New Technologies for Managing Macular Degeneration Patients

Greg A. Caldwell, OD, FAAO

Woo U – Distance Learning Event

Wednesday, November 9, 2022

Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
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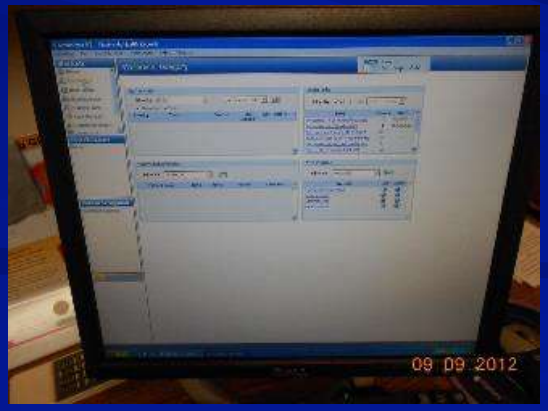
Optometric Education Consultants

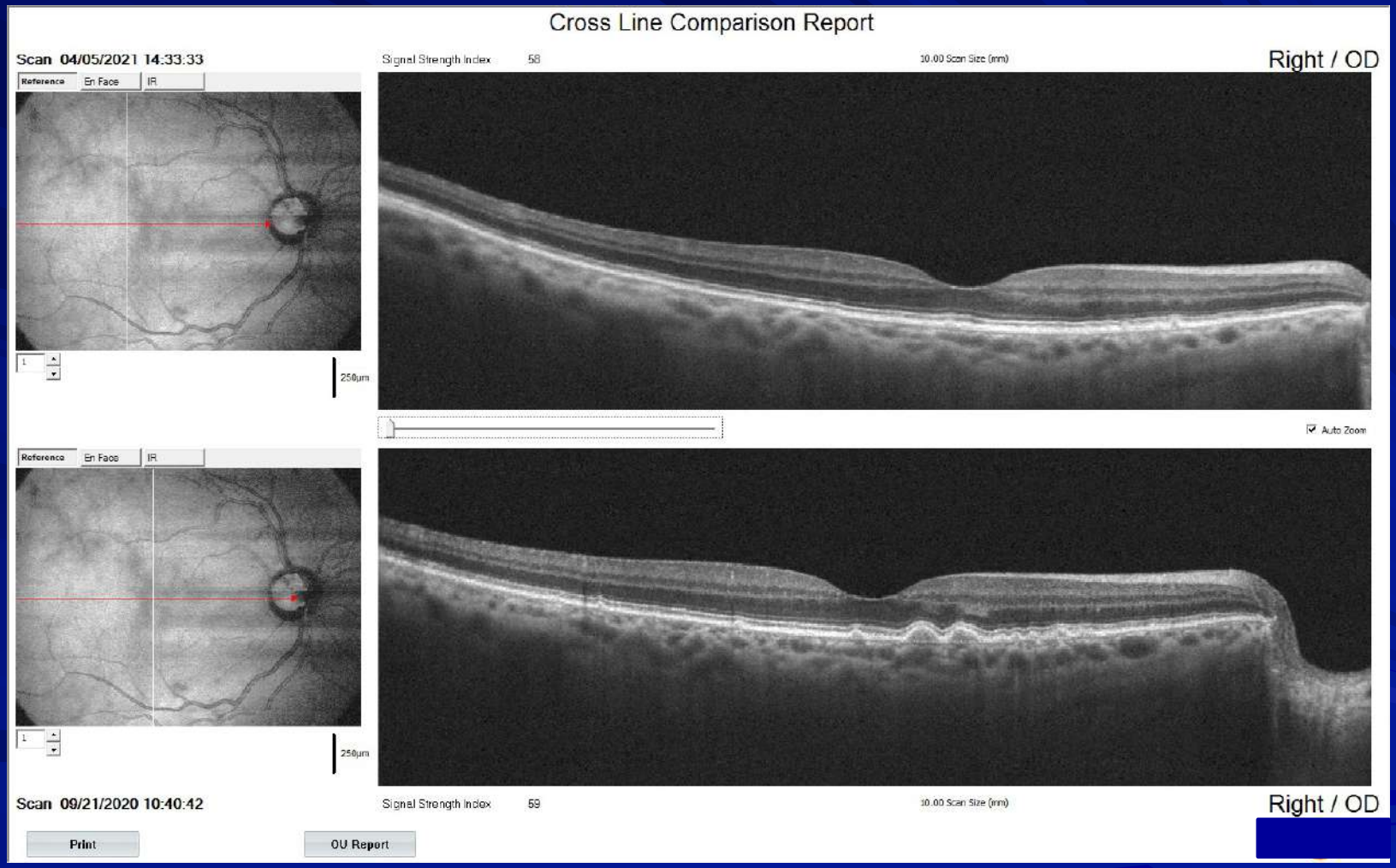
My Practice

I am a clinician first then a scientist

- Some are scientists first then clinician
- I need to simplify for patient and patient care.
- Science is great, but not good if there isn't a clinical application.
- Some lectures are science based without clinical application.
- My lecture will be a hybrid. Showing clinical applications of the science



It is wonderful to have someone who's juggling so many aspects of optometry [scientific, clinical experience, teacher & lecturer]. It is refreshing and very informative. -Sarah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Right / OD
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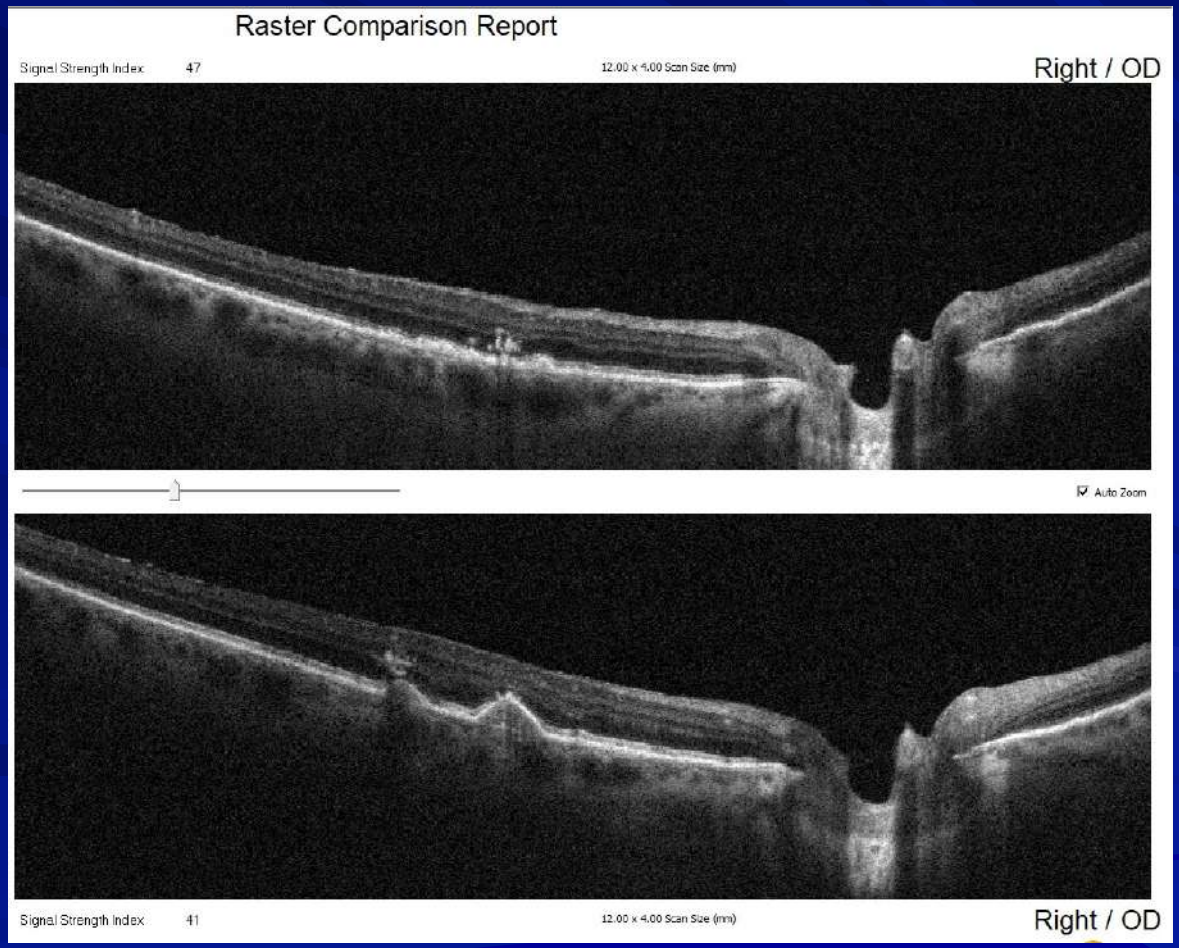
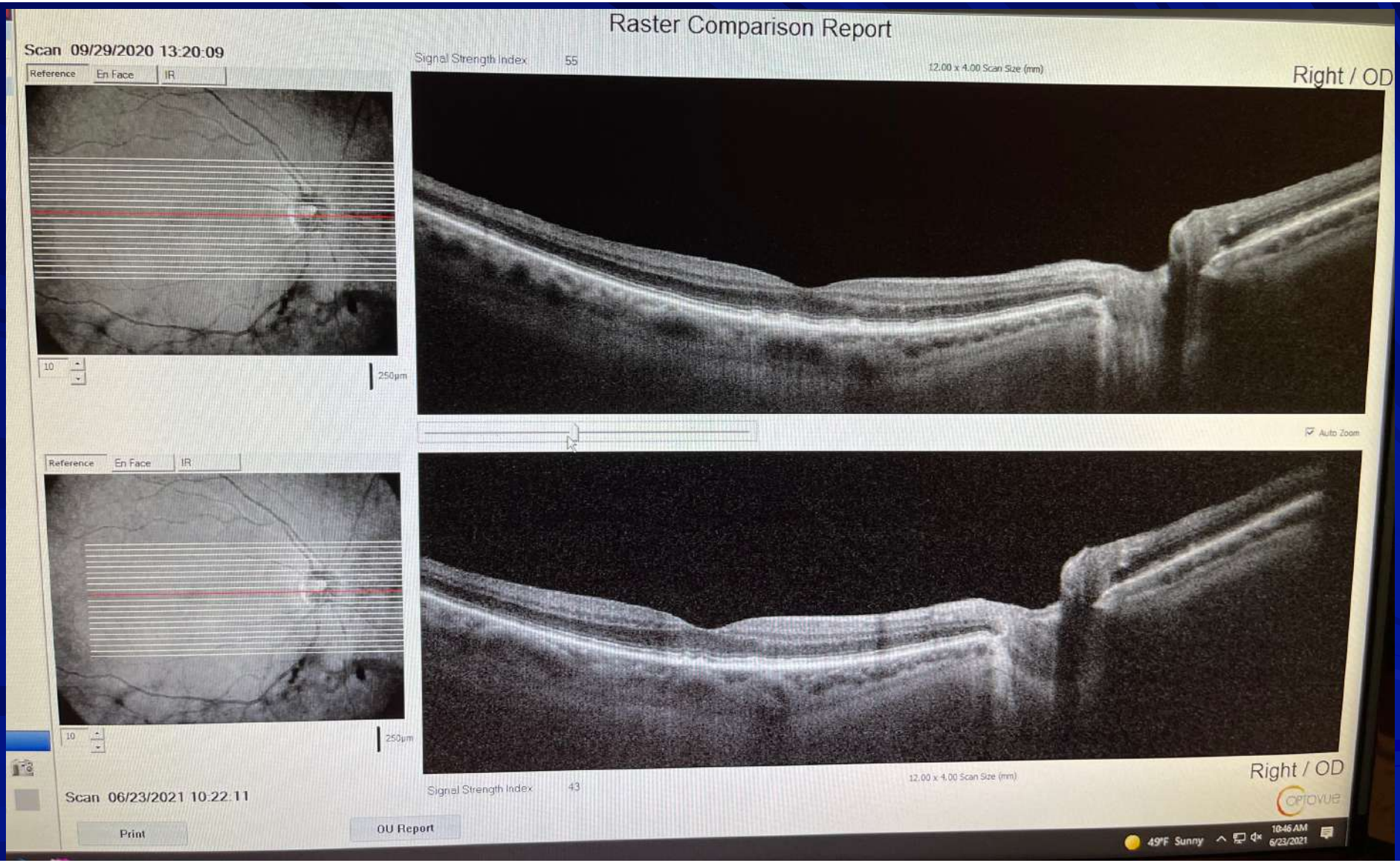
April 27, 2021 – January 26, 2022 (9 months)




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
OPTOVUE
Print
OU Report
49°F Sunny
10:46 AM
6/23/2021

AMD Dominance

- In 2010, the World Health Organization estimated that 5% of the world's blindness was due to AMD
- Leading cause of blindness over 55-year-old in USA
- 11 million people in USA have AMD, 22 million by 2050
  - Approximately 1 in 14 **people** over the age of 40 **has** some degree of **macular degeneration**
  - Over 60, 1 in 8 (12.5%)
  - Over 80, 1 in 3 (33 %)
- More cases of AMD than Alzheimer's, breast cancer, and Parkinson's combined
- The leading cause of blindness and vision loss in Caucasians
- Affect 1 in 5 families
- Hereditary strongest genetic linkage of any major diseases

Eye Care Professional Landscape

- 58,000 eye care professionals
  - 40,000 optometrists
  - 18,000 ophthalmologists
    - About 10% are retinal specialists

Optometrists and All Eye Care Professionals Responsibility

- Rethink our responsibility related AMD diagnosis and management
- Commit to that we will do better in
  - Early detection
  - Treatment
- Know, execute, and employ current clinically appropriate Practice Guidelines
  - Those that preserve vision
  - Don't wait until vision has been lost
- Closely monitor and treat the early detected disease
  - If progresses to advanced AMD, better opportunity to save vision

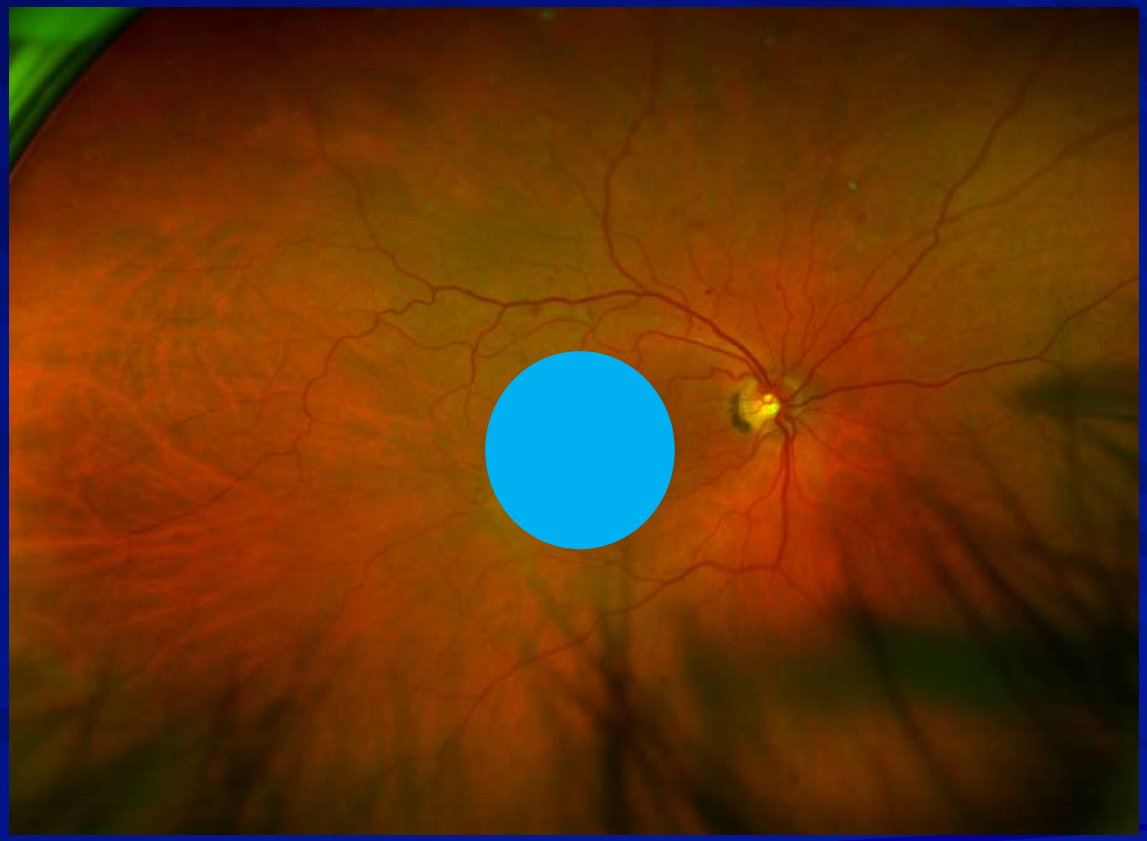
Tools for Diagnosis, Management, and Treatment of AMD

- Comprehensive eye exam – structural, some functional
- Fundus photography and FAF - structural
- OCT and OCT Angiography – structural
- Dark adaptation – functional
- Carotenoid levels – molecular

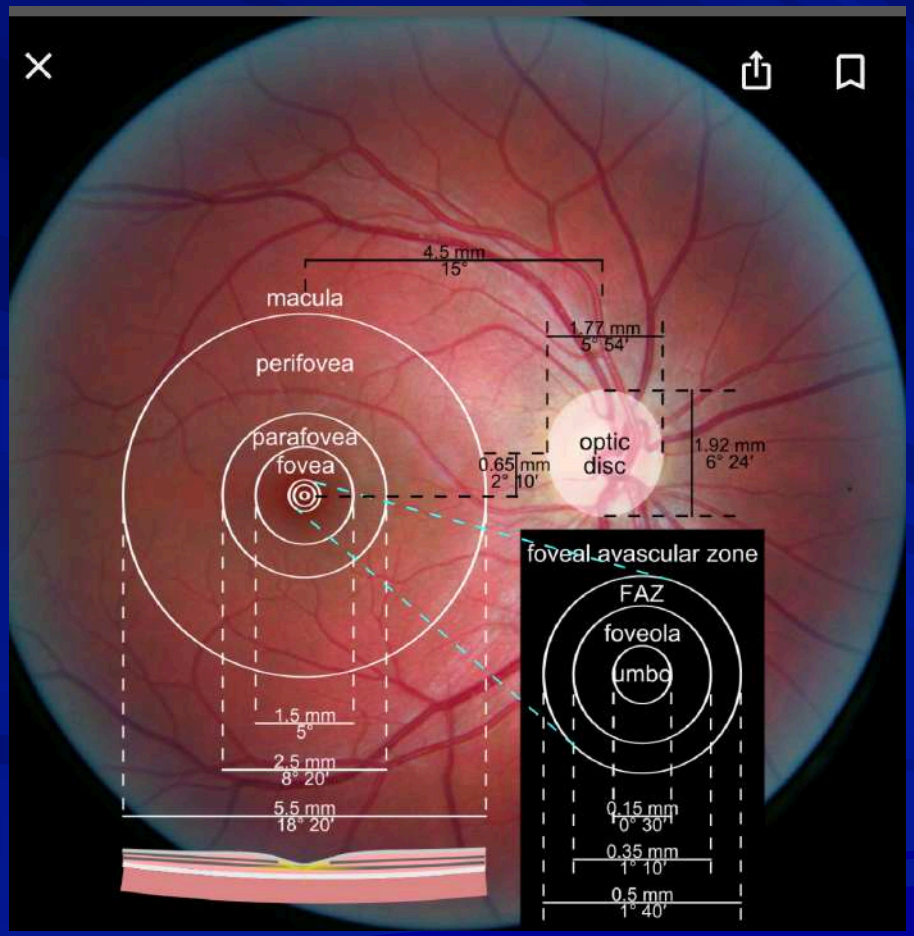
Instruments for comprehensive AMD patient care

- Slit lamp/DFE - structural, some functional
- Camera – structural
- OCT- structural
- OCT Angiography –structural
- Dark adaption – functional
- Contrast sensitivity – functional
- PHP – structural
- Macula pigment eval – skin not MPOD - molecular
- Genetic testing – molecular

Where is the macula?



How large is the macula?



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)

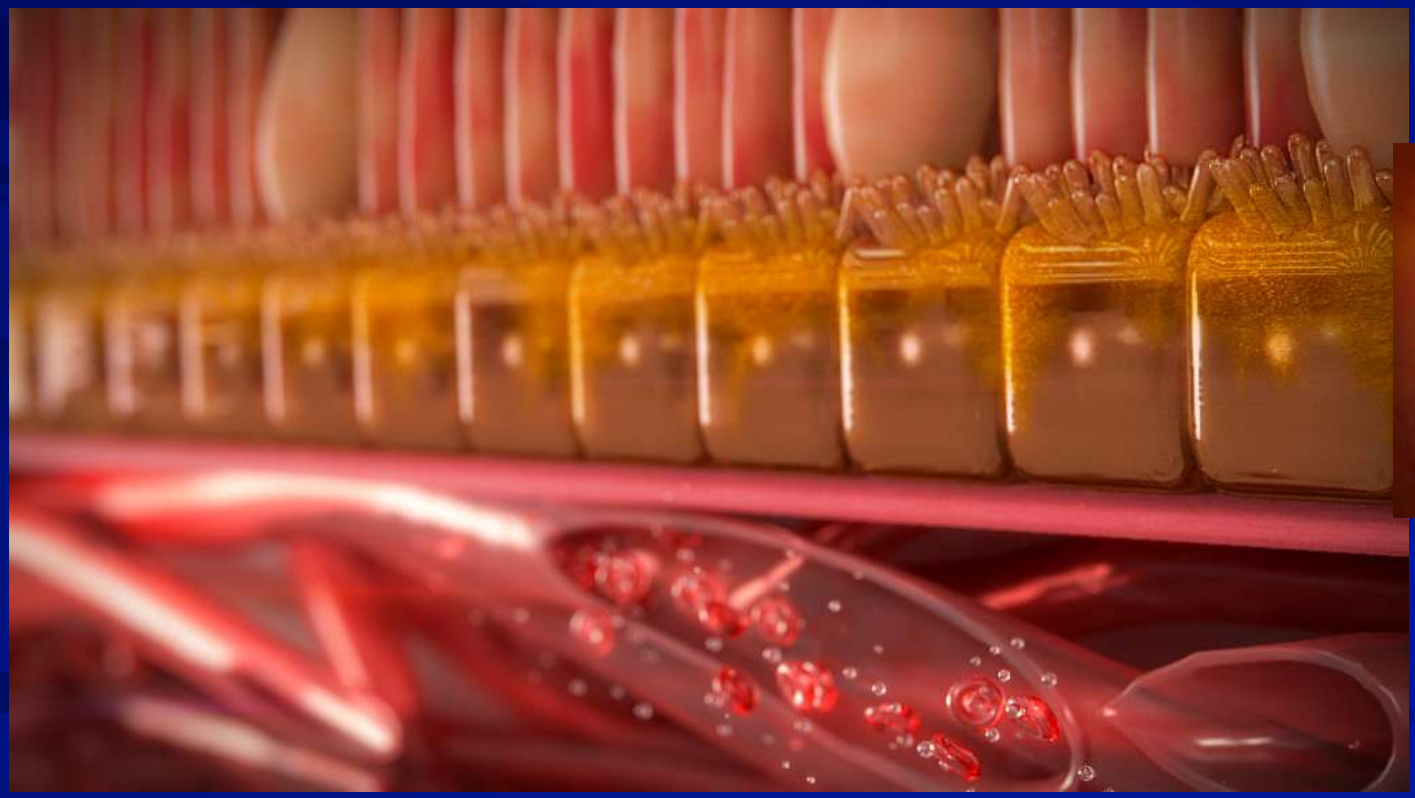
54-year-old man

- Dad is getting intravitreal injections every 6-8 weeks for wet AMD and I was told I am too young and that I have "drumezum"
  - ★ Patient: "Can we do something now?"
  - ★ Me: You have come to the right person – if you are willing to make lifestyle changes if indicated
- Genetic testing
- Skin carotenoids
- Dark Adaption
- Contrast Sensitivity
- OCT
- OCT Angiography

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

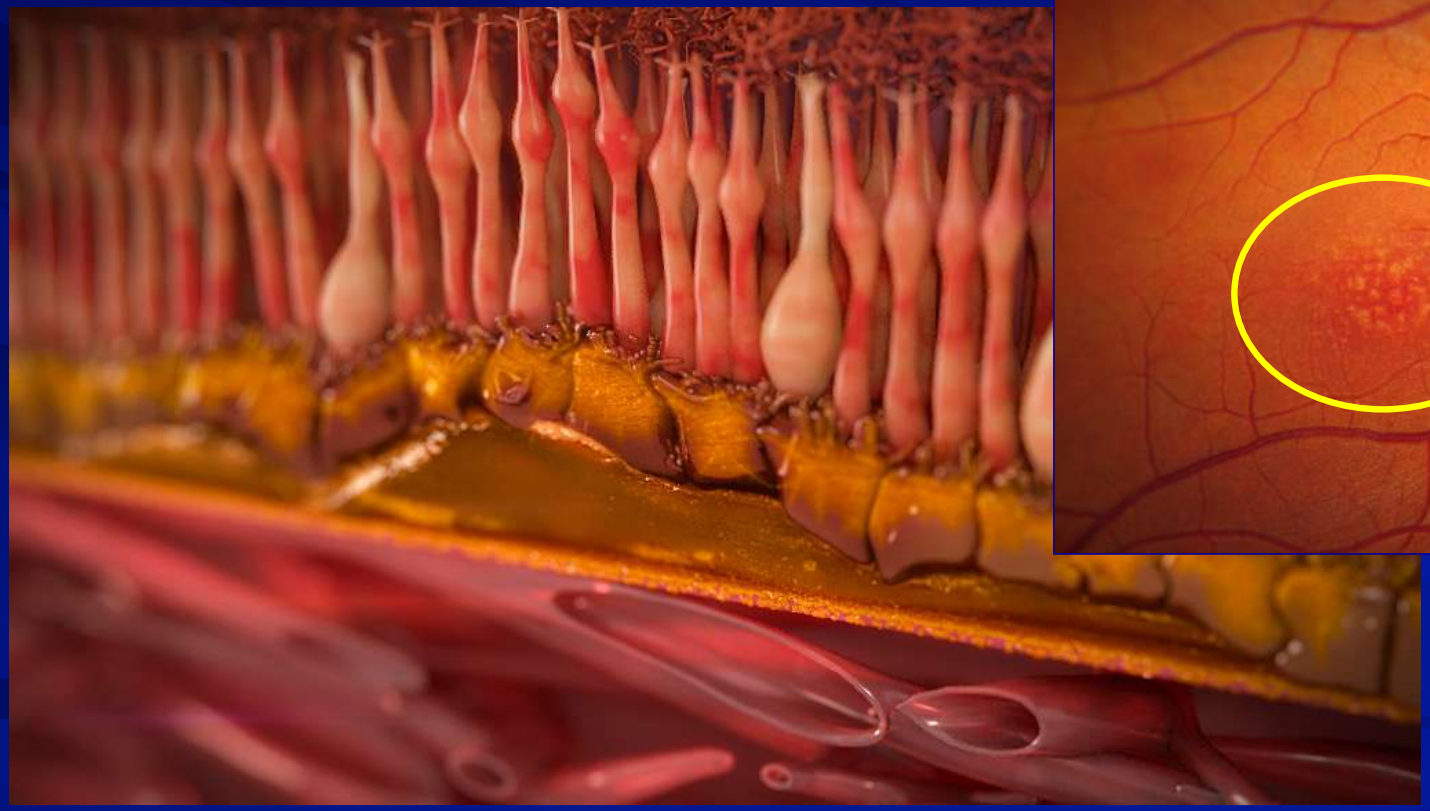
Healthy choriocapillaris, Bruch's, RPE, and Photoreceptors

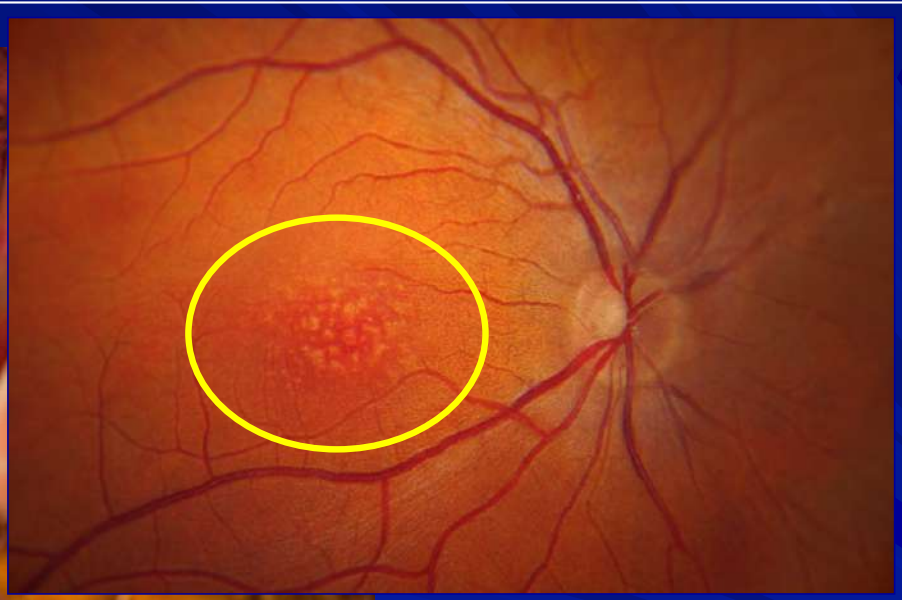


Cholesterol barrier deposited along Bruch's and RPE

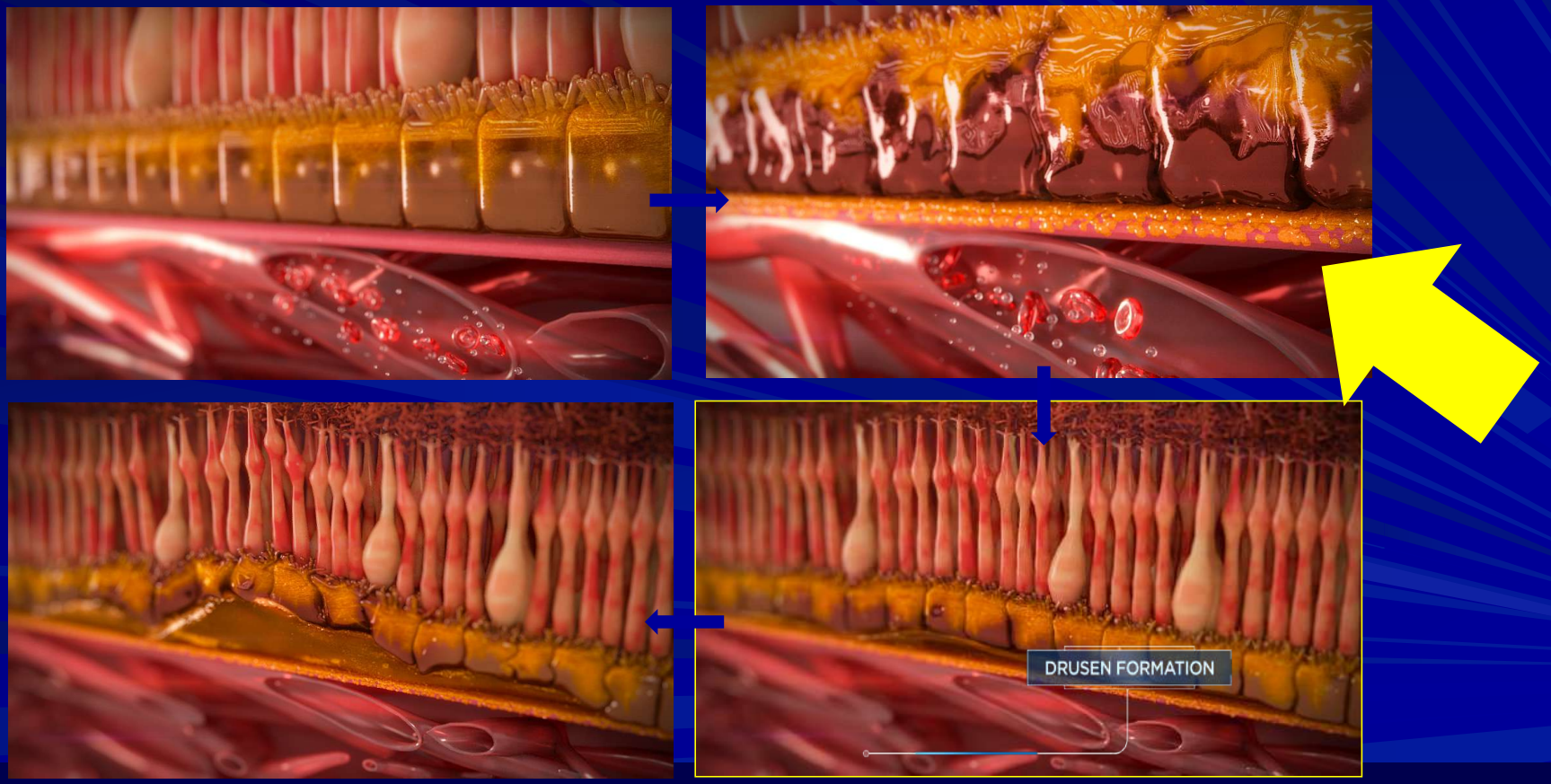
RPE Secretes even more cholesterol and degenerates

Finally, visibly evident drusen on fundus evaluation

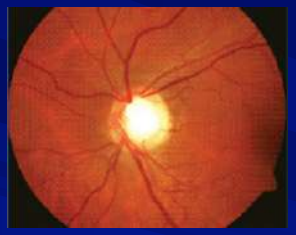
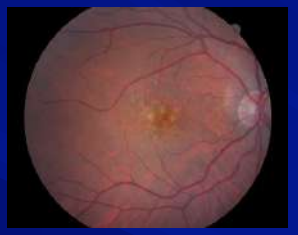




AMD is a Disease Process that Starts Below the Surface



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
  - Adaptation Time – Heru
- 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%

The Role of Contrast Sensitivity in AMD

- **Contrast Sensitivity** is affected in early AMD
  - In many diseases, including AMD, traditional visual acuity testing does not fully reflect the patient's symptoms
- There is evidence that it may degrade prior to observable structural changes in the retina
- When AMD leads to significant visual dysfunction, CS testing can give insight into the level of difficulty a patient is likely to encounter in activities of daily living [1]
- In one AMD study, increases in central drusen were correlated with decreasing CS results, yet all subjects maintained 20/20 VA [2]
- Heru's contrast sensitivity application uses a tumbling E presentation on a light background (85 cd/m^2) with a shrinking staircase thresholding strategy
- Heru test time is 25 – 45 seconds per eye

1, 2. Roark, M.W., *Add Contrast Sensitivity Testing for AMD*. (2020). Optometric Management - Add Contrast Sensitivity Testing for AMD

Early Detection

Dark Adaptation and Contrast Sensitivity

Dark Adaptation

54-year-old man

- Dad is getting intravitreal injections every 6-8 weeks for wet AMD and I was told I am too young and that I have "drumezum"
  - ★ Patient: "Can we do something now?"
  - ★ Me: You have come to the right person – if you are willing to make lifestyle changes if indicated
- Genetic testing
- Skin carotenoids
- Dark Adaption
- Contrast Sensitivity
- OCT
- OCT Angiography

DNA Sciences

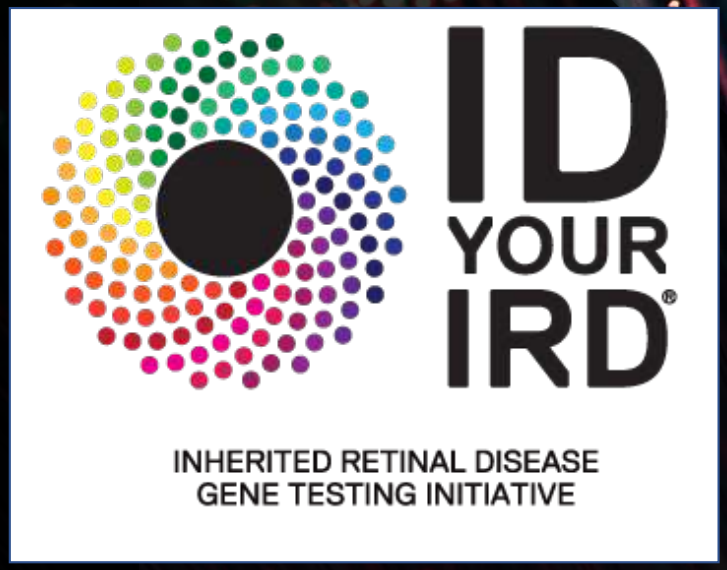
- Genomics = all of our genes
- Genetics = individual genes

- Epigenetics – the study of how our cells control gene activity without changing the DNA
  - Internal and external environments


Ocular Genetic Testing

Generalized Ocular Testing
Inherited Retinal Disease and Spark Therapeutics

- Panel tests for mutations in approximately 300 genes associated with inherited retinal disease (IRD)
  - More commonly tested for:
    - ***Retinitis pigmentosa***
    - ***Leber congenital amaurosis***
    - ***Stargardt disease***
  - Commonly associated symptoms
    - Nyctalopia
    - Central and/or peripheral field loss
    - Color vision deterioration and/or loss
    - Severe photophobia



*****ID your IRD does NOT currently test for genes associated with AMD*****

Generalized Ocular Testing

Inherited Retinal Disease and Spark Therapeutics

ID YOUR IRD® Testing Panel

The only way to confirm that your patient has an inherited retinal disease (IRD) is with a genetic test. Through the **ID YOUR IRD gene testing initiative**, Spark Therapeutics supports people living with certain IRDs by providing genetic information that can empower their decisions. The ID YOUR IRD panel tests for mutations in **approximately 300 genes** associated with IRDs.

Visit **IDYOURIRD.com** for more information or to order free[1] test kits.

GENE	DISEASE CATEGORY[1]	GENE	DISEASE CATEGORY[1]
ABCA4	Stargardt disease, autosomal recessive Cone or cone-rod dystrophy, autosomal recessive[1]	BBS1	Bardet-Biedl syndrome, autosomal recessive[1]
ABCC8*	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	BBS2	Bardet-Biedl syndrome, autosomal recessive[1]
ABHD12	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	BBS4	Bardet-Biedl syndrome, autosomal recessive[1]
ACBD5	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	BBS5*	Bardet-Biedl syndrome, autosomal recessive[1]
ACO2	Optic atrophy, autosomal recessive Infantile cerebellar-retinal degeneration, autosomal recessive[1]	BBS7	Bardet-Biedl syndrome, autosomal recessive[1]
ADAM9	Cone or cone-rod dystrophy, autosomal recessive[1]	BBS9	Vitelliform macular degeneration (Best disease), autosomal dominant and recessive Retinitis pigmentosa, autosomal dominant and recessive[1]
ADAM10*	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	C1QTNF5	Macular dystrophy, autosomal dominant[1]
ADAR2*	Retinitis pigmentosa, autosomal recessive[1]	CA4	Bardet-Biedl syndrome, autosomal recessive
ADAR1*	Usher syndrome, autosomal recessive[1]	CABP4	Retinitis pigmentosa, autosomal dominant[1]
ADIPOR1	Retinitis pigmentosa, autosomal dominant Bardet-Biedl syndrome, autosomal recessive[1]	CACNA1F	Congenital stationary night blindness, autosomal recessive[1]
AGBL5	Retinitis pigmentosa, autosomal recessive[1]	CACNA2D4	Cone or cone-rod dystrophy, X-linked[1]
AHI1	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	CACNB4	Cone or cone-rod dystrophy, autosomal recessive[1]
AHR	Retinitis pigmentosa, autosomal recessive[1]	CAPN5	Other retinopathy, autosomal dominant[1]
AIPL1	Cone or cone-rod dystrophy, autosomal dominant Leber congenital amaurosis, autosomal recessive[1]	CC2D2A	Syndromic/systemic disease with retinopathy (excluding ciliopathies)[1]
ALMS1	Syndromic/systemic diseases with retinopathy, autosomal recessive Alstrom syndrome, autosomal recessive[1]	CCT2	Leber congenital amaurosis, autosomal recessive[1]
ANKRD39	Retinitis pigmentosa, autosomal recessive[1]	CDH3	Other retinopathy, autosomal recessive[1]
ARL2BP	Joubert syndrome, autosomal recessive[1]	CDHR1	Usher syndrome, autosomal recessive and digenic recessive[1]
ARL3	Retinitis pigmentosa, autosomal dominant[1]	CEP164	Cone or cone-rod dystrophy, autosomal recessive[1]
ARL6	Retinitis pigmentosa, autosomal recessive[1]	CEP250	Bardet-Biedl syndrome, autosomal recessive[1]
ARL6IP6	Joubert syndrome, autosomal recessive[1]	CEP290	Joubert syndrome, autosomal recessive[1]
ARMC9*	Joubert syndrome, autosomal recessive[1]	CEP78	Cone or cone-rod dystrophy with hearing loss, autosomal recessive[1]
ARSG	Usher syndrome, autosomal recessive[1]	CERKL	Infantile nephronophthisis with occasional retinopathy[1]
ASRGL1	Other retinopathy, autosomal recessive[1]	CEP164	Syndromic/systemic diseases with retinopathy, occasional exception[1]
ATF6	Cone or cone-rod dystrophy, autosomal recessive[1]	CEP250	Usher syndrome, autosomal recessive[1]
ATOH7	Nonsyndromic congenital retinal nonattachment, autosomal recessive (also RNR7)[1]	CEP290	Leber congenital amaurosis, autosomal recessive Bardet-Biedl syndrome, autosomal recessive[1]
BBS1	Joubert syndrome, autosomal recessive Meckel syndrome, autosomal recessive[1]	CERKL	Cone or cone-rod dystrophy, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]
BBS2	Retinitis pigmentosa, autosomal recessive Bardet-Biedl syndrome, autosomal recessive[1]	CFAP418*	Cone or cone-rod dystrophy, autosomal recessive[1]
BBS1	Retinitis pigmentosa, autosomal recessive Bardet-Biedl syndrome, autosomal recessive[1]	CHM	Choroideremia, X-linked[1]
BBS2	Bardet-Biedl syndrome, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]	CNGA1	Deafness alone or syndromic, autosomal recessive[1]
		CNGB1	Retinitis pigmentosa, autosomal recessive Bardet-Biedl syndrome, autosomal recessive[1]
		CNGB3	Achromatopsia, autosomal recessive[1]

GENE	DISEASE CATEGORY[1]	GENE	DISEASE CATEGORY[1]
CLN3	Juvenile neuronal ceroid lipofuscinosis, autosomal recessive[1]	GNAT1	Congenital stationary night blindness, autosomal recessive[1]
CLN5	Retinitis pigmentosa, autosomal recessive Usher syndrome, autosomal recessive[1]	GNAT2	Cone or cone-rod dystrophy, autosomal recessive[1]
CLN6*	Leber congenital amaurosis, autosomal recessive[1]	GNB3	Congenital stationary night blindness, autosomal recessive[1]
CLN8*	Retinitis pigmentosa, autosomal recessive[1]	GNPTG	Mucolipidosis, autosomal recessive[1]
CNGA1	Achromatopsia, autosomal recessive Cone or cone-rod dystrophy, autosomal recessive[1]	GPR125	Joubert syndrome, autosomal recessive[1]
CNGB1	Retinitis pigmentosa, autosomal recessive[1]	GPR179	Congenital stationary night blindness, autosomal recessive[1]
CNGB3	Achromatopsia, autosomal recessive Cone or cone-rod dystrophy, autosomal recessive[1]	GRK1	Retinitis pigmentosa, autosomal recessive[1]
CNNM4	Cone or cone-rod dystrophy, autosomal recessive Jalili syndrome, autosomal recessive[1]	GRM6	Retinitis pigmentosa, autosomal recessive[1]
COL11A1*	Stickler syndrome, autosomal dominant Marshall syndrome, autosomal dominant[1]	GUCA1A	Retinitis pigmentosa, autosomal recessive[1]
COL11A2	Stickler syndrome, autosomal dominant[1]	GUCA1B	Cone or cone-rod dystrophy, autosomal dominant[1]
COL18A1	Knobloch syndrome, autosomal recessive[1]	GUCY2D	Leber congenital amaurosis, autosomal recessive[1]
COL2A1	Stickler syndrome, autosomal dominant[1]	HARS1	Usher syndrome, autosomal recessive[1]
COL4A3	Stickler syndrome, autosomal recessive[1]	HGSNAT	Sanfilippo syndrome, autosomal recessive[1]
COL4A4	Stickler syndrome, autosomal recessive[1]	HK1	Retinitis pigmentosa, autosomal dominant[1]
COL4A7	Stickler syndrome, autosomal recessive[1]	HMX1	Oculoauricular syndrome, autosomal recessive[1]
COL9A1	Stickler syndrome, autosomal recessive[1]	IDH3A	Retinitis pigmentosa, autosomal recessive[1]
COL9A2	Stickler syndrome, autosomal recessive[1]	IDH3B	Retinitis pigmentosa, autosomal recessive[1]
COL9A3	Stickler syndrome, autosomal recessive[1]	IFT122	Cranioectodermal dysplasia, autosomal recessive[1]
CPLANE1	Joubert syndrome, autosomal recessive[1]	IFT140	Mainzer-Saldino syndrome, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]
CRB1	Leber congenital amaurosis, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]	IMPDH1	Retinitis pigmentosa, autosomal dominant[1]
CRX	Leber congenital amaurosis, autosomal recessive[1]	INPP5E	Joubert syndrome, mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM syndrome), autosomal recessive[1]
CSPP1	Syndromic/systemic diseases with cortical malformation, commonly nonsyclinic[1]	INPPL1	Joubert syndrome, mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM syndrome), autosomal recessive[1]
CTNNA1	Macular dystrophy, autosomal dominant[1]	IQCB1	Senior-Loken syndrome, autosomal recessive[1]
CWC27	Retinitis pigmentosa with or without skeletal abnormalities[1]	IVD	Isovaleric acidemia, autosomal recessive[1]
CYP4V2	Other retinopathy, autosomal recessive[1]	JAG1	Alagille syndrome, autosomal dominant[1]
DHDDS	Retinitis pigmentosa, autosomal recessive[1]	KCNJ13	Leber congenital amaurosis, autosomal recessive[1]
DHX38	Retinitis pigmentosa, autosomal recessive[1]	KCNV2	Cone or cone-rod dystrophy, autosomal recessive[1]
DRAM2	Macular dystrophy, autosomal recessive[1]	KIAA1549	Optic atrophy, autosomal recessive[1]
DTNBP1	Leber congenital amaurosis, autosomal recessive[1]	KIAA1840	Joubert syndrome, autosomal recessive[1]
EIF2B1	Diffuse leukoencephalopathy with neuroaxonal spheroids and pigmented glia (Alexander disease), autosomal dominant[1]	KIAA1549	Retinitis pigmentosa, autosomal recessive[1]
ELOVL4	Stargardt disease, autosomal dominant[1]	KIF11	Microcephaly, chorioretinopathy, lymphedema, or mental retardation, autosomal dominant[1]
EMC1	Retinitis pigmentosa, autosomal recessive[1]	KIF7	Joubert syndrome, autosomal recessive[1]
ENKD1*	Serotonin retinitis pigmentosa, autosomal recessive[1]	KIZ	Retinitis pigmentosa, autosomal recessive[1]
EYS	Retinitis pigmentosa, autosomal recessive[1]	KLHL7	Retinitis pigmentosa, autosomal dominant[1]
FAM161A	Retinitis pigmentosa, autosomal recessive[1]	LCA5	Leber congenital amaurosis, autosomal recessive[1]
FAM161A	Childhood onset syndromic retinitis pigmentosa, autosomal recessive[1]	LRAT	Leber congenital amaurosis, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]
FAM221A	Infantile nystagmus, X-linked[1]	LRIT3	Congenital stationary night blindness, autosomal recessive[1]
FLCN*	Macular dystrophy, autosomal dominant[1]	LRP5	Syndromic/systemic diseases with osteoporosis, autosomal recessive (Osteoporosis-pseudoglioma, autosomal recessive)[1]
FZD4	Other retinopathy, autosomal dominant[1]	LRPP6	Familial exudative vitreoretinopathy, autosomal recessive and dominant[1]
G3PP	Leber congenital amaurosis, autosomal recessive[1]	LZTFL1	Bardet-Biedl syndrome, autosomal recessive[1]
GNAT1	Congenital stationary night blindness, autosomal dominant[1]	MAK	Retinitis pigmentosa, autosomal recessive[1]
GNAT2	Cone or cone-rod dystrophy, autosomal recessive[1]	MAP9/ARL6	Other rod monopathy, autosomal dominant[1]
GNB3	Congenital stationary night blindness, autosomal recessive[1]	MERTK	Retinitis pigmentosa, autosomal recessive[1]
GNPTG	Sanfilippo/systemic diseases with retinopathy, autosomal recessive[1]		

GENE	DISEASE CATEGORY[1]	GENE	DISEASE CATEGORY[1]
MFRP	Syndromic/systemic diseases with optic atrophy, autosomal dominant Chronic Mal-Y-Teeth Disease, autosomal recessive and dominant[1]	PEX7	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
MMP	Other retinopathy, autosomal recessive[1]	PEX10	Peroxisome biogenesis disorder, autosomal recessive[1]
MMP20	Dental (Tooth) syndrome, autosomal recessive[1]	PEX12	Peroxisome biogenesis disorder, autosomal recessive[1]
MKS1	Joubert syndrome, autosomal recessive Meckel syndrome, autosomal recessive[1]	PEX16	Peroxisome biogenesis disorder, autosomal recessive[1]
MPDZ	Retinitis pigmentosa, autosomal dominant[1]	PEX19	Peroxisome biogenesis disorder, autosomal recessive[1]
MTTP	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	PEX1 / PEX6	Peroxisome biogenesis disorder, autosomal recessive[1]
MYO7A	Usher syndrome, autosomal recessive[1]	PEX2	Peroxisome biogenesis disorder, autosomal recessive[1]
NDP	Norrie disease, X-linked[1]	PEX26	Peroxisome biogenesis disorder, autosomal recessive[1]
NEK2	Retinitis pigmentosa, autosomal recessive[1]	PEX3	Peroxisome biogenesis disorder, autosomal recessive[1]
NEUROD1	Retinitis pigmentosa, autosomal recessive[1]	PEX5	Peroxisome biogenesis disorder, autosomal recessive[1]
NMNAT1	Leber congenital amaurosis, autosomal recessive[1]	PEX6	Peroxisome biogenesis disorder, autosomal recessive[1]
NPHP1	Bardet-Biedl syndrome, autosomal recessive[1]	PEX26	Peroxisome biogenesis disorder, autosomal recessive[1]
NPHP3	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]	PHKA1	Syndromic/systemic diseases with retinopathy, X-linked[1]
NPHP4	Senior-Loken syndrome, autosomal recessive[1]	PITPNM3	Cone or cone-rod dystrophy, autosomal dominant[1]
NR2E3	Retinitis pigmentosa, autosomal recessive Enhanced s-cone syndrome, autosomal recessive[1]	PLA2G5	Other retinopathy, autosomal recessive[1]
NR2F1	Bosch-Boonstra-Schaaf optic atrophy syndrome, autosomal dominant[1]	PLK4	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
NRL	Retinitis pigmentosa, autosomal dominant[1]	PNPLA6	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
NRX	Congenital stationary night blindness, X-linked[1]	POC1B	Cone or cone-rod dystrophy, autosomal recessive[1]
OAT	Other retinopathy, autosomal recessive[1]	POMGNT1	Retinitis pigmentosa, autosomal recessive[1]
OCA2	Oculocutaneous albinism, autosomal recessive[1]	PRCD	Retinitis pigmentosa, autosomal recessive[1]
OFD1	Joubert syndrome, X-linked recessive Retinitis pigmentosa, X-linked recessive[1]	PRDM13	Cerebellar ataxia or degenerative, autosomal recessive[1]
OPA1	Hereditary optic atrophy, autosomal dominant Syndromic/systemic diseases with optic atrophy, autosomal dominant Behr syndrome, autosomal recessive[1]	PRDM7	Cone or cone-rod dystrophy, autosomal dominant[1]
OPA3	Optic atrophy and cataract, autosomal dominant[1]	PRPF3	Retinitis pigmentosa, autosomal dominant[1]
OPN1SW	Other retinopathy, autosomal dominant[1]	PRPF4	Retinitis pigmentosa, autosomal dominant[1]
OTX2	Leber congenital amaurosis, autosomal dominant[1]	PRPF6	Retinitis pigmentosa, autosomal dominant[1]
PAX2	Optic nerve hypoplasia and colobomatous macular dysplasia, autosomal dominant[1]	PRPF31	Retinitis pigmentosa, autosomal dominant[1]
PAX6	Aniridia, autosomal dominant[1]	PRPF8	Retinitis pigmentosa, autosomal dominant[1]
PCARE	Cone or cone-rod dystrophy, autosomal recessive[1]	PRPH2	Cone or cone-rod dystrophy, autosomal dominant Retinitis pigmentosa, autosomal dominant[1]
PDE6A	Retinitis pigmentosa, autosomal recessive[1]	PRPS1	Nonsyndromic sensorineural deafness, X-linked recessive Charcot-Marie-Tooth disease, X-linked recessive[1]
PDE6B	Retinitis pigmentosa, autosomal recessive[1]	QARS	Cone or cone-rod dystrophy, autosomal recessive[1]
PDE6C	Achromatopsia, autosomal recessive[1]	RAX2	Cone or cone-rod dystrophy, autosomal recessive[1]
PDE6G	Retinitis pigmentosa, autosomal recessive[1]	RBP3	Retinitis pigmentosa, autosomal recessive[1]
PDE10A	Retinitis pigmentosa, autosomal recessive[1]	RBP4	Other retinopathy, autosomal recessive[1]
PDE12	Retinitis pigmentosa, autosomal recessive[1]	RCBTB1	Other retinopathy, autosomal dominant[1]
PDZD7	Usher syndrome, autosomal recessive and digenic recessive[1]	RD3	Leber congenital amaurosis, autosomal recessive[1]
PEX1	Zellweger syndrome, autosomal recessive[1]	RDH5	Cone or cone-rod dystrophy, autosomal recessive[1]
PEX2	Peroxisome biogenesis disorder, autosomal recessive[1]	RDH12	Leber congenital amaurosis, autosomal recessive Retinitis pigmentosa, autosomal dominant[1]
PEX5	Peroxisome biogenesis disorder, autosomal recessive[1]	REEP6	Retinitis pigmentosa, autosomal recessive[1]
PEX7	Peroxisome biogenesis disorder, autosomal recessive[1]	RGR	Retinitis pigmentosa, autosomal recessive[1]
PEX10	Peroxisome biogenesis disorder, autosomal recessive[1]	RGS9	Other retinopathy, autosomal recessive[1]
PEX12	Peroxisome biogenesis disorder, autosomal recessive[1]	RGS9BP	Other retinopathy, autosomal recessive[1]
PEX14	Peroxisome biogenesis disorder, autosomal recessive[1]	RHO	Retinitis pigmentosa, autosomal dominant[1]

GENE	DISEASE CATEGORY[1]	GENE	DISEASE CATEGORY[1]
RIMS1	Cone or cone-rod dystrophy, autosomal dominant[1]	TEAD1	Retinitis pigmentosa, autosomal dominant[1]
RLBP1	Retinitis pigmentosa, autosomal recessive[1]	TIMP3	Congenital stationary night blindness, autosomal recessive[1]
ROM1	Retinitis pigmentosa, autosomal dominant[1]	TOPORS	Other retinopathy, autosomal dominant[1]
RP1	Retinitis pigmentosa, autosomal dominant[1]	TTC8	Syndromic/systemic diseases with retinopathy, autosomal recessive Joubert syndrome, autosomal recessive[1]
RP1L1*	Occult macular dystrophy, autosomal dominant Retinitis pigmentosa, autosomal recessive[1]	TTLL5	Retinitis pigmentosa, autosomal recessive[1]
RP2	Retinitis pigmentosa, X-linked[1]	TTPA	Cone or cone-rod dystrophy, autosomal recessive[1]
RPE65	Retinitis pigmentosa, autosomal recessive Leber congenital amaurosis, autosomal recessive[1]	TUB	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
RPGR	Cone or cone-rod dystrophy, X-linked[1]	TULP1	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
RPGRIP1	Cone or cone-rod dystrophy, autosomal recessive[1]	TUBGCP4	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
RPGRIP1L	Joubert syndrome, autosomal recessive[1]	TUBGCP6	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
RS1	Retinoschisis, X-linked[1]	TULP1	Leber congenital amaurosis, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]
RTN4IP1	Optic atrophy, autosomal recessive[1]	TYR*	Oculocutaneous albinism, autosomal recessive[1]
SAG	Congenital stationary night blindness, autosomal recessive Retinitis pigmentosa, autosomal recessive and dominant[1]	TYRP1	Oculocutaneous albinism, autosomal recessive[1]
SAMD11	Retinitis pigmentosa, autosomal recessive[1]	UNC119	Cone or cone-rod dystrophy, autosomal dominant[1]
SCLT1	Retinitis pigmentosa, autosomal recessive[1]	USH1C*	Usher syndrome, autosomal recessive[1]
SDCCAG8	Bardet-Biedl syndrome, autosomal recessive[1]	USH1G	Usher syndrome, autosomal recessive[1]
SEMA4A	Cone or cone-rod dystrophy, autosomal dominant[1]	USH2A	Usher syndrome, autosomal recessive Retinitis pigmentosa, autosomal recessive[1]
SLC24A1	Congenital stationary night blindness, autosomal recessive[1]	VCAN	Wagner syndrome, autosomal dominant[1]
SLC25A46	Oculoauricular syndrome, autosomal recessive[1]	WDR19	Cohen syndrome, autosomal recessive[1]
SLC39A5	Retinitis pigmentosa, autosomal recessive[1]	WDPCP	Syndromic/systemic disease with retinopathy, autosomal recessive[1]
SNRNP200	Retinitis pigmentosa, autosomal dominant[1]	WDR19	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
SPATA7	Leber congenital amaurosis, autosomal recessive[1]	WFS1	Syndromic/systemic diseases with optic atrophy, autosomal recessive and dominant Wolfram syndrome, autosomal recessive[1]
SPP2	Retinitis pigmentosa, autosomal dominant[1]	WHRN	Usher syndrome, autosomal recessive[1]
TCTN1	Joubert syndrome, autosomal recessive[1]	ZNF408	Retinitis pigmentosa, autosomal recessive[1]
TCTN2	Joubert syndrome, autosomal recessive Meckel syndrome, autosomal recessive[1]	ZNF423	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]
TCTN3	Joubert syndrome, autosomal recessive[1]	ZNF513	Retinitis pigmentosa, autosomal recessive[1]
TEAD1	Choroidal atrophy or degeneration, autosomal dominant[1]		
TMEM67	Syndromic/systemic diseases with optic nerve atrophy, X-linked Joubert Syndrome, autosomal recessive[1]		
TMEM70	Macular dystrophy, autosomal dominant[1]		
TMEM107	Joubert syndrome, autosomal recessive Meckel syndrome, autosomal recessive[1]		
TMEM126A	Optic atrophy, autosomal recessive[1]		
TMEM138	Joubert syndrome, autosomal recessive[1]		
TMEM216	Joubert syndrome, autosomal recessive Meckel syndrome, autosomal recessive[1]		
TMEM237	Syndromic/systemic diseases with retinopathy, autosomal recessive[1]		
TOPORS	Retinitis pigmentosa, autosomal dominant[1]		
TPP1	Infantile neuronal ceroid lipofuscinosis (CLN2), autosomal recessive Late neuronal ceroid lipofuscinosis, autosomal recessive[1]		
TRIM32*	Senior-Loken syndrome 8 (cerebellar ataxia and retinal dystrophy), autosomal recessive[1]		
TRIP13	Syndromic/systemic diseases with retinopathy, autosomal dominant Familial Cockayne syndrome, autosomal dominant and recessive[1]		
TRNT1*	Bardet-Biedl syndrome, autosomal recessive[1]		

Visit **IDYOURIRD.com** for more information or to order free[1] test kits.

References: 1. Target GR Editors. S. Varela G.L. Genetic/Genomic Interactions Research. https://www.ncbi.nlm.nih.gov/books/NBK1116/. Updated September 1, 2010. Accessed September 29, 2016. 2. Online Catalog of Human Genes and Genetic Disorders. Updated September 30, 2016. Accessed September 30, 2016.

Spark

Age-Related Degeneration Genetic Testing

Peer-Reviewed Published Studies

Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models. *IOVS* 53.3 (2012): 1548-1556.

CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology* 120.11 (2013): 2317-2323.

Validation of a prediction algorithm for progression to advanced macular degeneration subtypes. *JAMA ophthalmology* 131.4 (2013): 448-455.

Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic risk allele number in the Age-Related Eye Disease Study. *Ophthalmology* 122.1 (2015): 162-169.

Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis. *British Journal of Ophthalmology* 100.12 (2016): 1731-1737.

CFH and ARMS2 genetic risk determines progression to nvAMD after antioxidant and zinc supplementation. *Proc National Academy of Sciences* 115.4 (2018): E696-E704.

Age-Related Degeneration Testing

Arctic Medical Laboratories (https://arcticdx.com)

Vita Rx Risk®
PREDICT AND PROTECT®

Vita Risk® is a DNA test measuring the two main genetic variations (three genetic variations in two genes) that interact with common vitamin/mineral supplements containing zinc. People in one genetic group have increased risk of progression of age-related macular degeneration, to wet AMD.

Does my patient carry the genetic variations associated with vision loss when using chronic supplements such as AREDS?

*****Patients positive for VitaRisk are advised to avoid long-term AREDS/AREDS2 supplements***

Age-Related Degeneration Testing

Arctic Medical Laboratories (https://arcticdx.com)

Macula Risk®
PREDICT AND PROTECT®

Macula Risk® is a DNA test combining many of the genes (15 genetic variations in 12 genes) associated with the progression of age-related macular degeneration (AMD). The genetic result is integrated into a formula developed from research at Tufts Medical Center and includes a patient's age, AMD disease status, height, weight, sex, age, and smoking history, which provides a basis for progression risk.

What is the likelihood of my patient progressing to advanced AMD?

Should my patient avoid chronic zinc supplementation?

*****Predictive algorithm touts 89% accuracy @ 2, 5 and 10-year time points***

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2 of 3 PATIENT'S RISK OF ED AMD **LOW**

CONTRIBUTION TO RISK RESULTS

The AMD Lifetime Risk is calculated based upon the patient's genetics, ocular findings, demographic and behavior status. The table below lists the patient's individual factors contributing to their individual risk.

RISK FACTORS

DESCRIPTION OF CONTRIBUTION

PATIENT FACTOR MEASURED	LOWER RISK	MODERATE RISK	HIGHER RISK	PATIENT RESULTS
AMD Grading	0-2 Factors	3 Factors	4 Factors	LOWER
Genetic Markers	Low	Moderate	High	LOWER
Race	Non-White	-	White	HIGHER
Smoking Status	Never	Past	Current	LOWER
BMI Score	<25	25-29	≥30	HIGHER
Gender	Male	-	Female	LOWER
Age (years)	55-64	65-74	≥75	LOWER

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	12/01/2021	0-1235	P-1192

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AMD LIFETIME RISK REPORT age related macular degeneration — Visible GENOMICS

RISK FACTORS

GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	X
		GT	Moderate Risk	
		TT	Higher Risk	
CFH (Complement Factor H)	rs1061170	TT	Highly Protective	X
		CT	Moderately Protective	
		CC	Higher Risk (Reference)	
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	X
		GG	Higher Risk (Reference)	
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	X
		GC	Moderate Risk	
		CC	Higher Risk	

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	[redacted]	[redacted]	[redacted]

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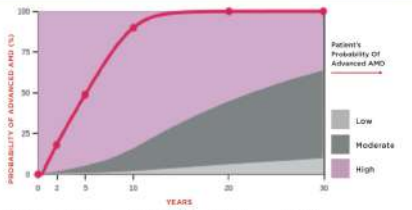
CURRENT AGE **60** RISK OF ADVANCED AMD

PATIENT'S PROBABILITY OF ADVANCED AMD **HIGH**

2 YEARS	18%
5 YEARS	49%
10 YEARS	90%
20 YEARS	100%
30 YEARS	100%



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George Miles, M.D., Ph.D.	11/24/2021	0-1200	P-1196

AMD PROGRESSION REPORT age related macular degeneration — Visible GENOMICS

RISK FACTORS

DESCRIPTION OF CONTRIBUTION

PATIENT FACTOR MEASURED	LOWER RISK	MODERATE RISK	HIGHER RISK	PATIENT RESULTS
AMD Grading	0-2 Factors	3 Factors	4 Factors	MODERATE
Genetic Markers	Low	Moderate	High	HIGHER
Race	Non-White	-	White	HIGHER
Smoking Status	Never	Past	Current	MODERATE
BMI Score	<25	25-29	≥30	HIGHER
Gender	Male	-	Female	LOWER
Age (years)	55-64	65-74	≥75	HIGHER

GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	
		GT	Moderate Risk	
		TT	Higher Risk	X
CFH (Complement Factor H)	rs1061170	TT	Highly Protective	
		CT	Moderately Protective	X
		CC	Higher Risk (Reference)	
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	
		GG	Higher Risk (Reference)	X
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	
		GC	Moderate Risk	
		CC	Higher Risk	X

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	11/24/2021	0-1200	P-1196

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2 of 3 PATIENT'S RISK OF ED AMD **MODERATE**

CONTRIBUTION TO RISK RESULTS

The AMD Lifetime Risk is calculated based upon the patient's genetics, ocular findings, demographic and behavior status. The table below lists the patient's individual factors contributing to their individual risk.

RISK FACTORS

DESCRIPTION OF CONTRIBUTION

PATIENT FACTOR MEASURED	LOWER RISK	MODERATE RISK	HIGHER RISK	PATIENT RESULTS
AMD Grading	0-2 Factors	3 Factors	4 Factors	LOWER
Genetic Markers	Low	Moderate	High	MODERATE
Race	Non-White	-	White	HIGHER
Smoking Status	Never	Past	Current	LOWER
BMI Score	<25	25-29	≥30	LOWER
Gender	Male	-	Female	HIGHER
Age (years)	55-64	65-74	≥75	LOWER

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	11/24/2021	0-1239	P-1195

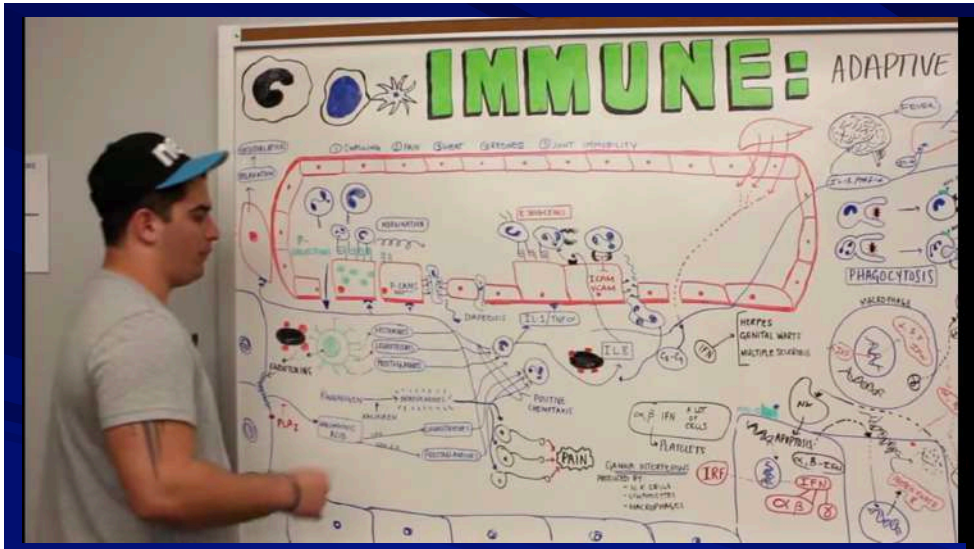
AMD LIFETIME RISK REPORT age related macular degeneration — Visible GENOMICS

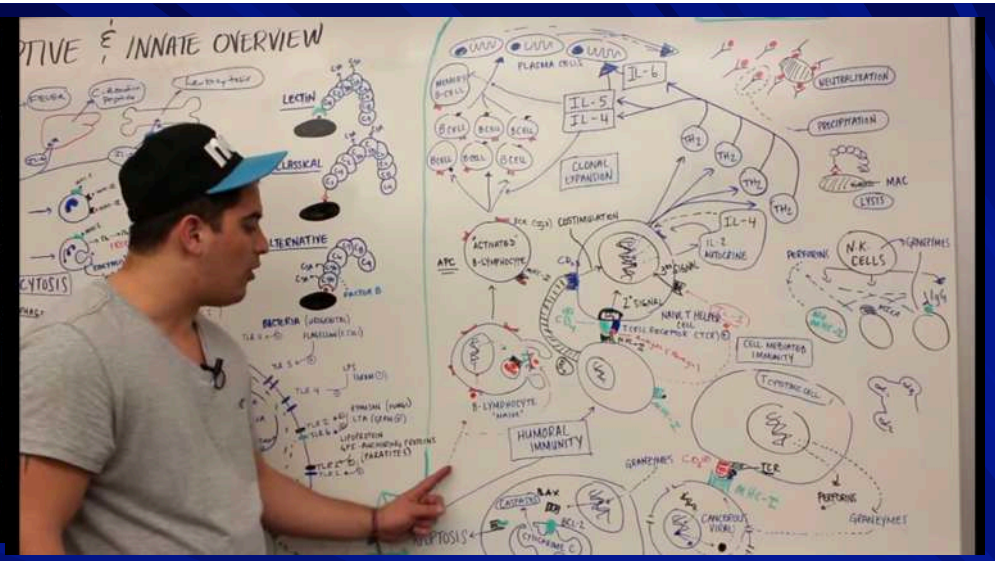
RISK FACTORS

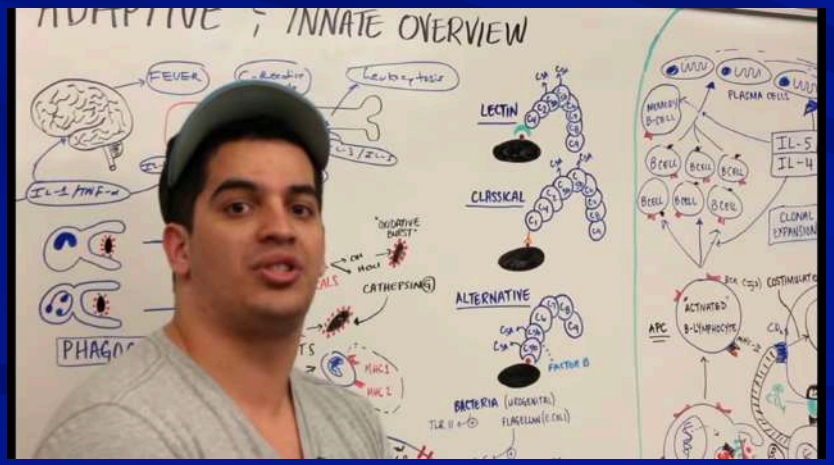
GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	
		GT	Moderate Risk	X
		TT	Higher Risk	
CFH (Complement Factor H)	rs1061170	TT	Highly Protective	X
		CT	Moderately Protective	
		CC	Higher Risk (Reference)	
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	X
		GG	Higher Risk (Reference)	
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	
		GC	Moderate Risk	X
		CC	Higher Risk	

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	[redacted]	[redacted]	[redacted]







Ninja Nerd Science
YouTube

Complement factor H in AMD: Bridging genetic associations and pathobiology

Christopher B. Toomey [a, b, 1] ... Catherine Bowes Rickman [a, b]

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https://doi.org/10.1016/j.preteyeres.2017.09.001

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Abstract

Age-Related Macular Degeneration (AMD) is a complex multifactorial disease characterized in its early stages by lipoprotein accumulations in Bruch's Membrane (BrM), seen on fundoscopic exam as drusen, and in its late forms by neovascularization ("wet") or geographic atrophy of the Retinal Pigmented Epithelial (RPE) cell layer ("dry"). Genetic studies have strongly supported a relationship between the alternative complement cascade, in particular the common H402 variant in Complement Factor H (CFH) and development of AMD. However, the functional significance of the CFH Y402H polymorphism remains elusive. In this

FEEDBACK

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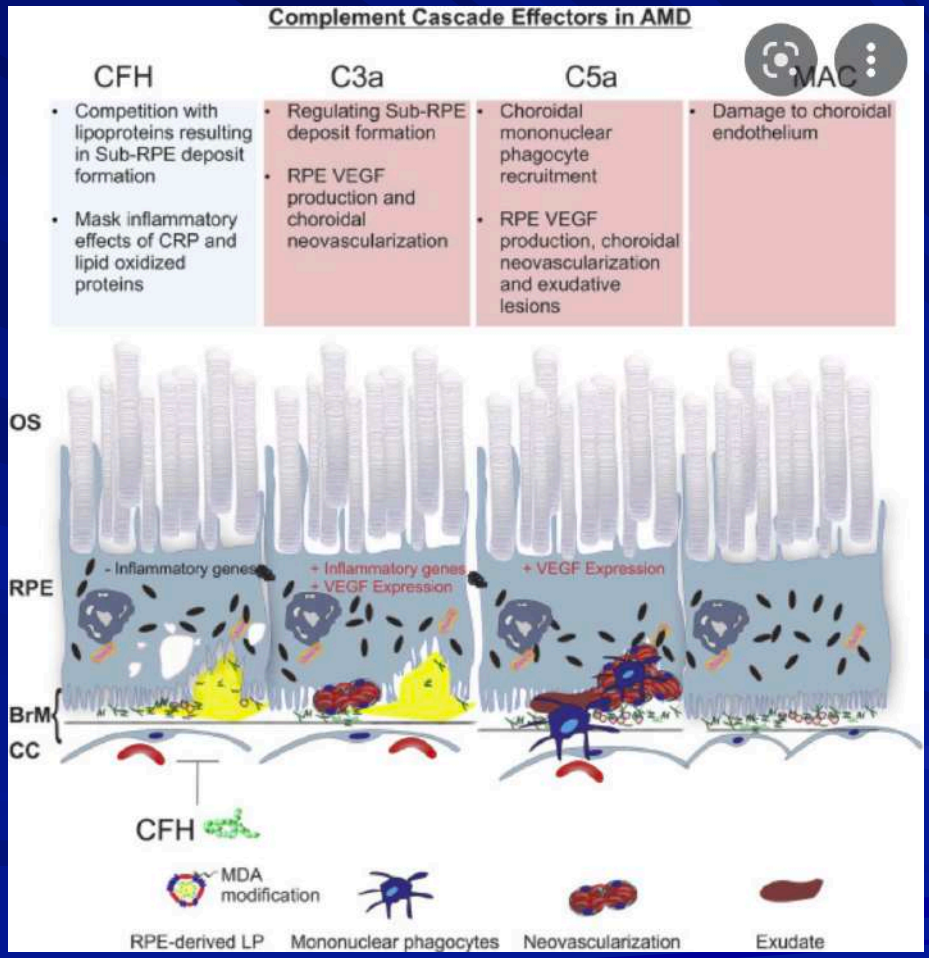

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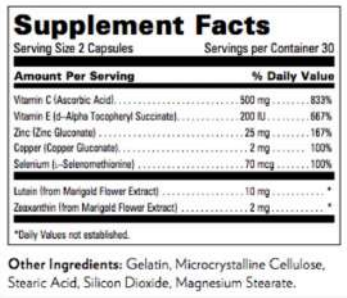
AREDS/AREDS2 Frequently Asked Questions

Ingredients



Supplement Facts

Serving Size 2 Capsules — Servings per Container 30

Amount Per Serving		% Daily Value
Vitamin C (Ascorbic Acid)	500 mg	833%
Vitamin E (d-Alpha Tocopheryl Succinate)	200 IU	667%
Zinc (Zinc Gluconate)	25 mg	167%
Copper (Copper Gluconate)	2 mg	100%
Selenium (L-Selenomethionine)	70 mcg	100%
Lutein (from Marigold Flower Extract)	10 mg	*
Zeaxanthin (from Marigold Flower Extract)	2 mg	*

*Daily Values not established.

Other Ingredients: Gelatin, Microcrystalline Cellulose, Stearic Acid, Silicon Dioxide, Magnesium Stearate.

What is the basis for the concentration of zinc in the AREDS supplements? What concentration should I take?

In the AREDS trial, the 80 mg zinc dose (alone or in combination with antioxidant vitamins) was found to be effective compared to a placebo. Although zinc was found to be an essential component of the AREDS formulation, some nutritional experts recommended a lower dose. In the AREDS2 trial, there was no placebo control. Instead, participants were given the option to take the original formula or to be randomly assigned to receive a modified version, such as a formula containing 25 mg zinc. The investigators did not find a difference in the effects of 80 mg vs. 25 mg zinc. Because AREDS2 did not include a placebo control, results from AREDS, placebo-controlled trial, are still considered the gold standard.

Zinc is found in vegetables, grains, and meat. Vegetables and grains contain other molecules that can prevent zinc absorption and thus reduce its bioavailability. Supplements contain purified zinc, without these competing molecules. Although the chemical form of zinc affects its rate of absorption in the stomach, it is not clear how this affects bioavailability (i.e., the amount of zinc that reaches the retina). For more on this topic, please see the zinc fact sheet from the NIH Office of Dietary Supplements.

PubMed.gov

Advanced

Randomized Controlled Trial

Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic risk allele number in the Age-Related Eye Disease Study

Carl C Awh et al. Ophthalmology. 2015 Jan.

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Abstract

Objective: To evaluate the impact of complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) risk alleles on the observed response to components of the Age-Related Eye Disease Study (AREDS) formulation.

Design: Genetic and statistical subgroup analysis of a randomized, prospective clinical trial.

Participants: White patients from the AREDS with category 3 or 4 age-related macular degeneration (AMD) with available DNA (n = 989).

Results: Patients with 2 CFH risk alleles and no ARMS2 risk alleles progressed more with zinc-containing treatment compared with placebo, with a hazard ratio (HR) of 3.07 (P = 0.0196) for zinc and 2.73 (P = 0.0418) for AREDS formulation (AF). Seven-year treatment-specific progression rates were: placebo, 17.0%; zinc, 43.2% (P = 0.023); and AF, 40.2% (P = 0.039). Patients with 0 or 1 CFH risk alleles and 1 or 2 ARMS2 risk alleles benefited from zinc-containing treatment compared with placebo, with an HR of 0.514 for zinc (P = 0.012) and 0.569 for AF (P = 0.0254). Seven-year treatment-specific AMD progression rates were as follows: placebo, 43.3%; zinc, 25.2% (P = 0.020); and AF, 27.3% (P = 0.011). Zinc and AF treatment each interacted statistically with these 2 genotype groups under a Cox model, with P values of 0.000999 and 0.00366, respectively. For patients with 0 or 1 CFH risk alleles and no ARMS2 risk alleles, neither zinc-containing treatment altered progression compared with placebo, but treatment with antioxidants decreased progression (HR, 0.380; P = 0.034). Seven-year progression with placebo was 22.6% and with antioxidants was 9.17% (P = 0.033). For patients with 2 CFH risk alleles and 1 or 2 ARMS2 risk alleles, no treatment was better than placebo (48.4%).

Conclusions: The benefit of the AREDS formulation seems the result of a favorable response by patients in only 1 genotype group, balanced by neutral or unfavorable responses in 3 genotype groups.

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RESEARCH ARTICLE | OPEN ACCESS

CFH and *ARMS2* genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation

Demetrios G. Vavvas, Kent W. Small, Carl C. Awh, +2, and Rafal Kustra Authors Info & Affiliations

January 8, 2018 | 115 (4) E696-E704

https://doi.org/10.1073/pnas.1718059115

Genetic Polymorphisms of *CFH* and *ARMS2* Do Not Predict Response to Antioxidants and Zinc in Patients with Age-Related Macular Degeneration

Independent Statistical Evaluations of Data from the Age-Related Eye Disease Study

Melissa J. Assel, MS,[1,2] Fan Li, MS,[1,2] Ying Wang, PhD,[1,2] Andrew S. Allen, PhD,[1,2] Kirk A. Baggerly, PhD,[3,4] Andrew J. Vickers, PhD[1,2]

Purpose: Considerable controversy has erupted in recent years regarding whether genotyping should be part of standard care for patients with age-related macular degeneration (AMD) who are being considered for treatment with antioxidants and zinc. We aimed to determine whether genotype predicts response to supplements in AMD.

Design: Three separate statistical teams reanalyzed data derived from the Age-Related Eye Disease Study (AREDS), receiving data prepared by the AREDS investigators and, separately, data from investigators reporting findings that support the use of genotyping.

Participants: The population of interest was AREDS participants with AMD worse than category 1 and genotyping data available. Data from the 2 groups overlap imperfectly with respect to measurements made; the largest common set involved 979 participants for whom the same *CFH* and *ARMS2* single nucleotide polymorphisms were measured by both groups.

Methods: Each team took a separate but complementary approach. One team focused on data concordance between conflicting studies. A second team focused on replicating the key claim of an interaction between genotype and treatment. The third team took a blank slate approach in attempting to find baseline predictors of treatment response.

Main Outcome Measures: Progression to advanced AMD.

Results: We found errors in the data used to support the initial claim of genotype–treatment interaction. Although we found evidence that high-risk patients had more to gain from treatment, we were unable to replicate any genotype–treatment interactions after adjusting for multiple testing. We tested 1 genotype claim on an independent set of data, with negative results. Even if we assumed that interactions in fact did exist, we did not find evidence to support the claim that supplementation leads to a large increase in the risk of advanced AMD in some genotype subgroups.

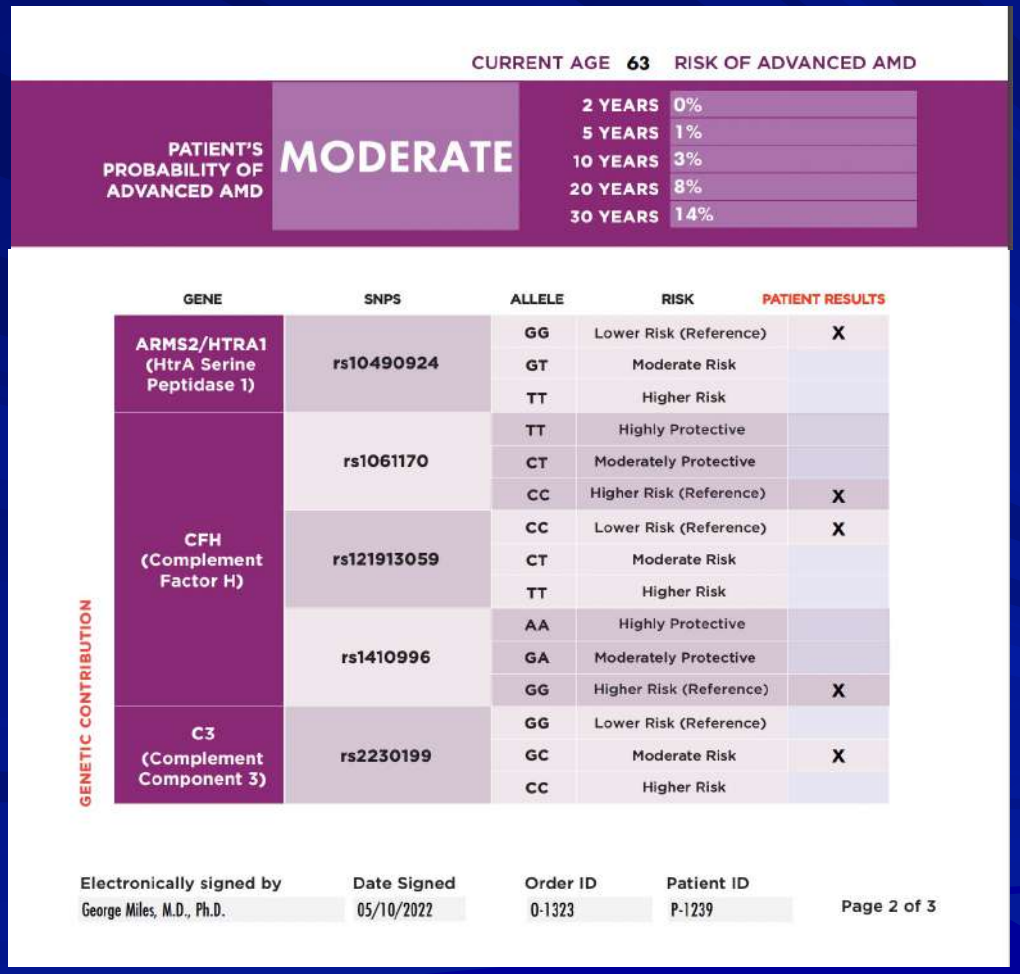
Conclusions: Patients who meet criteria for supplements to prevent AMD progression should be offered zinc and antioxidants without consideration of genotype. Ophthalmology 2018;125:397-397 © 2017 by the American Academy of Ophthalmology

Supplemental material available at www.aaojournal.org.

The Age-Related Eye Disease Study (AREDS) was a large, multicenter, double-blind randomized trial to determine whether high-dose antioxidants, zinc, or their combination could reduce the risk of progression of age-related macular degeneration (AMD) in older patients. Excluding patients in AMD category 1, for whom the event rate was less than 1%, the combination of zinc and antioxidants was found to reduce the risk of progression to advanced AMD (odds ratio, 0.68; 95% confidence interval [CI], 0.49–0.93; $P = 0.002$).[1] The publication of the trial results led to rapid changes in practice, with at-risk patients routinely prescribed the zinc and antioxidant combination noted in the trial.

In 2008, Klein et al[2] published a pharmacogenomic study suggesting that the effects of antioxidants and zinc on AMD in AREDS may be influenced by genotype.

Would You Recommend AREDS2?



CURRENT AGE 63 RISK OF ADVANCED AMD

PATIENT'S PROBABILITY OF ADVANCED AMD: **MODERATE**

2 YEARS	0%
5 YEARS	1%
10 YEARS	3%
20 YEARS	8%
30 YEARS	14%

GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	X
		GT	Moderate Risk	
		TT	Higher Risk	
CFH (Complement Factor H)	rs1061170	TT	Highly Protective	
		CT	Moderately Protective	
		CC	Higher Risk (Reference)	X
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	
		GG	Higher Risk (Reference)	X
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	
		GC	Moderate Risk	X
		CC	Higher Risk	

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	05/10/2022	0-1323	P-1239

Page 2 of 3

AREDS/AREDS2 Frequently Asked Questions

Taking the AREDS formulas

Are the AREDS vitamins right for me?

In clinical trials, the AREDS and AREDS2 formulas benefited people with intermediate or late AMD. There was no benefit for people with early AMD or for people who do not have AMD.

Your primary care physician or eye care provider is in the best position to advise you on how treat your AMD. You may wish to discuss AREDS/AREDS2 supplements with your health care providers to decide which, if any, supplements are right for you.

Will taking the AREDS or AREDS2 supplements prevent AMD?

Nutritional supplements cannot prevent AMD. However, the AREDS/AREDS2 supplements may delay progression of intermediate to advanced AMD and may help you keep your vision longer. The participants AREDS trial have now been followed for more than 10 years, and the benefits of the AREDS formulation have persisted over this time.

Additional Resources

AREDS and AREDS2 Information

Age-Related Eye Disease Studies

AREDS/AREDS2 - Background and Design

AREDS/AREDS2 Nutritional Supplements

AREDS/AREDS2 News

Information about AMD

Age-Related Macular Degeneration

Will taking the AREDS or AREDS2 supplements prevent AMD?

Nutritional supplements cannot prevent AMD. However, the AREDS/AREDS2 supplements may delay progression of intermediate to advanced AMD and may help you keep your vision longer. The participants AREDS trial have now been followed for more than 10 years, and the benefits of the AREDS formulation have persisted over this time.

Can I take a daily multivitamin if I am taking one of the AREDS/AREDS2 formulas?

Yes. The AREDS and AREDS2 formulas do not substitute for multivitamins. In AREDS, two-thirds of the study participants took multivitamins along with the AREDS formulation. In AREDS2, almost nine of ten participants took multivitamins.

Endogenous and Exogenous Antioxidants

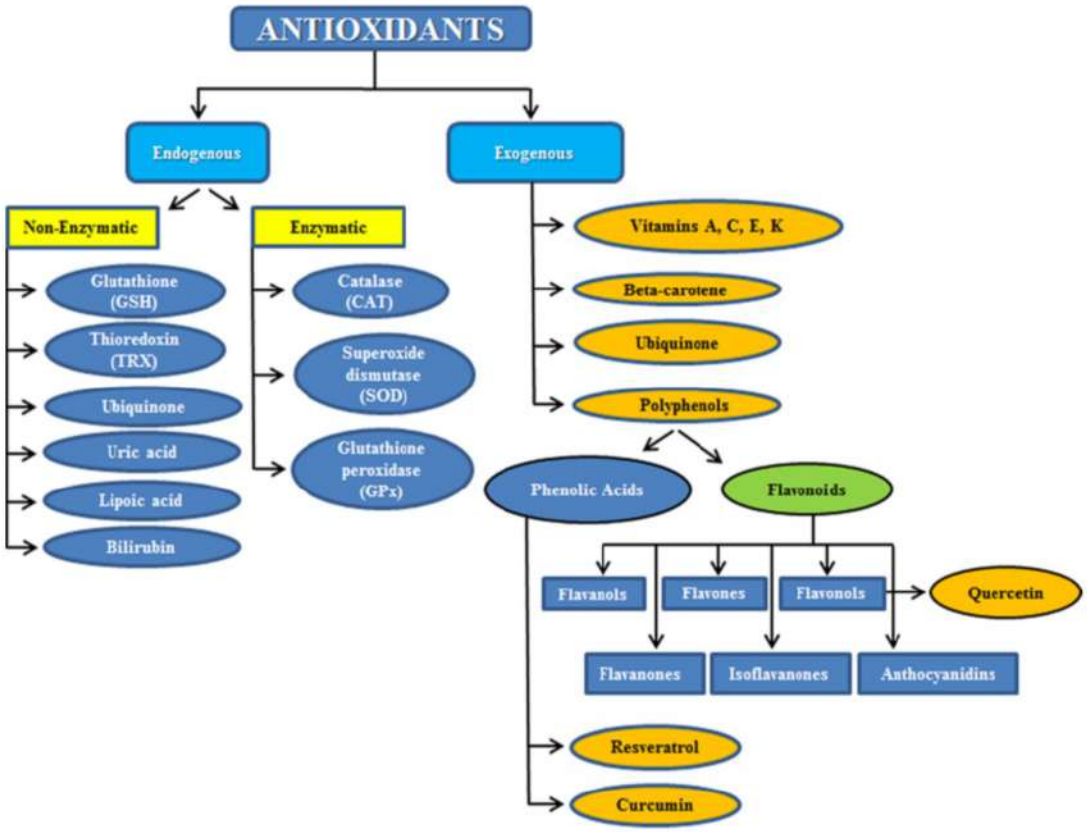
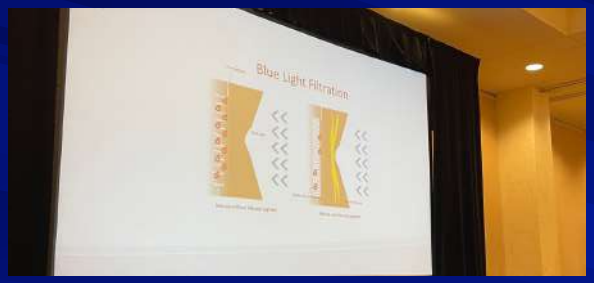
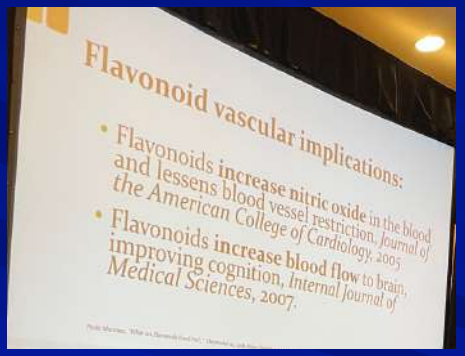


Figure 1: Subdivision between endogenous and exogenous antioxidants.

Carotenoids

- Why do hear so much about carotenoids
- Melonie Clemmons, OD May 20, 2022 AACO Nashville





Treating Half the Retina?

Oxidative Medicine and Cellular Longevity

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

Review

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

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

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].

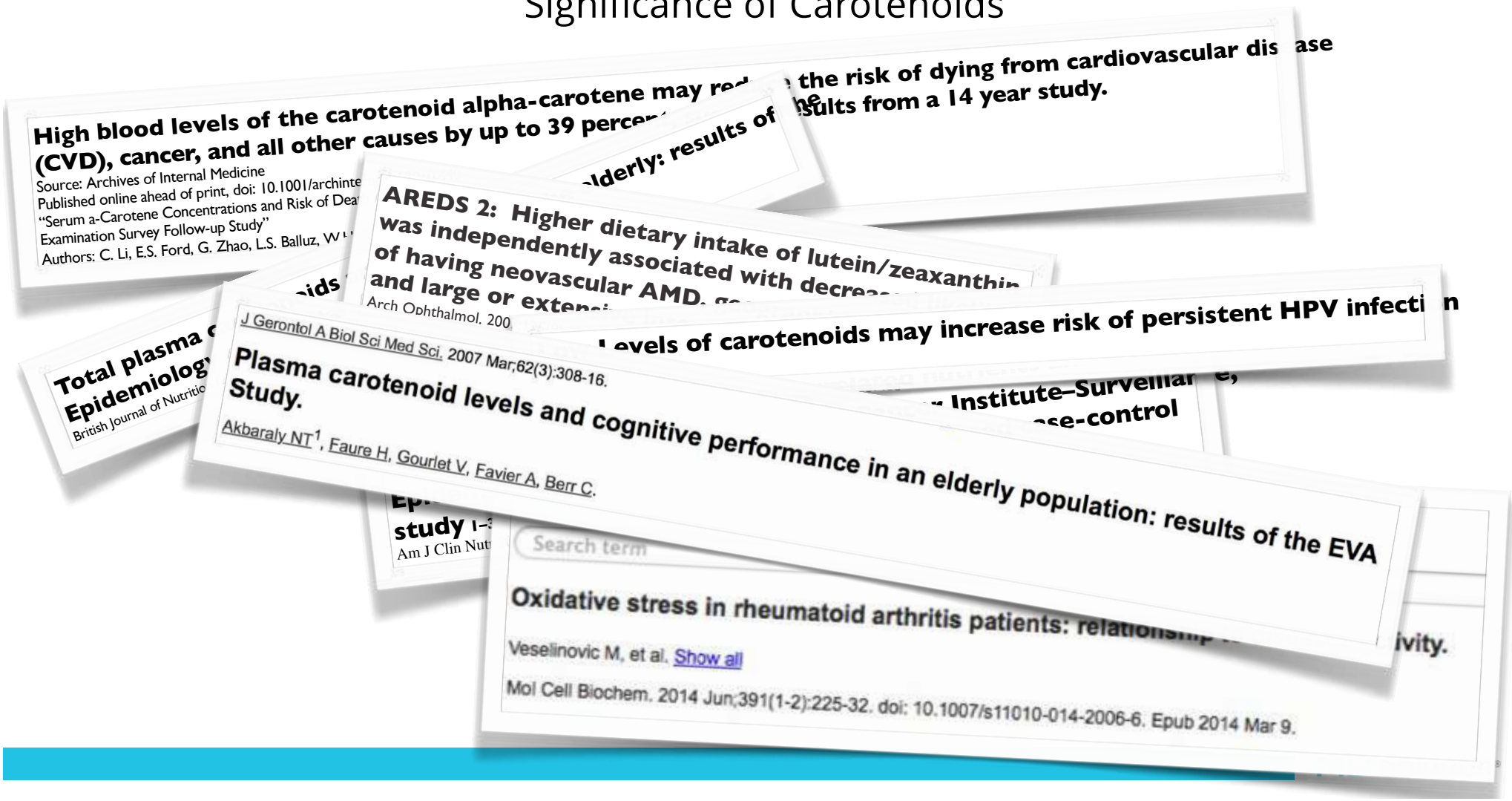
ASSESSMENT OF CAROTENOIDS

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.

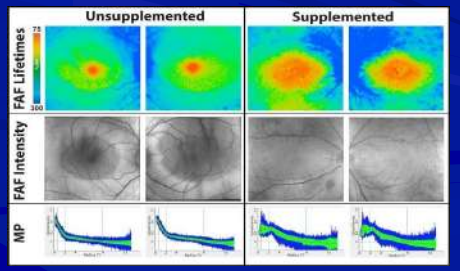
A large variety of methods are used to assess carotenoid status in humans, most of which are focused on the eye, but carotenoids can also be measured in tissue outside of the eye, such as the skin, blood, and the brain. Measurements of ocular carotenoids can be distinguished between subjective (psychophysical) 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).

Significance of Carotenoids



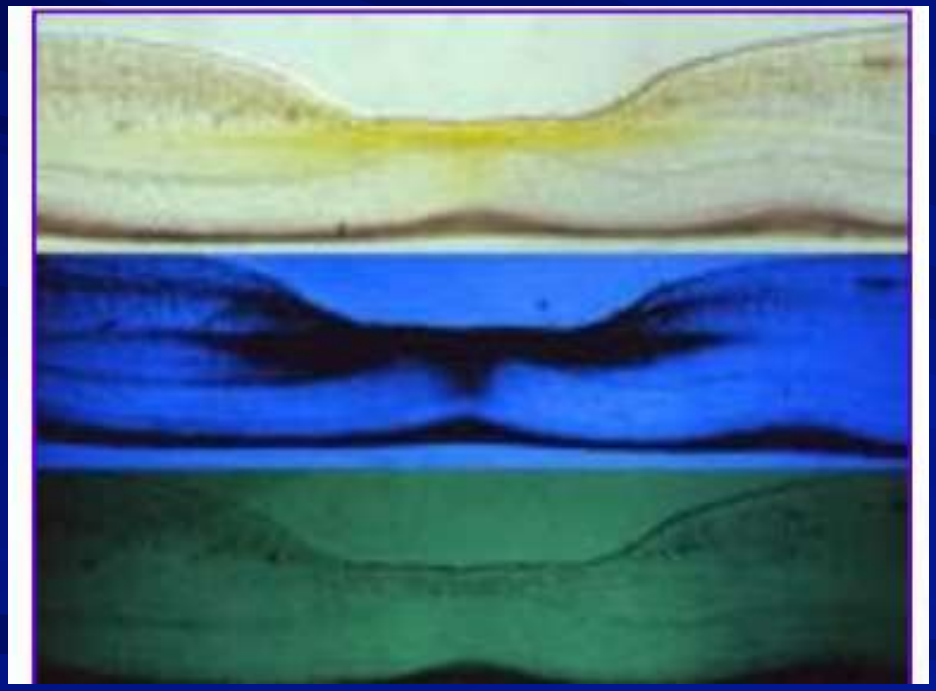
Measuring Macular Pigment

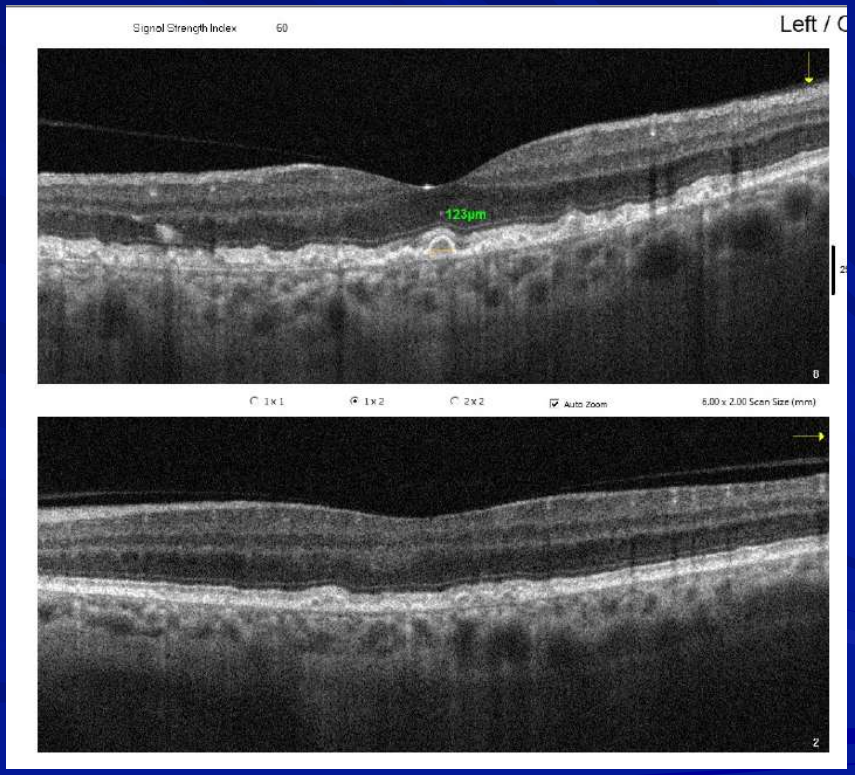
- Retina macula biopsy
- Clinical Imaging
  - ★ Subjective
    - ZeaVision MPSII
    - Guardion Mapcat SF
  - ★ Clinical
    - ZeaVision MPR
    - Zeiss Visucam 200
    - Spectralis HRA+OCT
    - Spectralis MPOV



Thank you! Dr. Chris Putnam

Macular Pigment





Macular Pigment

Imaging lutein and zeaxanthin in the human retina with confocal resonance Raman microscopy

Binxing Li[a], Evan W. George[a], Gregory T. Rognon[a], Aruna Gorusupudi[a], Arunkumar Ranganathan[a], Fu-Yen Chang[a], Linjia Shi[a], Jeanne M. Frederick[a], and Paul S. Bernstein[a,1]

[a]Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT 84132

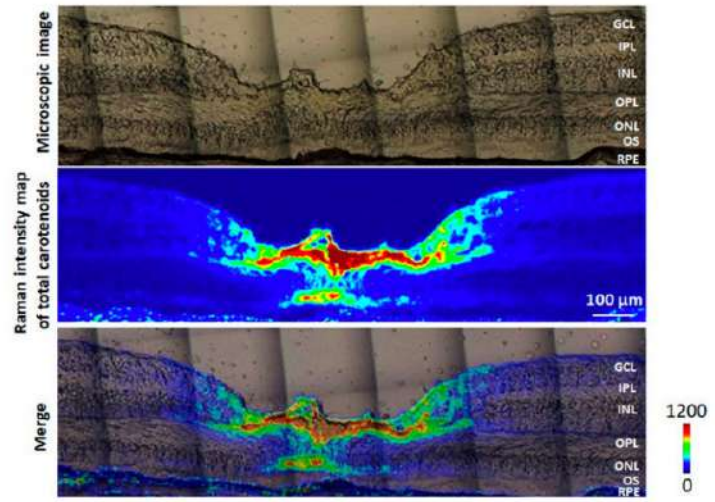
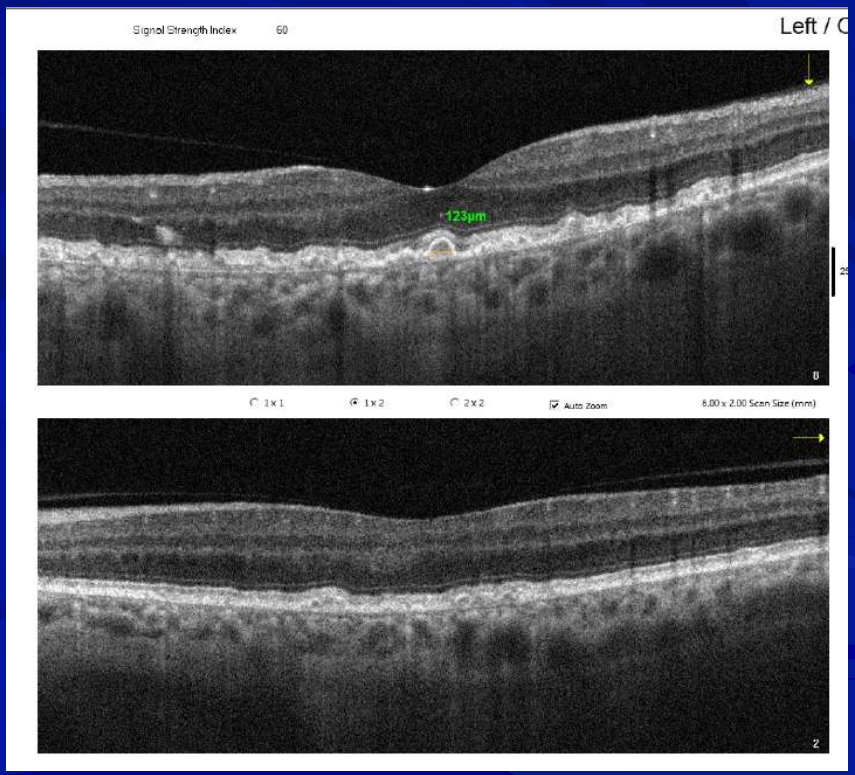


Fig. 4. Distribution of total carotenoids in a human retinal section. (*Top*) A



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

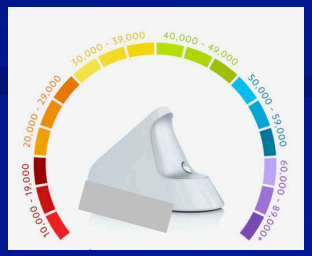
Carotenoid Levels

ARVO
The Association for Research in Vision and Ophthalmology

Scanner correlates to blood and macular pigment

read study

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



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;58:3616–3627. 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

Raman Spectroscopy

478nm PHOTONS ARE EMITTED FROM THE SCANNER

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

ARVO STUDY

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

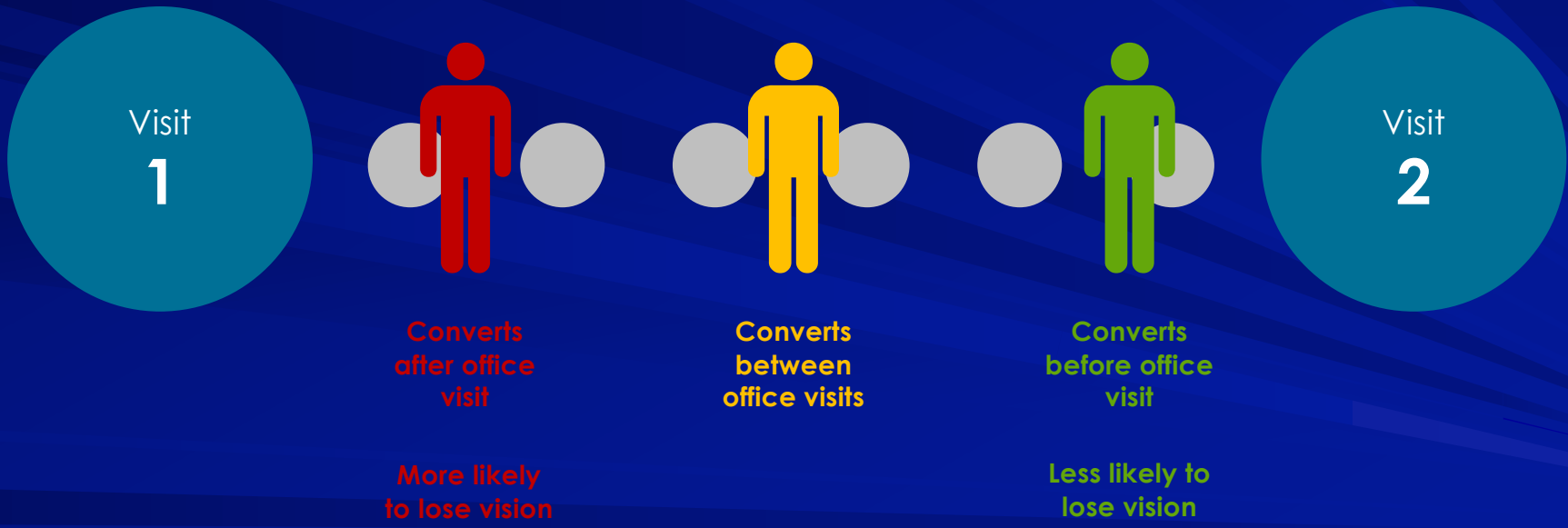
Conclusions:

"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.

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

AREDS
Dry AMD
Baseline

20/25
20/32

Wet AMD
Onset

BUT WHERE DID
WE START?

Preventable Vision Loss

Saving Lines

On average, those diagnosed at driving vision maintain vision

(CATT 1 & 2 year data)

+11.6/
+6.6
2 Years
ANCHOR/MARINA

+1.7
4 Years
HORIZON

-8.6
7.3 Years
7-Up Study

ForeseeHome Study Results[1]

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

Current Standard of Care

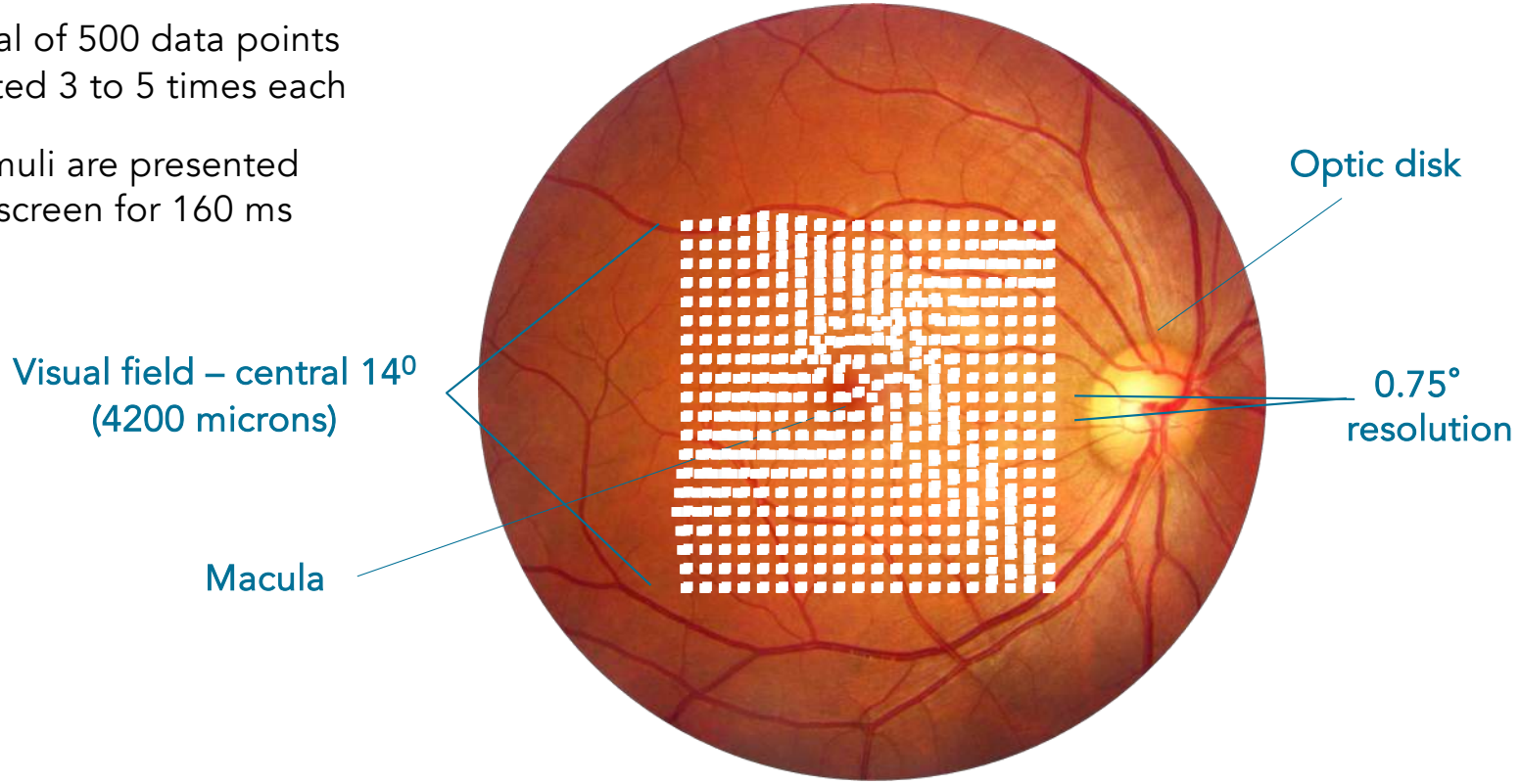
- 20/83 average VA[2]
- 13-41% 20/40 or better[3]
- 2.9-4.2 disc area size lesions[3]

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(5):268-273.

Notal Vision- PERIMETRY: The ForeseeHome Test

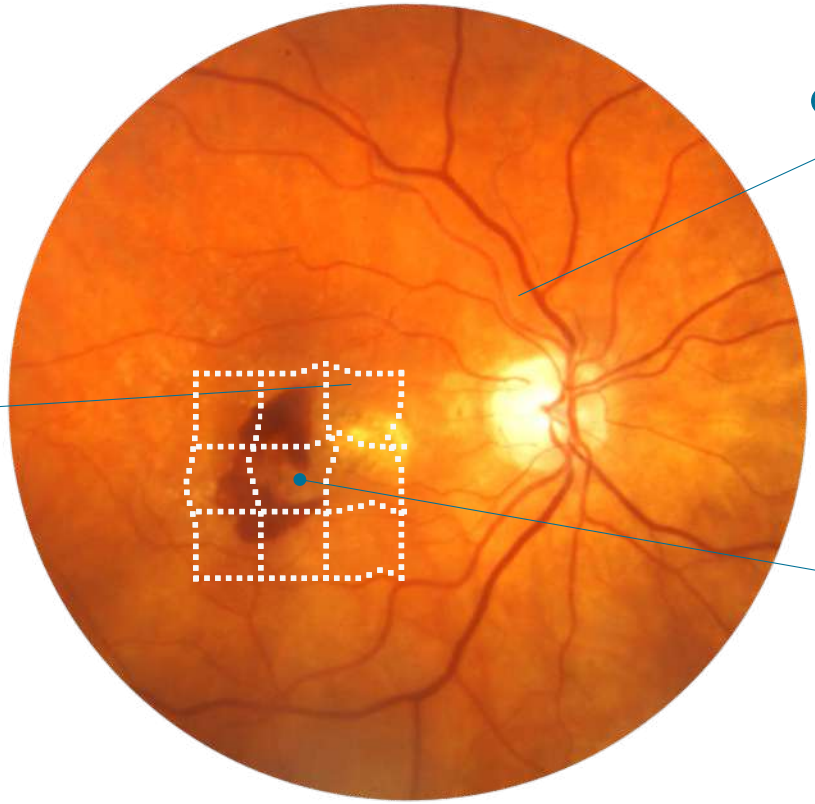
Total of 500 data points tested 3 to 5 times each

Stimuli are presented on screen for 160 ms



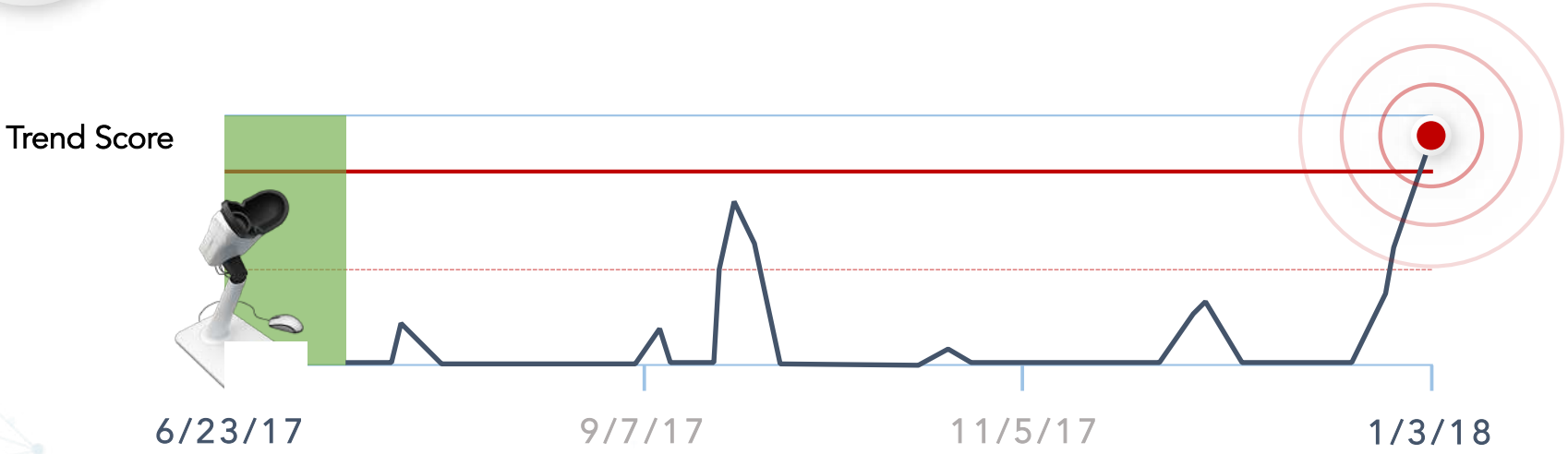
Once pathology is suspected, the area is bracketed to localize and quantify pathology

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

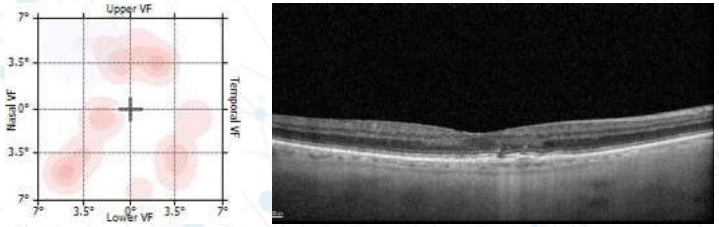


CASE 1 →

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

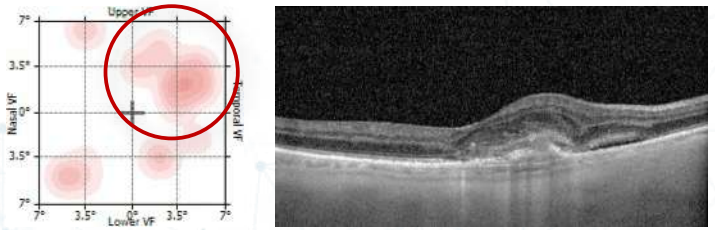


STARTED TESTING



ALERTED

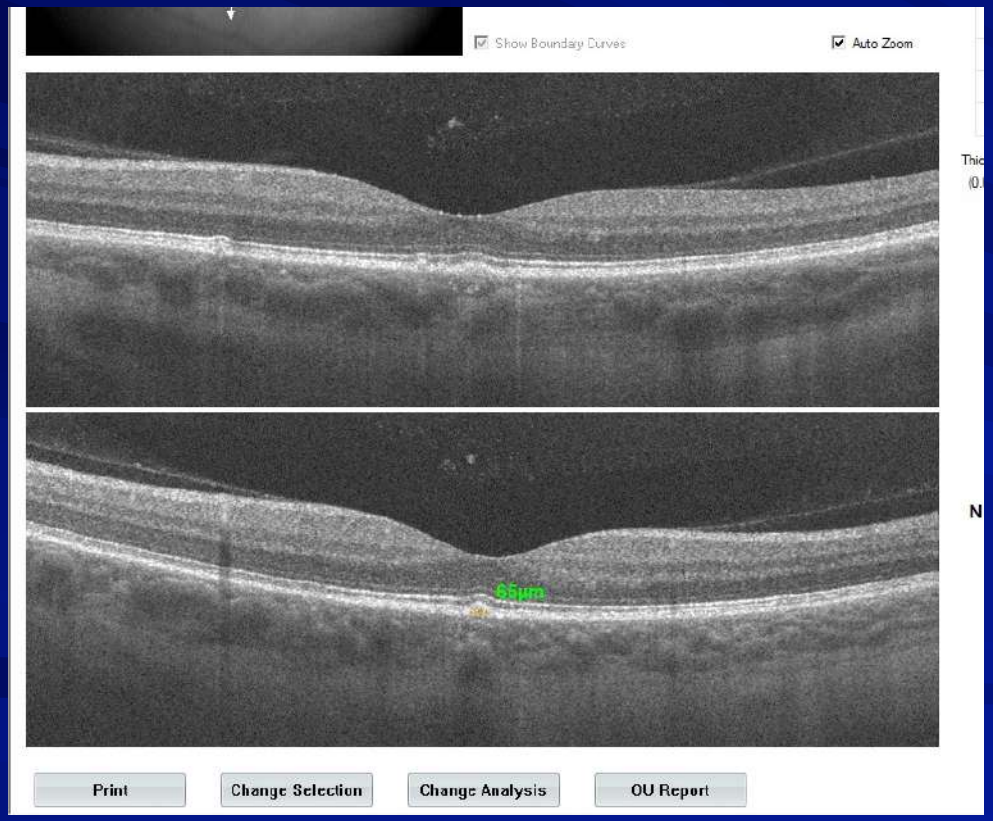
20/60 OD and asymptomatic



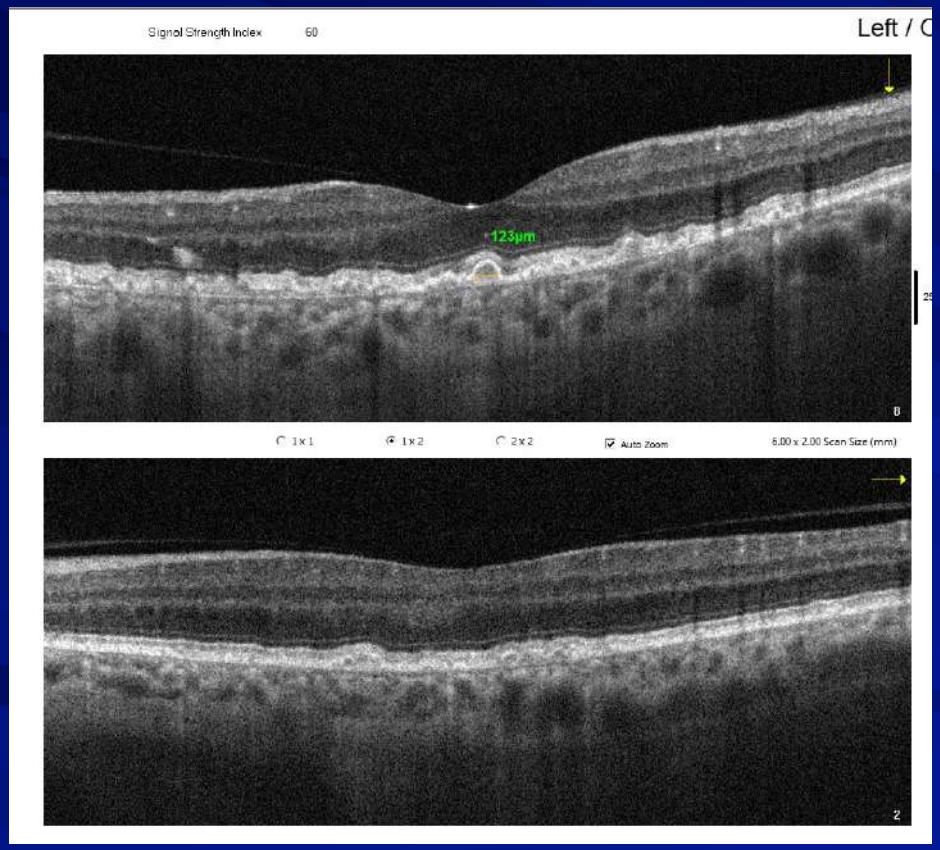
OCT in AMD

- Need spectral domain to follow intermediate or worse AMD
- Able to identify OCT predictors of progression
- Especially in identifying OCT predictors of progression
  - Hyper-reflective foci
  - Reticular pseudodrusen
  - Nascent geographic atrophy
  - Sub-RPE hyper-reflective columns
  - Drusen substructures
  - Drusen load and regression

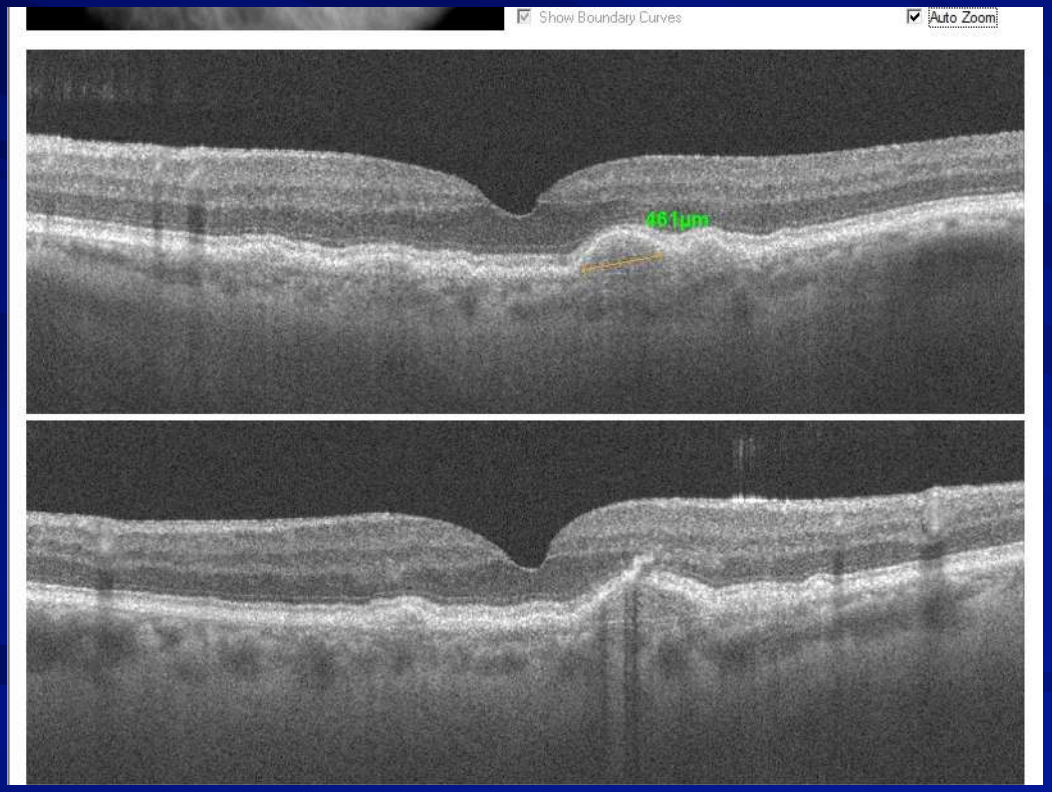
Measure the Drusen with Your OCT



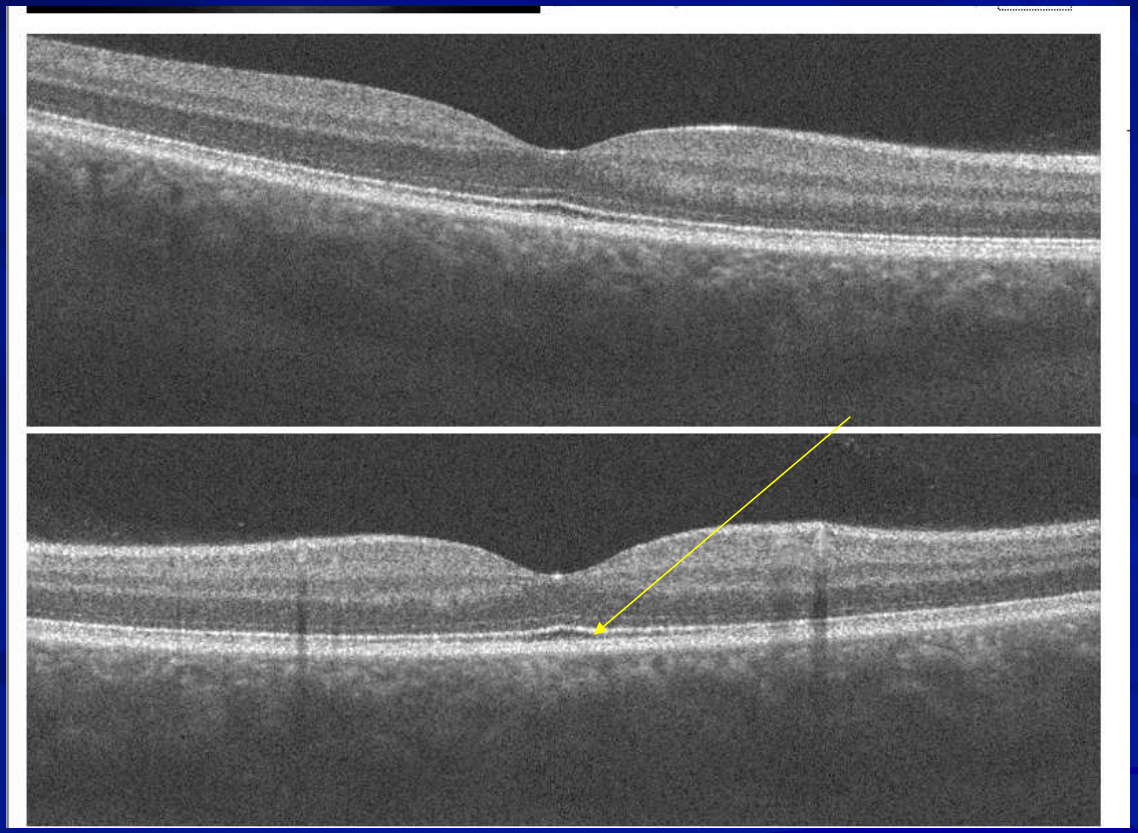
Measure the Drusen with Your OCT



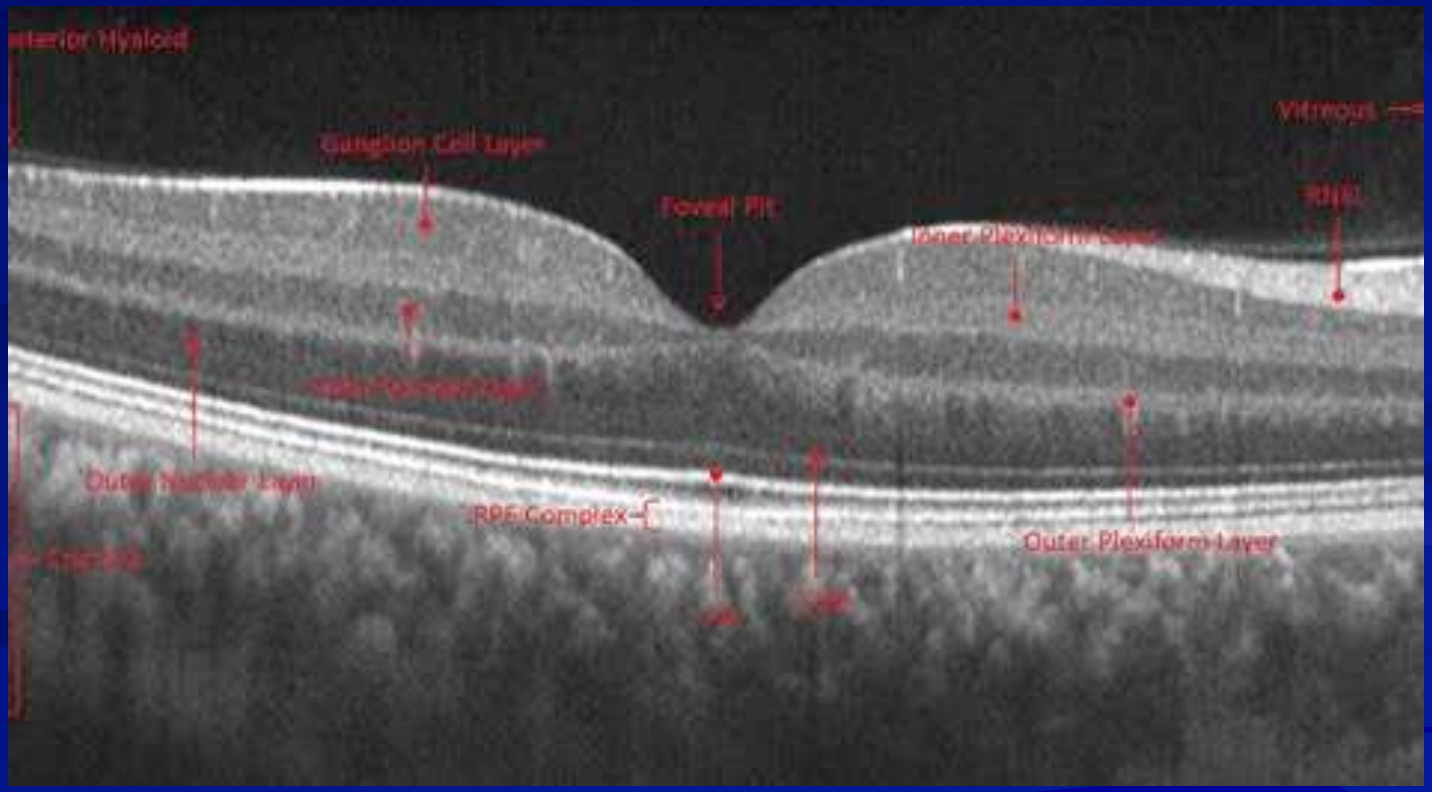
Measure the Drusen with Your OCT

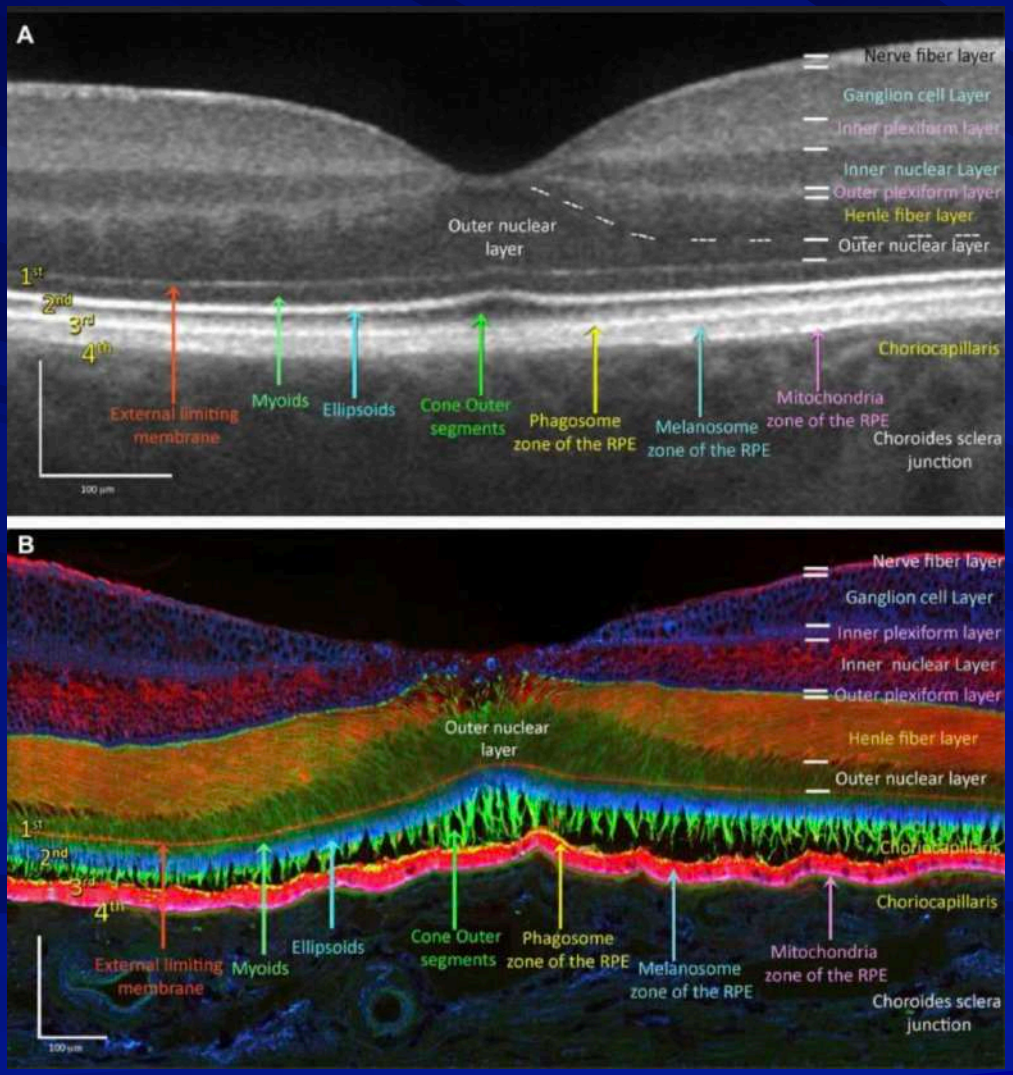


What is this layer called?



The ellipsoid zone (EZ) is considered to be **formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors**. However, it was previously known as the junction between the photoreceptor IS/OS).





Progress in Retinal and Eye Research
Volume 77, July 2020, 100828

Interpretation of OCT and OCTA images from a histological approach: Clinical and experimental implications

Nicolás Cuenca [a, b, 1] ... Isabel Pinilla [f, 1]

Show more

Outline | Share | Cite

https://doi.org/10.1016/j.preteyeres.2019.100828

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Abstract

Optical coherence tomography (OCT) and OCT angiography (OCTA) have been a techn

FEEDBACK

Fun Facts I Have Learned About the Mitochondria

- Mitochondria produce energy from organic matter
- Live about 100 days
- They produce 90% of energy in the body
- In return they product 90% of the free radicals
- When they become dysfunction when get many clinical consequences
- Mitochondria are very sensitive to reactive oxygen and need antioxidant support
- Mitochondria are one of cellular organelles
  - Electron transport chain – uses co-enzyme 10, and many other micronutrients
  - Brain cell has 1-2 million/single neuron
  - Heart cell has 5,000/cell
  - Liver cell has 1000-2000/cell
  - Photoreceptors 498/cell
  - RPE cells >700/cell


Neuron. Author manuscript; available in PMC 2018 Nov 1.
Published in final edited form as:
Neuron. 2017 Nov 1; 96(3): 651–666.
doi: 10.1016/j.neuron.2017.09.055

PMCID: PMC5687842
NIHMSID: NIHMS909951
PMID: 29096078

Mitostasis in neurons: Maintaining mitochondria in an extended cellular architecture

Thomas Misgeld[1,2,3,4] and Thomas L. Schwarz[5,6]

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nature › scientific reports › articles › article

Article | Open Access | Published: 22 September 2021

The 3D organisation of mitochondria in primate photoreceptors

Matthew J. Hayes, Dhani Tracey-White, Jaime Hoh Kam, Michael B. Powner & Glen Jeffery

Scientific Reports 11, Article number: 18883 (2021) | Cite this article

913 Accesses | 21 Altmetric | Metrics

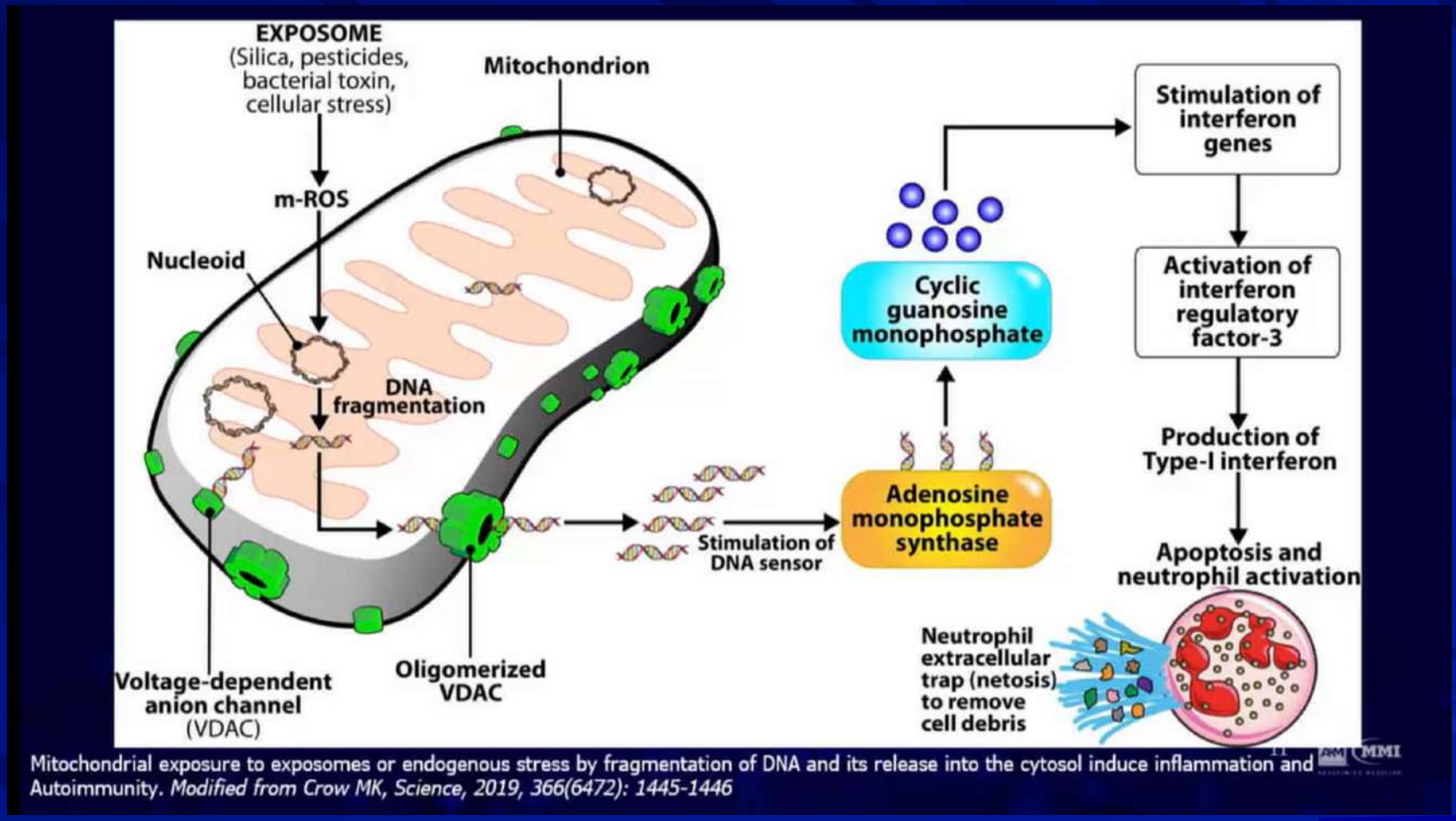
The ellipsoid contains a densely-packed array of mostly elongated mitochondria arranged broadly parallel to the long axis of the photoreceptor. The cell contained **498 individual mitochondria**

Inflamm-aging

One of the consequences of failing mitochondria due to aging, beyond mtROS, is the release of mtDNA. Plasma levels of mtDNA increase gradually after the fifth decade of life, correlating with elevated levels of pro-inflammatory cytokines (i.e., TNF-α, IL-6, RANTES, and IL-1ra)

These data indicate that mtDNA may promote the production of pro-inflammatory cytokines in aging. Because cell stress, senescence and death are a part of the pathophysiology of aging designing new therapeutic strategies against circulating mtDNA, or other mtDAMPs, or their cognate receptors (e.g., TLRs or FPR1) may be a viable strategy to approaching IA and its associated conditions.

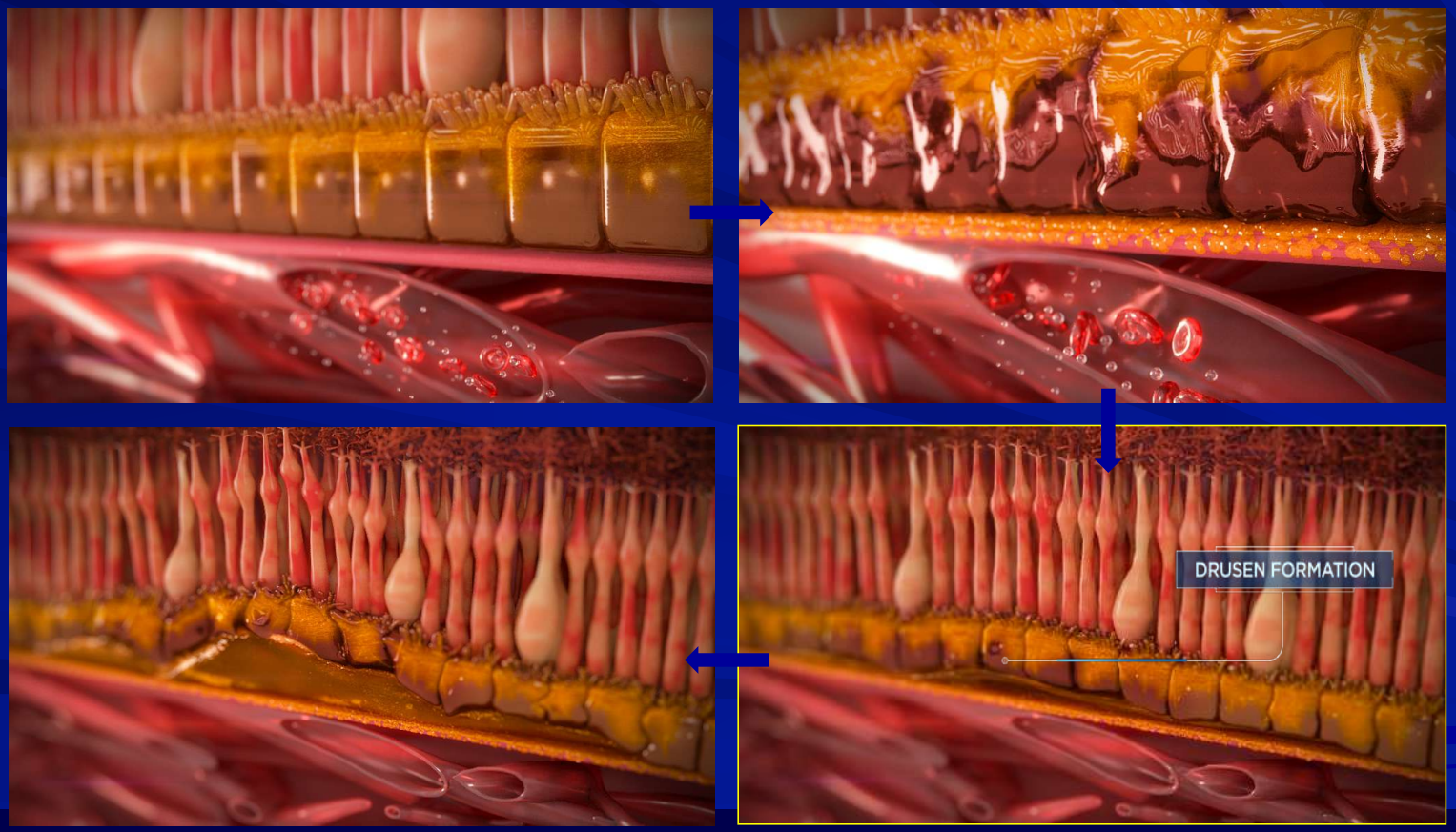
Credit to: Elroy Vojdani, MD - Dead Batteries: The Role of Mitochondrial Dysfunction in Immunological Decline - Emerging Diagnostic Tools and Nutraceutical Interventions



Mitochondrial exposure to exposomes or endogenous stress by fragmentation of DNA and its release into the cytosol induce inflammation and Autoimmunity. *Modified from Crow MK, Science, 2019, 366(6472): 1445-1446*

Credit to: Elroy Vojdani, MD - Dead Batteries: The Role of Mitochondrial Dysfunction in Immunological Decline - Emerging Diagnostic Tools and Nutraceutical Interventions

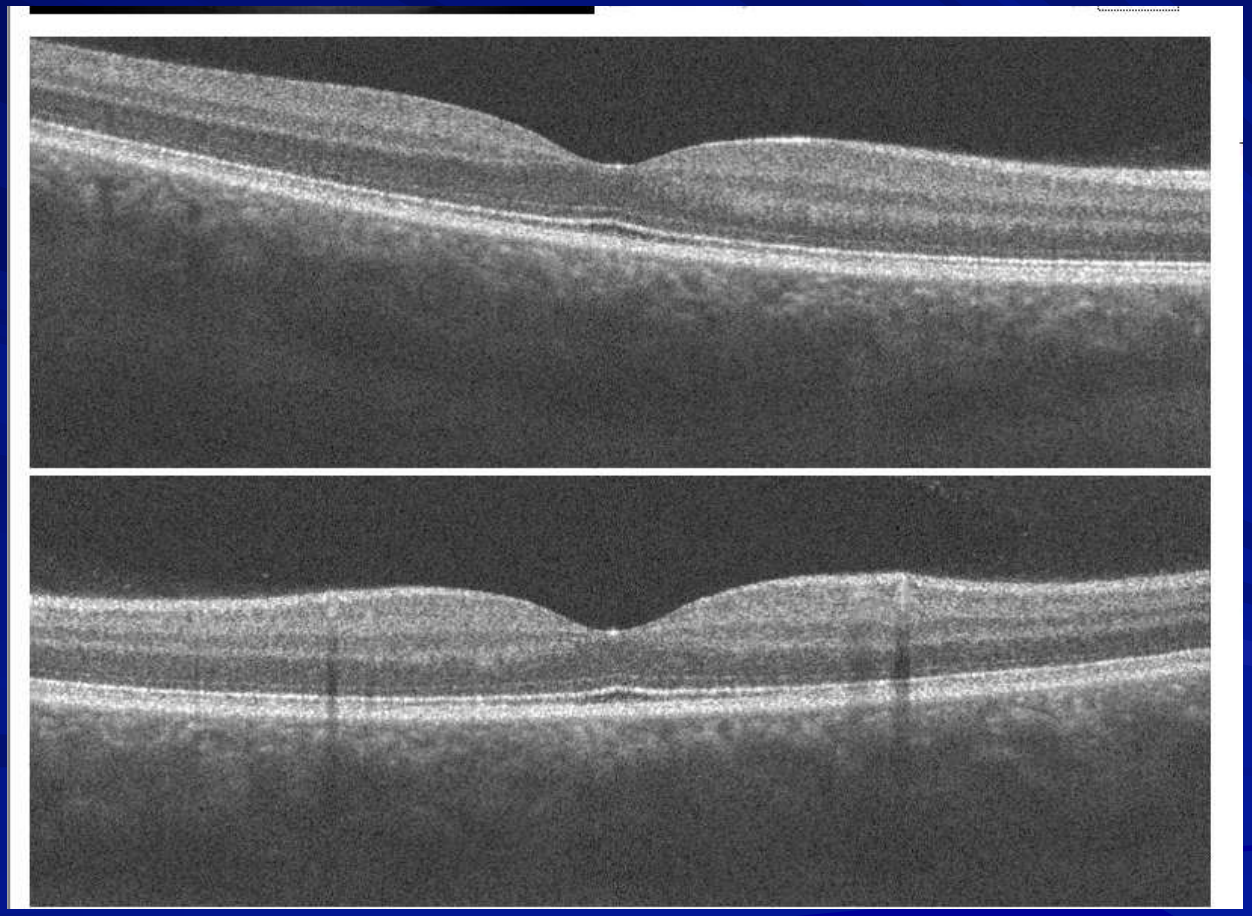
AMD is a Disease Process that Starts Below the Surface



OCT in AMD

- Need spectral domain to follow intermediate or worse AMD
- Able to identify OCT predictors of progression
- Especially in identifying OCT predictors of progression
  - Hyper-reflective foci
  - Reticular pseudodrusen
  - Nascent geographic atrophy
  - Sub-RPE hyper-reflective columns
  - Drusen substructures
  - Drusen load and regression

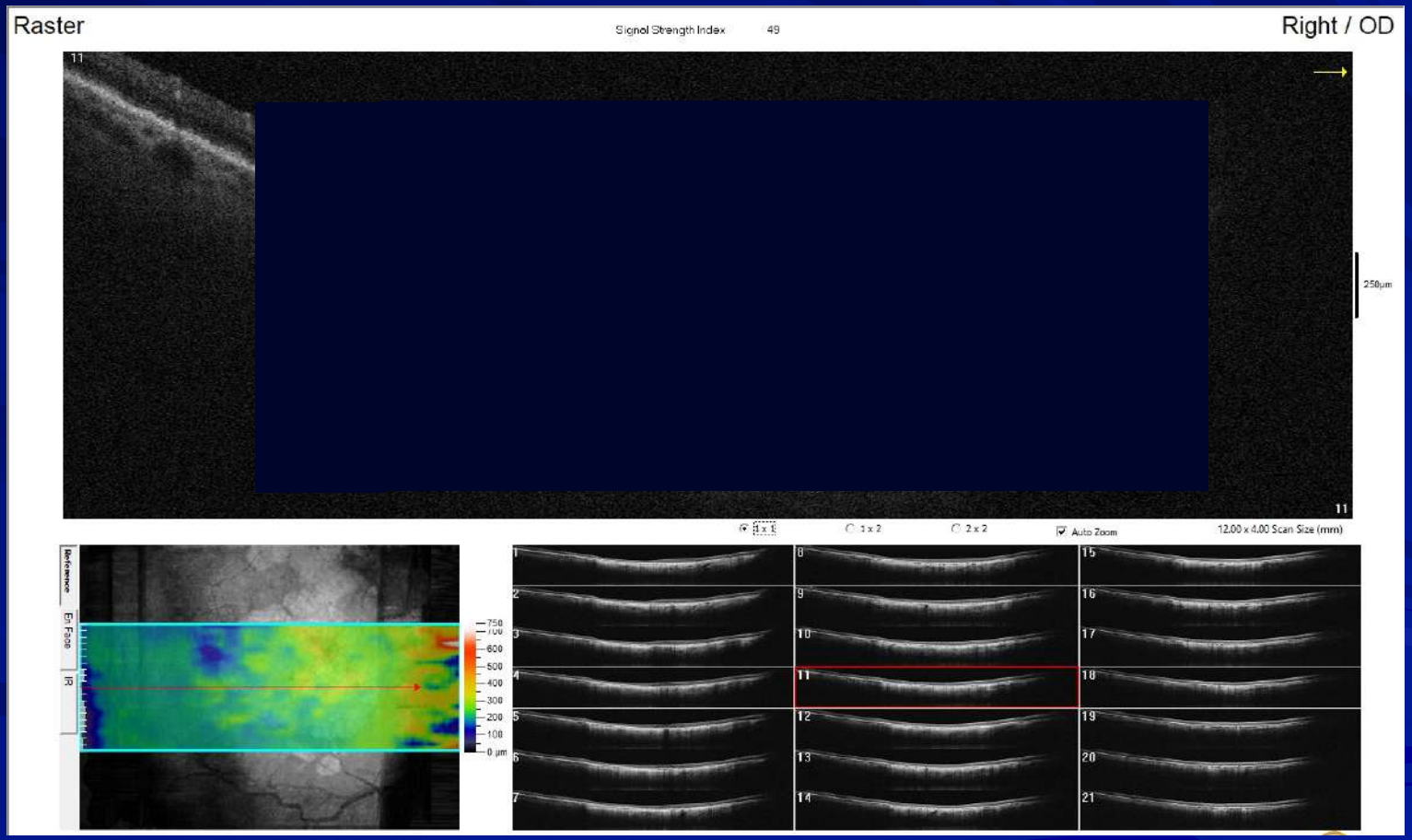
Hypo versus Hyper Reflectance



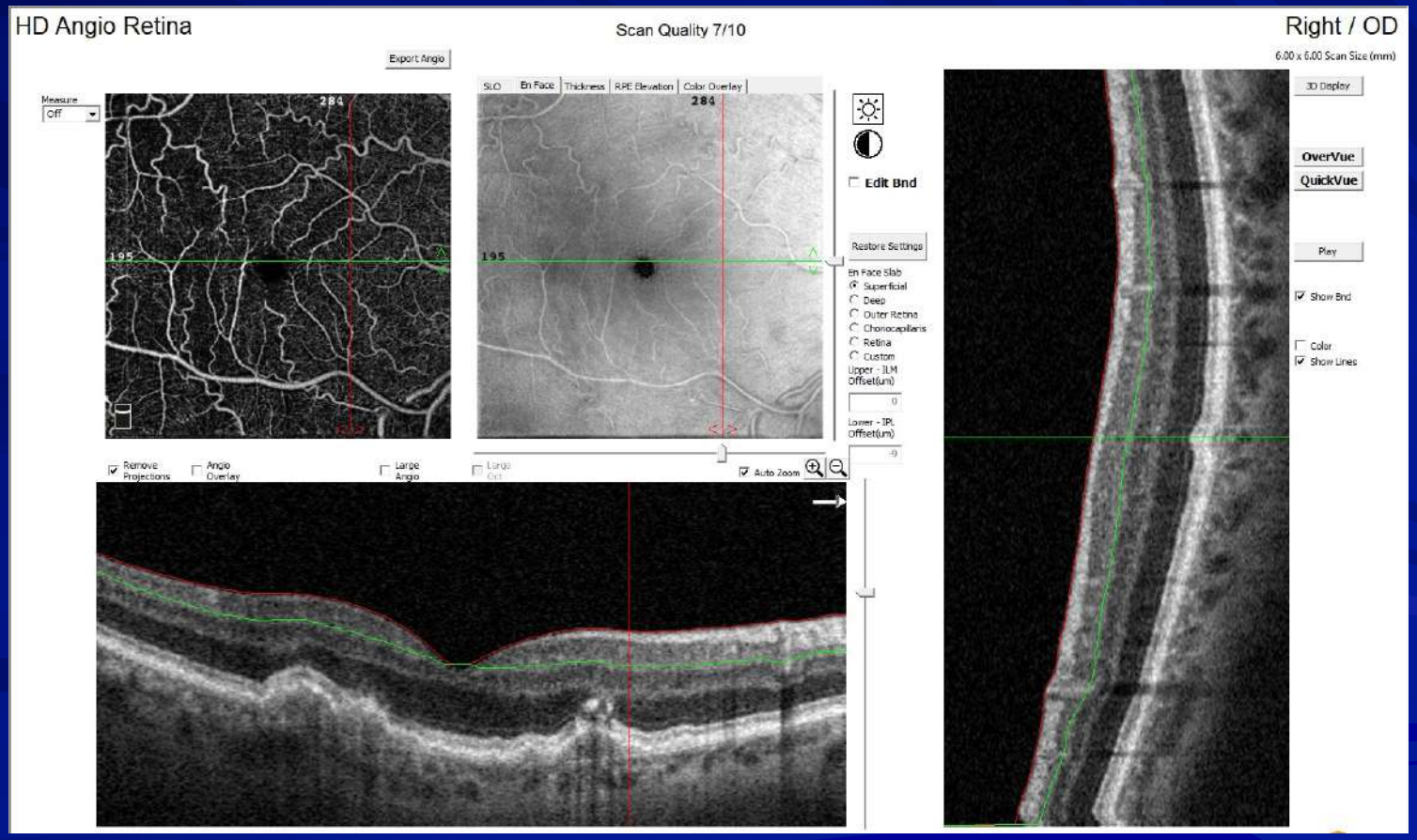
Can We Learn From These Pictures?

Can We Learn From These Pictures?

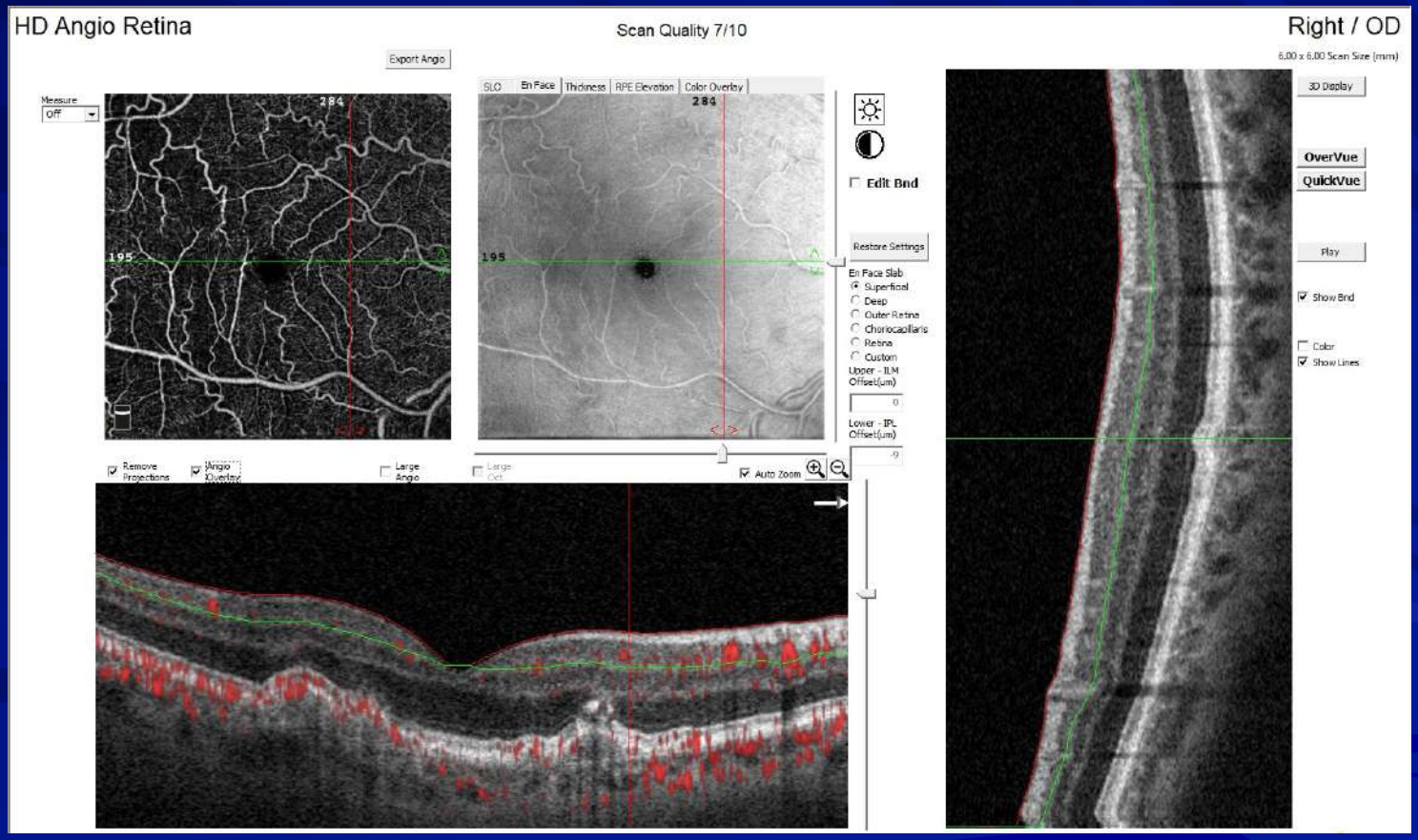
Hypo versus Hyper Reflectance



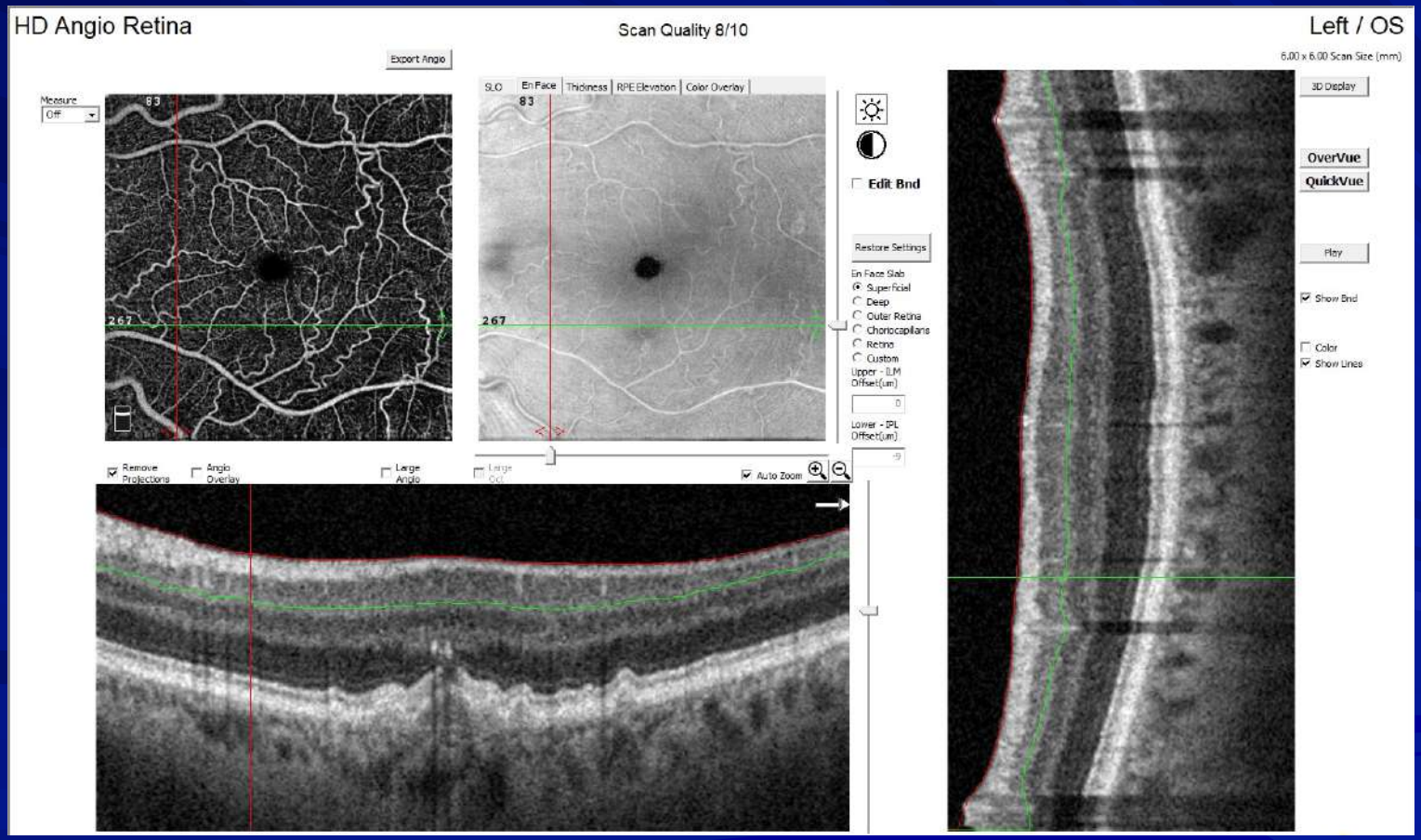
Case 1 - OCT Predictors of Progression



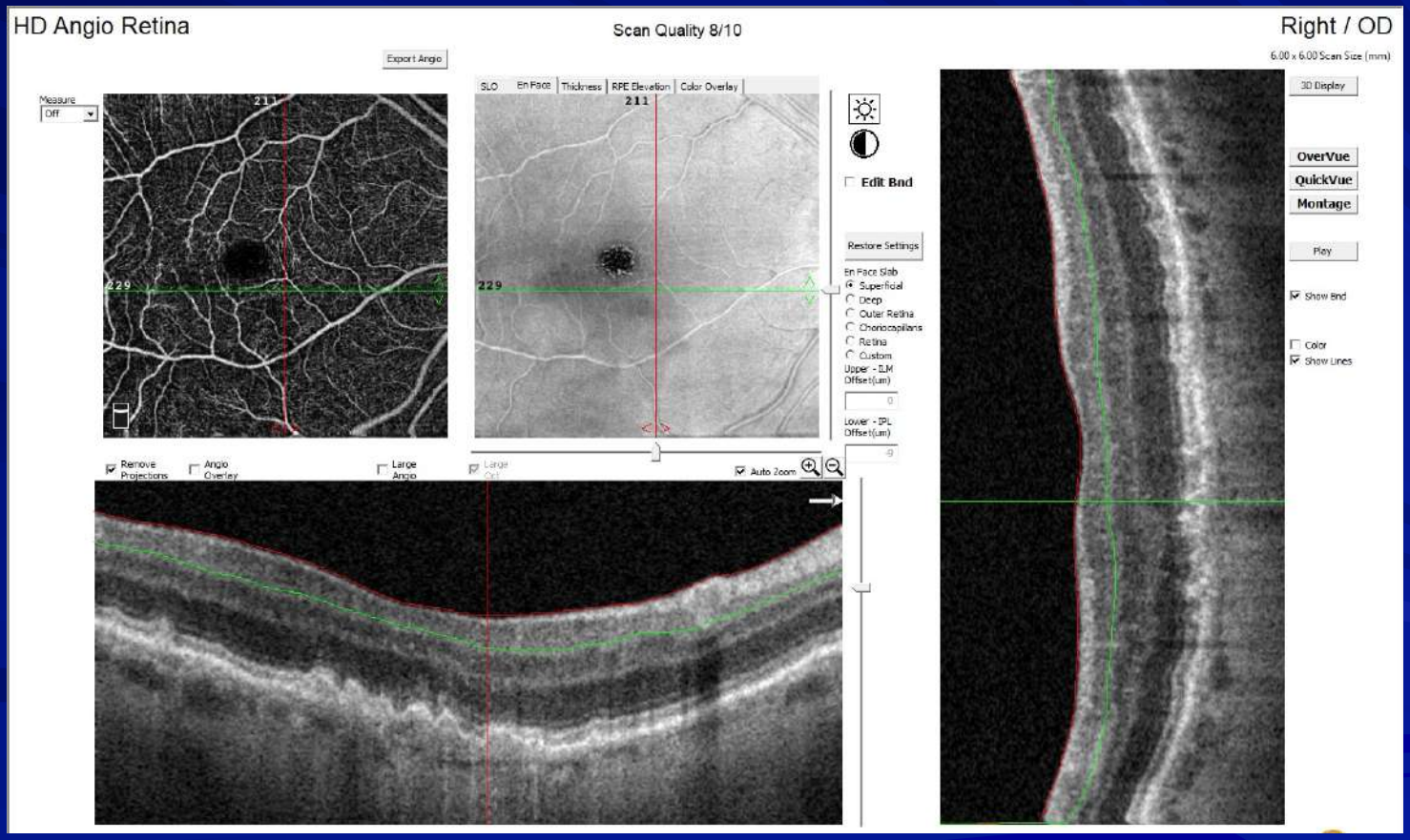
Case 1 - OCT Predictors of Progression



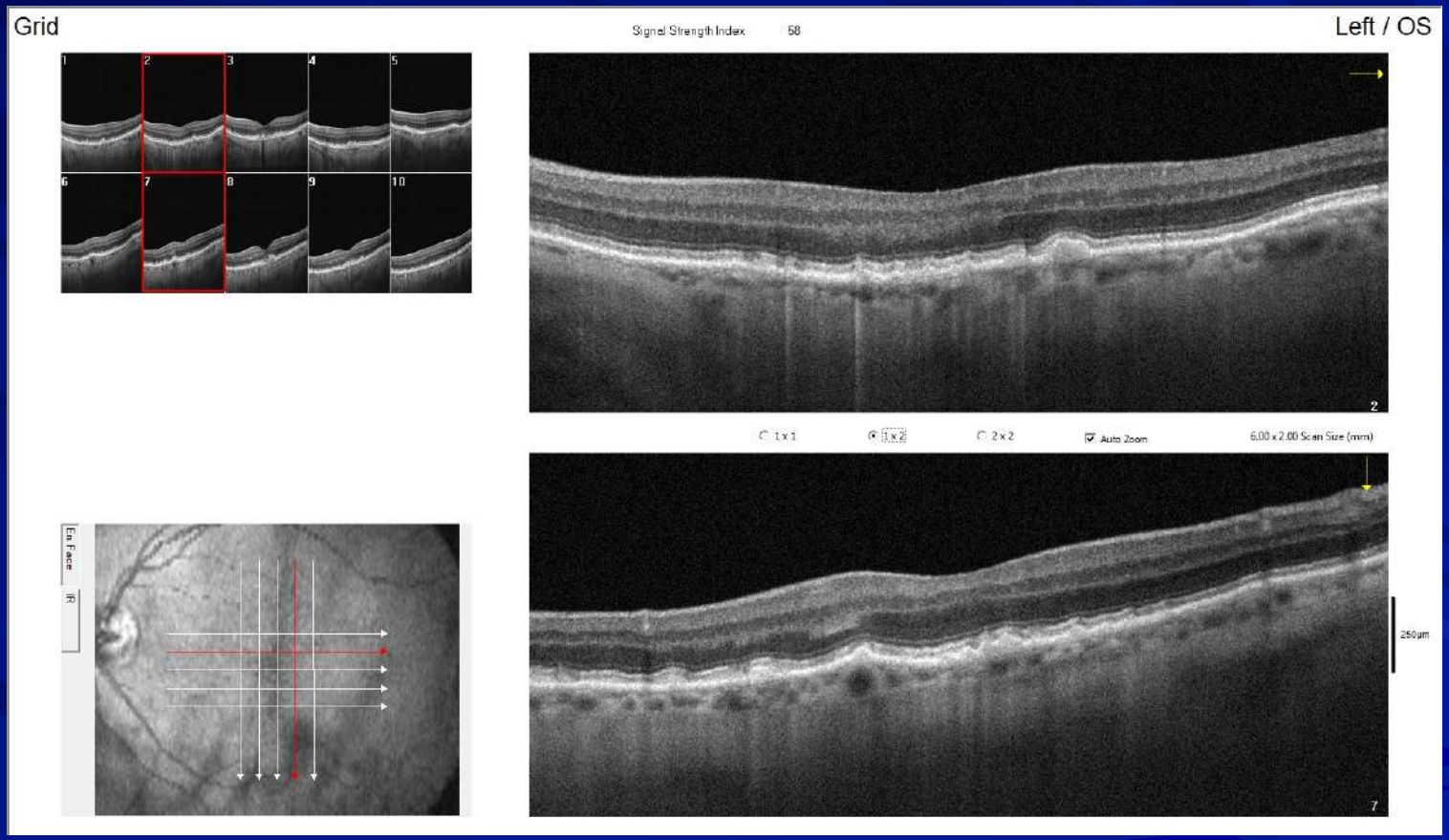
Case 1 - OCT Predictors of Progression



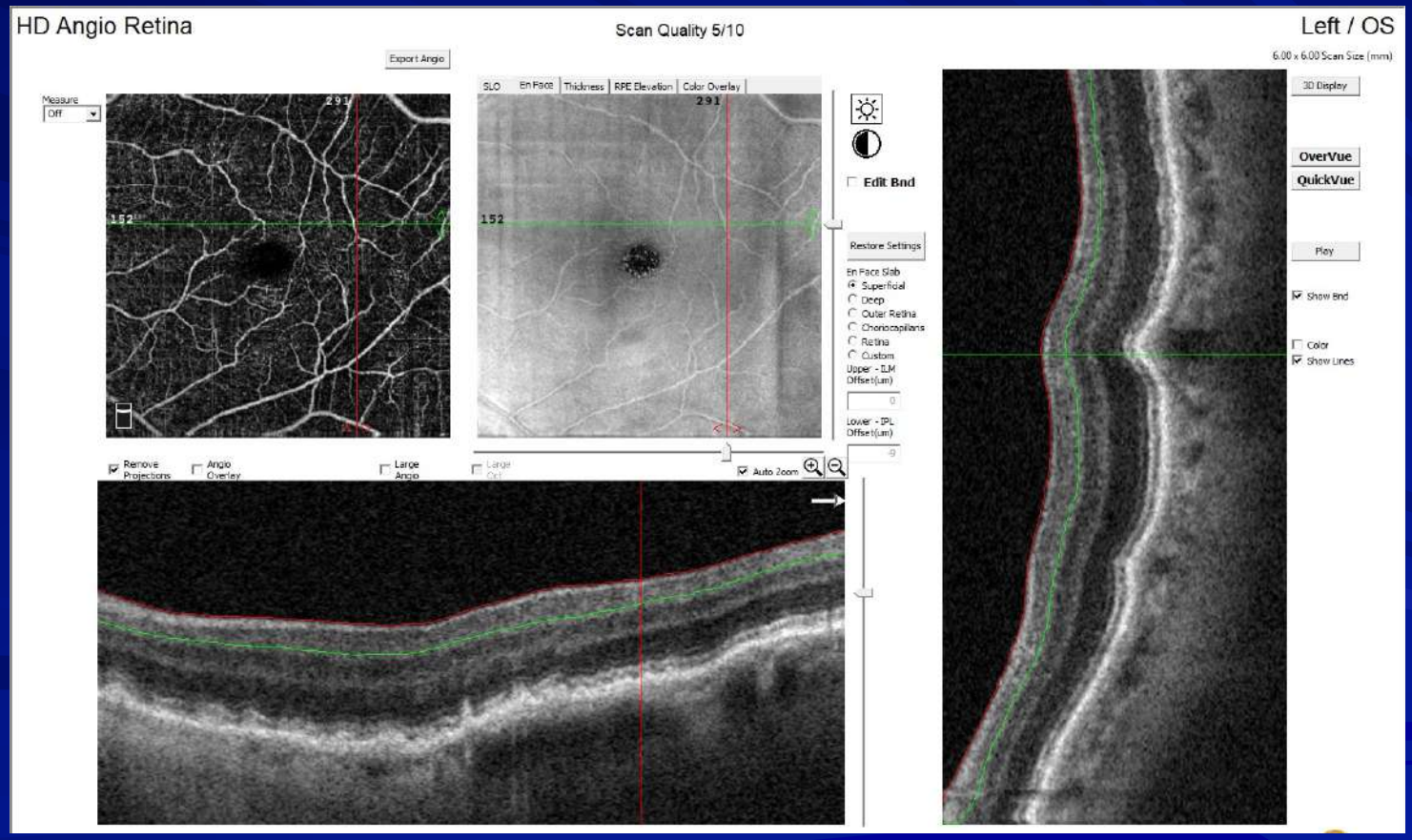
Case 2 - OCT Predictors of Progression



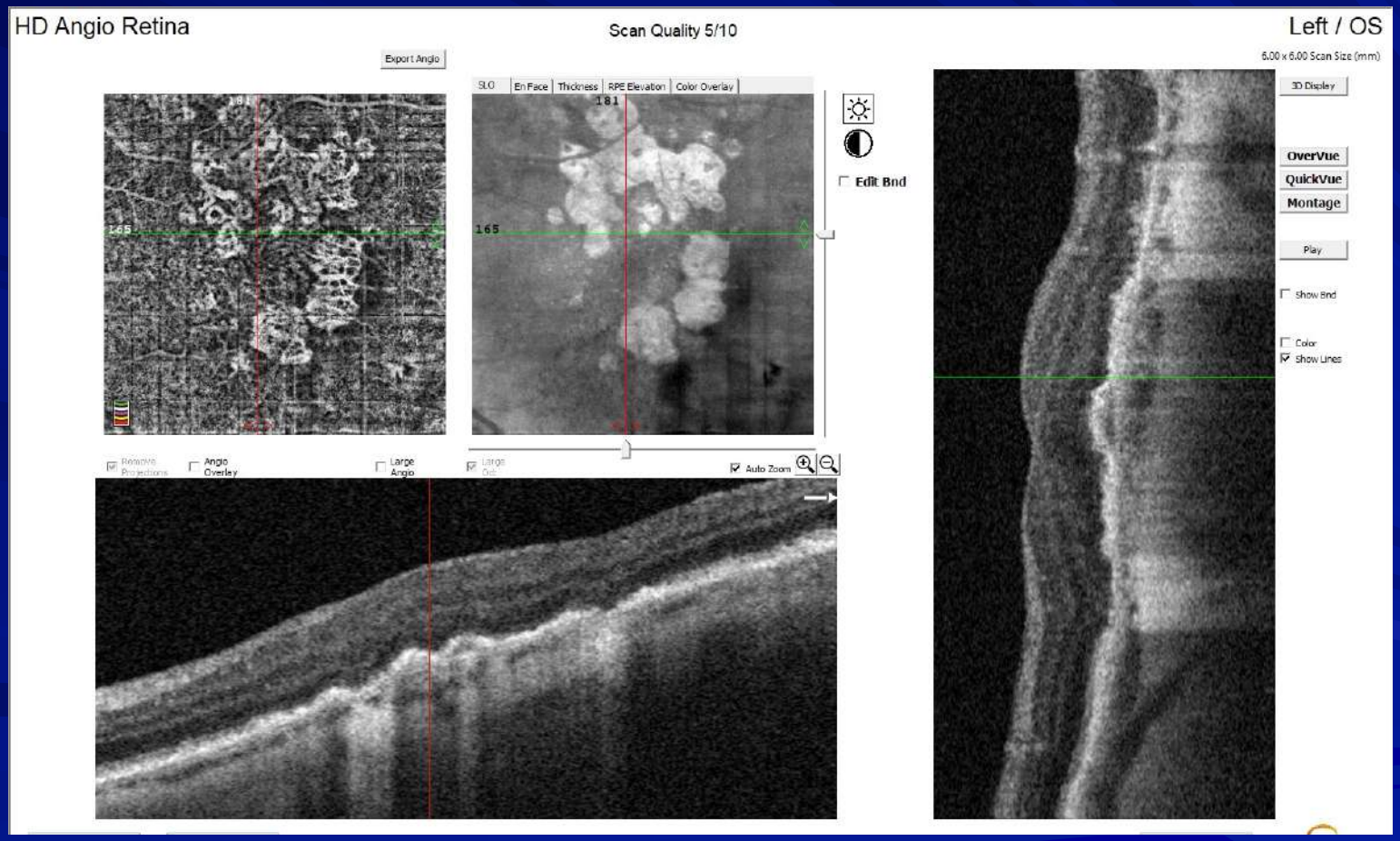
Case 2 - OCT Predictors of Progression



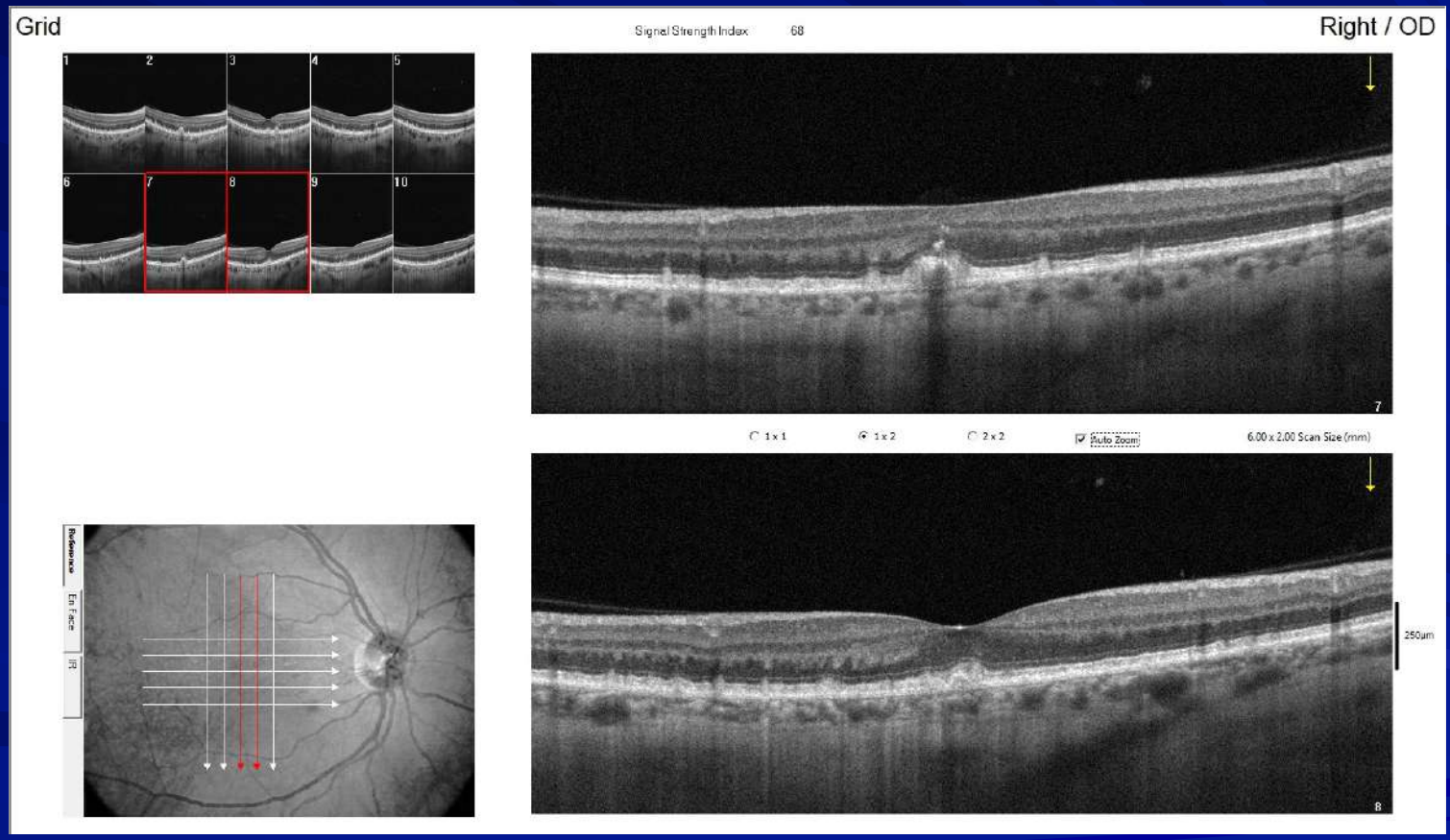
Case 2 - OCT Predictors of Progression



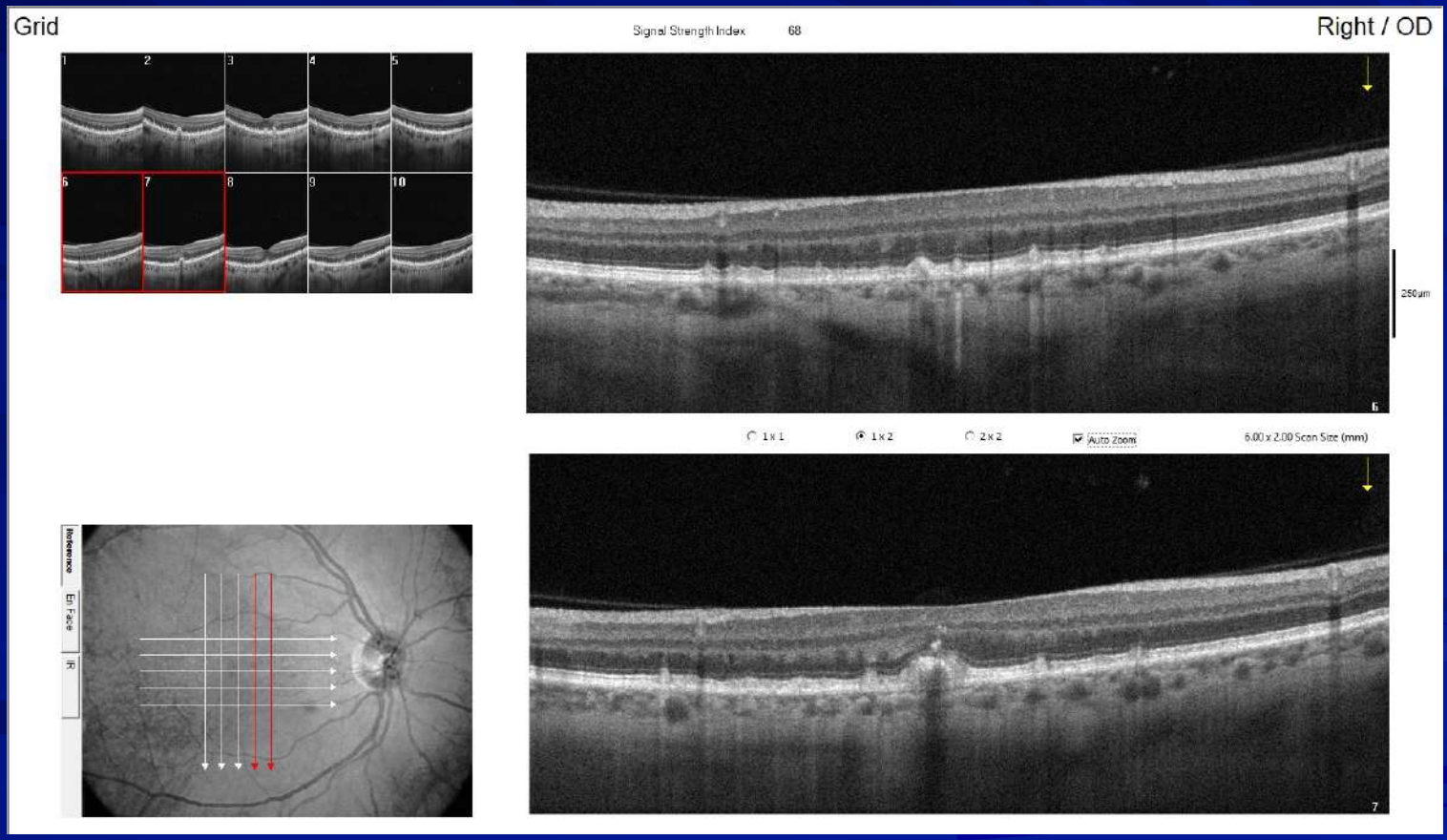
Case 3 - OCT Predictors of Progression



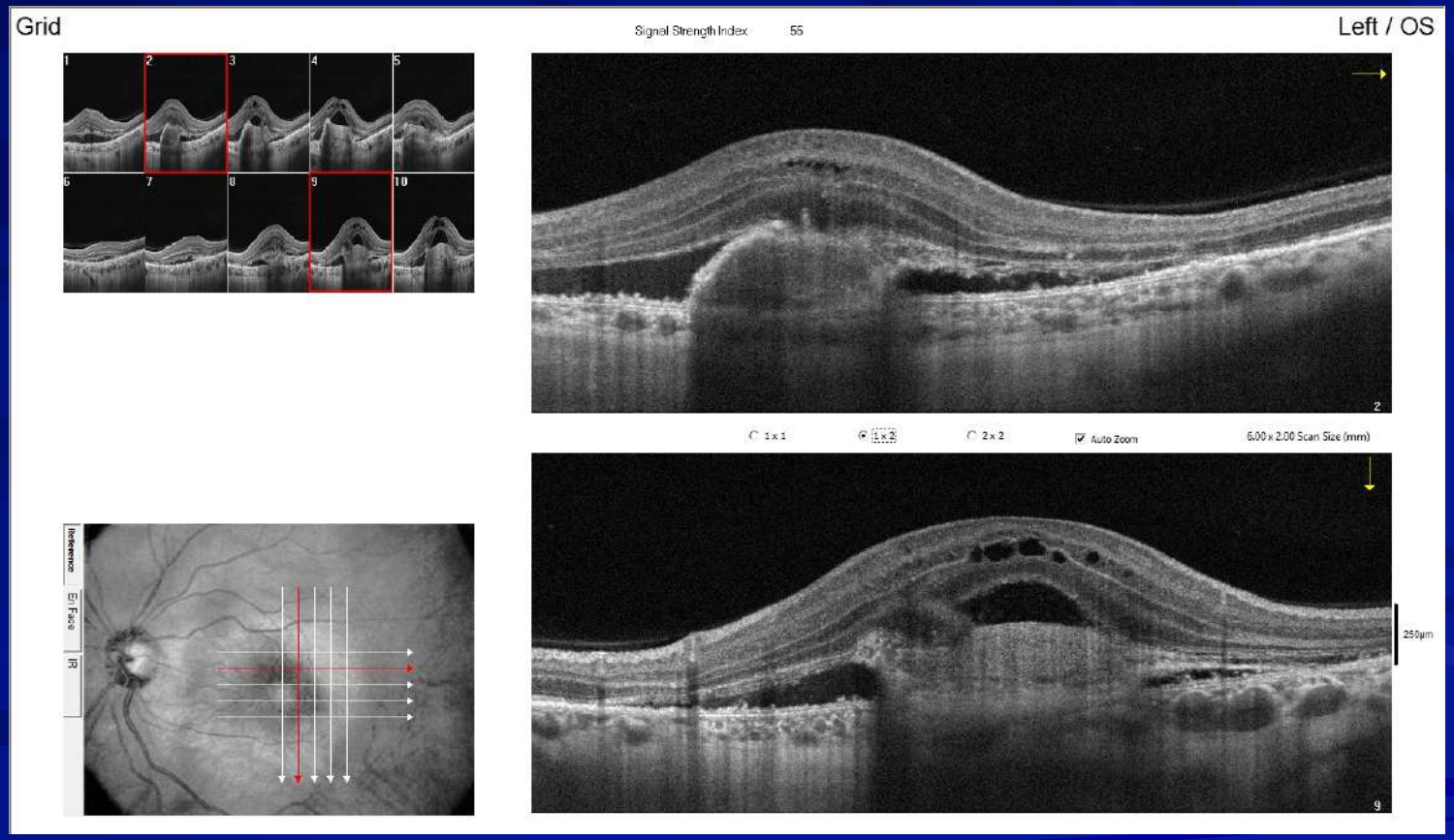
Case 4 - OCT Predictors of Progression



Case 4 - OCT Predictors of Progression



Case 4 - OCT Predictors of Progression



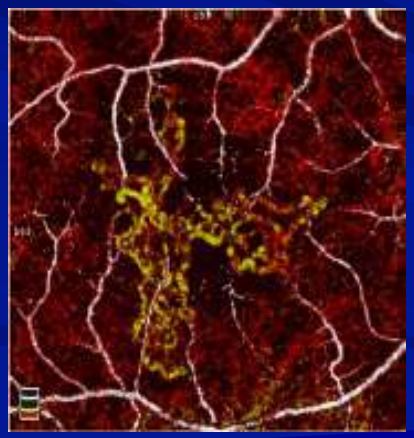
OCT Angiography in AMD
Structure Test

- Able to identify occult or classic CNV before they leak
- Non-invasive technique
- Subclinical CNV or "Occult non-exudative CNV"
  - Risk of exudation at 12 months is 15.2 times greater compared to eyes without subclinical CNV

OCT Angiography
A New Approach to Protecting Vision

- Non-invasive visualization of individual layers of retinal vasculature
- Pathology not obscured by fluorescein staining or pooling
- Image acquisition requires less time than a dye-based procedure
- Reduced patient burden allows more frequent imaging to better follow disease progression and treatment response

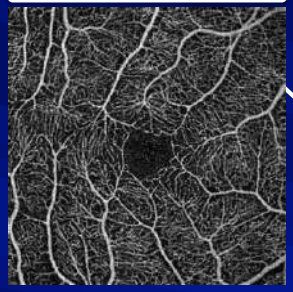
FA of CNV



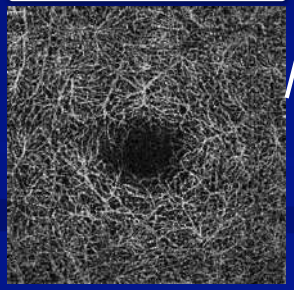
OCTA of CNV

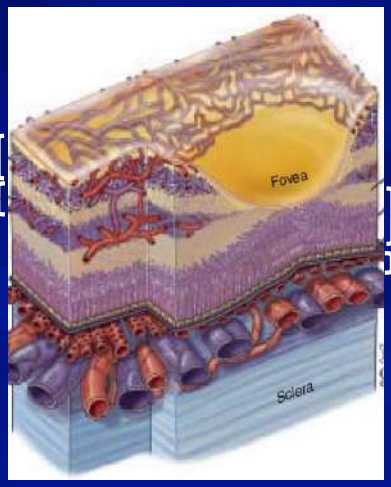
Enface OCT-A Slabs Based on Retinal Anatomy

Superficial Plexus (ILM – IPL)



Deep Plexus (INL – OPL)

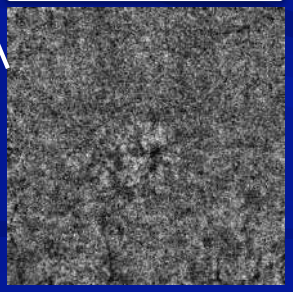




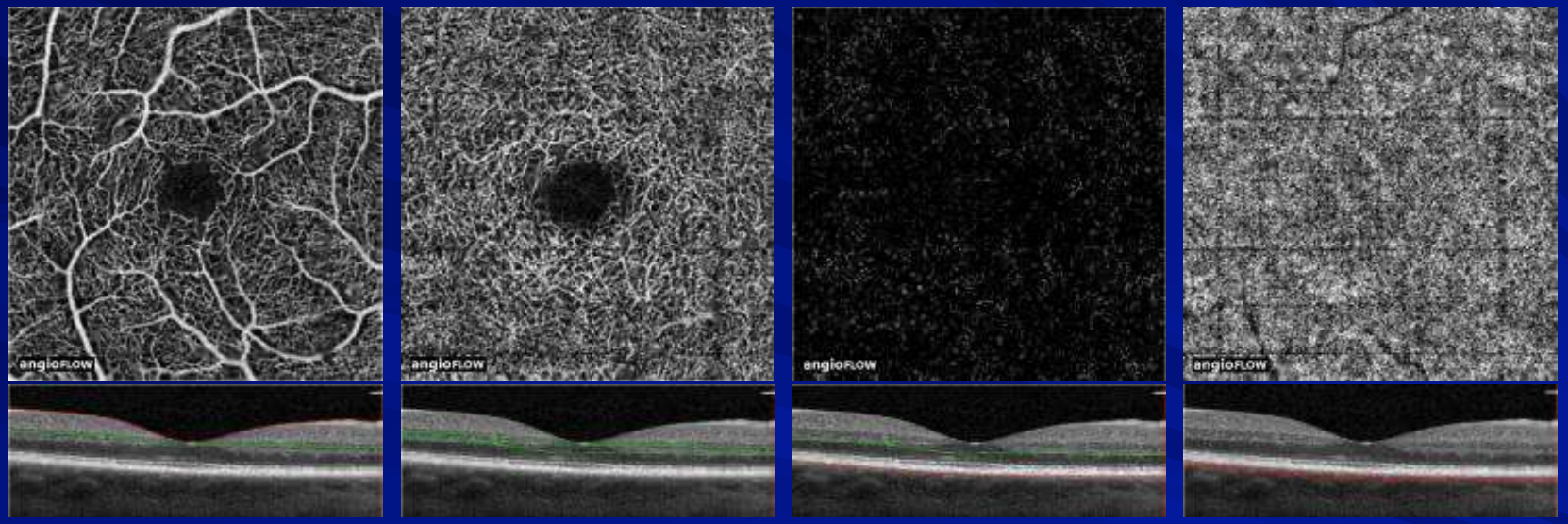
En Face Visualization of Layers Based on Retinal Anatomy

Outer Retinal Zone (ONL – BM)

Choroid Capillaris



Normal Retinal Vasculature



Superficial Capillary Plexus

3μm Below ILM → 15 μm Below IPL

Deep Capillary Plexus

15μm Below ILM → 70 μm Below IPL

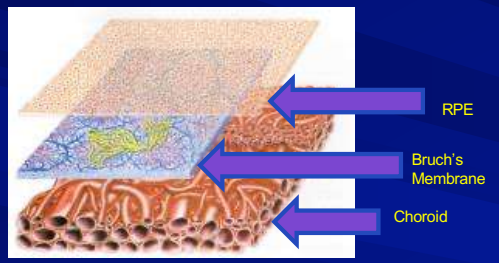
Outer Retina

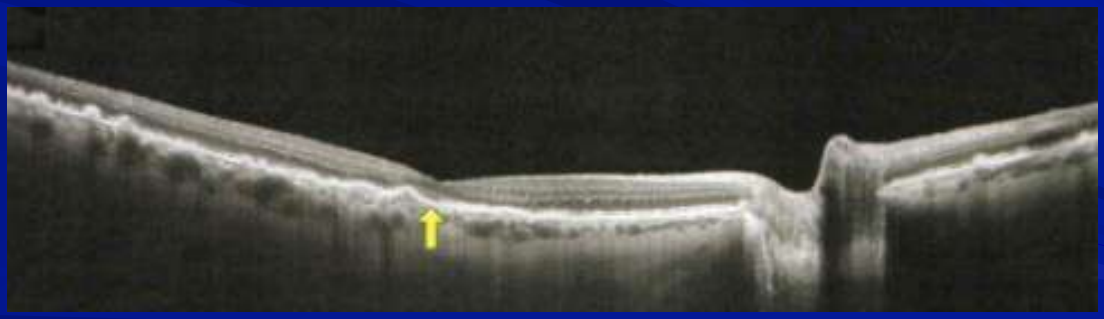
70μm Below IPL → 30 μm Below RPE Reference

Choriocapillaris

30 μm Below RPE Reference → 60 μm Below RPE Reference

Type 1 "Occult" CNV

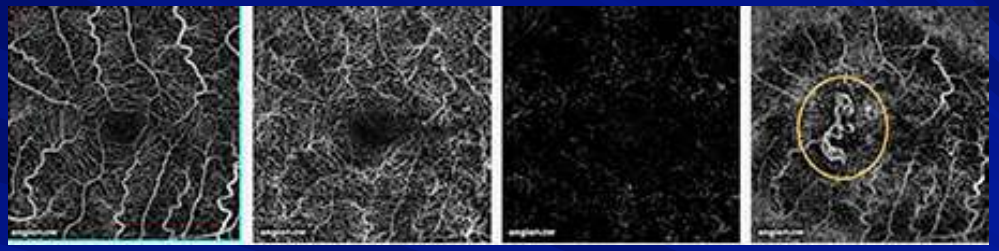


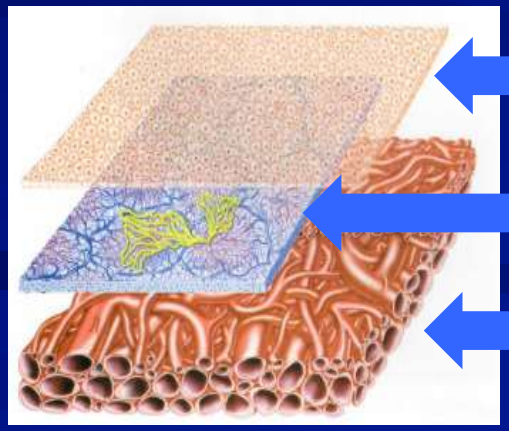


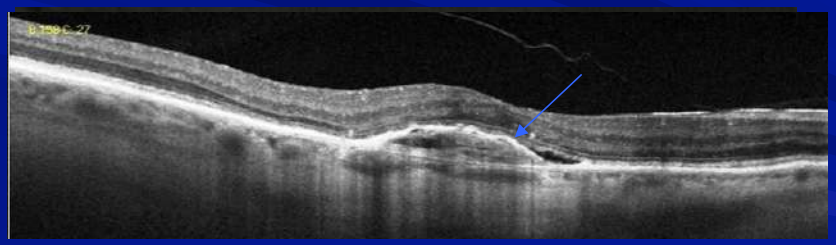
- New vessels develop in the choroid
- New vessels located below RPE and above Bruch's membrane

Type 1 "Occult" CNV

- New vessels develop in the choroid
- New vessels located **BELOW RPE** and ABOVE Bruch's membrane

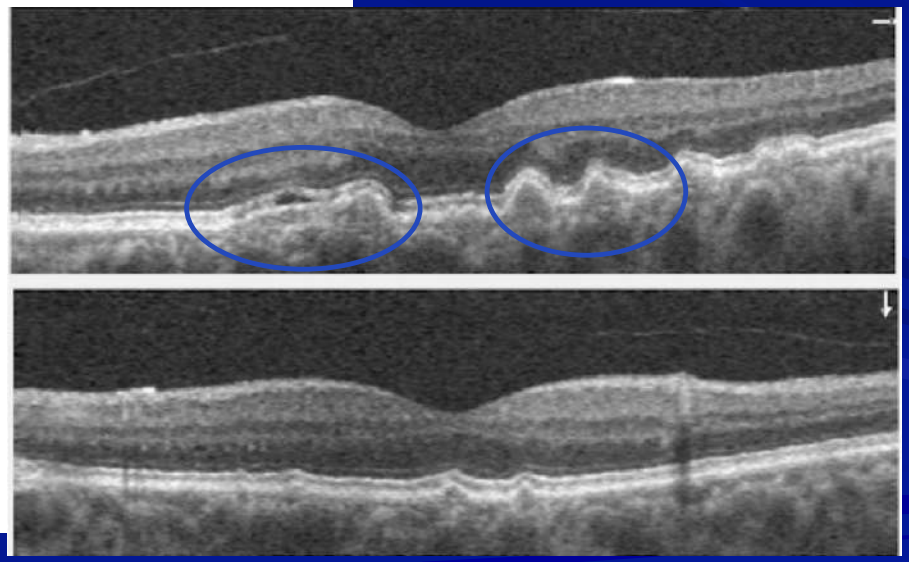




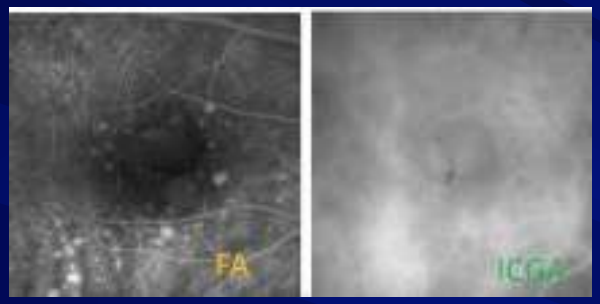


CNV?

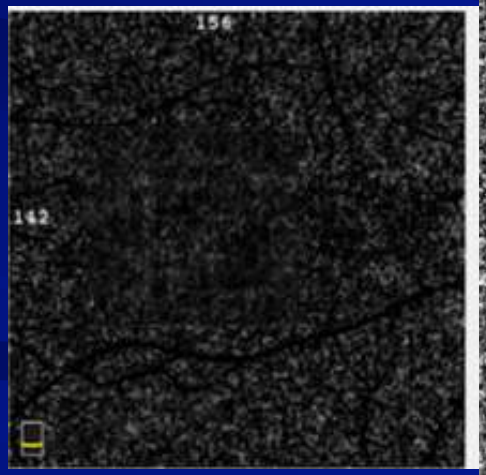
72 y/o Hispanic male
20/30
History of "Dry AMD"

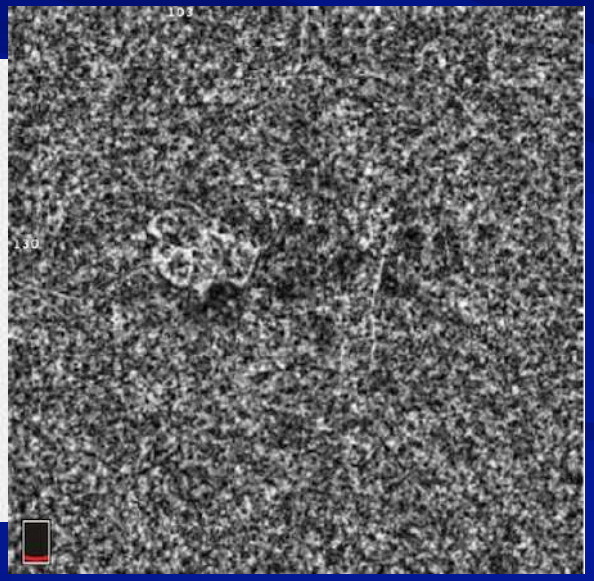


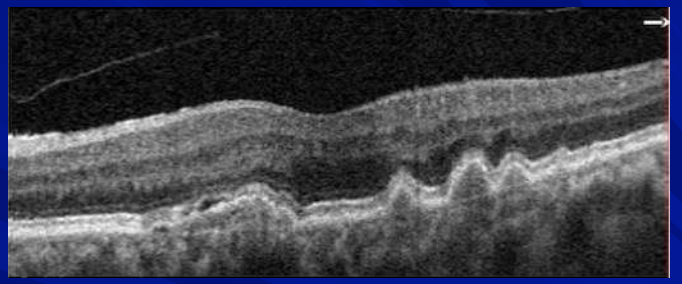
Multimodal imaging and OCTA

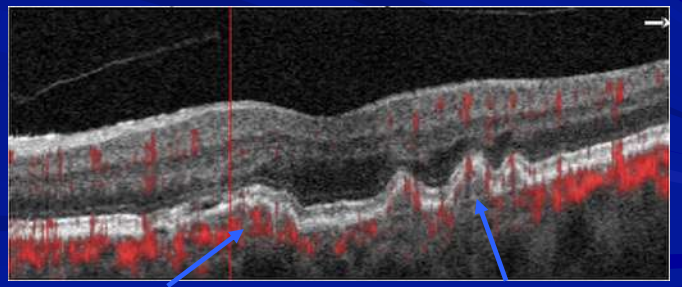


VAGUE???



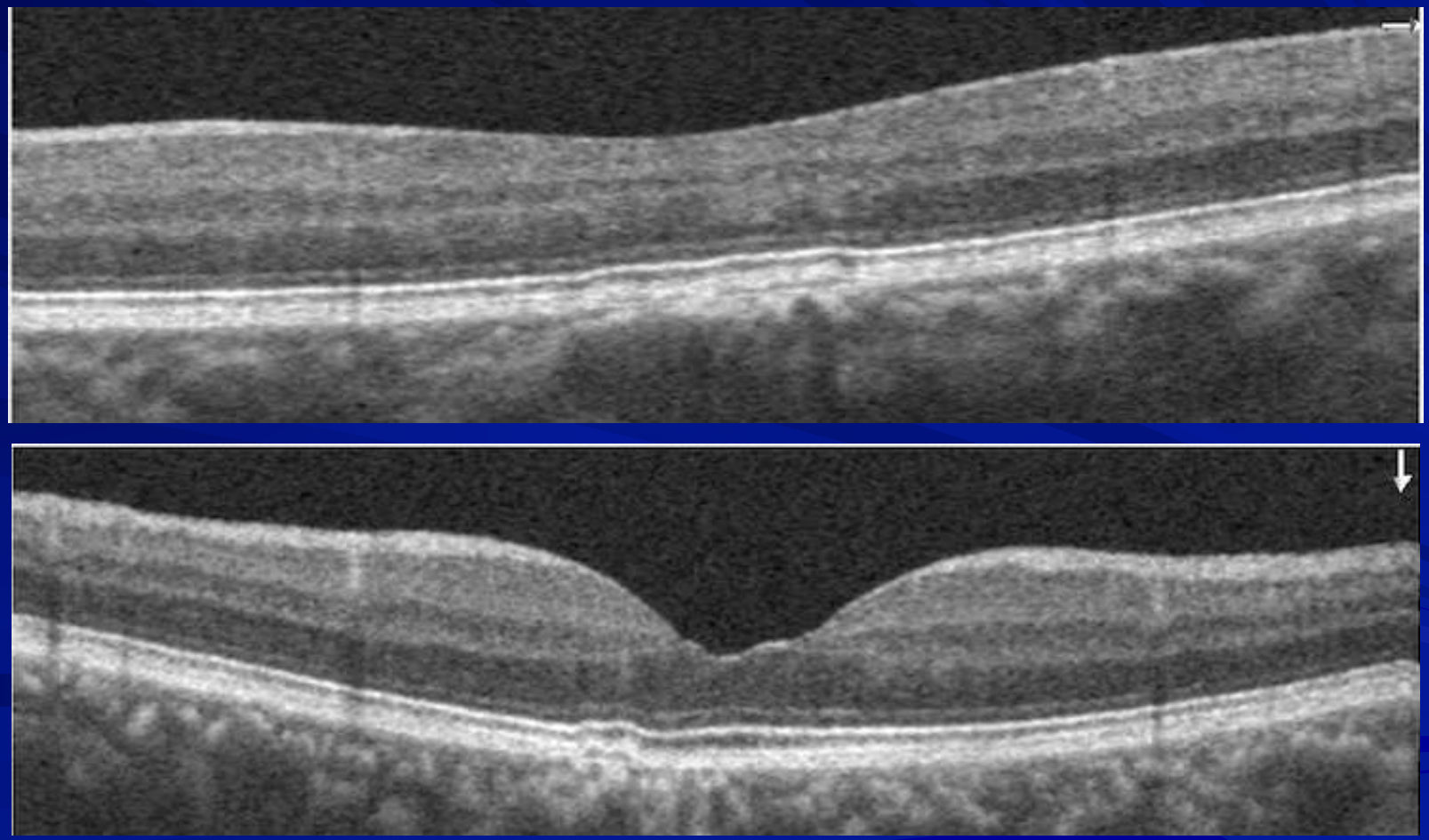


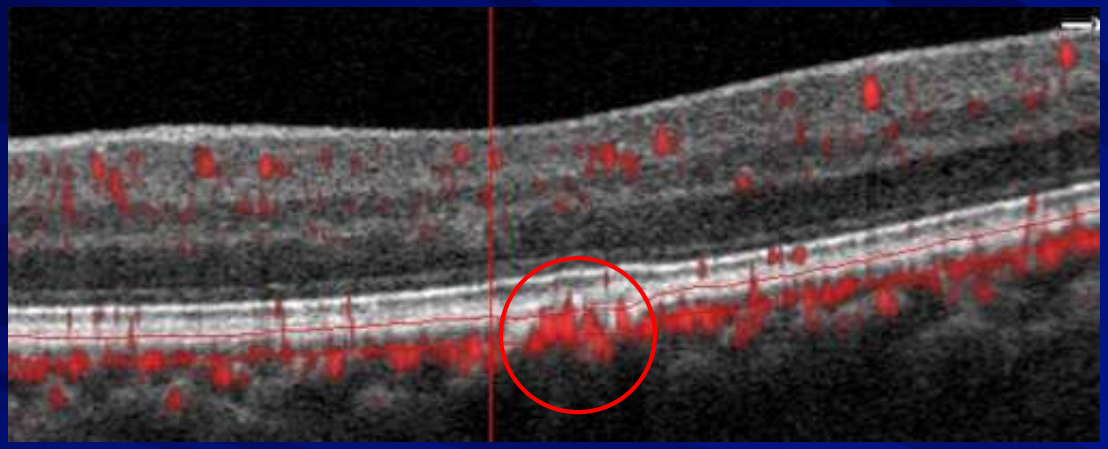


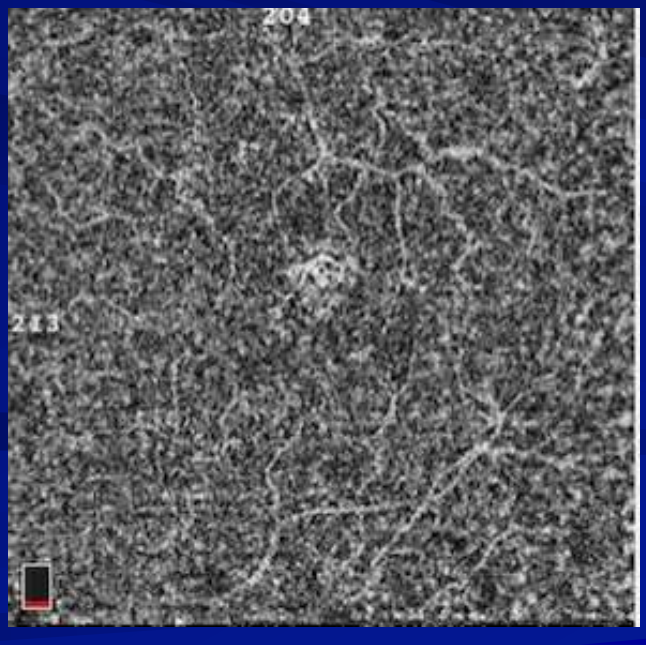


Vascularized Non-vascularized

And the not so obvious ones…

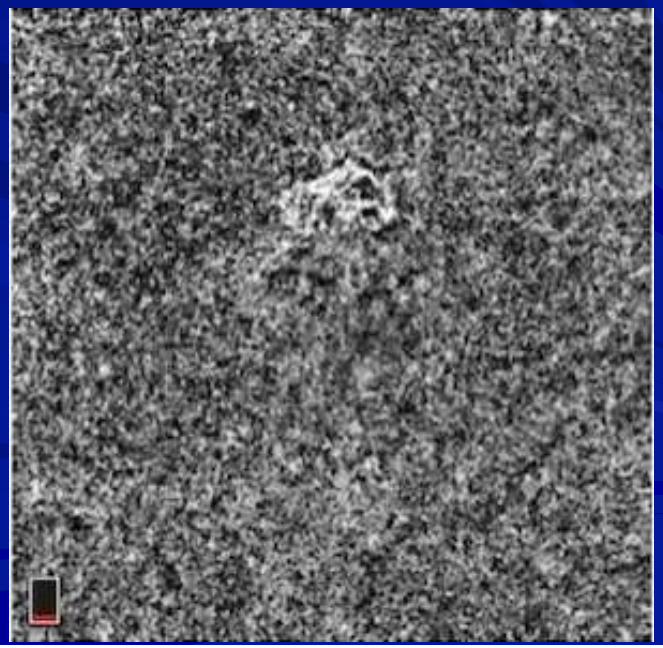




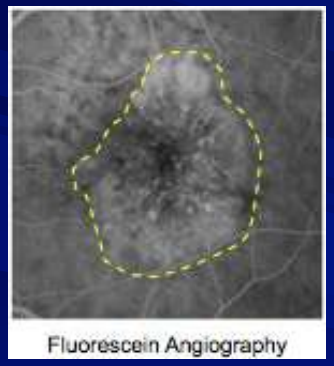


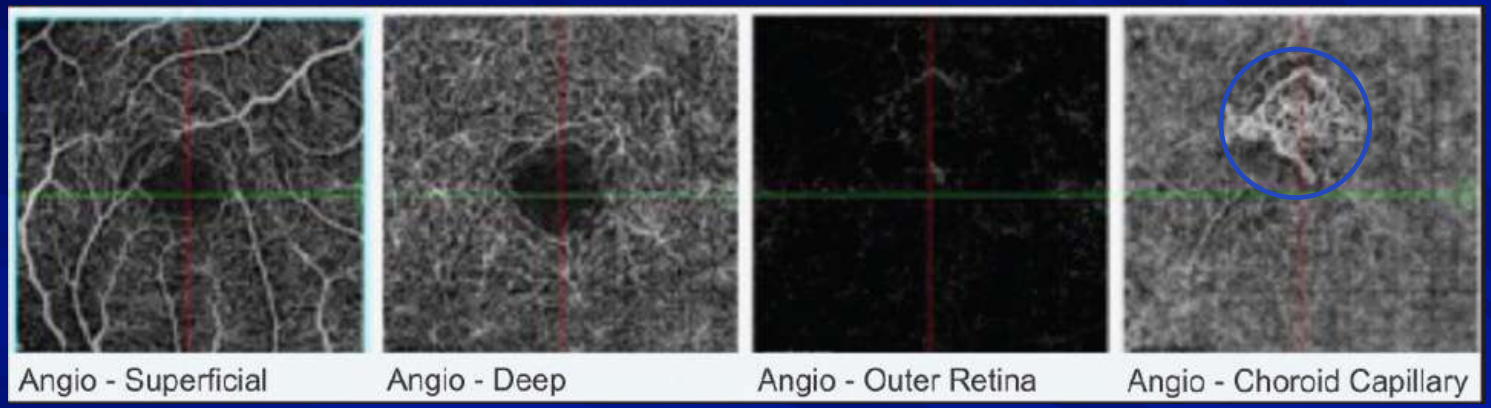
6x6

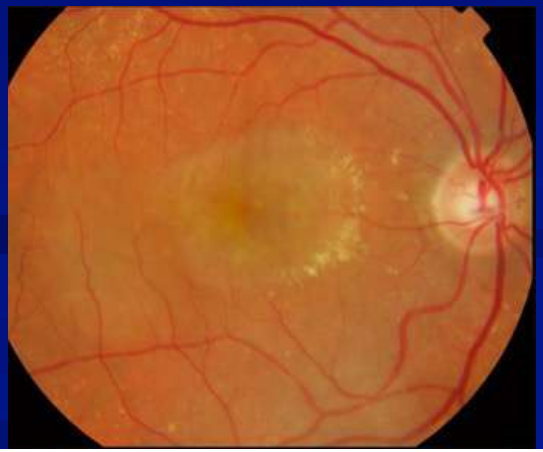
3x3

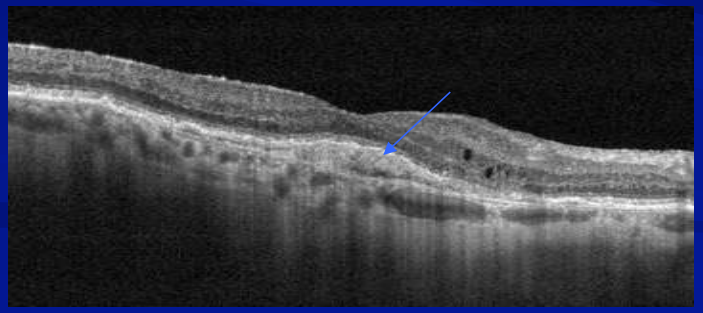


Case example: 70 y/o WM, AMD


Fluorescein Angiography

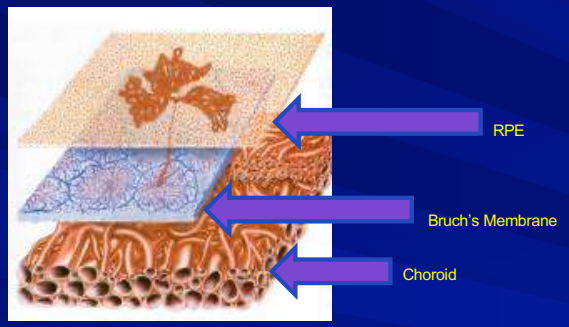


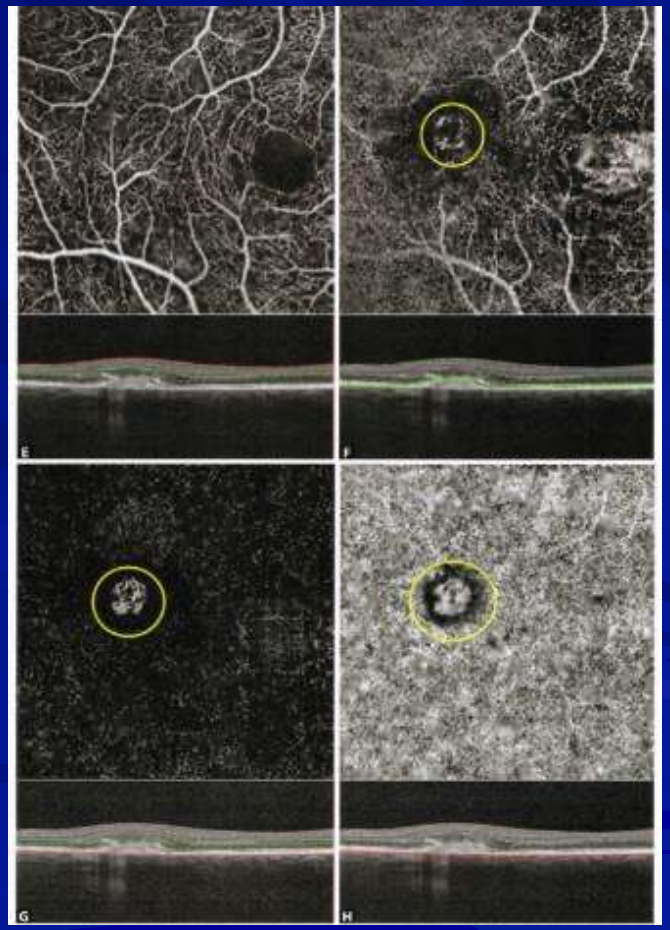




Below the RPE

Type 2 "Classic" CNV

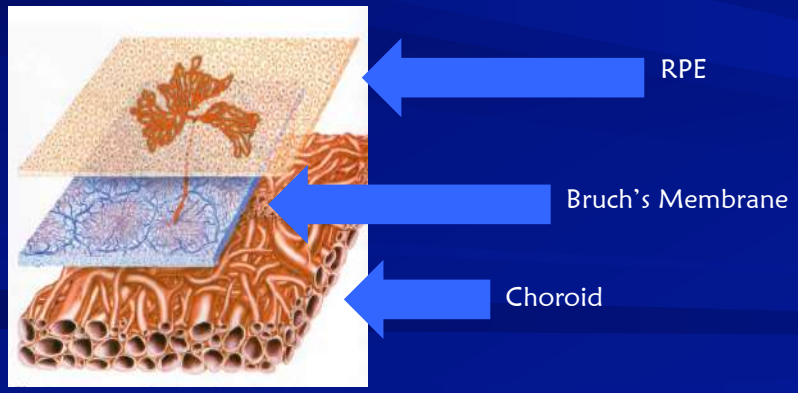


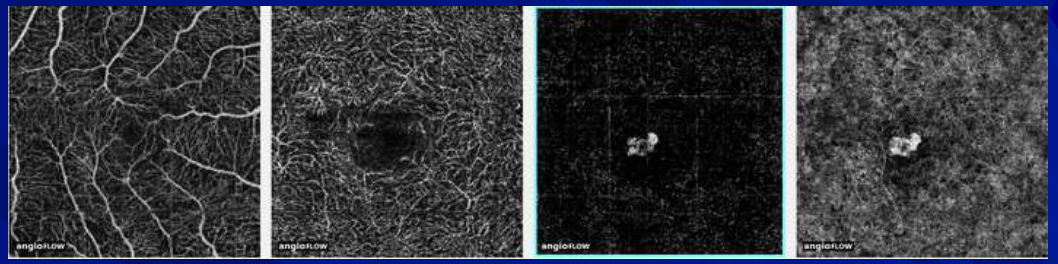


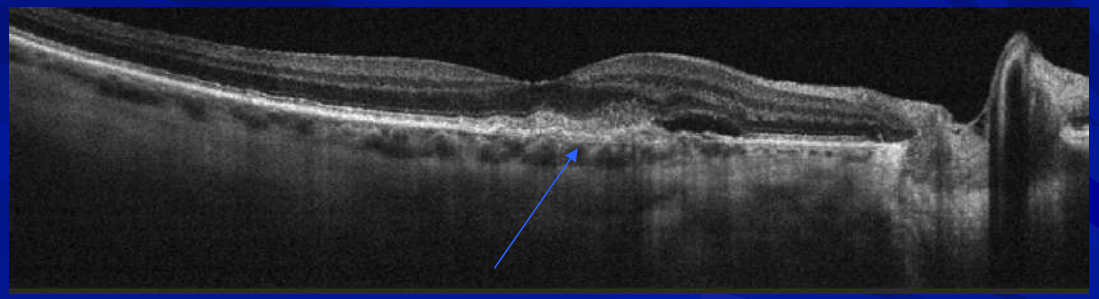
- New vessels develop in choroid
- New vessels located above the RPE and above Bruch's membrane

Type 2 "Classic" CNV

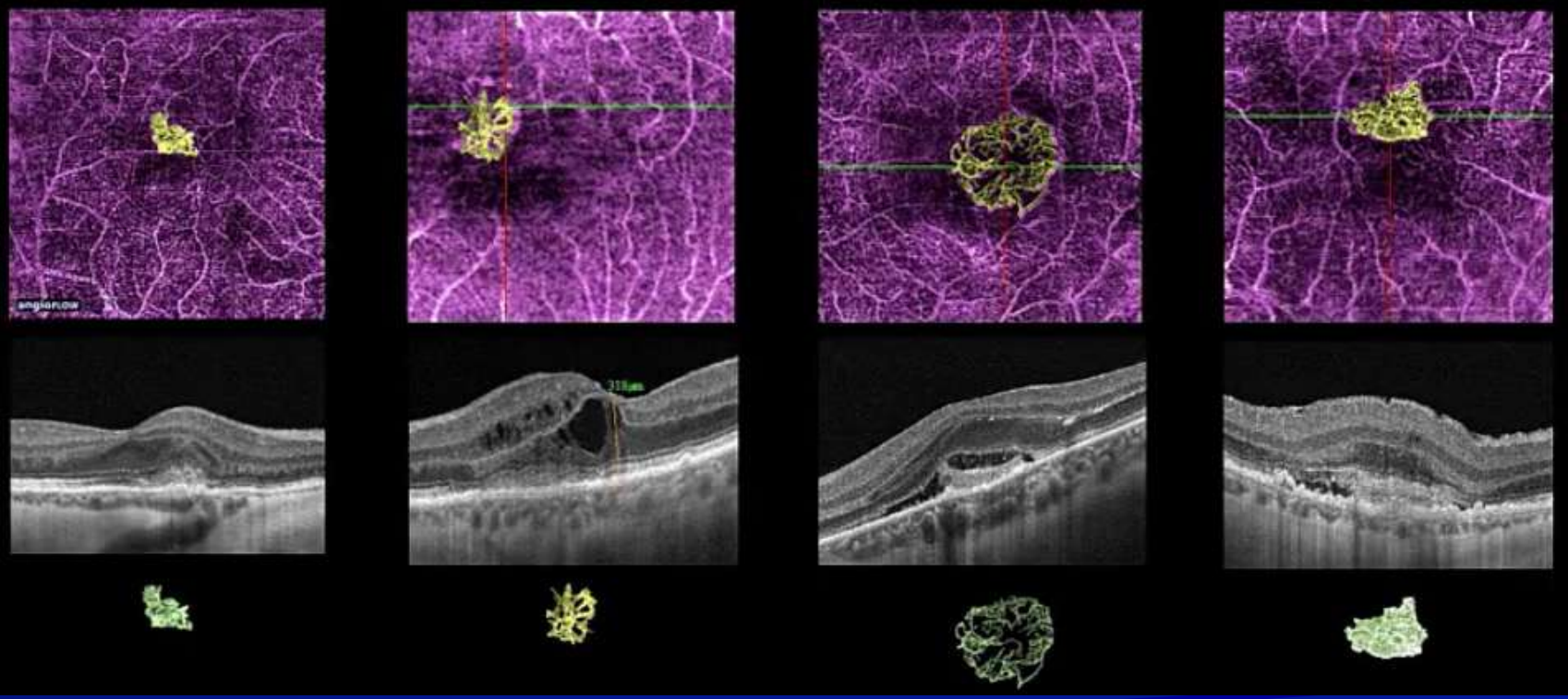
- New vessels develop in choroid
- New vessels located **ABOVE the RPE** and ABOVE Bruch's membrane



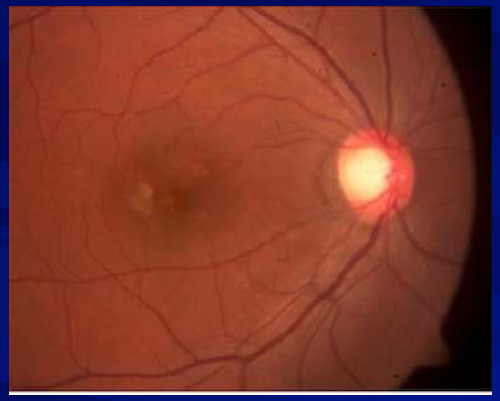


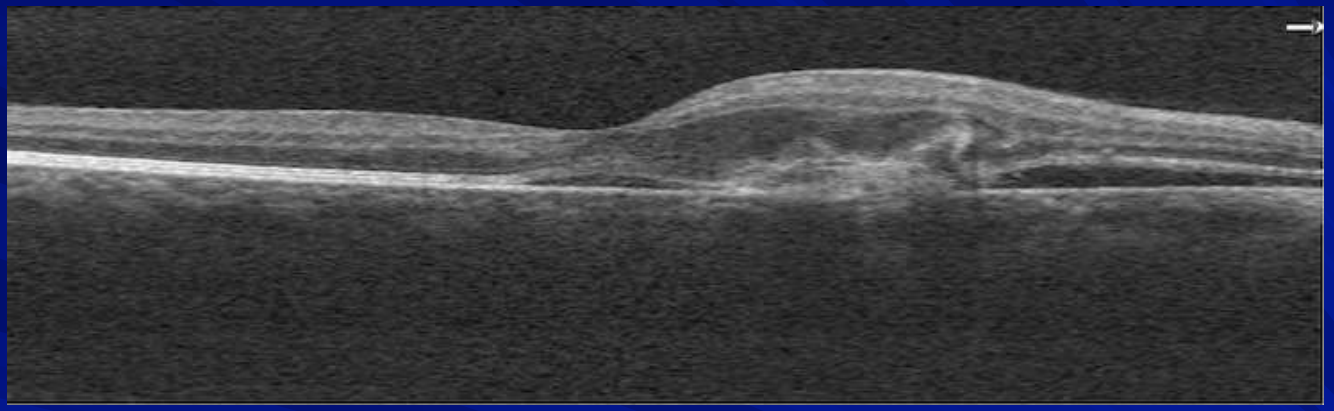


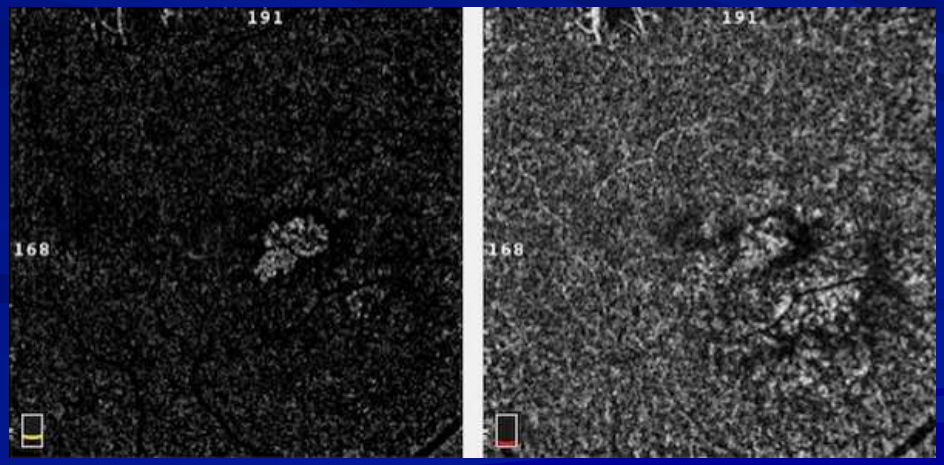
Type 2 CNV: Above RPE, Smaller than Type 1, Avascular Zone Always Involved.
Very Heterogeneous Shapes



48 y/o WM 2-week history of "dark spot" OD





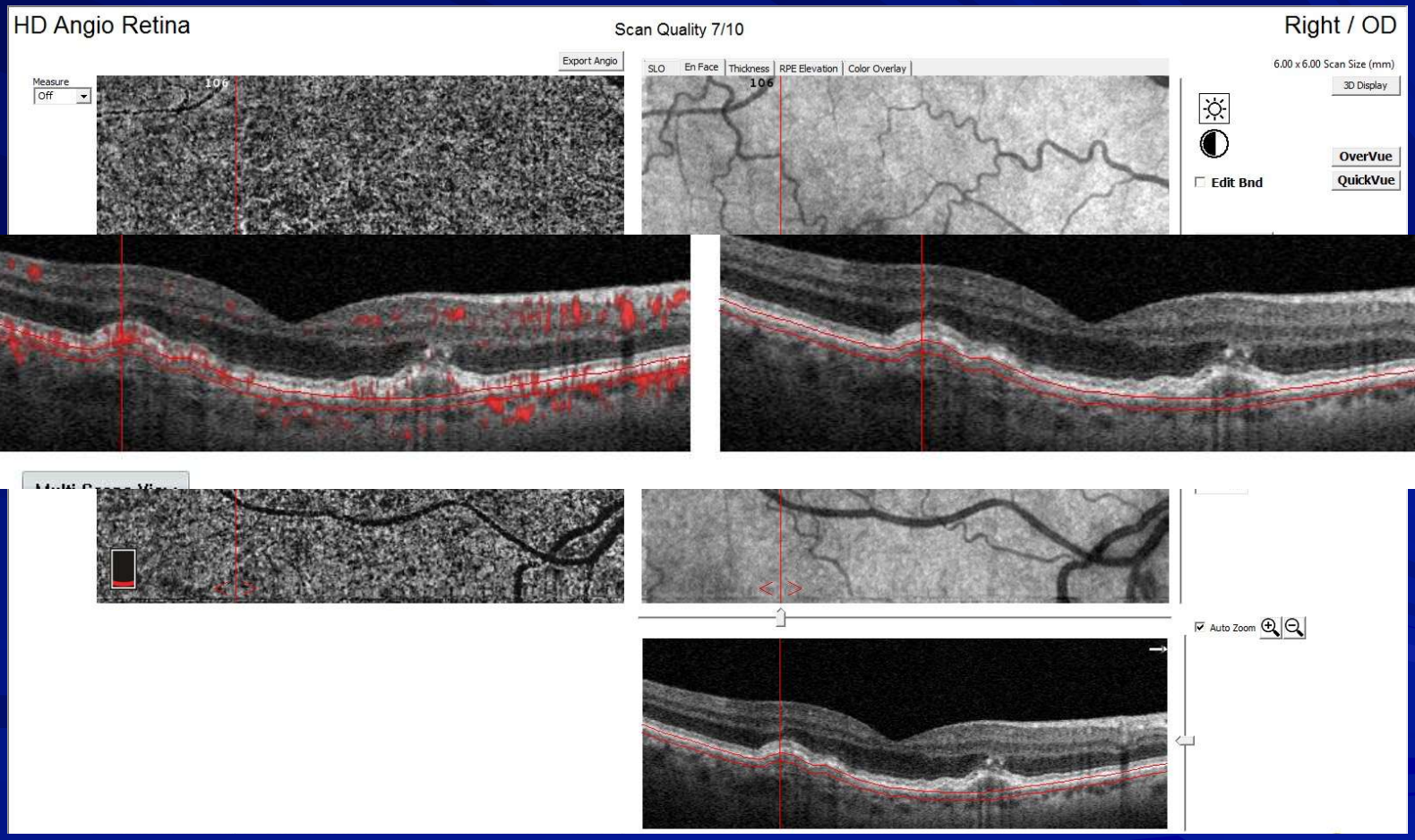


OCT Angiography

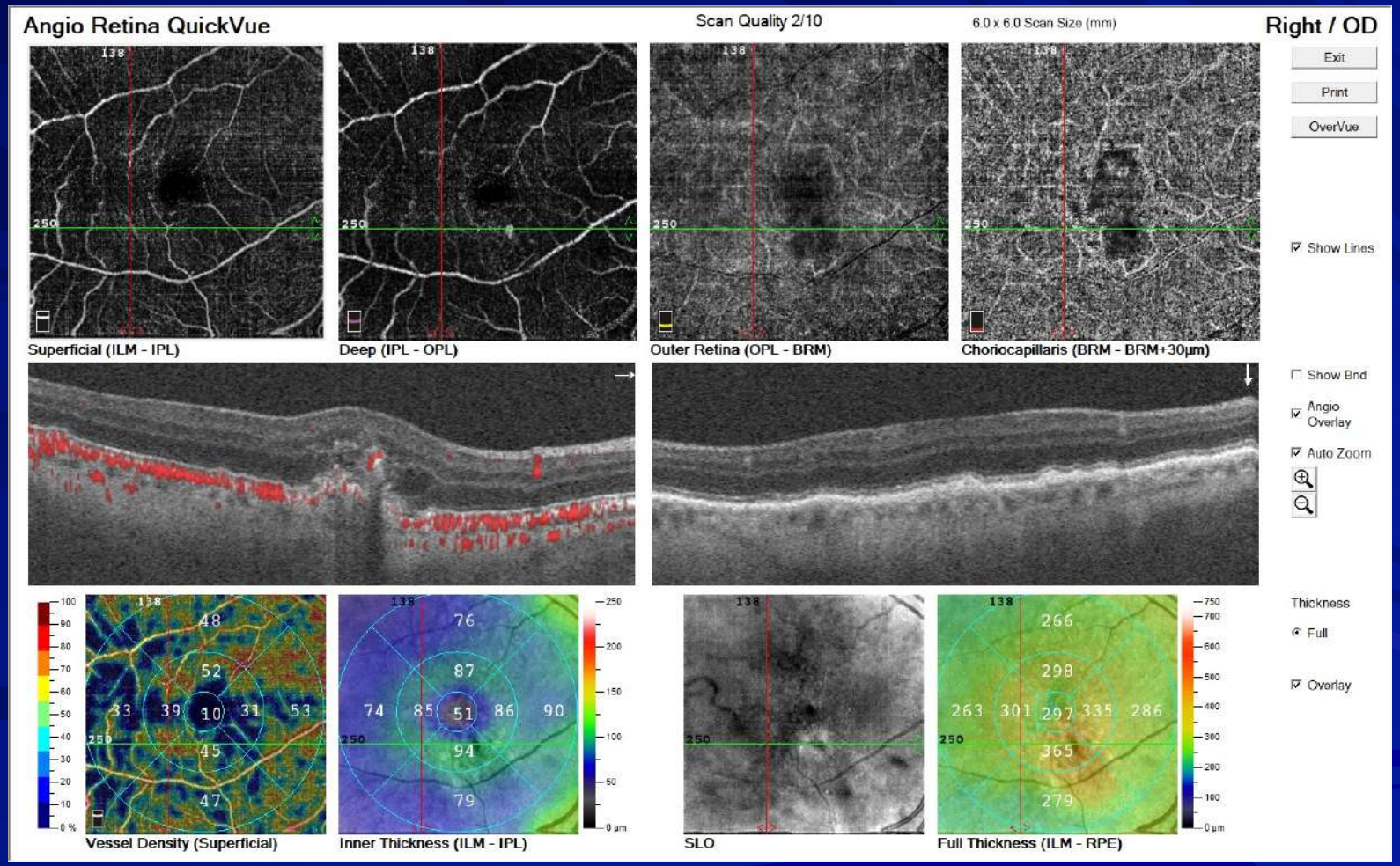
Subclinical CNV or “Occult non-exudative CNV”

Risk of exudation at 12 months is 15.2 times greater compared to eyes without subclinical CNV

Which is More Suspicious?

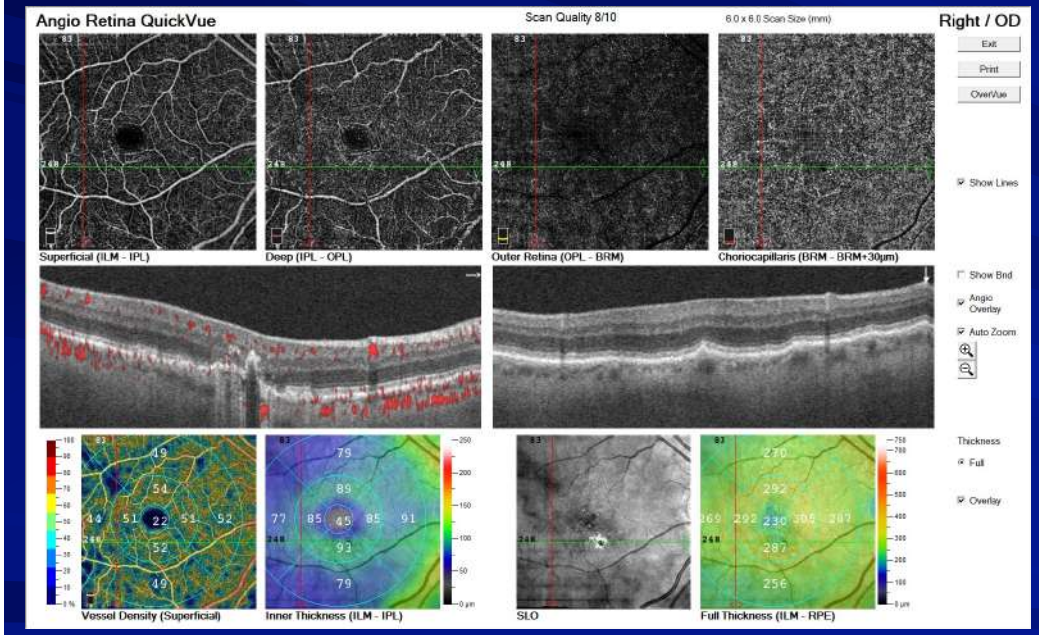


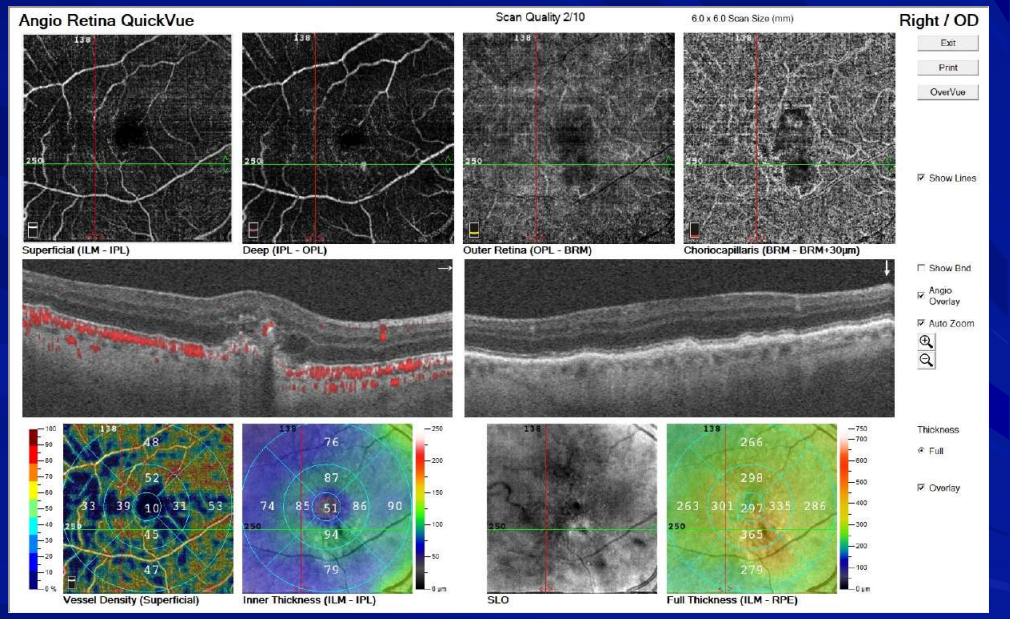
OCT Angiography Evaluation AMD

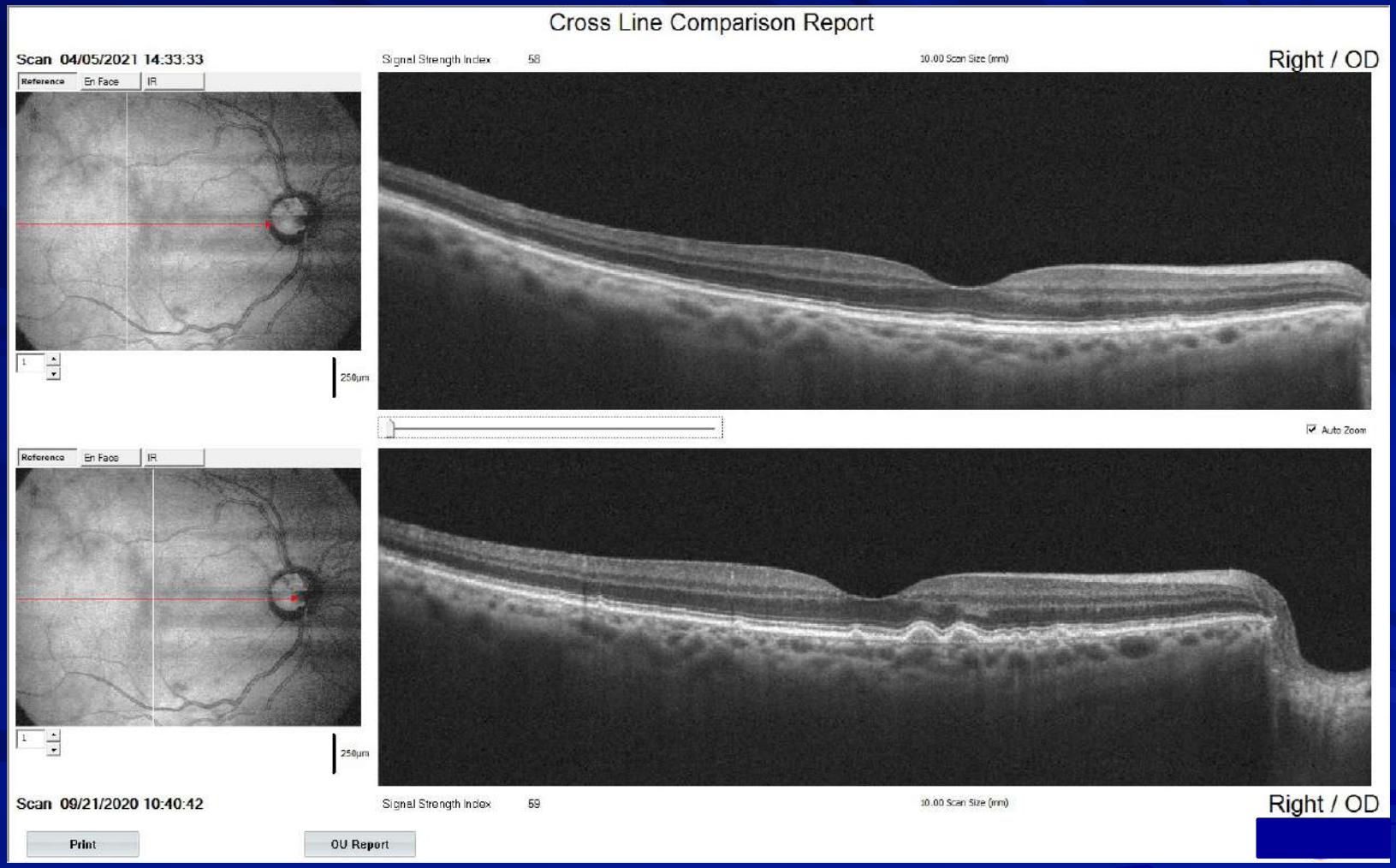


OCT Angiography Evaluation AMD

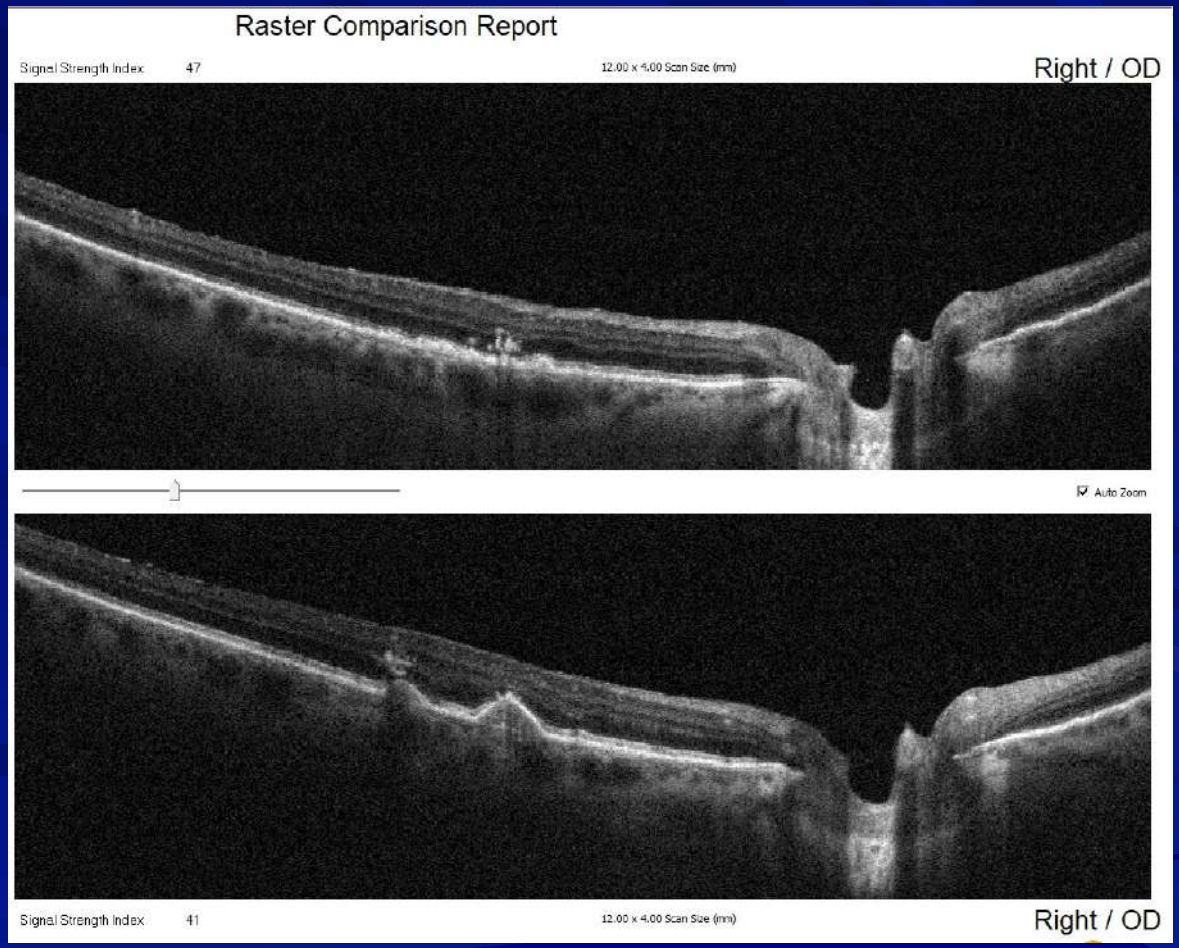
After and Before Bevacizumab (Avastin)

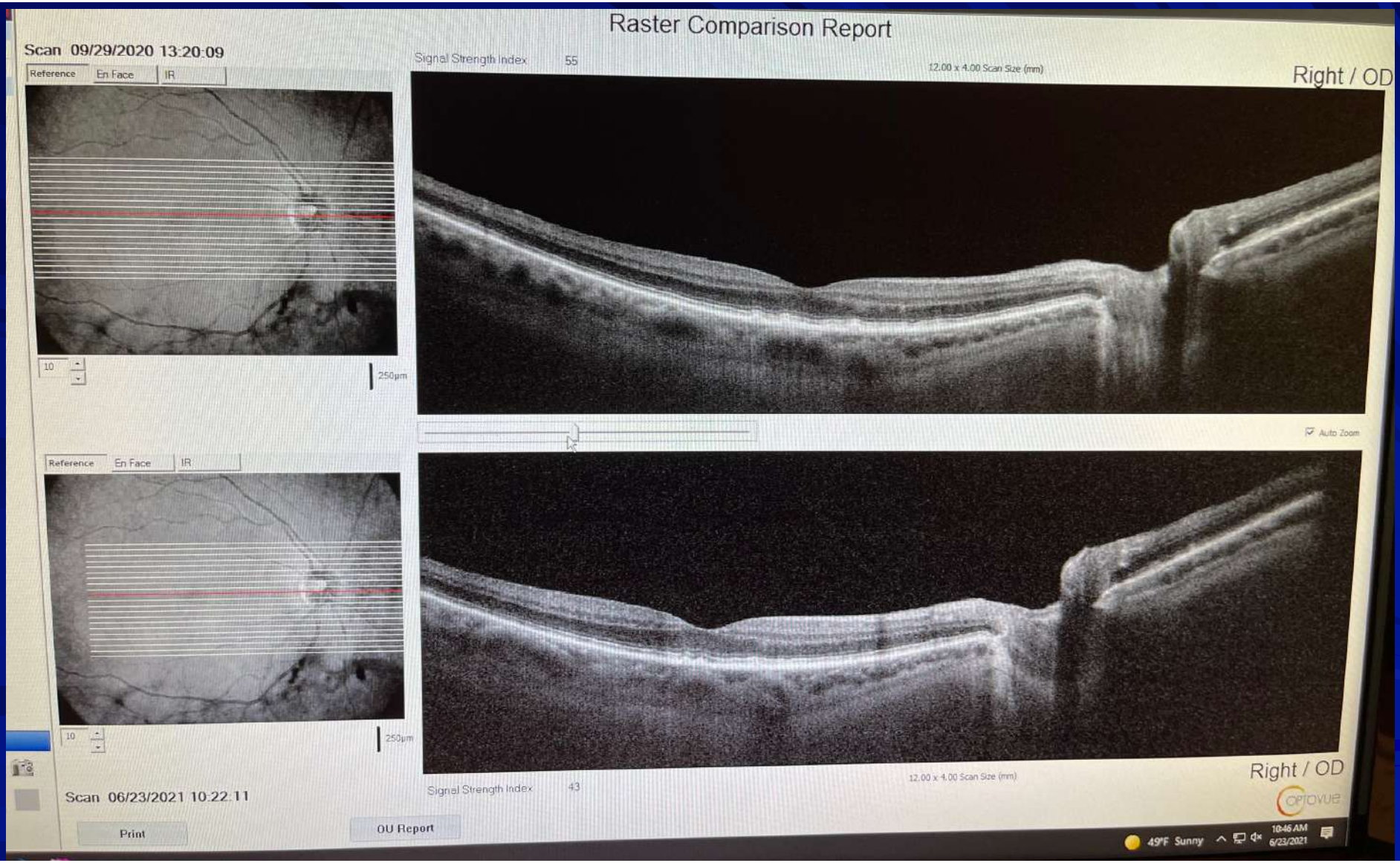




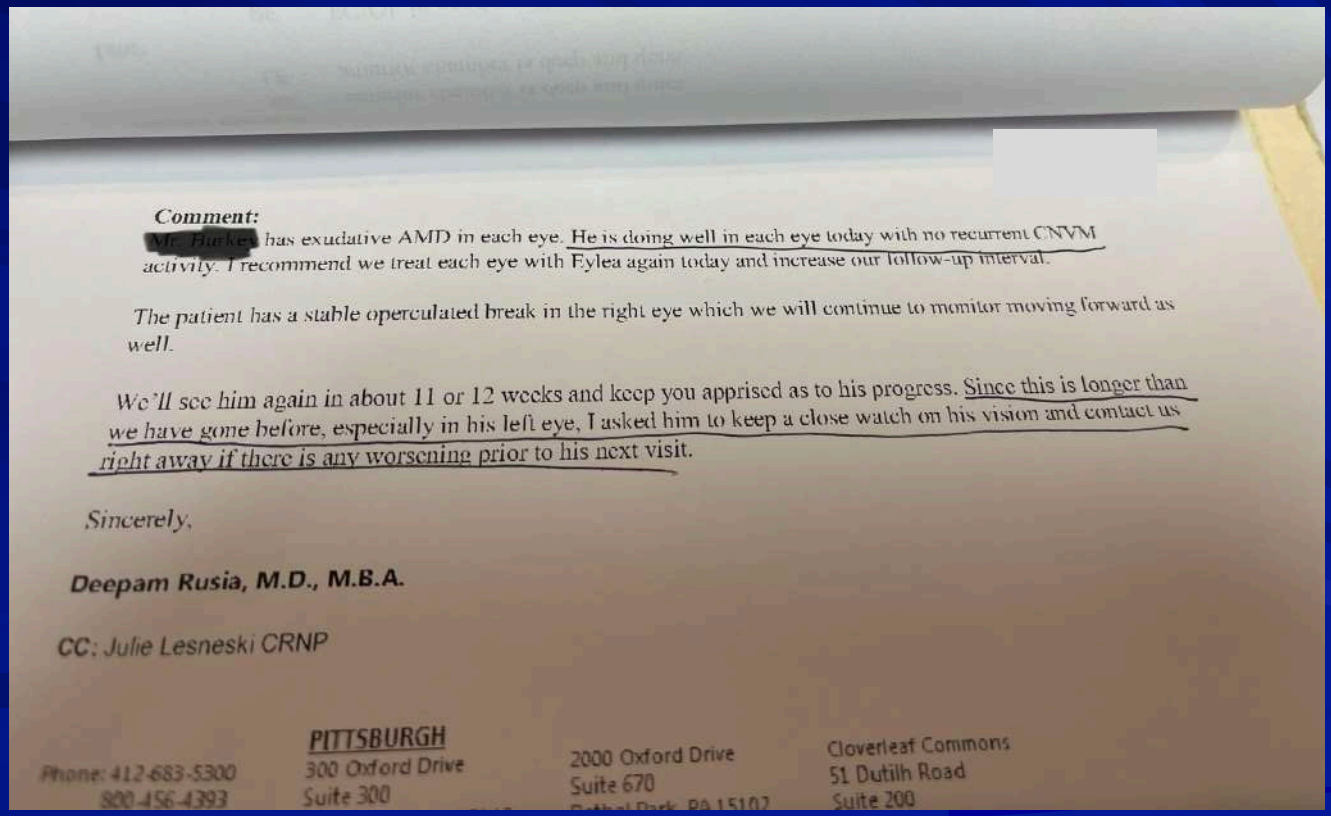

Cross Line Comparison Report
Scan 04/05/2021 14:33:33
Signal Strength Index 58
10.00 Scan Size (mm)
Right / OD
Reference
En Face
IR
250µm
Auto Zoom
Scan 09/21/2020 10:40:42
Signal Strength Index 59
10.00 Scan Size (mm)
Right / OD
Print
OU Report

April 27, 2021 – January 26, 2022 (9 months)




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
OPTOVUE
Print
OU Report
49°F Sunny
10:46 AM
6/23/2021

Treat and Extend!



Comment:

[redacted] has exudative AMD in each eye. He is doing well in each eye today with no recurrent CNVM activity. I recommend we treat each eye with Eylea again today and increase our follow-up interval.

The patient has a stable operculated break in the right eye which we will continue to monitor moving forward as well.

We'll see him again in about 11 or 12 weeks and keep you apprised as to his progress. Since this is longer than we have gone before, especially in his left eye, I asked him to keep a close watch on his vision and contact us right away if there is any worsening prior to his next visit.

Sincerely,

Deepam Rusia, M.D., M.B.A.

CC: Julie Lesneski CRNP

PITTSBURGH

Phone: 412-683-5300
800-456-4393

300 Oxford Drive
Suite 300

2000 Oxford Drive
Suite 670

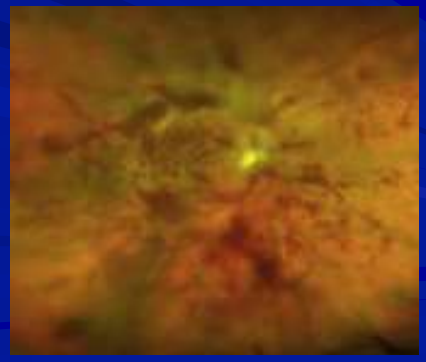
Cloverleaf Commons
51 Dutilh Road
Suite 200

Treatments for Choroidal Neovascularization (CNV)

- Current Anti-VEGF treatments
  - Bevacizumab (Avastin)
    - Humanized full length monoclonal antibody
    - AMD
  - Ranibizumab (Lucentis)
    - Humanized monoclonal antibody fragment
    - AMD, DME, DR, RVO
  - Aflibercept (Eylea)
    - Fusion protein
    - AMD, DME, DR
  - brolucizumab-dbll (Beovu)
    - Humanized single-chain antibody fragment
    - Up to 3 months dosing intervals, most are 4-6 weeks
      - 50% remained 3 months after 1 year
  - Pegaptanib (Macugen)
    - RNA aptamer
    - AMD

Beovu (brolucizumab)

- Indication: injection is used for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)
  - Offers a 3-month dosing schedule in the first year of treatment
- Warning issued by the American Society of Retinal Specialists about a series of intraocular inflammation events—some of which led to severe vision loss
- On April 8, 2020, Novartis announced its completion of the review, which included an assessment by an external, independent Safety Review Committee
- Complications: n=1098
  - Intraocular inflammation (IOI) - 4.6% (n=50)
  - IOI + retinal vasculitis – 3.3% (n=36)
  - IOI + retinal vasculitis –retinal (artery) vascular occlusion – 2.1% (n=23)
  - Vision loss of 15 letters or more - <1%



Byooviz™ (ranibizumab-nuna)

- Reference drug Ranibizumab (Lucentis™)
  - Ten manufacturers are working on Ranibizumab biosimilar (as of 2021)
- Samsung Bioepis, South Korea
  - First ophthalmology biosimilar approved by US-FDA in September 2021
    - Others have been approved around the world
  - Treat wet AMD, Macular Edema following RVO, and myopic CNVM,
  - A randomized phase 3 multicenter, parallel-group double-masked study compared efficacy, safety, pharmacokinetics & Immunogenicity of Byooviz with the reference Ranibizumab in patients of nAMD.
  - 705 patients were enrolled and randomized (1:1) to receive Byooviz or reference Ranibizumab every 4 weeks through week 48.
  - The safety and immunogenicity profile of SB11 and reference ranibizumab were comparable at all points up to week 52

Thank You and Questions!

New Technologies for Managing Macular Degeneration Patients

Greg A. Caldwell, OD, FAAO

Woo U – Distance Learning Event

Wednesday, November 9, 2022