Macular Degeneration Updates

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Financial Disclosures

- NONE

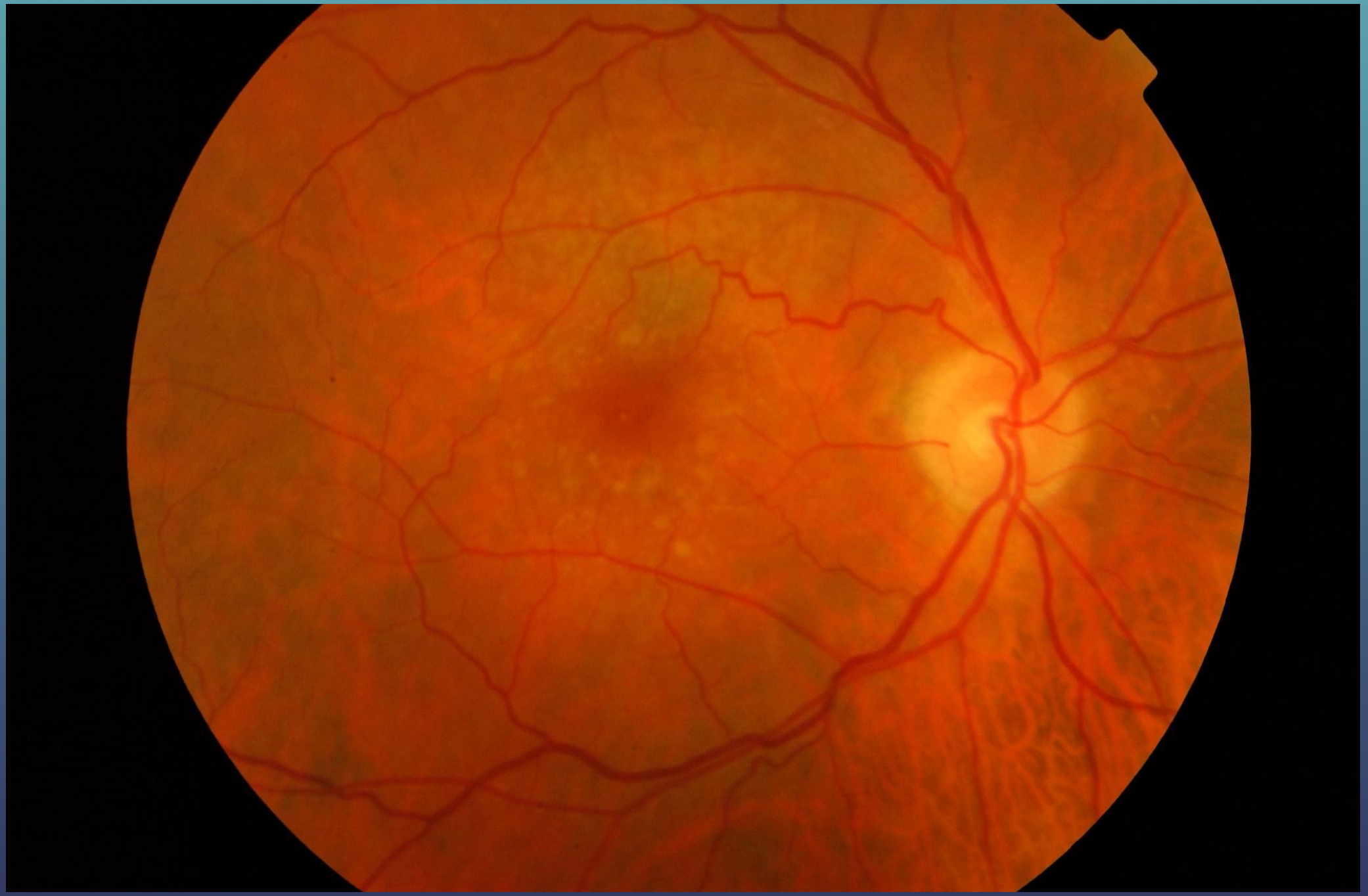
Overview

- Dry AMD
- Wet AMD
- Current Therapies
- Future Therapies
- ForeseeHome

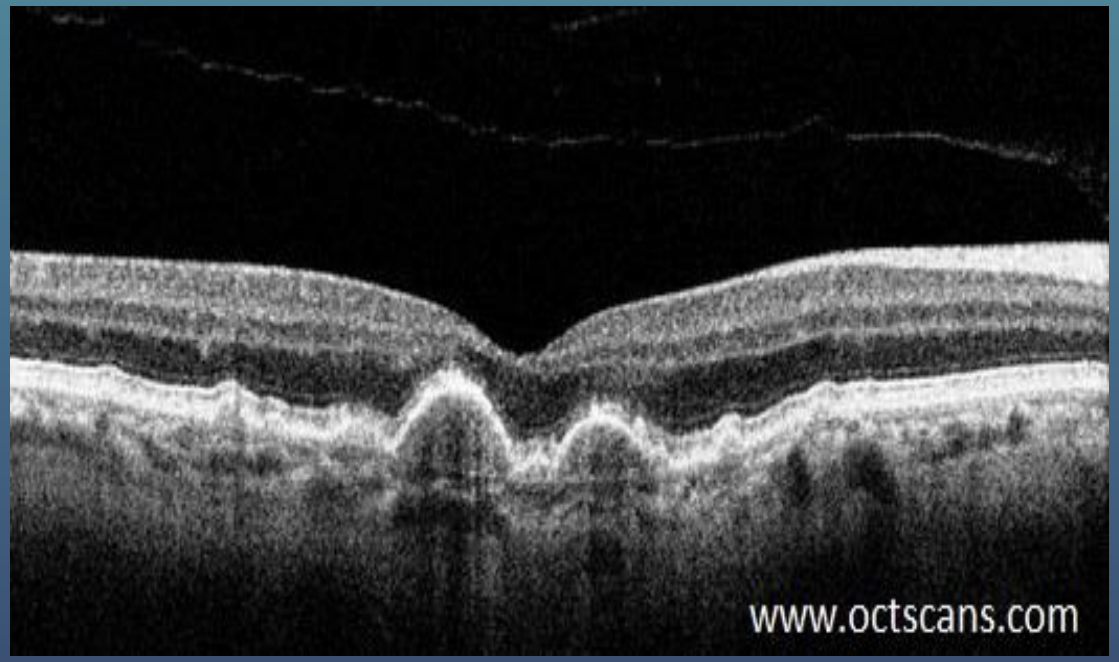
AMD Demographics

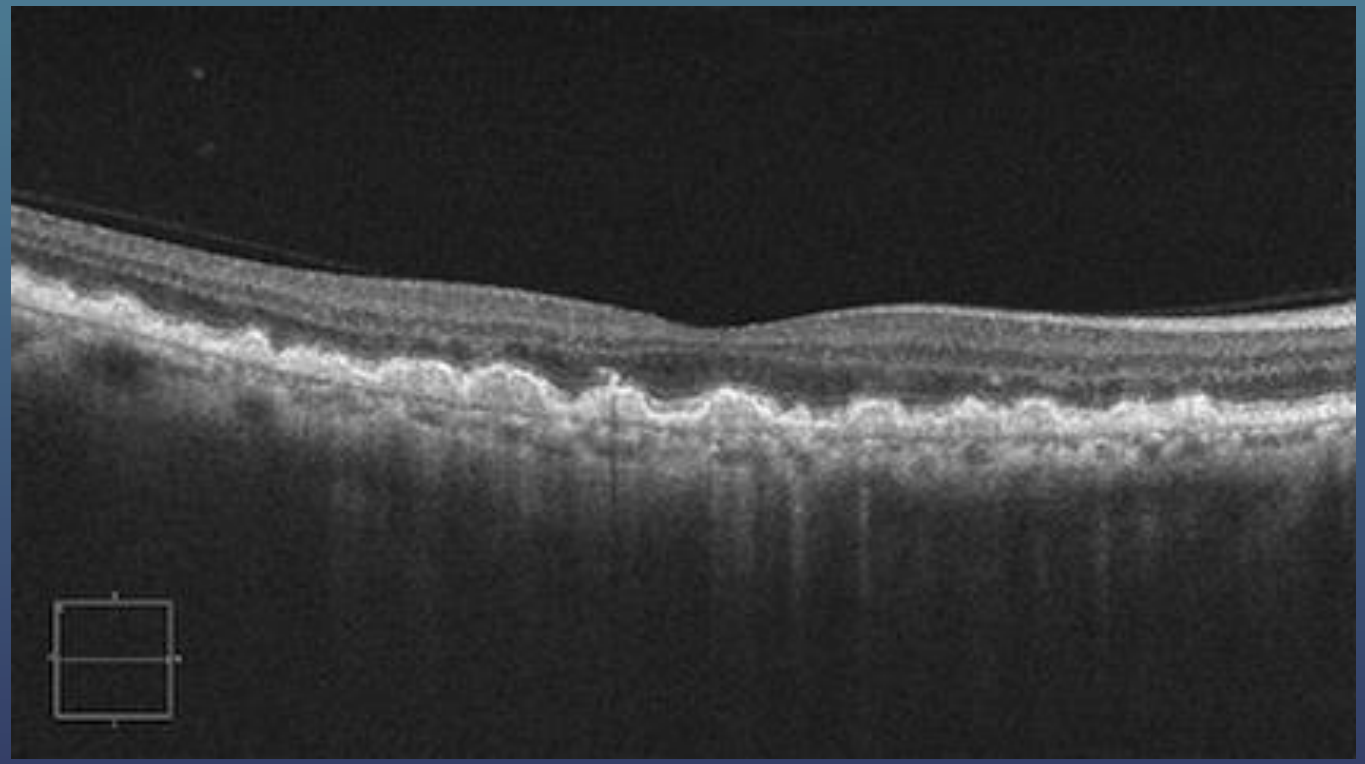
- NEI: 15 million Americans have AMD
- Leading cause of vision loss in adults 60 or older

AMD



AMD



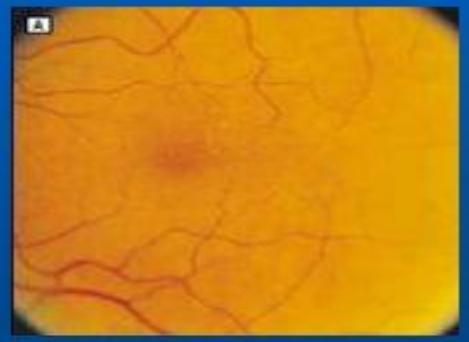


Risk Factors

- Family history of the disease
- Smokers
- Obese
- High blood pressure
- More common in Caucasians
- Over 50 years old

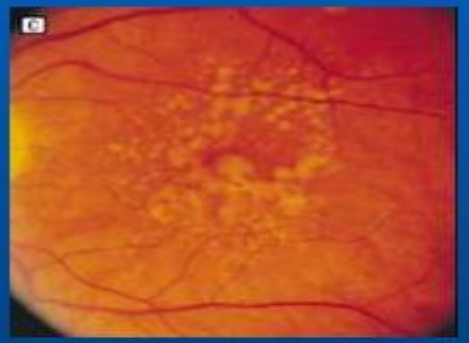
Age-Related Macular Degeneration (AMD)

Early



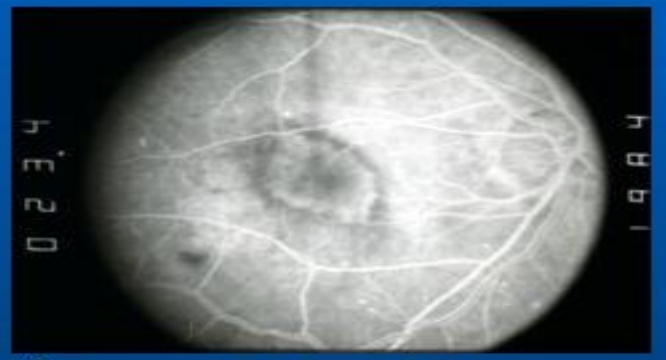
Multiple small or a few intermediate drusen

Intermediate

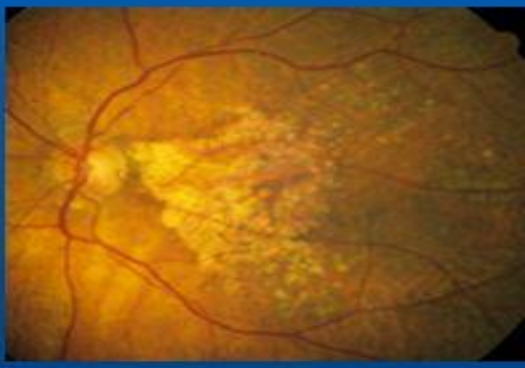


Extensive intermediate drusen

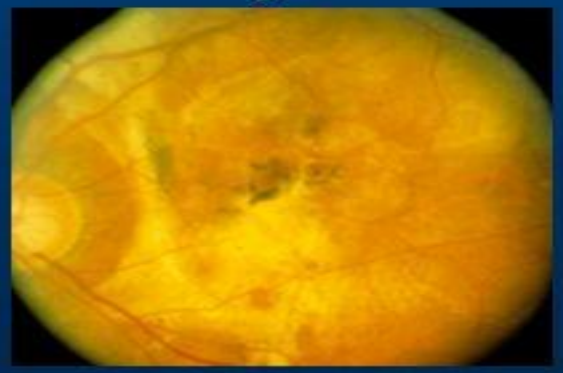
Advanced



Choroidal Neovascularization



Geographic Atrophy



Subretinal Fibrosis

AMD

- Presence of at least intermediate size drusen (>63 um)

AMD

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  - 125 µm is the width of an average large vein at the disc margin

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- RPE changes (hypo/hyperpigmentation)

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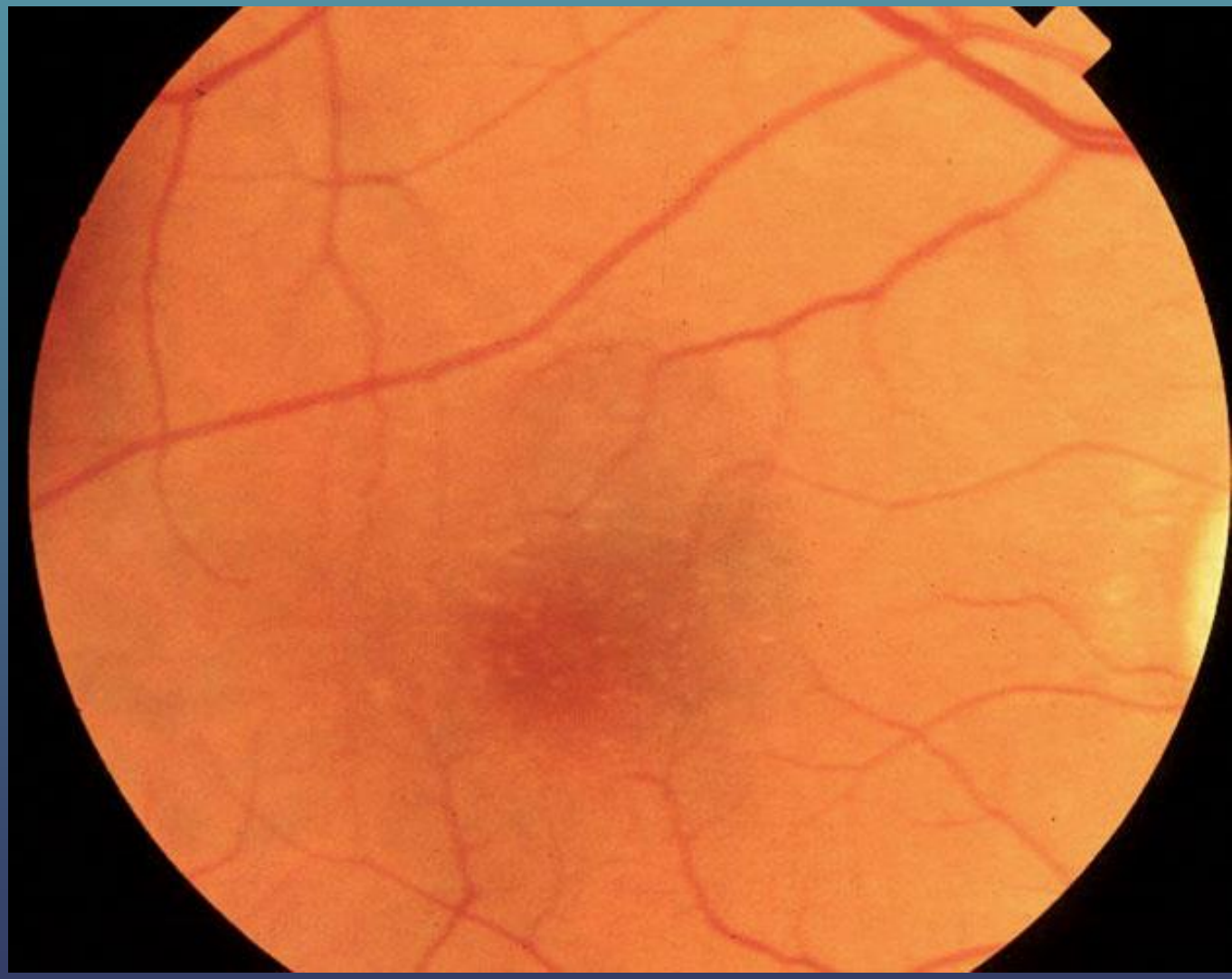
- Reticular pseudodrusen

AMD

- Presence of at least intermediate size drusen (>63 um)
  - 125 µm is the width of an average large vein at the disc margin
- RPE changes (hypo/hyperpigmentation)
- Reticular pseudodrusen
- Presence of any of the following
  - GA
  - Choroidal Neovascularization
  - Polypoidal choroidal vasculopathy
  - Retinal angiomatous proliferation

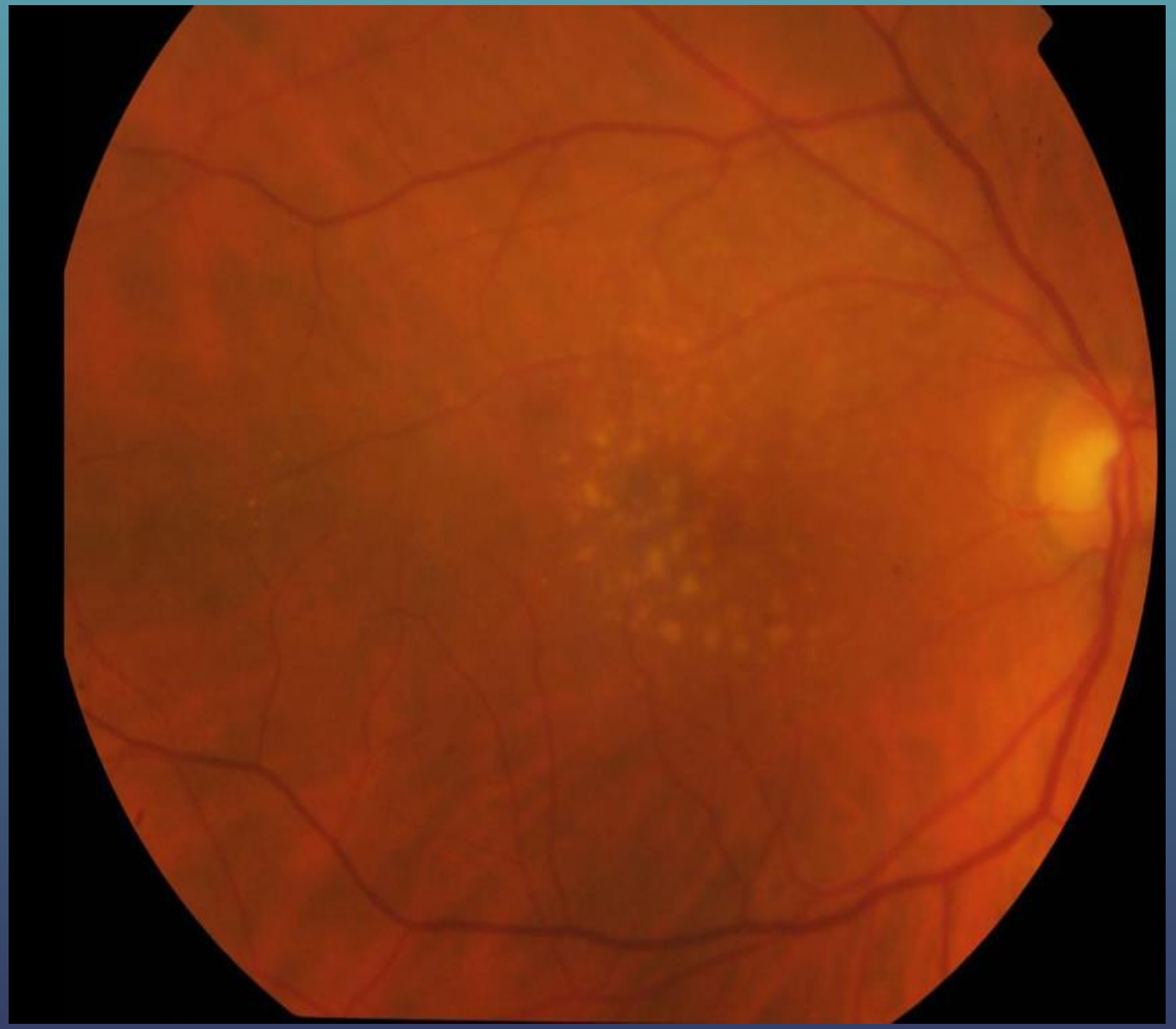
Early AMD

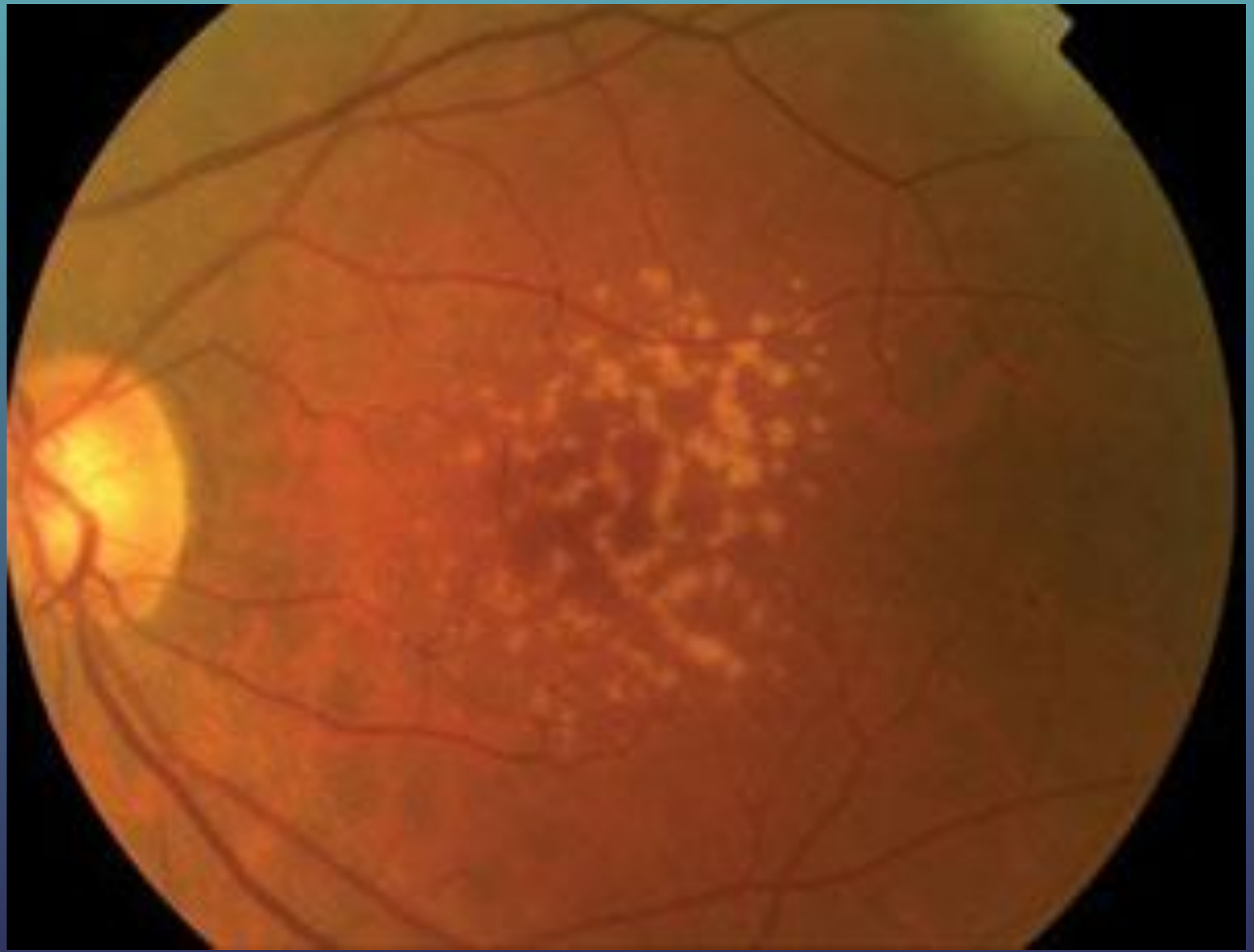
- Multiple small drusen (<63 um)
- A few intermediate drusen (63-124 um)
- Mild RPE abnormalities



Intermediate AMD

- Numerous intermediate drusen
- At least one large druse (>125um)
- Geographic atrophy not involving the center of fovea



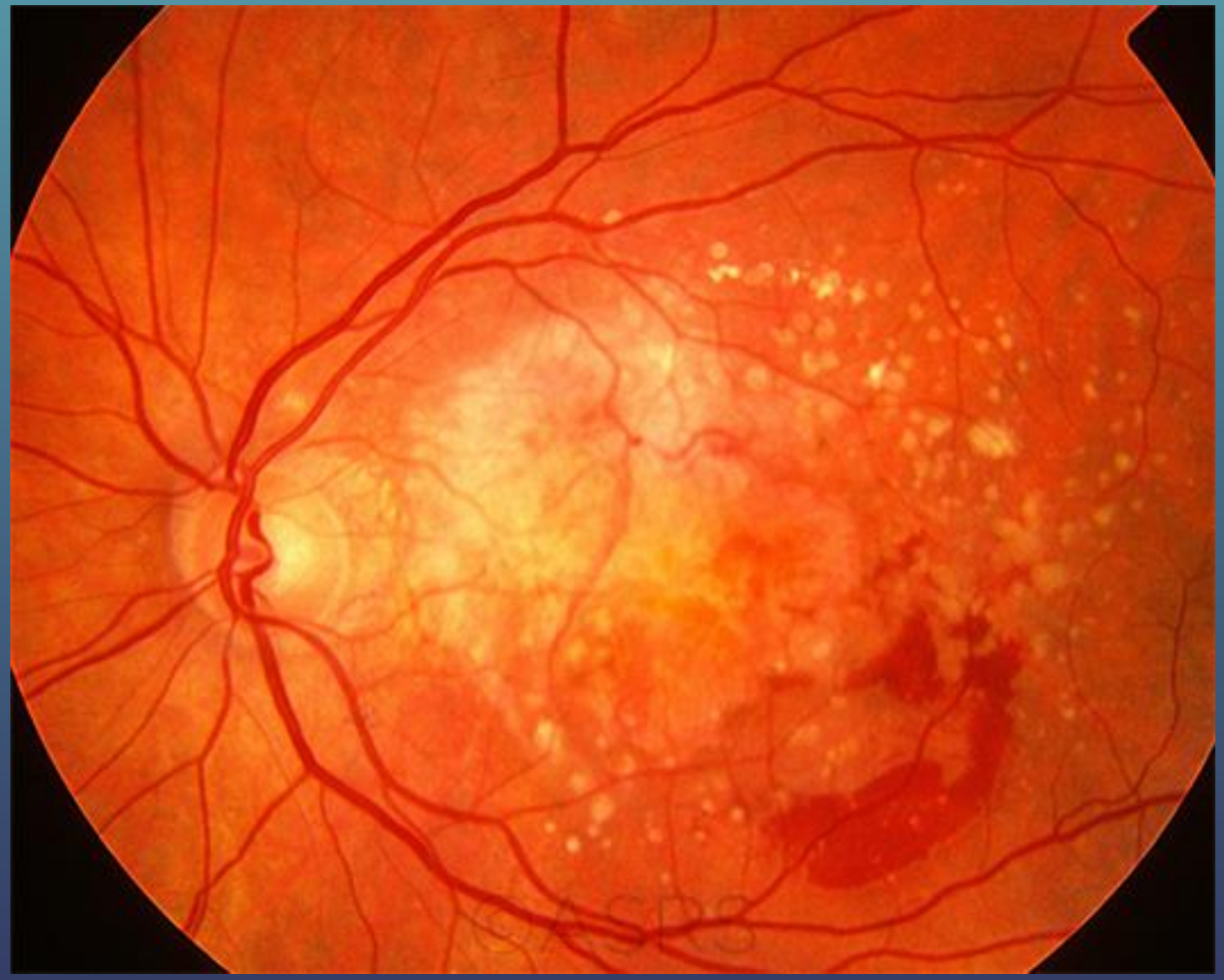


Advanced AMD

- GA involving foveal center

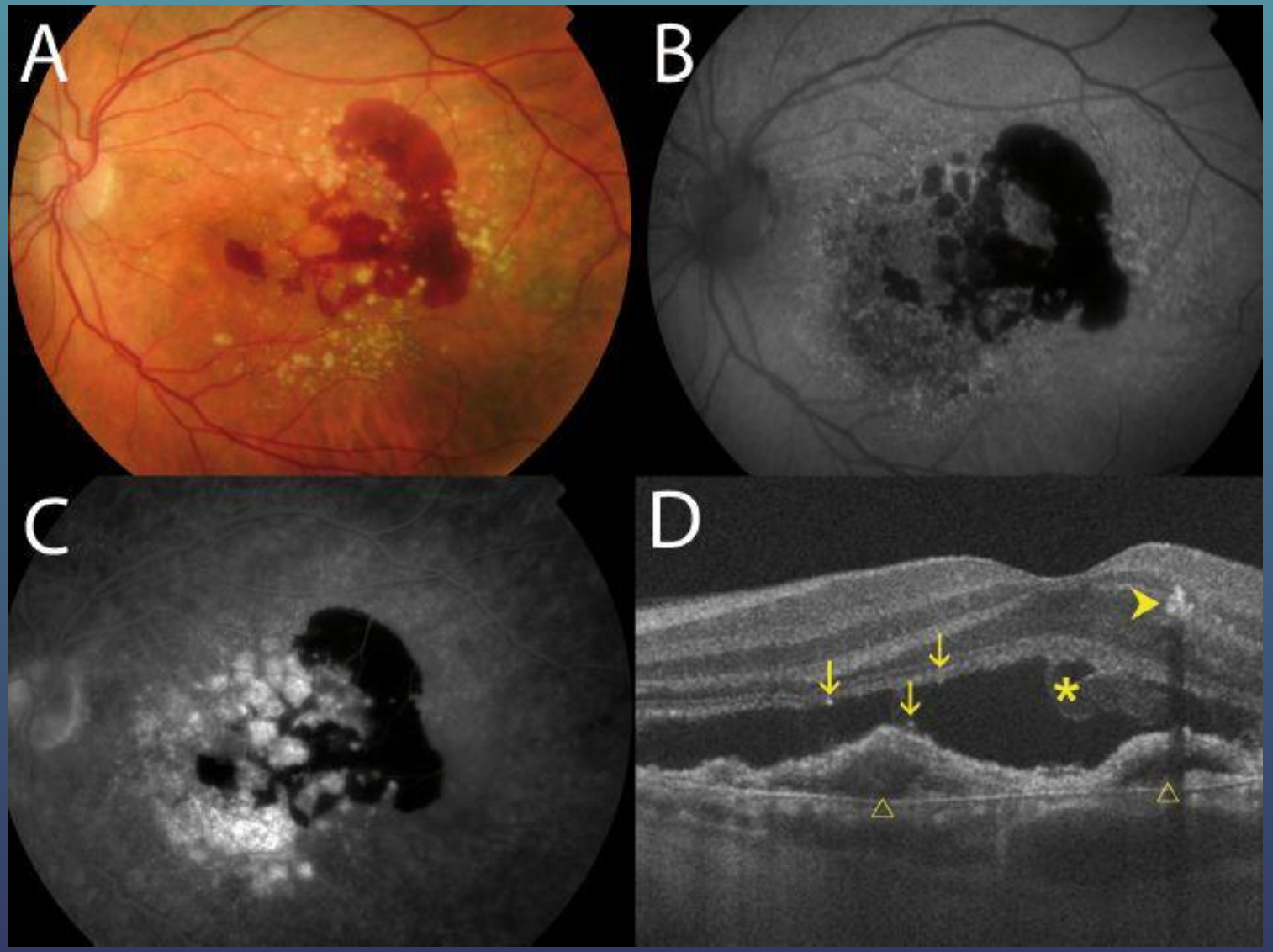
Advanced AMD

CNV



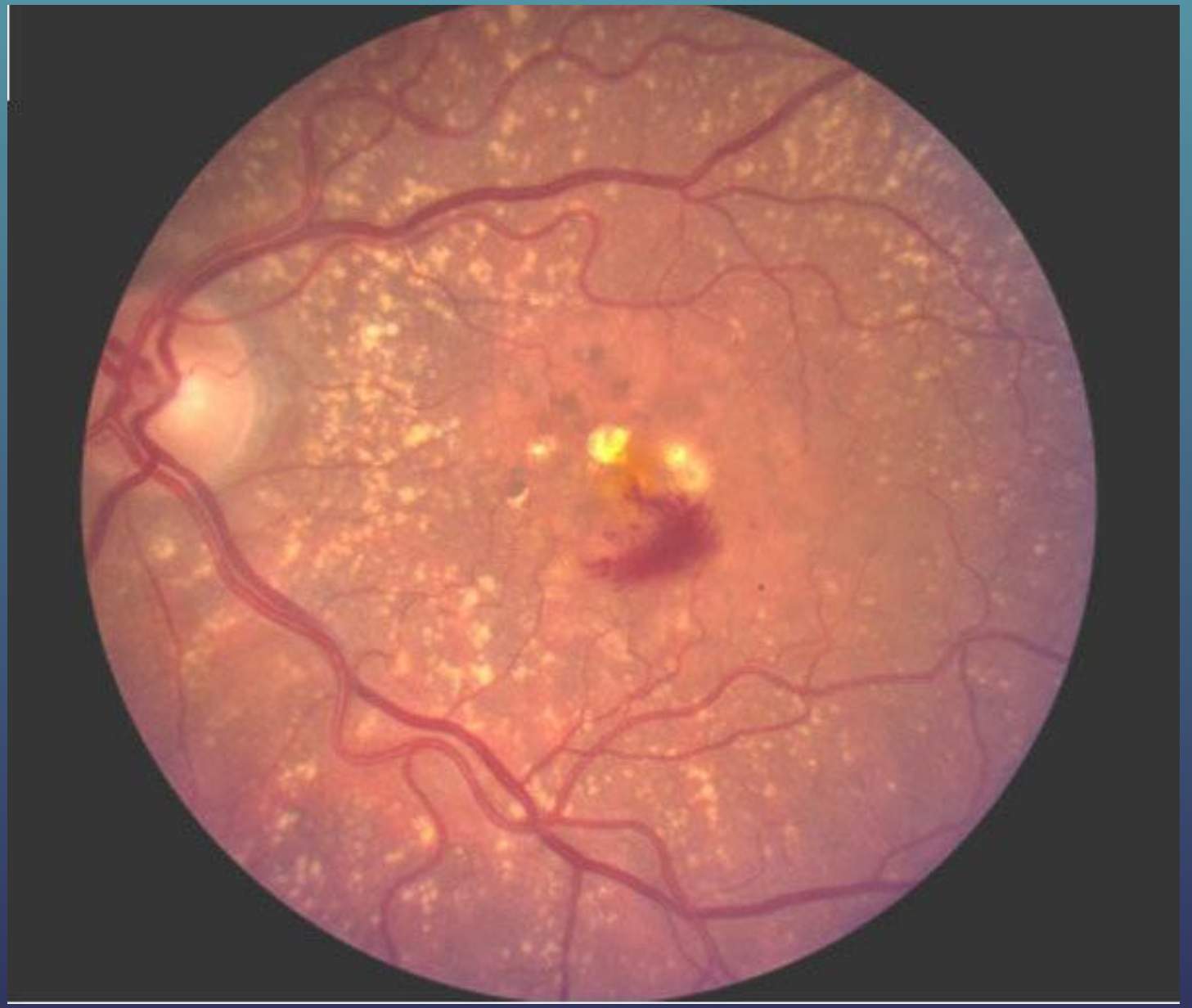
Advanced AMD

Serous and/or hemorrhagic detachment of neurosensory retina or RPE



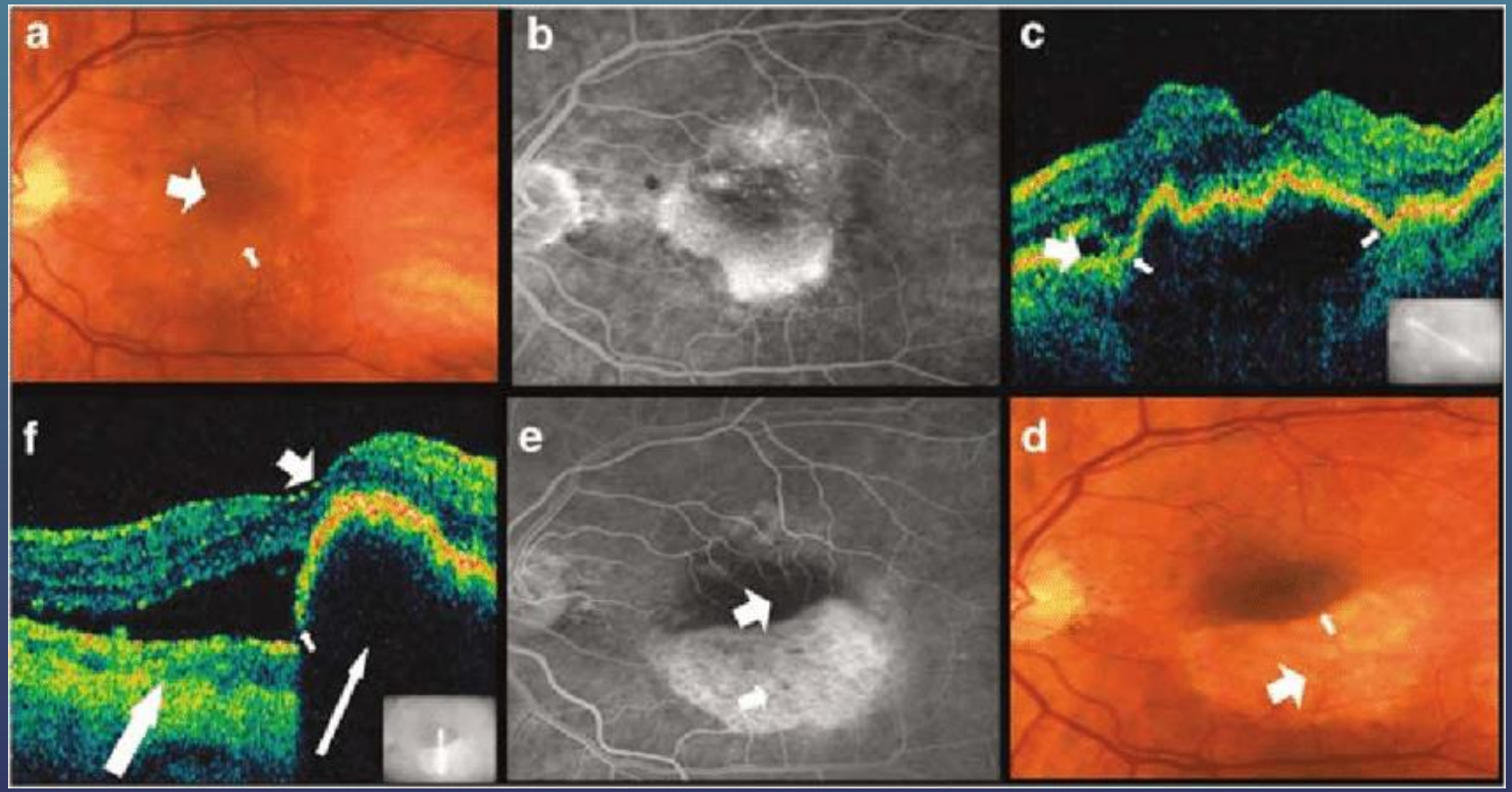
Advanced AMD

Retinal Hard Exudates (2/2 chronic intravascular leakage)



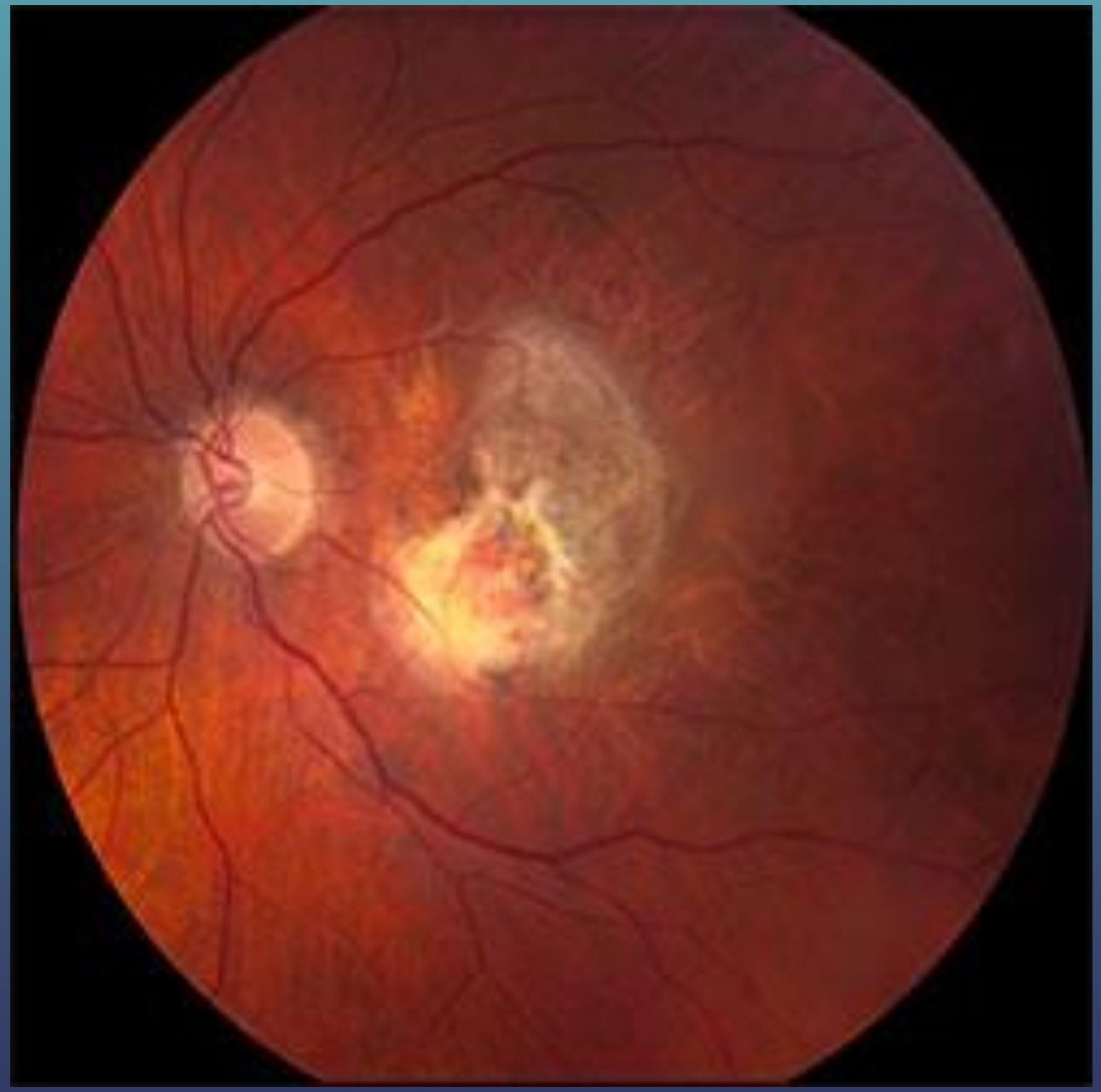
Advanced AMD

Subretinal and sub-RPE fibrovascular proliferation

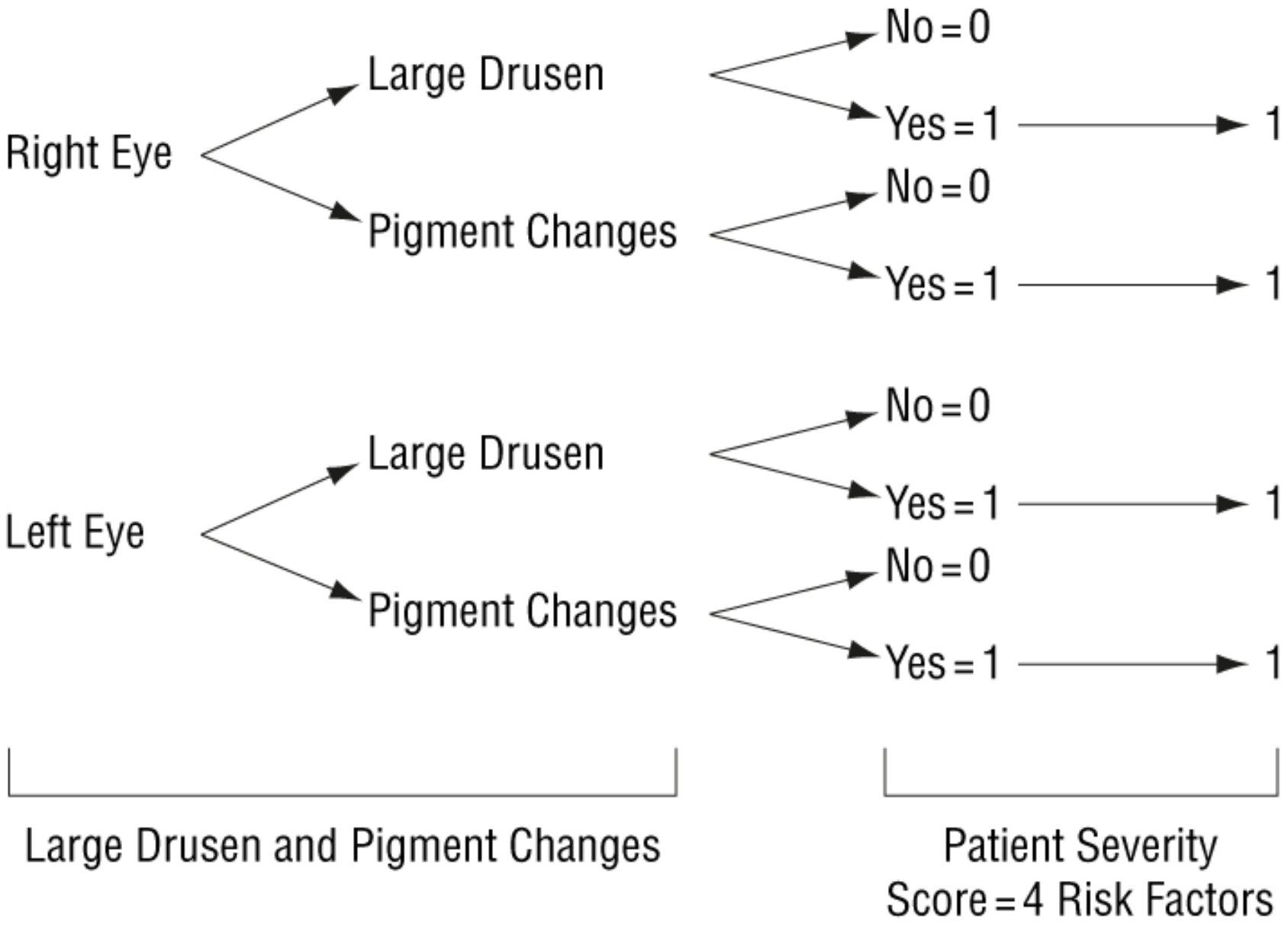


Advanced AMD

Disciform Scar



Simplified Severity Scale

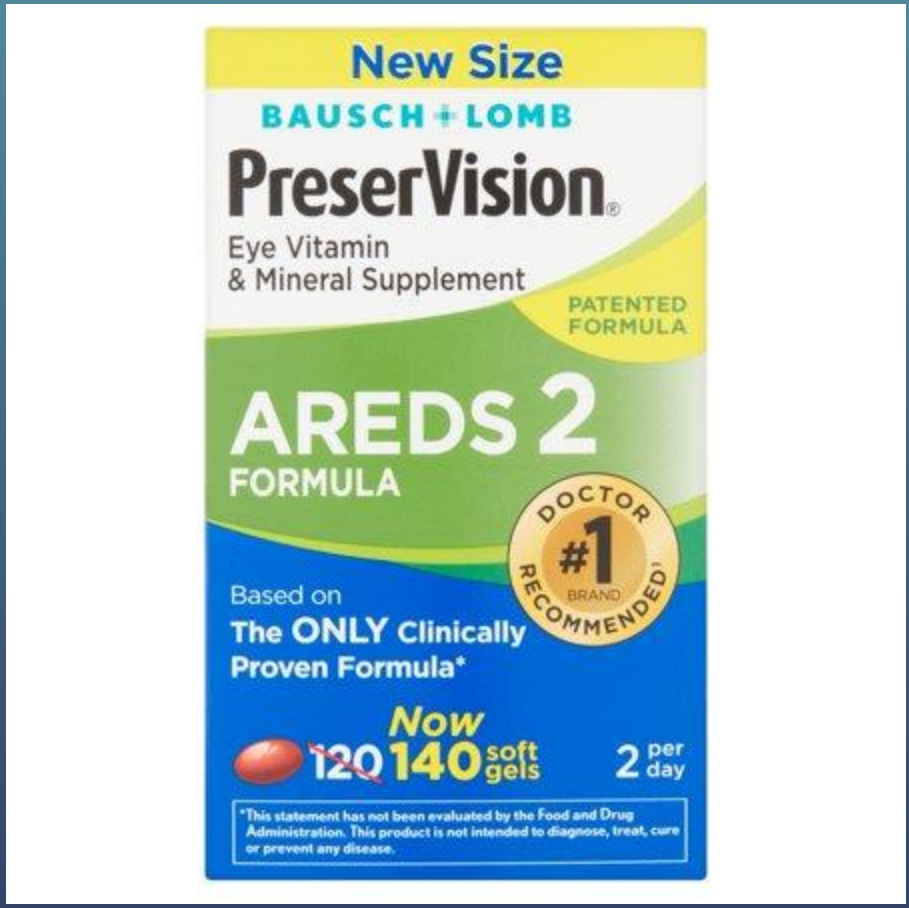

Right Eye
Large Drusen
No = 0
Yes = 1
1
Pigment Changes
No = 0
Yes = 1
1
Left Eye
Large Drusen
No = 0
Yes = 1
1
Pigment Changes
No = 0
Yes = 1
1
Large Drusen and Pigment Changes
Patient Severity
Score = 4 Risk Factors

Five-Year Rates of Advanced AMD (In One or Both Eyes for Patients With Both Eyes at Risk)

	Patients Without Advanced AMD in Either Eye at Baseline*			Patients with Advanced AMD in One Eye at Baseline†		
Risk Factors	No. at Risk	No.	%	No. at Risk	No.	%
0	1466	6	0.4			
1	635	20	3.1			
2	455	55	11.8	149	22	14.8
3	328	85	**25.9**	178	63	**35.4**
4	317	150	**47.3**	273	145	**53.1**

Dry AMD Treatment:

- Antioxidant vitamin and mineral supplementation as per AREDS/AREDS2 trials should be considered in patients with intermediate or advanced AMD

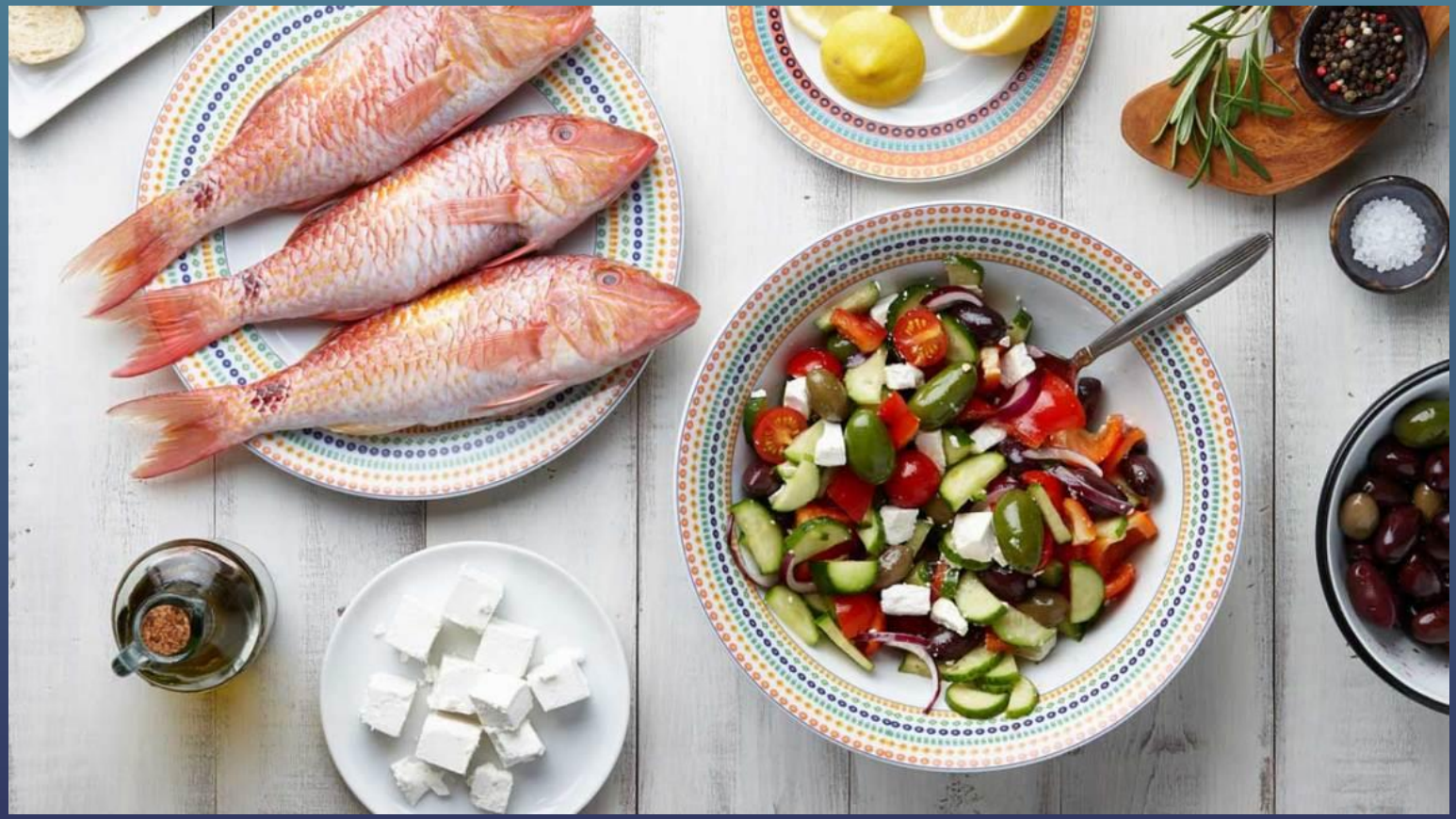


Supplements	Amount (QD)		Comments (percentage DV*)
	AREDS2	AREDS	
Vitamin C	500 mg	500 mg	840
Vitamin E	400 IU	400 IU	1340
Zinc	80 mg	80 mg	540
Copper	2 mg	2 mg	100
Beta-carotene	X	15 mg	**
Lutein	10 mg	X	**
Zeaxanthin	2 mg	X	**

*Percentage DV based on a 2000-calorie diet, **DV not established.
DV=Daily value; AREDS2=Age-related eye disease study 2; AREDS=Age-related eye disease study

Dry AMD Treatment:

- Eat a well balanced diet, rich in fruit, vegetables, Mediterranean diet




GLOBAL HEALING CENTER
9 Health Benefits
of a Vegetarian Diet

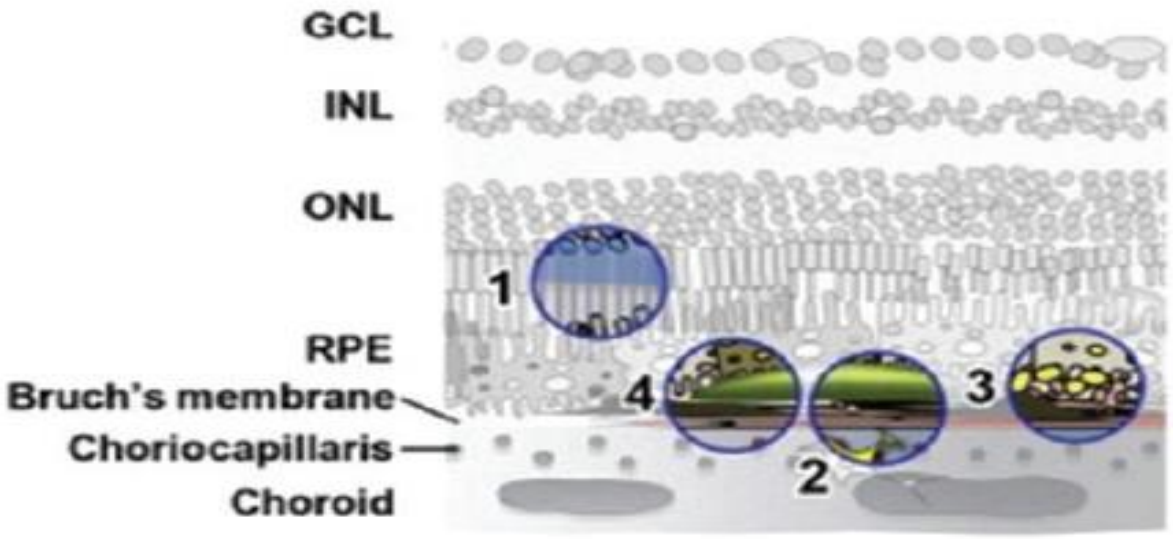
Dry AMD Treatment:

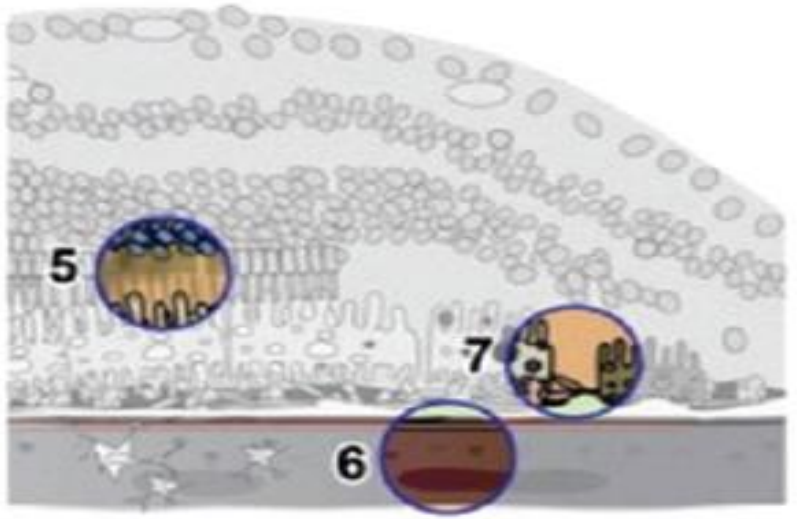
- Exercising 3x/week can decrease risk of wet AMD by 70%

Dry AMD Possible Future Treatments:

- Lampalizumab
- APL-2 (complement C3 inhibitor): Pending Phase 3
- Brimonidine
- Atorvastatin
- Photomodulation
- Minocycline

Pathways and Therapeutic Targets in Dry AMD





1. **Visual cycle toxic by-products**
   - Visual cycle modulators
2. **Inflammation, complement, and ECM**
   - mTOR inhibitors
   - Complement inhibitors
   - MMP inhibitors
3. **Lipoprotein accumulation**
   - LDL-lowering drugs
4. **Beta-amyloid accumulation**
   - Anti-amyloid beta
5. **Oxidative stress**
   - Anti-oxidants
   - Neuroprotectant
6. **Choriocapillaris atrophy**
   - Choroidal perfusion enhancers
7. **RPE and photoreceptor loss**
   - Stem cell therapy
   - Neurotrophins

Drugs	Mechanism of action	Sponsor	Trial subjects	Clinical phase	Clinical trial identifier
Trimetazidine	Anti-ischemic agent with cytoprotective effects (oral)	Institut de Recherches internationales Servier	Drusen in study eye, wet AMD in follow eye	Phase III	ISRCTN99532788 (completed - not published)
MC-1101	Increase choroidal blood flow (topical)	MacuCLEAR	Dry AMD	Phase II/III	NCT02127463 (ongoing)
NT-501:encapsulated CNTF	Neuroprotection: rescues photoreceptors from degeneration (intravitreal)	Neurotech Pharmaceuticals	Geographic atrophy	Phase II	NCT00447954 (completed at April, 2011)
Brimonidine tartrate	Neuroprotection: alpha-2 adrenergic receptor agonist (intravitreal)	Allergan	Geographic atrophy	Phase II	NCT00658619 (completed at March, 2013)
Tandospirone (AL-8309B)	Neuroprotection: 5-HT1A receptor agonists (selective serotonin 1A receptor agonist) (topical)	Alcon	Geographic atrophy	Phase III	NCT00890097 (terminated at June 2014)
RN6G	Neuroprotection: binds and eliminates amyloid β (IV)	Pfizer	Geographic atrophy	Phase I	NCT00877032 (completed - not published at March, 2015) NCT01003691 (completed at March, 2013)
GSK 933776	Neuroprotection: binds and eliminates amyloid β (INF)	GSK	Geographic atrophy	Phase II	NCT01342926 (ongoing)
Fenretinide	Visual cycle inhibitors: Retinol analog inhibits binding of retinol (oral)	Sirion Therapeutics	Geographic atrophy	Phase II	NCT00429936 (completed at June 2010)
Emixustat HCl (ACU-4429) SEATTLE	Visual cycle inhibitors: Nonretinoid inhibits isomerization of retinol (oral)	Acucela	Geographic atrophy	Phase II Phase II/III	NCT01002950 (completed at Feb, 2014) NCT01802866 (ongoing)

CNTF=Ciliary neurotrophic factor; IV=Intravenous; AMD=Age-related macular degeneration; INF=Interferon; GSK=GlaxoSmithKline

Drugs	Mechanism of action	Sponsor	Trial subjects	Clinical phase	Clinical trial identifier
POT-4/AL-78898A	Inhibits complement component 3 (intravitreal)	Potentia/alcon	Wet AMD Advanced neovascular lesions	Phase I	NCT00473928 (completed at March, 2010)
ARC1905	Aptamer against complement component 5 (intravitreal)	Ophthotech	Geographic atrophy and/or drusen	Phase I	NCT00935883 (completed at November, 2013)
Eculizumab	Monoclonal Antibody against complement component 5 (IV)	Alexion	Geographic atrophy and/drusen	Phase II	NCT00935883 (completed at January, 2015)
FCFD4514S	Fab derived from a monoclonal antibody against complement factor D (intravitreal)	Genetech/Roche	Geographic atrophy	Phase I	NCT00973011 (completed at February, 2012)
Glatiramer acetate (Copaxone, Teva)	Induces glatiramer acetate-specific suppressor T-cells and downregulates inflammatory cytolines (subcutaneous)	Kaplan Medical Center New York Eye and Ear Infirmary	Drusen	Phase II, III Phase I	NCT00466076 (unknown April, 2007) NCT00541333 (suspended at May 2013)
Fluocinolone acetonide (iluvien)	Glucocorticoid-mediated Suppression of inflammation (intravitreal)	Alimera sciences	Geographic atrophy	Phase II	NCT00695318 (terminated at May 2015)
LFG 316	Inhibits complement component 5 (intravitreal)	Novartis	Geographic atrophy Dry AMD	Phase II	NCT01527500 (completed at December, 2015)
TA 106	Antigen-binding fragment from a monoclonal antibody against complement factor B	Taligen Therapeutics	Dry AMD	Preclinical	None

IV=Intravenous; AMD=Age-related macular degeneration

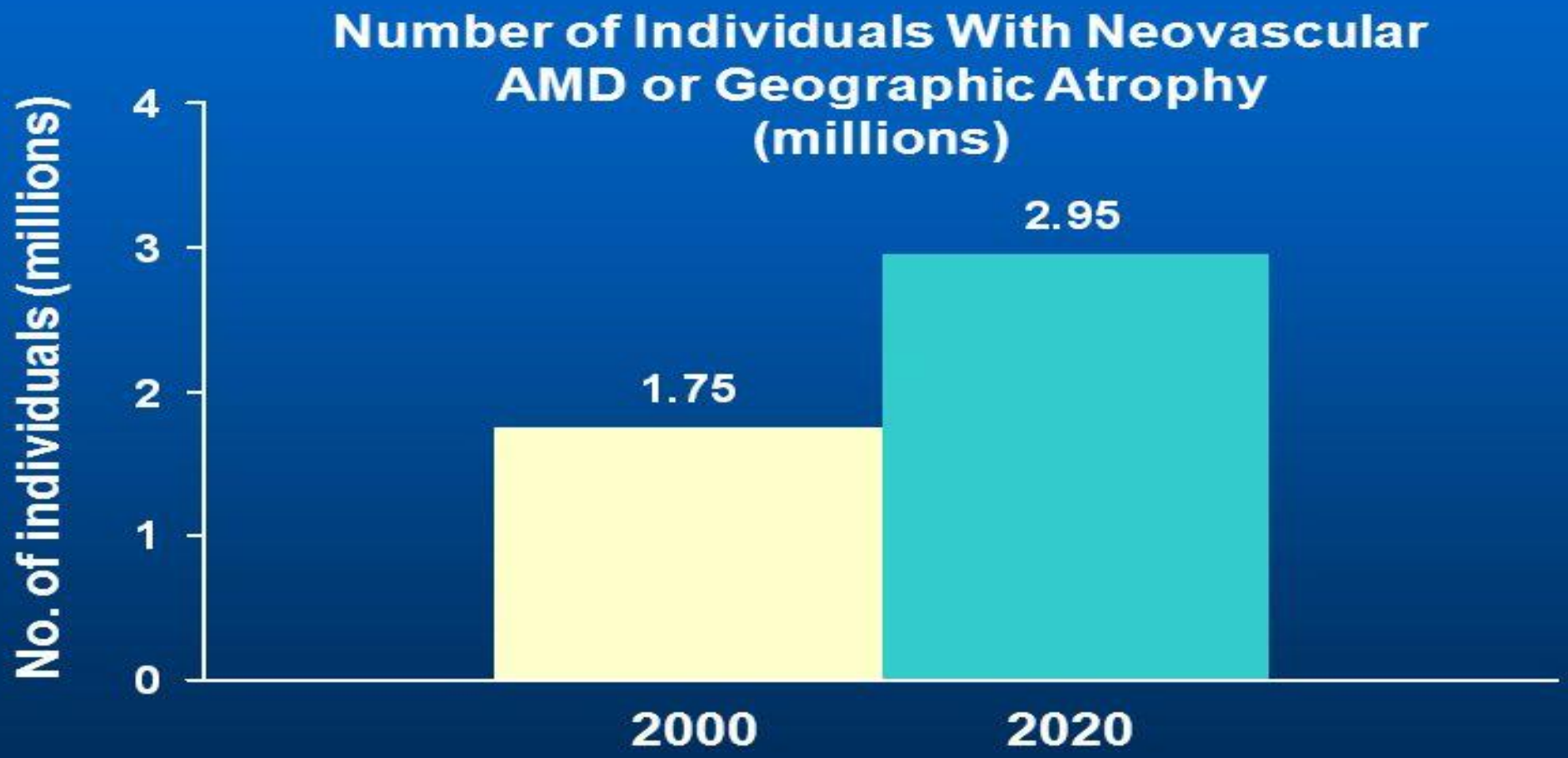
GA trials:

- Prevention of progression to GA
- Slow down the growth of GA
- Bringing back whatever has been lost in GA

Wet AMD

- Although around 80% of AMD patient have dry AMD, the wet form is responsible for 90% of severe vision loss associated with AMD.

Advanced AMD
Major Public Health Problem



Wet AMD

- The hallmark feature of the wet or neovascular form of age-related macular degeneration (nvAMD) is the **presence of choroidal (or retinal) neovascularization (CNV).**

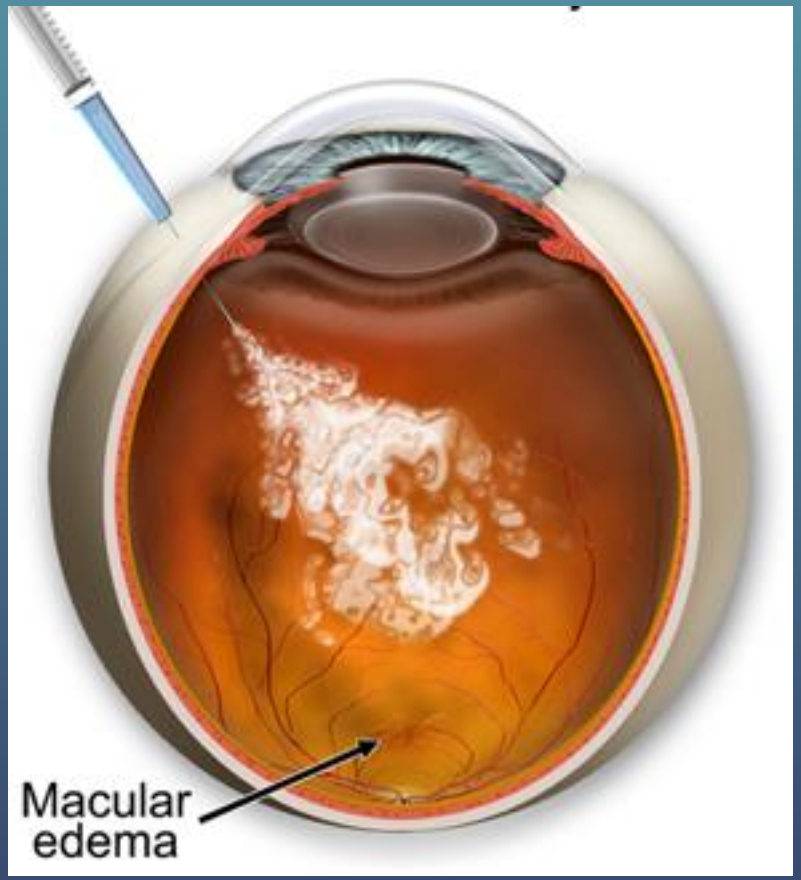
Wet AMD

- If left untreated, CNV may result in significant central vision loss due to complications including exudation, leakage, and ultimately **subretinal fibrosis** causing remarkable **photoreceptor loss**.

Treatment of Wet AMD

- Pegaptanib (Macugen: VISION trials)
- Ranibizumab (Lucentis: MARINA/ANCHOR)
- Aflibercept (Eylea: VIEW)

- Off label: Bevacizumab (Avastin: CATT)



Goal of Treatment:

- Maintain disease remission while minimizing side effects and treatment burden

Treatment Modules:

- Monthly
  - Continuous fixed monthly regimens associated with best visual outcomes

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Treatment Modules:

- Monthly
  - Continuous fixed monthly regimens associated with best visual outcomes
- PRN
  - Failed to preserve vision gains comparable to monthly gains (CATT)
- Treat and Extend
  - 65% of US ASRS members prefer this method
  - Goal is to establish an individual patient's optimal interval since many eyes show predictable pattern of recurrence
    - 10-20% need monthly
    - 10-20% show extended disease quiescence

Treatment Modules:

Some may require injections at shorter than q4 week intervals

Wet AMD Future Therapies:

- Long-Acting Anti-VEGFs
- Sustained Delivery Treatments
- Topical Treatments
- Oral-Anti-VeGFs
- Gene Therapy

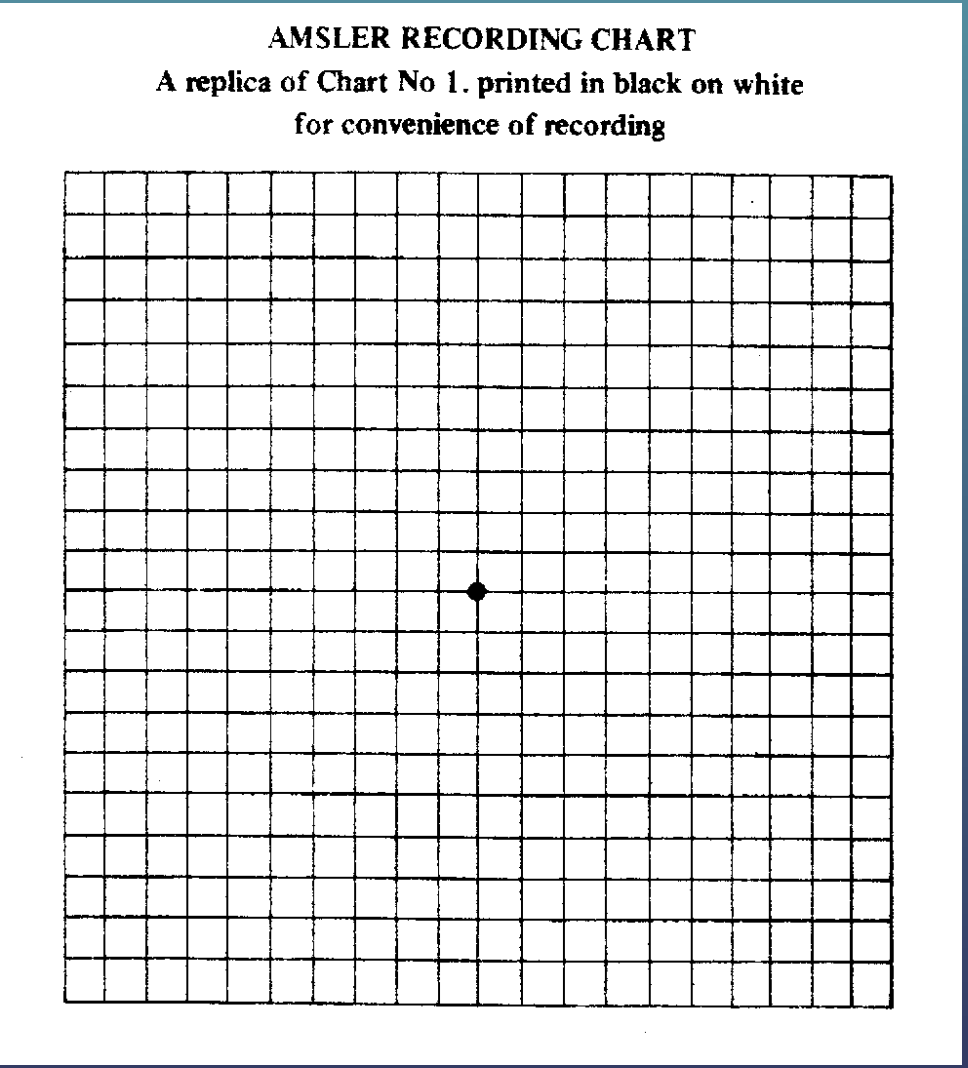
Table 1. AMD Therapies in the Research Pipeline

Compound	Company	Stage of Development	Structure/Mechanism of Action
Brolucizumab	Novartis	Phase III	small MW humanized single-chain Fab anti-VEGF-A
Abicipar pegol	Allergan	Phase III	DARPin antagonist of VEGF-A
OPT-302	Ophthea	Phase IIb	anti-VEGF-C/VEGF-D
Pegpleranib (Fovista)	Ophthotech	Phase III did not meet end point	anti-PDGF-B aptamer
Rinucumab-aflibercept	Regeneron	Phase II did not meet end point	anti-PDGF-B/anti-VEGF co-formulation
DE-120	Santen	Phase II	dual TKI of VEGF-A/PDGF
Nesvacumab-aflibercept	Regeneron	Phase II	Ang-2/VEGF-A mAb co-formulation
RG7716	Roche	Phase II	bispecific Ang-2/VEGF-A antibody
ARP-1536	Aerpio	Preclinical	Tie-2 receptor activation (via VE-PTP inhibition)
X-82	Tyrogenex	Phase II	oral anti-VEGF-A/PDGFR
Pazopanib	GlaxoSmithKline	Phase IIb did not meet endpoint	TKI of VEGF-A/PDGF
PAN-90806	PanOptica	Phase I/II	TKI of VEGF-A/PDGF
Regorafenib	Bayer Healthcare	Phase IIa did not meet endpoint	TKI of VEGF-A/PDGF
LHA510	Alcon	Phase II	VEGF-A inhibitor
Ranibizumab PDS	Genentech	Phase II	refillable port of VEGF-A mAb
GB-102	GrayBug Vision	Preclinical	bioerodible nanoparticles encapsulate TKI of VEGFR/PDGFR
NT-503 ECT	Neurotech	Phase II terminated	VEGF-A receptor fusion protein
Hydrogel depot	Ocular Therapeutix	Preclinical	sustained-release anti-VEGF-A
Durasert	pSivida	Preclinical	TKI of VEGF-A/PDGF
ENV1305	Envisia Therapeutics	Preclinical	sustained-release anti-VEGF-A
AVA-101	Adverum Biotechnologies	Phase IIa results were mixed	AAV sFLT
AVA-201	Adverum Biotechnologies	Preclinical	AAV sFLT
ADVM-022/ADVM-032	Adverum Biotechnologies	Preclinical	AAV encoding anti-VEGF-A cDNA
AAV2-sFLT01	Genzyme (Sanofi)	Phase I	AAV sFLT
RGX-314	Regenxbio	Preclinical	AAV8 encoding anti-VEGF-A
Retinostat	Oxford Biomedica	Phase I	EIAV encoding endostatin and angiostatin

Wet AMD Take Home Point

- It is a chronic disease
- Meds might not all be equal
- Recurrence is different per patient

Amsler Grid (recording chart)



ForeSee Home

ForeseeHome FDA Indication for Use

- ForeseeHome is intended for use in the detection and characterization of **central and paracentral metamorphopsia** (visual distortion) in patients with age-related macular degeneration.

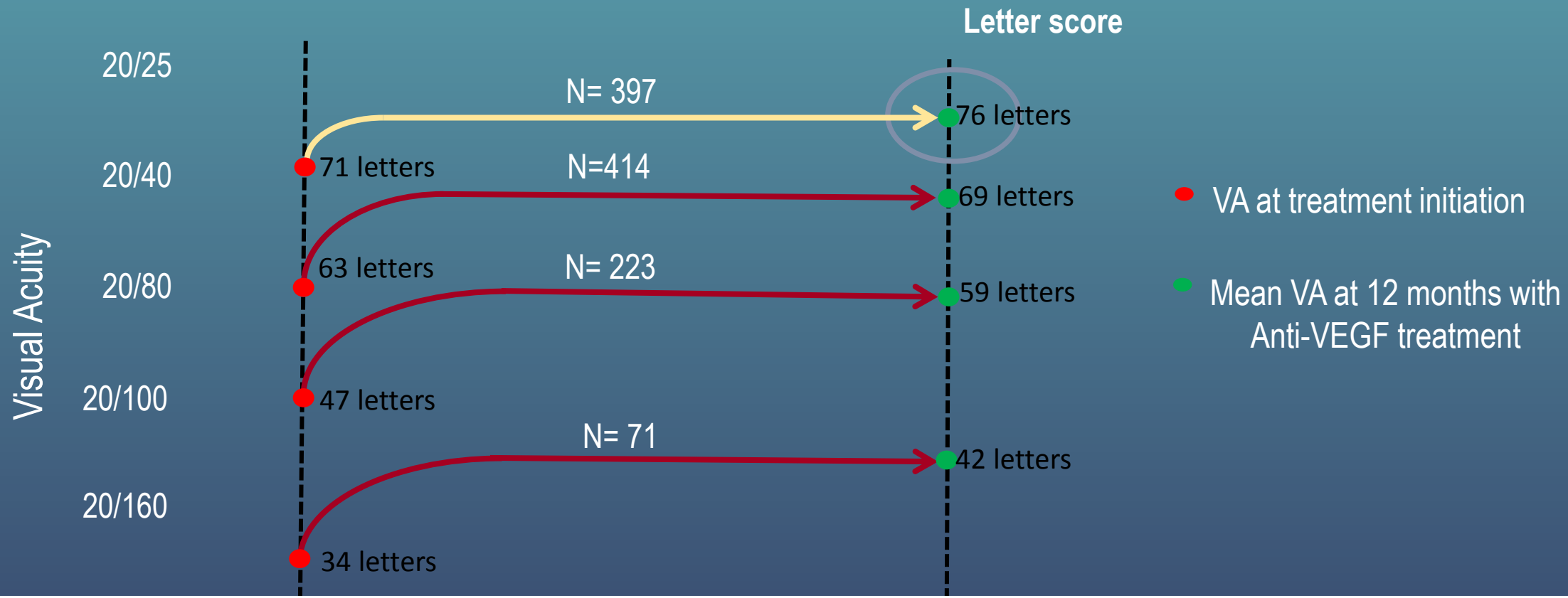
ForeseeHome FDA Indication for Use

The ForeseeHome AMD Monitoring Program is available by prescription only to dry AMD patients at risk of developing CNV

Analyses from 5 Landmark Studies have Demonstrated that Several Baseline Characteristics Predict VA Outcomes

Baseline Measure	CATT *1 year*	HARBOR *1 year*	MARINA *2 years*	ANCHOR *1 year*	TAP/VIP *1 year*
CNV lesion size/leakage area	✔	✔	✔	✔	✔
BCVA	✔	✔	✔	✔	
Age	✔	✔	✔	✔	
SRF presence	✔	✔			
RPE elevation	✔				
Occult CNV	✔				
GA presence	✔				
Foveal thickness	✔				

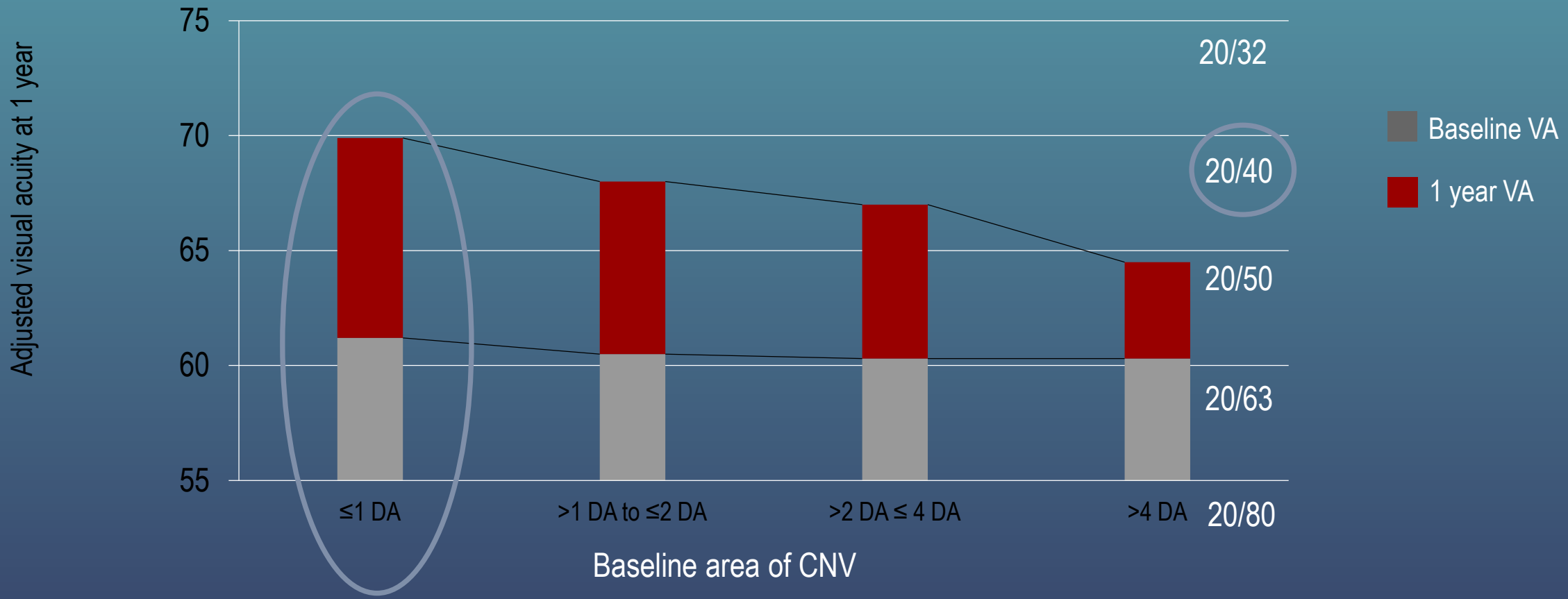
CATT : Mean Visual Acuity at 1 Year



"The detection of CNV before there is a large loss of vision remains important even in the era of highly effective treatment." – CATT Study Group

degeneration. Ophthalmology. 2013 Jan;120(1):122-9

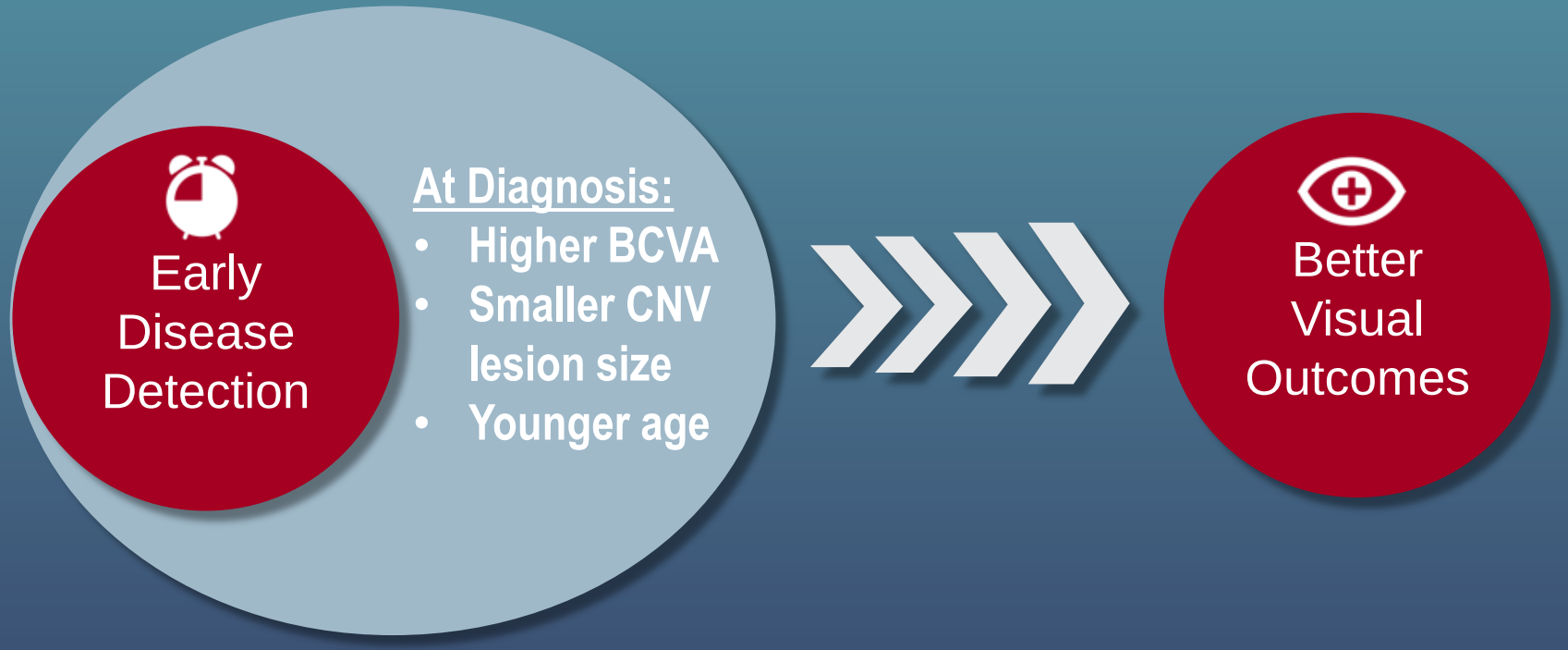
CATT : Adjusted Mean VA at 1 Year vs. CNV Area at Baseline



Smaller, younger lesions demonstrated a better VA outcome at 1 year

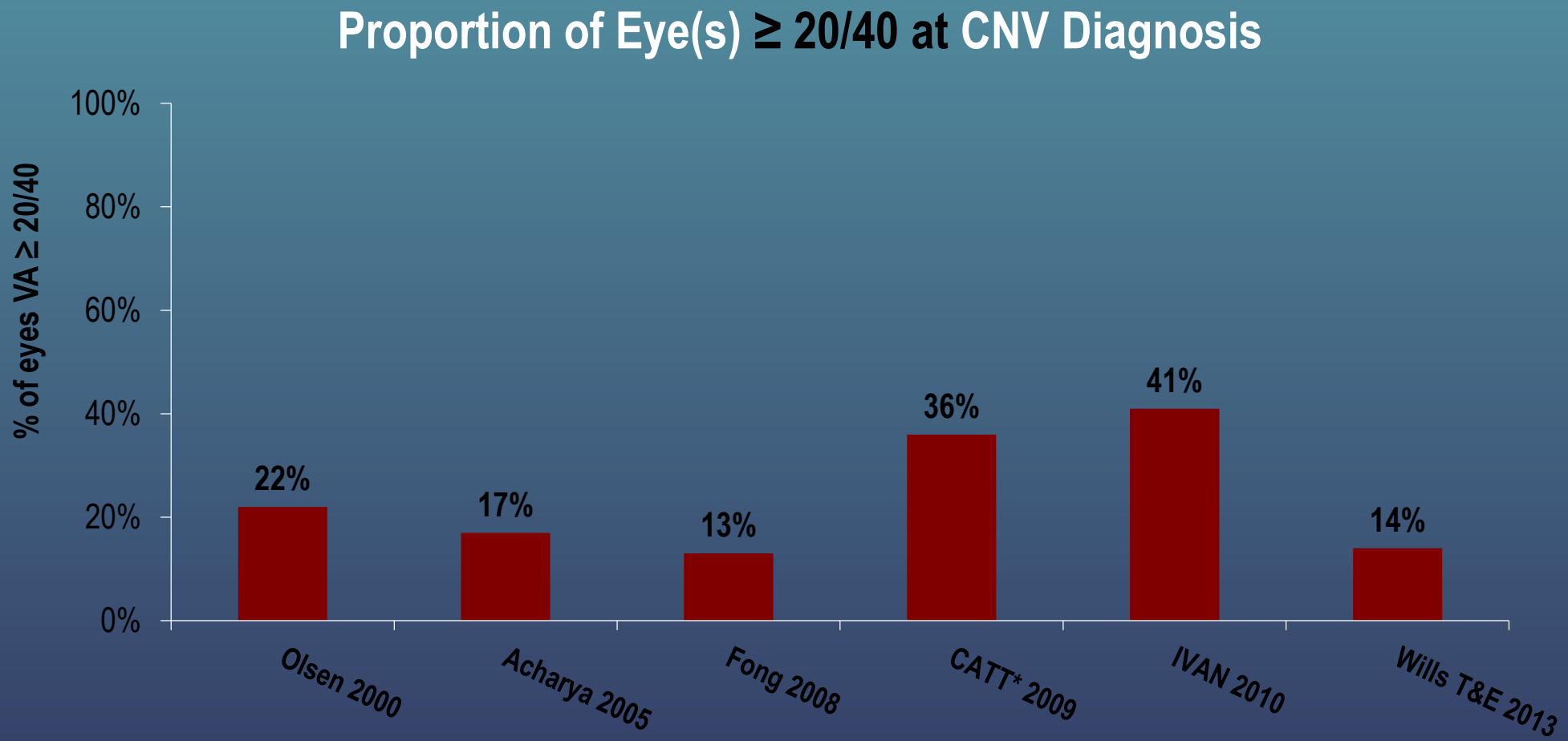
Ying GS, et. al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology. 2013 Jan;120(1):122-9

Baseline Characteristics that Predict BETTER VISION OUTCOMES are associated with EARLY DETECTION



Irreversible vision loss can occur when there is a delay in diagnosis and treatment.

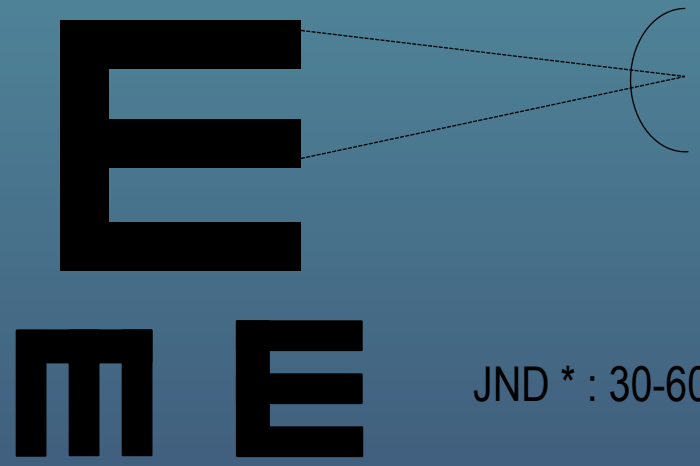
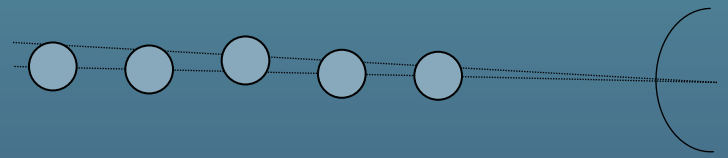
A limited number of newly diagnosed CNV eyes are detected early



*All but CATT included eyes with VA of 20/20 or worse (CATT included ≤20/25)

Core Technology Based on Hyperacuity

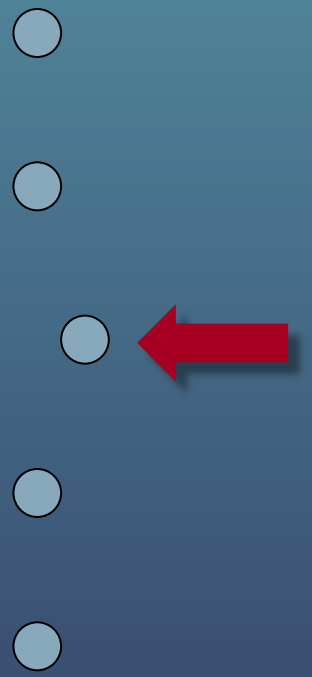
Greater sensitivity for detecting minute vision changes in AMD

Visual acuity (resolution)	Hyperacuity (Vernier acuity)
	
JND * : 30-60 ‘’	JND * : 3-6 ‘’
= Two-points discrimination	**= Detection of misaligned objects**
Low sensitivity **Age-dependent** **Blur-dependent**	**High sensitivity** **Resistant to age** **Insensitive to blur**

JND * : just noticeable difference

Preferential Hyperacuity Perimetry (PHP)

Technology is Based on Vernier Acuity



The human ability to perceive minute differences in the relative spatial localization of two objects

The brain is exceptionally sensitive to such deviation

In the fovea, hyperacuity ability is in the range of 3-6” (sec) of arc (~10x better than standard acuity)

PHP Home-based Technology:

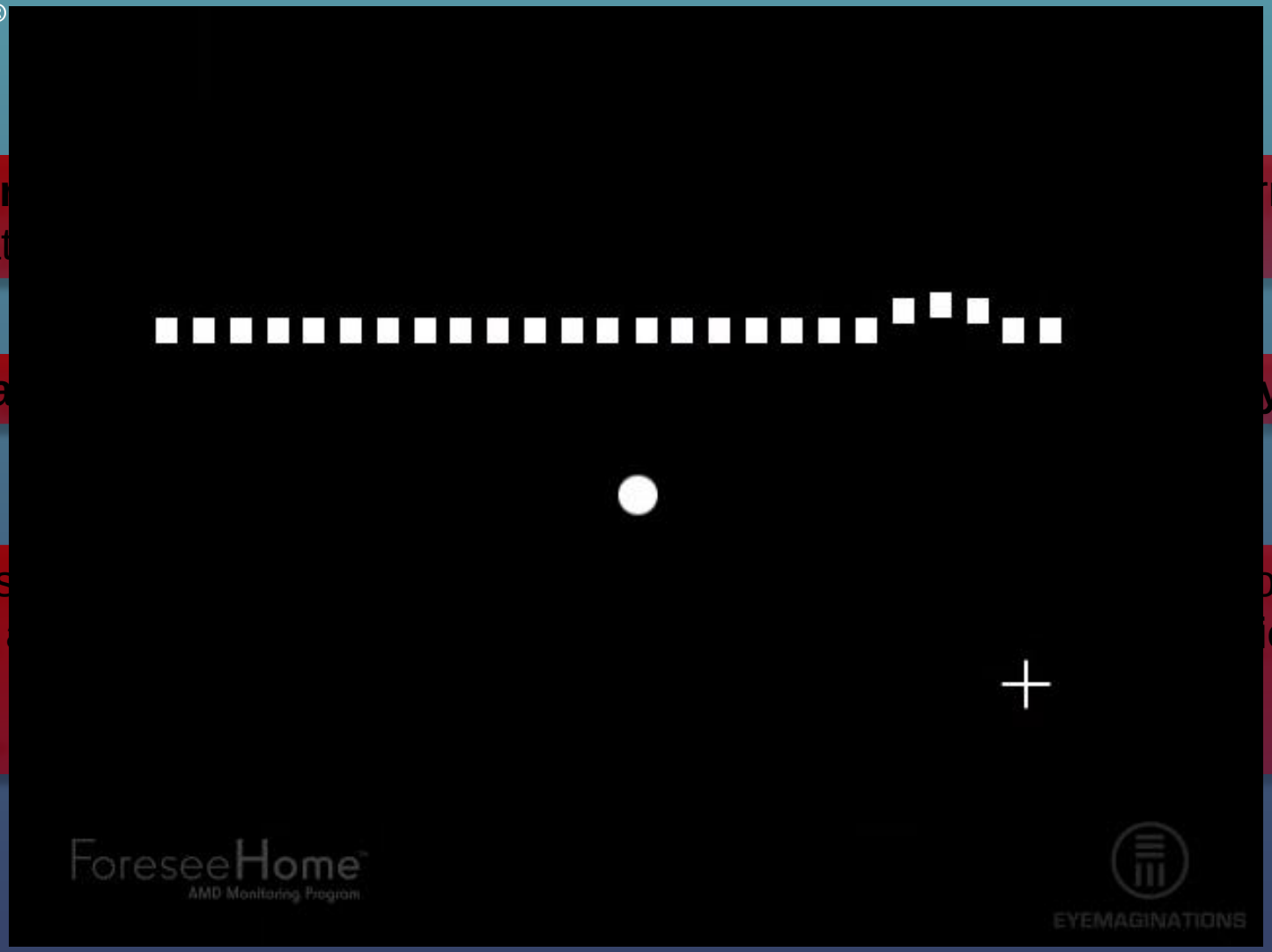
ForeseeHome®

First FDA-clear rmediate
AMD patients at

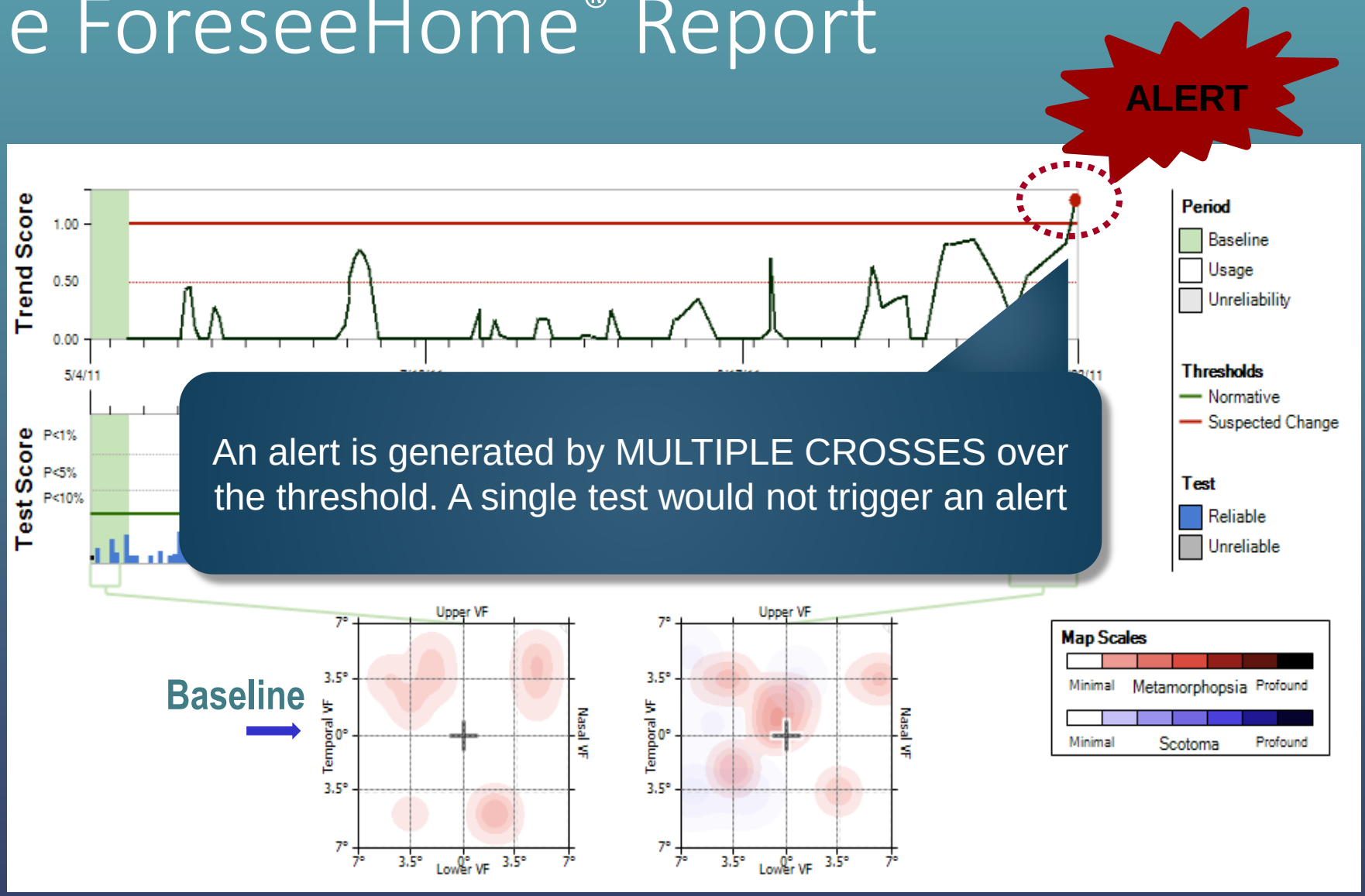
Can detect cha y visual
symptoms.

Ability to assess on
competing with ion test.

Pathological >



The ForeseeHome® Report



The ForeseeHome® Process

Patient completes the brief non-invasive test daily; ~3 mins per eye.

A baseline reference score and map is generated within the first few weeks; daily test results are sent to the Notal Data Monitoring Center.

When a statistically significant change is detected, Doctor is alerted and follow up plan is initiated.

Physicians are sent monthly reports and can view patient data via a website. The reports can be used as a follow-up tool during clinic visits.

MORE ABOUT THE ALERT…

- The ordering physician receives the alert (standard protocol)
- In addition, alerts can be sent simultaneously to the ordering physician AND patients by physician consent. The patient is alerted that a statistically significant change in testing has occurred, and is asked to contact their eyecare provider as soon as possible.

The HOME Study

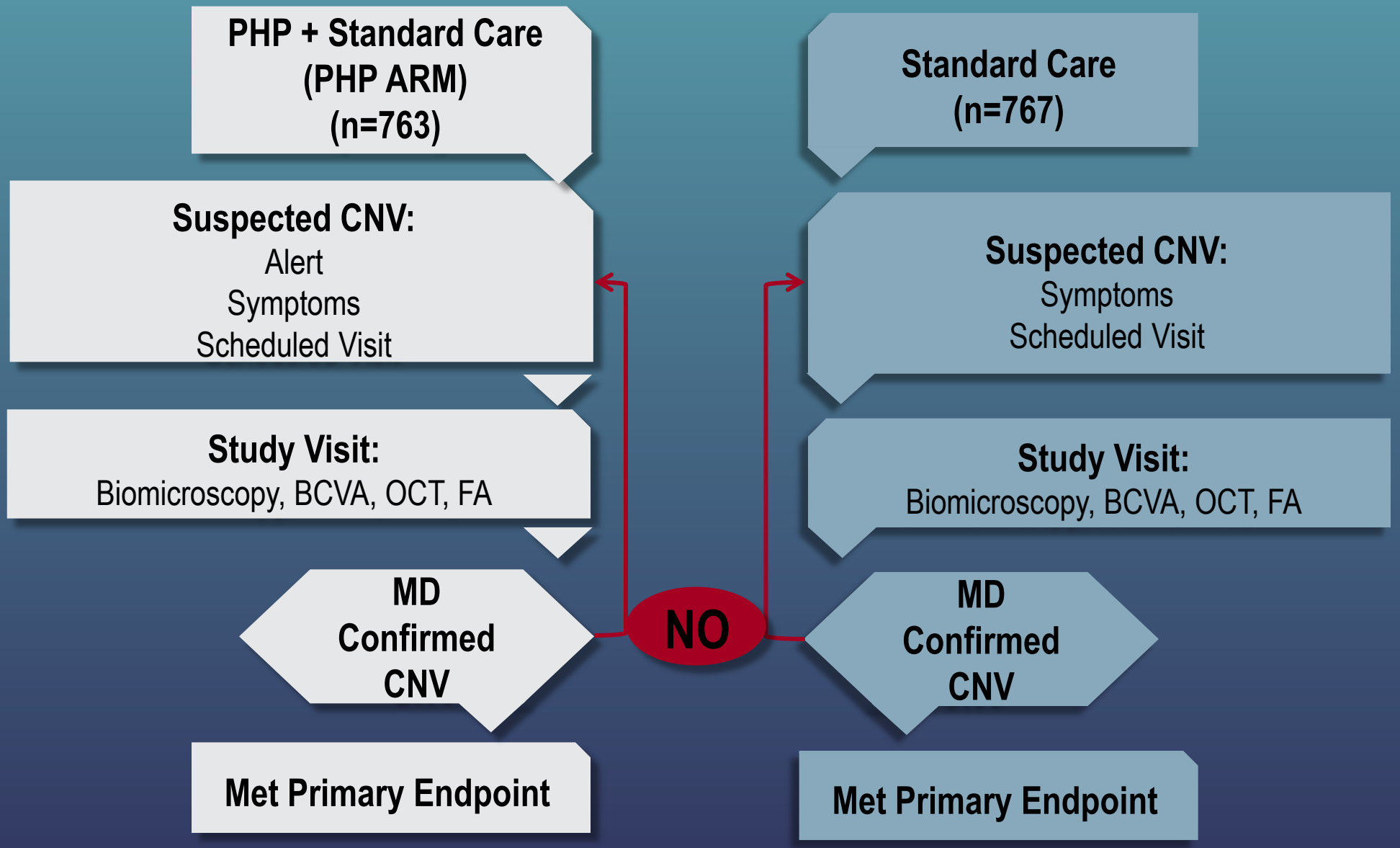
Study Methods & Demographics

Does home monitoring with PHP (ForeseeHome) plus standard care result in earlier detection of progression to CNV when compared to standard care alone?

- **Inclusion:** Dry AMD patients with 3 or 4 risk factors per AREDS scale
  - ≥ 1 large druse (≥125 microns)
  - VA ≥ 20/60
  - No CNV, scarring, or central GA in the study eye(s)
- **1520 patients** enrolled from 44 AREDS2 centers

Unprecedented number of patients for a medical device study

Study Design



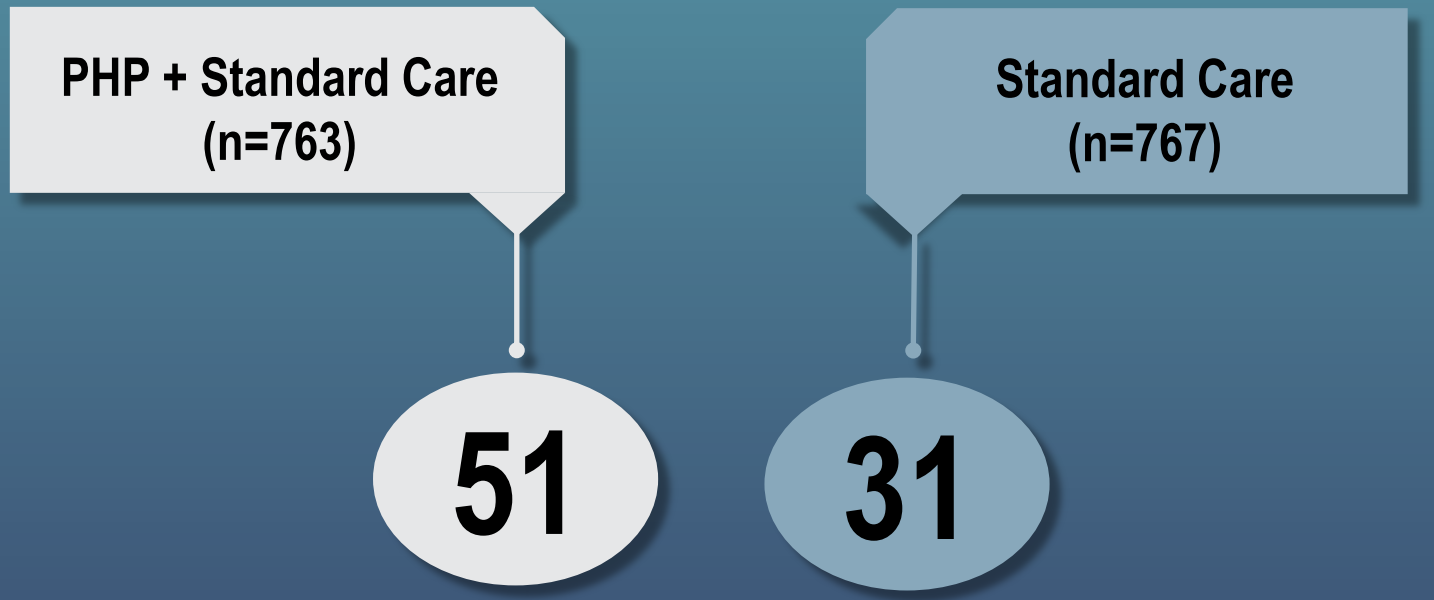
Outcome Measures

Primary Outcome: Change in VA from baseline to time of incident CNV

- **Secondary Outcomes**
  - Additional VA outcomes (i.e. proportion maintaining ≥20/40 at diagnosis)
  - Sensitivity and specificity (“First to alert” and false positive alert rate)
  - Lesion characteristics at the time of CNV diagnosis – not reported until full dataset available

CNV Events at 22 Months, April 2013

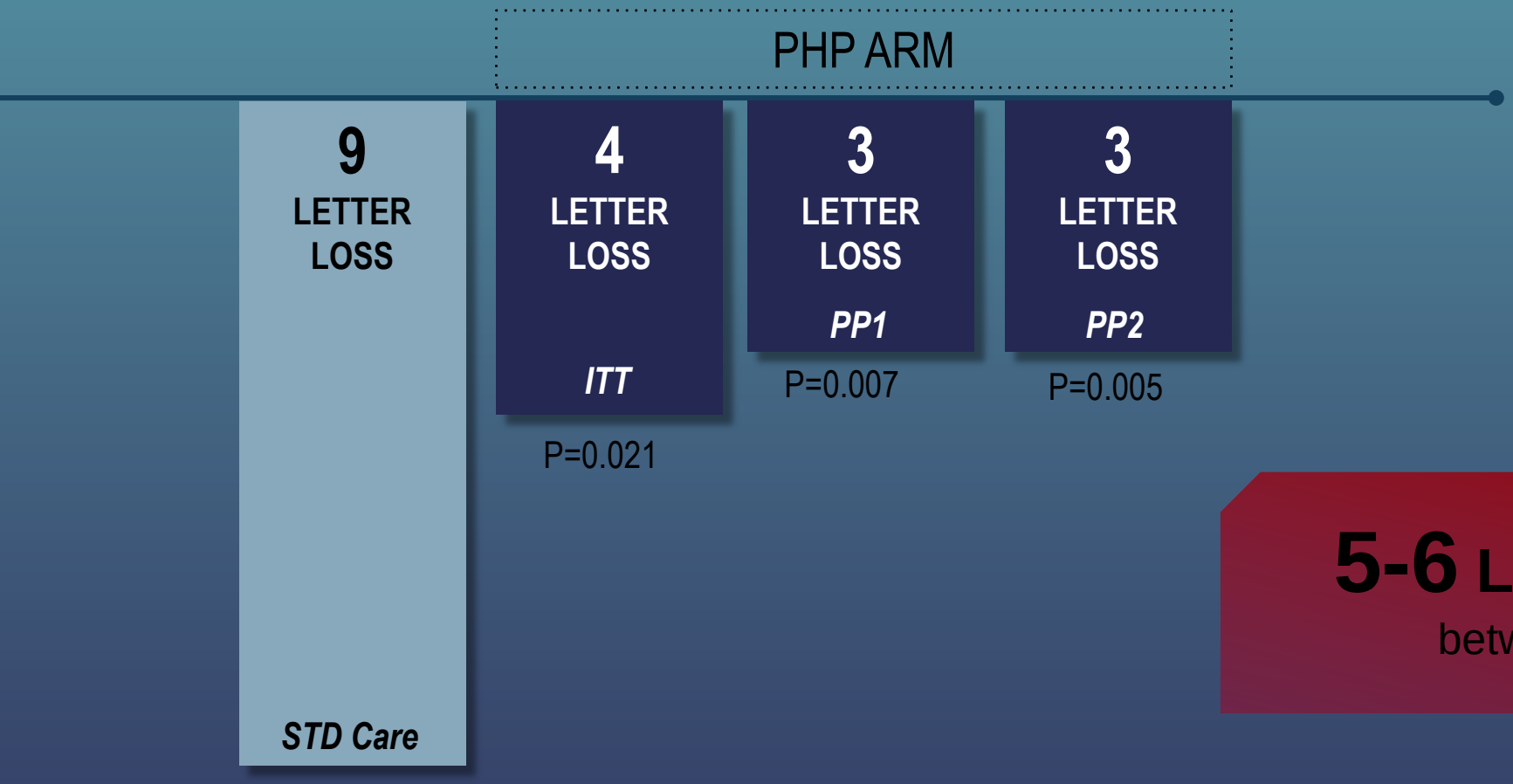
Intent to Treat (ITT) Population



As a result of earlier detection, CNV EVENTS ACCUMULATED FASTER in the PHP arm vs. STD care

CNV events confirmed by physician at time point when DSMC recommended study termination for efficacy
ITT population: Includes all assigned to PHP whether using or not

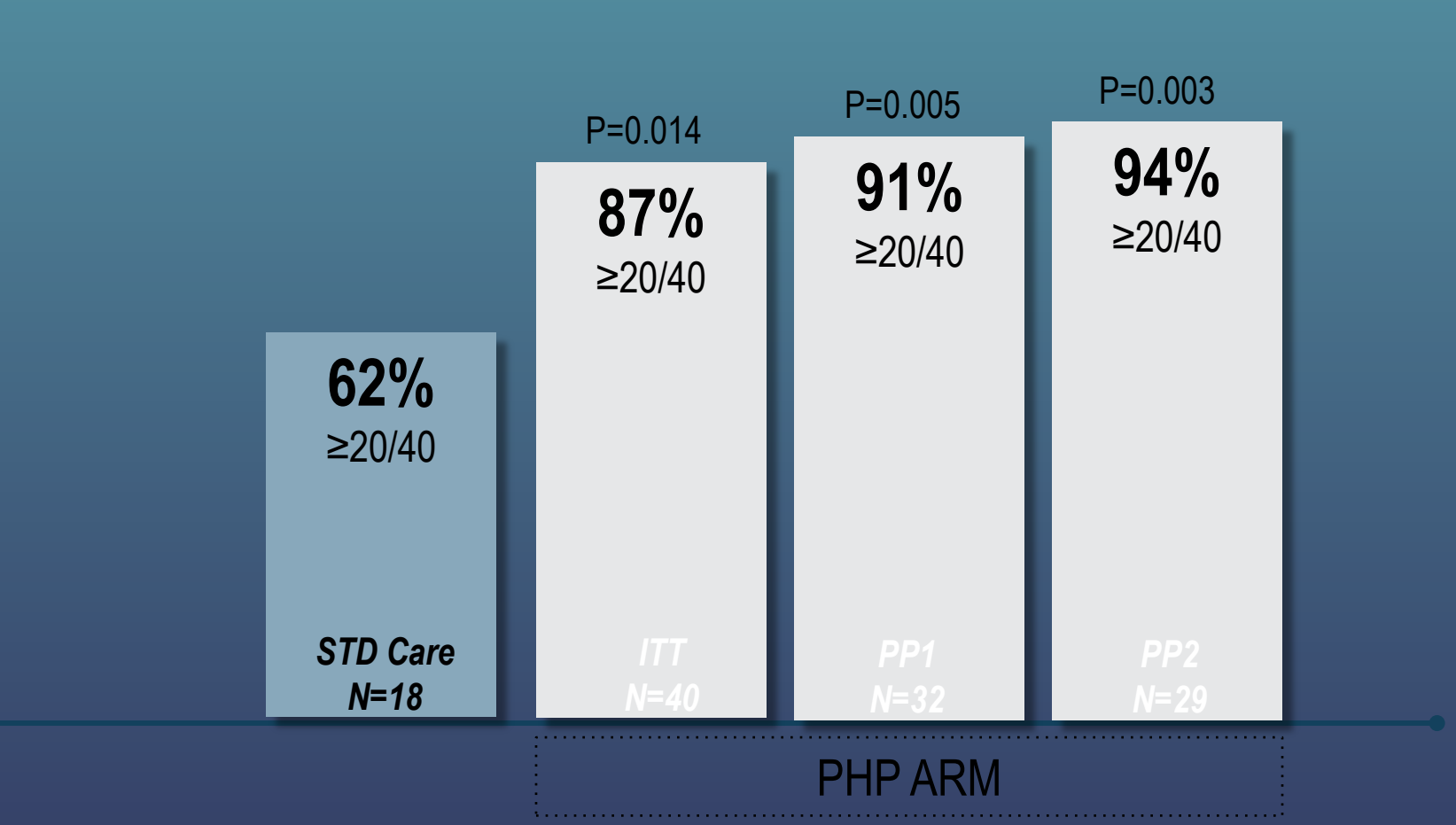
Change in VA Score from Baseline at CNV Detection



5-6 LETTER DIFFERENCE
between PHP arm & STD care

ITT population: Includes all assigned to PHP whether using or not
PP population: (1) Real life after est. baseline; (2) Minimal recommended practice

Proportion of Eyes Maintaining ≥20/40 at CNV Detection



Up to 50%
INCREASE
in patients within the PHP arm vs. STD care

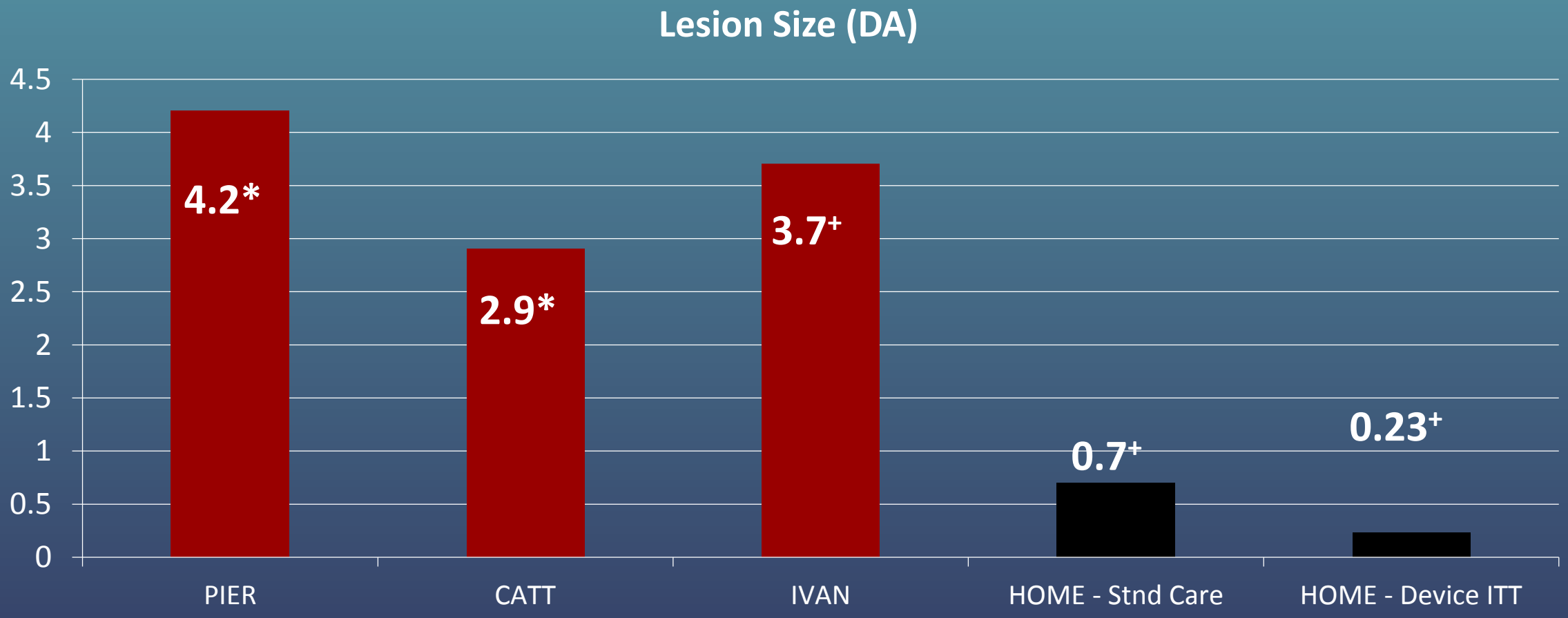
ITT population: Includes all randomized to PHP arm whether using or not
PP population: (1) using device at the time of the event; (2) Recommended testing of at least 2 times per week, and using at the time of the event

Performance of PHP

79% of PHP arm participants had no false alerts over the period of 1.4 years (study duration)

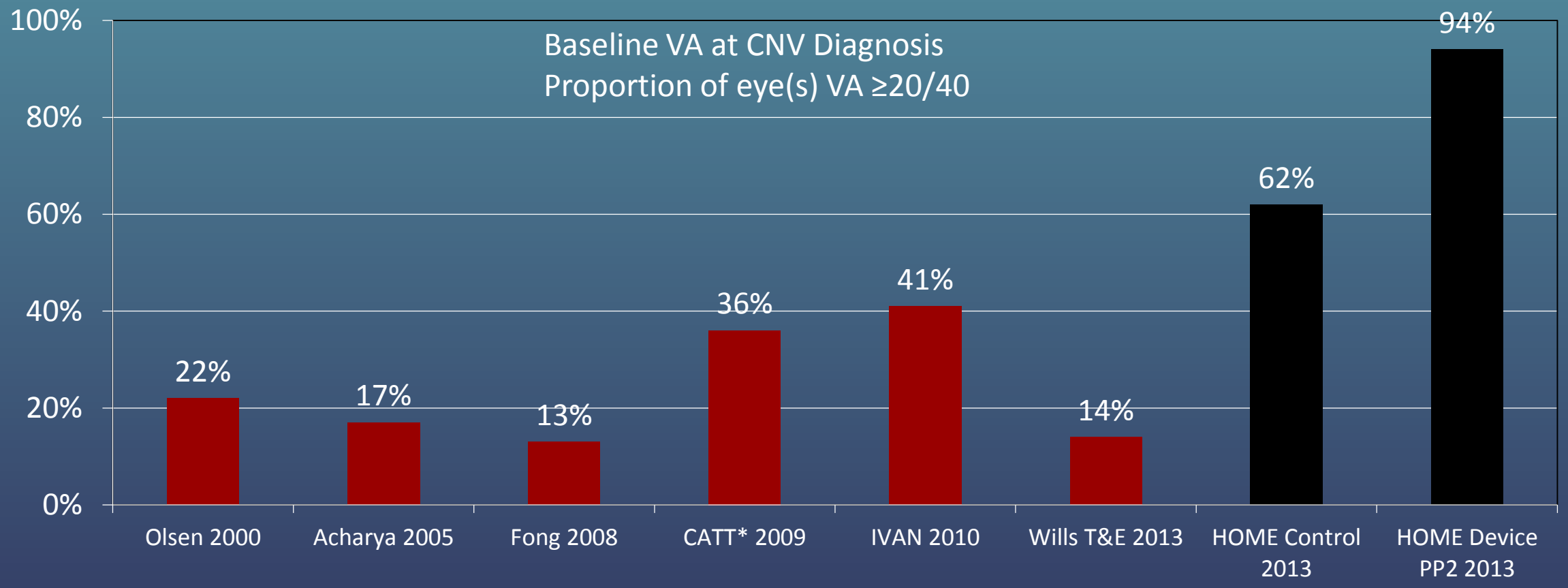
An average of 1 false alert may occur in 1 patient over 4 YEARS of continual testing for that patient

ForeseeHome diagnoses CNV with smaller lesion size



* Mean + Median

Incorporation of ForeseeHome facilitates earlier detection of CNV in a greater proportion of patients



***All but CATT included eyes with VA of 20/20 or worse (CATT included ≤20/25)**

One of the very few studies in Ophthalmology that has been stopped due to POSITIVE EFFICACY

DSMC RECOMMENDATION

- On April 30, 2013, the DSMC reviewed the study results and concluded that study eyes at risk of AMD progression presented to their study sites with SIGNIFICANTLY BETTER VISION WHEN THEIR NEOVASCULAR AMD DEVELOPMENT WAS DETECTED BY THE FORESEEHOME DEVICE as compared to standard monitoring.
- Therefore, the DSMC UNANIMOUSLY RECOMMENDED EARLY TERMINATION OF THE STUDY AS THEY WERE CONFIDENT THAT THE STUDY HAD MET ITS PRIMARY OBJECTIVE; namely, demonstrating that eyes at high risk of progression to neovascular AMD can be identified with better levels of vision when they are detected by use of the home monitoring device as compared to standard methods.

Laser Photocoagulation of Subfoveal Recurrent Neovascular Lesions in Age-Related Macular Degeneration Results of a Randomized Clinical Trial. *Arch Ophthalmol.* 1991; 109(9):1232-41.

Medicare Coverage for ForeseeHome

Achieved November 2015

Dry Intermediate AMD patients at High Risk for Progression to CNV

BCVA of 20/60 or better

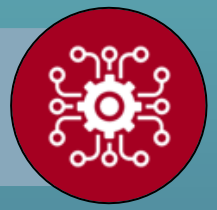
ICD-10 Codes:

- H 35.31 1 2 (Dry Intermediate, Right Eye)
- H 35.31 2 2 (Dry Intermediate, Left Eye)
- H 35.31 3 2 (Dry Intermediate, Bilateral)

Candidates may include:

- Dry AMD eyes (bilateral) with intermediate sized drusen and hyperpigmentation
- Dry AMD in one eye (testing eye) and Wet AMD in fellow eye

WHY DO I USE PHP?



- **Provides the highest quality care I can provide my intermediate dry AMD patients**
- Increases likelihood that my patients will be able to remain independently able to drive, read, and enjoy their quality of life
- Reinforces that they are at risk for wet AMD and provides a better understanding of their disease

WHO ARE THE IDEAL CANDIDATES?

- Intermediate AMD eye(s) at risk for progressing to CNV
- 20/60 BCVA or better in monitoring eye(s)
- No CNV, scarring or central GA in monitoring eye(s)
- **In SHORT: Intermediate dry AMD; those recommended an AREDS2 vitamin formulation**

Thank you

- Samckim@gmail.com