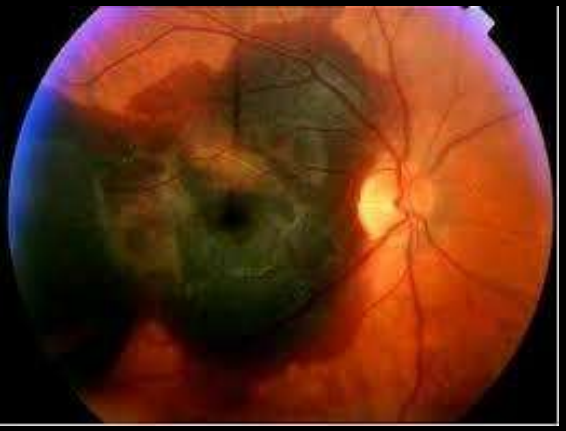
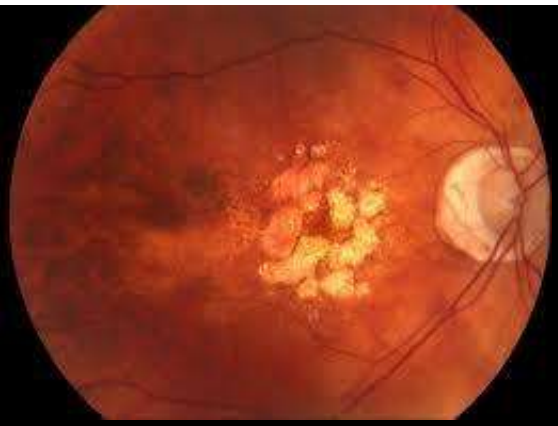
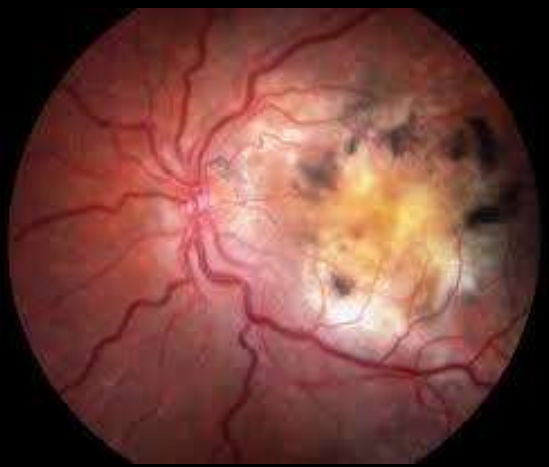




AMD: Current Science and Trends in Diagnosis and Treatment

Jeffry D. Gerson, O.D., F.A.A.O.
Grin Eye Care
jgerson@hotmail.com

Julie Rodman, O.D., M.S., F.A.A.O.
Professor, Nova Southeastern University
rjulie@nova.edu



Disclosures: Gerson

- I am/have been a member of an Ad board or speaker's bureau or been paid honoraria by/for…
  - Allergan, Arctic Dx, AstaReal, Bausch Health, Essilor, Genentech, Luneau Technologies, Macular Degeneration Association, Maculogix, Optos, Optovue, Regeneron, VSP, &/or Zeavision

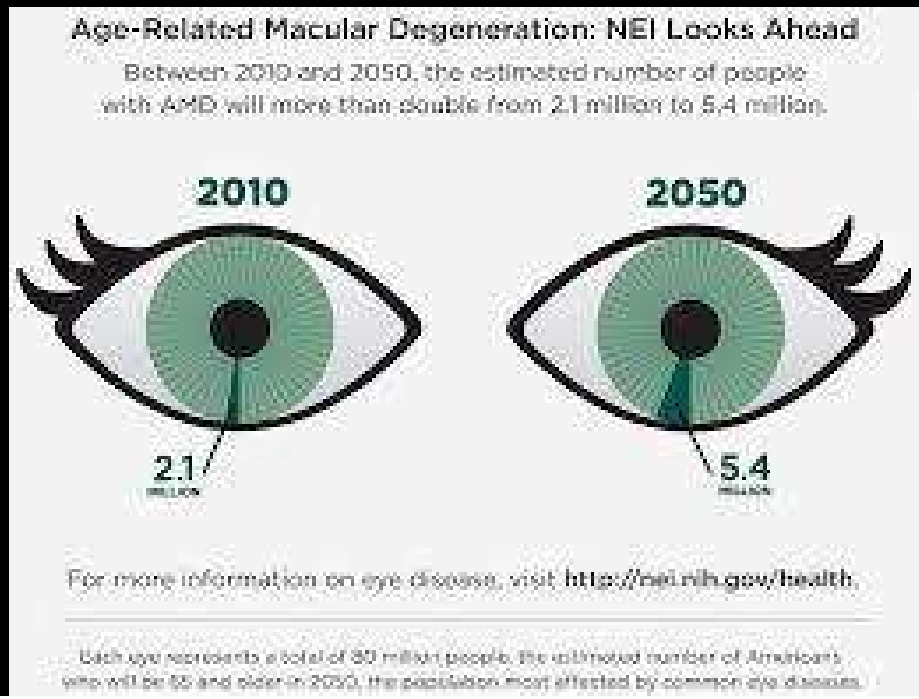
Disclosures: Rodman

- Optovue, Maculogix, iCare

These affiliations will have **no** effect on the content of this lecture

Conclusion/Take Away

- Prevention and early detection are key to ultimate patient success
  - That's what we do
- Treatment of advanced AMD is not good in the long term
  - We refer for this…



Another important conclusion

- Future Direction: There will be more AMD, less MD's and we will NEED to be more proactive an involved
- We need to be comfortable spending time discussing AMD with our patients
  - More education equals more proactive equals better outcomes
  - We may need to listen some also
    - Take clues to help guide

Trivia

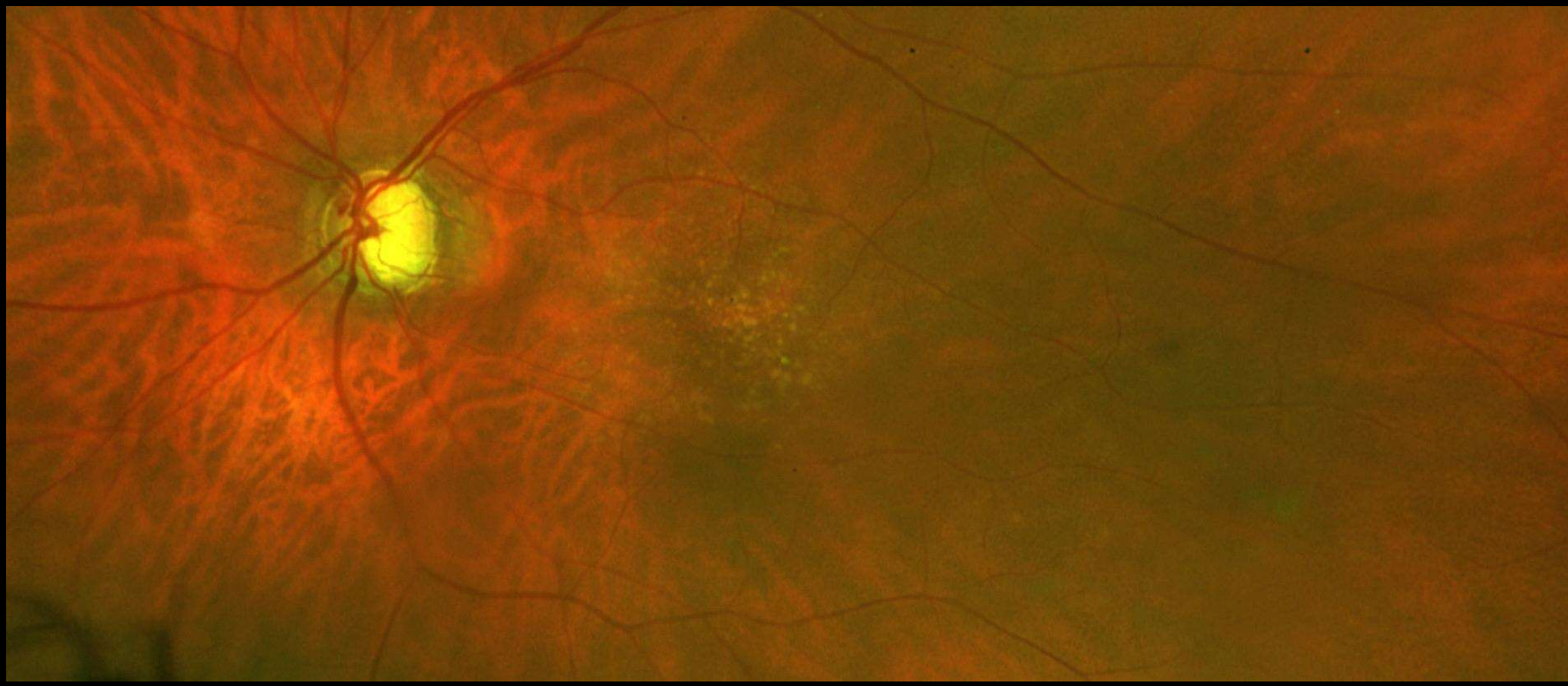
- What is “NUNA”

Where do you practice?

- Private OD practice
- OD/MD practice
- Institution

- We all see the same patients!

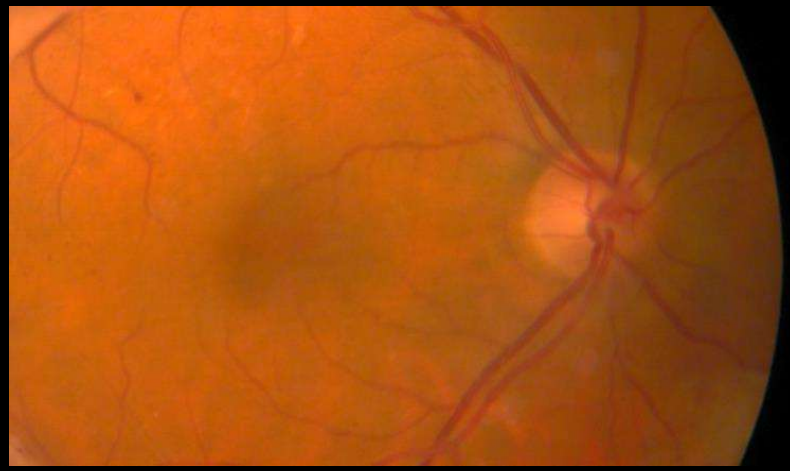
Start with a case…..



- 80 y/o (stubborn) male
- Same appearance OU
- 20/25- OU
- What do you want to know?

One more case

- 68y/o w T2DM



- No real complaints, but ”I don’t like driving at night”
- 20/20, no family history

- What if I told you that they failed their DA screening?

Presenting for routine exam

It is Our Responsibility to Communicate AMD Diagnosis with Our Patients

- Deliver a simple and objective message to your patients.
- No need to apologize.
- Help them understand why they may have trouble seeing or driving at night.
- Early diagnosis should be considered good news!

We found something early and can do something about it!

We'll come back to this later…

How do we find AMD?

- Must start with clinical exam
  - What exactly is the minimum findings to "qualify" for AMD?

What is “pre-AMD”

- Well defined “prediabetes” that triggers interventions
- Do we have such a thing with AMD?
  - Should we?
  - Could we?
  - Why would we?

We do not diagnose AMD early enough!

- Several recent papers pointing out that AMD goes undiagnosed!
- 60% of 95 pts in Anterior Seg MD pts had AMD based on OCT (case vs. hx vs no hx)[2]
- Up to 40% over age 60 in OD practice with subclinical AMD[3]

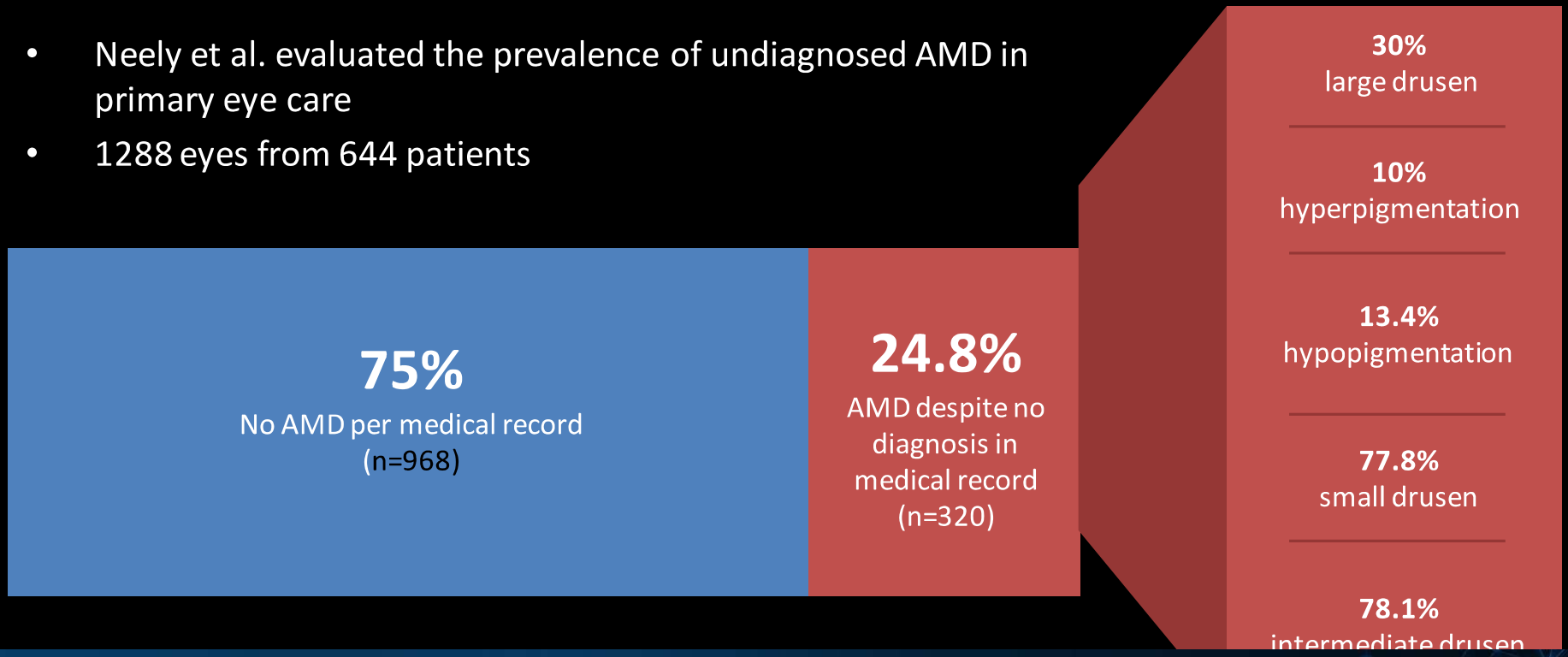
SO WHAT?

Who Cares?

2. Weiss and Henderson. Subclinical AMD. ARVO 2017 poster B0194 3. Unpublished as of this date

Intermediate AMD may often go undiagnosed

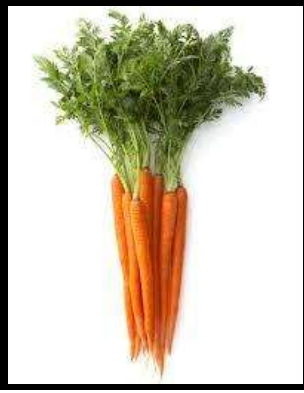
- Neely et al. evaluated the prevalence of undiagnosed AMD in primary eye care
- 1288 eyes from 644 patients



If eyes go undiagnosed, patients may not be prescribed the right treatment plan.
The study concluded that better detection strategies may be needed for early AMD.

What's up Doc?

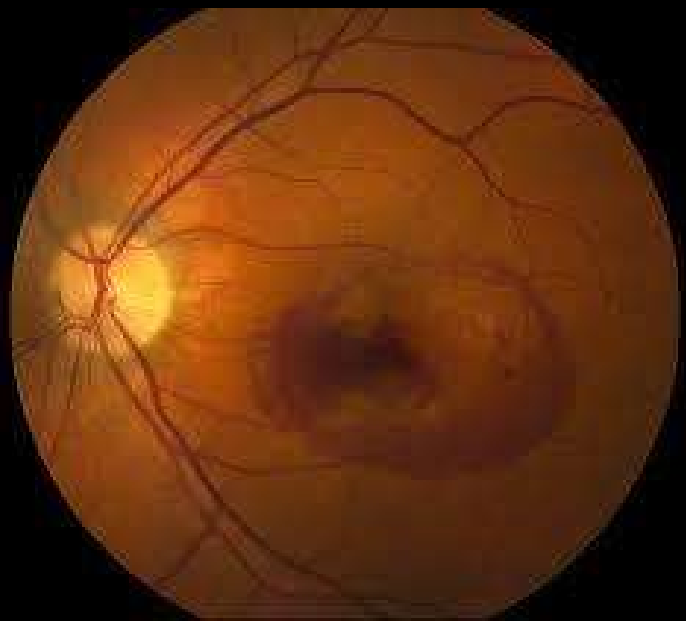
- Most people think that _____ is the best food for their eyes and will help their vision.
- Carrots can be part of a healthy diet, and are high in beta carotene.
- Foods with L/Z likely better for health and vision!



Age Related Macular Degeneration

Risk Factors

- Smoking (truly avoidable risk)
- Aging (33% over age 75)
- Family history (50% lifetime risk vs. 10-12% without)
- Hypertension / Cardiovascular Dz
- Race (Caucasian females)
- Obesity / high cholesterol
- Sun Exposure: Blue light



Risk Factor vs Diagnostic testing

- Risk Factor: Gives ideas of risk moving forward
  - MPOD, genetics, smoking, Hx
- Diagnostic testing: Identifies presence of disease
  - OCT, clinical exam, DARK ADAPTATION

This is an important concept/distinction!!

SMOKING is a HUGE RISK Factor

Beave

Blue M

Rotter

ases risk

vomen.

to 10

mokers.

or

at 5

nt

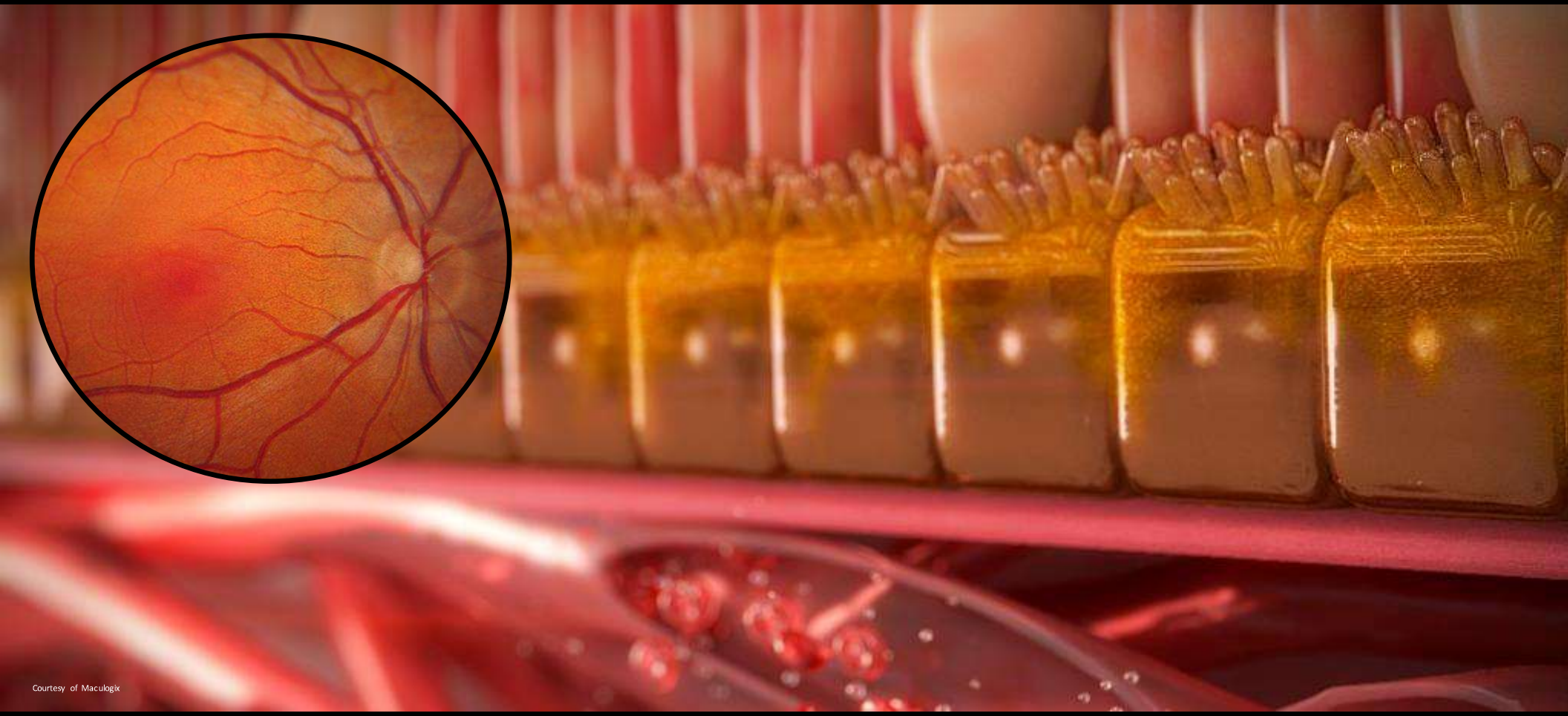
rs

Clinical Risk Factors: Per Blue Mountains Eye Study

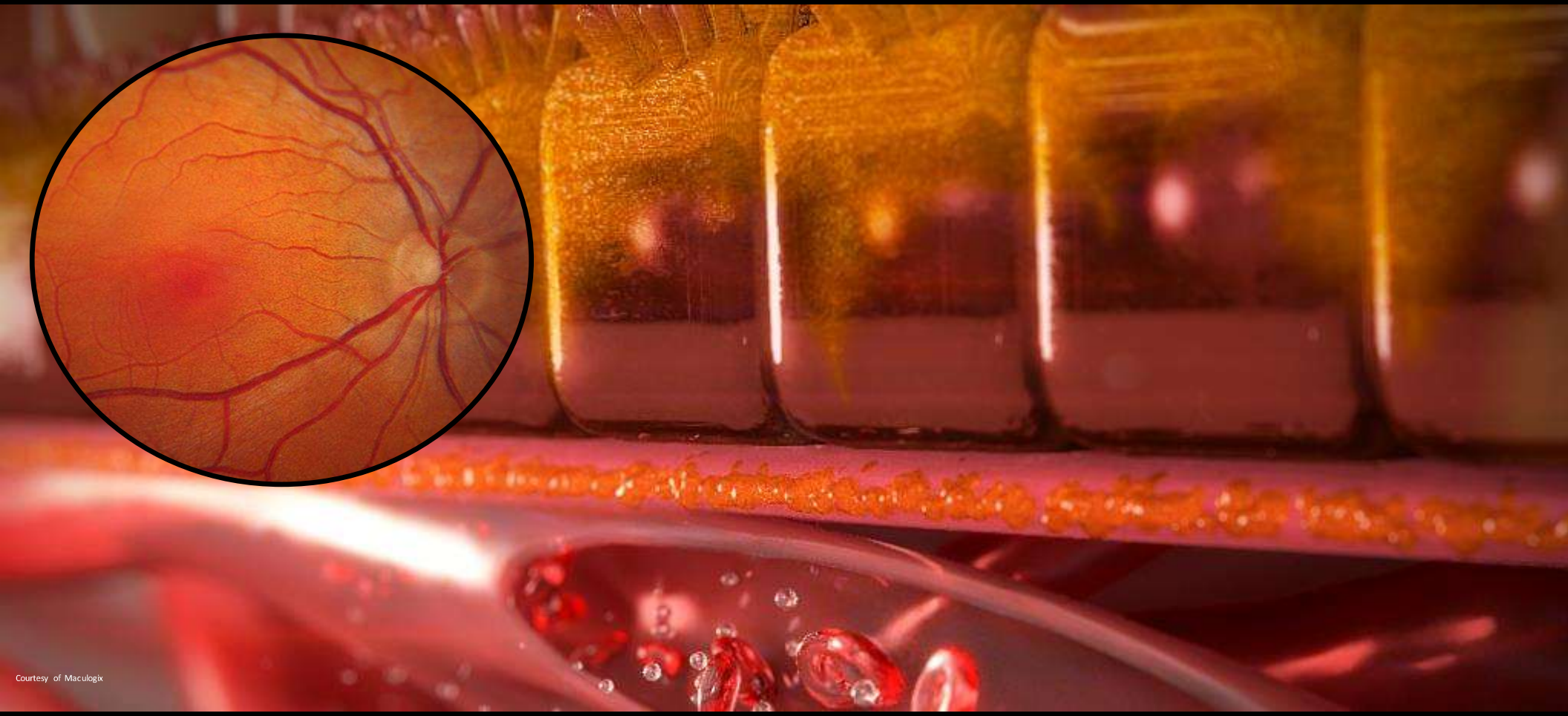
- Large Drusen and Pigmentary change are most predictive for late AMD
- No large drusen or pigmentary changes: <1% of advanced AMD in 5 yrs
- Large Drusen and pigmentary changes: >50% of advanced AMD
- Those in highest tertile of L/Z: approx 1mg/d had 65% reduced incident Neovasc. AMD

Let’s review the pathophysiology of AMD

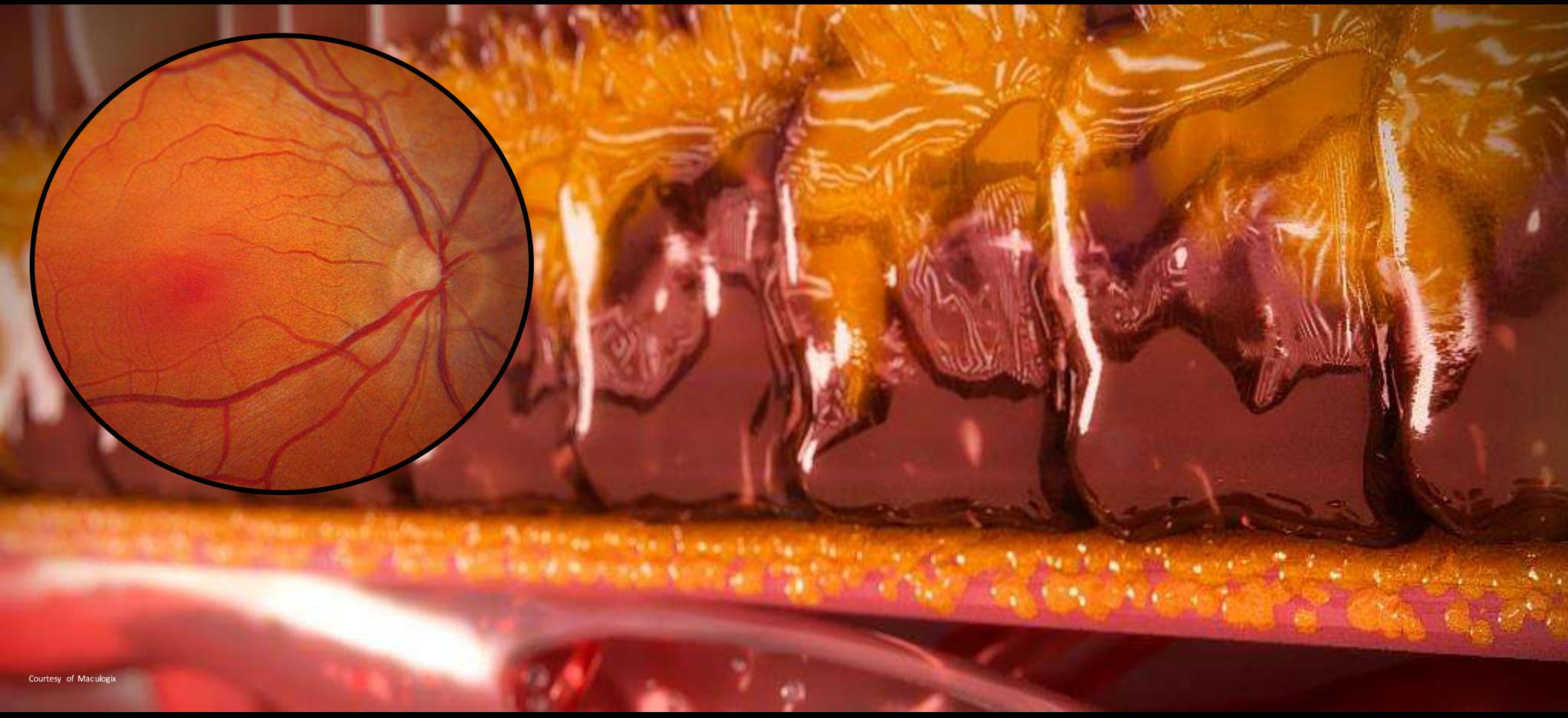
Healthy Choriocapillaris, Bruch's, RPE, and Photoreceptors



Cholesterol Barrier Deposited Along Bruch's and RPE



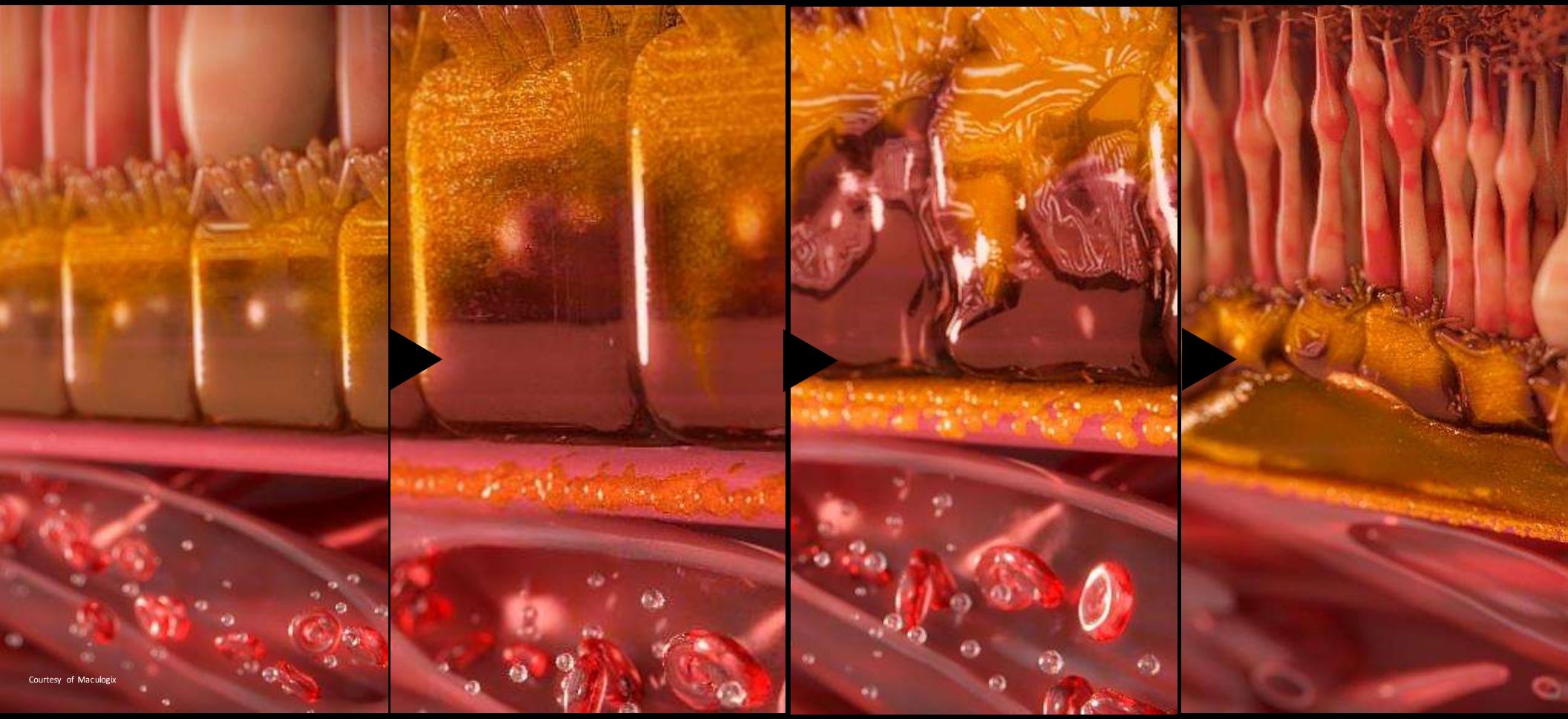
RPE Secretes Even More Cholesterol and Degenerates



Visibly Evident Drusen on Fundus Evaluation

Courtesy of Maculogix

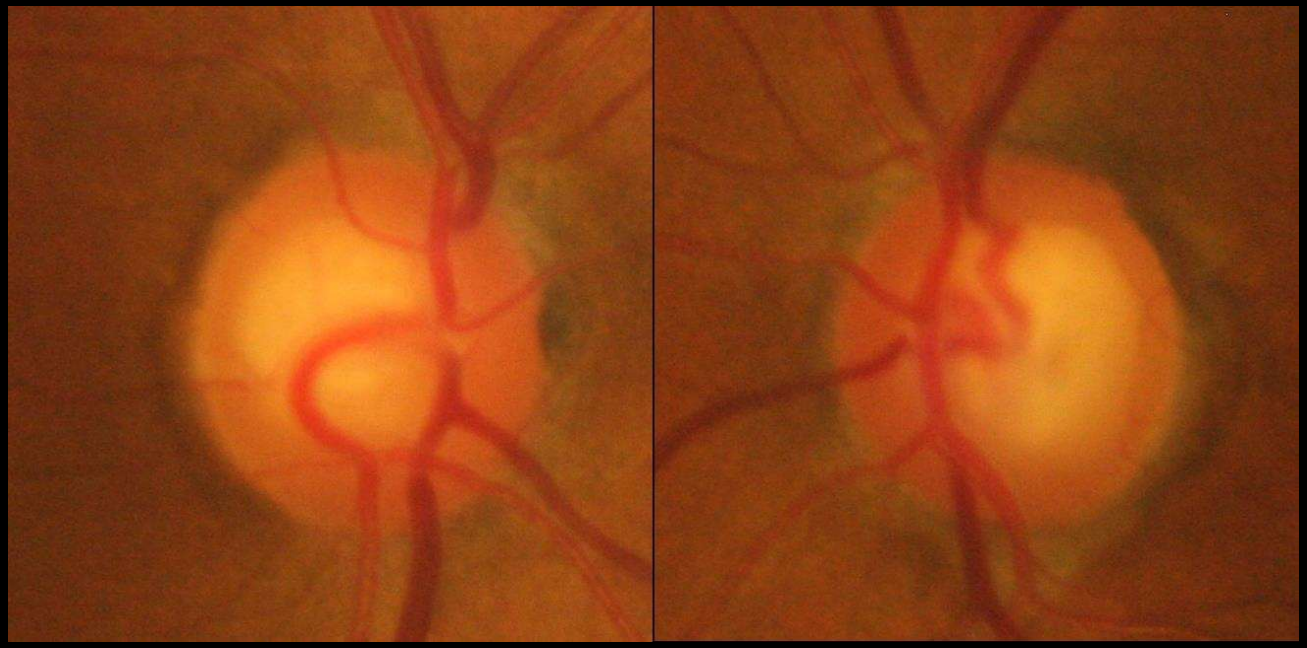
Disease Process of AMD Starts Below the Surface



How can we do a better job?

Integrate new and innovative testing!!

65-year-old African-American female

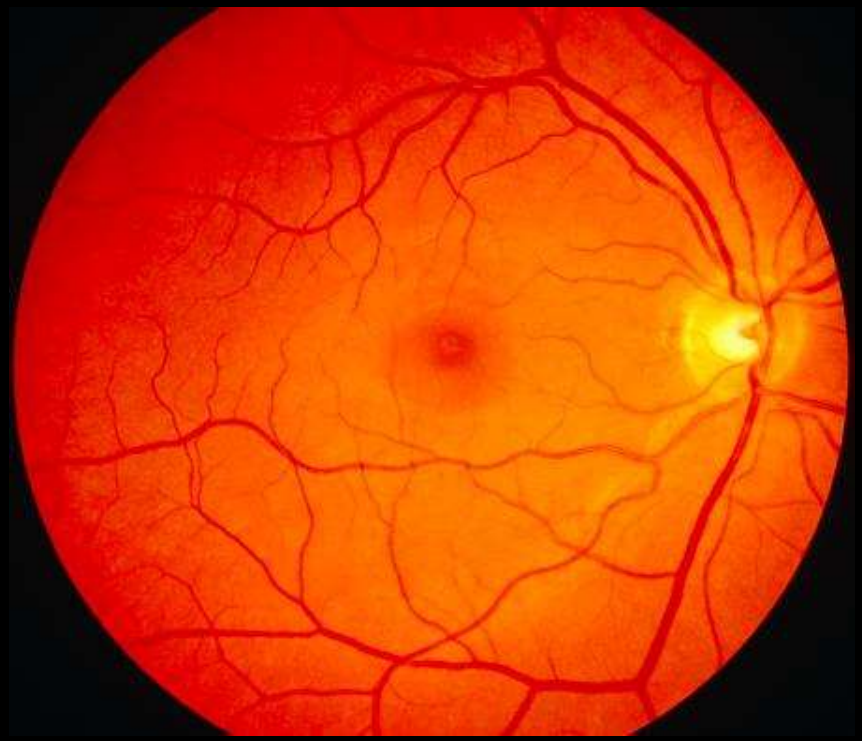


- 20/20 vision
- Normal family and personal ocular history
- No complaints

What would you do? Normal? Abnormal?

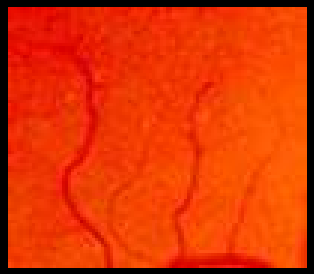
Would you ever manage this patient without this testing??

70-year-old Caucasian female



- 20/20 vision
- Normal family and personal ocular history
- Some difficulty seeing at night

What about this one?



Is there any testing that you may want to do??

Types of AMD Tests:

Structural Testing – assessment that evaluates the physical structure of the retina

Functional Testing – assessment that evaluates how the retina is working

Structural Testing

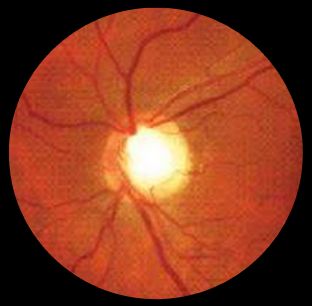
- ✓ Clinical Examination with Slit Lamp
- ✓ Fundus Fluorescein Angiography (FFA)
- ✓ Optical Coherence Tomography (OCT)
- ✓ Fundus Autofluorescence Imaging (AF)

VS

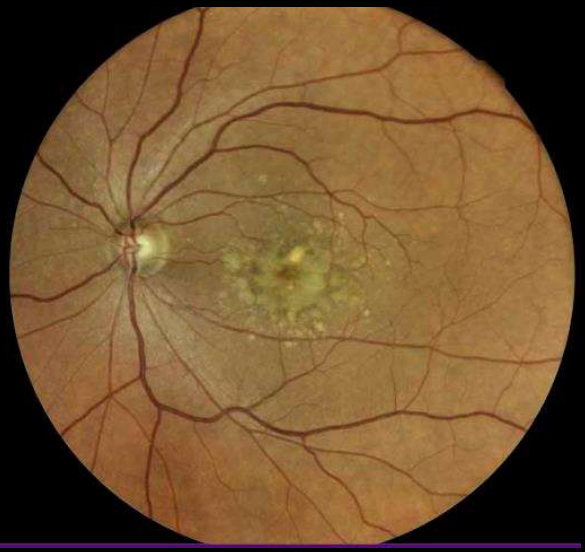
Functional Testing

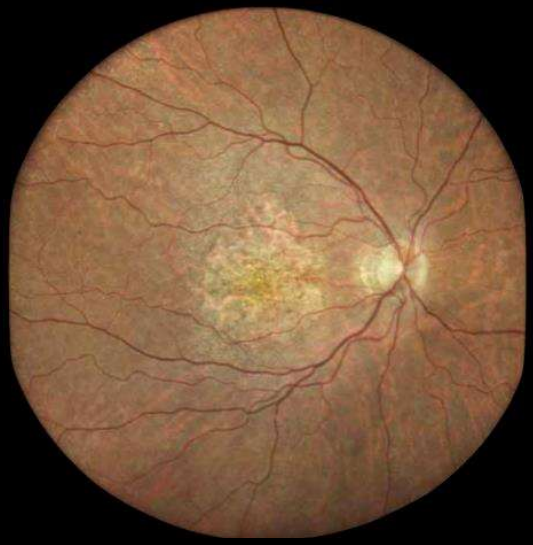
- ✓ Dark adaptation

Standard of Care Comparison: Two Multifactorial Diseases

	GLAUCOMA	AMD
Structure	 Cup-to-Disc Ratio	 Drusen
Function	 Visual Field	 Dark Adaptation
Risk	Intraocular Pressure (IOP) Corneal Thickness Demographics and Family History	Macular Pigment Optical Density Contrast Sensitivity Genetic Testing Demographics, Family History, Lifestyle

Clinical Examination with Slit Lamp



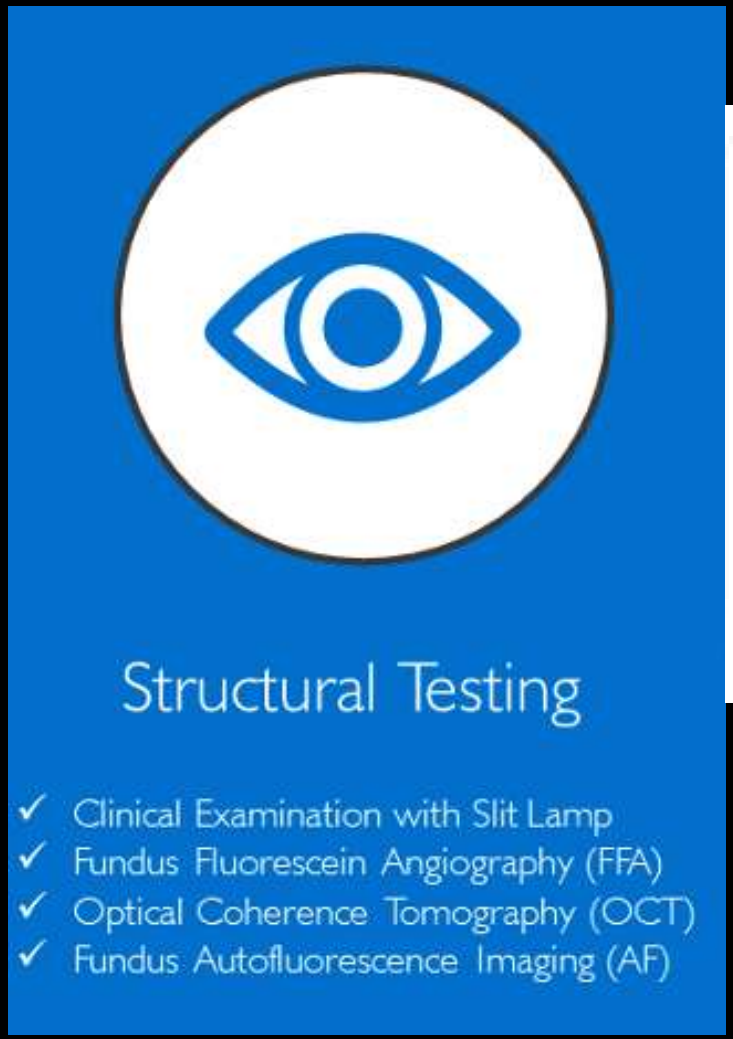


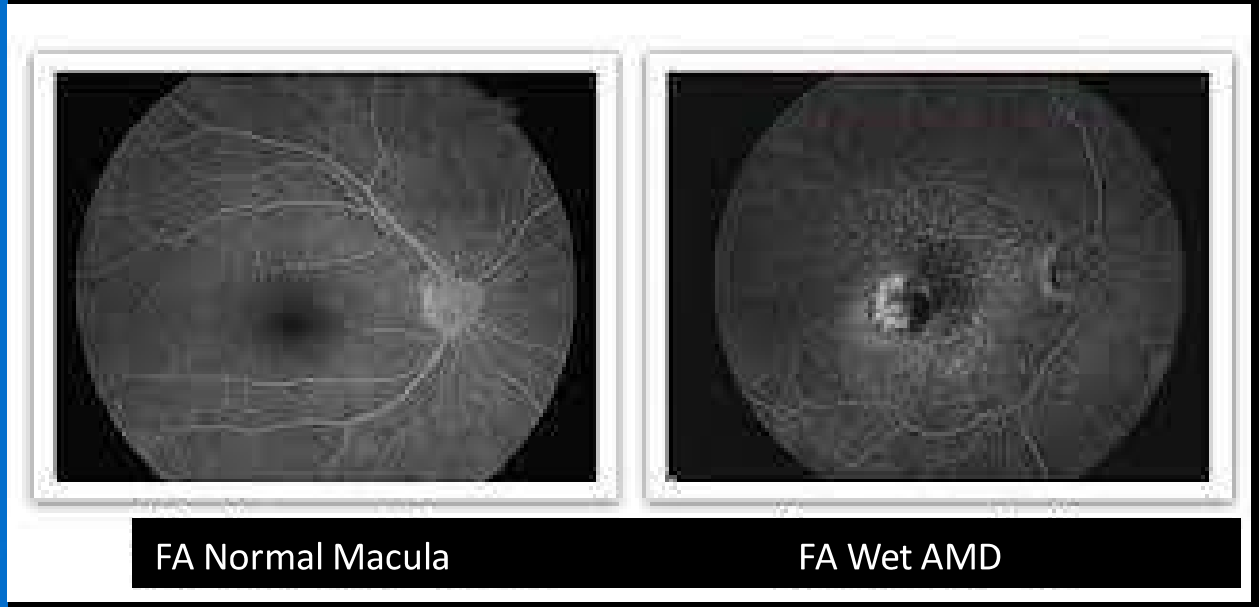
Images courtesy of iCare

Structural Testing

- ✓ Clinical Examination with Slit Lamp
- ✓ Fundus Fluorescein Angiography (FFA)
- ✓ Optical Coherence Tomography (OCT)
- ✓ Fundus Autofluorescence Imaging (AF)

Fundus Fluorescein Angiography (FFA)

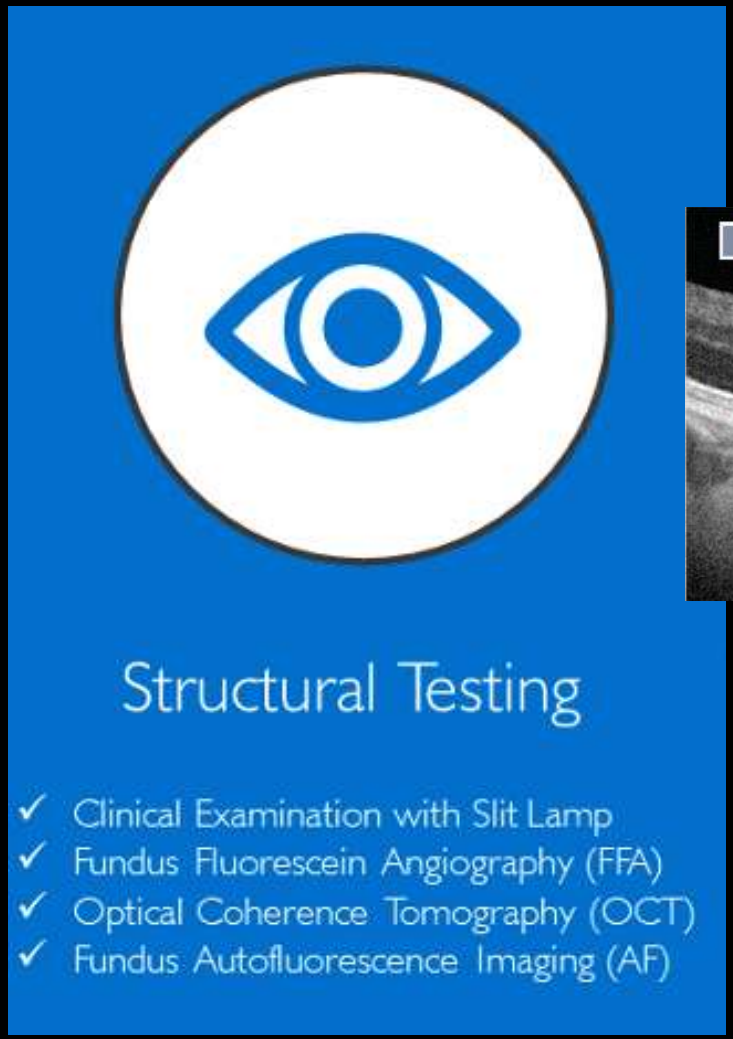




Size, type, location of CNV
Wet versus Dry

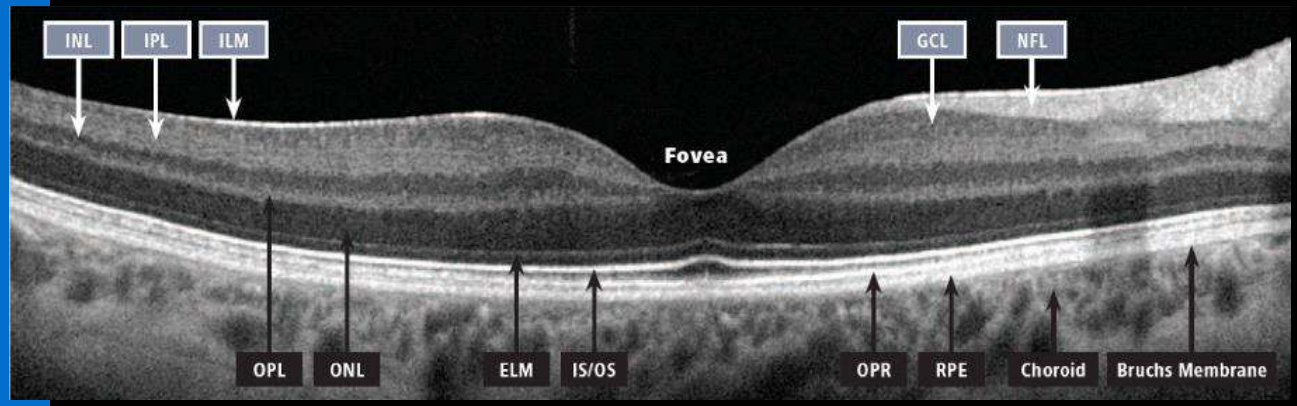
https://www.cureamd.org/dry-wet-amd-signs-symptoms-diagnosis/attachment/fa-normal-vs-wet-amd/

Optical Coherence Tomography (OCT)

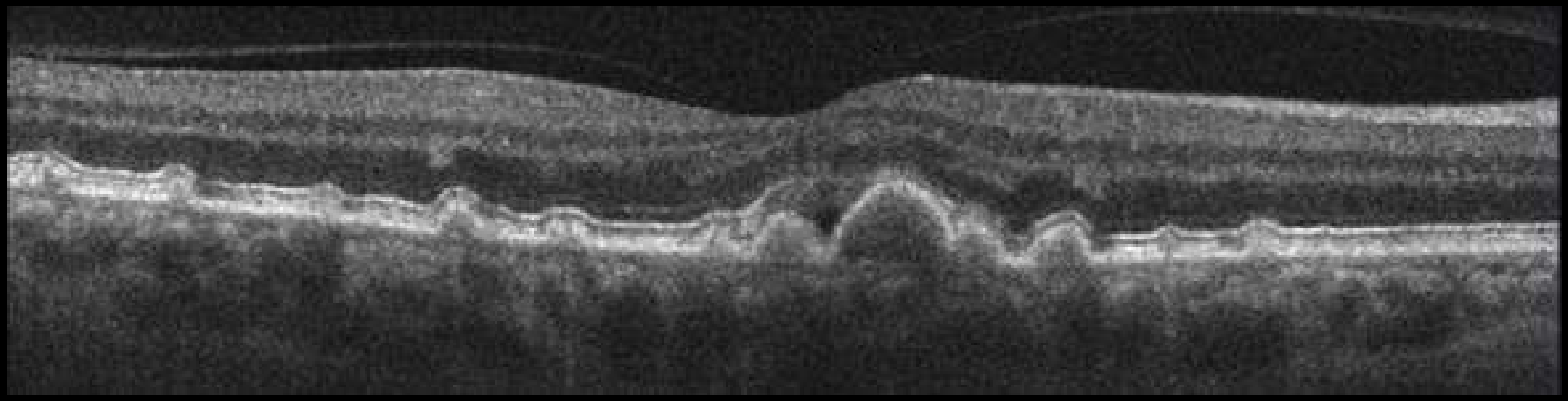


Structural Testing

- ✓ Clinical Examination with Slit Lamp
- ✓ Fundus Fluorescein Angiography (FFA)
- ✓ Optical Coherence Tomography (OCT)
- ✓ Fundus Autofluorescence Imaging (AF)

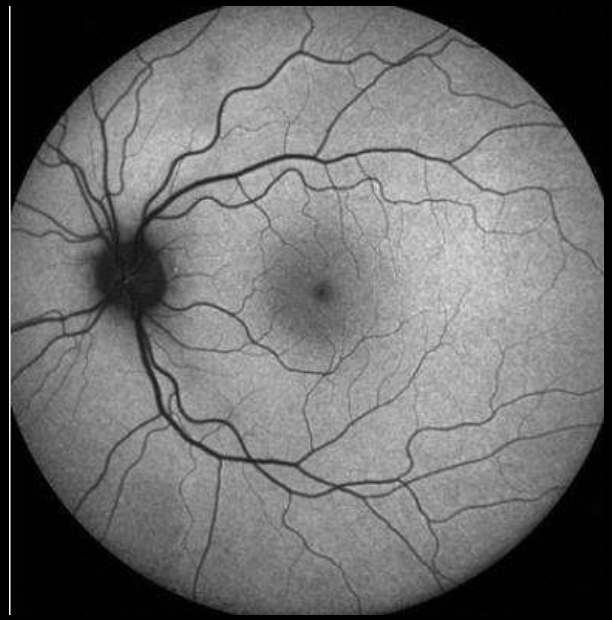


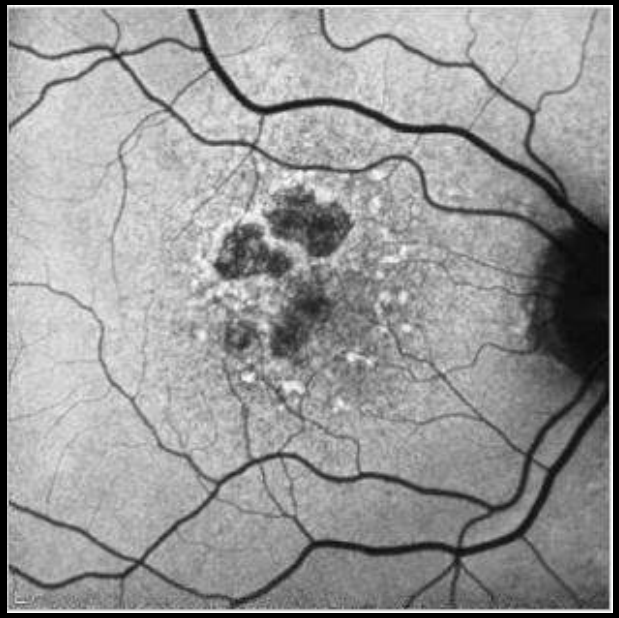
Drusen, pigmentary changes, CNVM, geographic atrophy



Fundus Autofluorescence Imaging (AF)

Visualize health and integrity of the RPE





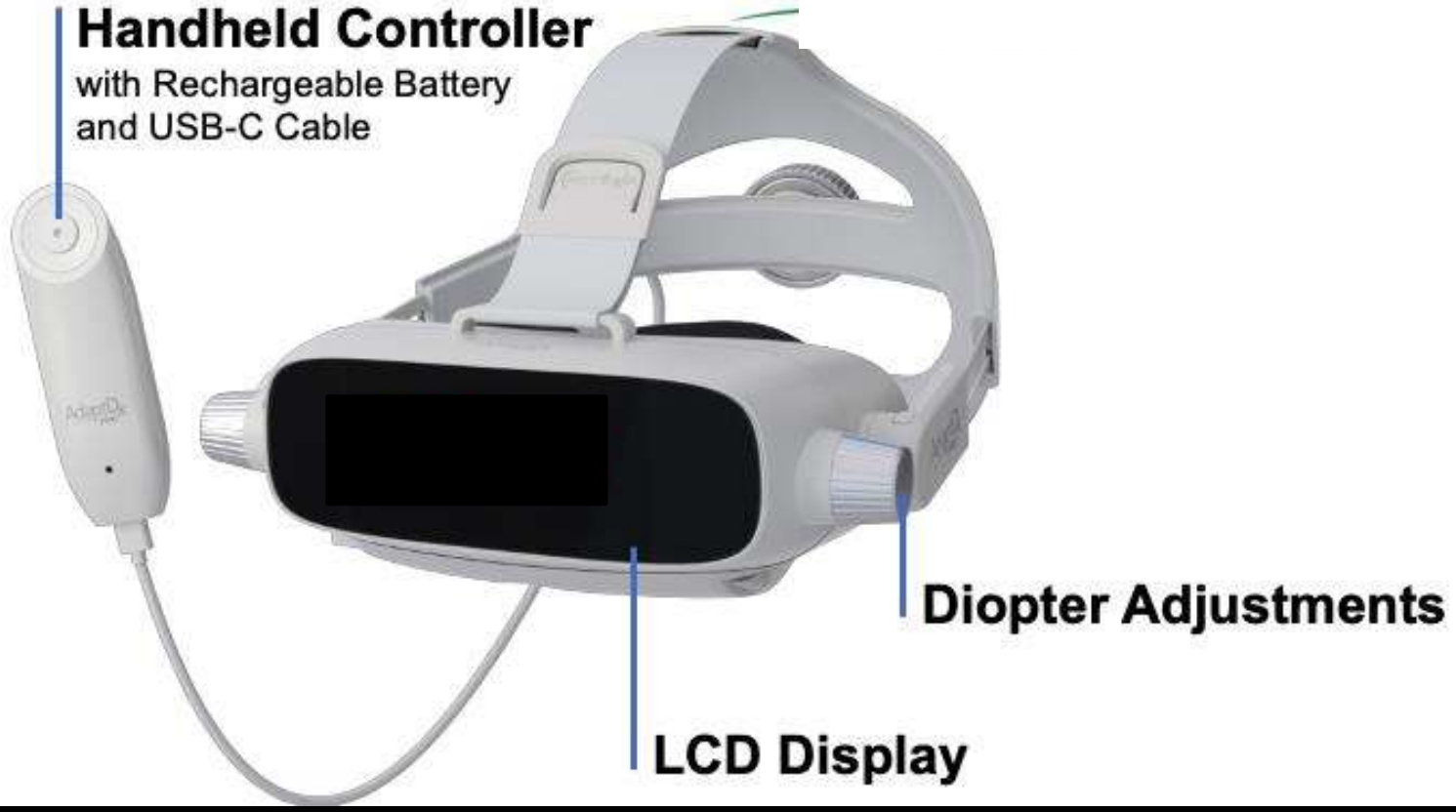
Structural Testing

- ✓ Clinical Examination with Slit Lamp
- ✓ Fundus Fluorescein Angiography (FFA)
- ✓ Optical Coherence Tomography (OCT)
- ✓ Fundus Autofluorescence Imaging (AF)

Functional Testing

- ✓ Dark adaptation

Impaired Dark Adaptation is Earliest Biomarker of AMD


Handheld Controller
with Rechargeable Battery
and USB-C Cable
Diopter Adjustments
LCD Display

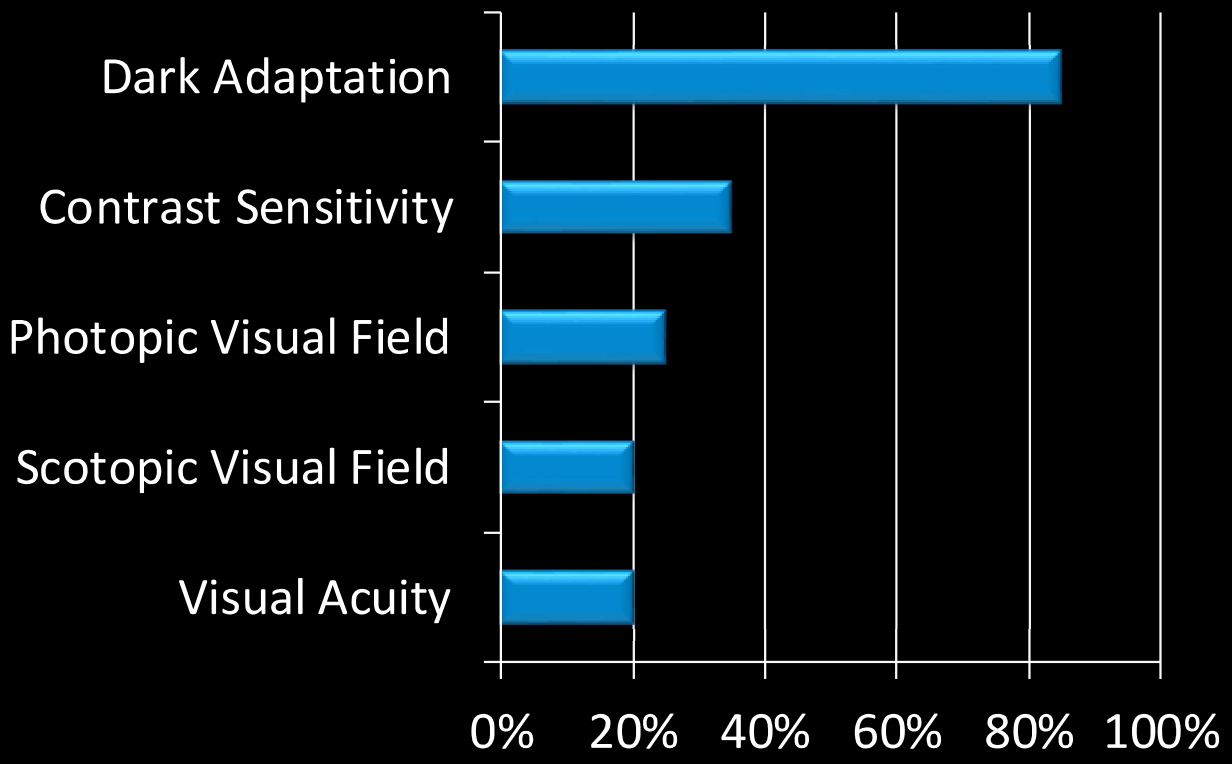
Staging Test

- Impairment increases with AMD severity

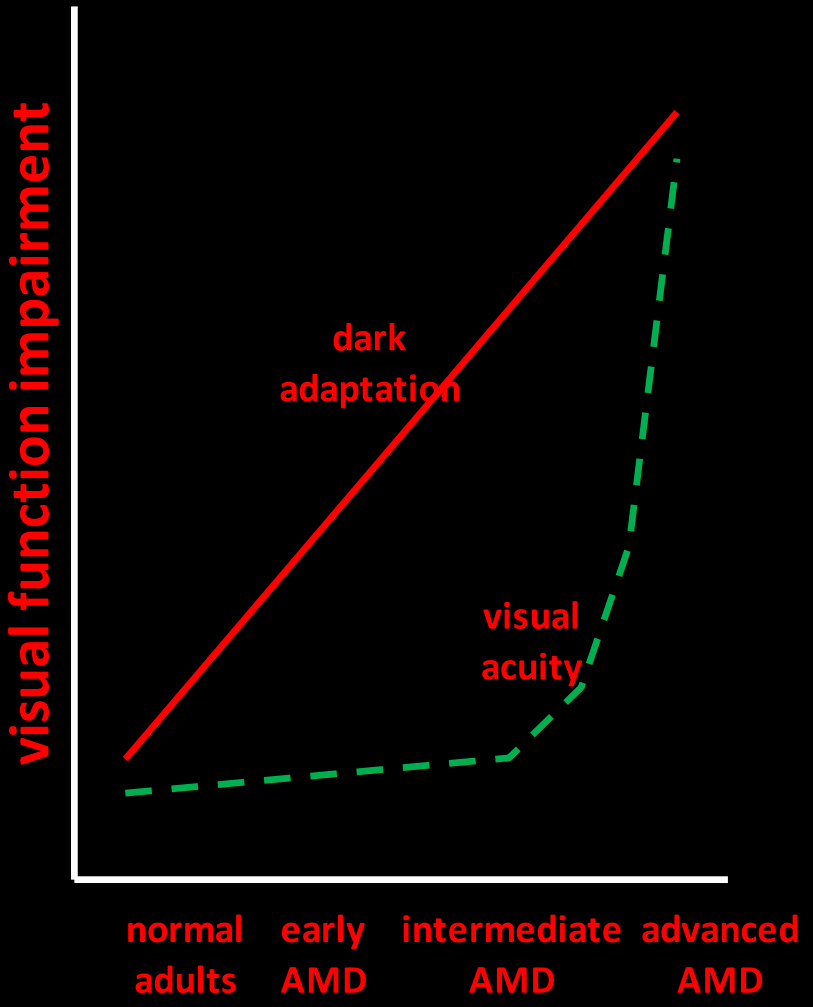
Stage	Rod Intercept
Normal	5.7 ± 1.9 minutes
Early AMD	12.9 ± 6.1 minutes
High-Risk AMD	16.6 ± 5.2 minutes
Late AMD	19.0 ± 4.5 minutes

- Odds of having High-Risk AMD increase 11.9% per minute ($p = 0.0015$)

Diagnostic Sensitivity



Akin to stress test in cardiology…rest and then try to perform..



Owsley et al. (2001) Ophthalmology 108:1196

My experience with dark adaptation

- IRB approved, publication pending
- 39/100 “normal” macula patients over age of 60 with impaired dark adaptation.

- The big question with that:
  SO NOW WHAT…..

Dark adaptation has changed how I practice

- Likely the first (unrealized) symptom of AMD
  - "I don't like to drive at night anymore"
- I do it on all patient over age 60
- If fail screening, return for extended testing
- Discussion of pre-emptive measures to take and back to taking care of self…..

So What??? Why do we care??

QUALITY OF LIFE!!

THAT IS WHAT WE PRACTICE!!

The Beckman Classification

4 Stages of AMD

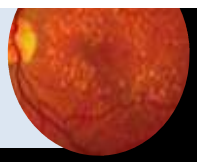
No AMD

No drusen or small drusen ≤ 63 µm
No AMD pigmentary abnormalities

Subclinical AMD **RI**

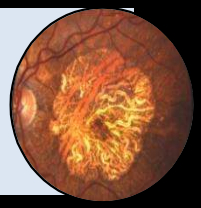
No drusen or small drusen ≤ 63 µm
No AMD pigmentary abnormalities
Impaired dark adaptation

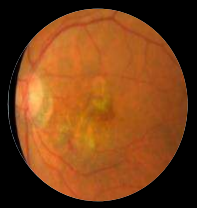
Intermediate AMD



1 large druse > 125 µm and/or
Any AMD pigmentary abnormalities

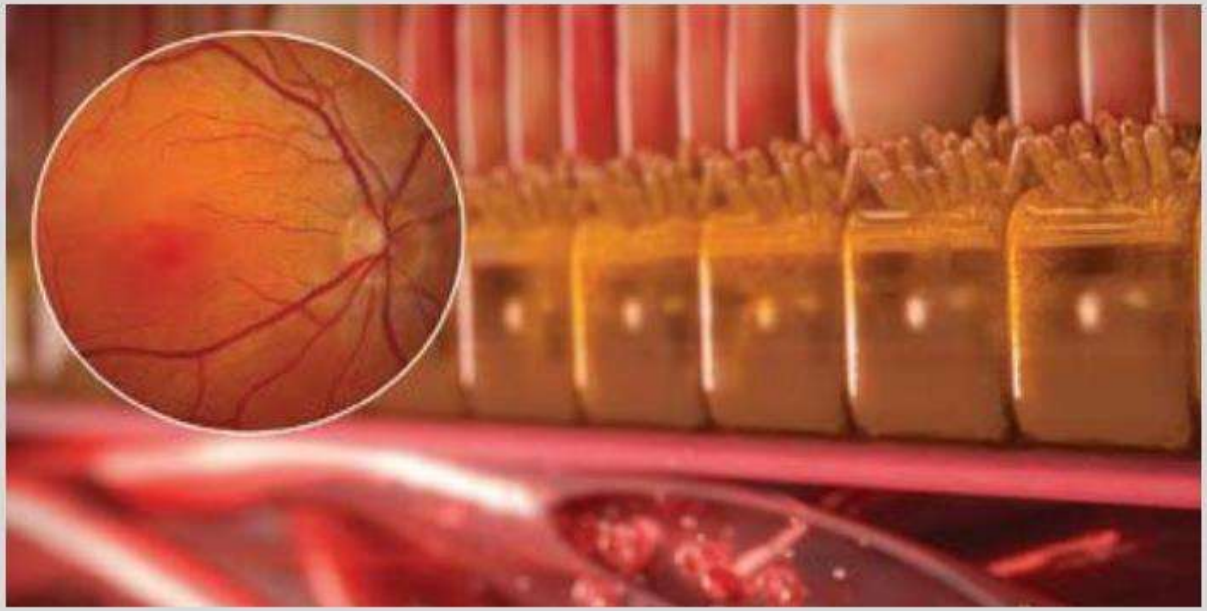
Advanced AMD





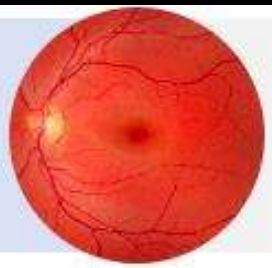
2 forms: Geographic Atrophy and Neovascular AMD

Geographic Atrophy Neovascular AMD



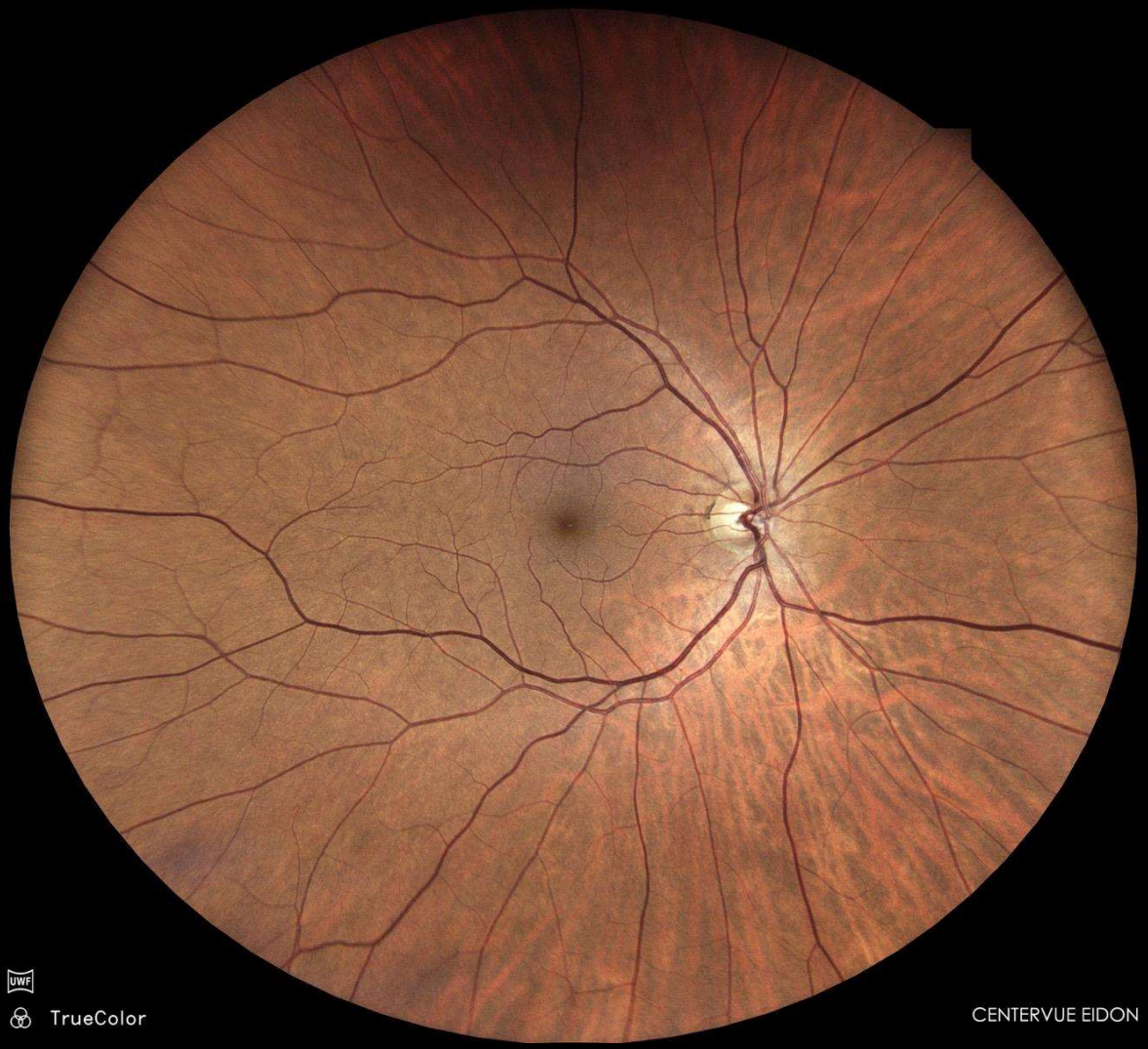
No AMD: Normal fundus appearance. Healthy choriocapillaris, Bruch's membrane, RPE, and photoreceptors.

No AMD



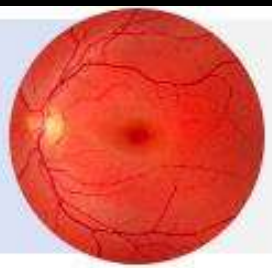
No drusen or small drusen ≤ 63 µm

No AMD pigmentary abnormalities



What might this look like clinically?

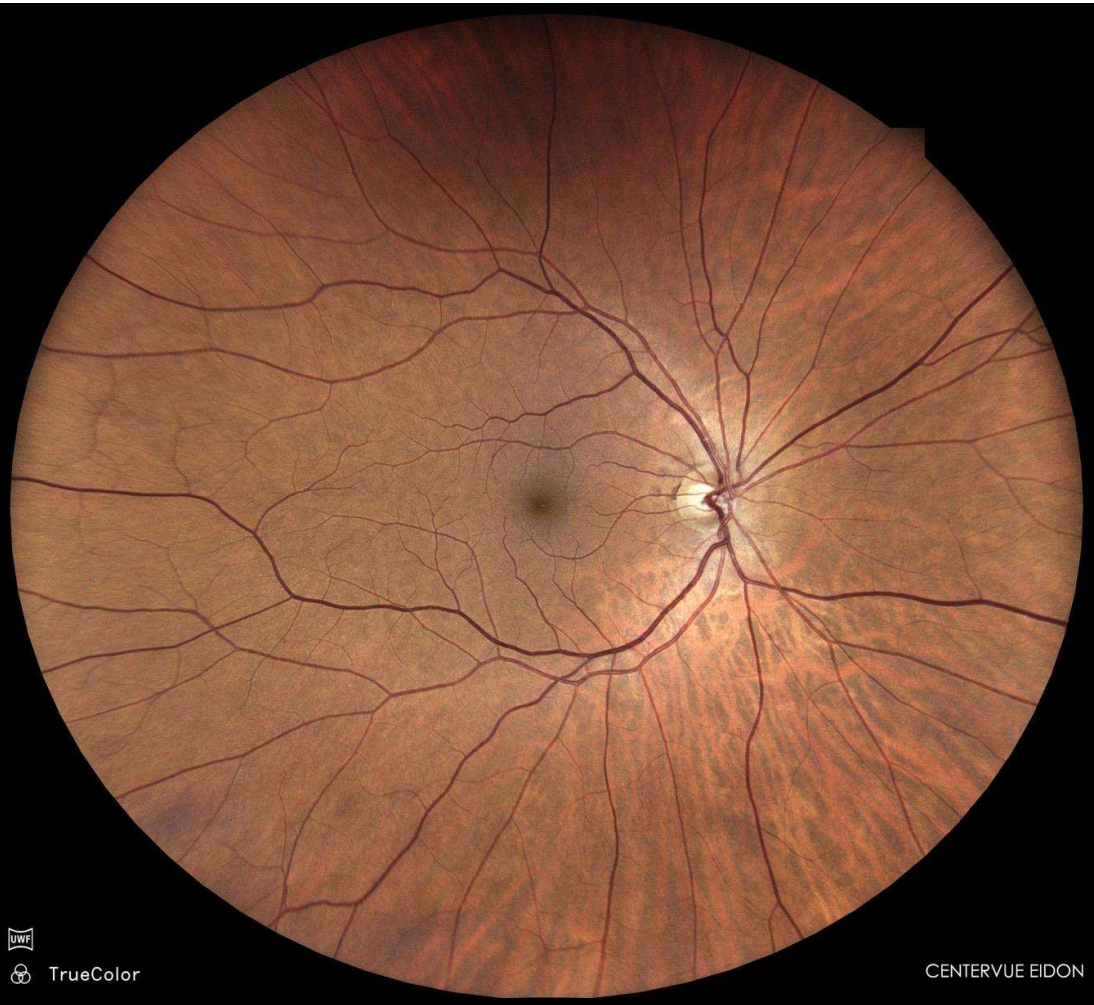
NORMAL fundus appearance



No AMD

No drusen or small drusen ≤ 63 µm

No AMD pigmentary abnormalities

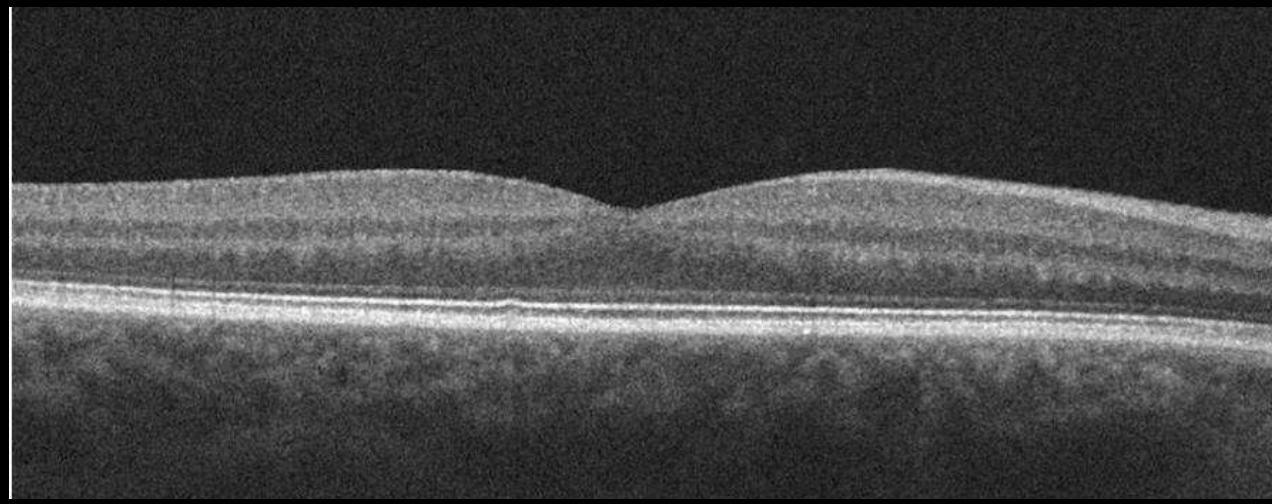


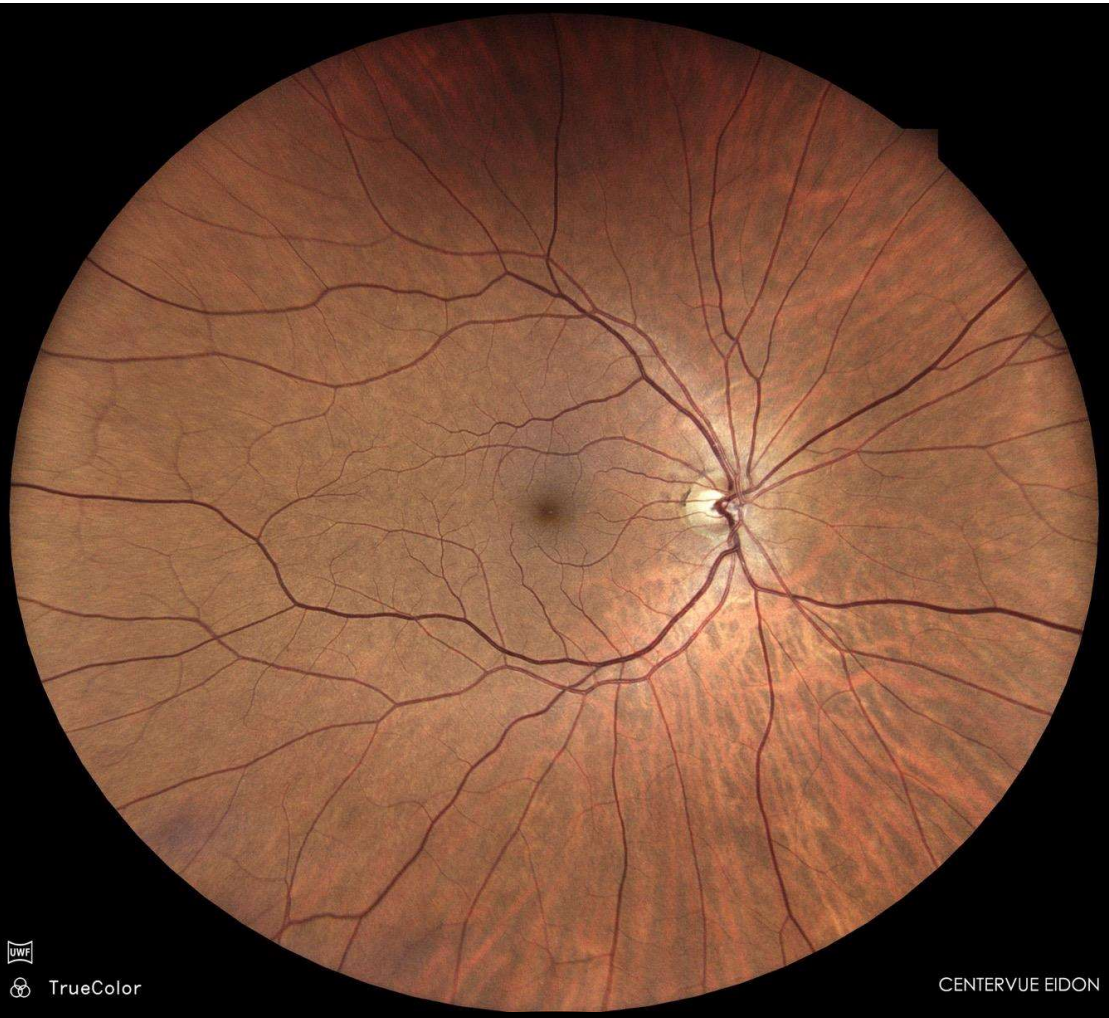
UWF

TrueColor

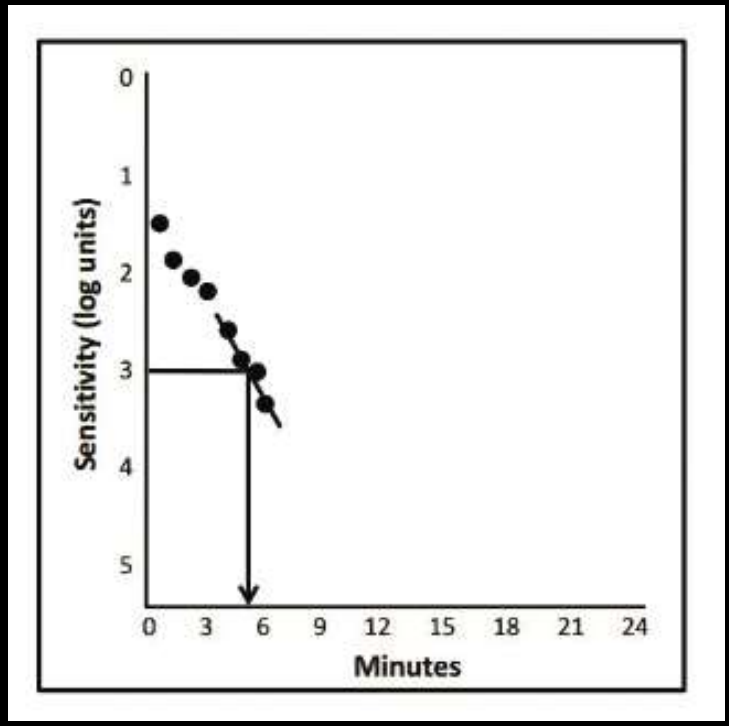
CENTERVUE EIDON

Image courtesy of iCare

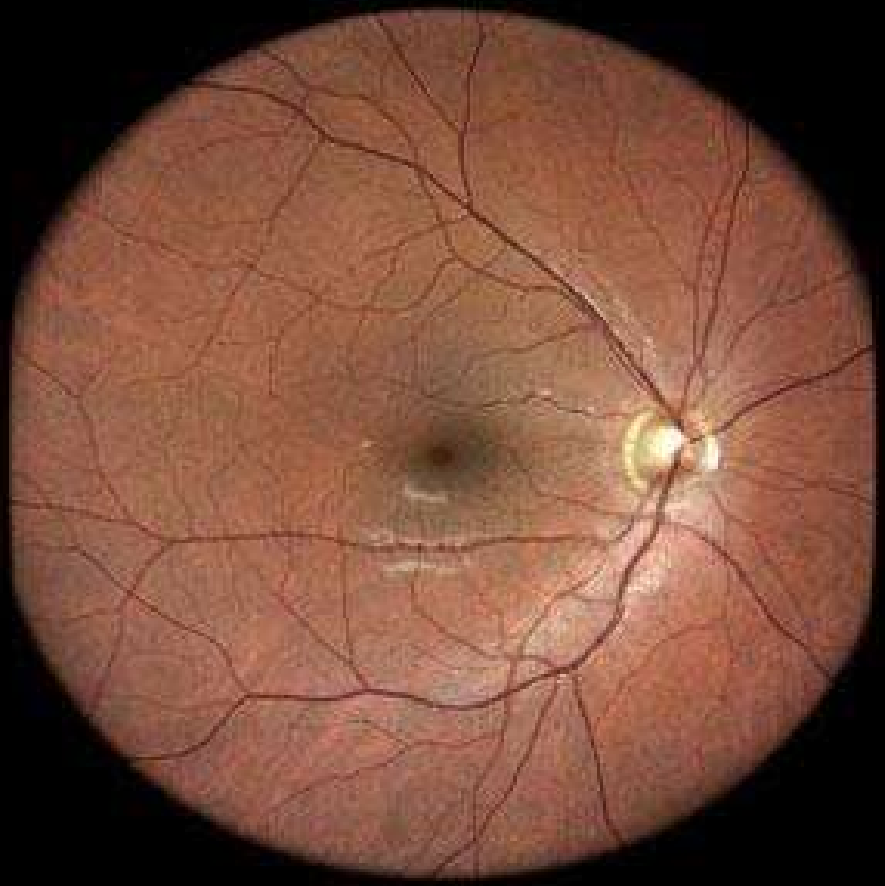




What about this patient's dark adaptation?



Normal!!

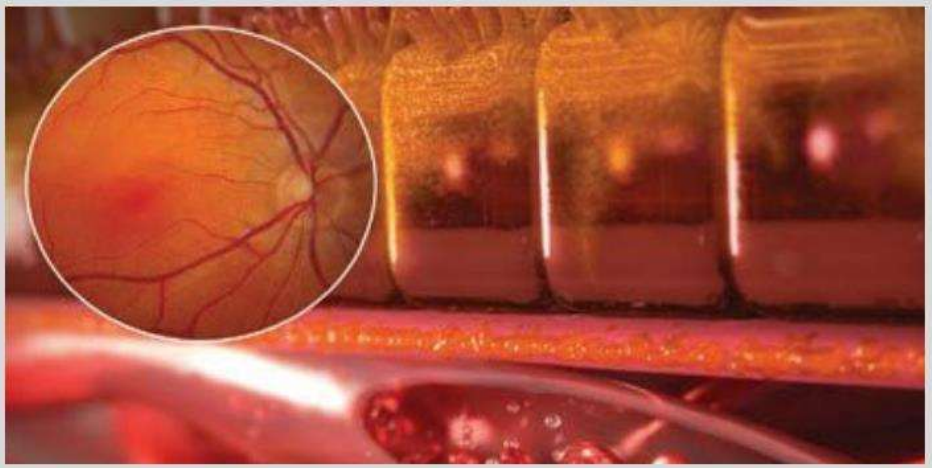


What about this one?

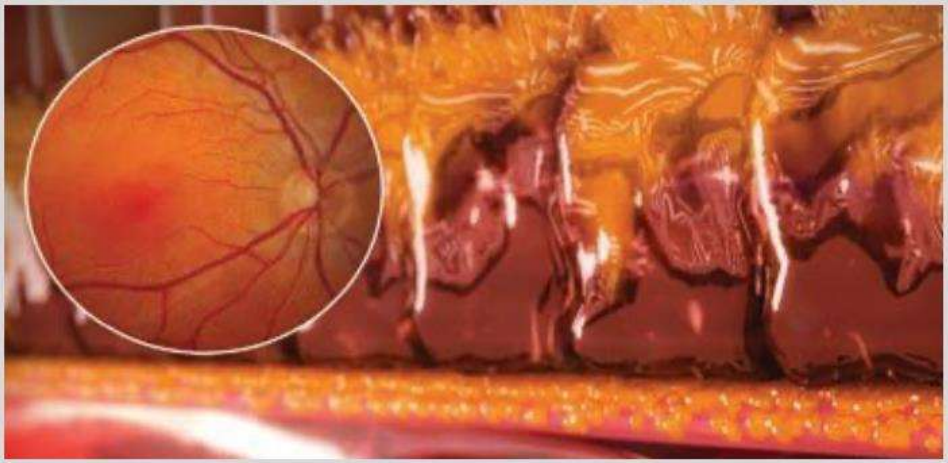
Normal

?

Subclinical AMD



Subclinical AMD: Normal fundus appearance. Invisible layers of cholesterol are forming along Bruch's membrane, blocking transport of vital nutrients and impairing dark adaptation function.



Subclinical AMD: Normal fundus appearance. Cholesterol continues to build, along with functional impairment.

Subclinical AMD **RI**

No drusen or small drusen ≤ 63 µm
No AMD pigmentary abnormalities
Impaired dark adaptation

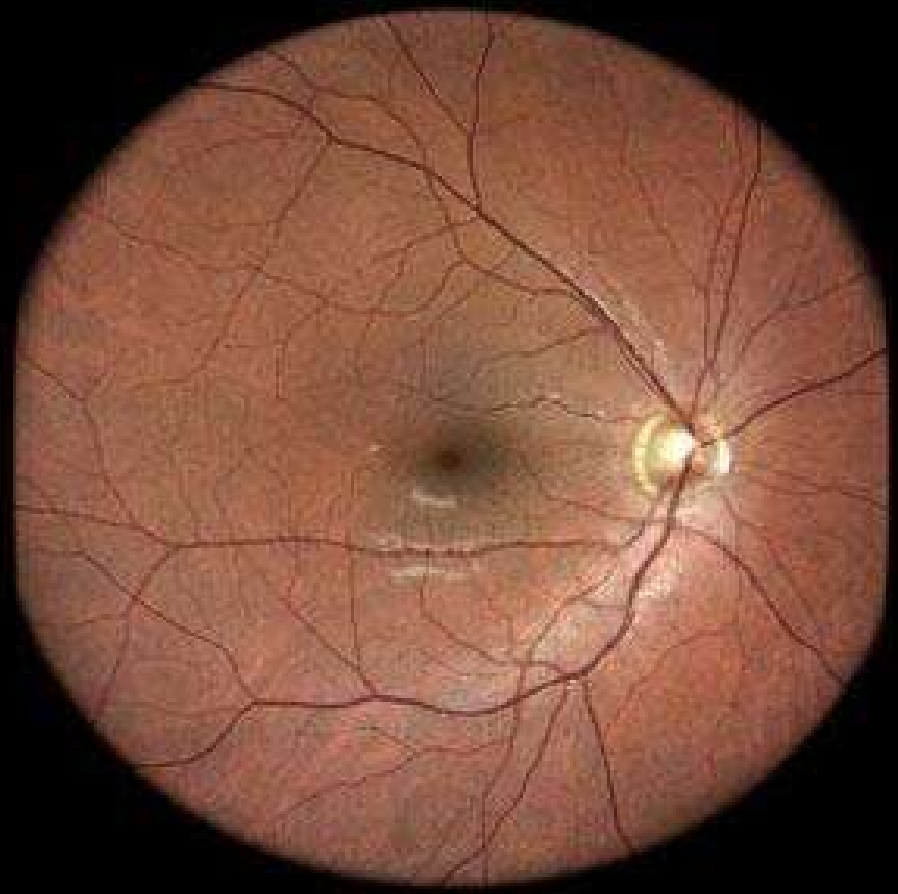
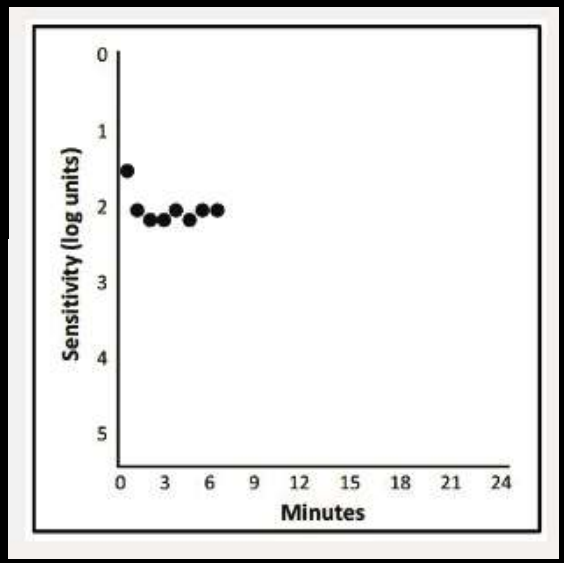


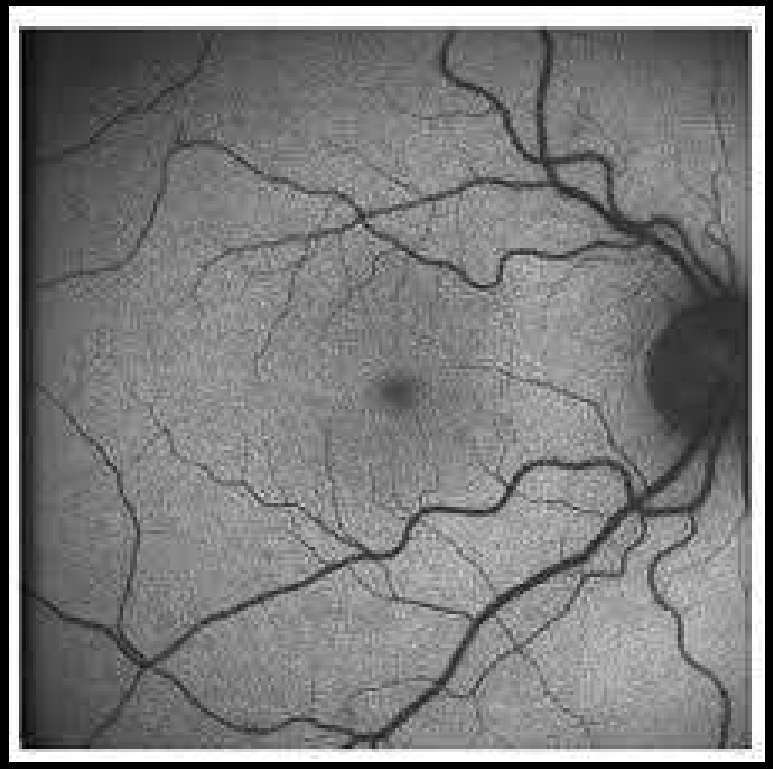
Image courtesy of iCare

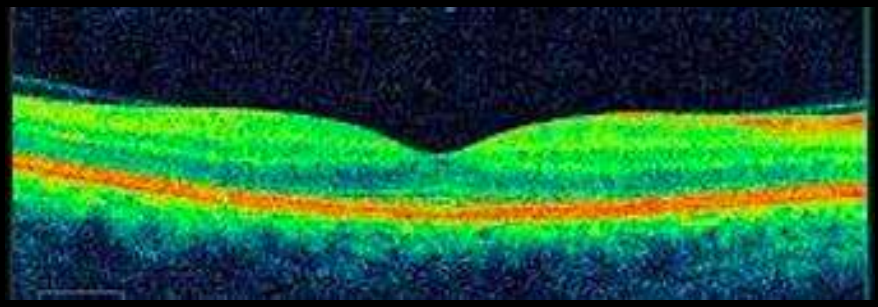
At the subclinical stage, patients demonstrate abnormal dark adaptation but still exhibit no evidence of drusen formation or retinal pigment epithelial defects

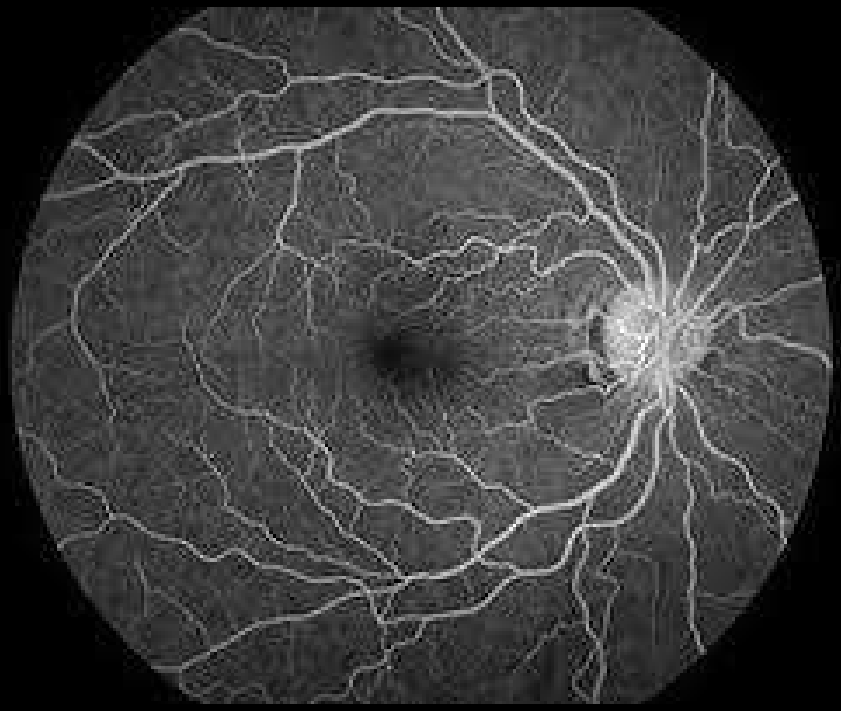


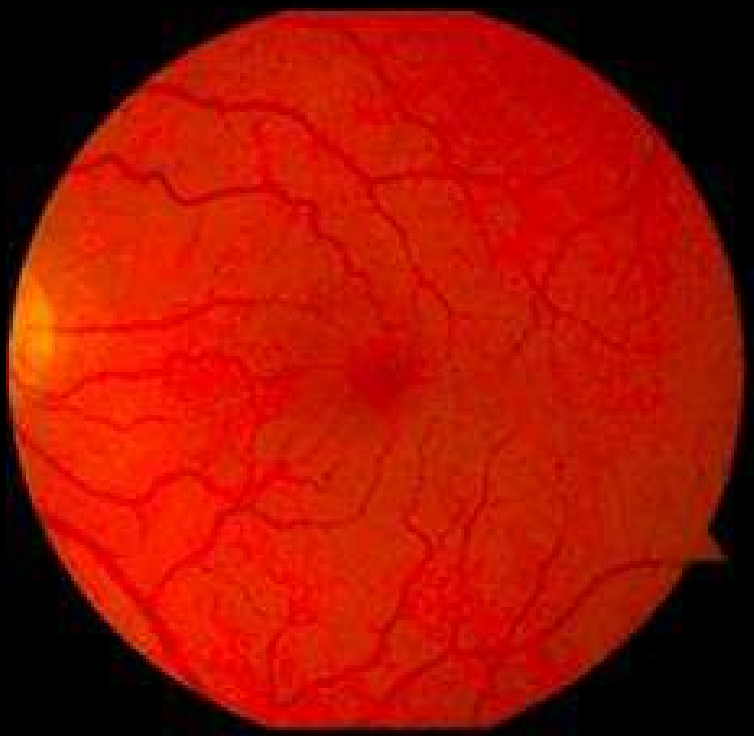
What about this one?

Yet....

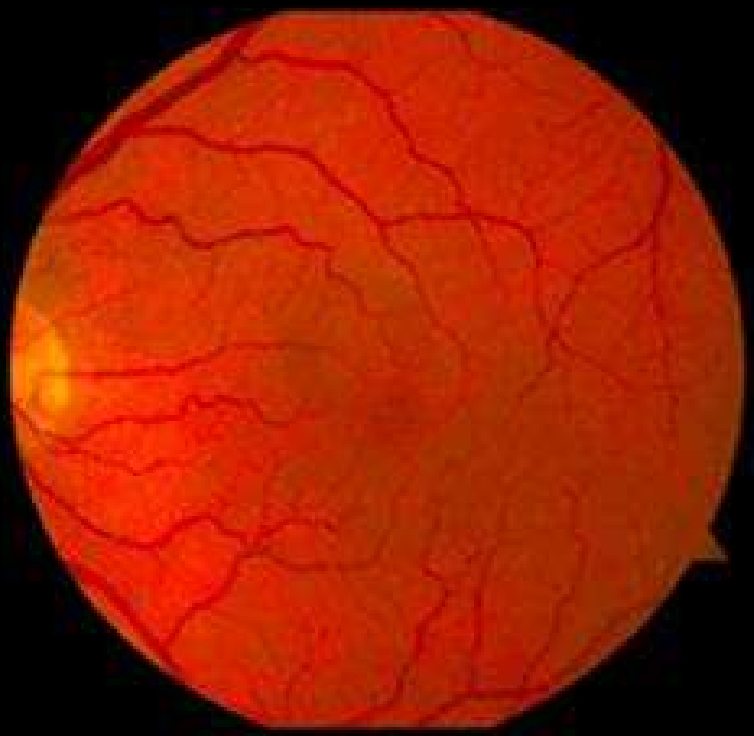




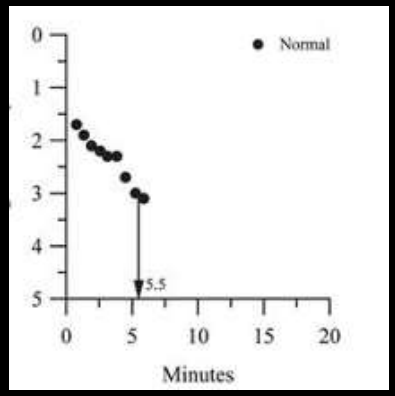




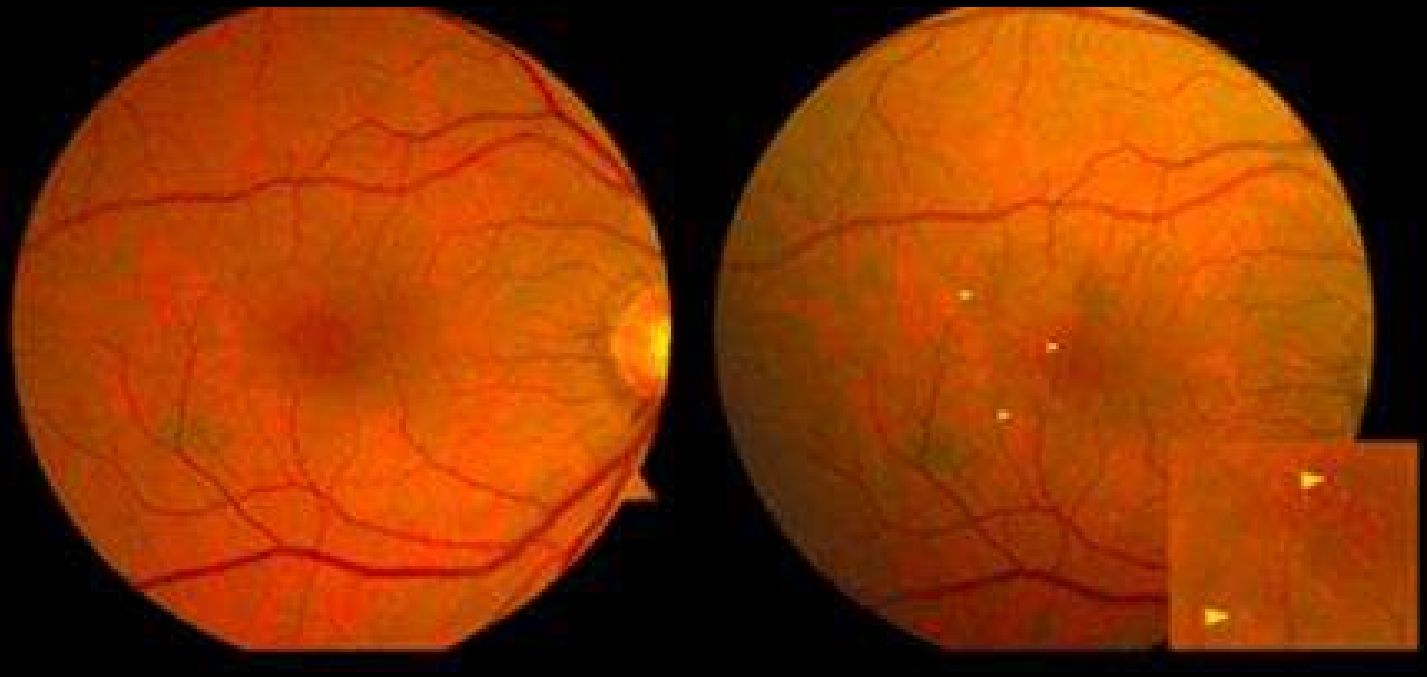
Baseline



Three years later

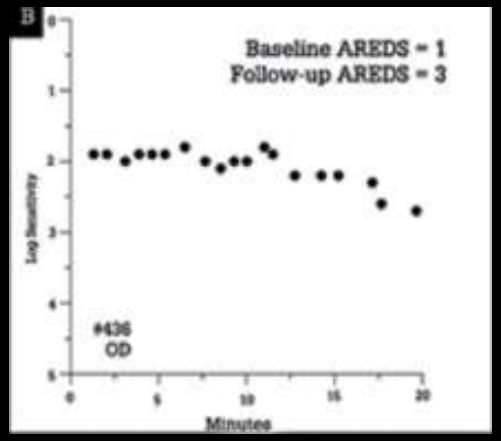


A patient with a normal fundus at baseline had normal dark adaptation and a normal fundus both at baseline and three years later



Baseline

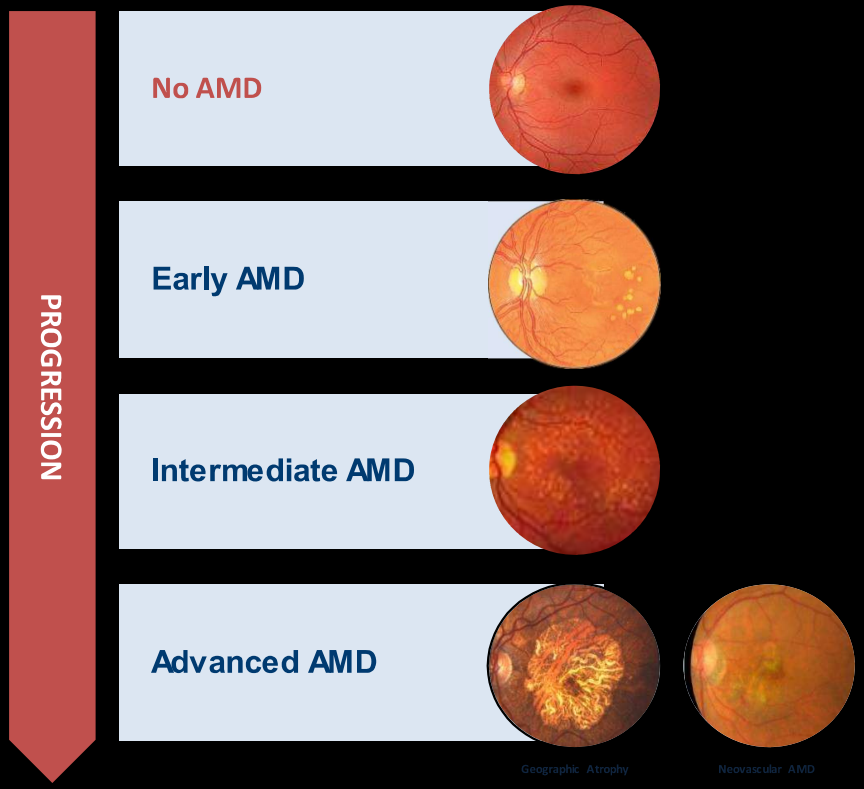
Three years later



Another patient had a normal fundus but poor dark adaptation at baseline. Three years later, this patient had dev eloped drusen characteristic of AMD.

The Beckman Classification

4 Stages of AMD



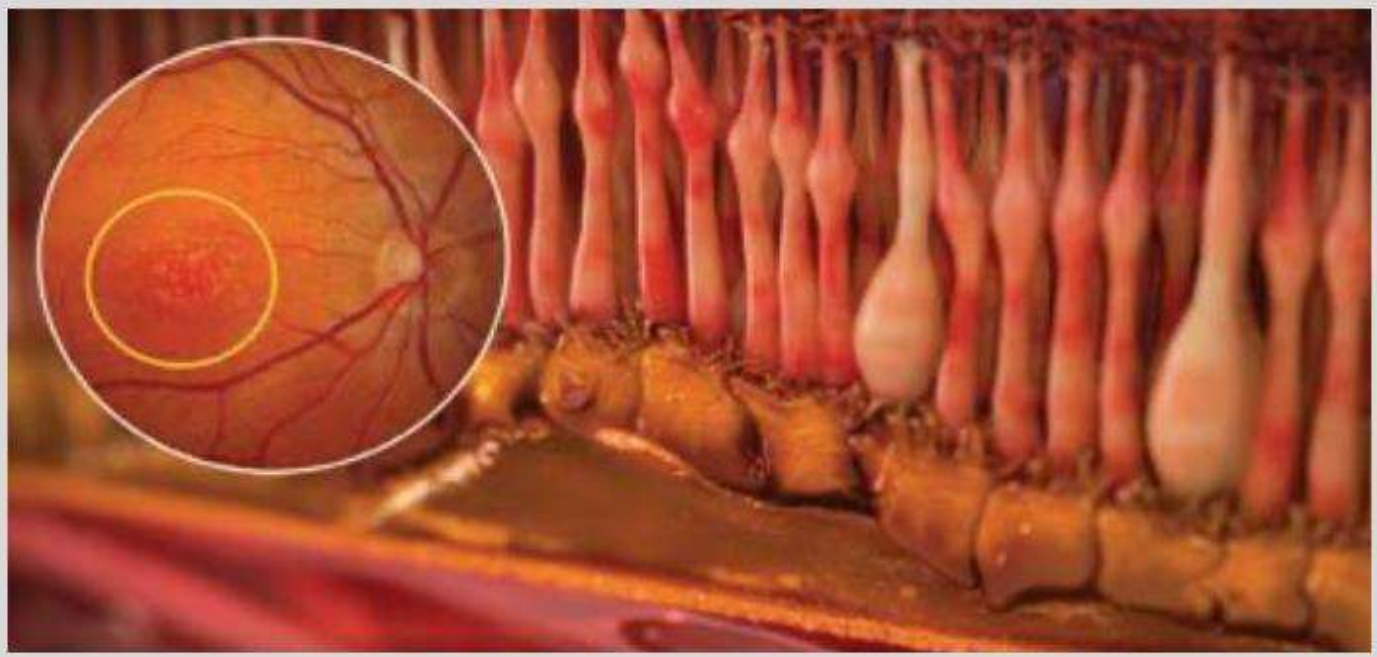
No drusen or small drusen ≤ 63 µm
No AMD pigmentary abnormalities

Medium drusen > 63 µm and ≤ 125 µm
No AMD pigmentary abnormalities

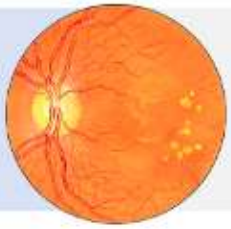
1 large druse > 125 µm and/or
Any AMD pigmentary abnormalities

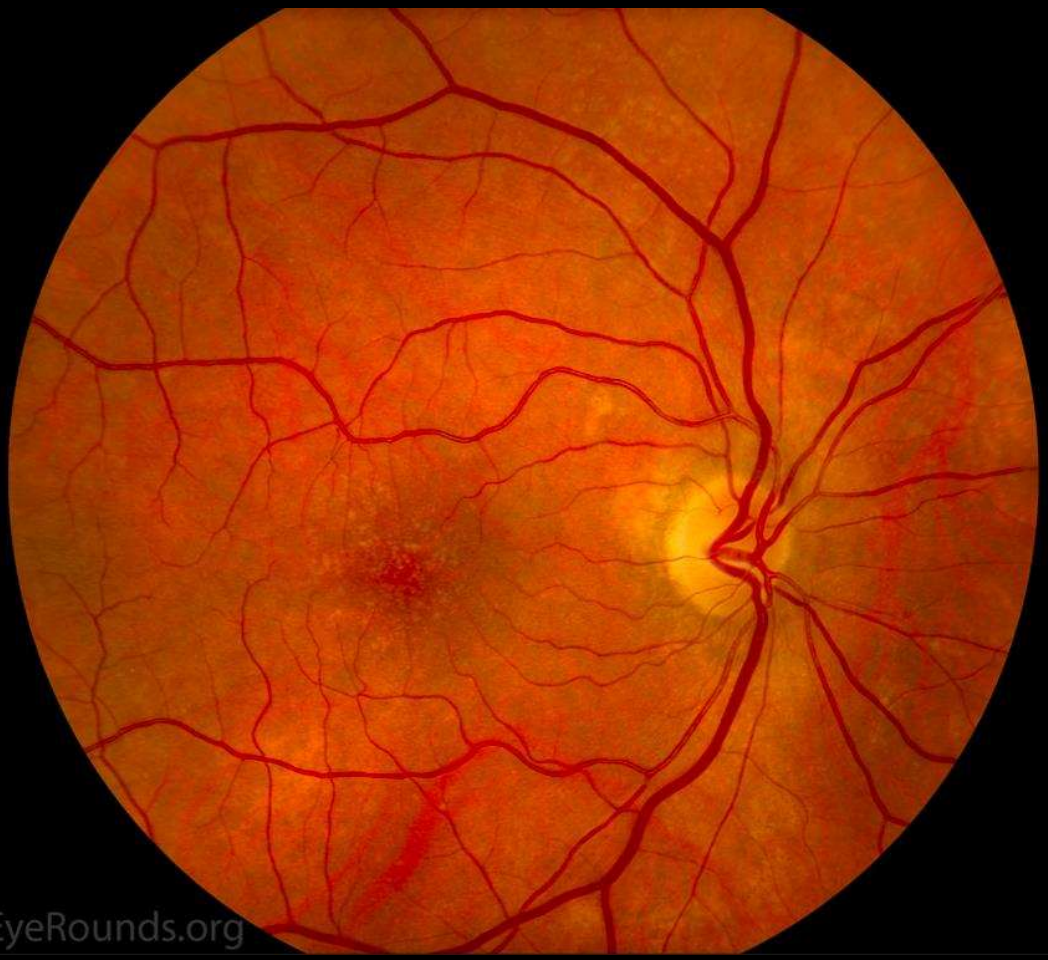
2 forms: Geographic Atrophy and Neovascular AMD

- sources: AMD, age-related macular degeneration. Ferris FL, et al. Ophthalmology. 2013;120(4):844-851.



Early AMD: Visibly evident drusen on fundus evaluation. Functional impairment continues to worsen.

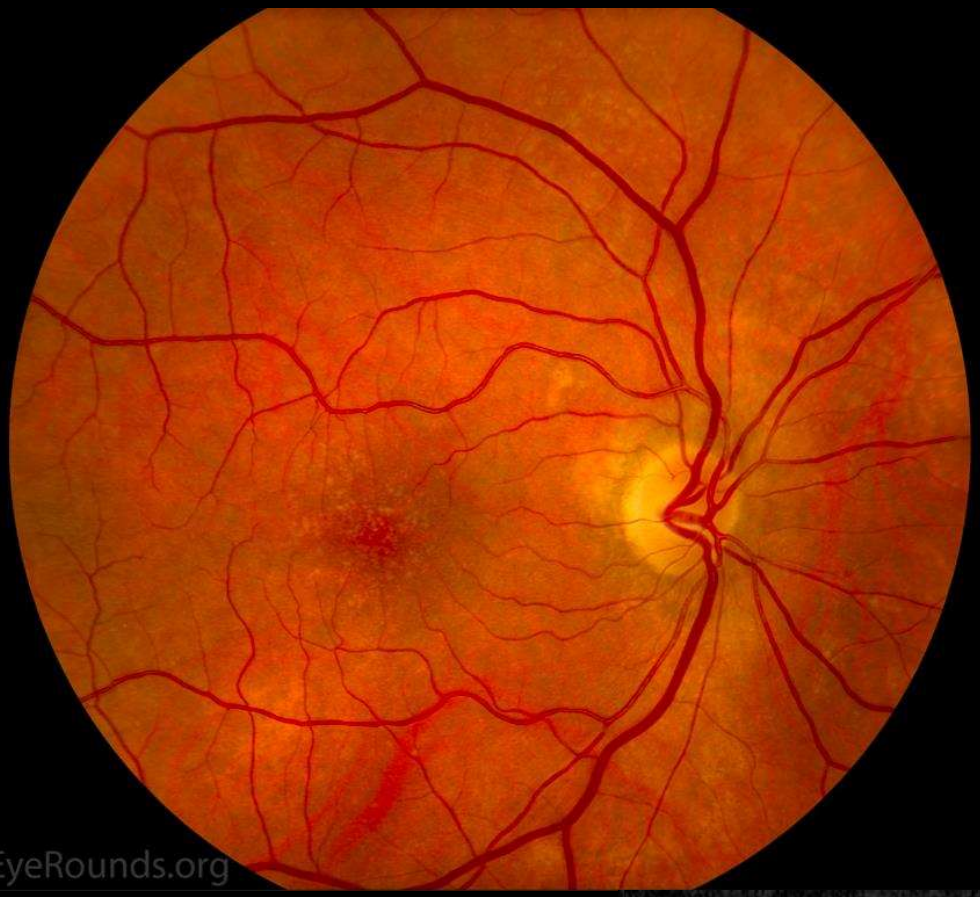
Early AMD		Medium drusen > 63 µm and ≤ 125 µm No AMD pigmentary abnormalities

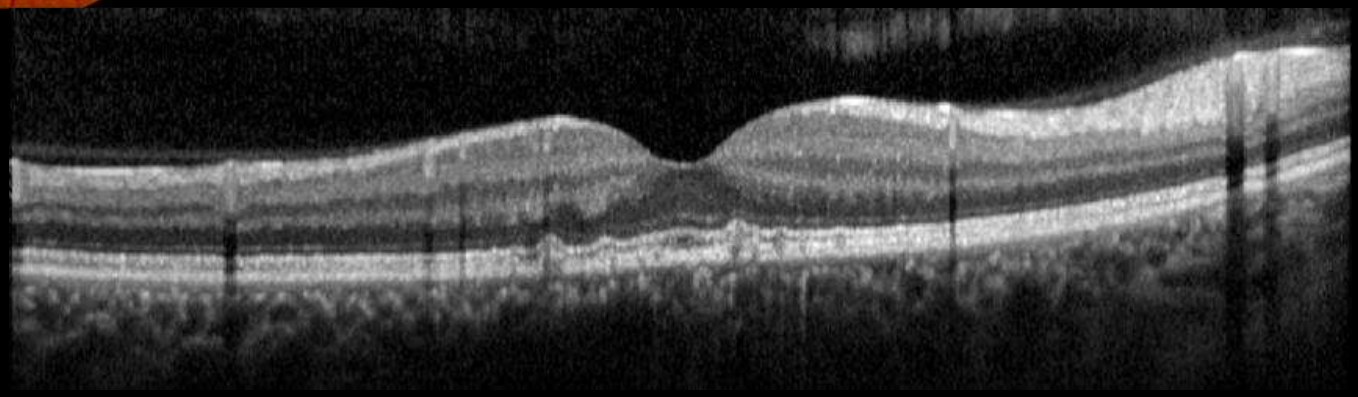


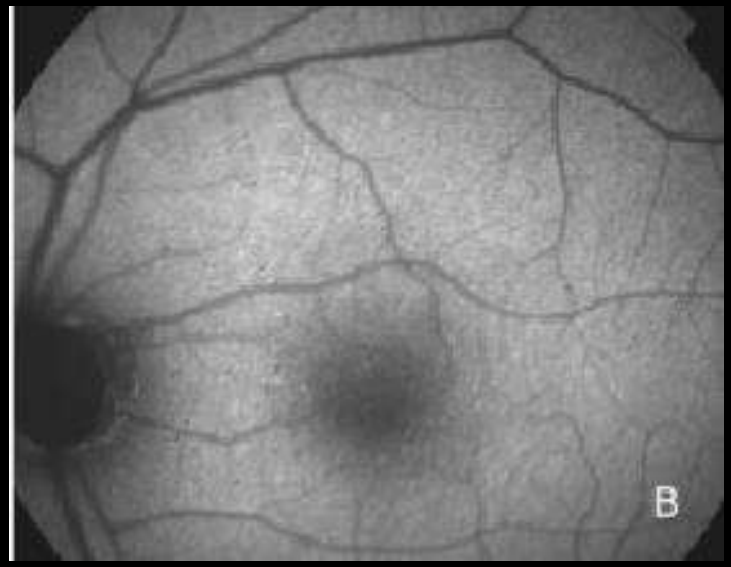
78 y/o WF
HTN
Former smoker
BCVA 20/20

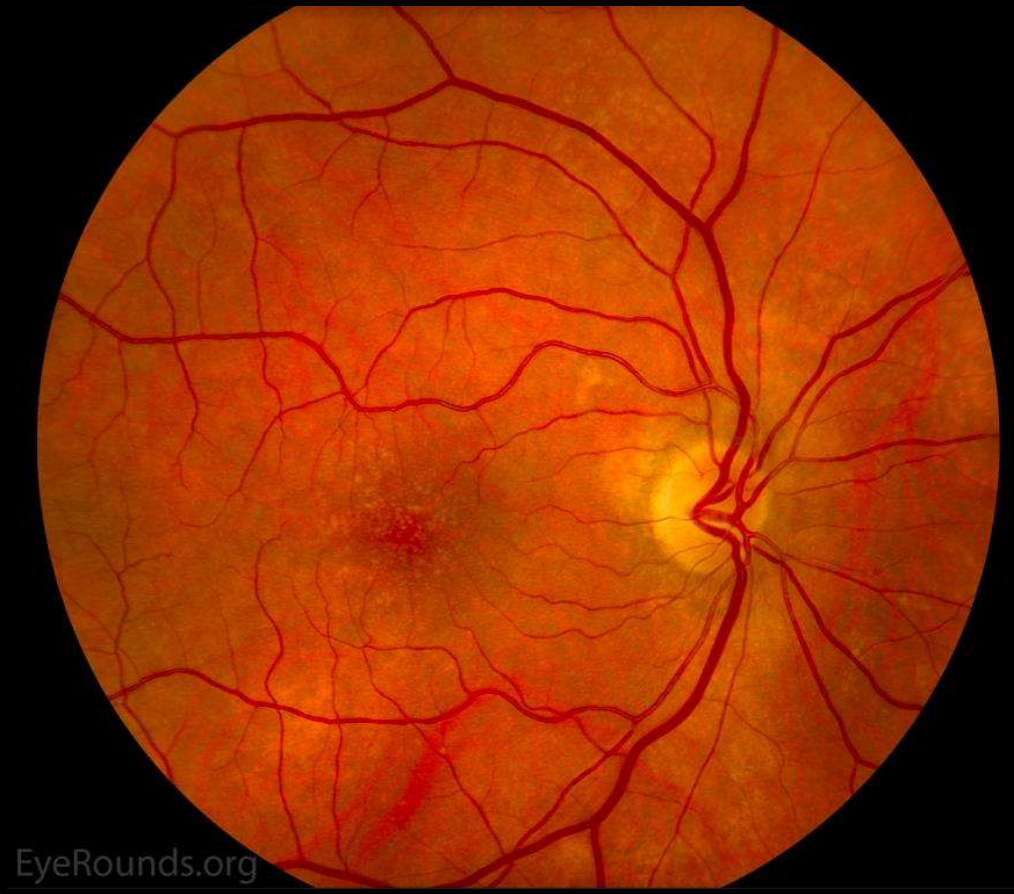
Early AMD

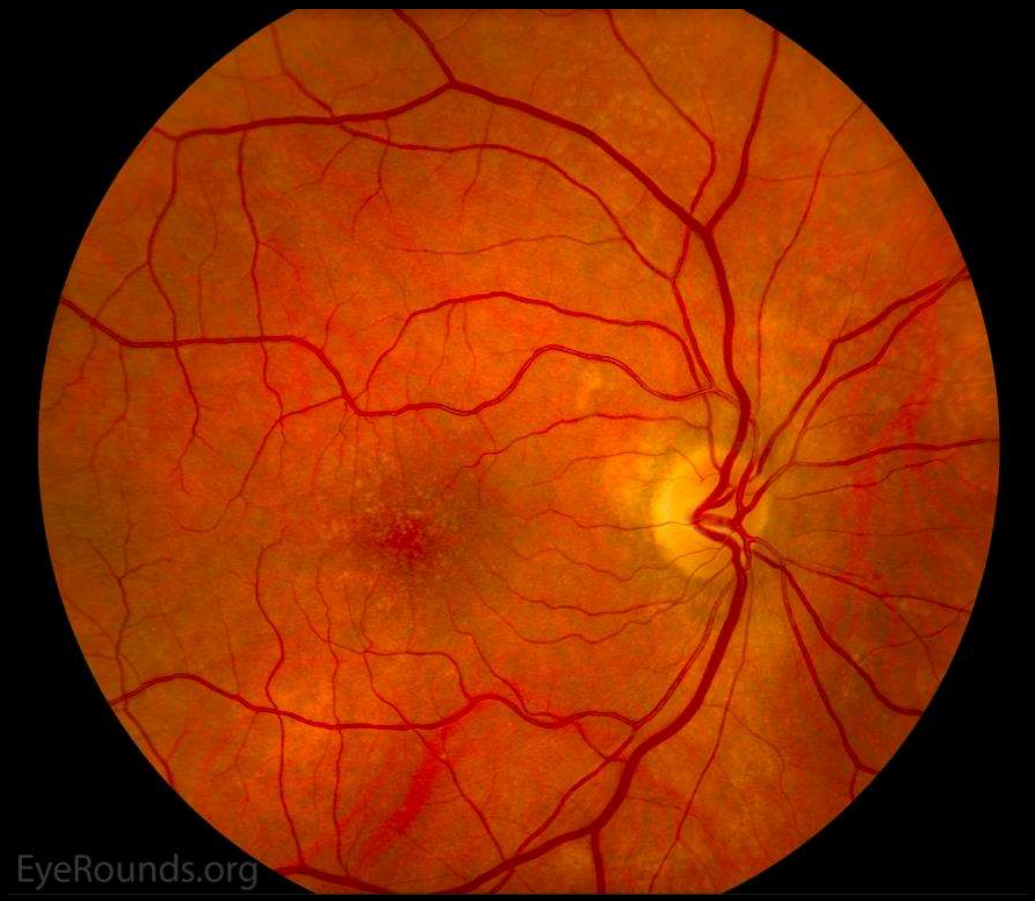
Medium drusen > 63 µm and ≤ 125 µm
No AMD pigmentary abnormalities


EyeRounds.org



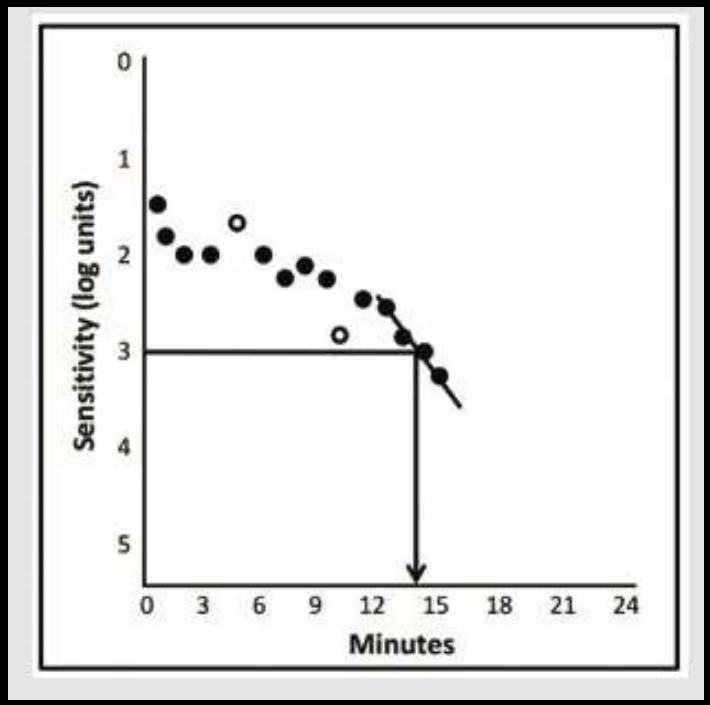

B


EyeRounds.org



Abnormal!!

What about this patient's dark adaptation?

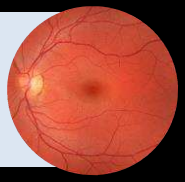


The Beckman Classification

4 Stages of AMD

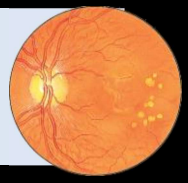
PROGRESSION

No AMD



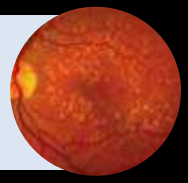
No drusen or small drusen ≤ 63 µm
No AMD pigmentary abnormalities

Early AMD



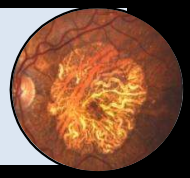
Medium drusen > 63 µm and ≤ 125 µm
No AMD pigmentary abnormalities

Intermediate AMD

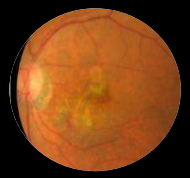


1 large druse > 125 µm and/or
Any AMD pigmentary abnormalities

Advanced AMD



Geographic Atrophy



Neovascular AMD

2 forms: Geographic Atrophy and Neovascular AMD

- sources: AMD, age-related macular degeneration. Ferris FL, et al. Ophthalmology. 2013;120(4):844-851.

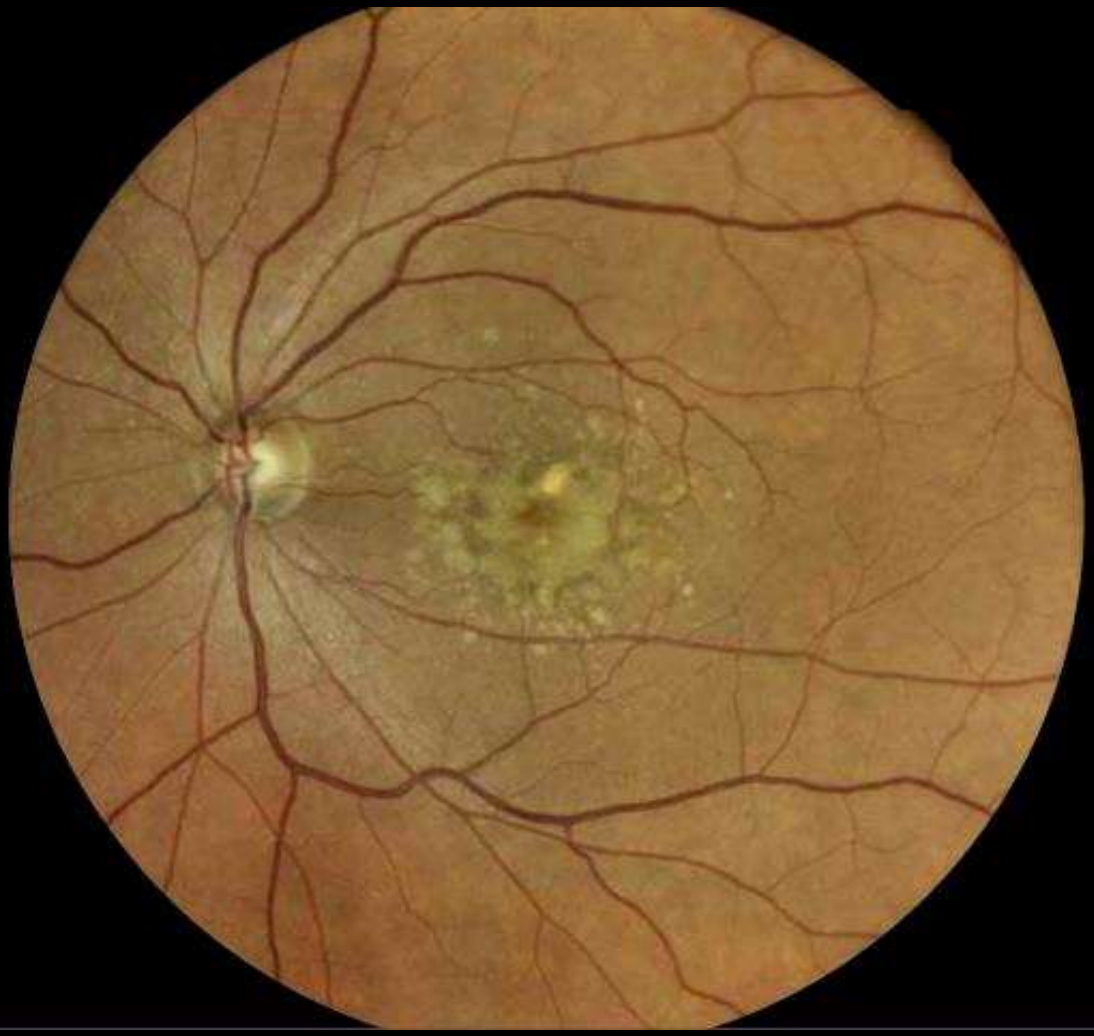
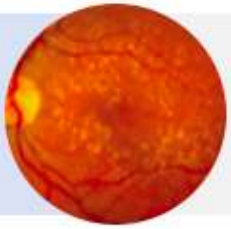


Image courtesy of ICare

What might this look like clinically?

Intermediate AMD



1 large druse > 125 µm and/or
Any AMD pigmentary abnormalities

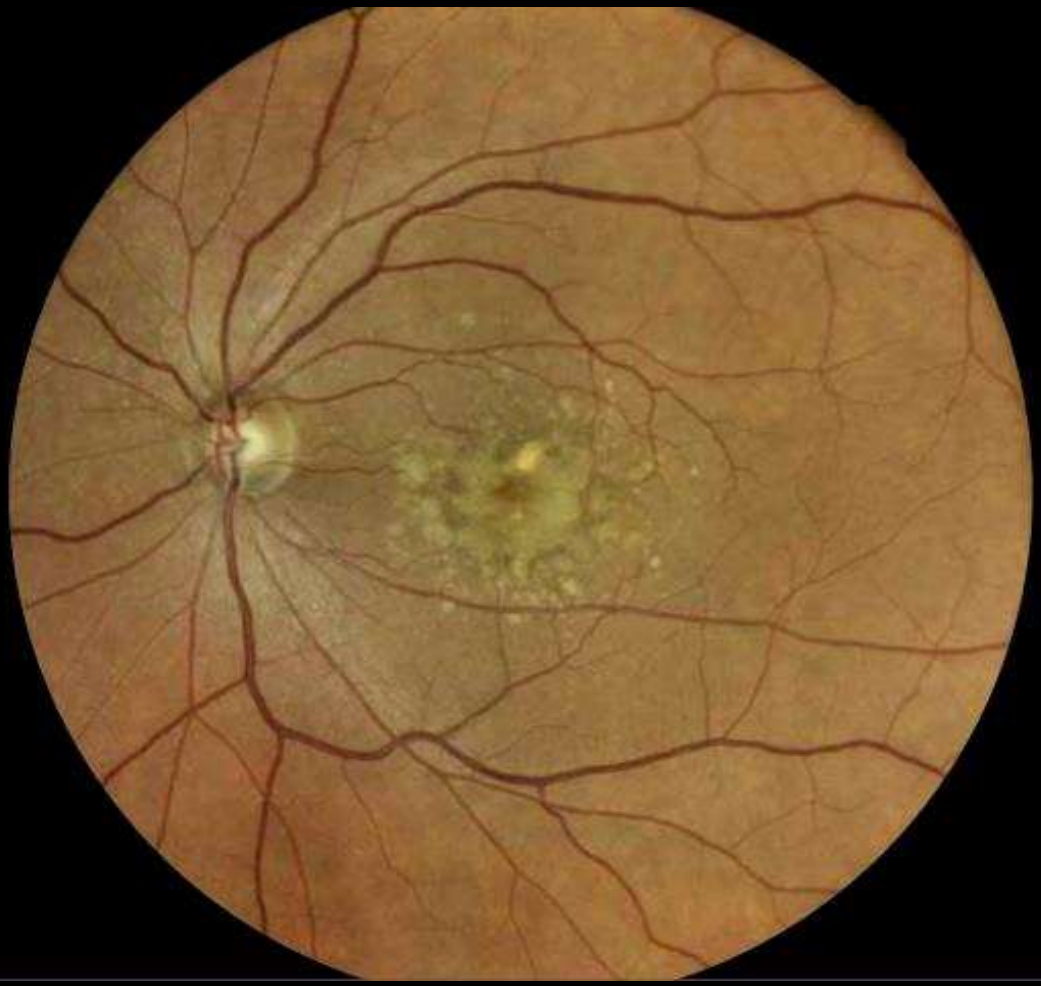
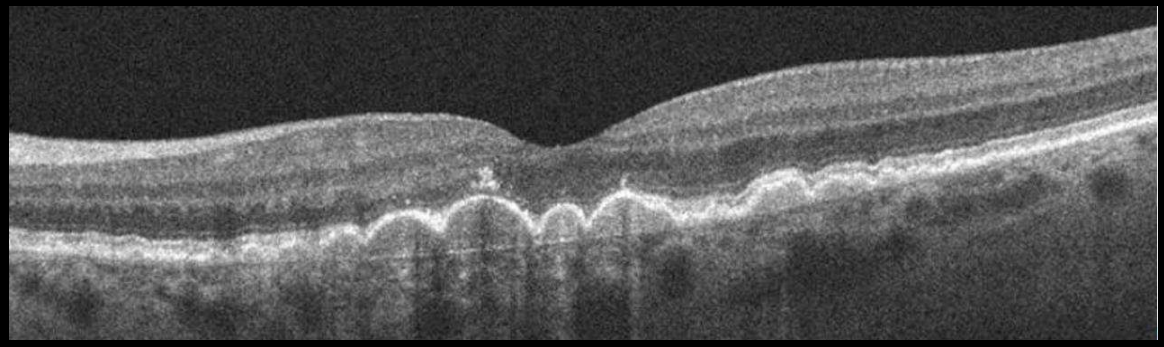
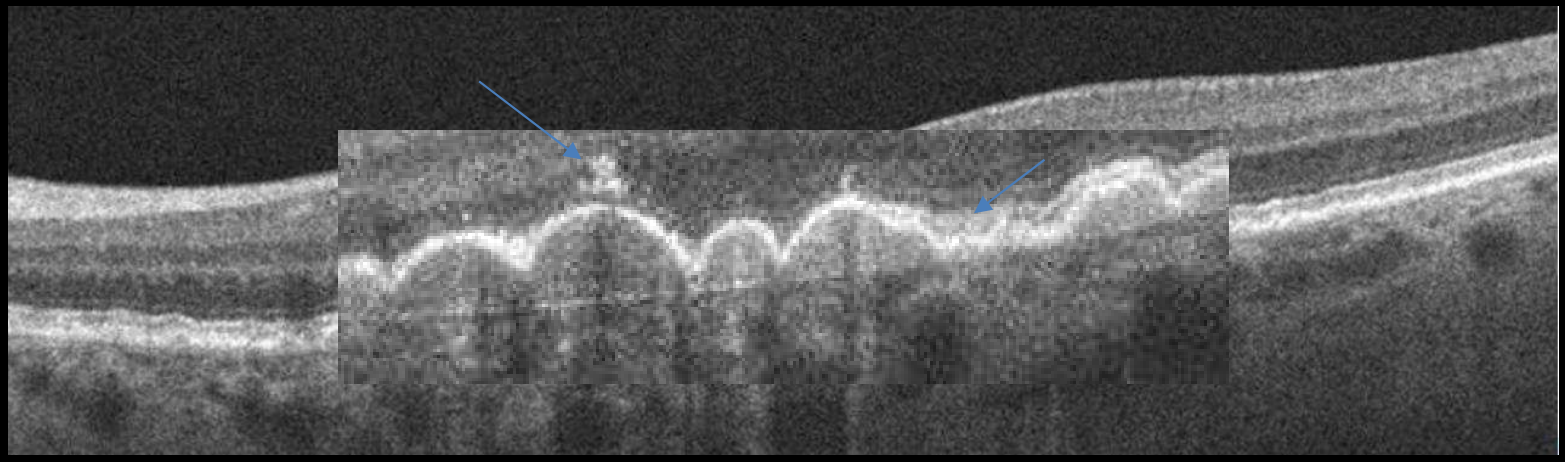
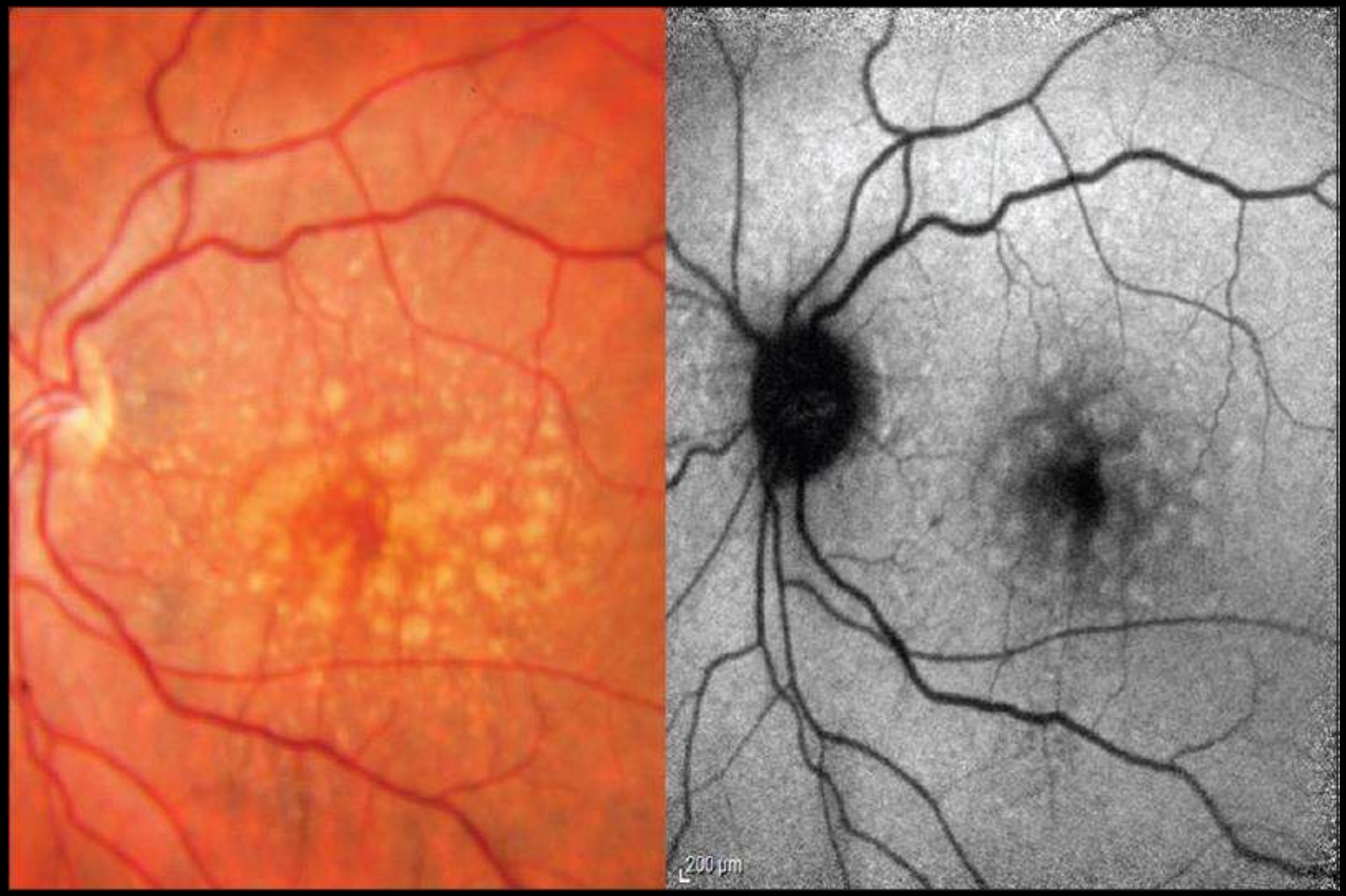


Image courtesy of iCare





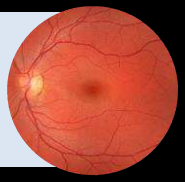

200 µm

The Beckman Classification

4 Stages of AMD

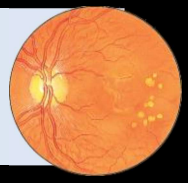
PROGRESSION

No AMD



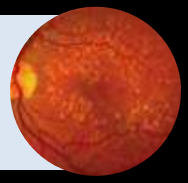
No drusen or small drusen ≤ 63 µm
No AMD pigmentary abnormalities

Early AMD



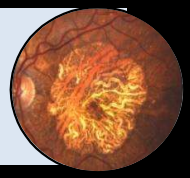
Medium drusen > 63 µm and ≤ 125 µm
No AMD pigmentary abnormalities

Intermediate AMD

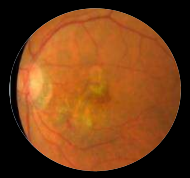


1 large druse > 125 µm and/or
Any AMD pigmentary abnormalities

Advanced AMD



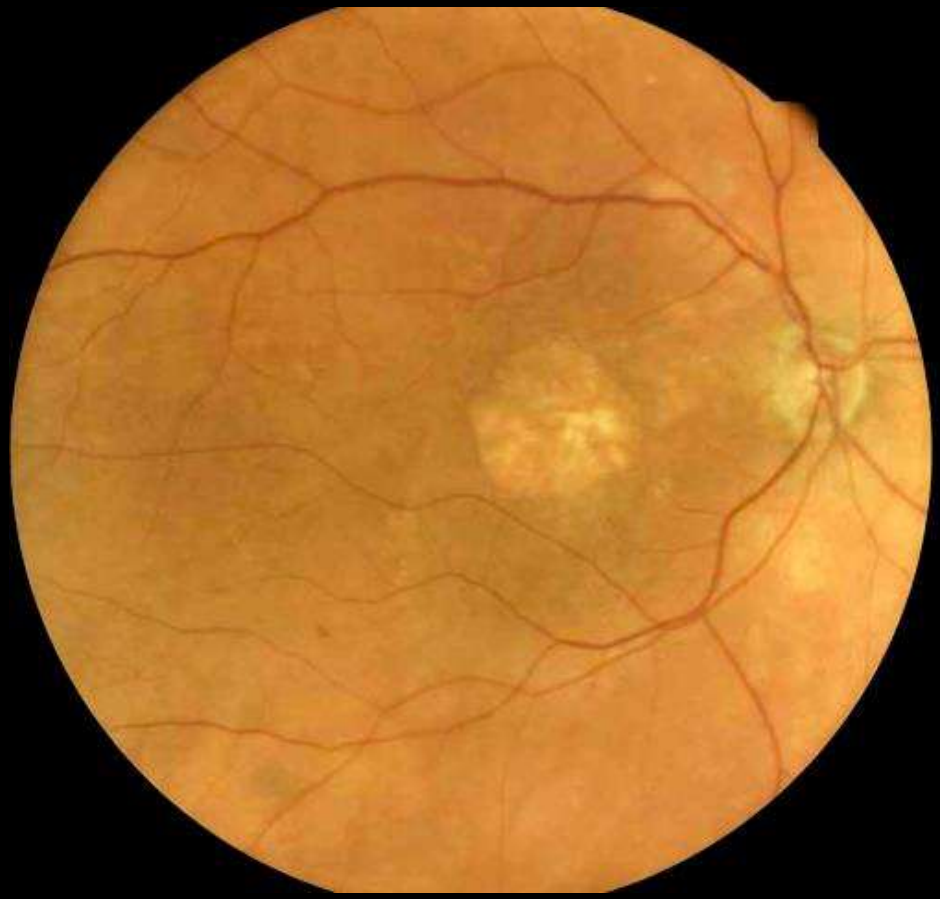
Geographic Atrophy

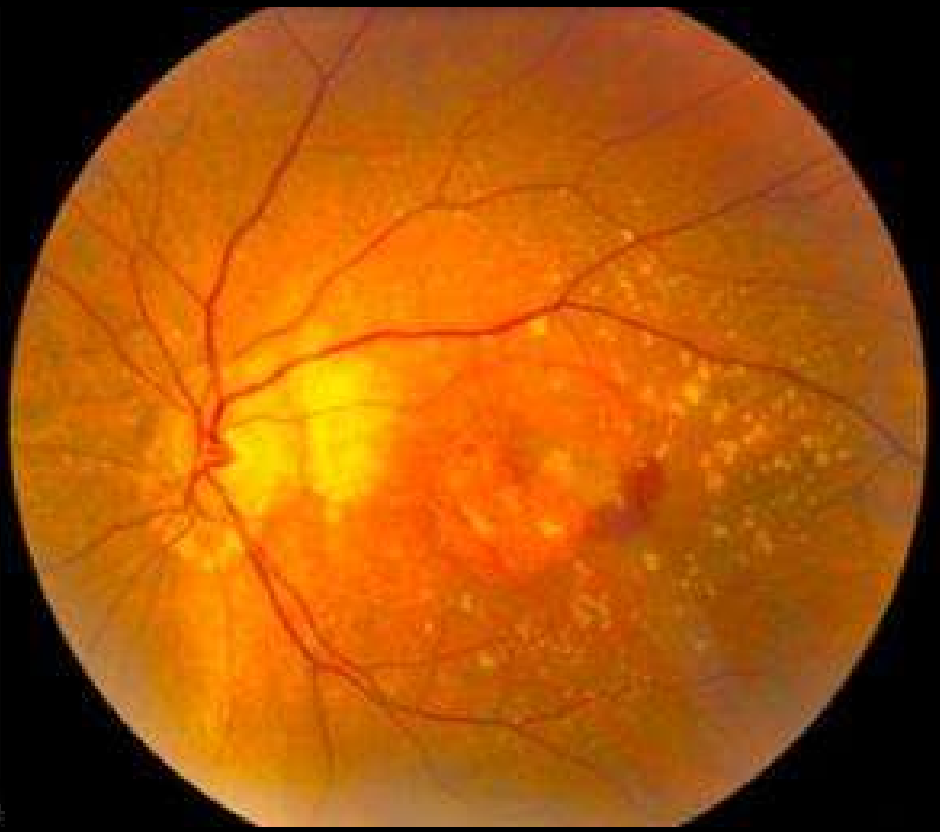


Neovascular AMD

2 forms: Geographic Atrophy and Neovascular AMD

- sources: AMD, age-related macular degeneration. Ferris FL, et al. Ophthalmology. 2013;120(4):844-851.



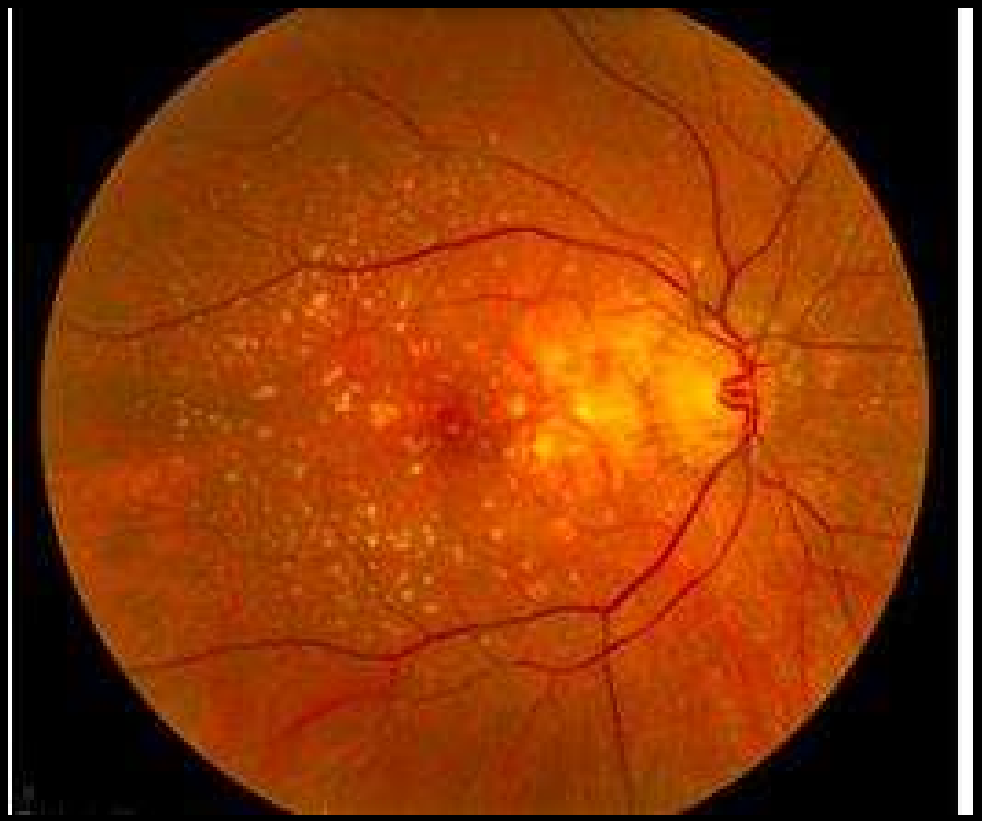


Advanced AMD

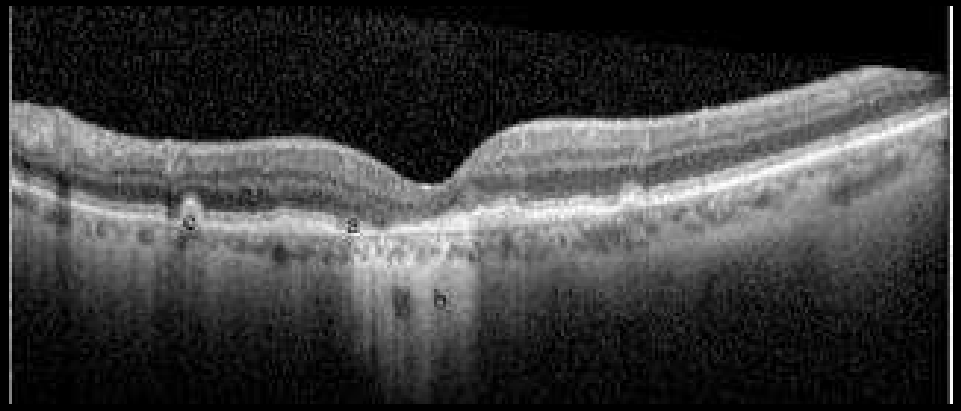
Geographic Atrophy

Neovascular AMD

2 forms: Geographic Atrophy and Neovascular AMD

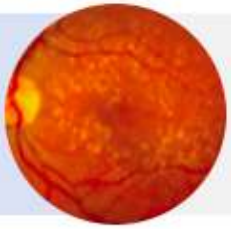


Geographic Atrophy outside of fovea



https://webeye.ophth.uiowa.edu/eyeforum/tutorials/AMD-medical-student/

Intermediate AMD



1 large druse > 125 µm and/or
Any AMD pigmentary abnormalities

Advanced AMD

Geographic Atrophy

Neovascular AMD

2 forms: Geographic Atrophy and Neovascular AMD

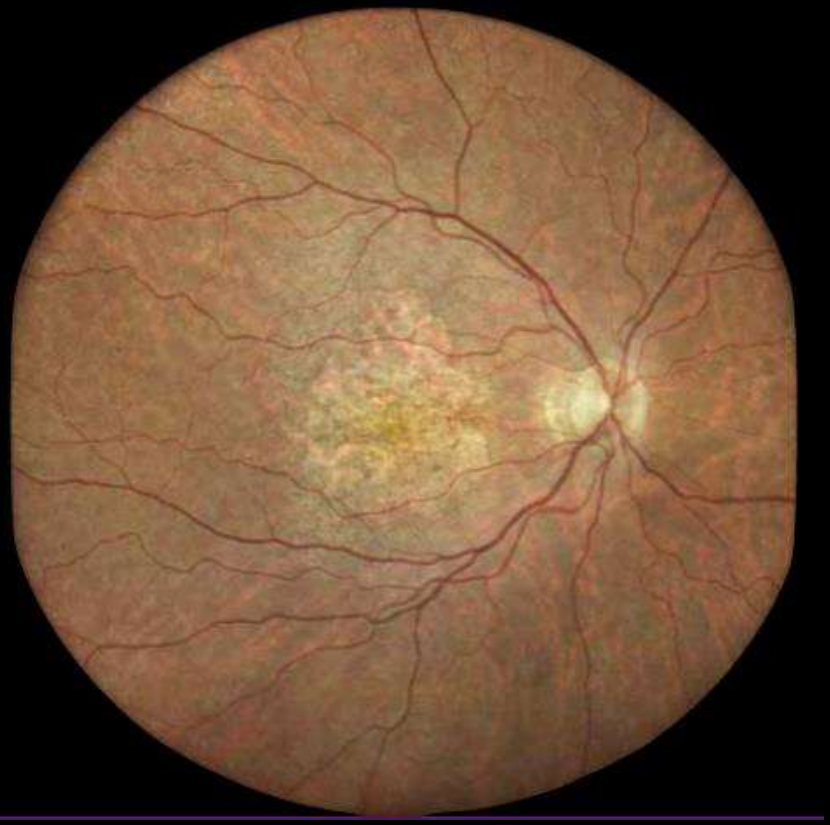
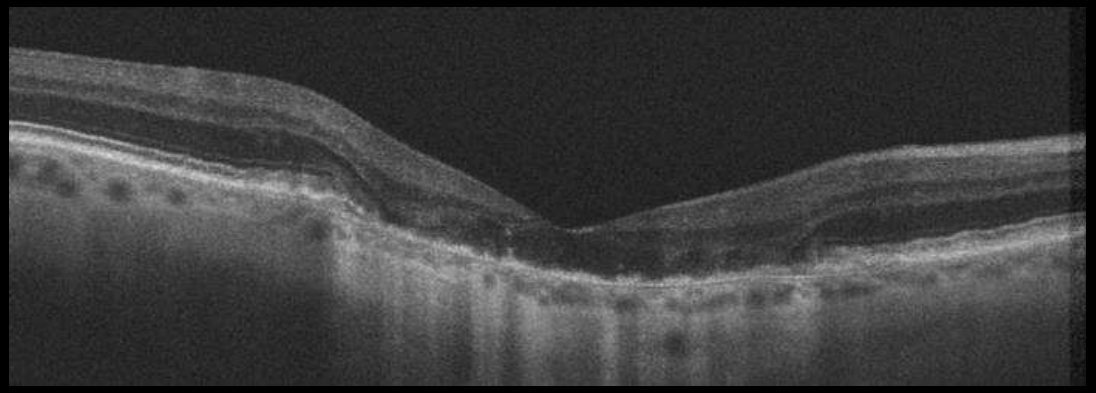


Image courtesy of iCare

Geographic Atrophy involving fovea



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwebeye.ophth.uiowa.edu%2Feyeforum%2Fatlas%2Fpages%2FAMD.htm&psig=AOvVaw2p6Lr2yq KKzXVXPLpQ&ust=1616799501966000&source=images&cd=vfe&ved=2ahUKEwid7fW Px8zvAhXNMFMKHYAHA8IQr4kDegUIAR DSAQ

Advanced AMD

Geographic Atrophy

Neovascular AMD

2 forms: Geographic Atrophy and Neovascular AMD

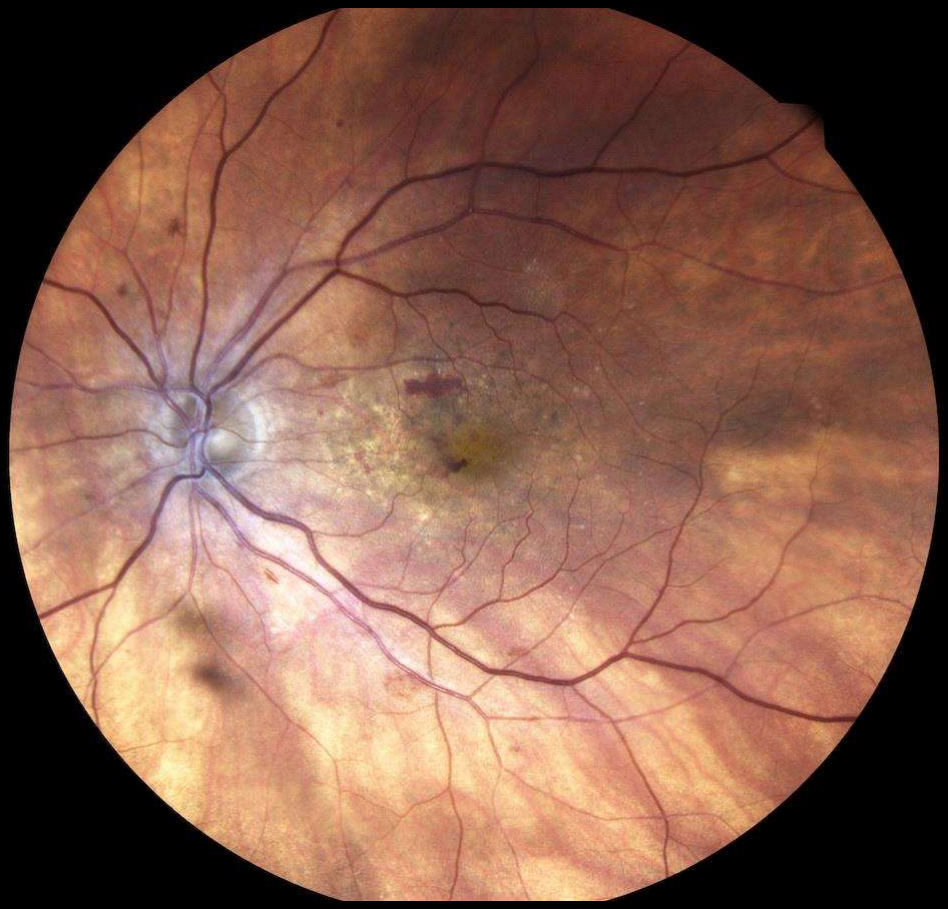
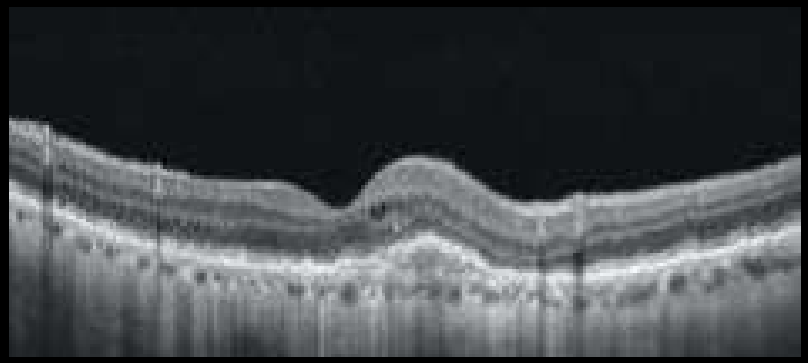


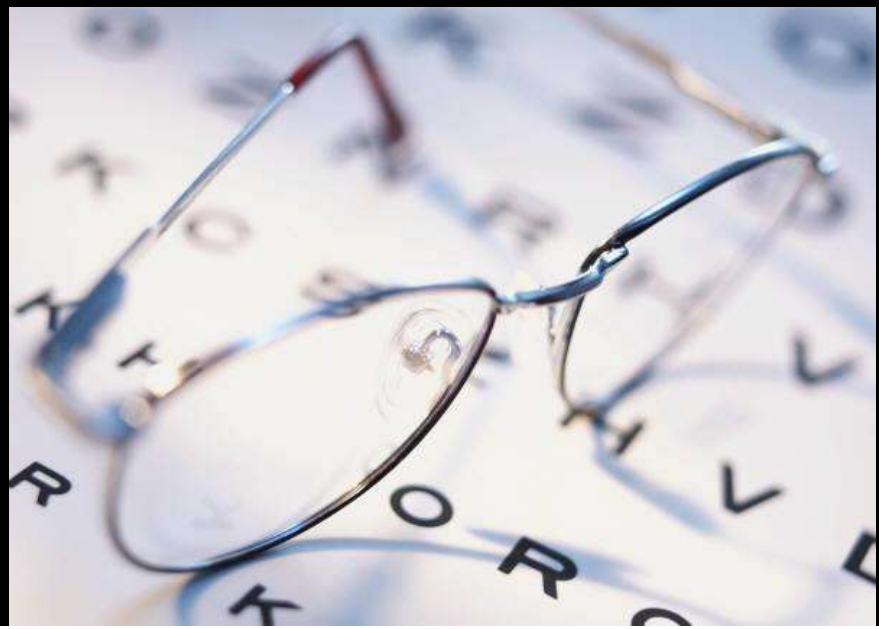
Image courtesy of iCare

Neovascular AMD



Is 20/20 good enough?

- No…that is quantity not quality
- Adequate MPOD can improve
  - contrast sensitivity: especially in dark conditions
  - light sensitivity
  - visual acuity
  - shape discrimination



Survey of this audience

- Who recommends:
  - Lutein
  - Zeaxanthin
  - MesoZ
  - Fish oil
- Who dispenses from their office any of above?

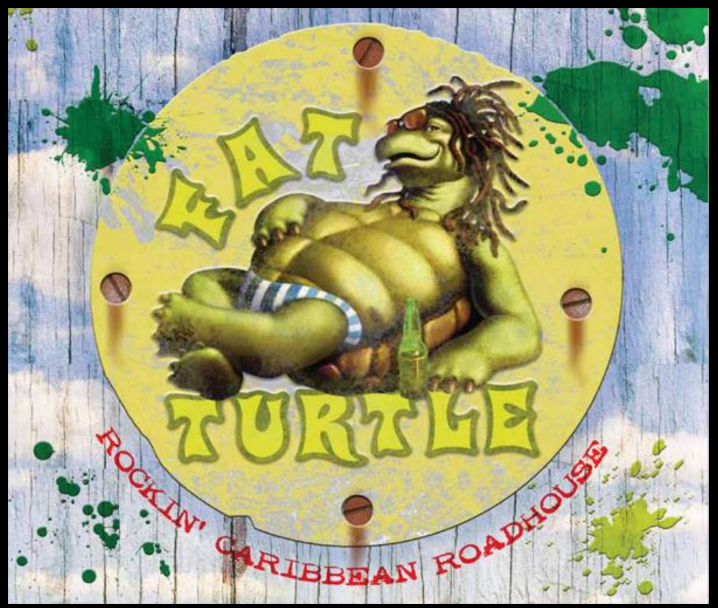
MPOD

- **Macular Pigment Optical Density**
- The 2 macular pigments are from yellow and orange carotenoids (L&Z)
  - Unable to be synthesized by humans
  - Found in highest concentration in fovea
  - Accumulation can protect RPE and photoreceptors
- Lower MPOD associated with lower carotenoid intake/serum levels, females, smoking, diabetes, increased BMI, AMD
- Measurable
- May even help with light sensitivity

Reference: Macular pigments, update and measurement. Malinovsky V, Geirhart D.

The 3rd Carotenoid?

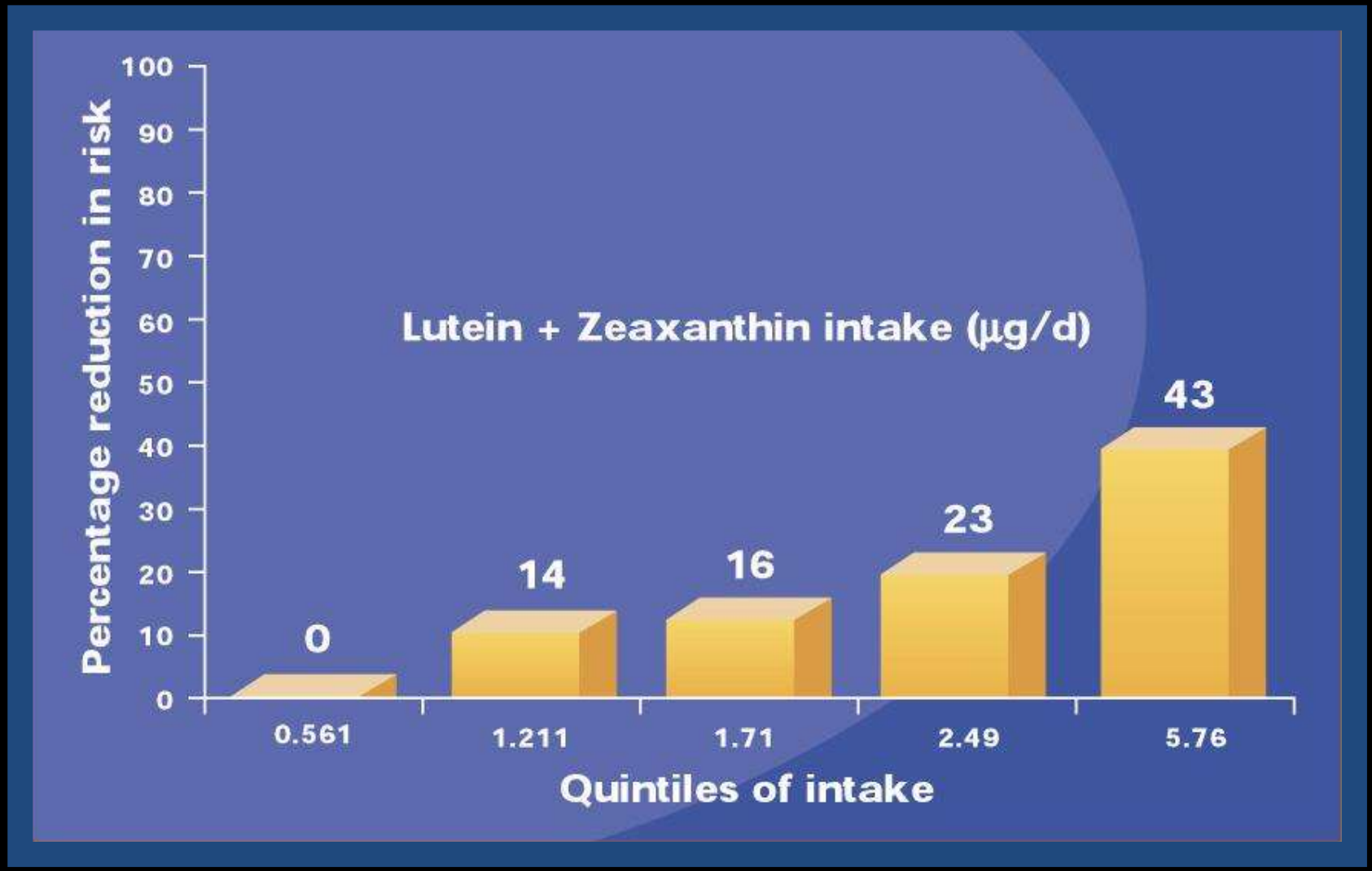
- What about Mesozeaxanthin?
  - It is not dietary (in relevant quantities)
  - In combination with other carotenoids, improves CSF (about the same as just 2)



Simplistic view of MPOD

- Biomarker of overall (macular) health and potential function
  - MPOD happens to be indicator of health beyond macula/AMD
    - Heart health
    - Skin health
    - COGNITIVE ABILITY
    - Diabetes status / DR status

Effect of Lutein + Zeaxanthin On risk of Advanced AMD



Which fruits/veggies should I eat?

- Historically, recommendations are made for green leafy veggies
  - Maize has highest % of lutein, and Orange pepper/Goji Berries has highest % of Zeaxanthin
  - High amounts were also found in: kiwi fruit, grapes, spinach, orange juice, zucchini and different kinds of squash
    - Note: different colors of f/v involved
    - F&V affecting MPOD: Br J Ophthalmol. 1998 Aug;82(8):907-10.

  Note, Mesozexanthin is found in food sources, but not in meaningful quantities

Realistic Dietary Sources of L/Z

Romaine lettuce 2.3 mg

Broccoli 1.7 mg

Spinach 12 mg

Kale 40 mg

L/Z values based on a 100 g serving

U.S. Department of Agriculture, Agricultural Research Service. 2010. USDA National Nutrient Database for Standard Reference, Release 23. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/ba/bhnrc/ndl

Bottom line:

- Fact:
  - MPOD is measureable and modifyable
    - Modify w diet, supplements and other lifestyle
  - MPOD is a piece of the puzzle
- Question:
  - Who should be tested
  - Who should be supplemented
    - Age vs risk factor vs diet…..

How can we make it “easy” to talk about MPOD and AMD lifestyle

- The recommendations on how to prevent or try to “control” AMD are no different than what a cardiologist or internist would recommend
- Cognitive Function is important to everybody and improved MPOD is correlated with
  - Higher plasma L/Z equaled better cognition, memory and executive function, and higher Z imiproved processing speed[1]
  - Higher MPOD = better memory, faster reaction times, faster at tasks[2]

1. Feeney et al. Plasma L/Z and Cognition. J Gerontol A Biol Sci Med, 2017, Vol 00 no 00 1-6. 2. Feeney et al. MPOD and cognition. Neurobiology of Aging. In press

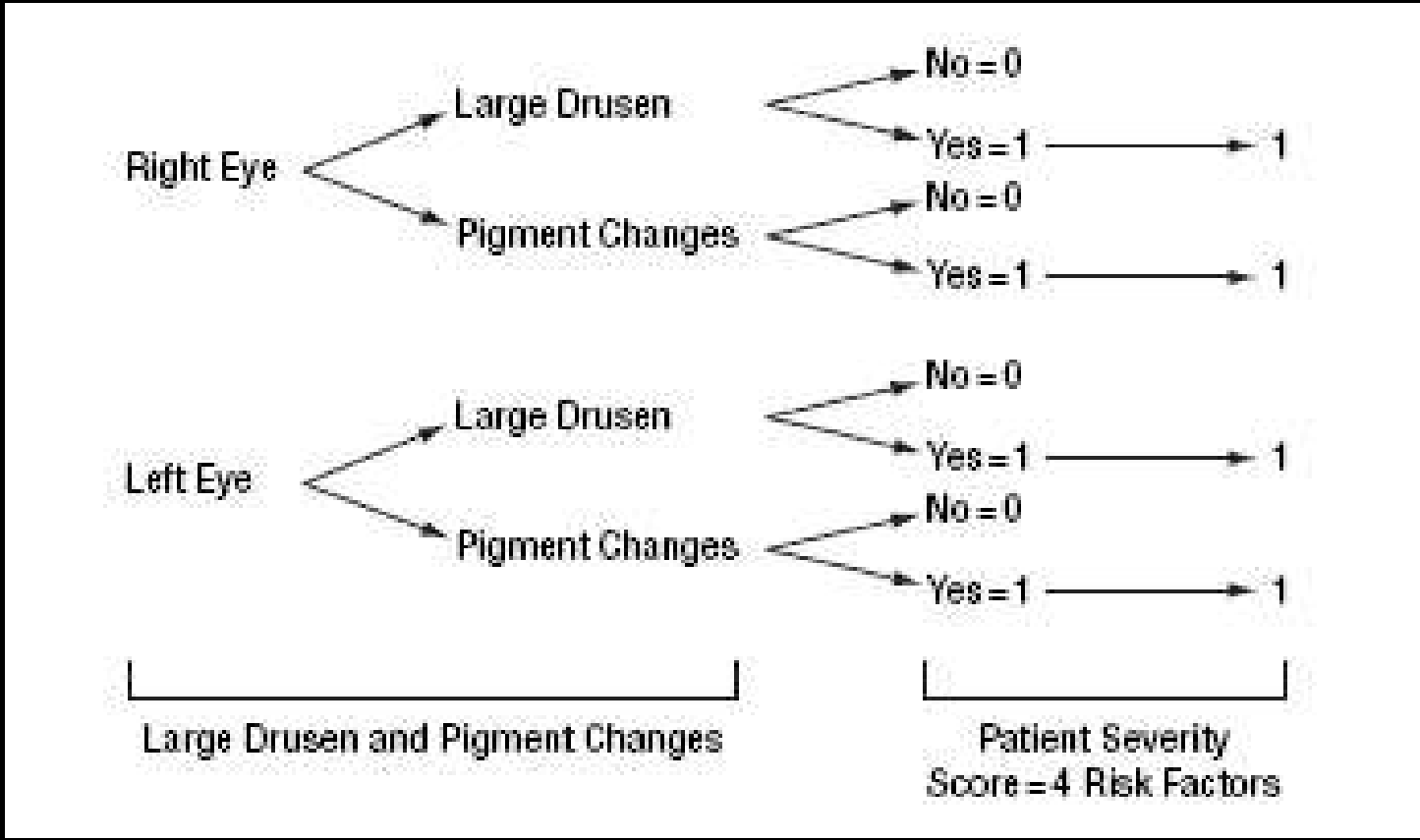
What did AREDS 2 tell us (abridged version?

- Addition of L/Z “helpful”
- Reduction of Zinc “not helpful”
- Omega 3 “not helpful”
- Beta-Carotene not helpful
- MesoZeaxanthin was not tested
-

- Bottom line; about 67% still convert regardless of intervention…..

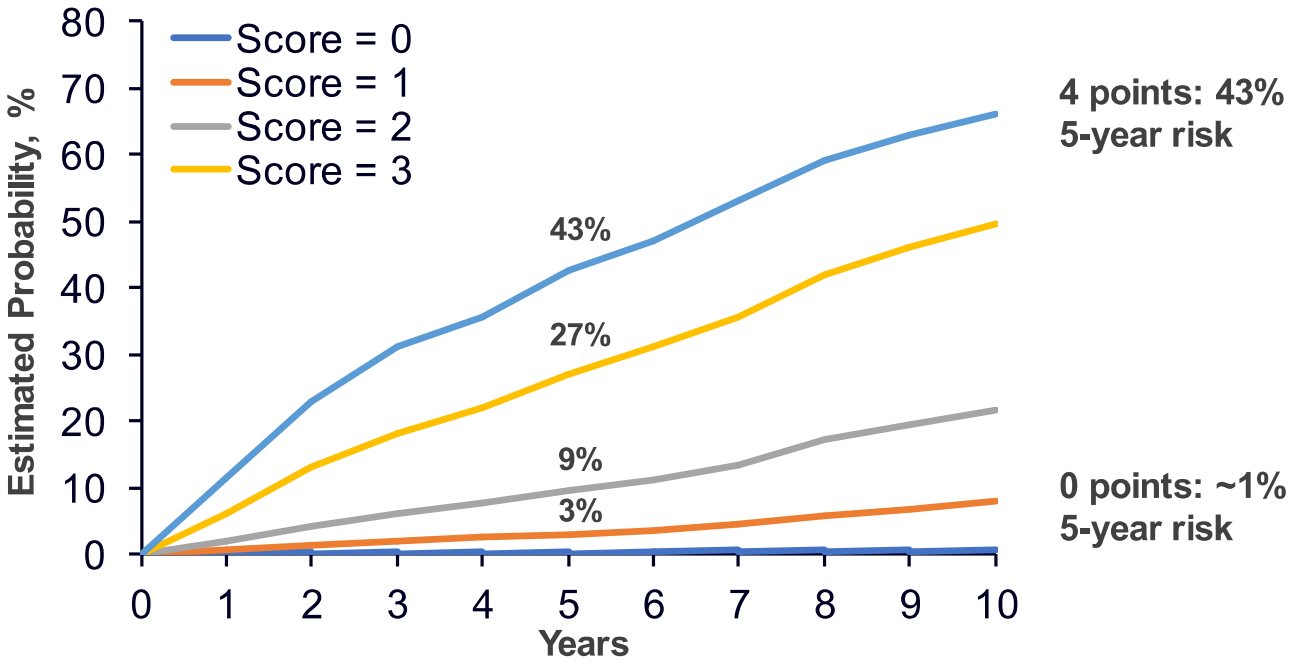
AREDS Simple System 0 to 4 Points

- Treating AMD is important because patients tend to progress with time
- The AREDS study implemented a helpful patient severity scale



NIH Public Access from *Arch Ophthalm*AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study.
ol. 2005;123:1570–1574.

Risk of Progression to Advanced AMD

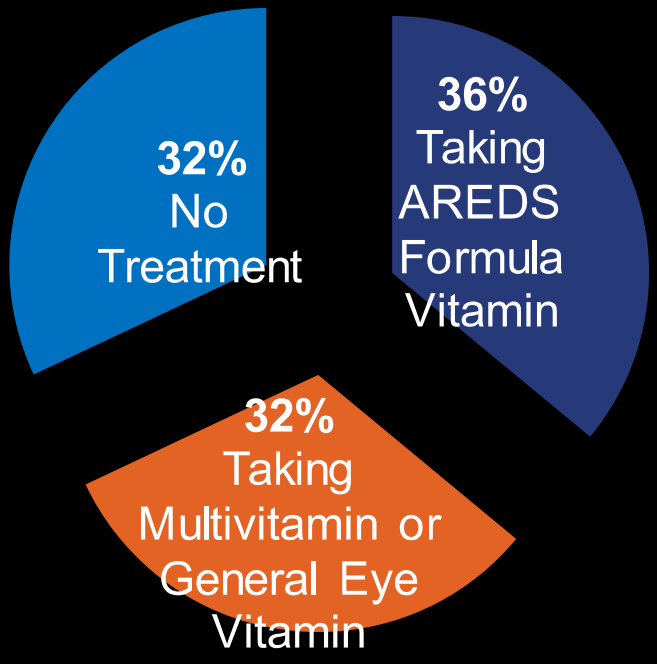


AMD, age-related macular degeneration.
Ferris FL et al. *Arch Ophthalmol.* 2005;123:1570-1574.

64% of Patients with Moderate to Advanced AMD are Not Taking an AREDS Formula Vitamin

Key Barriers

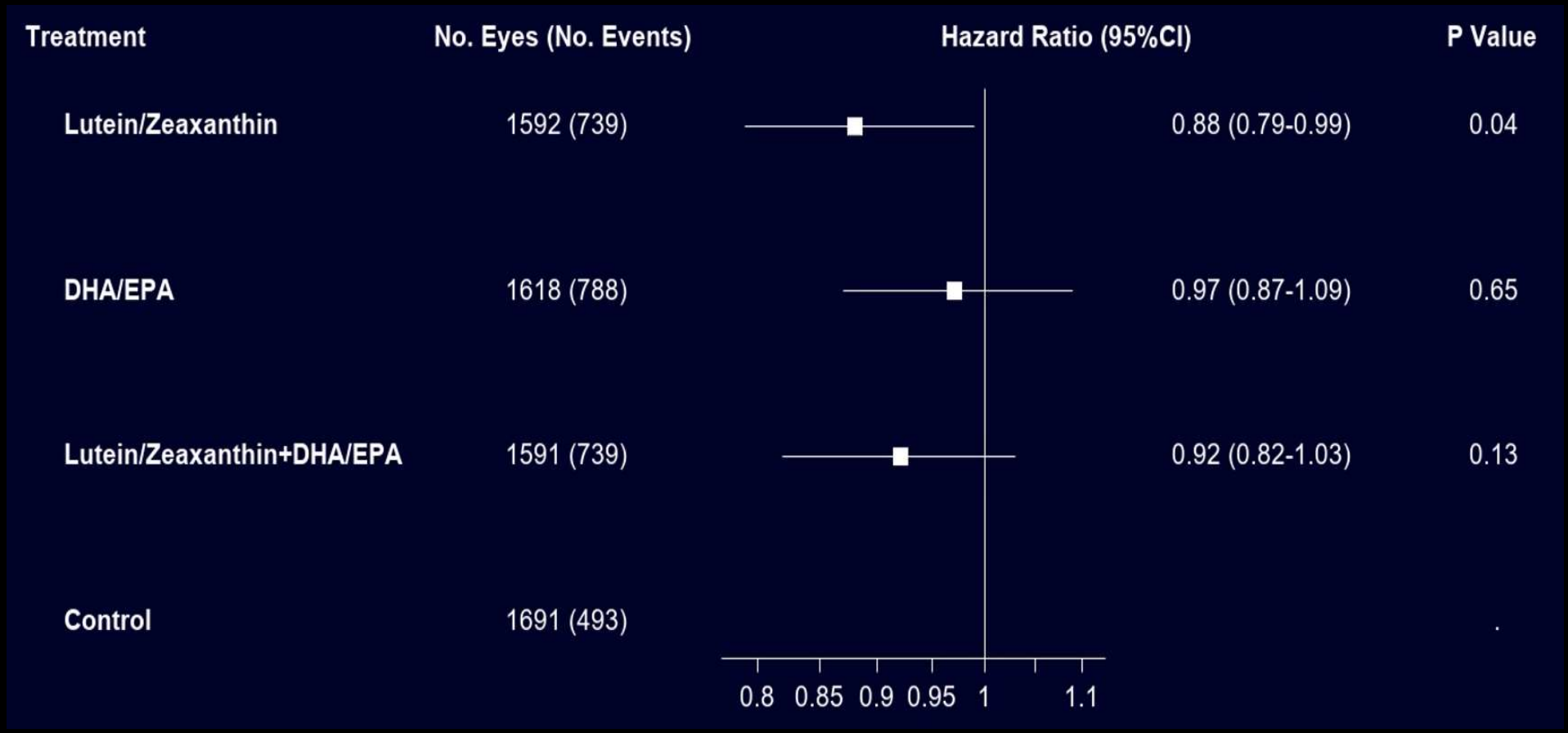
- Lack of awareness of vitamins based on the AREDS Study
- Lack of doctor recommendation



Each patient not on an AREDS formula vitamin is an opportunity to do the right thing

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study.
IRI AMD Custom Survey, April 2017 n=347

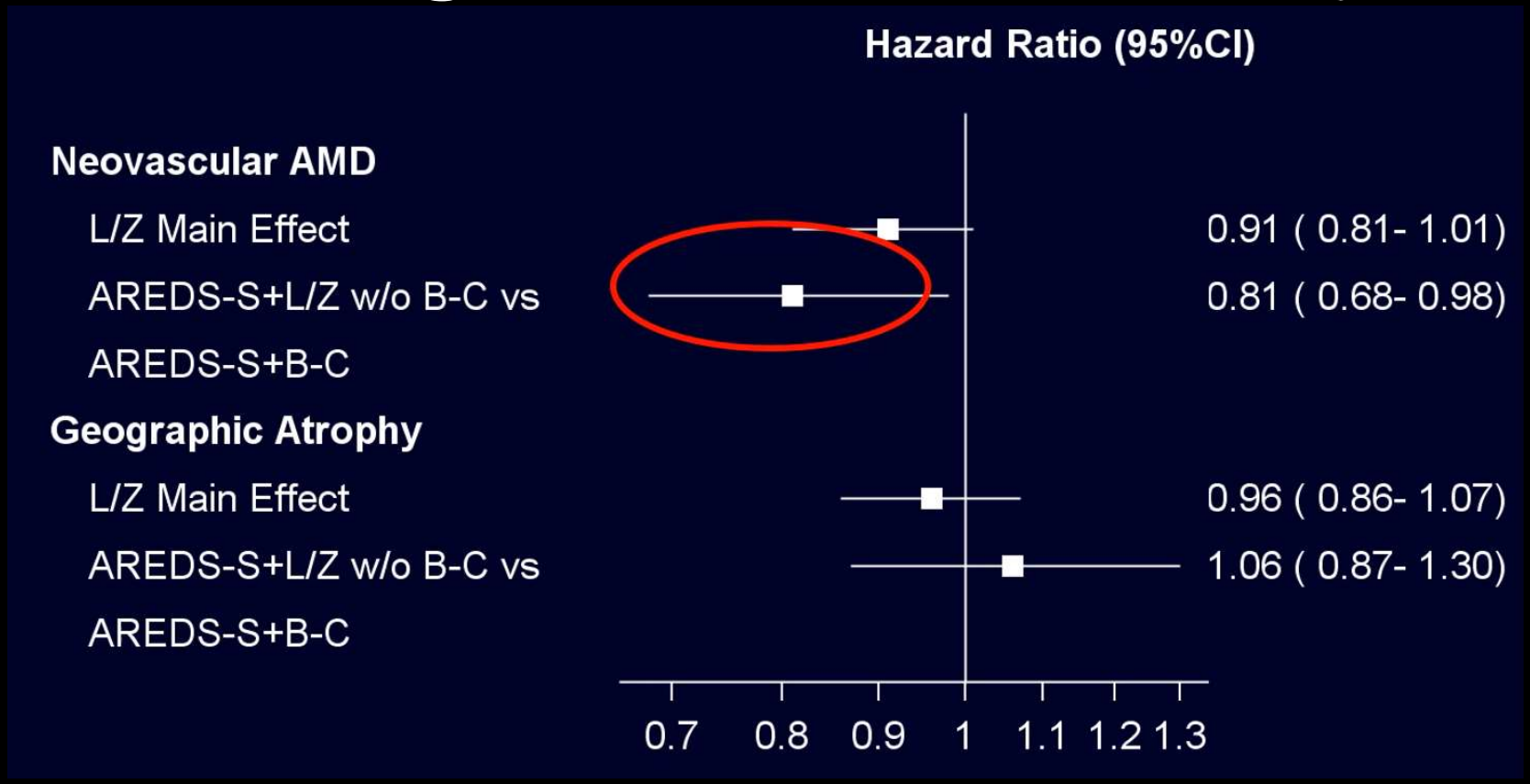
At 10 years, Participants Taking AREDS2 Supplements with L/Z had ~10% Reduced Progression to Late AMD



Significant effect of L/Z also appears at 5 years

AMD, age-related macular degeneration; AREDS2, Age-related Eye Disease Study 2; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; L/Z, lutein/zeaxanthin.

Participants Taking AREDS2 Supplements with L/Z + No Beta-carotene had ~20% Reduced Progression to NV AMD (10 Years)



Significant effect of L/Z + No beta-carotene also appears at 5 years

AMD, age-related macular degeneration; AREDS2, Age-related Eye Disease Study 2;B-C, beta-carotene; CI, confidence interval; L/Z, lutein/zeaxanthin; NV, neovascular; OCT, optical coherence tomography.

Most recent AREDS2 report

- Progression of GA in AMD : Report 16
  - 17.3% developed GA over study 4.4 yrs
  - In eyes w incident GA, incidence of NVAMD was 29%
  - If noncentral GA, progression to central GA was 57%

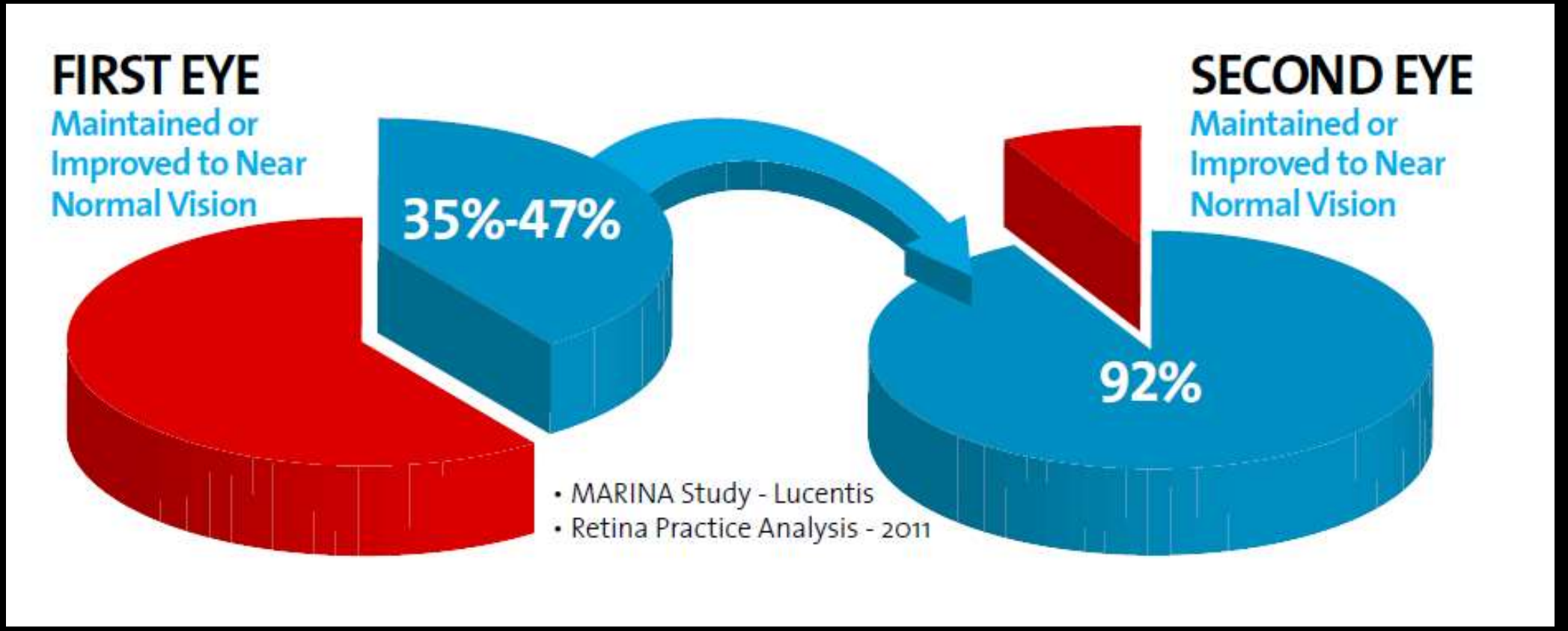
- Natural history of drusenoid PED's associated w ARMD Report 17
  - DPED associated w risk for late AMD : HR 2.36
  - 67% developed CNVM within 5yrs3x rate developing >3 lines of VA loss
  - 46% developed some vision loss within 5yrs

Keenan et al. Progress66656ion of GA in AMD. AREDS2 #16. Ophth 012/18. Yu et al. Natural History of Drusenoid PED in AMD: AREDS2 report 17. Ophth 2/2019.

The AMD Problem

Wet AMD
Initial Presentation
First Eye
80% are Blind
(20/200 or worse)

Save the First Eye



- Excellent results in the second eye need to be duplicated in patients' first eyes

RED signifies "lost vision" unable to be saved

Medical Utility – Why Should We Test?

- Early detection can save sight
- Genetics helps identify patients at risk of progression
- More frequent monitoring of high risk patients leads to earlier treatment and better visual outcomes

Not to mention pharacogenetics aka: The Zinc debate

Genes add Predictive Power

AUC – ROC 'C' Statistic Scores (AREDS 2 &3)

1. Toss a Coin = 0.5 (Baseline)
2. Eye Exam + Age = 0.732 (+46.4%)
3. Eye Exam + Age +BMI + Smoking = 0.757 (+10.7%)
4. Add Genetics = 0.8221 (+24.9%)

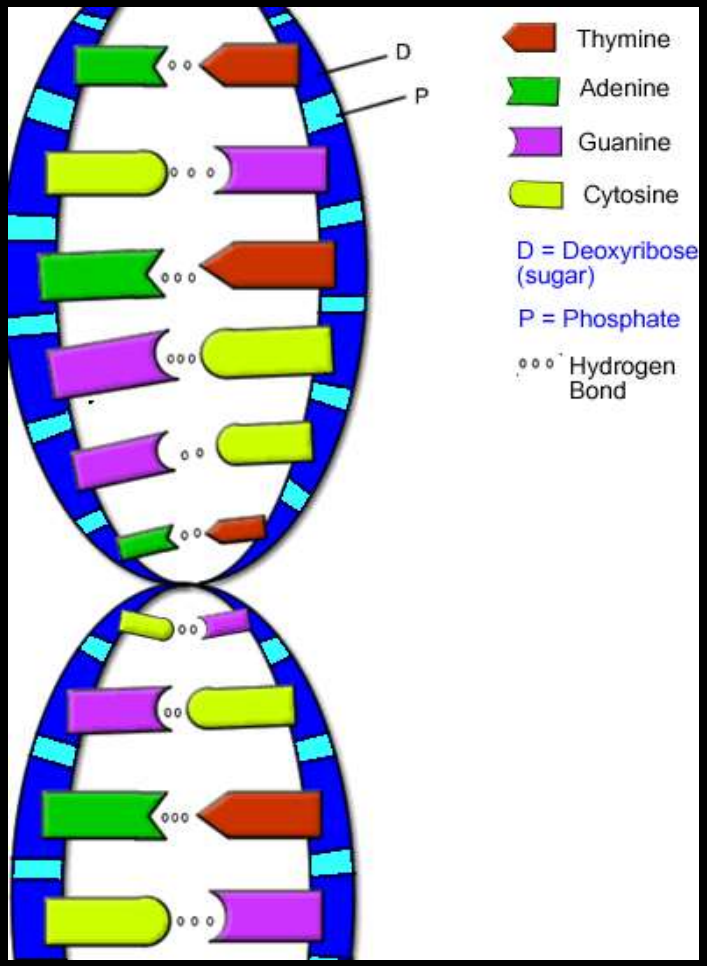
Genetic Testing adds 24.9% improvement

0.821-0.757/(0.757-**0.5**)*100 = 24.9%

J. M. Seddon, B. Rosner et al; IOVS May 2009

Is AMD in your DNA?

DNA



AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk[1]

In other words: AMD is >70% due to genetics!

Former Smokers: 1.29x
Current Smokers: 2.4X
Non-Smoker and CFH,Y402H: 7.6X
Current smoker and CFH,Y420H: **34X**

1.J.M. Seddon, B Rosner et al; IOVS May 2009

Arctic
MEDICAL LABORATORIES

801 Broadway NW
Grand Rapids MI 49504
Phone: 616-233-0622
Fax: 616-233-0693

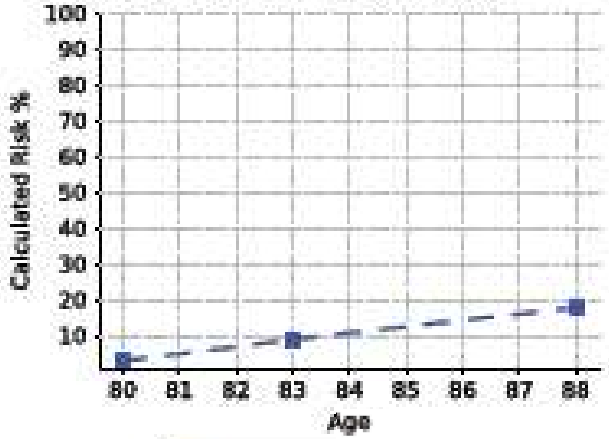
Accession:	AMLNXG-xxxxx	**Receiving Facilities:**	**Receiving Physicians:**
Patient:	Patient, Sample		
Date of Birth/Age:	July 13, 1934 / 78		
Gender:	Female		
Created:	January 23, 2013		
Smoking History:	Never		
Height/Weight/BMI:	5 feet 7.0 inches / 174 pounds / 27		
Specimen Type:	Buccal Swab		
AMD Status:	Right Eye (OD): Early / Left Eye (OS): Early		

Macula Risk NXG Lab Report

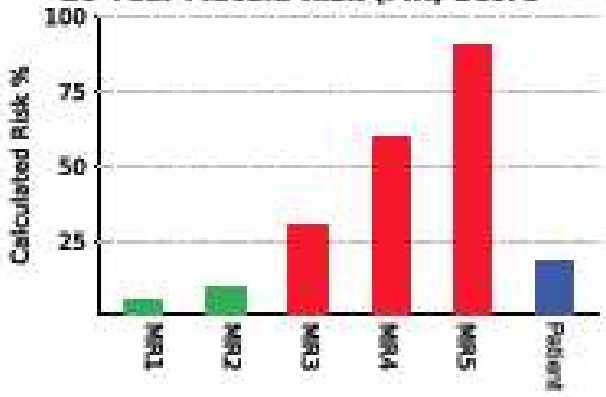
Risk of Conversion to GA or CNV (%) based on genetic and non genetic features

Category	2 Years	5 Years	10 Years
Patient, Sample	3	8	18
10 Year Macula Risk Score			3

2-10 Year Conversion Risk



10 Year Macula Risk (MR) Score



Macula Risk Score

Gene	SNP	Result	Gene	SNP	Result	Gene	SNP	Result
CFH	rs3766405	CC	C2	[illegible]	GG	COL8A1	rs13095228	TT
CFH	rs412852	CC	CFB	rs541862	AG	APOE	rs7412	--
CFH	rs1048663	GG	LIPC	rs10468017	CC	APOE	rs429358	--
CFI	rs10033900	CT	ABCA1	rs1883025	CT	TIMP3	rs9621532	AA
C3	rs2230199	GC	CETP	rs3764261	CC	ARMS2	372_5150#443ins	NN

Genetic Risk Subscore: 76% (range: 0 - 100, average = 50)

How do you calculate vitamin risk?

Raging debate

- The big debate in pharmacogenetics in AMD is ”Does it matter” and if so, who gets what?
- Several published papers:
- Awh et al: Genetics is EVERYTHING
- Chew et al: Genetics means NOTHING
- Seddon: Genetics means something
- Most recent: somewhat neutral: Genetics is critical

Personalized Medicine

- Each of your patients is an individual with their own potential needs
  - “This is the beginning of the end of worshiping at the altar of the large randomized placebo-controlled clinical trial. It introduces the era of personalized medicine based on, among other findings, genetic profile. “
    - Leo Semes, O.D., F.A.A.O.

Undetected AMD is a Significant Problem
Is Dark Adaptation testing real/relevant??

GRIN EYE CARE

The eye care you choose will make a difference you can see

Sample of 100 consecutive older adults (over age 60) with normal retinal health based on clinical exam were tested using AdaptDx.

39% (39 of 100) had previously undetected AMD

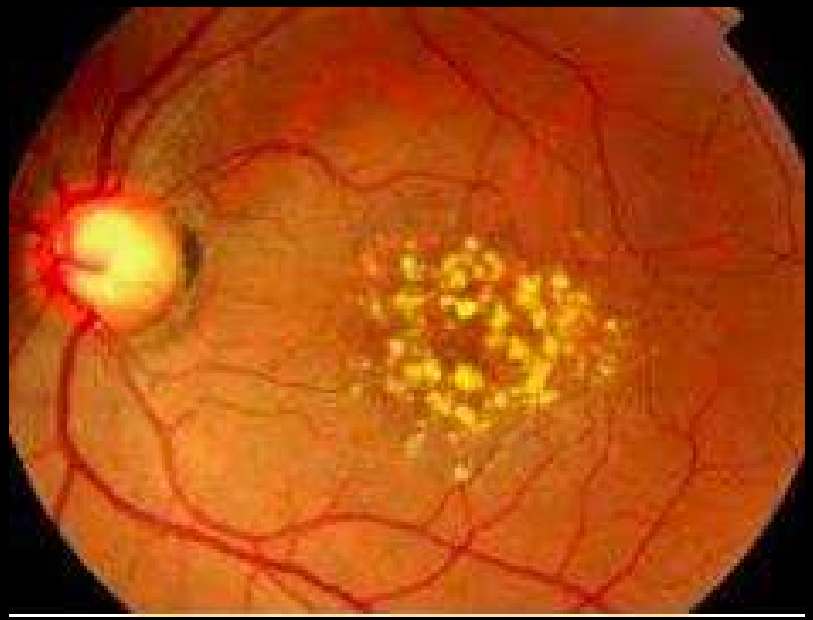
Jeffry Gerson, OD, Grin Eye Care. IRB approved. Publication pending

Peripheral AMD changes???

- Where do changes happen first in AMD
- Could it be in periphery?
- Correlating data may prove to allow earlier detection of AMD (and other diseases)

Is it truly only a disease of the posterior pole; particularly the macula?

Age-related macular degeneration may be more than a "macular" condition… one that involves the entire retina



Peripheral retina in AMD….

- Diagnosis relies on changes seen in macula
  - Beckman or AREDS classification
- **BUT**… there are many age-related changes in the periphery that may influence the development of macular lesions
- **OR**… the macular pathology itself may trigger peripheral changes that could influence treatment options

The AREDS2 OPERA

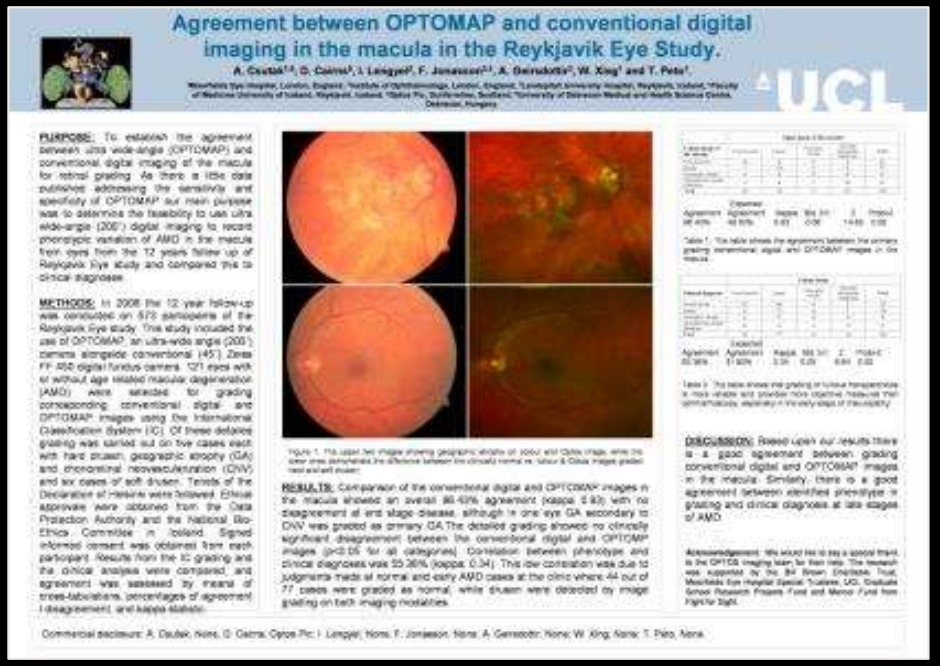
- AREDS2 looked at more than which vitamin to give patients
- It looked at peripheral retinal changes in AMD pts
  - 951 study eyes and 163 controls
  - % eyes with drusen in post pole/mid/far periph
  - Study: 97/78/64%
  - Control: 48/21/9%
- “Age-related macular degeneration may be more than a "macular" condition but one that involves the entire retina.”

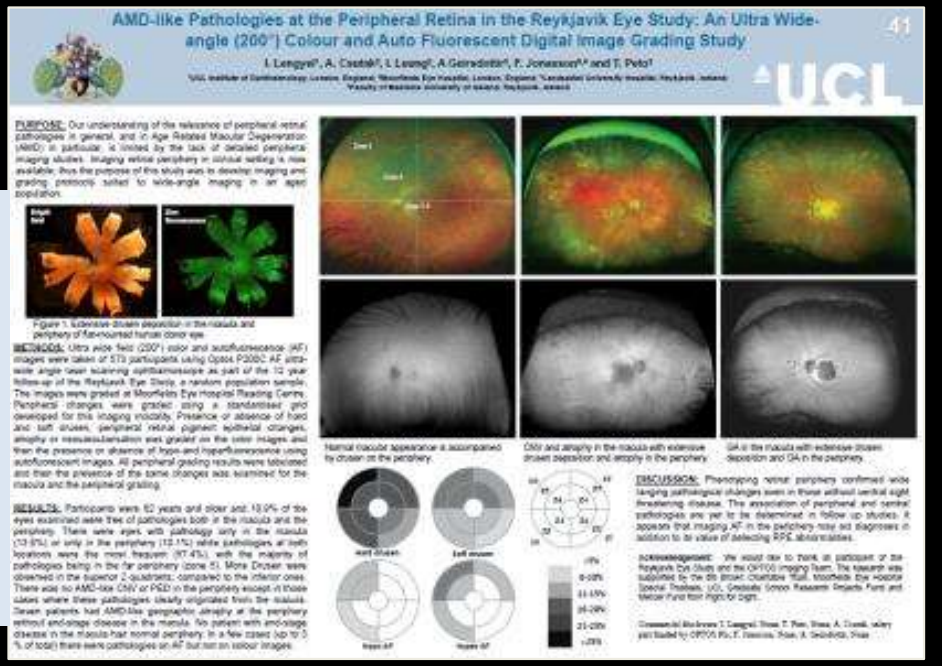
Opera writing committee. Periph Ret in AREDS2. Ophthalmology. 4/17

Reykjavik Eye Study

- 573 patients imaged at 12 year time period
- Color and AF imaging
- The peripheral retina was analysed and the study found:

In **77% of patients**, AMD related changes were visualised outside of the area of the Topcon photos


Agreement between OPTOMAP and conventional digital imaging in the macula in the Reykjavik Eye Study.


AMD-like Pathologies at the Peripheral Retina in the Reykjavik Eye Study: An Ultra Wide-angle (200°) Colour and Auto Fluorescent Digital Image Grading Study

Reticular Pigmentary Changes in an eye with AMD (L); Control (R)

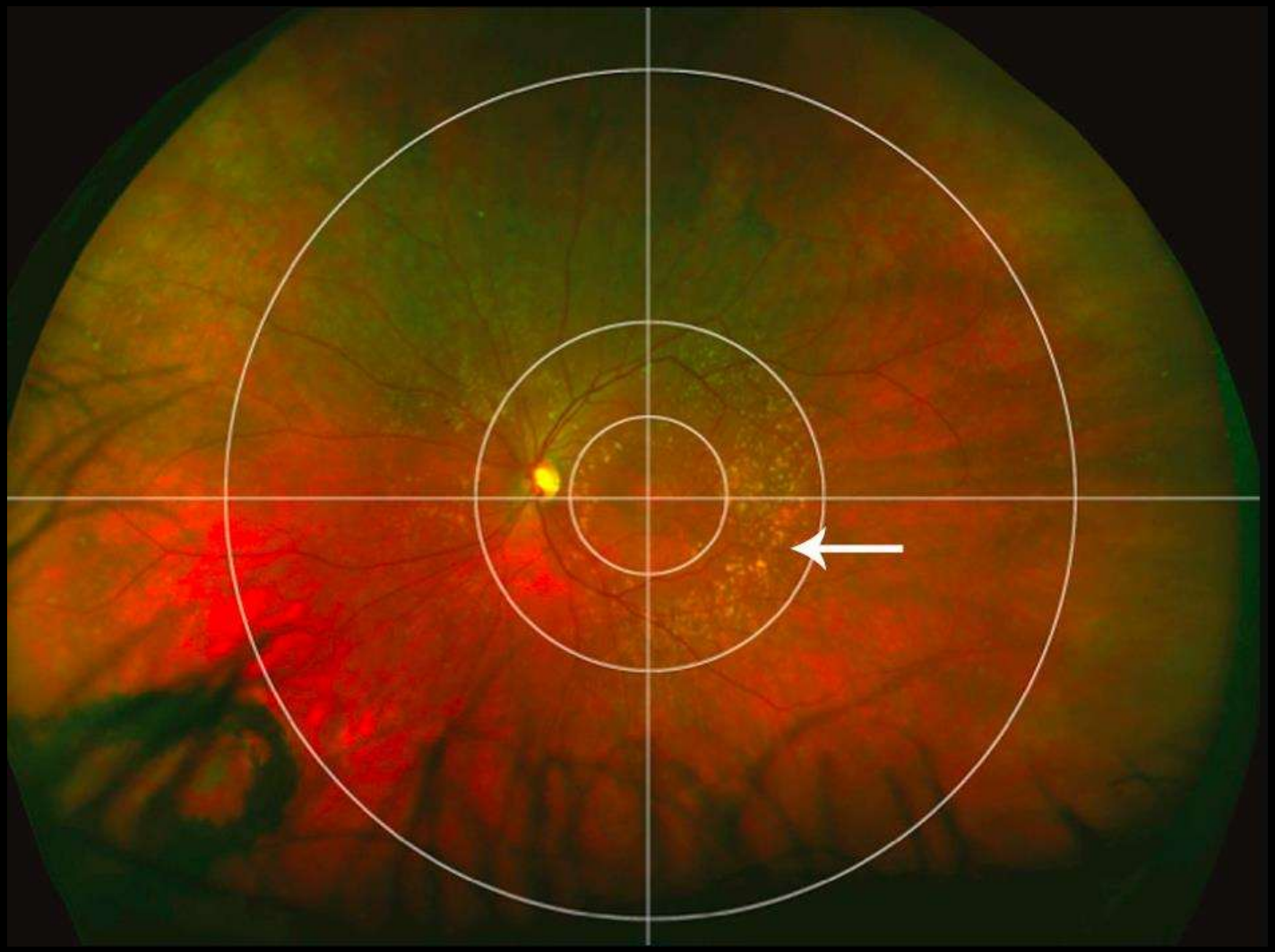
What are the implications of this data?

Laíns I, Park DH, Mukai R, et al. Peripheral changes associated with delayed dark adaptation in age-related macular degeneration. *Am J Ophthalmol*. 2018;190:113-124.

- The clinical significance of peripheral lesions in AMD remains incompletely understood
- Strong correlation between patients with prolonged dark adaptation and peripheral reticular pigmentary changes….

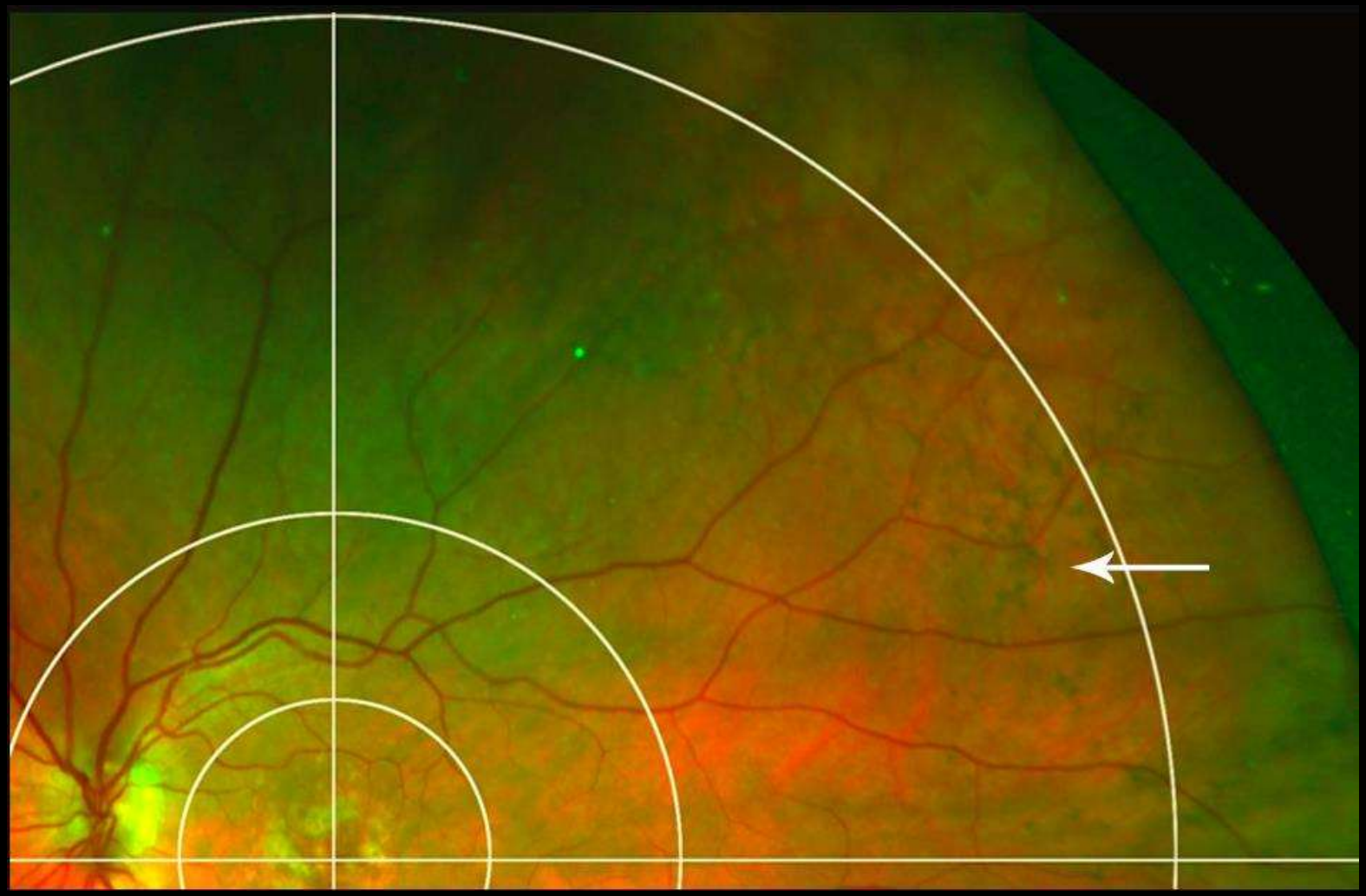
Suggests that peripheral changes may have a role to play not only in the diagnosis of AMD but also in determining prognosis of disease.

https://retinatoday.com/articles/2020-apr/ultra-widefield-imaging-for-age-related-macular-degeneration Laíns I, Park DH, Mukai R, et al. Peripheral changes associated with delayed dark adaptation in age-related macular degeneration. *Am J Ophthalmol.* 2018;190:113-124.



Minimal macular involvement…..

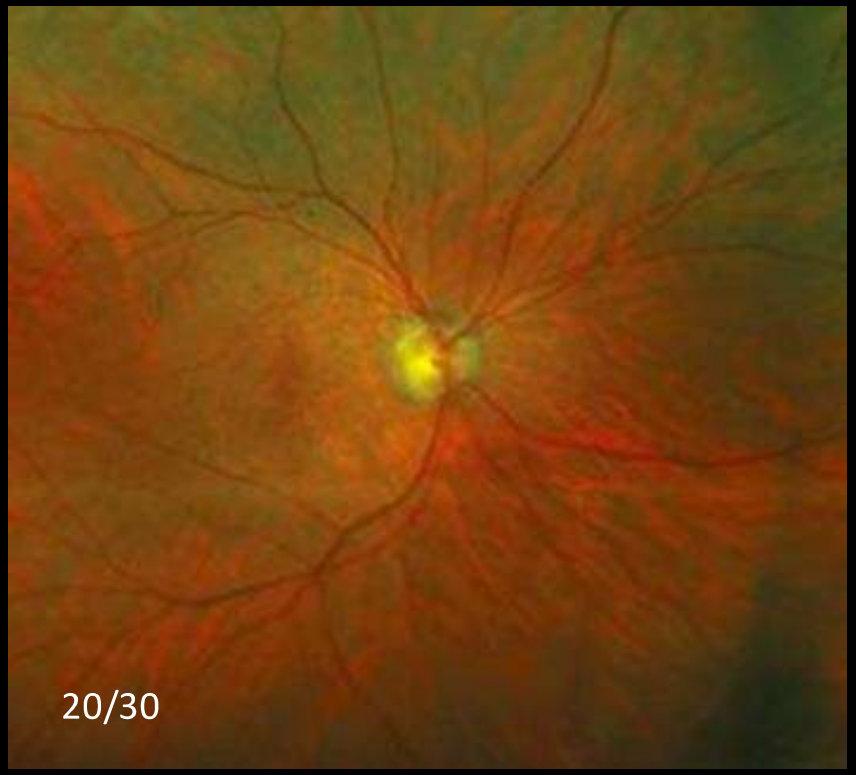
Drusen in the perimacular zone (all quadrants), as well as some drusen in midperipheral and far-peripheral zones



Significant macular involvement….

Reticular pigmentary changes, which occupy both the midperipheral and far-peripheral zones.

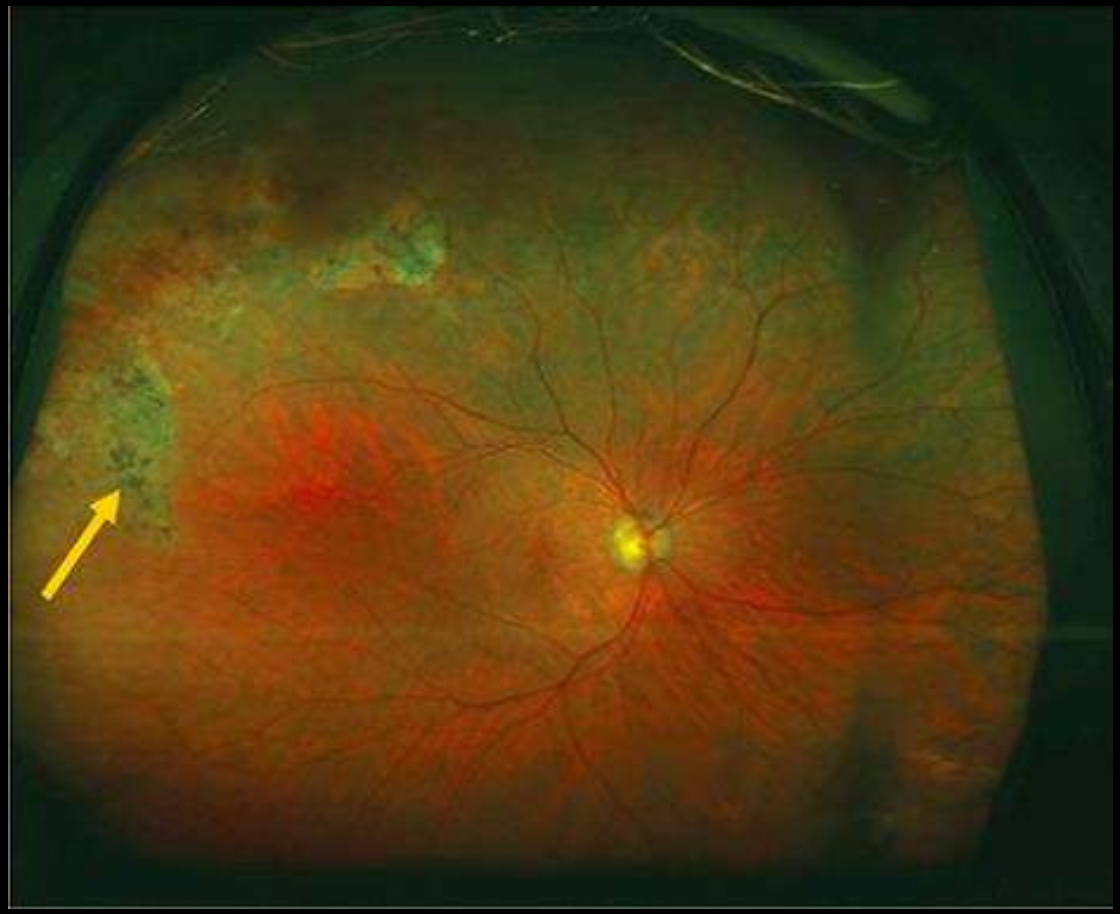
80-year-old Caucasian female
Routine eye exam

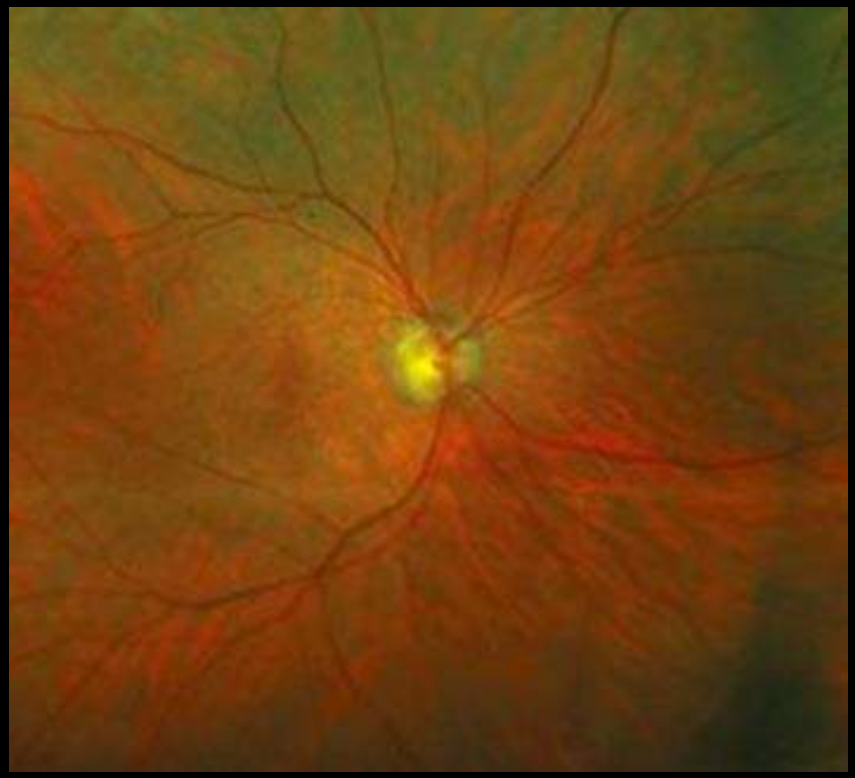


(+)20 history of smoking
(+)HTN, hypercholesterolemia

"I live in S. Fla and I LOVE the sun!!"

Looks great… RIGHT??

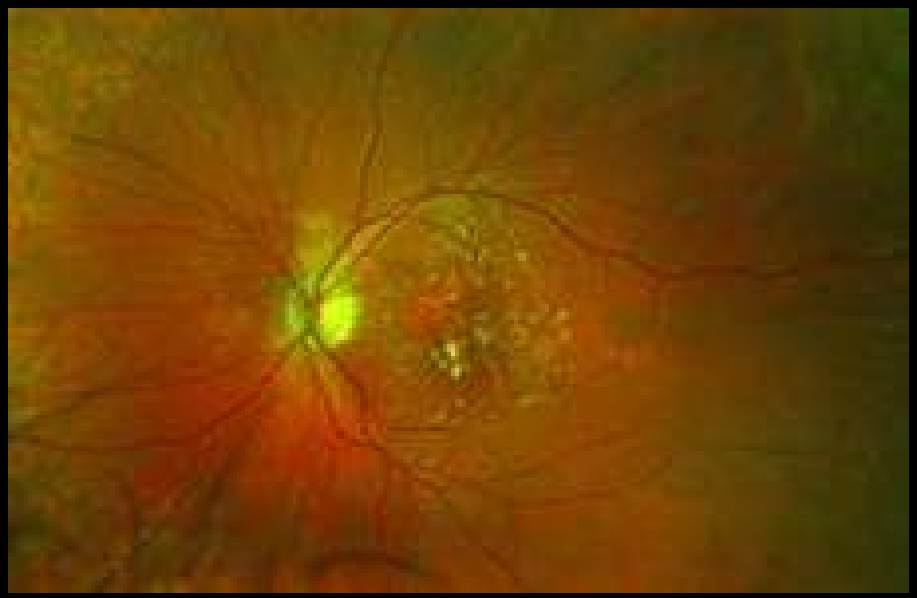




What is the relevance of these peripheral changes?
*Hypo and hyper pigmentation
*Drusen

Should we test dark adaptation???

A 74-year-old Hispanic Male
Longstanding h/o AMD



Geographic atrophy, drusen, pigmentary changes in posterior pole….

”My vision is stable..”

The importance of reticular pseudodrusen in the development of GA…

And the periphery???

Opera study

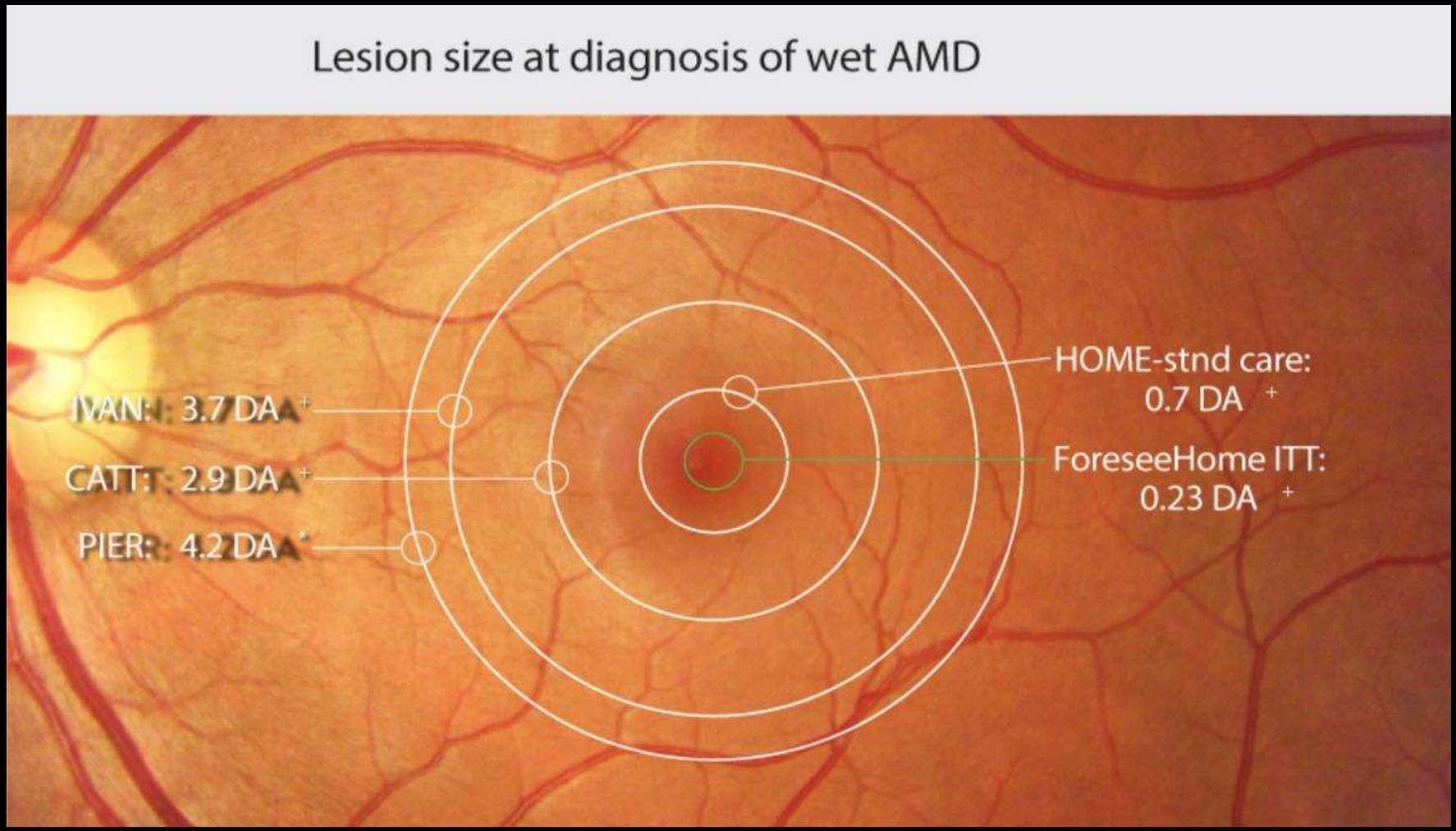
What is PHP?

HOME study

- Part of AREDS2
- 94% retained 20/40 or better when following protocol
- 51% more retained 20/40 compared to standard monitoring

- In home monitoring remotely read with alerts as needed
-

ForSee Home in “real life”



How much does PHP cost?

- No cost to you the practitioner
  - And no DIRECT benefit…but indirect benefit!
- Over 60% of Medicare patients pay ZERO!!!

What's next from Notal?

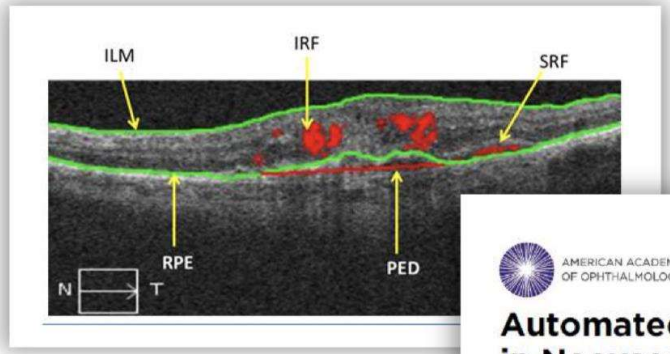
- Home OCT
- Will use a binary program to tell if there IS or IS NOT fluid
- Ultimately will likely be used in AMD and DM and any other macular condition

Home OCT

Using Artificial Intelligence to Personalize and Optimize Retinal Disease Management

Notal OCT Analyzer (NOA)

Validated Machine Learning Algorithms
Perform Automated Analysis



AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Automated Identification of Lesion Activity in Neovascular Age-Related Macular Degeneration

Usha Chakravarthy, PhD,[1,2] Dafna Goldenberg, MD,[3,4] Graham Young, BSc,[2] Moshe Havilio, PhD,[5] Omer Rafaeli, MD,[5] Gidi Benyamini, MBA,[5] Anat Loewenstein, MD[3,4]

92% Sensitivity and 93% specificity compared to 3-retina specialist reading center

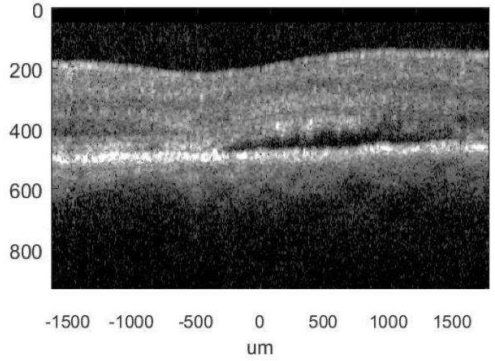
Home OCT

Home OCT cont.

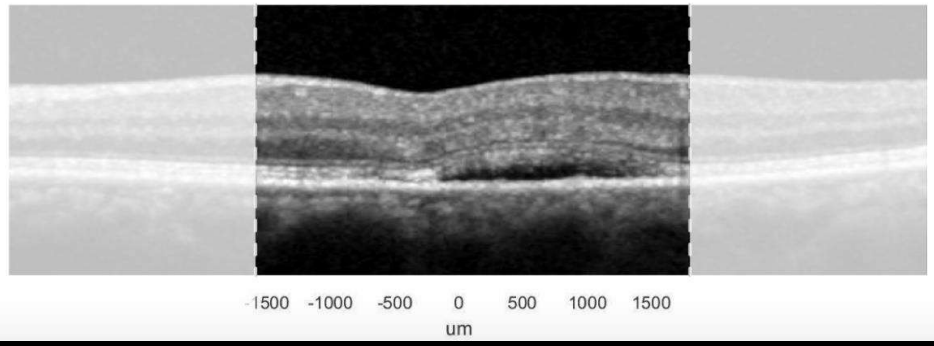
AI Driven Home OCT Creates a Decision Support Solution

- Spectral Domain OCT
- Easy-to-use, self-installed and self-operated
- Less than 10 seconds per eye
- Wirelessly uploads B-scans to cloud
- B-scans viewable by physician
- AI algorithm analyzes B-scans for fluid
- Change reports sent to physician

Home OCT

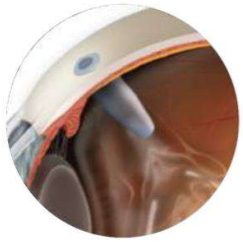
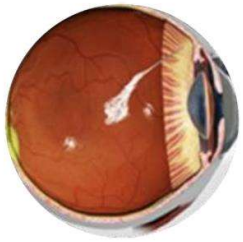


Heidelberg Spectralis



Why Home monitoring matters

Home Monitoring Optimizes Current and Emerging Treatment Modalities

SUSTAINED DELIVERY DEVICES	TOPICAL AND ORAL THERAPY	LONG-ACTING FORMULATIONS	EXTENDED BILATERAL WET REGIMEN
			
Most Advanced: Phase 3	**Most Advanced: Phase 2**	**Most Advanced: Post Phase 3**	**Up to 42% are Bilateral by 3 Years**
• Implant decision requires patient qualification • Eliminating visits requires confirmation of ongoing drug response	• Turns dosing over to patient • Eliminates visits • Compliance and drug response confirmation required	• Validation of drug response • Interval is adequate for a specific patient, and • Recurrence of fluid has not occurred	Extended regimens not feasible – lack of synchronization creates two follow-up schedules in absence of monitoring for recurrence of fluid

To make sure at least address…

- What is the treatment for wet AMD??

Relatively New…

- What's the newest approved Anti-Vefg injection? (9/20/21)
- Byooviz (Ranibizumab nuna by Samsung Biopls Co)
- First biosimilar approved in ophthalmology
- Approved based on study with 634 patients 1:1 to Lucentis
  - BCVA at wk 52 was +9.79 letters for the biosimilar & +10.41 for the reference product (–0.62; 95% CI)
  - The LS mean change in central subfield thickness was –139.55 mcm for Byooviz and –124.46 mcm for Lucentis (–15.09; 95% CI, –25.617 to –4.563)
  - At least 3 more Ranibizumab and 3 Aflibercept biosimilars in development

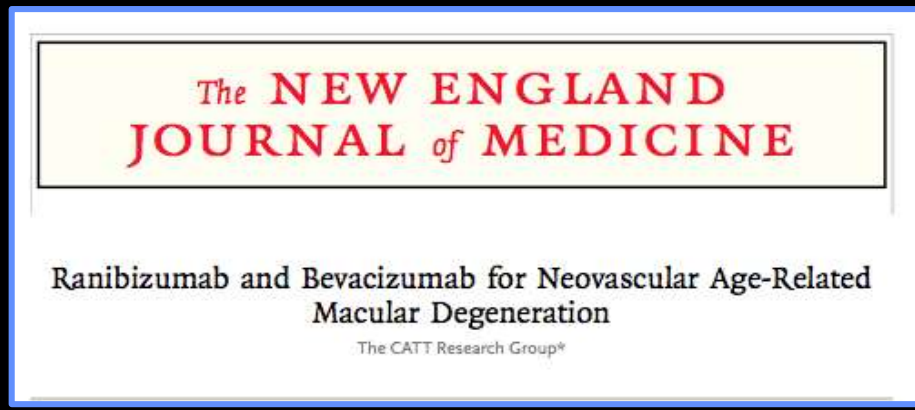
Biosimilar

- Per the FDA:

  A biosimilar is a biological product that is approved based on data showing that it is highly similar to a biological product already approved by the FDA (reference product) and has no clinically meaningful differences in terms of safety, purity and potency (i.e., safety and effectiveness) from the reference product, in addition to meeting other criteria specified by law.
  - FDA has approved 31 biosimilars in total
  - Other biosimilars discount price 15-30%

The Catt is out of the bag…

- CATT: Comparison of Lucentis monthly vs Lucentis PRN vs Avastin monthly vs Avastin PRN
- Bottom line: Monthly either slightly better than PRN either
- Lucentis essentially equal to Avastin in outcome measures
- Lucentis essentially equal to Avastin in Adverse events: both relatively low
- Avastin has significant economic benefits!



CATT Research Group. Lucentis vs Avastin in AMD. NEJM.4/28/2011.

Cost implications

Avastin per year

- Cost per injection: $50
- Monthly/yr: $600
- PRN: $350

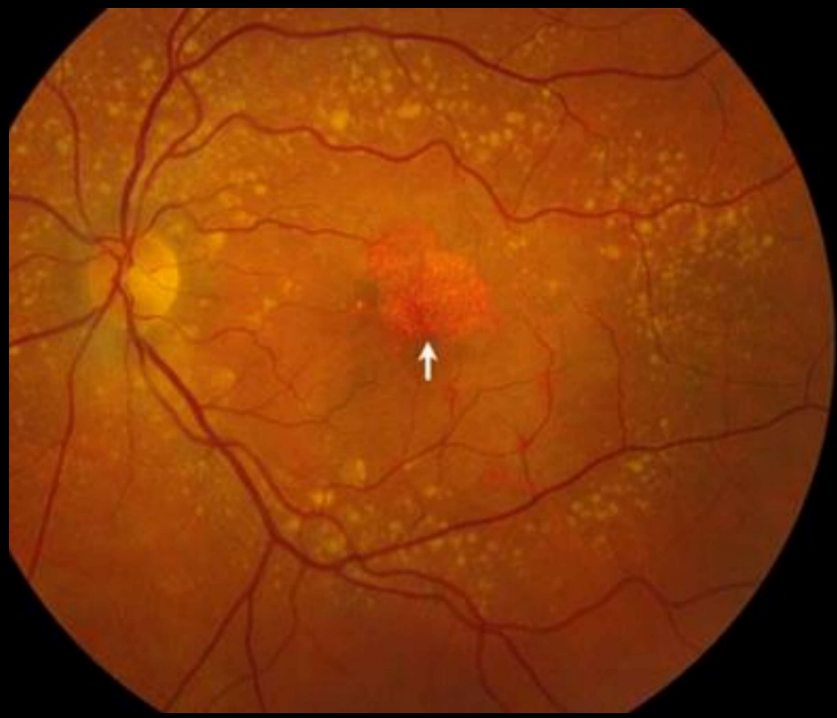
- 250,000 Americans:
- Monthly/yr: 150,000,000
- PRN/yr: 87,500,000

Lucentis per year

- Cost per injection: $2000
- Monthly/yr: $24000
- PRN: $14000

- 250,000 Americans:
- Monthly/yr: 6,000,000,000
- PRN/yr: 3,500,000,000

CATT



- Side effects
  - 40% Avastin vs 32% Lucentis
- Non-central GA was noted more often in LUCENTIS q1M grp vs Avastin prn grp, which interfere with reading
  - 26% lucentis q1M
  - 12% avastin PRN

CATT longer term

- Hopefully patients live longer than 2 years…
- At 5yrs, avg of 25 visits and 15 treatments[1]
  - 60% had some drug crossover
  - 50% at least 20/40, but 20% 20/200 or worse
  - Mean VA was -3 from baseline
  - GA in 41% and 36% CMT under 120microns

Maguire et al. CATT 5 yrs. Ophth 8/16.

Real bottom line

- Gains at 2 years
  - Monthly bevacizumab: 7.8-letter increase
  - Monthly ranibizumab: 8.8-letter increase
  - As-needed bevacizumab: 5.0-letter increase
  - As-needed ranibizumab: 6.7-letter increase
- Losses at 5 years
  - Bevacizumab, both regimens: 8.8-letter decrease from year 2
  - Ranibizumab, both regimens: 12.7-letter decrease from year 2
- ABOUT THE SAME!!!!
- Note: CATT DID NOT include Aflibercept

Great news for our patients and economy, but….

- Does CATT change the way we practice?
- Does it change our primary focus???

- Ideally, nobody would need Avastin or Lucentis!

  Avastin, Eylea and Lucentis sound great, so where do we fit in ……

Any drawbacks to injections

- 175 patients age 65-85yo
- Study participants took an iPad-based brain health assessment (BHA) to assess cognitive impairment
- Patients stratified: 0, 1-9, 10-20 and >20
- Likelyhood of cognitive impair vs 0 inject: 1.12/1.16/1.38 (memory, executive function and speed, visuospatial, and language)
- ? Could neurologic system be affected by anti-VEGF through retina/choroid complex?

Ray SK, Manz SN. Brain health assessment in macular degeneration patients undergoing intravitreal anti-VEGF injections (the BHAM study) – an interim analysis. *Retina*. Published online December 16, 2020. doi:10.1097/IAE.0000000000003066

Who gets Wet AMD in the first place

- Study of Medicare beneficiaries in 2014
- 7.8% were diagnosed with AMD
- 16.3% of diagnosed with AMD received at least 1 Anti-VEGF injection
- Dx of AMD was .26x for AA vs .56 Latino, .71 Asian vs Caucasians
- Anti-VEGF injections for AMD was .14 for AA vs .39 for Latino vs .52 for Asians

Mahr et al. Racial differences in AMD. Ophth Retina 2018;2:1188-1195.

Treat and Extend

- The concept has been employed for well over 5 years
- TREND[1]
  - 650 pts for 12 months: monthly vs Tx and extend
  - Treated with .5mg Lucentis
  - Less injections and visits in T&E vs Monthly
    - 8.7 vs 11.1 and 8.9 vs 11.2
    - +6.2 vs 8.1 in T&E vs monthly
    - T&E Statistically NON-INFERIOR
  - Better VA improvement in T&E group in TREX
    - Average just over 10 letters, same number of injections as TREND

1.Silva et al. Asia Pacific OA 3/17. Tx and Extend vs monthly. 2. Wykoff et al. **Prospective treat-and-extend TREX-AMD 1-year.** *Ophthalmology*. 2015; 122

Downside to Treat and Extend

- CANTREAT
  - Assessing injection frequency in wet AMD
  - Canadian based study comparing 6 or less per year (Group 1) to 7 or more per year (Group 2) of Ranibizumab
  - At 1 yr: Better overall VA in group 2
  - At 2 yrs: Better overall VCA in group 2
  - Crossover from group 2 to group 1 at 1yr: lost vision compared to group staying in group 2.

More on Anti-VEGF from ASRS

- Study of 49, 485 eyes getting injections for NvAMD by Williams
  - 40/25/35 Bevacizumab/Ranibizumab /Afliberecept
  - Less injections in those with worse vision and older pts
  - Vision plateaued with 10 injections in 1st year, lesser results w less injections
  - Real world: less injections and worse vision than in RCCT's

Long Term VA w Anti-VEGF

- A study of treatment naïve eyes receiving 3 injections over first 3 months
- Looking for early response: >70 letters (approx. 20/40)
- Good vision at 3 yrs was strongly associated w early response to at least 70 letters: HR 9.8x
- Gains in vision at 4 mos were 1.8x as likely to have good vision at 3yrs
- Eyes with gains at 4mos did better than those without: 65 vs 57 letters

Nguyen et al. Projection of long-term VA in NVAMD: Ophth. 1/19

What happens outside of a study

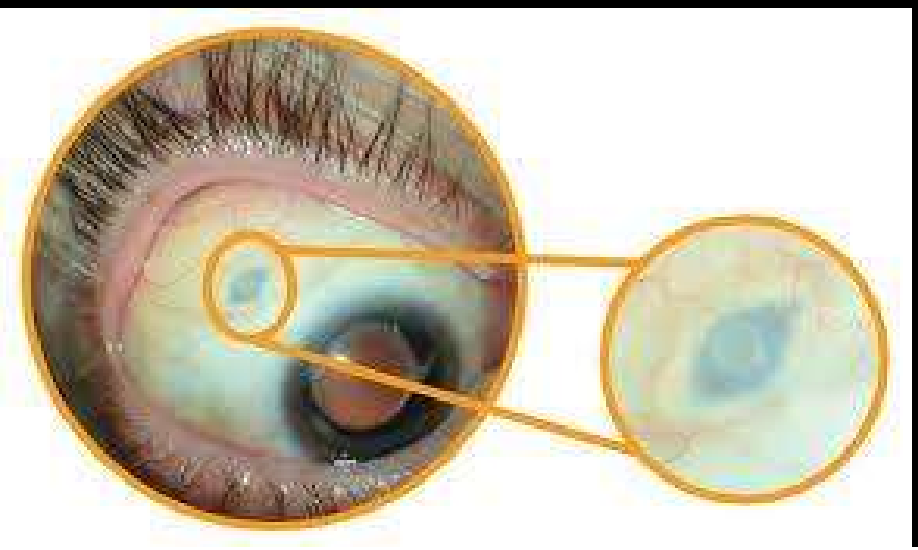
- Studies REQUIRE close f/u and strict protocols
- Once released from studies patients go back to "routine" care
- ASSESS (at Cole Eye Institute)
  - Trial with only 18 patients finishing year 3
  - Once treatment is "reduced" then vision drops
  - 5.5 to 16.7% at 20/200 or worse from 24 to 36 mos

What happens outside of a study

- Studies REQUIRE close f/u and strict protocols
- Once released from studies patients go back to “routine” care

How can we have longer duration?

- Genentech Port Delivery System (PDS)
- LADDER Study: :PHASE II reported
  - Refillable reservoir size of grain of rice surgically implanted
  - 63-80% didn't need refill for 6 mos depending on dosage
  - Comparable VA and macular thickness compared to injections
  - 50% gained at least 3 lines, 10% lost 3 lines



New Injections/drugs in trials

- Abicipar: Designed Ankyrin Repeat Protein (DARPin)
  - 8 and 12 wks vs monthly Ranibizumab enrolled
- Brolucizumab: Phase III complete. Smaller fragment
  - Approx 55% were able to go 12wks
  - HAWK/HARRIER: 6mg dose had better outcomes than Alfibercept at 2yrs: less fluid, longer intervals, and lower CST
- Pan 90806: topical formulation
  - Early promise, started Phase I in 5/18
- Faricimab by Genentech
  - Bi-phasic: Anti-VEGF and inactivator of Angiopoietin-2
  - Initial dosing at q16wks

What about topical treatments

- Squalamine gtts by Ohr Pharmaceuticals now in Phase 3 trial
- Phase 2 showed success and safety
  - Decrease in injections and improved vision
    - 40% vs 26% gain 3 lines
    - 11.0 vs 5.7 letters gained
  - Ultimately poor results and now not looking good

Results as reported from Phase II IMPACT study

GA Trials and Tribulations

- Lampilizumab
  - Injectable that failed in Phase 3
- Emixustat
  - Injectable that failed in trial
- Brimonidine
  - Topical or injectable: in trial
- APL-2 form Apellis
  - Injectable in phase 3 currently

What about a new oral for AMD?

- Statins are one of the most popular drug classes in the world for cholesterol
- Regression of HR AMD with Intensive Statin
  - 26 pts in study, 23 completed it on 80mg Atorvastatin monitored q3mo for at least 1 yr
    - 10/23 responders w 8/10 showing near resolution
    - Avg time to improvement is approx 11.5mos
    - None of pts developed to Adv AMD (calculator predicted 14%)
    - AMD response not related to Cholesterol response

Regression of AMD w Statin Tx. Vavvas et al. EBioMedicine. 2016.

New “news” on Aspirin

- Previous publications touting “dangers” of aspirin hastening conversion to CNVM
- More recently:
  - Long-term use of low-dose aspirin had no affect on incidence of NVAMD.

Rim et al. Long-term ASA and NVAMD. Ophth 2/2019.

What about long-term Lucentis f/u

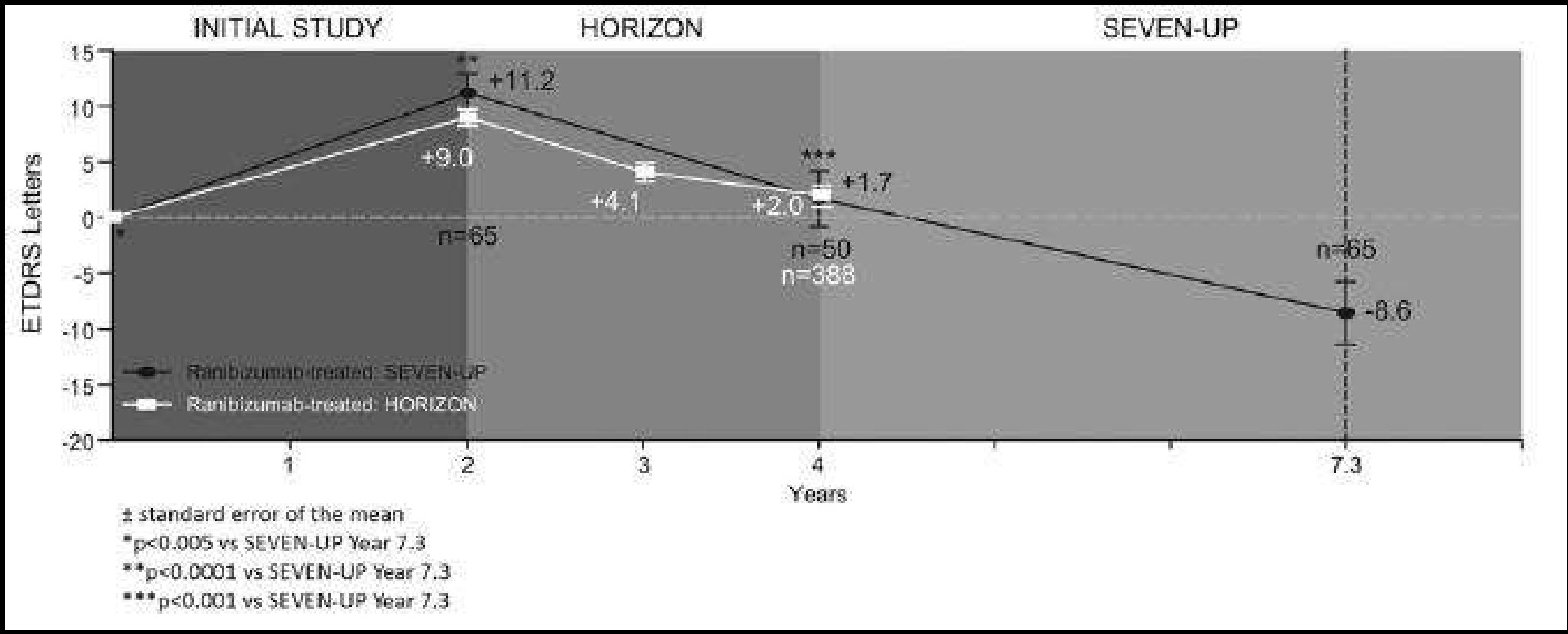
ARTICLE IN PRESS

Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON

A Multicenter Cohort Study (SEVEN-UP)

*Soraya Rofagha, MD, MPH,[1] Robert B. Bhisitkul, MD, PhD,[1] David S. Boyer, MD,[2] SriniVas R. Sadda, MD,[3] Kang Zhang, MD, PhD,[4] for the SEVEN-UP Study Group**

Not such a rosy bottom line..



What about GA?

- Underestimated impact on our patients

What's the best we have for now…

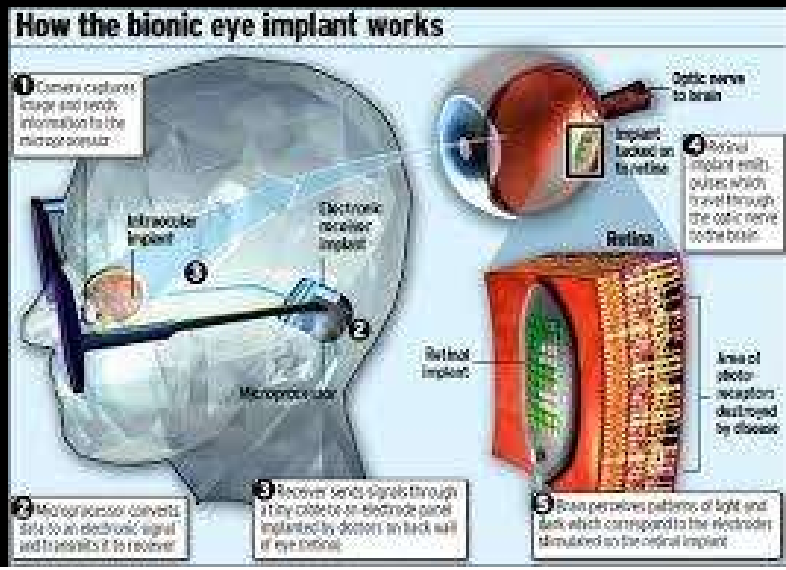
- Supplements
- Common questions I get:
  - When do you start supplements?
  - Is it worth supplementing early?
  - Should patients stop supplements when getting injections?

Topics to discuss

- Weight status
- Diet
  - Glycemic index
  - Fruits/veges
  - Fatty cold water fish
- Smoking
- Physical activity
- General health

When Medical treatment fails…

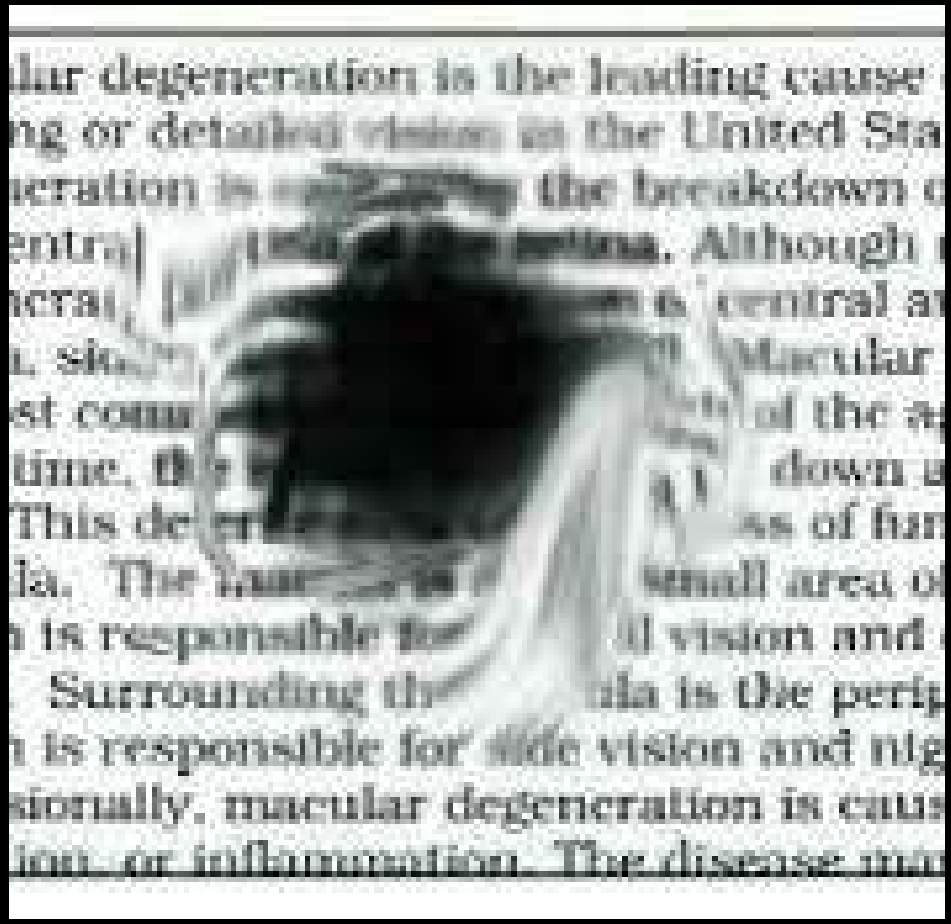
- Low vision is an important option
  - Traditional and newer / digital devices
    - ORCAM
  - Surgical options on the horizon
    - ARGUS2 retinal implant
  - Associations and support groups (MDA)



What if vision gets bad?

What about driving?

What about reading?



Low Vision options

Traditional bioptic

Function for those with POOR vision: Used for AMD in Australia

OrCam

- “reader” that can be connected to most frames
- Reads words on boxes, pages, signs
- Has ability to recognize specified items (money, products, faces…)
- Based on technology used to create driverless cars

OrCam in action

So….

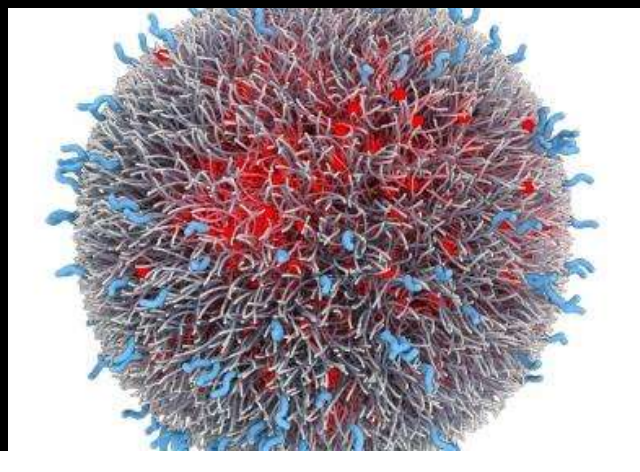
Find early…detect and alert…and do something!

Thank You!

Jeffry D. Gerson, O.D., F.A.A.O.
jgerson@Hotmail.com

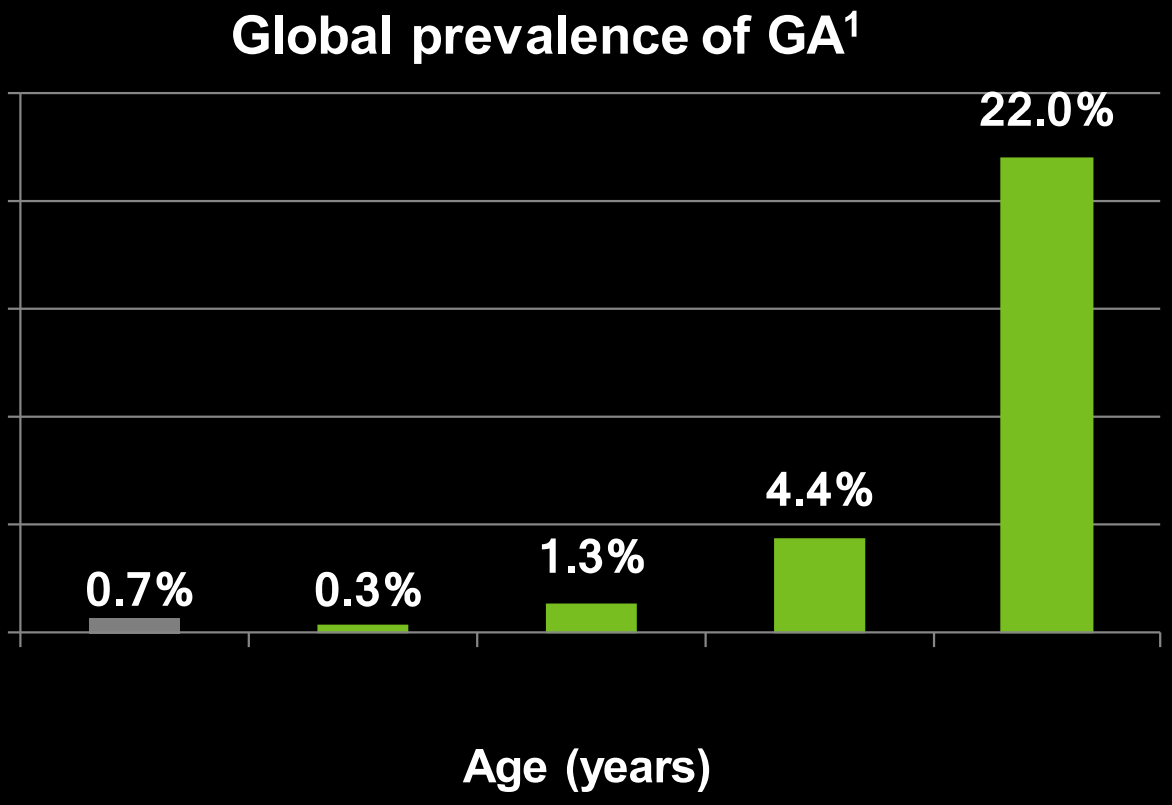
Nanoparticles

- Definition: Something less than 100 nanometers in size
  - A nanometer is 1 billionth of a meter (>25,000,000 /inch)
- Nanoparticles can be loaded w Avastin to deliver via drops to posterior segment[1]
- "The development of eye drops that can be safely and effectively used in patients would be a magic bullet – a huge breakthrough".



1. Davis et al. Topical Avastin in vivo. Small 3/14 Epub.

Significant Unmet Need for Treatment of Geographic Atrophy



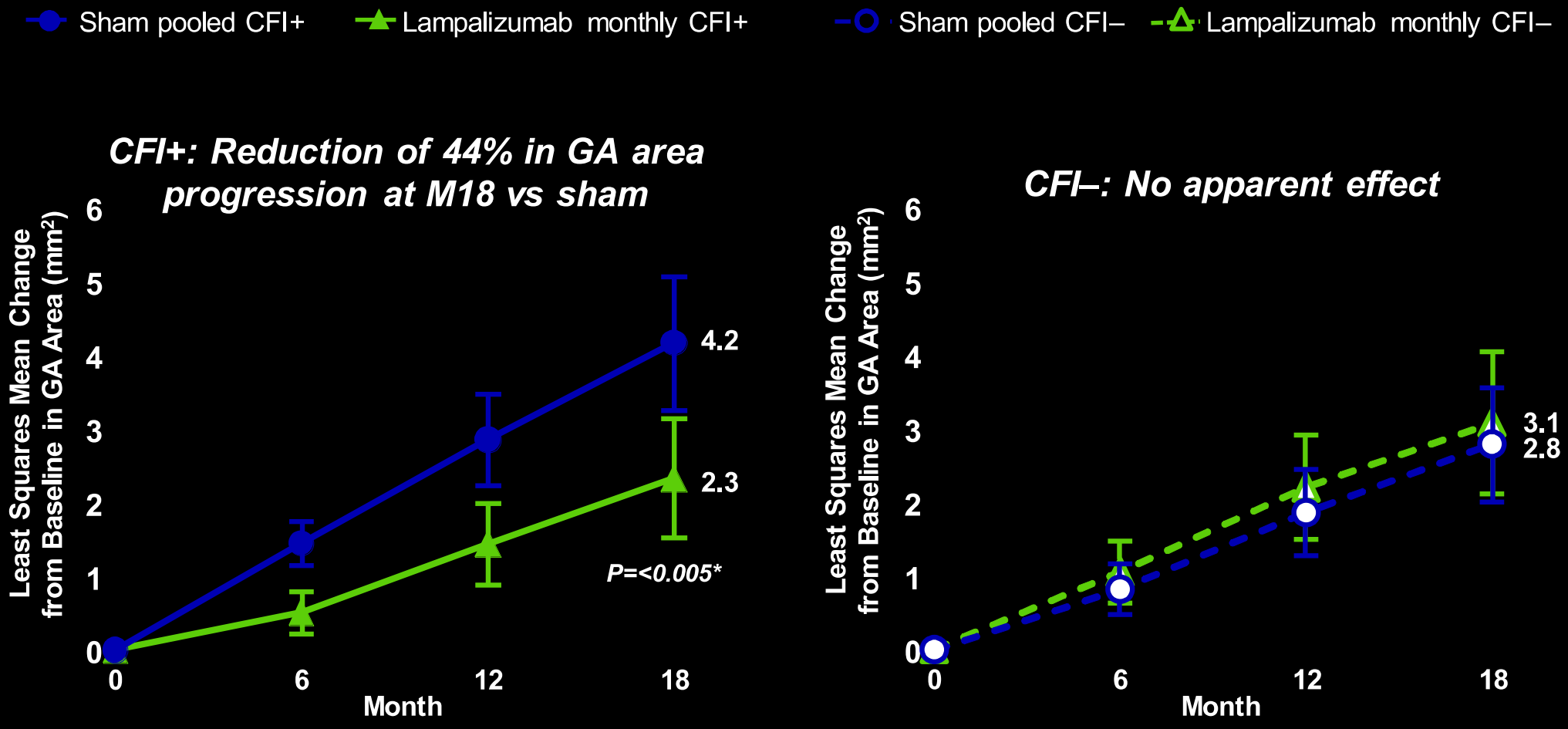
- GA currently affects more than 5 million people worldwide[1]
- Changes in alternative measures of visual function may be identified before deterioration in BCVA occurs[2]

1. Wong WL, et al. *Lancet Glob Health* 2014;2:e106-16; 2. Sunness JS, et al. *Ophthalmology* 1997;104:1677-91.

Differential Treatment Response: CFI+ vs CFI– Monthly Groups

Response to lampalizumab observed in the CFI+ group but not in the CFI– group

- The CFI biomarker may also be predictive of lampalizumab treatment response



*Not adjusted for multiplicity.

Conclusions

- MAHALO is the first study to demonstrate a positive treatment effect in GA due to AMD
- At the Month 18 endpoint:
  - 20% reduction in GA area progression in the lampalizumab monthly all-comers population vs sham
  - 44% reduction in GA area progression in the lampalizumab monthly CFI+ subpopulation vs sham
  - 18% reduction in GA area progression in the lampalizumab every other month CFI+ subpopulation vs sham
- Phase III trials are now enrolling based on positive phase II results

AMD Progression Leads to Permanent Central Vision Loss

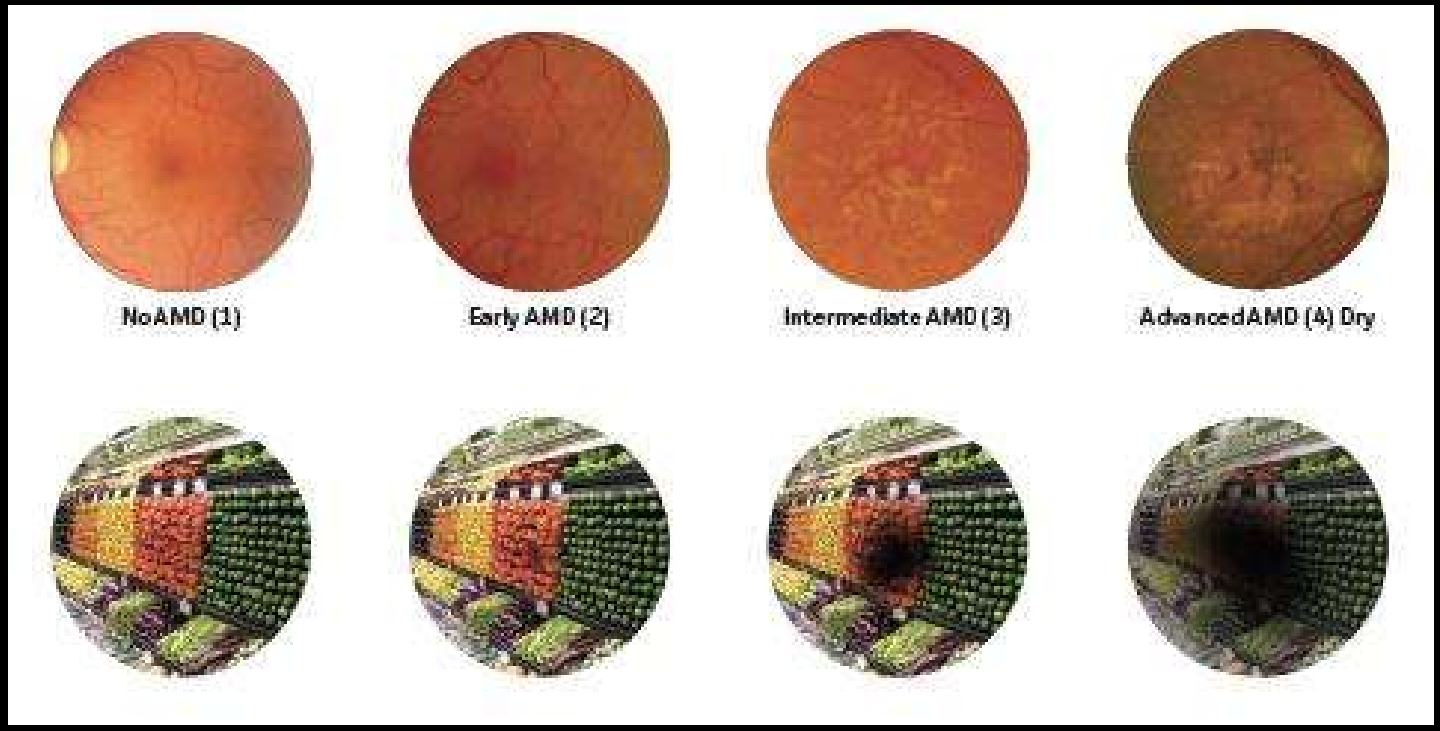
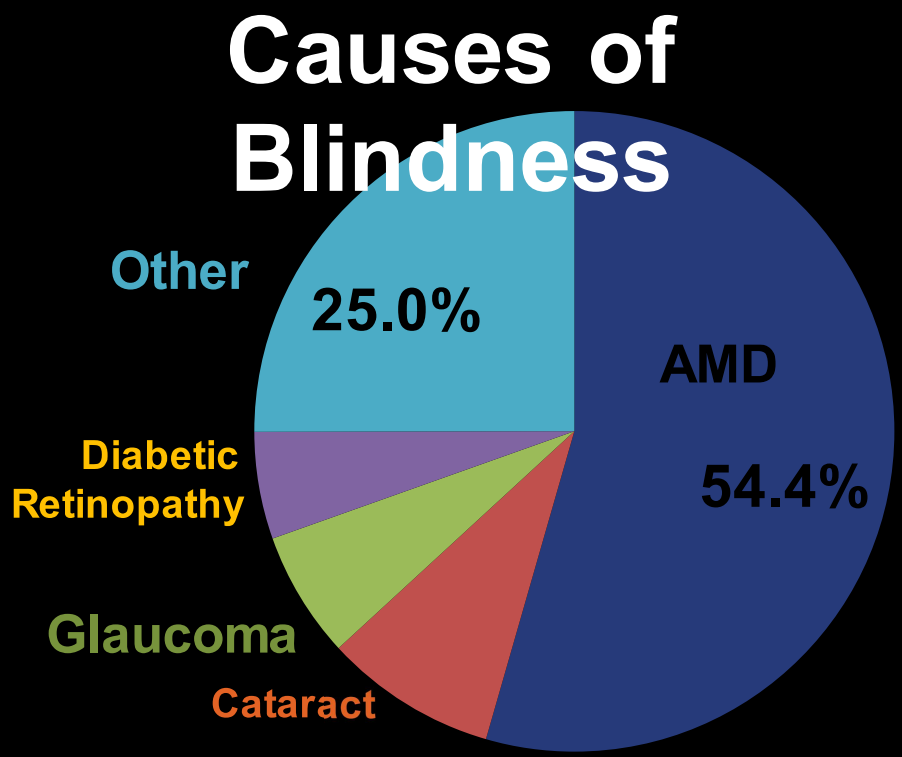


Image: Data on file. Bausch & Lomb Inc; Rochester, NY.

AMD: The Leading Cause of Blindness for Those Aged 65+

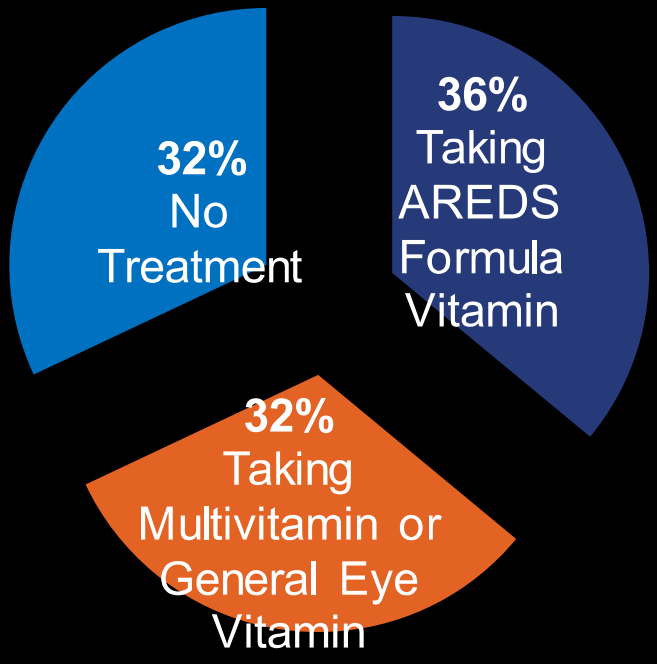


AMD=age-related macular degeneration.
Congdon N et al. *Arch Ophthalmol*. 2004;122:477-485. Friedman DS et al. *Arch Ophthalmol*. 2004;122(4):564-572.

64% of Patients with Moderate to Advanced AMD are Not Taking an AREDS Formula Vitamin

Key Barriers

- Lack of awareness of vitamins based on the AREDS Study
- Lack of doctor recommendation



Each patient not on an AREDS formula vitamin is an opportunity to do the right thing

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study.
IRI AMD Custom Survey, April 2017 n=347