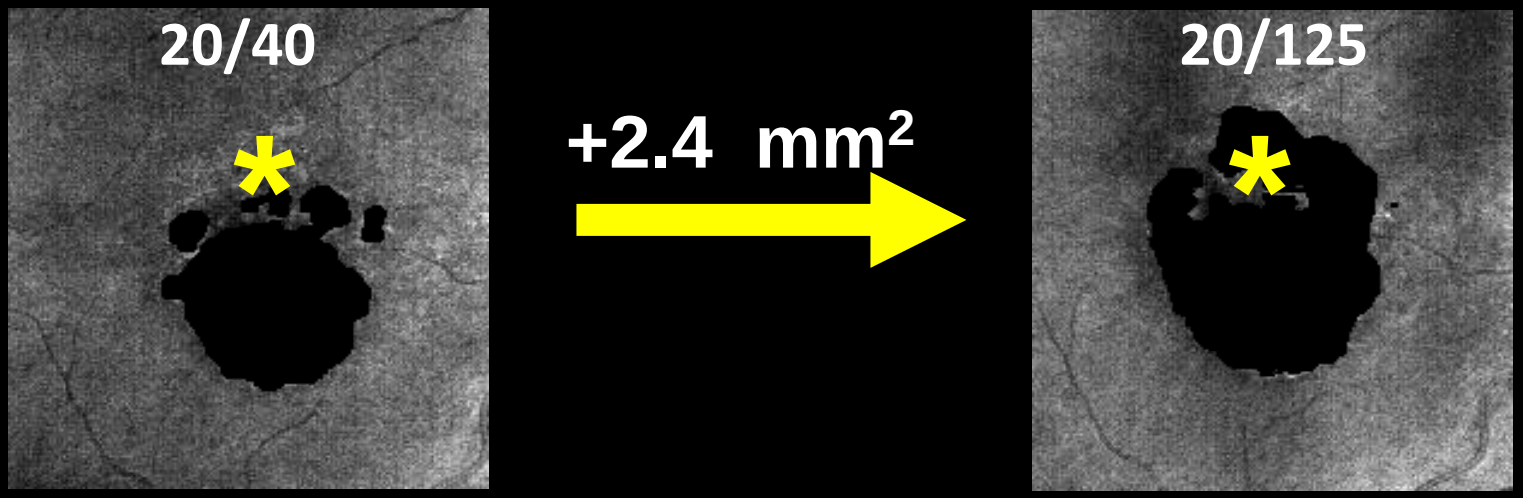
Vision loss ≠ disease progression



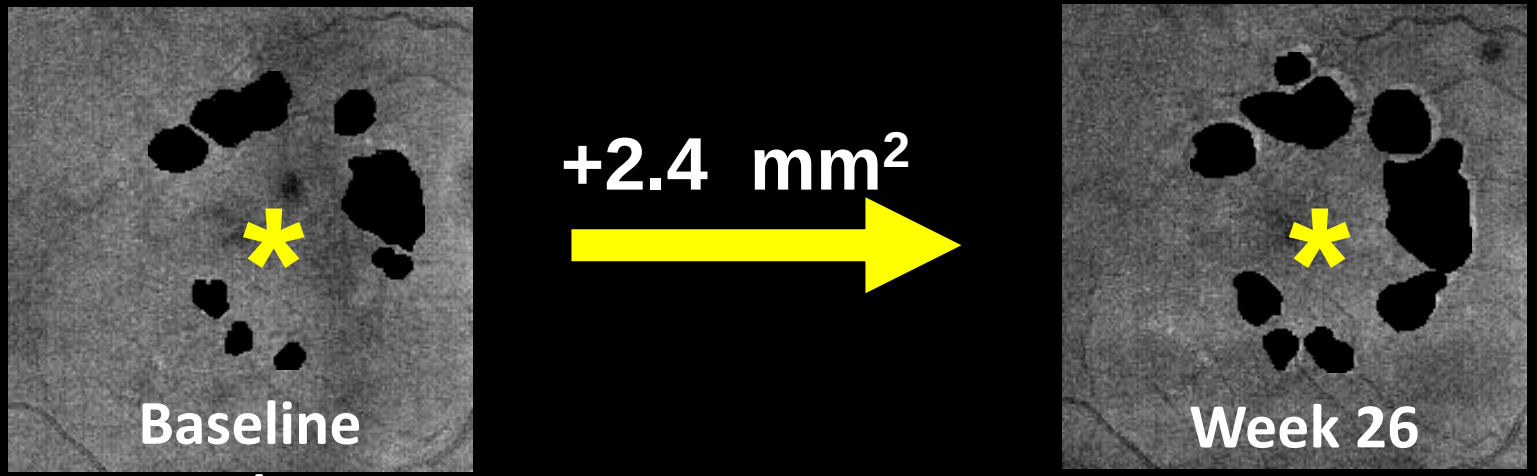
Baseline
20/25

+2.4 mm^2

Week 26
20/25



Central vision loss depends on proximity of GA to foveal center*



Phenotype Enrichment Depends on The Surrogate Endpoint

- Surrogate anatomic endpoints:
  - Growth of geographic atrophy (color, autofluorescence, or OCT *en face* imaging)
  - Progression to neovascular AMD
  - Change in drusen area and/or volume
  - Progression from drusen to GA (in AREDS, 95% of GA had drusen)
  - Progression of AREDS severity scale
  - Changes in retinal/RPE/choroidal anatomy using a variety of imaging strategies

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Growth of Geographic Atrophy

- Phenotype enrichment:
  - Autofluorescence patterns (e.g. banded)
  - Bilateral vs. unilateral GA
  - Disruption/atrophy of photoreceptors at margins of GA imaged by OCT
  - Decreased retinal sensitivity at margins of GA measured by microperimetry
  - Low luminance deficits
  - Presence/absence of reticular pseudodrusen (subretinal drusenoid deposits) or decreased choroidal thickness
  - Delayed dark adaptation

Growth of Geographic Atrophy

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  - **Disruption/atrophy of photoreceptors by OCT imaging at margins of G**
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  - **Delayed dark adaptation**

Enlargement Rates of GA using Fundus Autofluorescence (FAF)

FAF Patterns

'*None*'

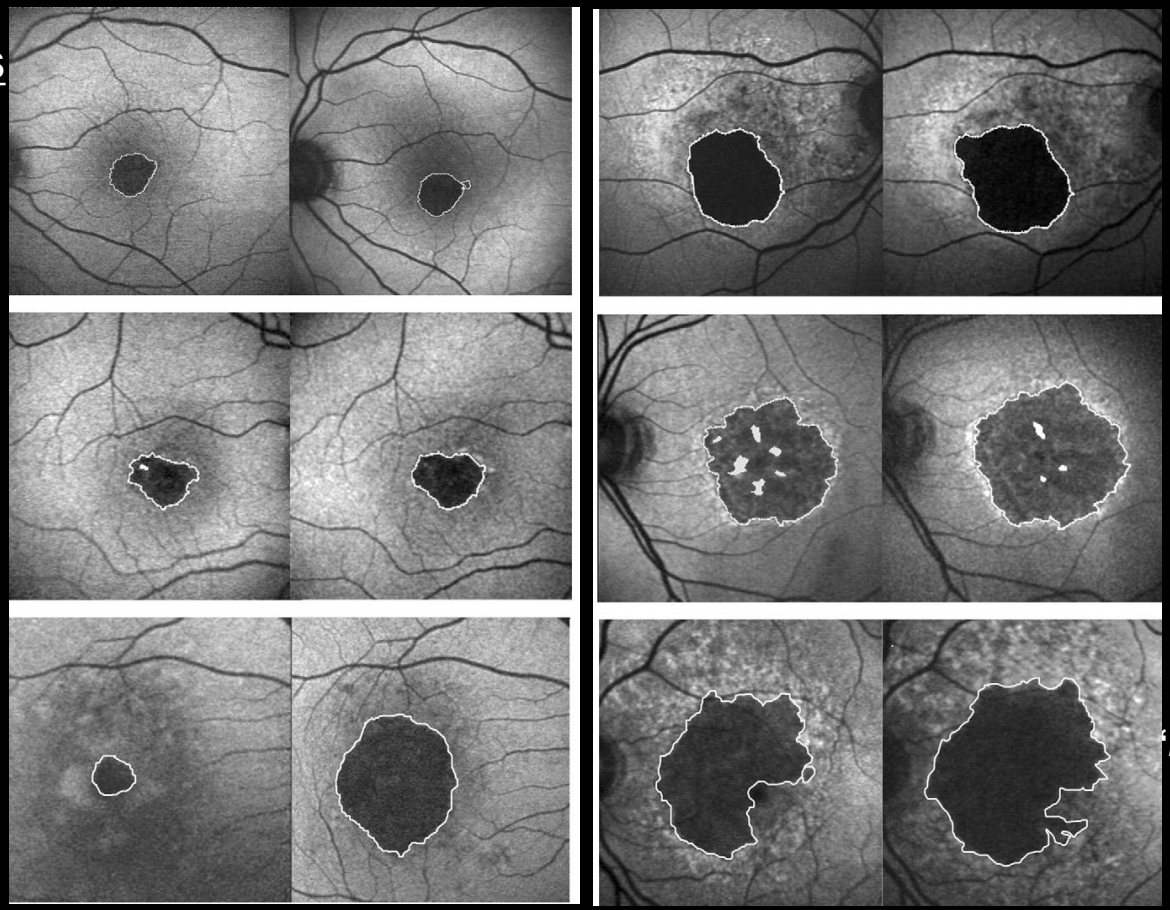
ER = 0.02 mm²/yr

'*Focal*'

ER = 0.36 mm²/yr

'*Patchy*'

ER = 1.84 mm²/yr



FAF Patterns

'*Diffuse*'

ER = 1.71 mm²/yr

'*Banded*'

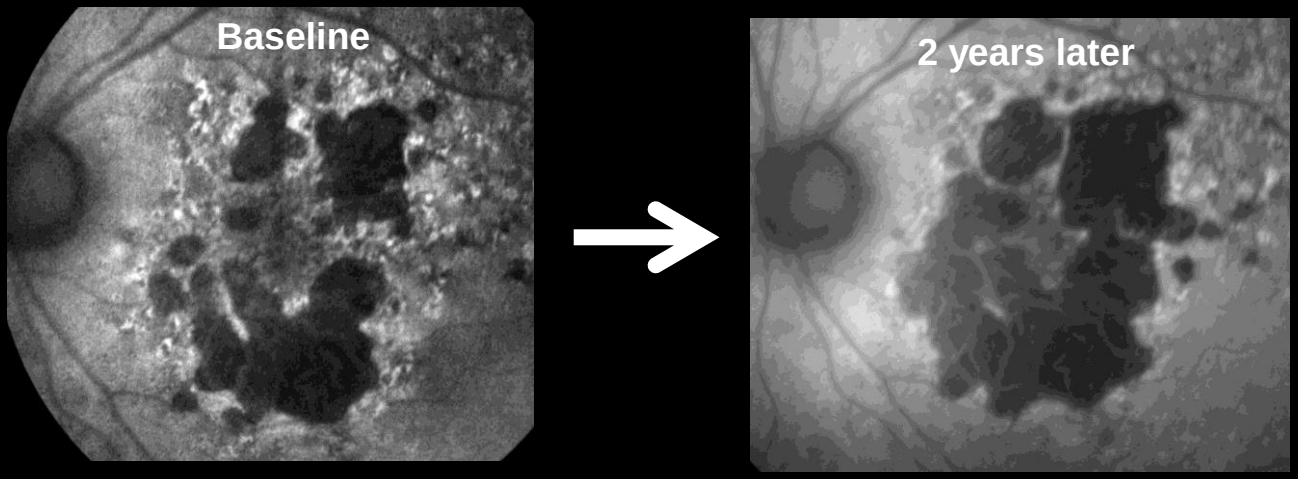
ER = 2.52 mm²/yr

'*Diffuse, Trickling*'

ER = 3.78 mm²/yr

Holz et al, *Am J Ophthalmol* 2007; 143: 463-472

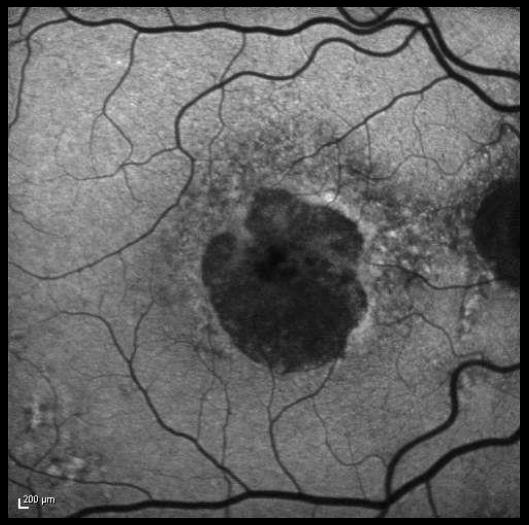
Example: Phase II and Phase III Lampalizumab Trials (Genentech/Roche)

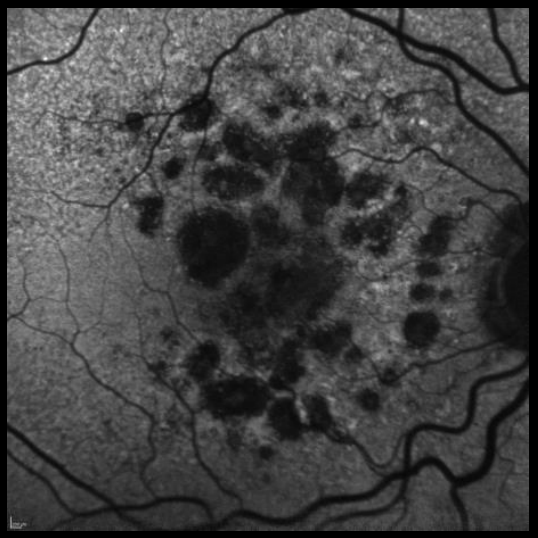


Enrollment criteria:

- Bilateral GA
- Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to the area of GA
- Area of GA: ≥ 1 disc area [DA]) and ≤ 7 DA (if multifocal then 1 focal lesion ≥ 0.5 DA)

Size vs. Unifocality vs. Multifocality

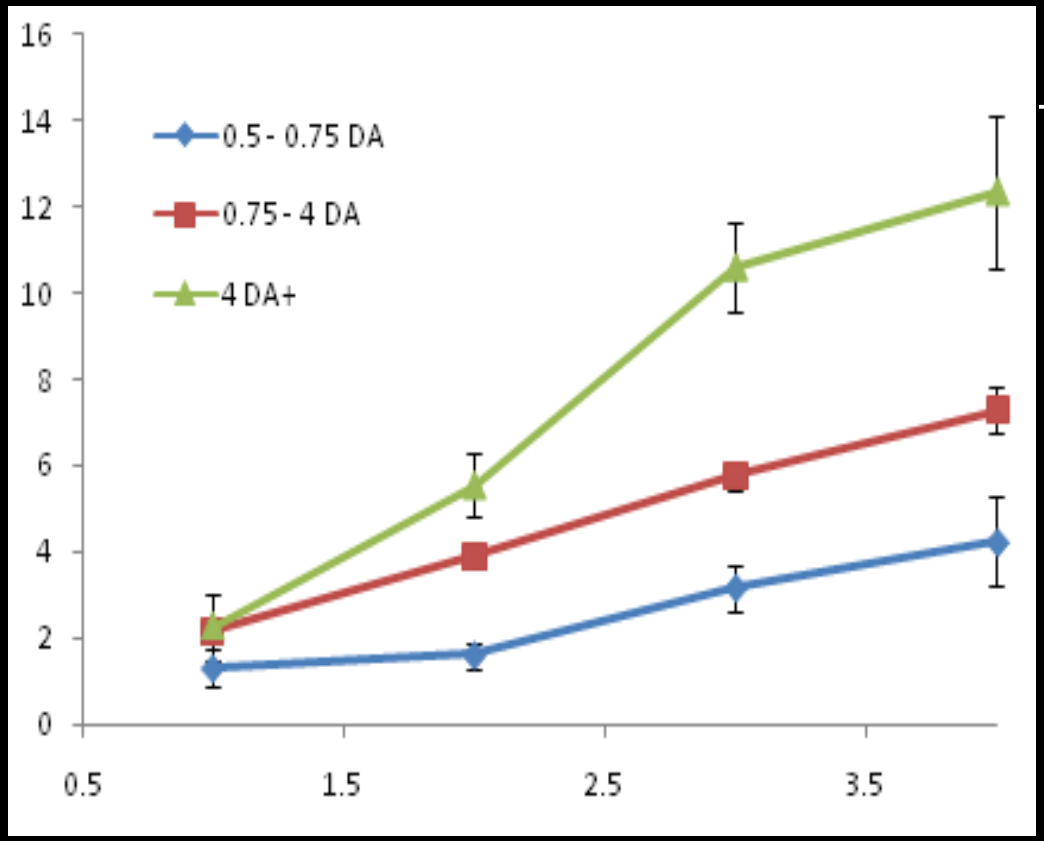




- Larger lesions appear to grow faster
- Multifocal lesions appear to grow faster
- Strategies to account for growth rate differences:
  - Square root transformation of area measurements
  - Correction for circularity index

AREDS Color Photo Measurements: Change in area of GA over 4 years

Change in Area (mm^2)



Time (Years)

Baseline Lesion Size

LARGE
>4 DA

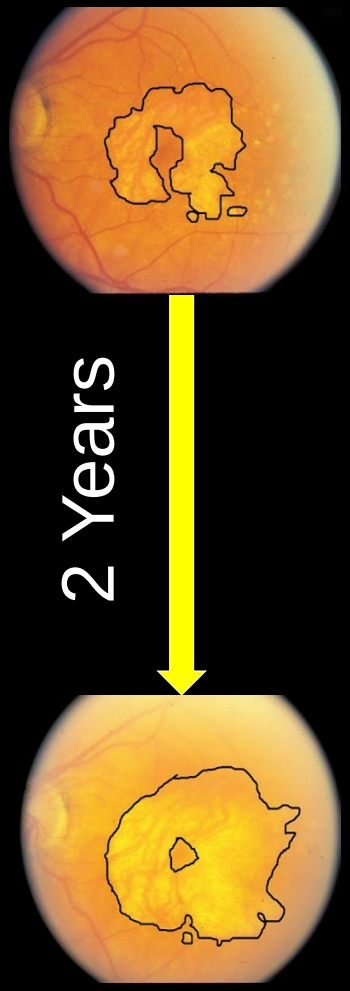
MEDIUM
0.75 - 4 DA

SMALL
0.5 - 0.75 DA

Growth rate depends on baseline lesion size

AREDS Report Number 26 Arch Ophthalmol. 2009; 127 (9) :1168-1174

Geographic Atrophy: The Growth Rate Dilemma



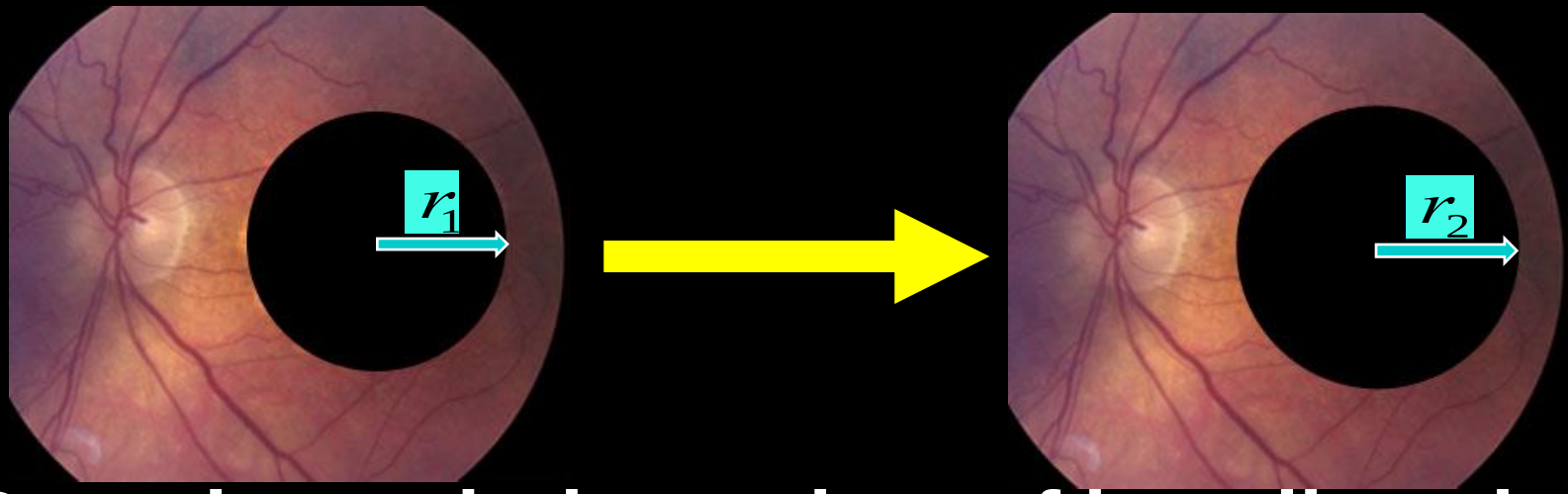
- Growth rate increases with lesion size and multifocality
- As lesions grow larger, they grow faster
- Multifocality/multilobularity changes as lesions grow
- Variability in test-retest measurements increases as the area of GA increases
- What's the solution for designing clinical trials?

Square Root Transformation Strategy: Difference in Areas = Difference in Radii

$$\sqrt{\text{Area}} = \sqrt{\pi r^2} = r\sqrt{\pi}$$

$$\Delta = r_2\sqrt{\pi} - r_1\sqrt{\pi}$$

$$\Delta = (r_2 - r_1)\sqrt{\pi}$$

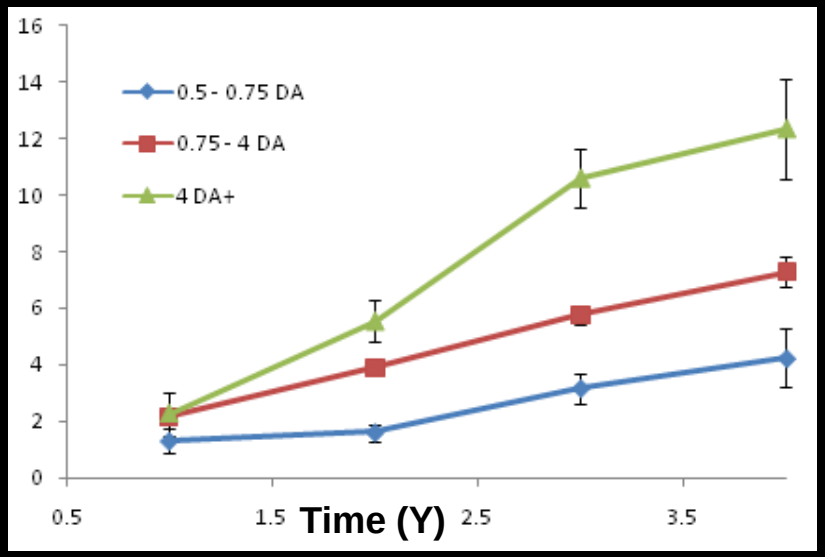


- Growth rate independent of baseline size
- Test-retest measurements independent of size

Yehoshua et al. Ophthalmology, April 2011; 118: 679-686

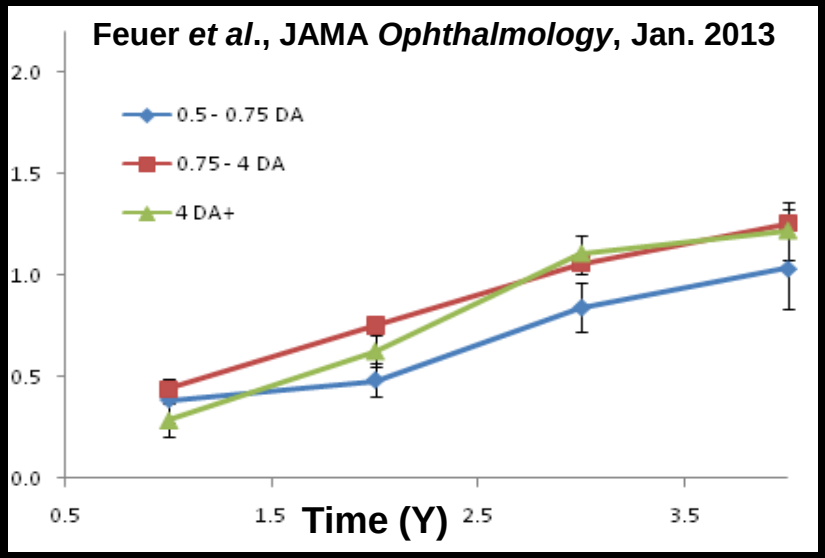
AREDS Database: Growth of GA over 4 Years (Courtesy of Emily Chew and Rick Ferris)

Change in Area (mm^2)



Feuer *et al*., JAMA *Ophthalmology*, Jan. 2013

Change in Square Root of Area (mm)

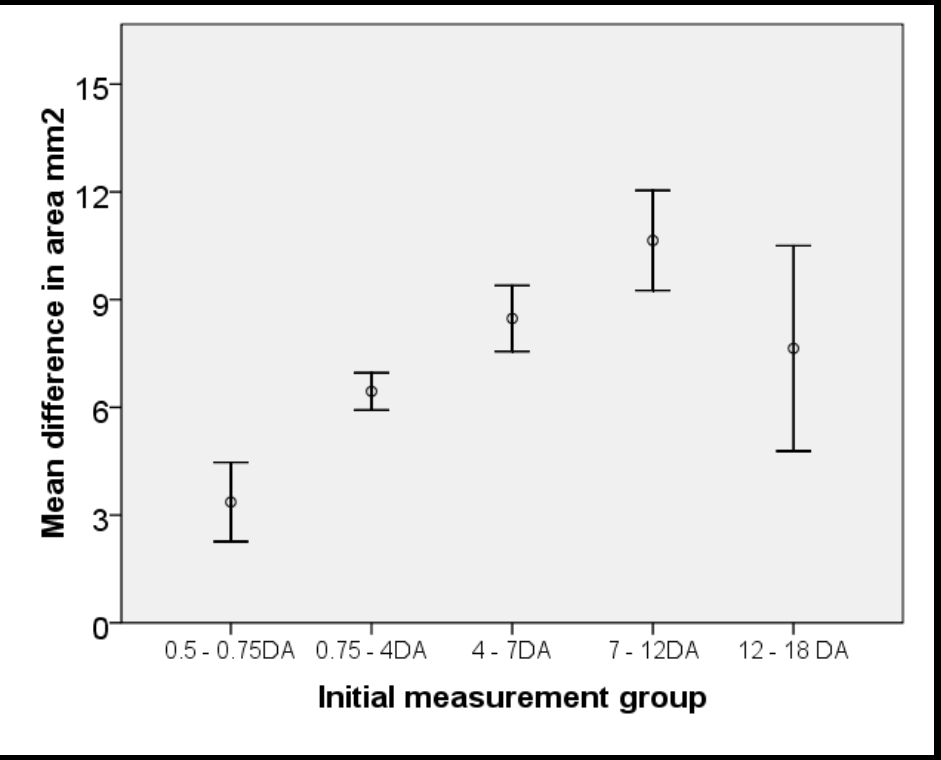


Growth rate no longer depends on size

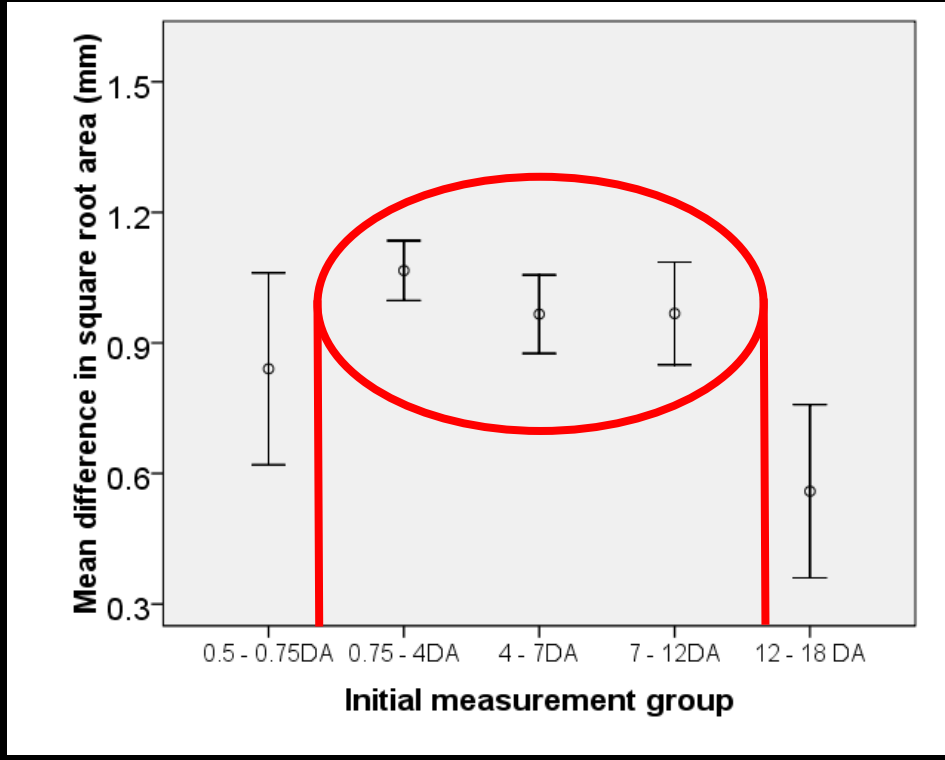
AREDS Color Fundus Database: Growth of GA over 4 Years

(Courtesy of Emily Chew and Rick Ferris)

Difference in Area Measurements



Difference in the Square Root Area Measurements



Confirms size range of GA for clinical trials

Non-Circularity Index (NCI) Helps Predict Progression of GA

Circularity Index as a Risk Factor for Progression of Geographic Atrophy

Amitha Domalpally, MD,[1] Ronald P. Danis, MD,[1] James White, BME,[1] Ashwini Narkar, MS,[1] Traci Clemons, PhD,[3] Fredrick Ferris, MD,[2] Emily Chew, MD[2]

Ophthalmology 2013;120:2666-2671

Definition of NCI:

$$\frac{\text{Actual Area}}{\text{Perimeter Area}}$$

Actual perimeter = $2\pi r_p$

r_p = radius of a circle with a perimeter equal to the perimeter from the actual GA

Perimeter Area = πr_p^2

If the GA lesion is a circle, then the NCI = 1

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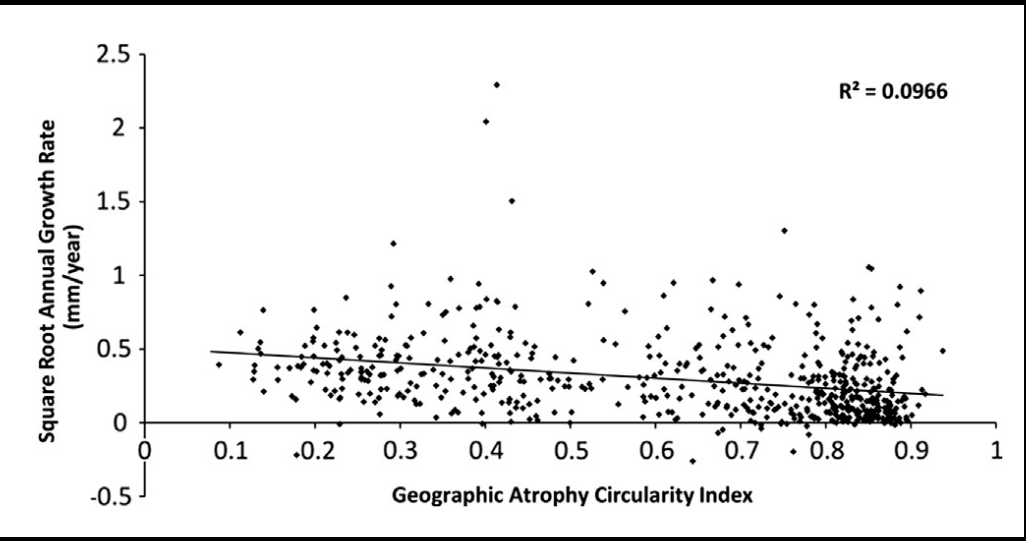

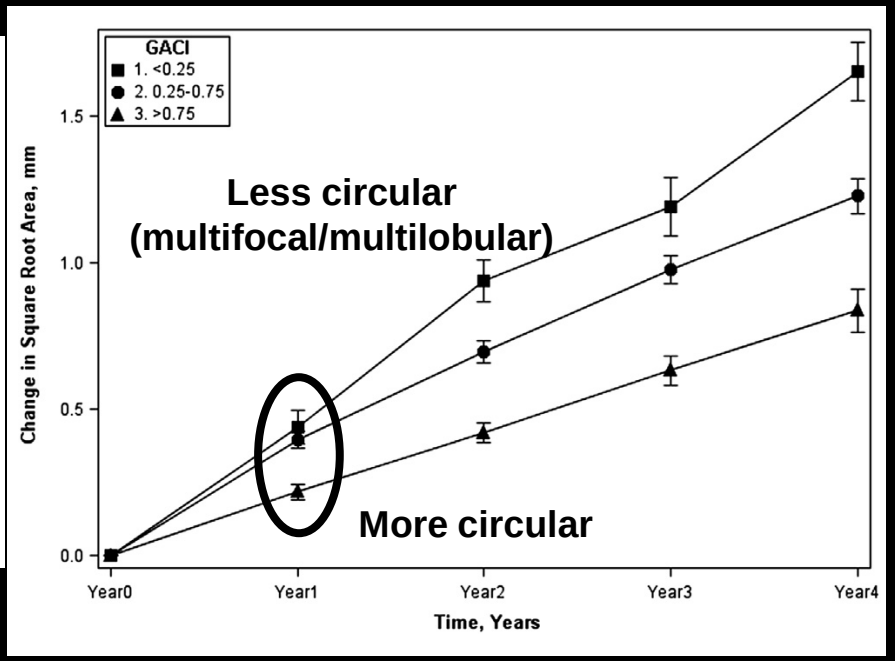

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  - Delayed dark adaptation

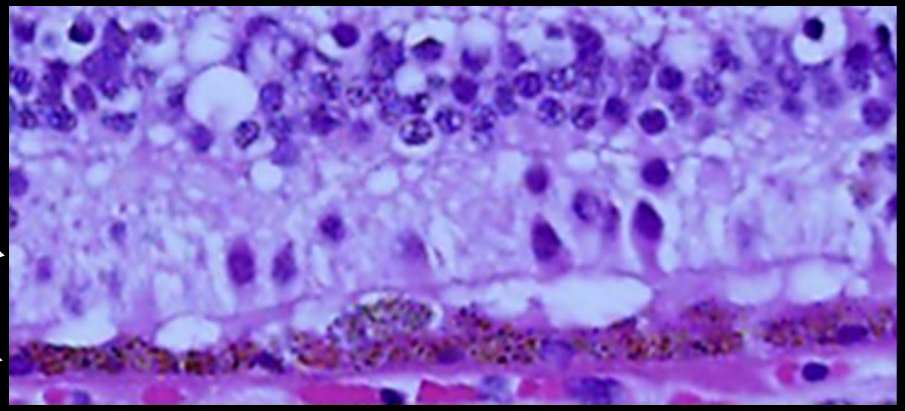
Abnormal Anatomy and Visual Function Extends Beyond the Margin of GA

- **Histopathology: Photoreceptor atrophy at variable distances from edge of GA**

Geographic Atrophy: A Histopathological Assessment
Bird et al., *JAMA Ophthalmol*. 2014;132(3):338-345.

Loss of photoreceptors 1400 µm from the edge of GA

Intact RPE



- **Electrophysiology and microperimetry: Photoreceptor dysfunction identified away from the edge of the GA**

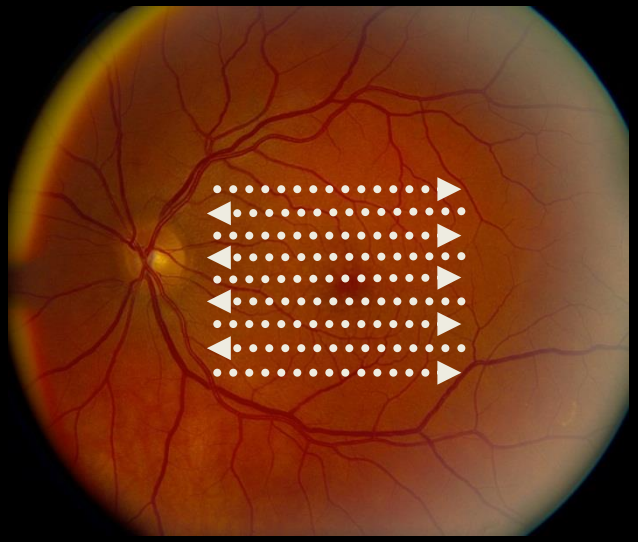
Bhutto I, Lutty G. Understanding AMD: relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. *Molecular aspects of medicine* 2012;33:295-317.

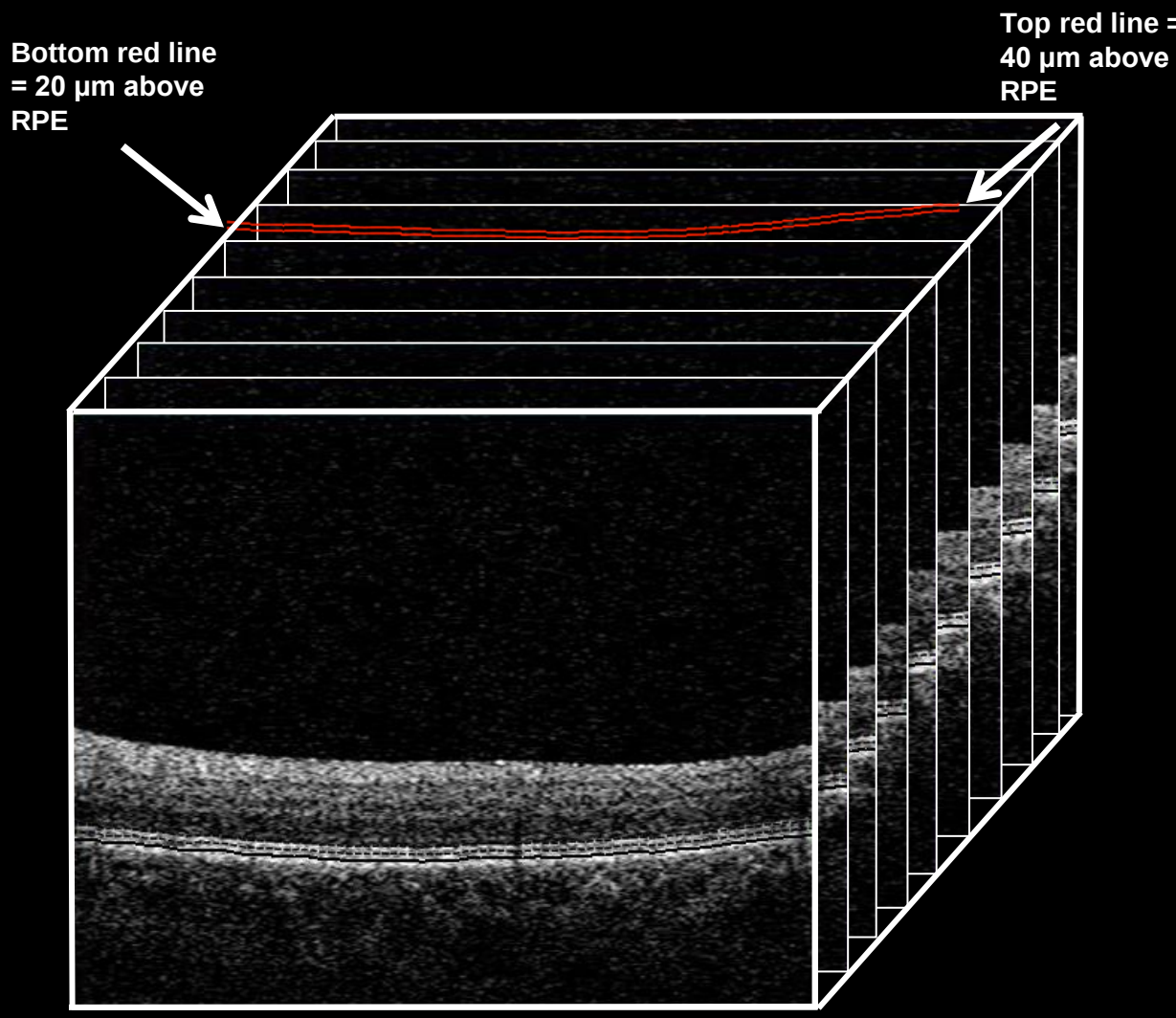
SD-OCT Imaging of the Outer Retina Can Show Disrupted Photoreceptors and Predict Progression of GA

- Ongoing prospective SD-OCT study
  - Eyes with GA secondary to AMD
  - Size of GA between 0.5 DA (1.8 mm^2) and 7 DAs (18 mm^2)
  - Followed for at least 1 year

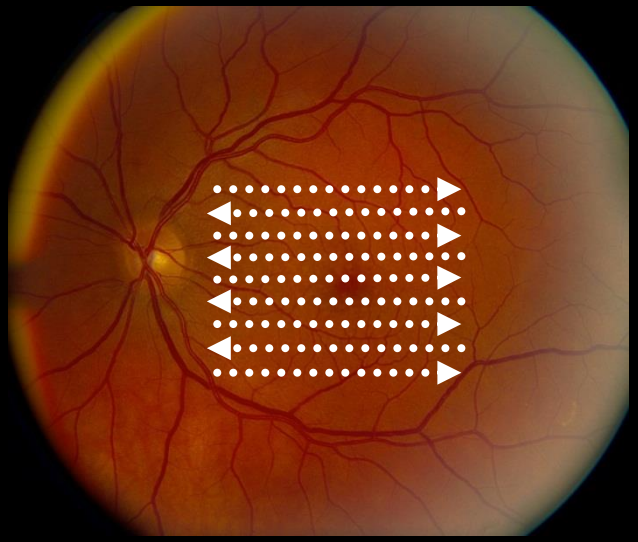
Nunes RP *et al.* Predicting the progression of geographic atrophy in age-related macular degeneration with SD-OCT en face imaging of the outer retina. Ophthalmic Surg Lasers Imaging Retina 2013;44(4): 344-59.

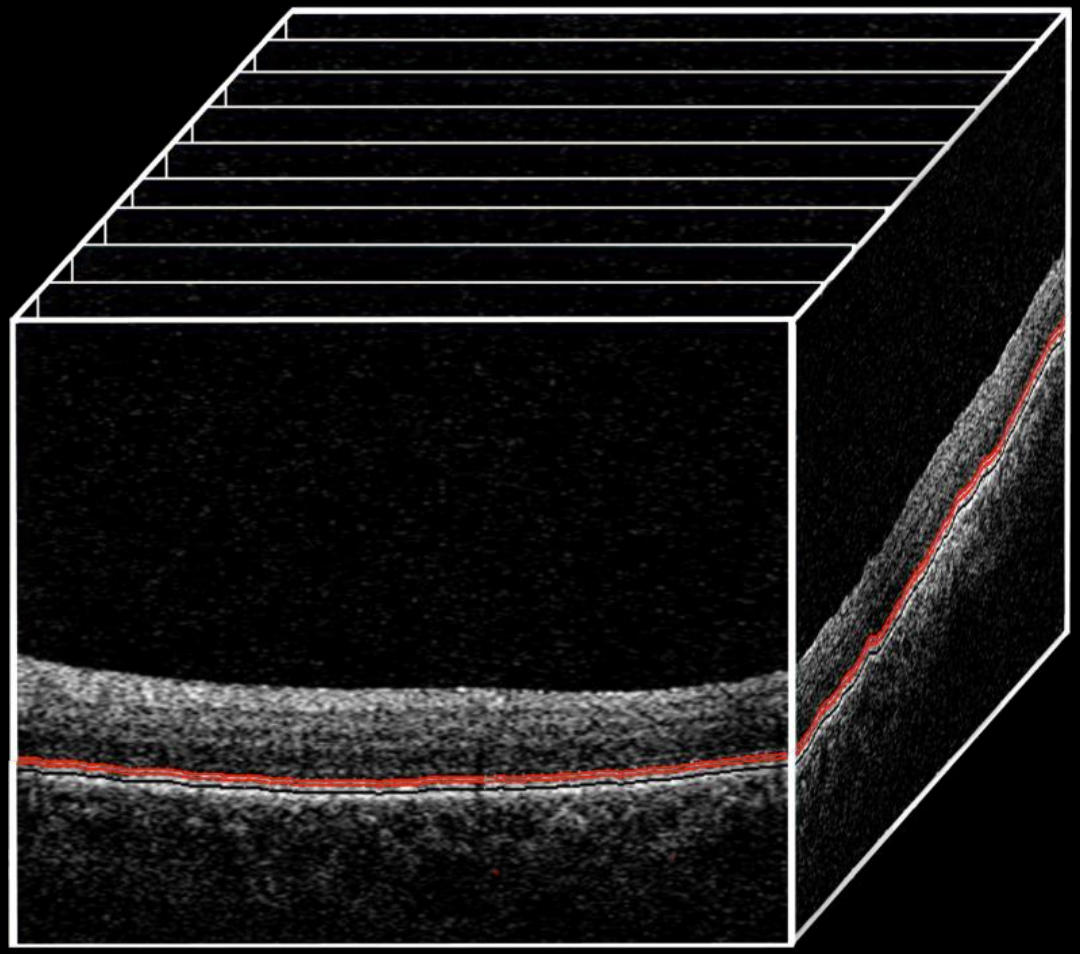
Outer Retinal IS/OS/EZ Slab *En Face* Image





20μm thick slab containing the IS/OS/EZ boundary





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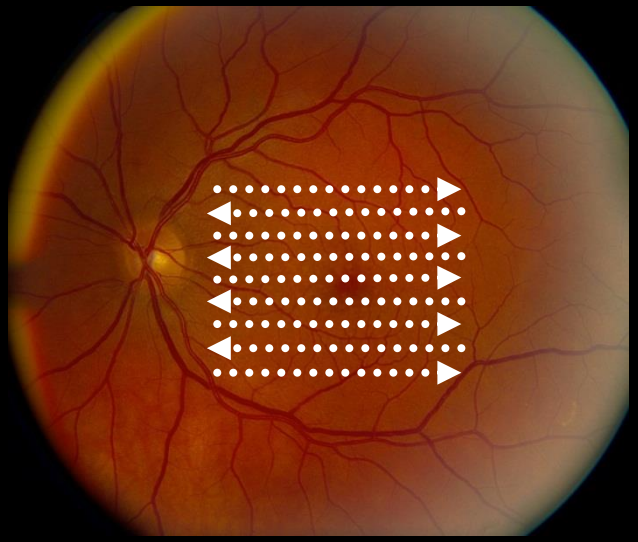
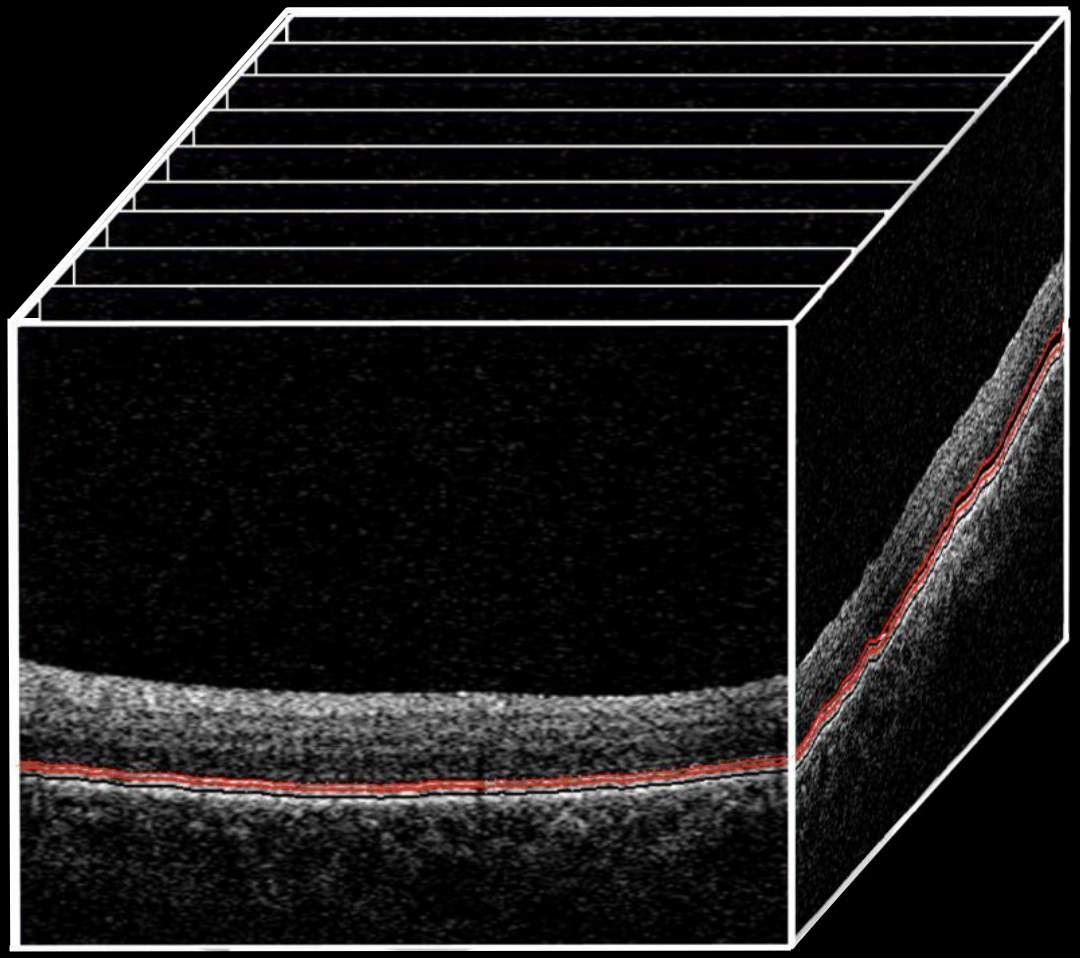
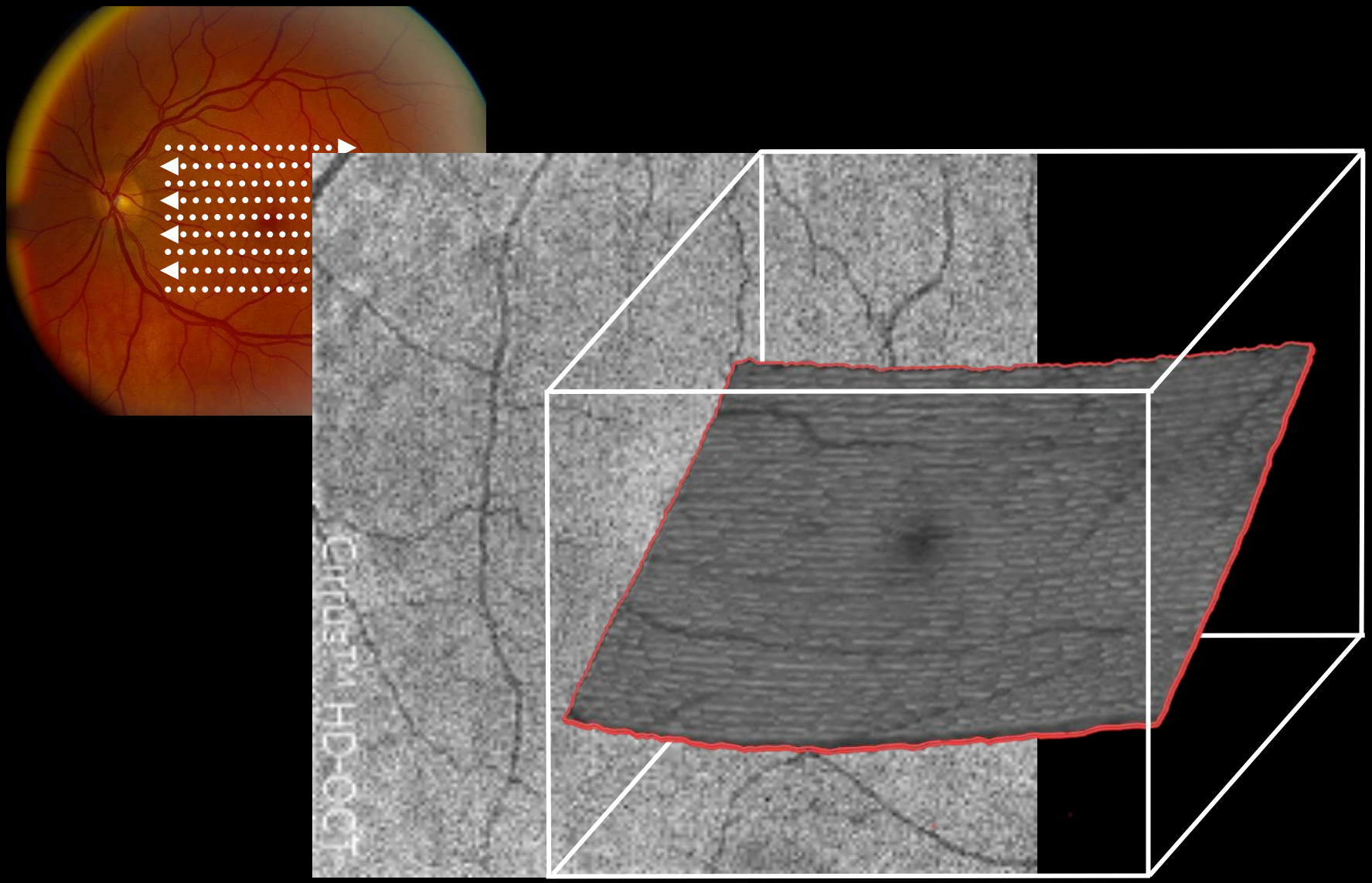




En Face Projection: IS/OS/EZ Region

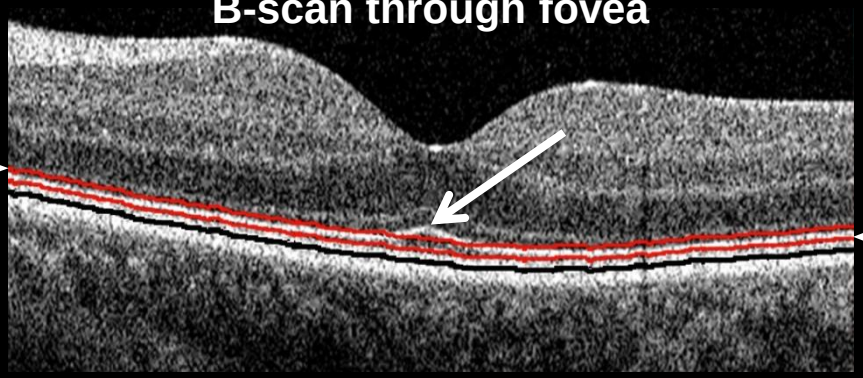


IS/OS/EZ Slab *En Face* Image

Top red line =
40 µm above RPE

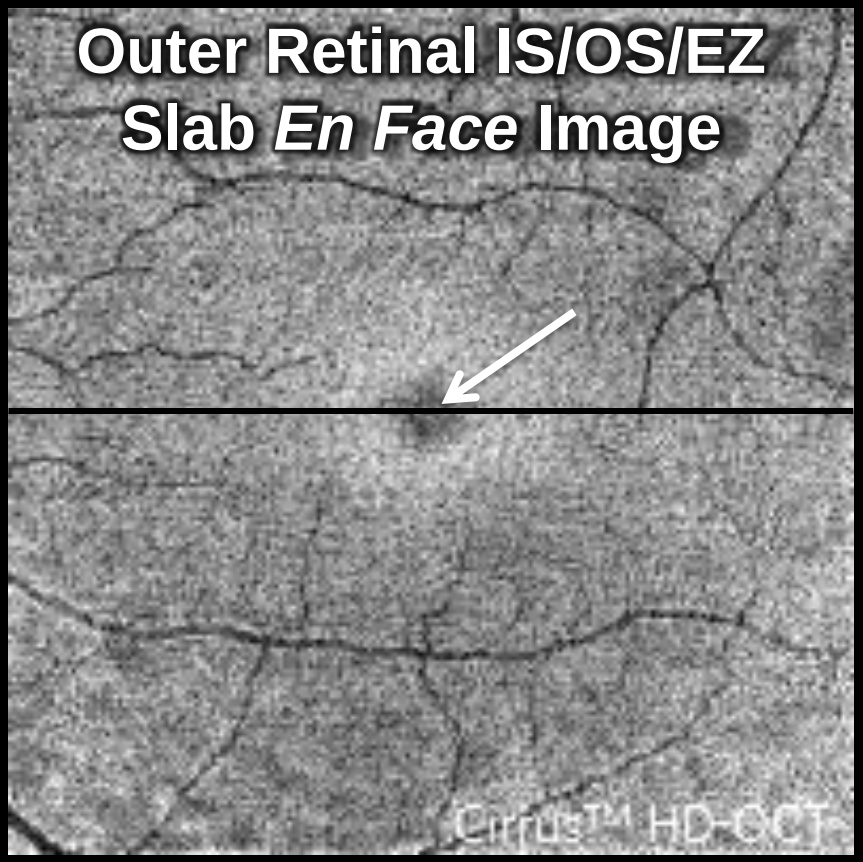
Black line = RPE

B-scan through fovea



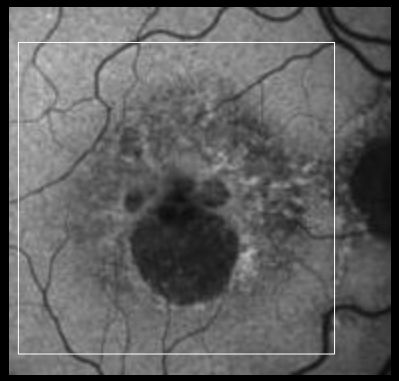
Bottom red line =
20 µm above RPE

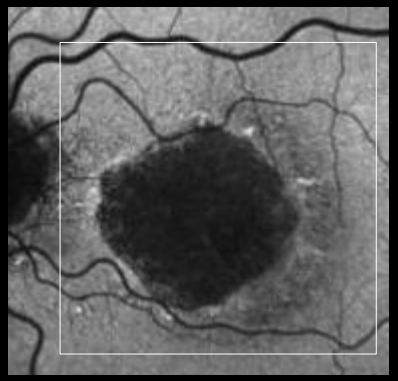
Location of B-scan



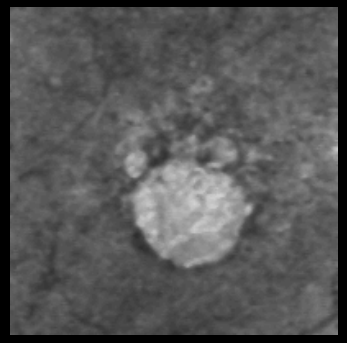
Case #1

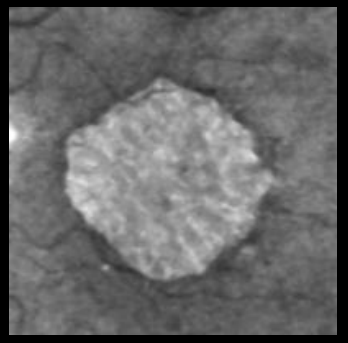
Color Images



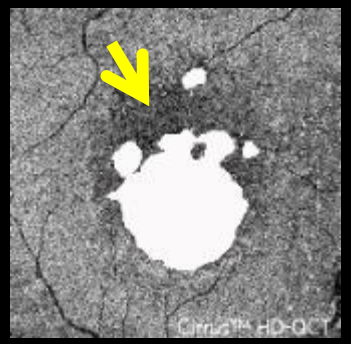


Heidelberg Autofluorescence Images





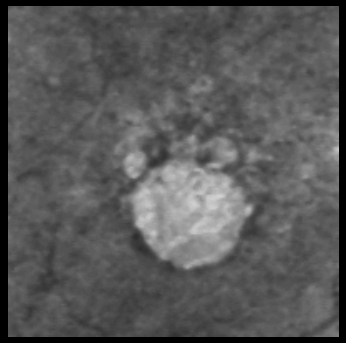
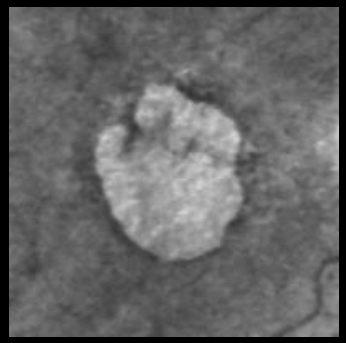
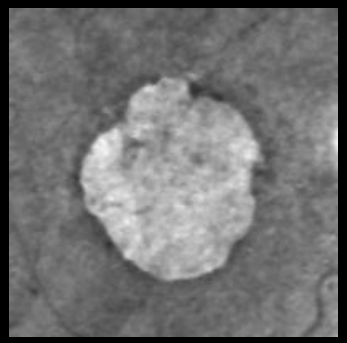
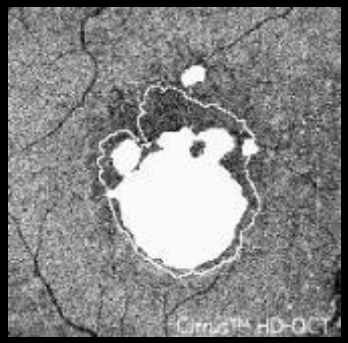
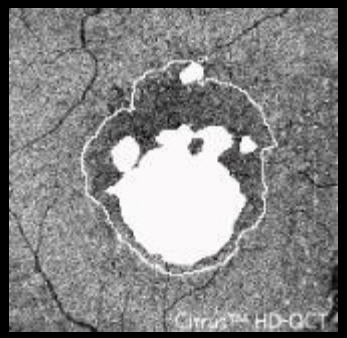
Sub-RPE Slab *En Face* Images (GA)



IS/OS/EZ Slab *En Face* Images (Focal Pattern)

2-2-10-ARR

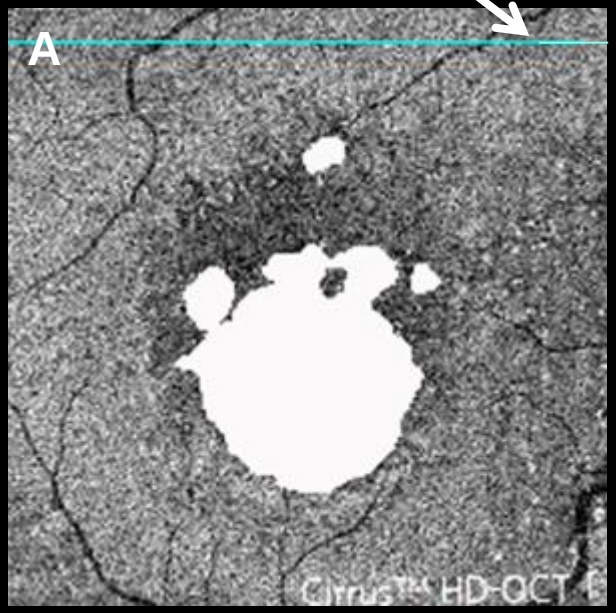
Growth of GA Over 1 Year: Focal Pattern

	Baseline	6 Months	12 Months
Sub-RPE Slab *En Face* Images (GA)			
Baseline IS/OS/EZ Slab *En Face* Images (Focal Pattern)			
	Baseline GA	Baseline GA + Growth at 6 months	Baseline GA + Growth at 12 months

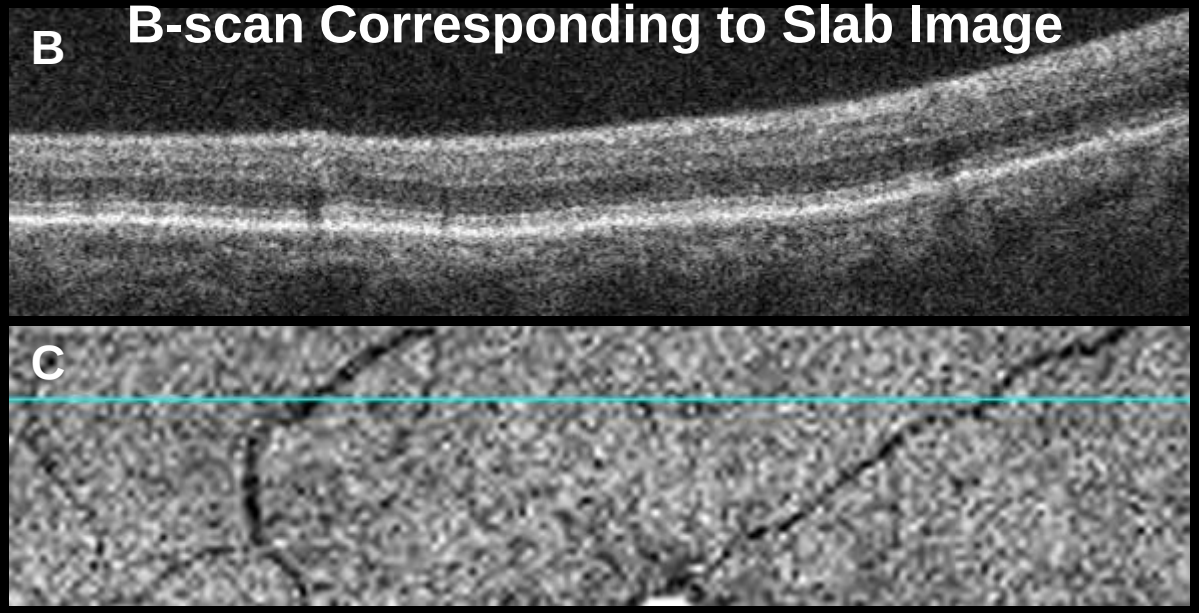
2-2-10-ARR

Correlation between B-Scan and Outer Retinal IS/OS/EZ Slab *En Face* Image

Location of B-scan



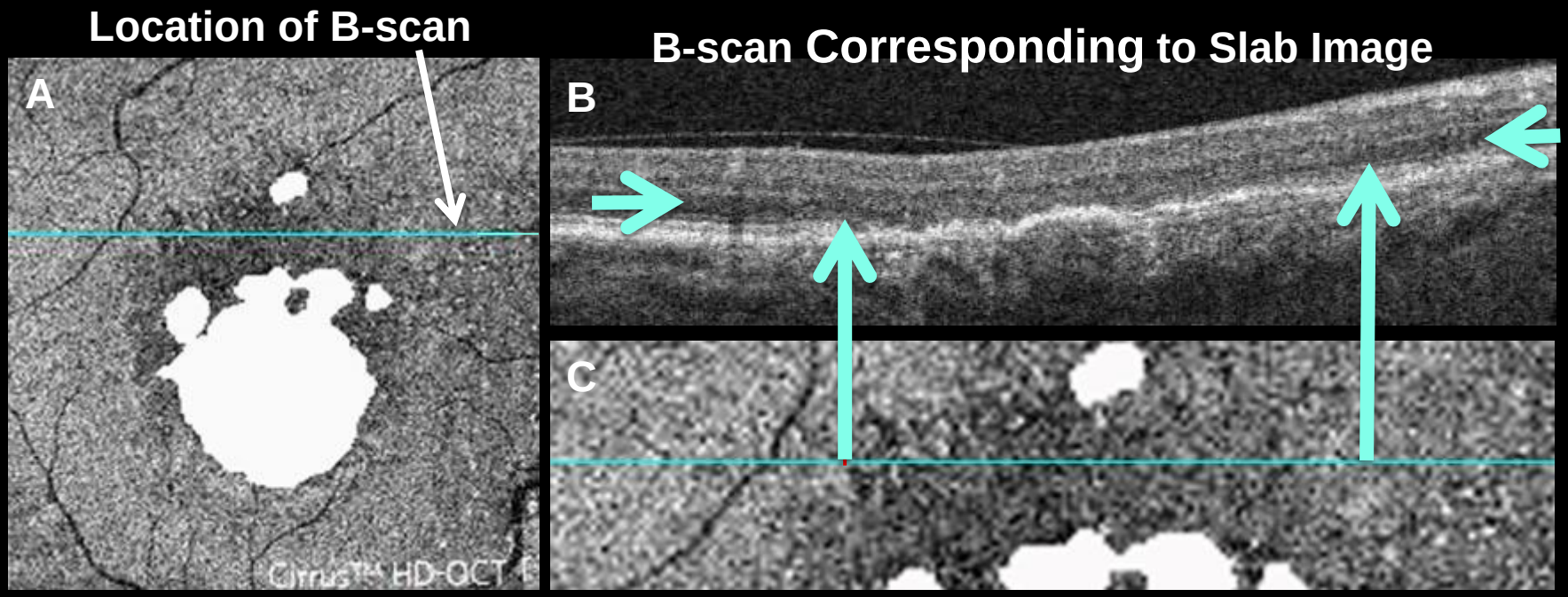
IS/OS/EZ Slab
En Face Image
(Focal Pattern)



Magnified IS/OS/EZ Slab *En Face* Image

2-2-10-ARR

Correlation between B-Scan and Outer Retinal IS/OS/EZ Slab *En Face* Image



IS/OS/EZ Slab *En Face* Image (Focal Pattern)

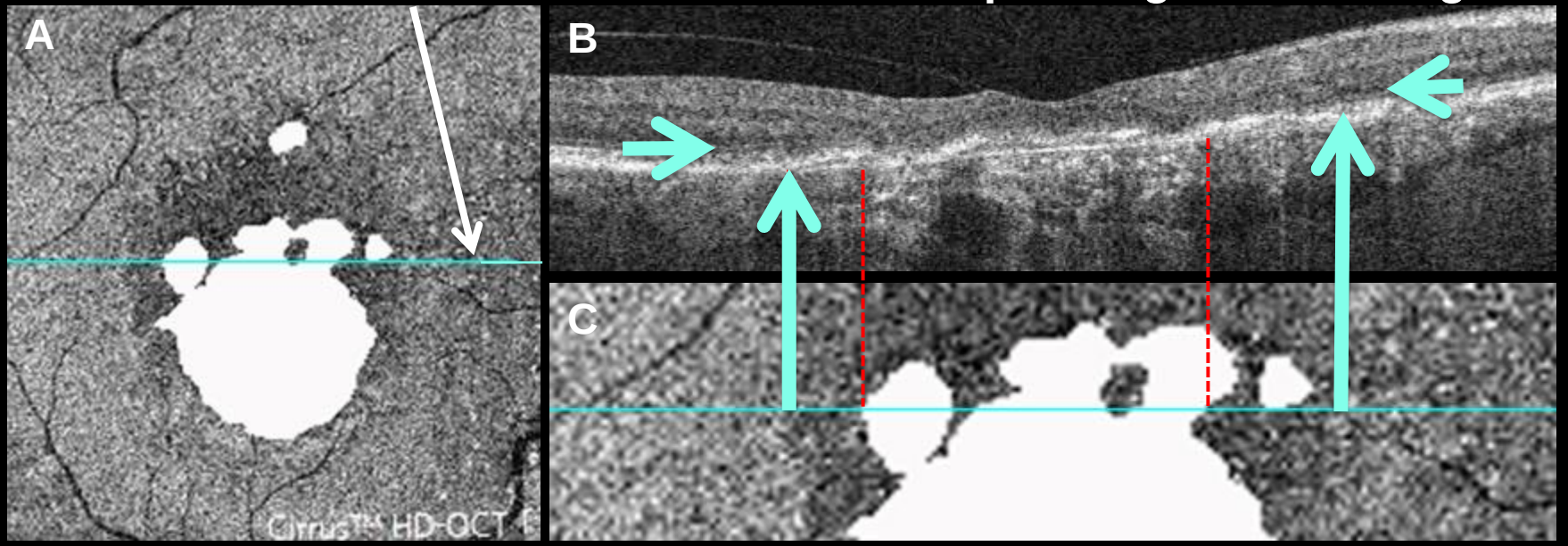
Magnified IS/OS/EZ Slab *En Face* Image

2-2-10-ARR

Correlation between B-Scan and Outer Retinal IS/OS/EZ Slab *En Face* Image

Location of B-scan

B-scan Corresponding to Slab Image

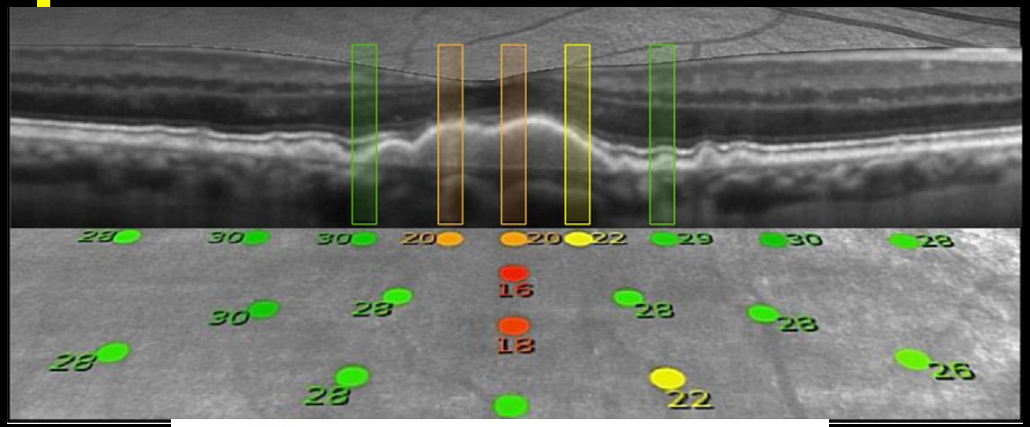


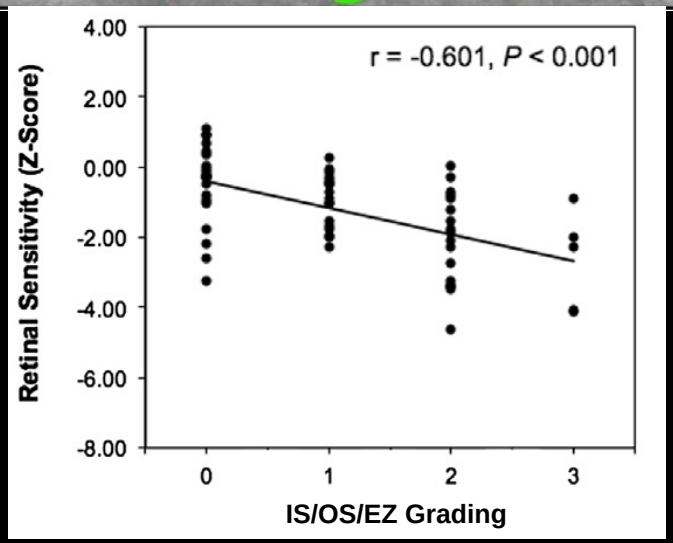
IS/OS/EZ Slab *En Face* Image (Focal Pattern)

Magnified IS/OS/EZ Slab *En Face* Image

Growth of IS/OS defect being used in ongoing CNTF trial in MacTel2

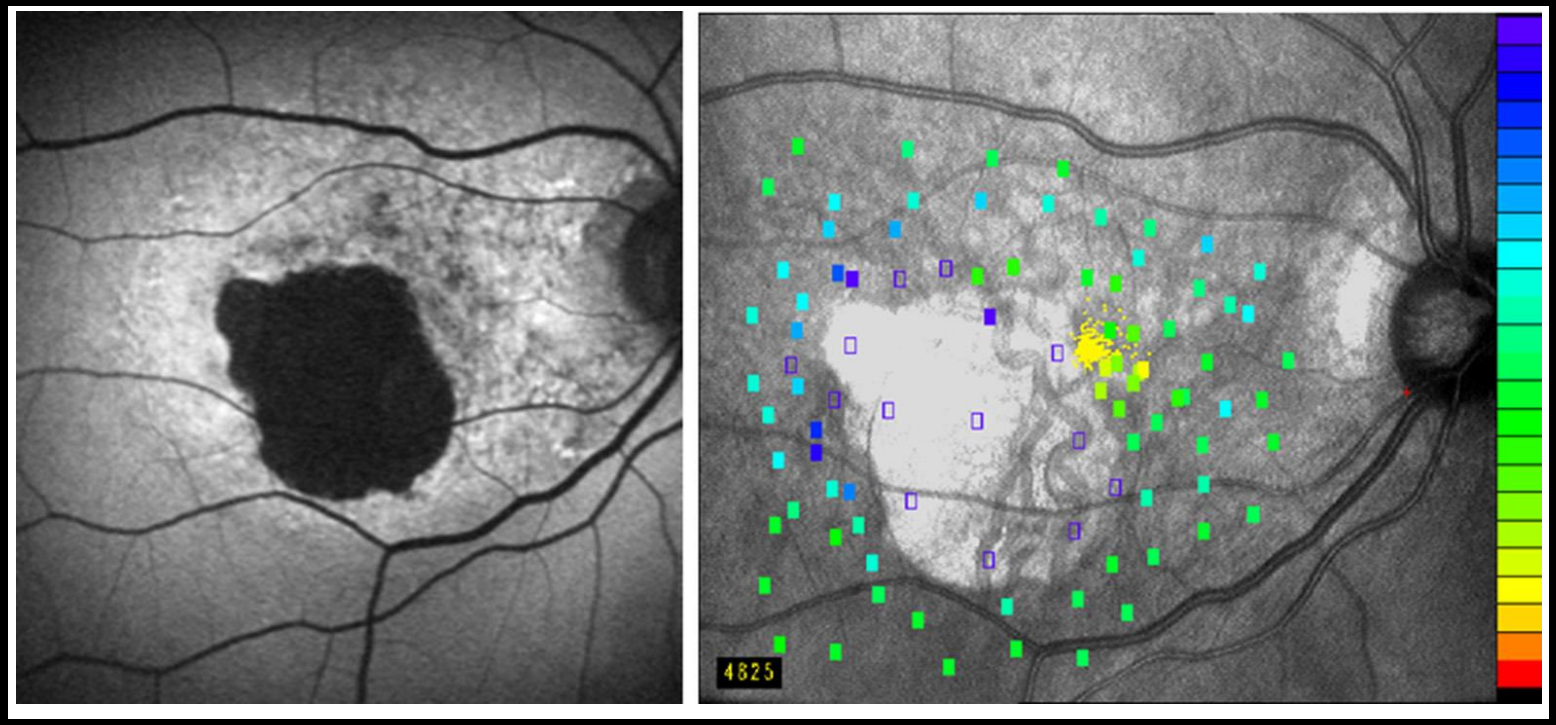
Loss of IS/OS/EZ Integrity Corresponds to Decreased Microperimetric Retinal Sensitivity





Wu Z, Ayton LN, Luu CD, Guymer RH. Relationship between retinal microstructures on optical coherence tomography and microperimetry in age-related macular degeneration. Ophthalmology 2014;121(7):1445-52.

Microperimetric Retinal Sensitivity Decreased Away from the Edge of GA



Loss of retinal sensitivity corresponds to perilesional area with increased autofluorescence

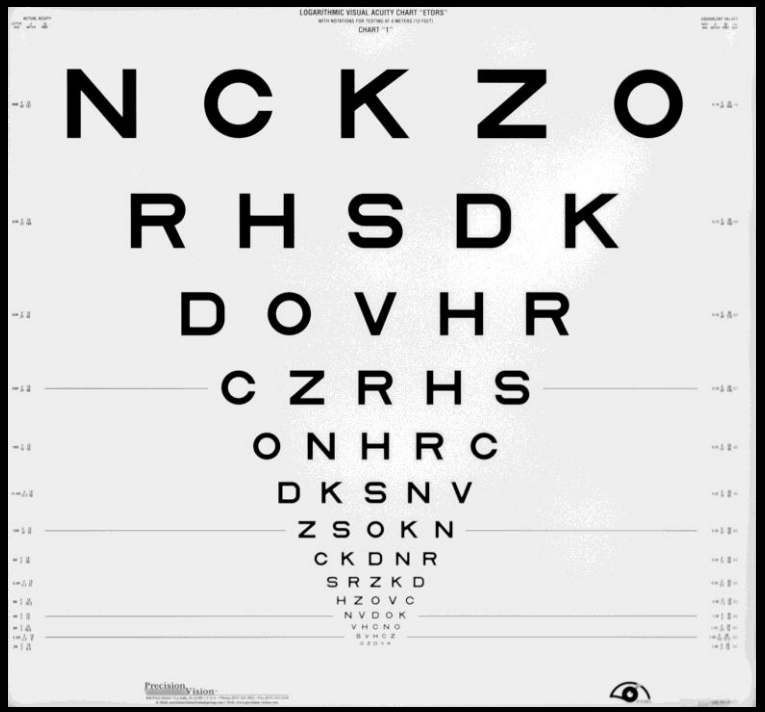
Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. Ophthalmology 2014;121(5):1079-91.

Growth of Geographic Atrophy

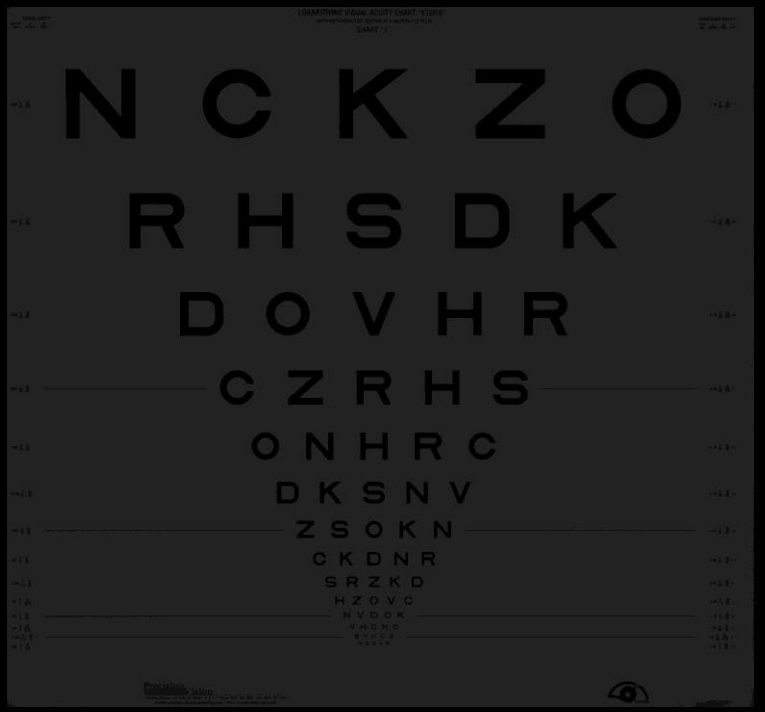
- **Phenotype enrichment:**
  - Autofluorescence patterns (e.g. banded)
  - Bilateral vs. unilateral GA
  - Disruption/atrophy of photoreceptors by OCT imaging at margins of GA
  - Decreased retinal sensitivity by microperimetry at margins of GA
  - Low luminance deficits
  - Presence/absence of reticular pseudodrusen (subretinal drusenoid deposits) or decreased choroidal thickness
  - Delayed dark adaptation

Low Luminance Deficit Testing

Normal Luminance ETDRS Acuity



Low Luminance ETDRS Acuity



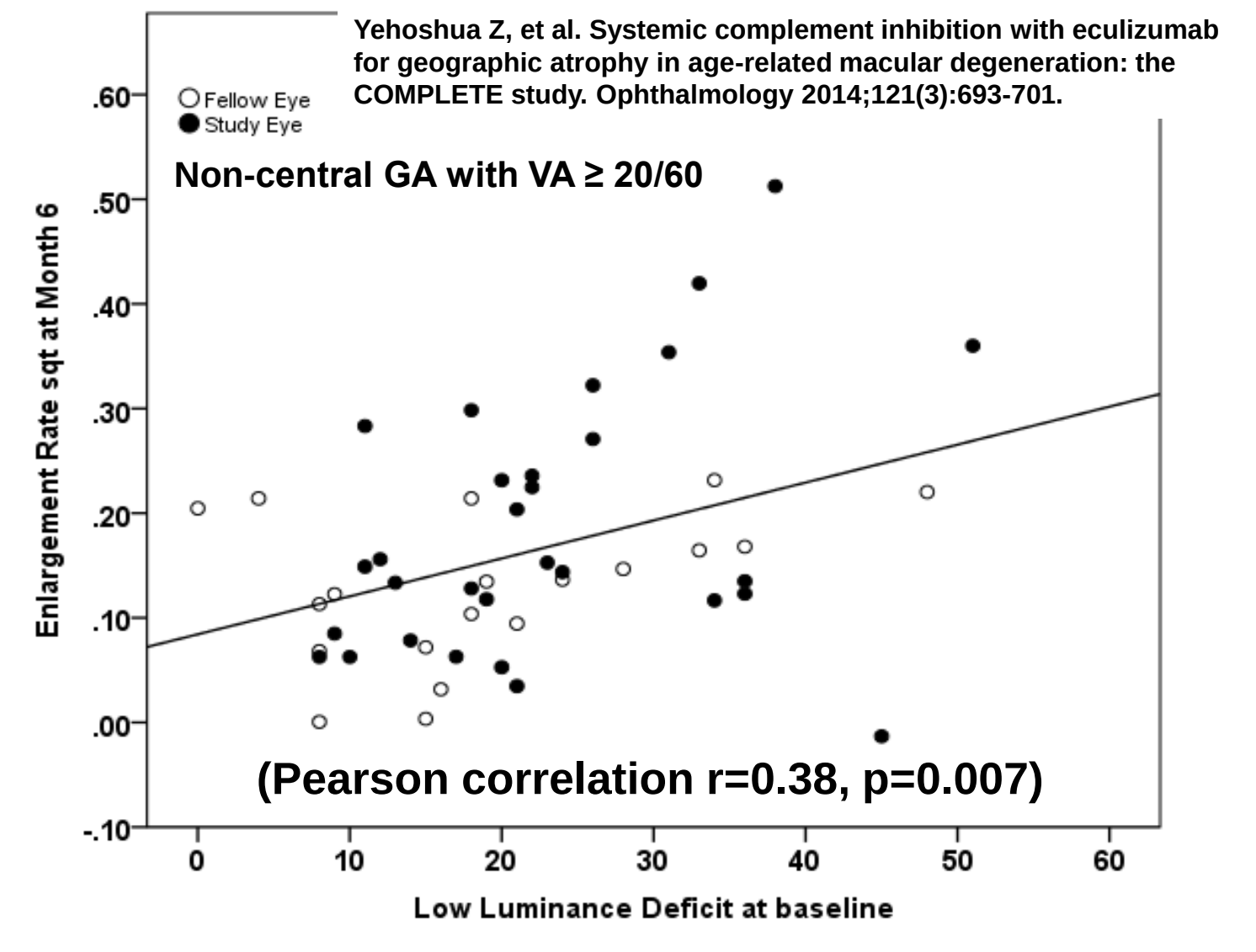
Low Luminance Deficit = Normal Luminance VA score - Low Luminance VA Score

Sunness JS , Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Ophthalmology. 2008 Sep;115(9):1480-8

2.0-log unit neutral density filter (filter lowers luminance by 100-fold), Kodak Wratten filter; Kodak, Rochester, NY

COMPLETE Study: Geographic atrophy

Low Luminance Deficit Predicts Growth Rate



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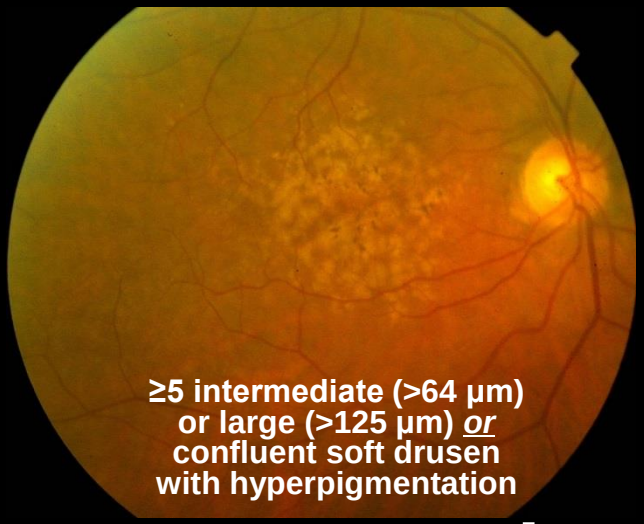
  - Delayed dark adaptation

Phenotype Enrichment Depends on The Surrogate Endpoint

- **Surrogate anatomic endpoints:**
  - **Growth of geographic atrophy (color, autofluorescence, or OCT *en face* imaging)**
  - **Progression to neovascular AMD**
  - **Change in drusen area and/or volume**
  - **Progression from drusen to GA (in AREDS, 95% of GA had drusen)**
  - **Progression of AREDS severity scale**
  - **Changes in retinal/RPE/choroidal anatomy using a variety of imaging strategies**

Anecortave Acetate Risk Reduction Trial (Alcon Research. Ltd/Novartis)



- Prevent progression from high-risk intermediate AMD (soft drusen, pigment hyperplasia within 3000µm) to wet AMD
- Wet AMD in fellow eye
- Incidence of sight-threatening CNV in 4 years estimated at 33%

Ferris FL, *et al.* A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. Arch Ophthalmol 2005;123(11):1570-4.

Anecortave Acetate Risk Reduction Trial (Alcon Research. Ltd/Novartis)

- 2596 patients enrolled worldwide
- At Month 48:
  - Estimated 80% power to detect a 30% reduction in CNV
  - Estimated 92% power to detect a 35% reduction in CNV
- After interim analysis at 2 years, study stopped, never published
- Successful enrollment proves feasibility of this surrogate study design

Ferris FL, *et al.* A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. Arch Ophthalmol 2005;123(11):1570-4.

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  - **Progression of AREDS severity scale**
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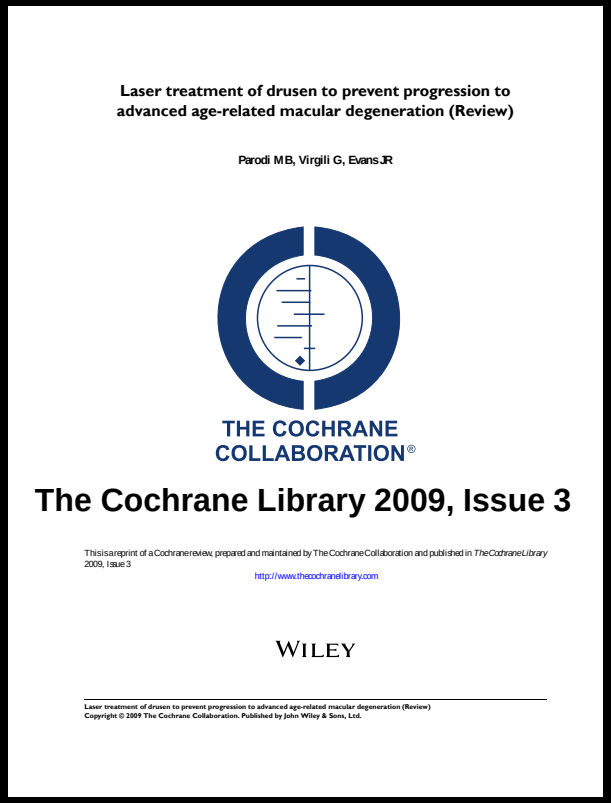
Treatment of Drusen with Laser: Slow Progression to VA loss, CNV, and GA



Laser treatment of drusen to prevent progression to advanced age-related macular degeneration (Review)

Parodi MB, Virgili G, Evans JR

THE COCHRANE COLLABORATION®

The Cochrane Library 2009, Issue 3

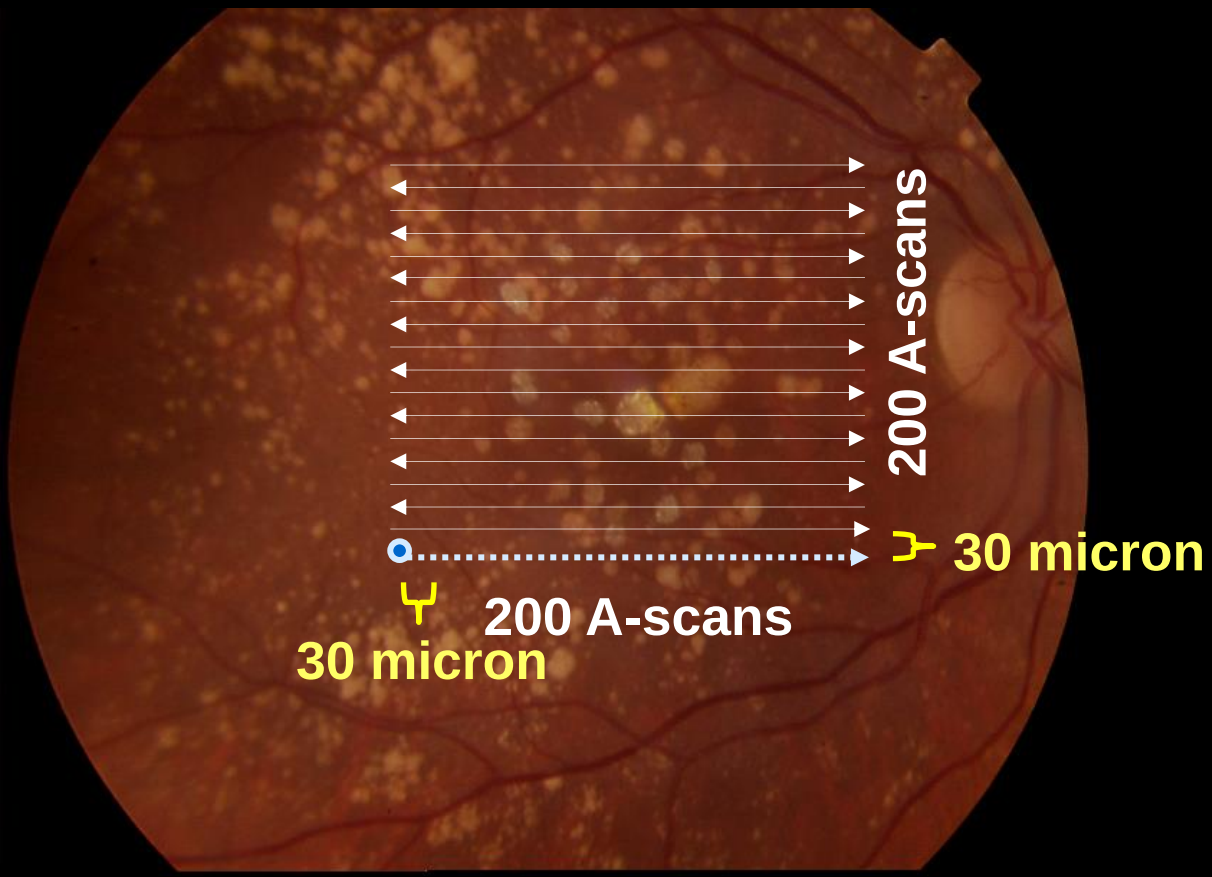
This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

http://www.thecochranelibrary.com

WILEY

- 9 studies, 2216 subjects randomized
- No evidence that disappearance of drusen reduced risk of developing CNV, GA or visual acuity loss

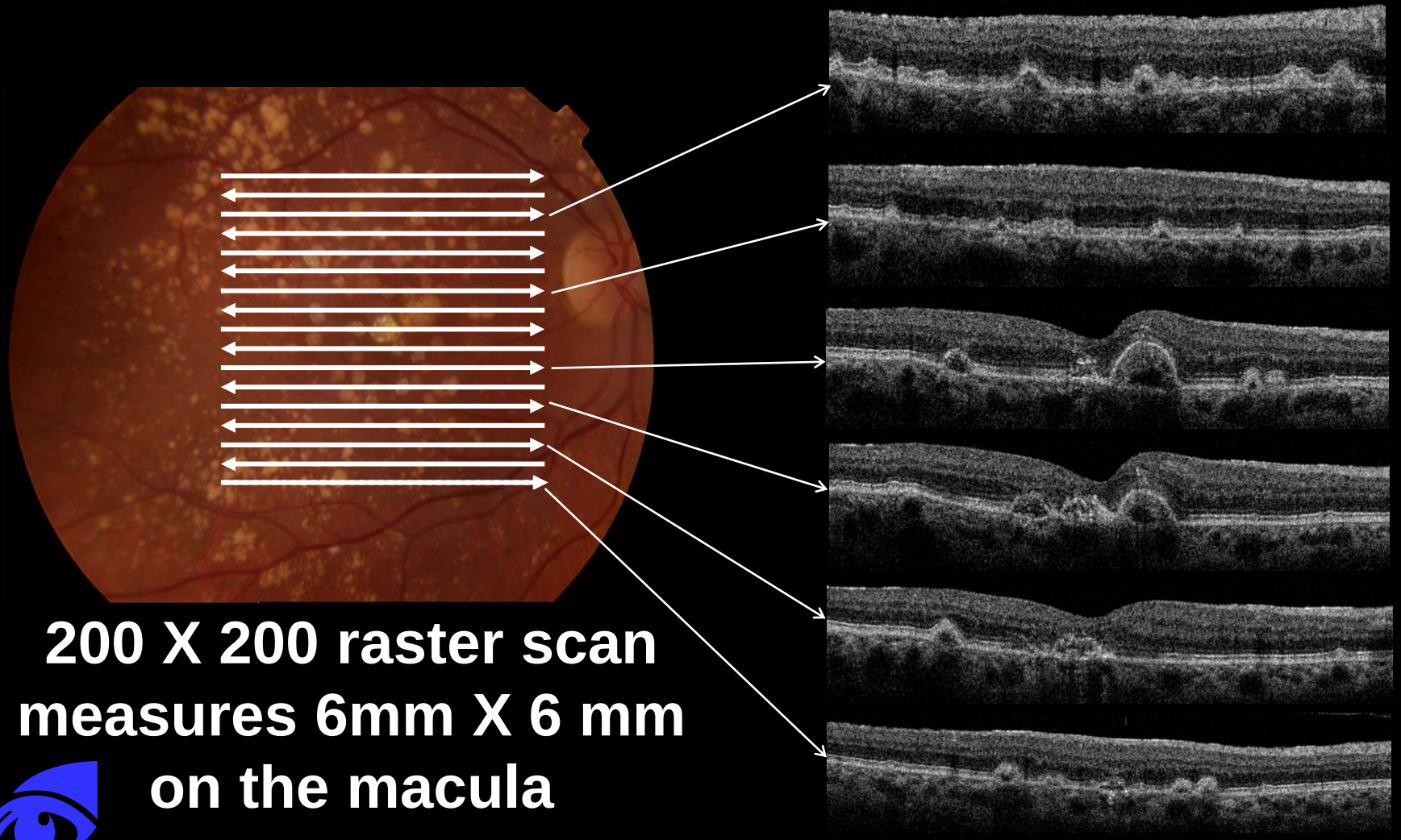
Cirrus SD-OCT Measurement of Drusen using the 200 X 200 Raster Scan Pattern: 6mm X 6mm



40,000 A-scans

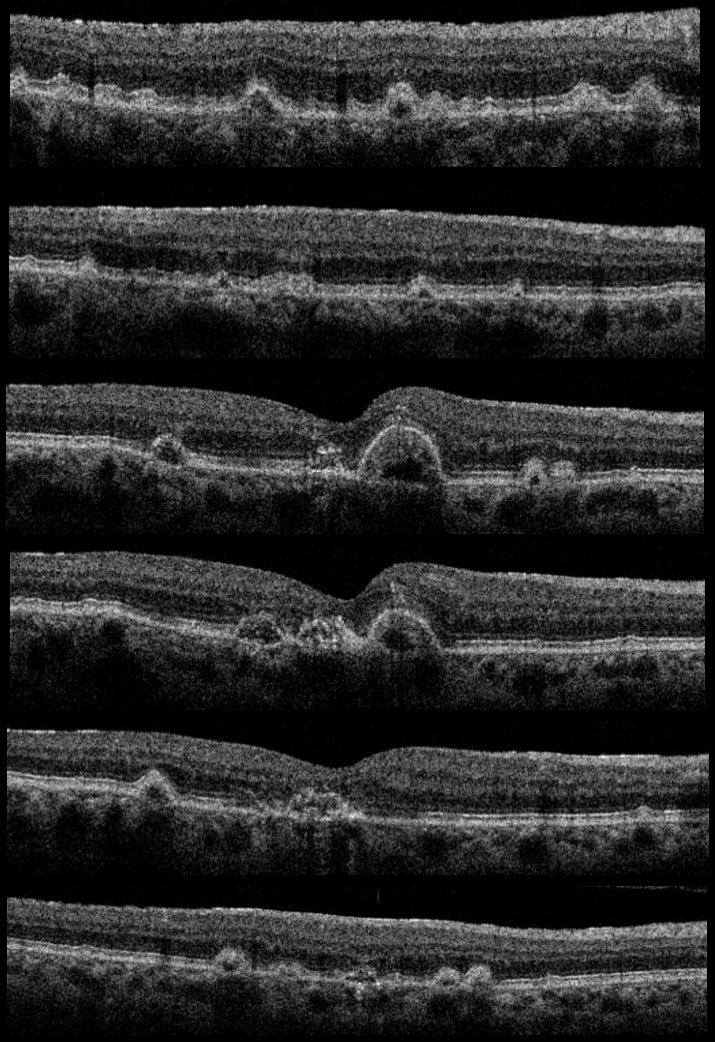
Equal distances between A-scans and B-scans

Cirrus SD-OCT Fundus Scanning Pattern
200 X 200 A-scans (6mm X 6mm)

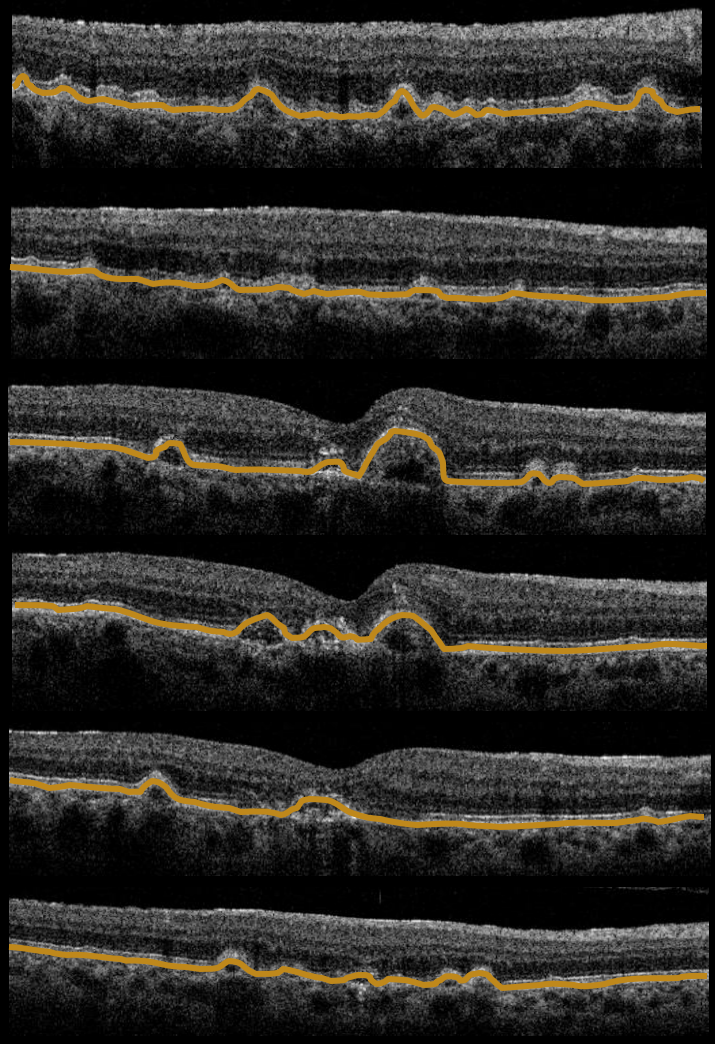


200 X 200 raster scan measures 6mm X 6 mm on the macula

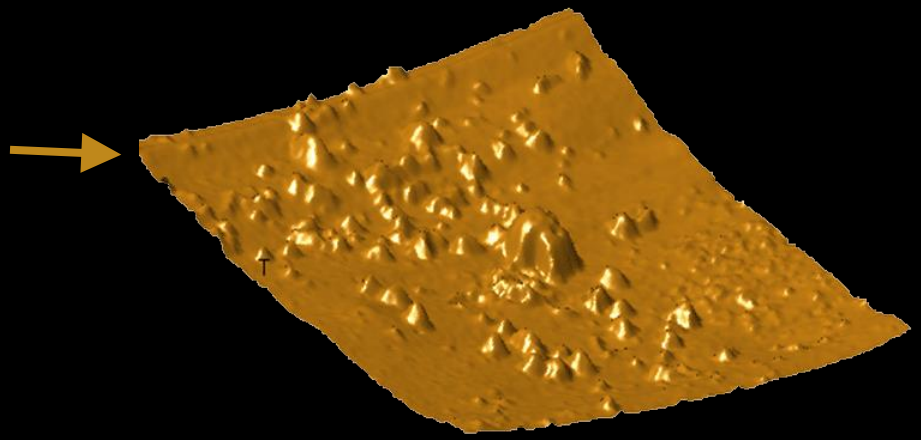
Segmentation Algorithms



Segmentation Algorithms



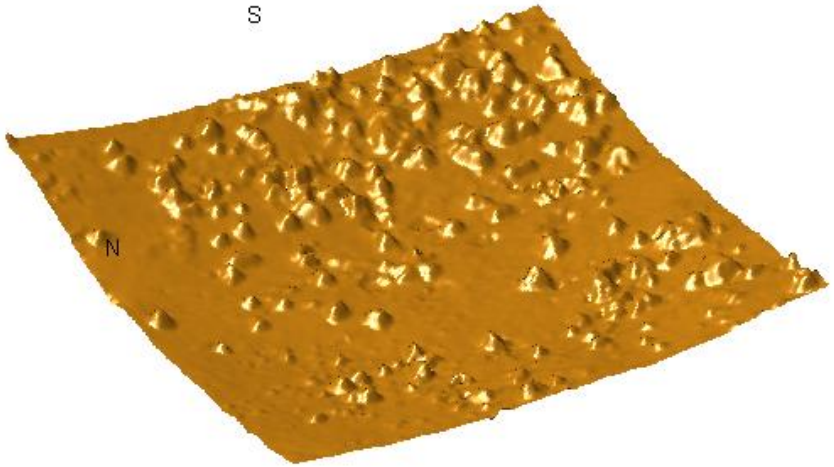
RPE Segmentation



Also available on the Topcon SDOCT instrument

Measuring RPE Elevations: Subtract “RPE Floor” from “RPE Elevations”

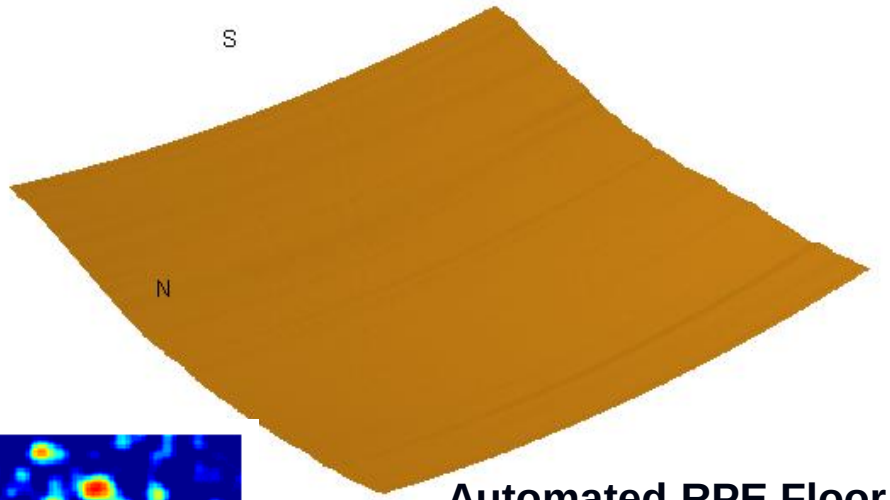
RPE Elevations



RPE Elevations

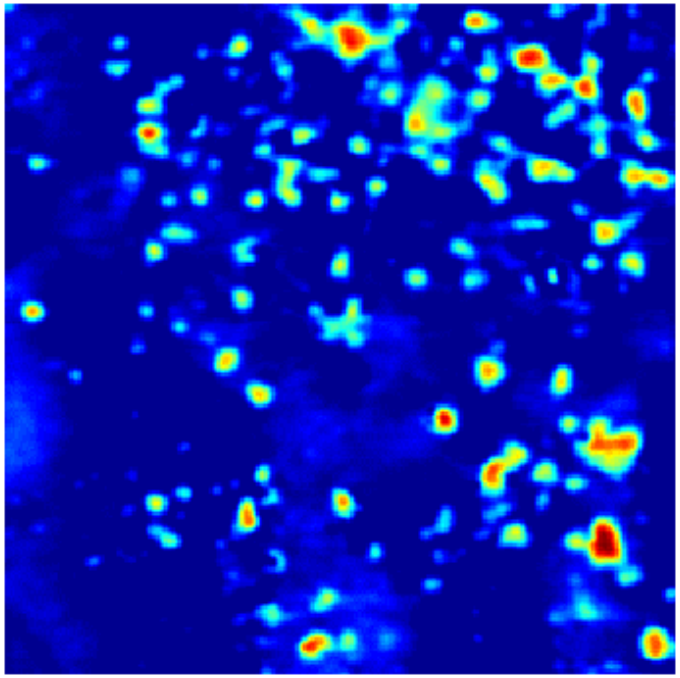
–

Virtual RPE Floor



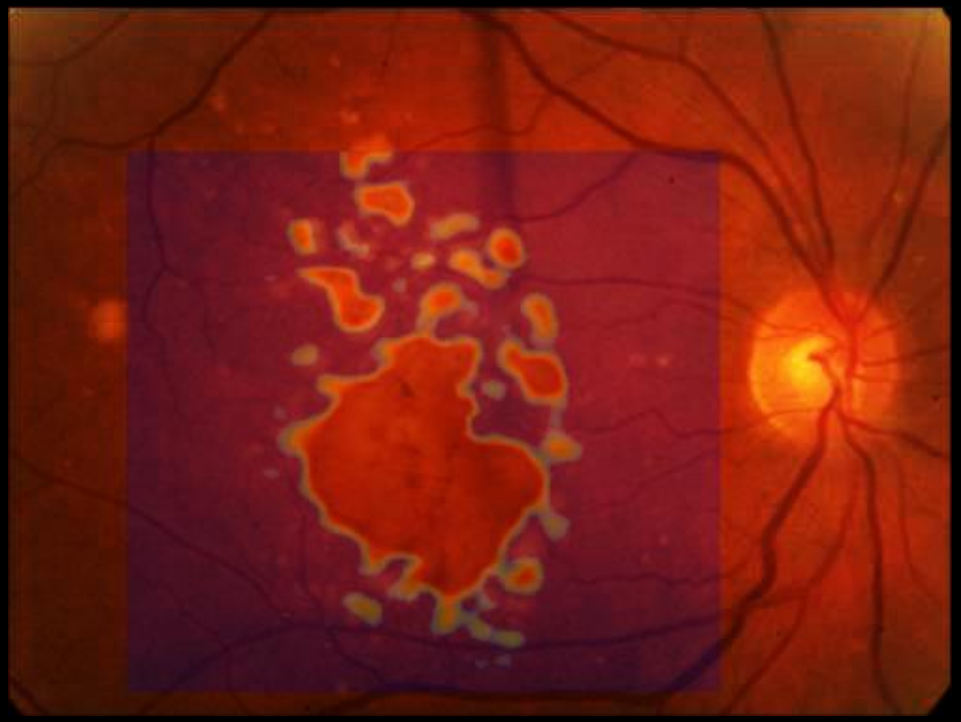
Automated RPE Floor

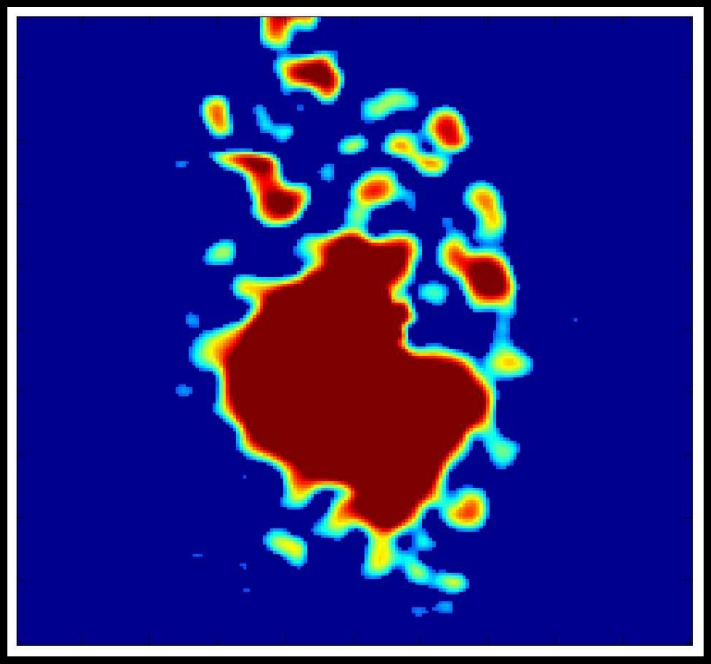
RPE Difference Map (Drusen)



Area and Volume Measurements

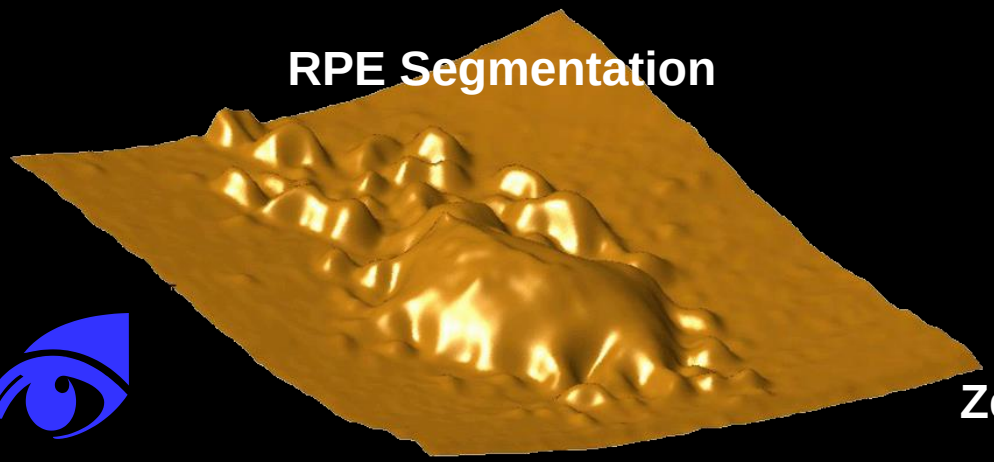
Drusen: Volume and Area Measurements





Area: 5.21 mm²

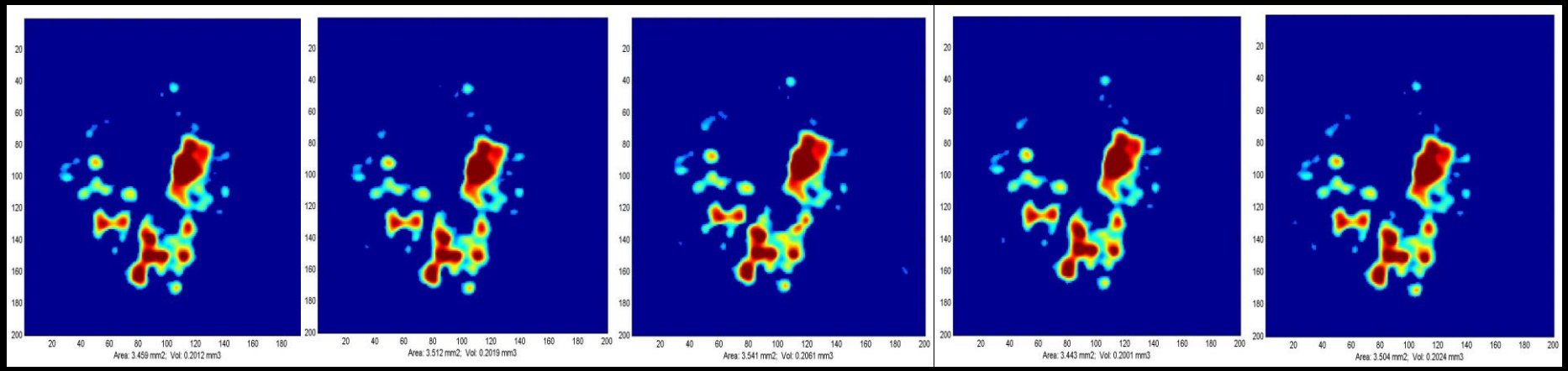
Volume: 0.899 mm³



Zeiss *Cirrus* SDOCT, Ver. 6.0 software

Reproducibility of Drusen Measurements

- 103 eyes from 74 patient
- 5 separate SD-OCT scans at the same visit
- Highly reproducible



Mean Area = 3.49mm^2 (SD=0.04)

Mean Volume = 0.202mm^3 (SD=0.002)

Gregori et al. Ophthalmology. 2011 Jul;118(7):1373-9

Natural History of Drusen in the Absence of Any Geographic Atrophy Using SDOCT Imaging

- 143 eyes
- Followed up to 24 months
- Different progression patterns observed
  - Increase: 48%/yr
  - Stable: 40%/yr
  - Decrease: 12%/yr

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

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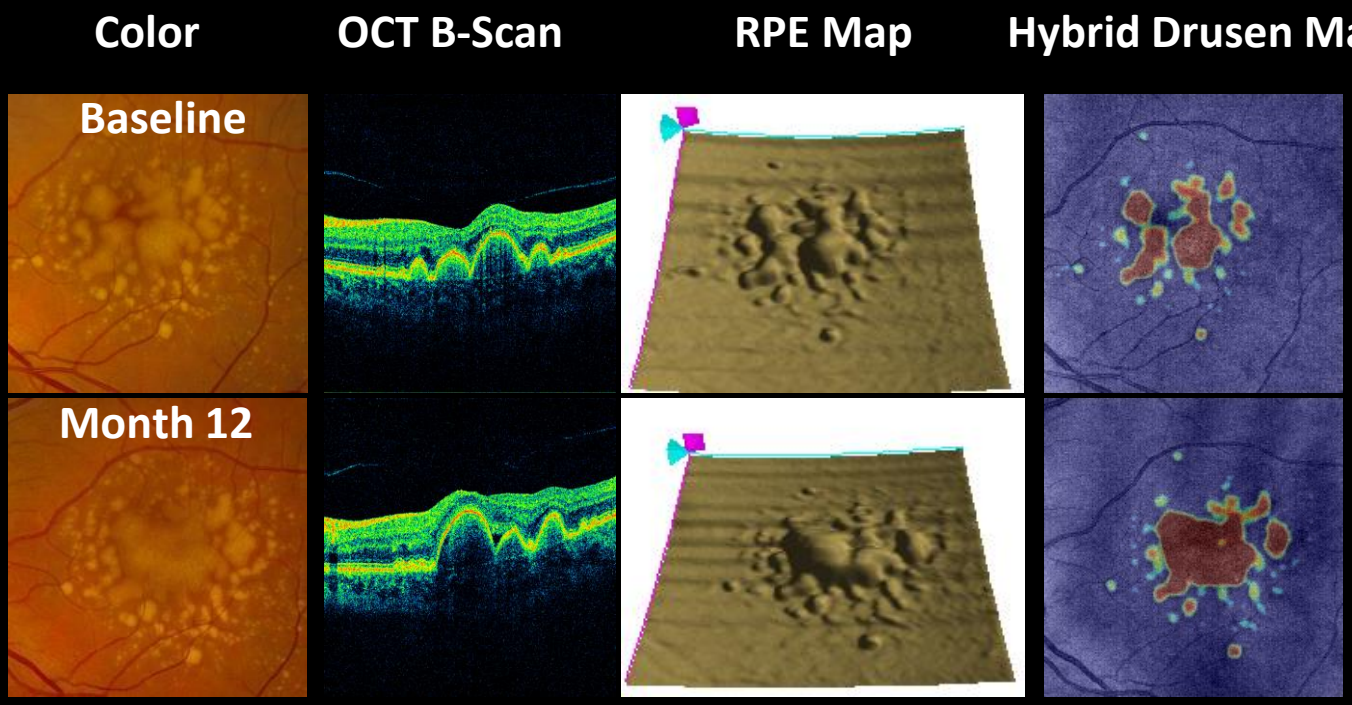
Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Increase in Drusen Area and Volume: 48%/yr



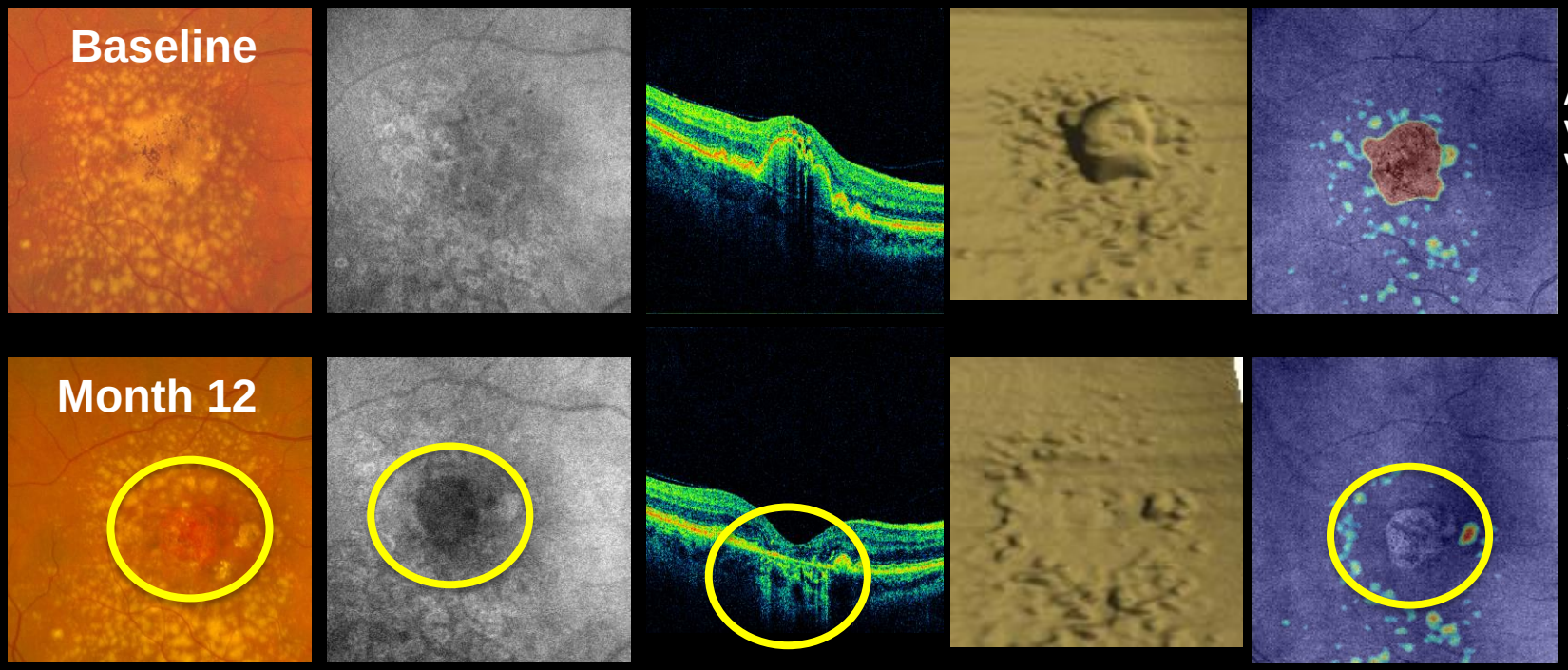
Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Decrease in Drusen Area and Volume: 3 Possible Outcomes

- Formation of geographic atrophy
- Formation of CNV
- No significant anatomic abnormality identified

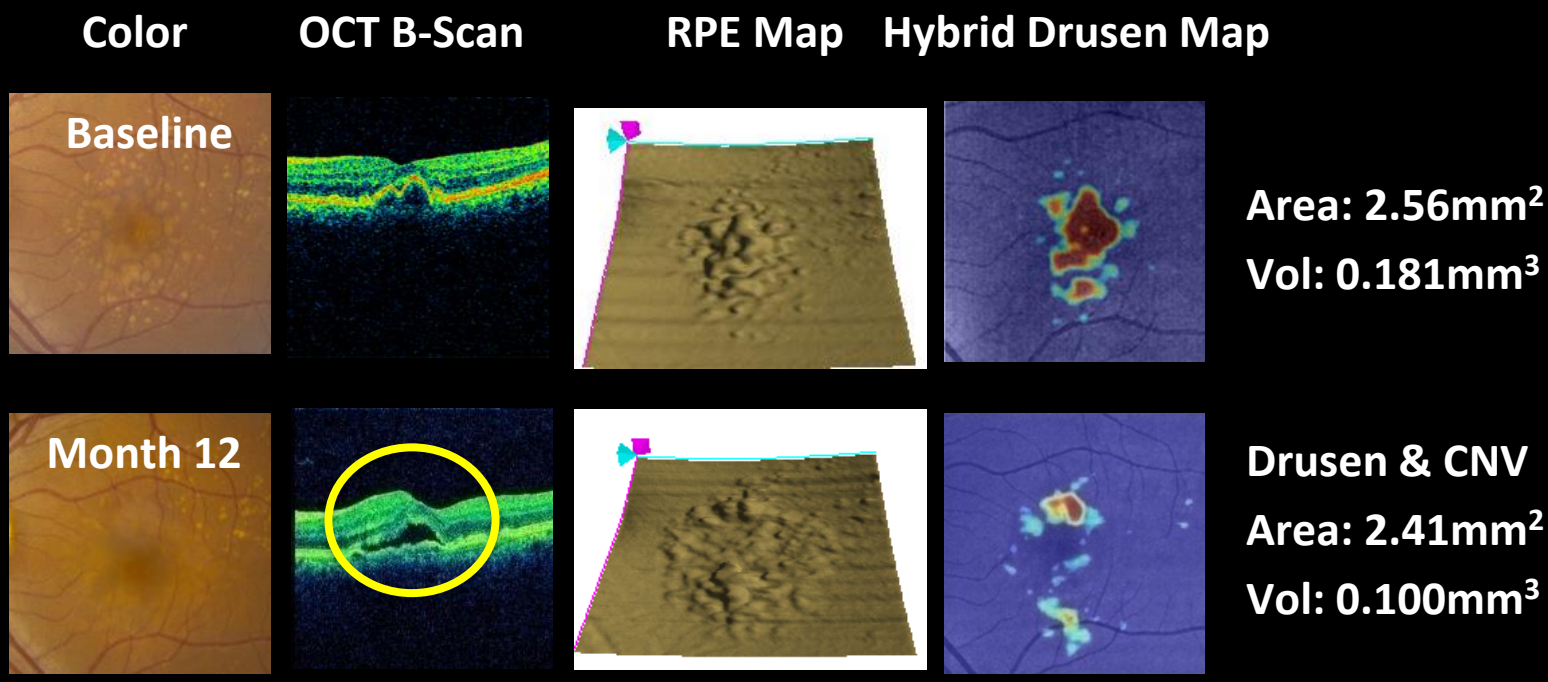
Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Decrease in Drusen Area and Volume with Formation of GA: 4.5%/yr



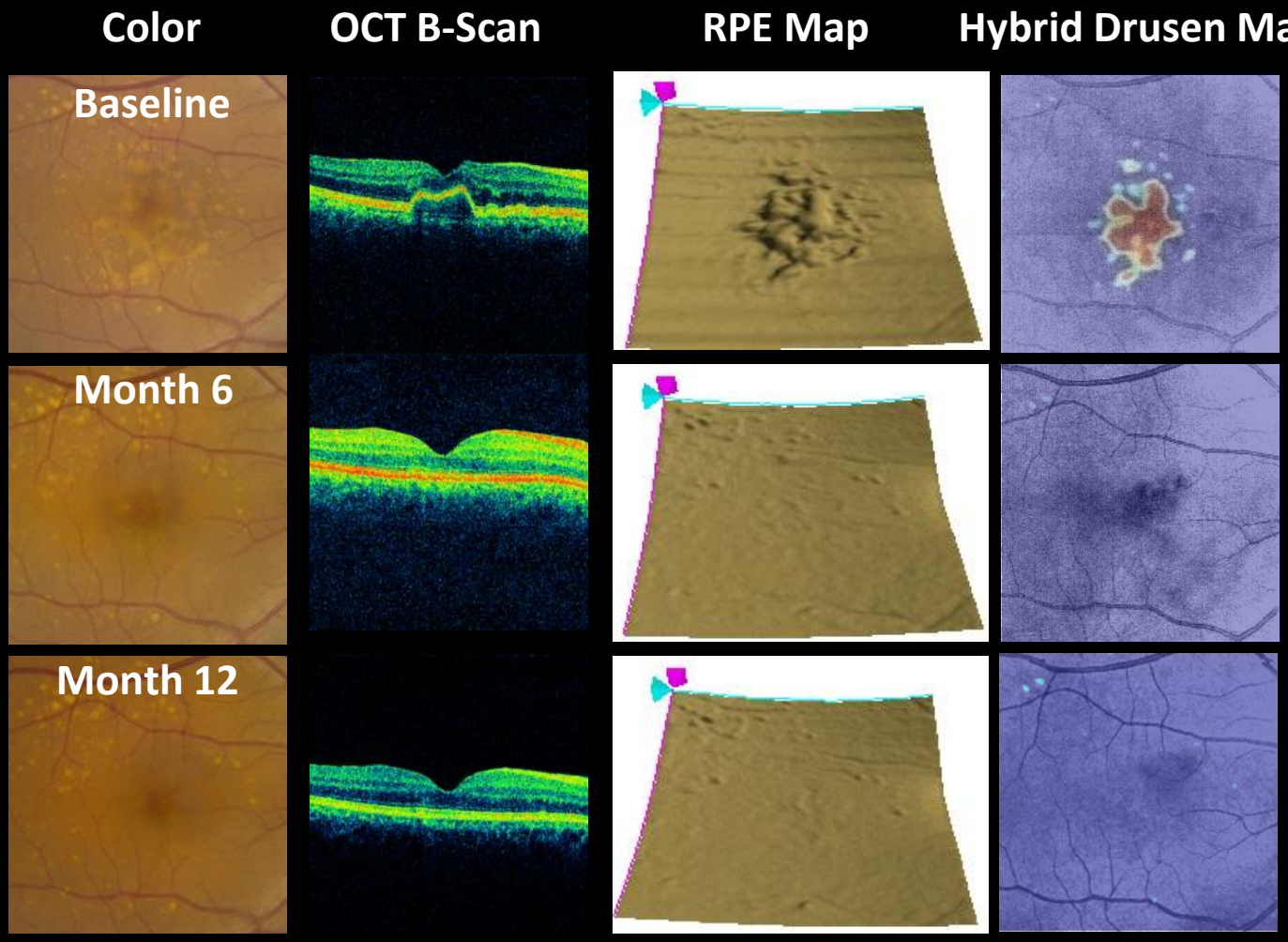
Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Decrease in Drusen Area and Volume with Formation of CNV: 3.5%/yr



Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Decrease in Drusen Volume > 50% Without Formation of GA or CNV: 4%/yr



Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Placement of 3 mm and 5 mm Diameter Circles Centered on the Fovea

Automatic algorithm registers the OCT fundus image with color fundus image

Gregori et al. Ophthalmology. 2011 Jul;118(7):1373-9

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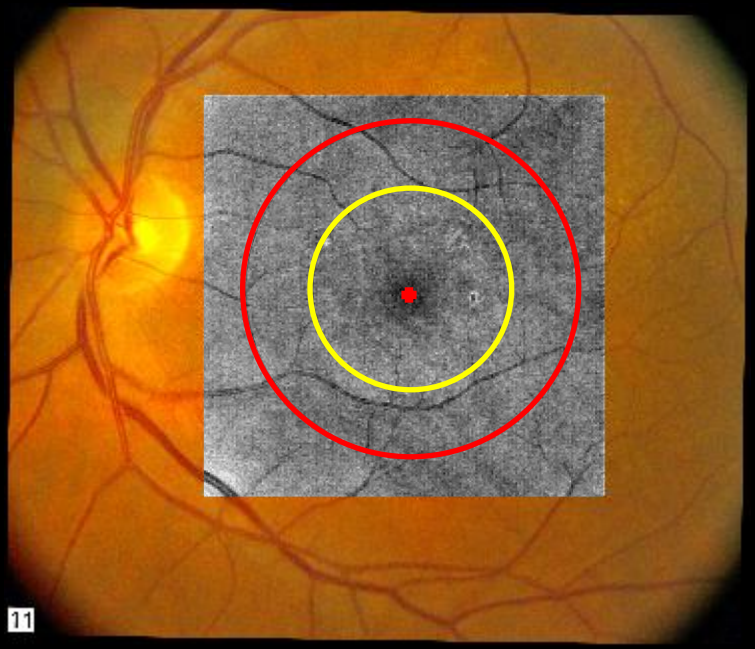

Gregori et al. Ophthalmology. 2011 Jul;118(7):1373-9

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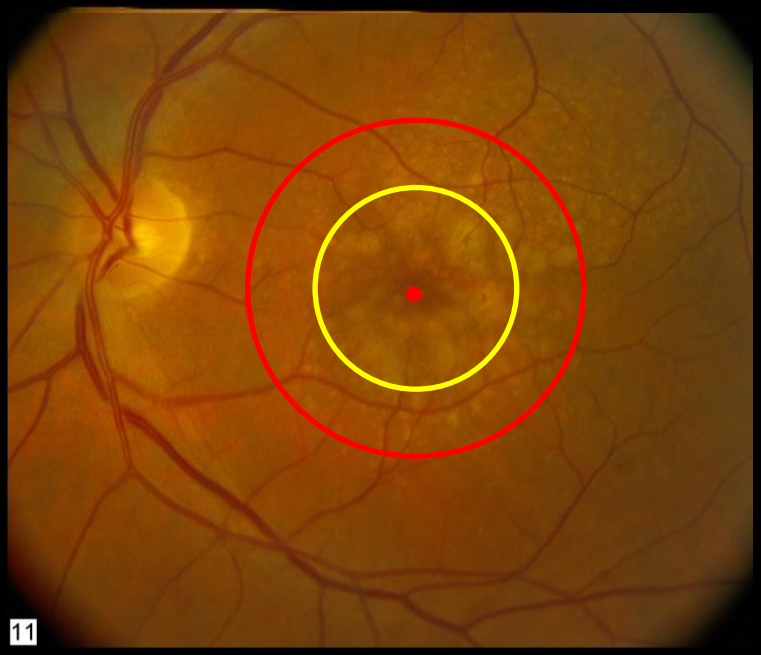
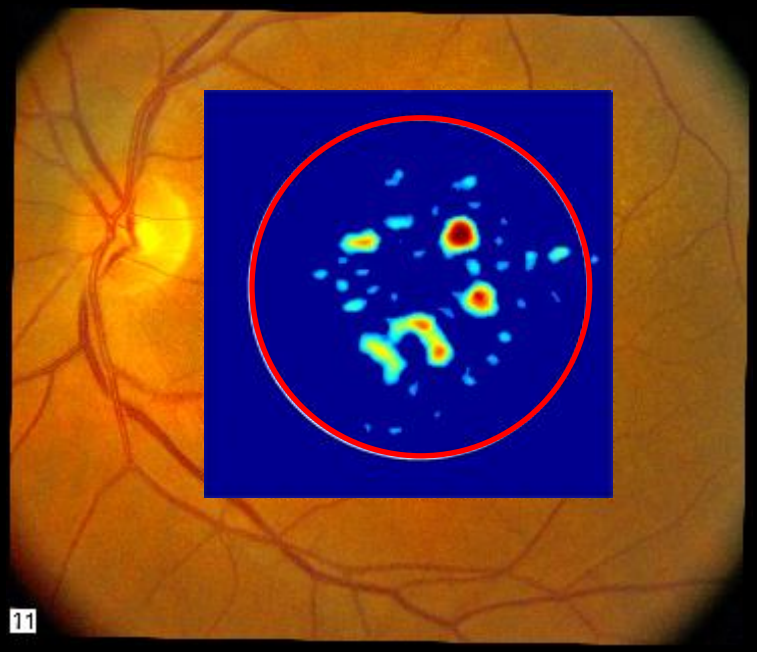


Gregori et al. Ophthalmology. 2011 Jul;118(7):1373-9

Quantification of Drusen with the 3 mm and 5 mm Diameter Circles Centered on the Fovea



Gregori et al. Ophthalmology. 2011 Jul;118(7):1373-9

Decrease in Drusen Volume > 50% Without Formation of GA or CNV as a Clinical Trial Endpoint

Natural History of Drusen Morphology in Age-Related Macular Degeneration Using Spectral Domain Optical Coherence Tomography

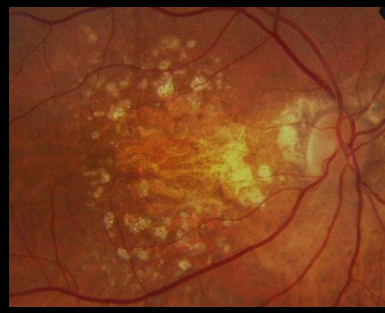
Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Table 7. Sample Size Table for Comparing Successful Outcomes in Treatment and Control Groups Depending on the Presumed Percent Treatment Success* and the Percent Power of a Study to Detect a Positive Outcome if One Exists

Ratio of Experimental to Control Randomized Eyes	Percent with Successful Outcomes in Control Group	Number of Eyes Needed in Each Group Based on the Anticipated Percent with Successful Outcomes* and the Desired Power to Detect the Outcome†					
		75%*		50%*		25%*	
		80% Power	90% Power	80% Power	90% Power	80% Power	90% Power
1:1	5%	9:9	11:11	18:18	23:23	59:59	75:75
2:1	5%	14:7	16:8	28:14	34:17	92:46	116:58

*A successful outcome was defined as shrinkage to <50% of baseline cube root volume without progression to geographic atrophy or neovascular disease.
†The number of eyes needed in each group was the same whether the follow-up interval was 6 or 12 months.

Phase II Eculizumab Study Bascom Palmer Eye Institute



Inclusion:

High Risk Drusen

OR

Geographic Atrophy

Drusen Cohort
N = 30
2:1 Randomization

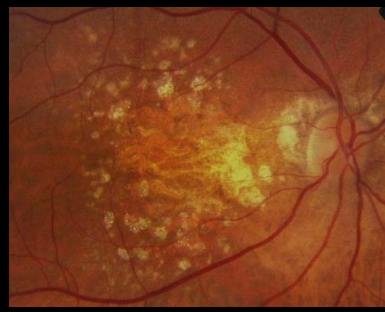
Eculizumab/Placebo

26 weeks

GA Cohort
N = 30
2:1 Randomization

Follow-up through one year

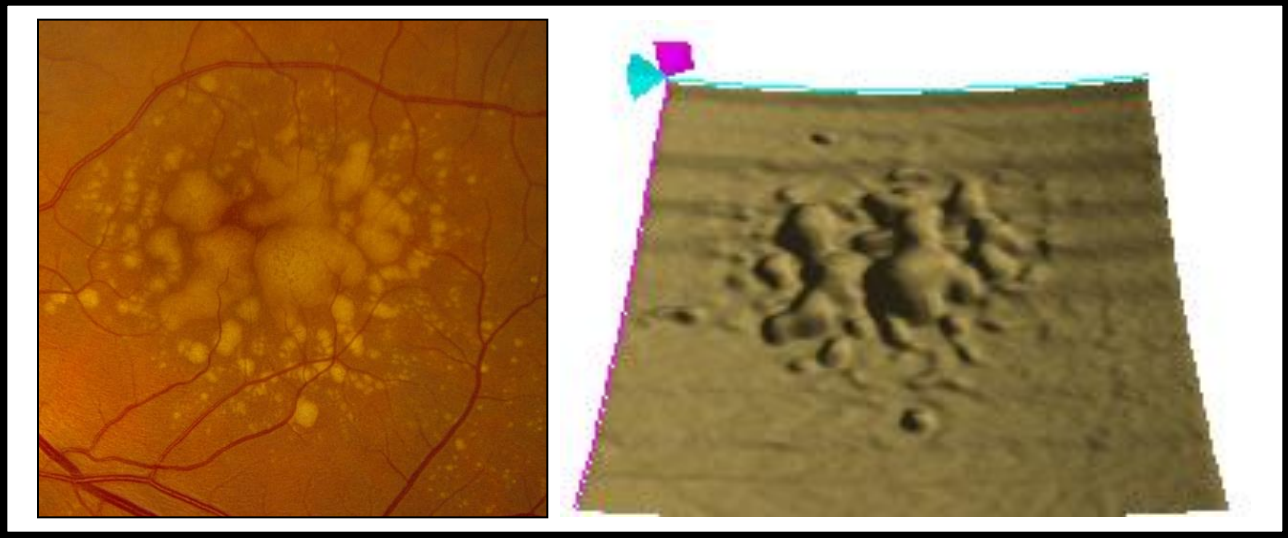
ClinicalTrials.gov Identifier: NCT0093588



Phase II Eculizumab Study: Bascom Palmer Eye Institute

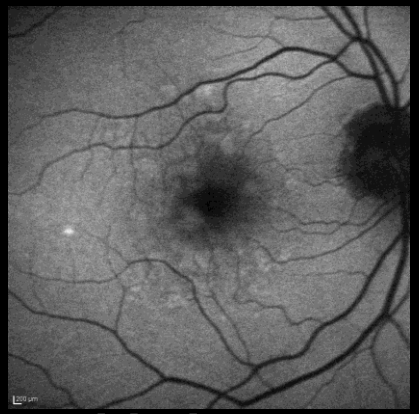
Drusen Cohort
N = 30

Visual Acuity: 20/63 or better
Drusen Volume ≥ 0.030 mm^3
No evidence of GA

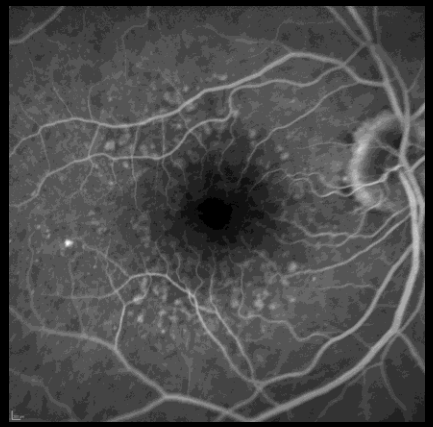


Color Fundus

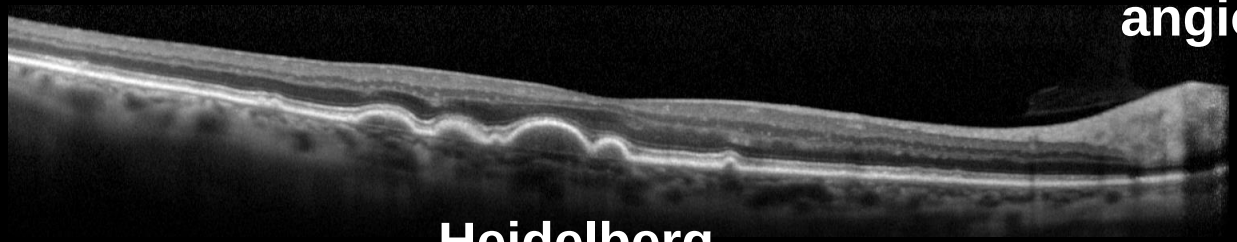
Topcon AF



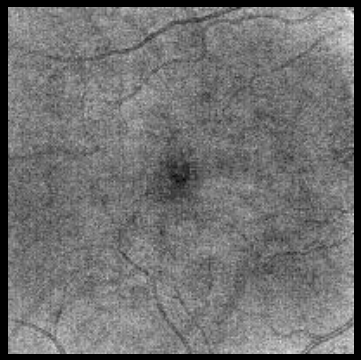
Heidelberg AF



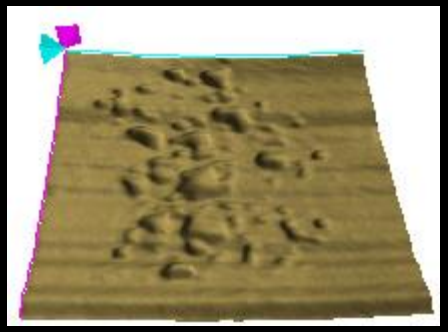
Fluorescein angiography



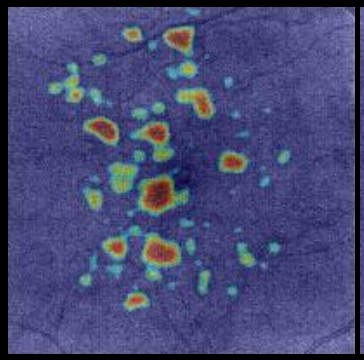
Heidelberg OCT



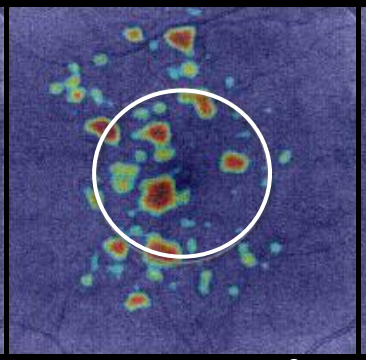
OCT Fundus Image



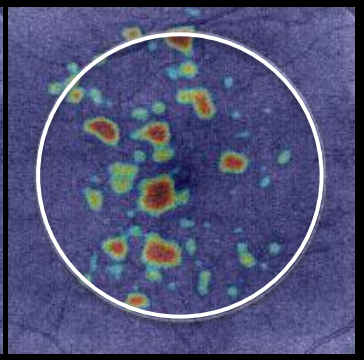
RPE map



Area : 4.29 mm^2
Vol : 0.208 mm^3



Area : 2.28 mm^2
Vol : 0.118 mm^3

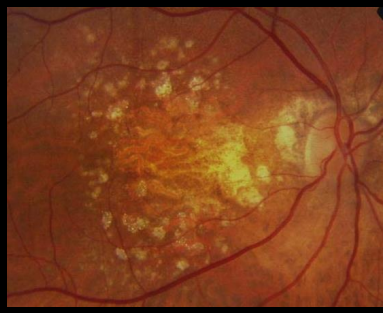


Area : 4.02 mm^2
Vol : 0.197 mm^3

Zeiss Cirrus Ver. 6.0 software

P1264_OD_100809

Phase II Eculizumab Study Bascom Palmer Eye Institute



Can Eculizumab Decrease Drusen Volume > 50% Without Formation of GA or CNV as a Clinical Trial Endpoint?

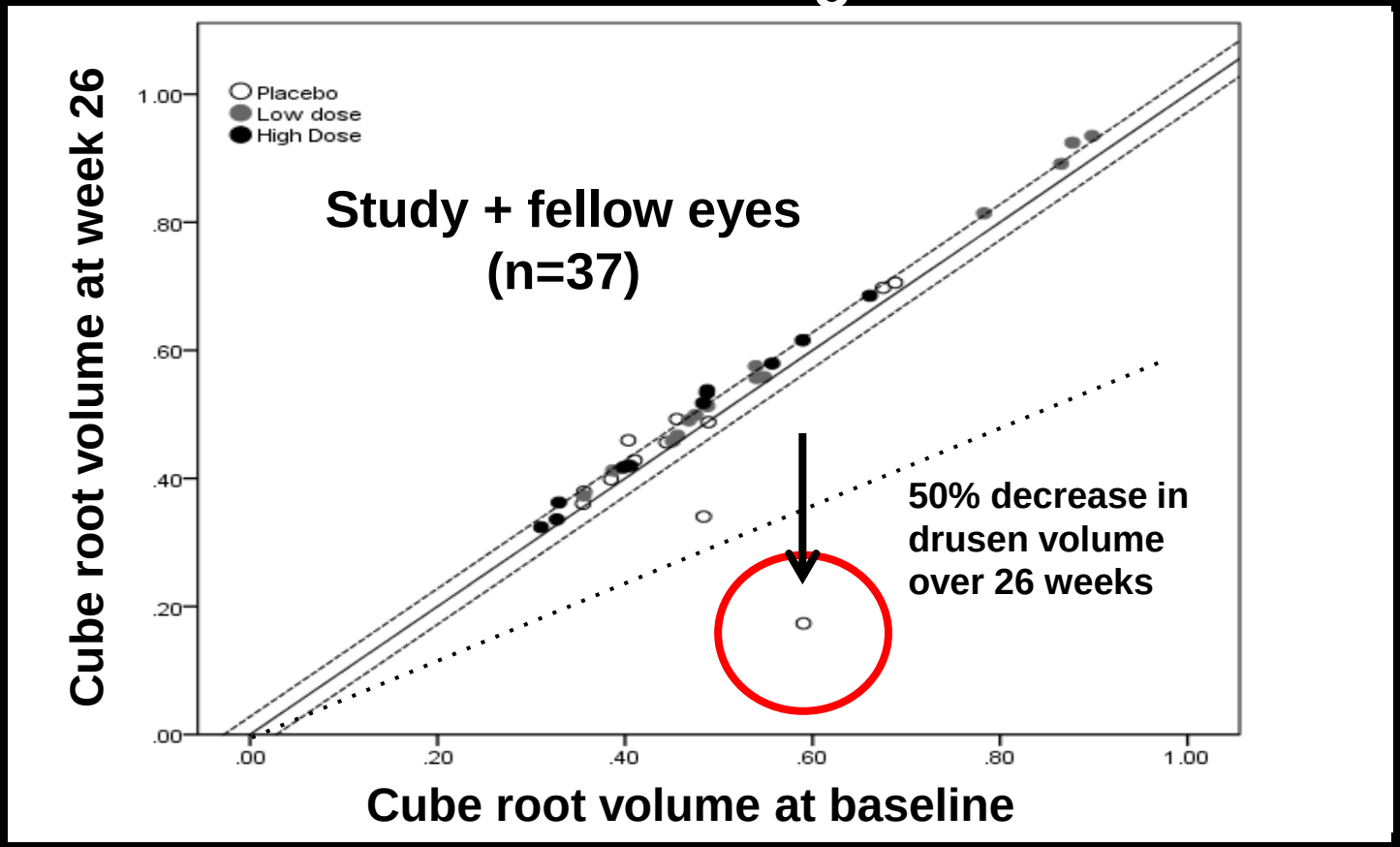
Change in Drusen Volume as a Novel Clinical Trial Endpoint for the Study of Complement Inhibition in Age-related Macular Degeneration

Carlos Alexandre de Amorim Garcia Filho, MD; Zohar Yehoshua, MD, MHA; Giovanni Gregori, PhD; Renata Portella Nunes, MD; Fernando M. Penha, MD, PhD; Andrew A. Moshfeghi, MD, MBA; Kang Zhang, MD, PhD; William Feuer, MS; Philip J. Rosenfeld, MD, PhD

Garcia et al., 2014, OSLI-RETINA, January/February Vol.45, No. 1

COMPLETE Study: Drusen Outcomes

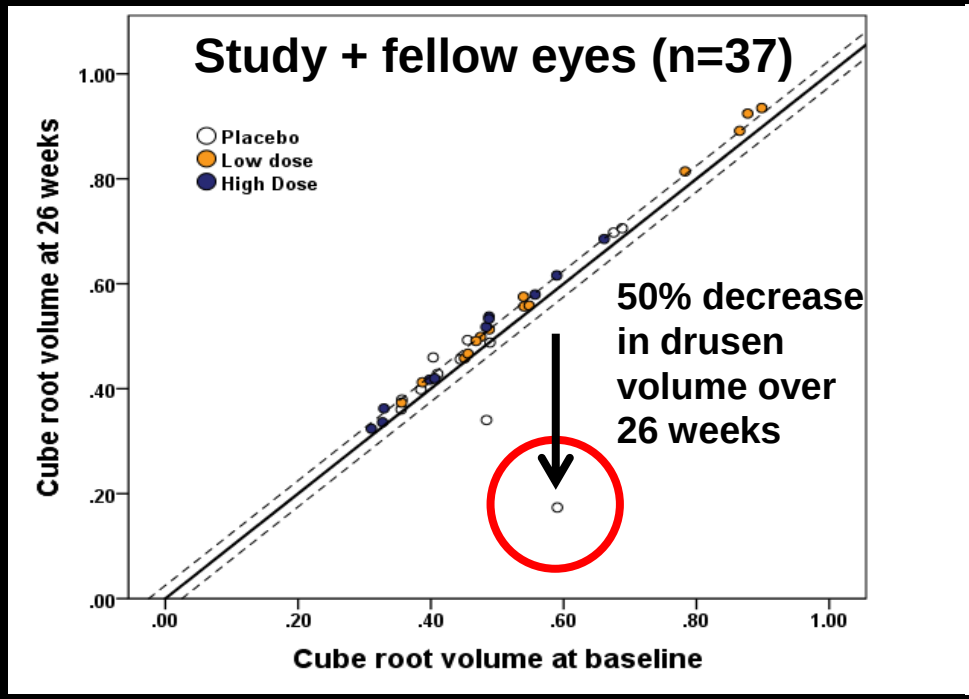
Drusen Volume Change at 26 Weeks



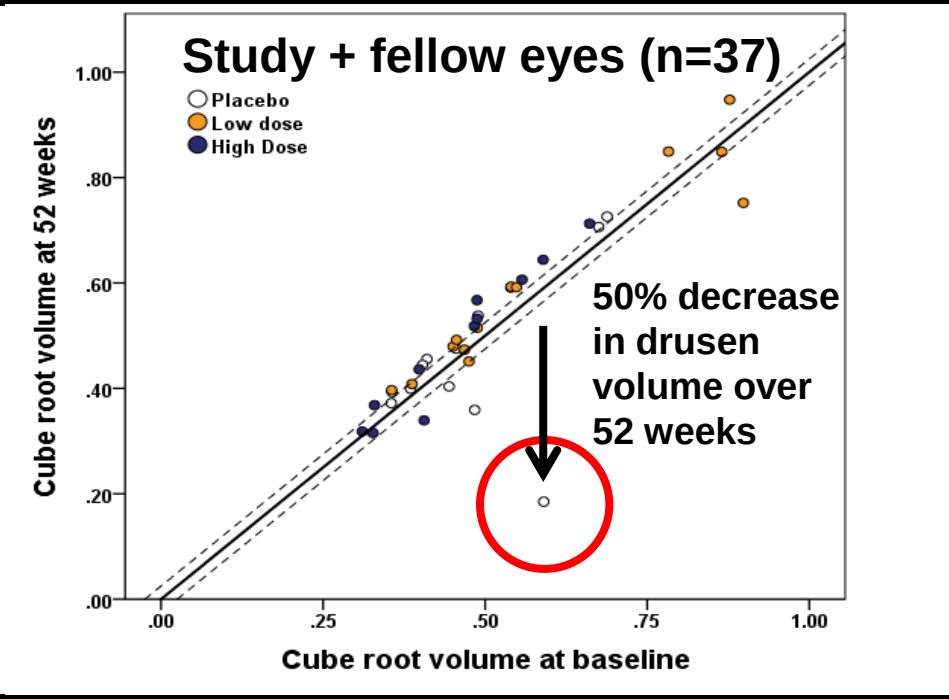
- Active vs placebo for drusen: p=0.15
- Outcome effectively ruled out a 22% or greater success rate for reducing drusen volume
  - based on the 95% confidence interval between treatment groups

COMPLETE Study: Change in Drusen Volume Over 52 weeks

Week 26 Outcome



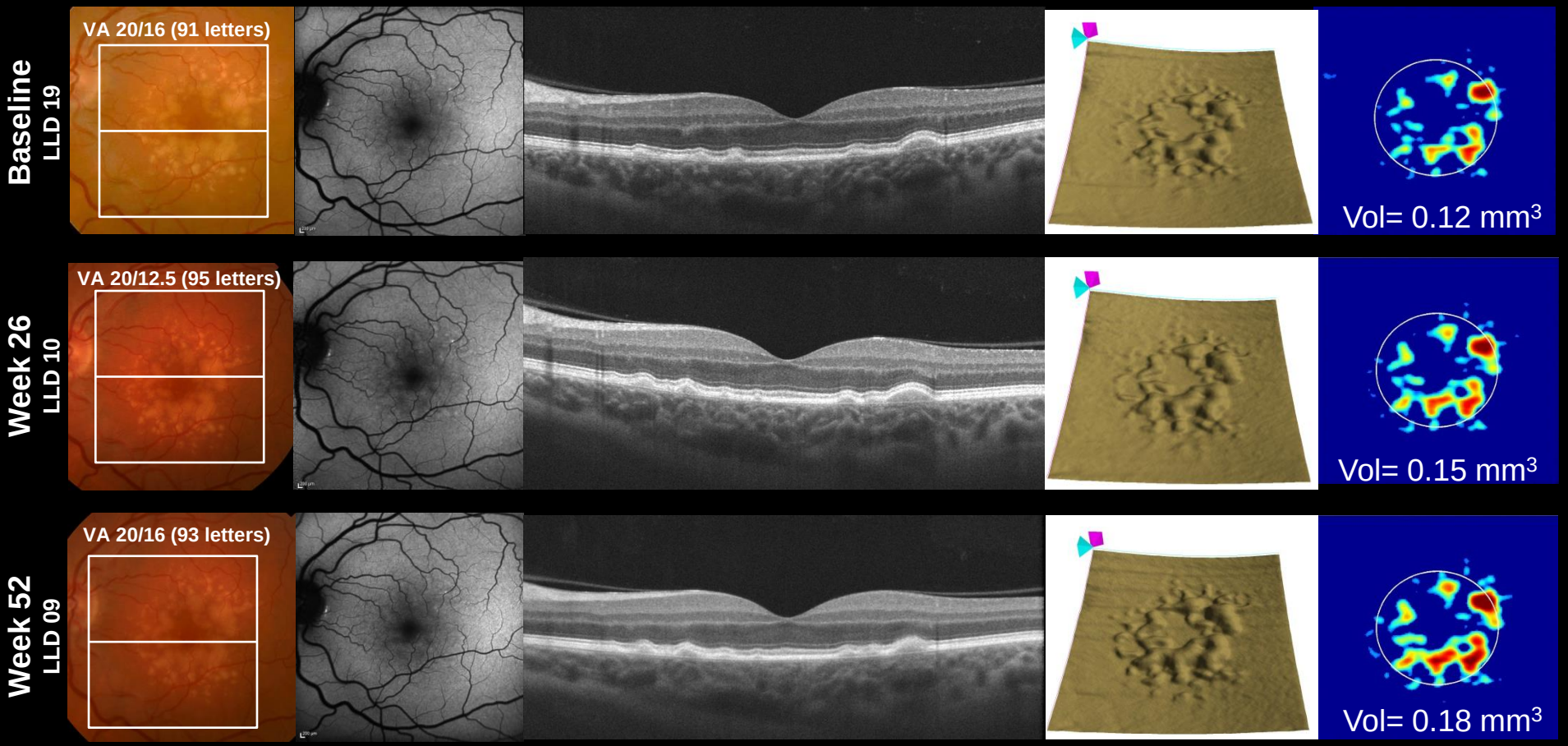
Week 52 Outcome



- Change in drusen volumes over 26 and 52 weeks consistent with natural history data

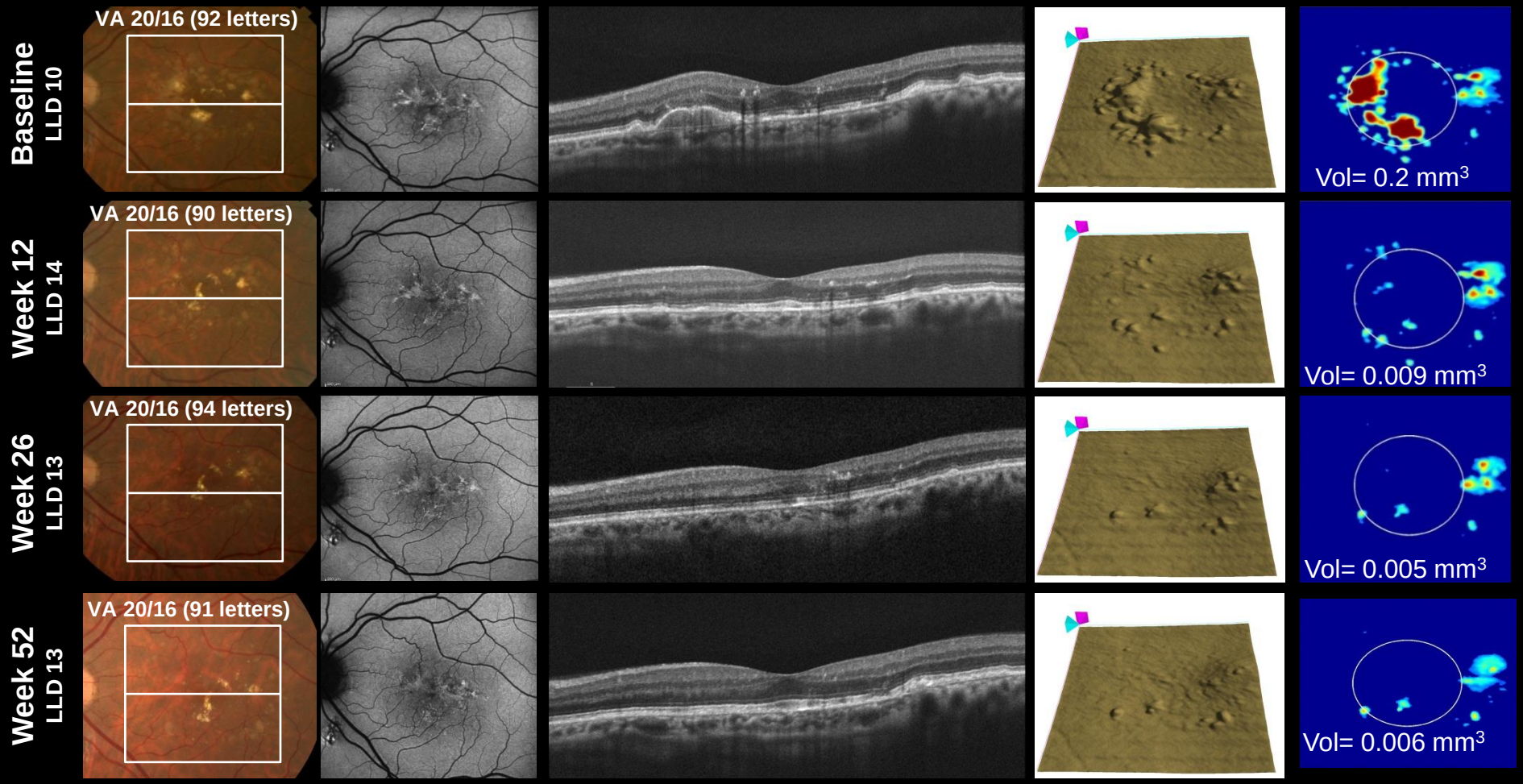
COMPLETE Study: Drusen Examples

Increase in Drusen Volume



COMPLETE Study: Drusen Examples

Decrease in Drusen Volume



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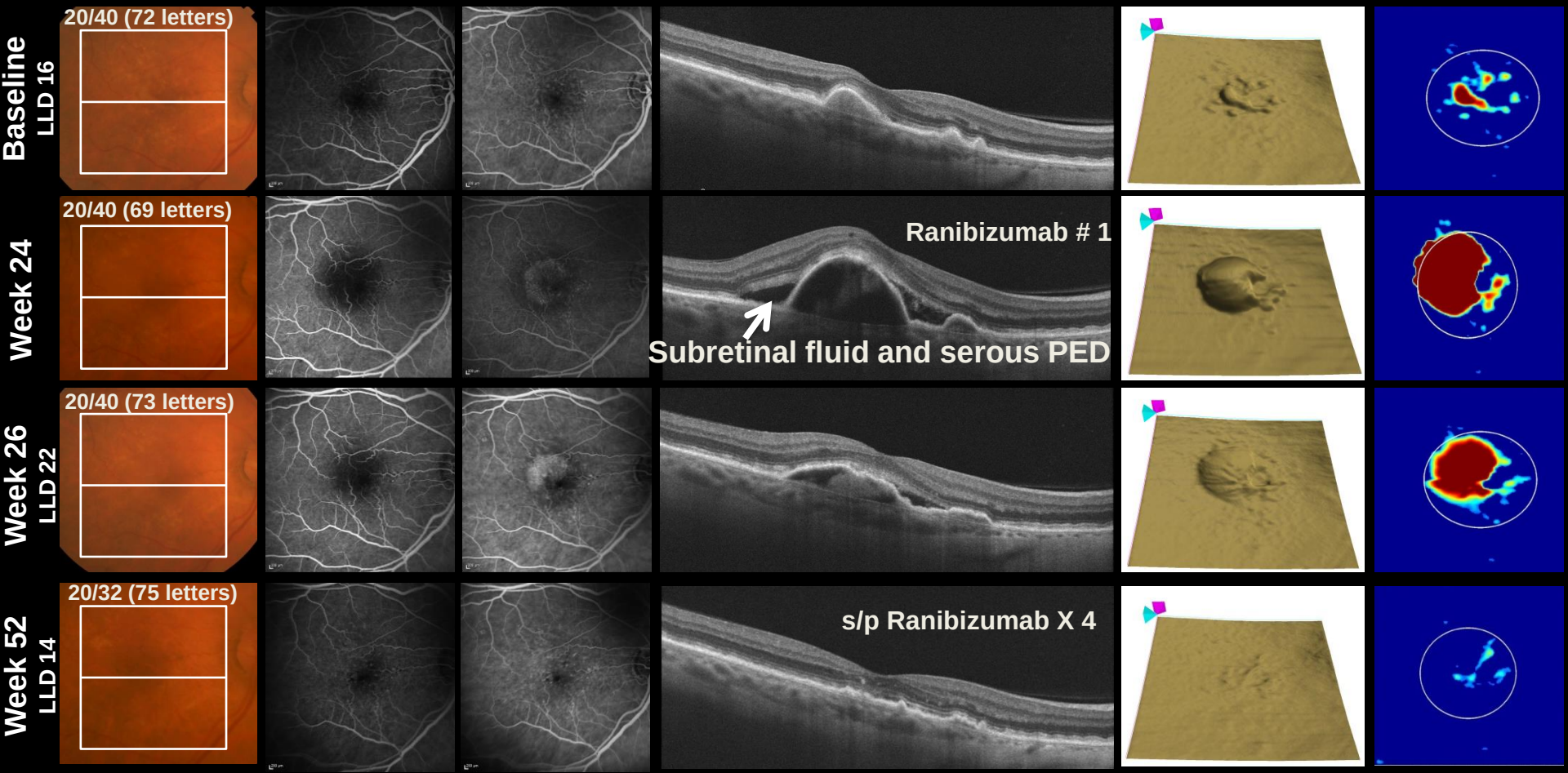
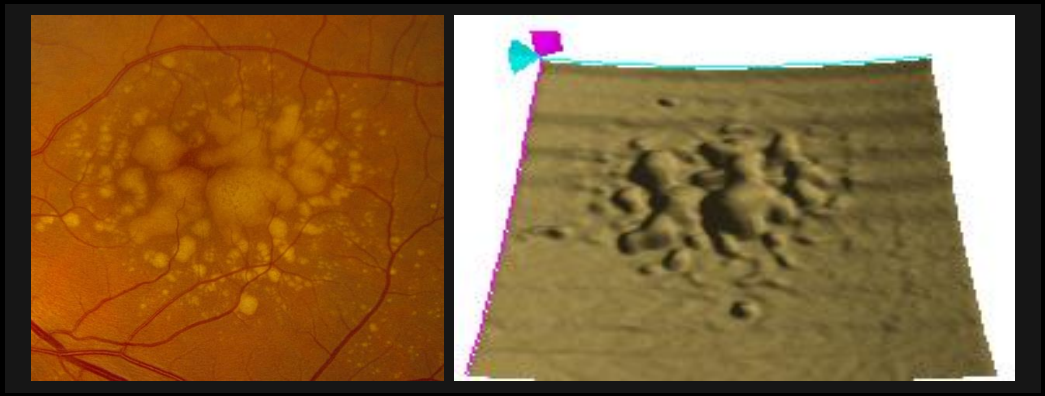
COMPLETE Study: Drusen Examples

Conversion to CNV



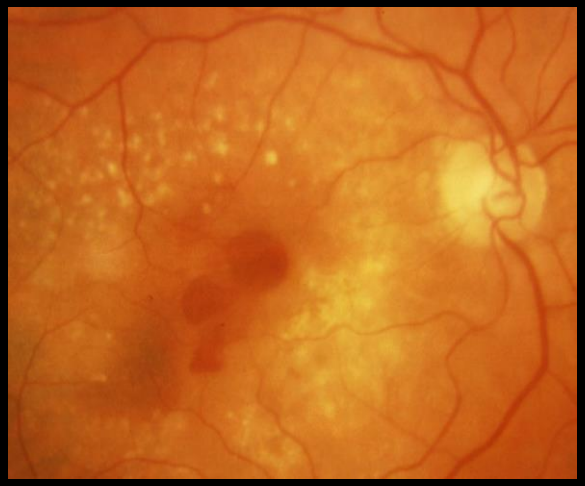
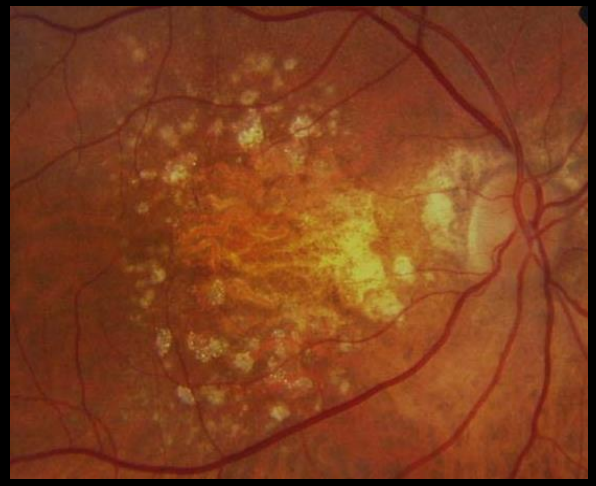
2 placebo eyes developed CNV (p=0.13)

Drusen Cohort: Primary Study Question



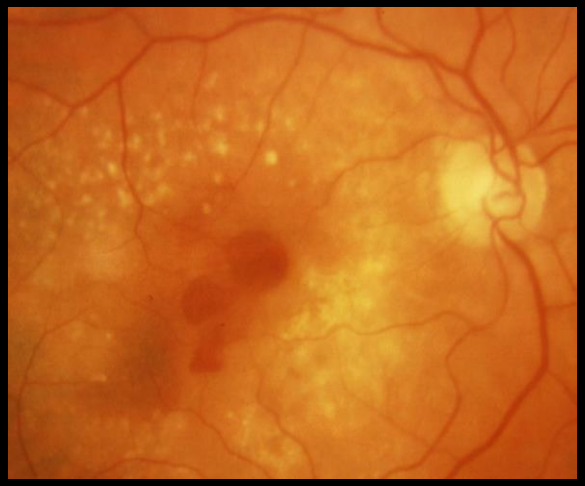
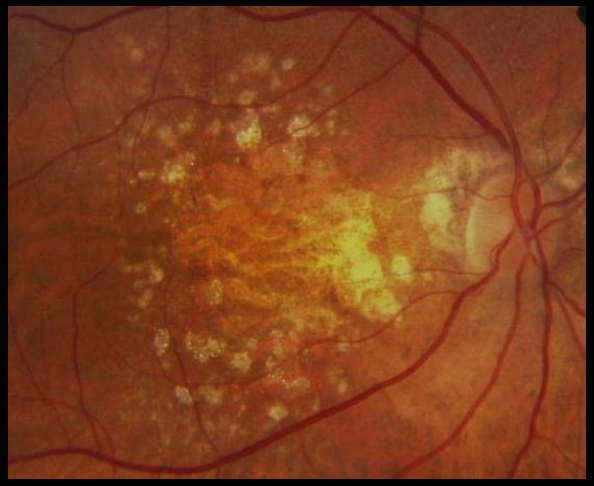
- Drusen Cohort
  - Biostatistician: “Trial is a success”
  - But, drug failed to meet primary endpoint

Novel Composite Clinical Trial Endpoint

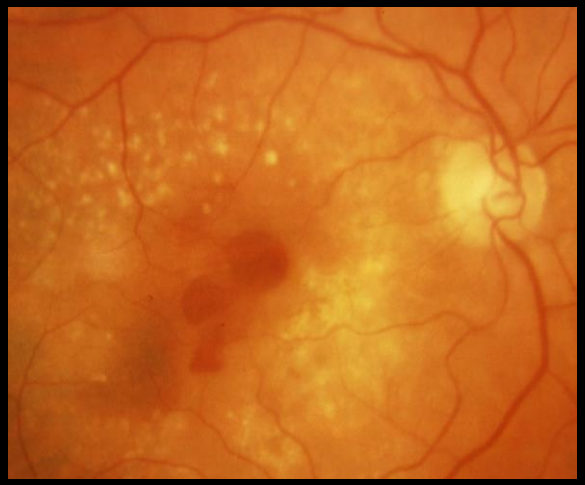
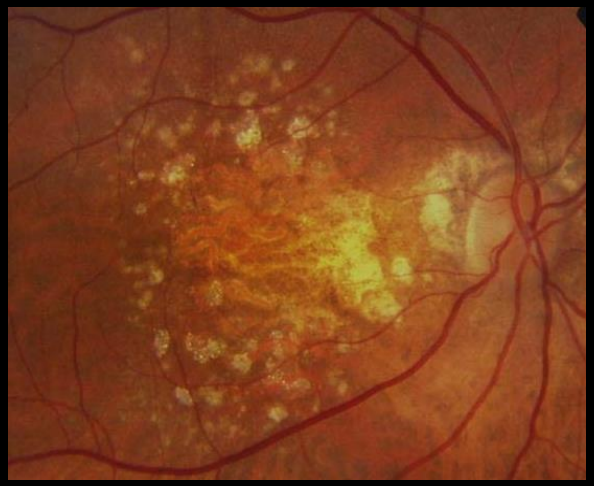
- In drusen-only eyes:
  - Growth is more common than regression
  - Growth leads to GA
  - Growth leads to CNV
  - Perhaps, a composite endpoint is best

Novel Composite Clinical Trial Endpoint

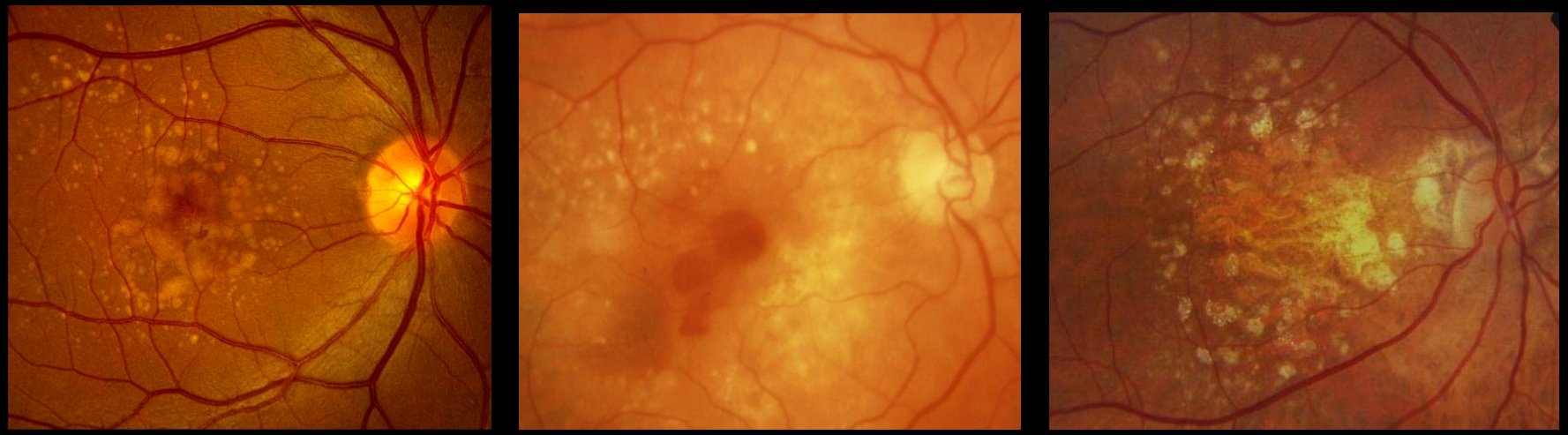
- In drusen-only eyes, failure defined as:
  - Growth of drusen volume/area
  - Formation of CNV
  - Conversion of drusen to GA

Novel Composite Clinical Trial Endpoint

- **Goal of therapy = Prevent failure**
  - **Prevent growth of drusen volume/area**
  - **Prevent formation of CNV**
  - **Prevent conversion of drusen to GA**

Novel Composite Clinical Trial Endpoint



Normal (placebo) failure rate is 60%

TABLE 4

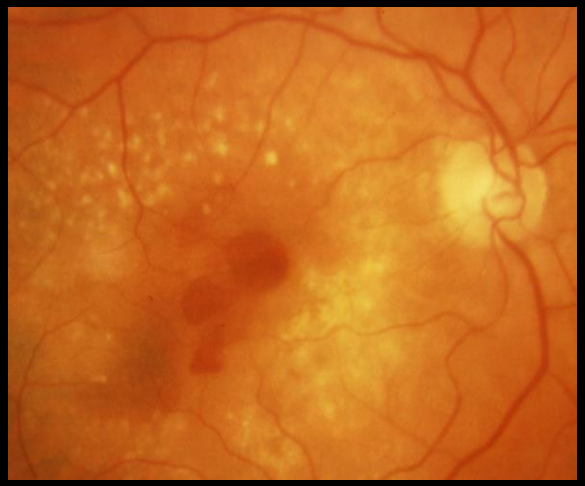
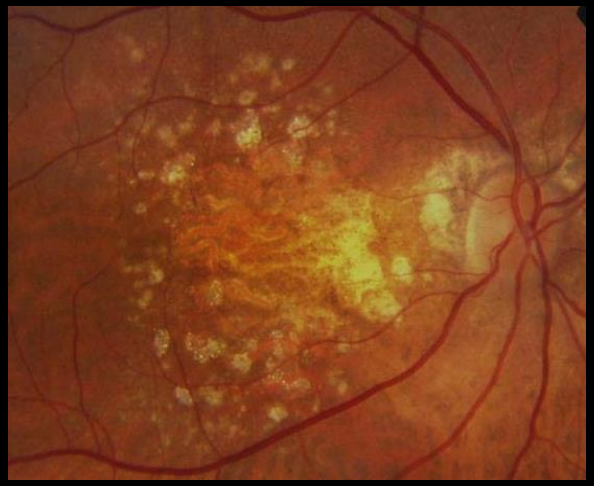
Sample Size Estimates for Each Treatment Group Based on the Predicted Percentage of Failures at 1 Year

	Number of Subjects Needed for Each Treatment Group Based on the Predicted Percentage of Failures in Actively Treated Group at 1 Year*			
Power	**30% Failure Rate**	**15% Failure Rate**	**5% Failure Rate**	**1% Failure Rate**
80%	48	21	13	11
90%	62	26	16	14

**Based on an estimated failure rate of 60% in the placebo group and 1:1 randomization. Failure was defined as growth of drusen volume and formation of any neovascularization or geographic atrophy at 1 year.*

Garcia et al., 2014, OSLI-RETINA, January/February Vol.45, No. 1

Novel Composite Clinical Trial Endpoint

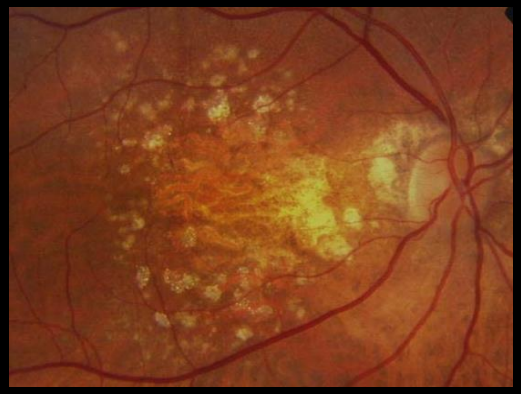
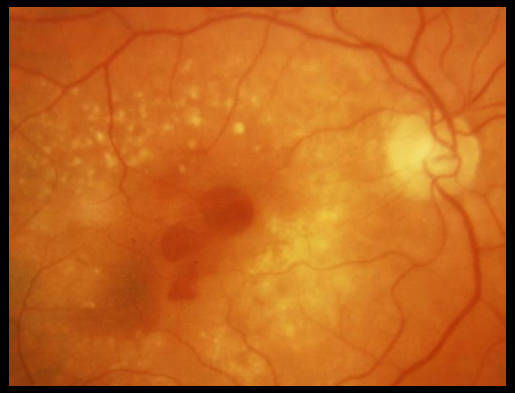




- Based on natural history data, which was validated in the COMPLETE Study:
  - For a study with 90% power
  - to detect a 50% reduction in failure rate
  - only 62 pts. needed per treatment arm
- Why study drusen progression rather than enlargement of GA?

Drusen Progression as an Endpoint

- Earlier stage disease than GA
- Treat earlier and preserve more vision
- Better defined population than GA?
- May be at a stage influenced more broadly by therapies (e.g. complement inhibition)
- Could prevent progression to CNV
- If treatment slows growth of GA, would it necessarily be effective in slowing progression of drusen to GA?
- Could open possibility of treating even earlier based on genetics plus phenotype

Important Take-Home Messages

- Phenotype enrichment depends on endpoint
- Growth of GA is the most commonly used surrogate endpoint for dry AMD trials
- Enrichment strategies include hyper-AF patterns, size, complexity, and genetics
- Limitations of GA include analysis of growth rate and its late stage (too late?)
- Surrogate endpoints using earlier stages (e.g. drusen) attractive for Phase 2 studies

Possible Future Scenarios

- Treatment successfully slows or stops the progression of GA
  - What's the labeled indication?
  - When will treatment be initiated?
  - Will early treatment prevent progression to GA or CNV?
- Treatment fails to slow or stop GA
  - Could treatment have prevented the progression to GA or formation of CNV?
  - If so, then goal would be to treat as early as possible