

AMD: The past, present and future

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Macular photocoagulation

- Argon Laser used to ablate the CNVM to prevent further leakage
- Subfoveal 1980
 - 20% of treated of pts had >6 lines of acuity loss at 5 yrs vs 37% untreated
 - Vision loss was immediate for treated group, vs more gradual for untreated group
 - At 42 mos, acuity levels equalized
 - At 5 years, acuity almost equal in both groups \cong 20/200
- **Balance long term level of function vs immediate loss of vision**

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Macular photocoagulation

- Extrafoveal (<200 um from fovea) 1982
 - MPS resulted in less vision loss for first two years, but due to high recurrence rate, effect decreased after
 - at 5 yrs, 48% of treated eyes vs 62 % of untreated eyes lost > 6 lines
 - At 5 yrs, va 20/125 in treated vs 20/200 untreated
- Juxta foveal (1-199 um from fovea) 1990
 - Small benefit in select pts
 - 52% of treated eyes lost > 6 lines vs 61% Untreated

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Photodynamic therapy

- FDA approved 2000
 - big breakthrough as first pharmacological treatment for wet amd
- Visudyne (verteporfin) is injected into the bloodstream
- When Dye reaches the CNVM, laser is used to activate the dye and destroy the CNVM
 - Issue is collateral healthy retina is also destroyed
- Has fallen out of favor and rarely used except in specific cases

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Photodynamic therapy

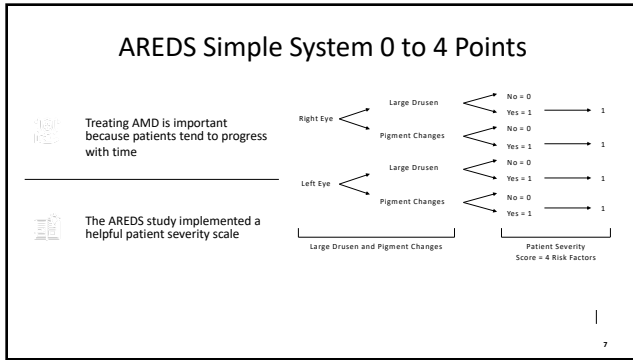
- TAP Study
 - Primary endpoint was percentage of eyes that loss less than 15 ETRDRS letters from baseline at 12 and 24 mos
 - 12 mos: 61% with treatment vs 46%
 - 24 mos: 53% vs 38%
- VIP/ VIM study
 - Looks at occult lesions or minimally classic lesions
 - Results mostly disappointing except with very small lesions

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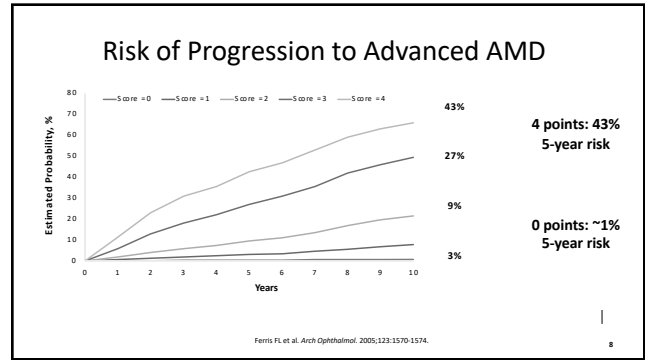
others

- Anecortave Acetate
- Rheophorsis
- laser

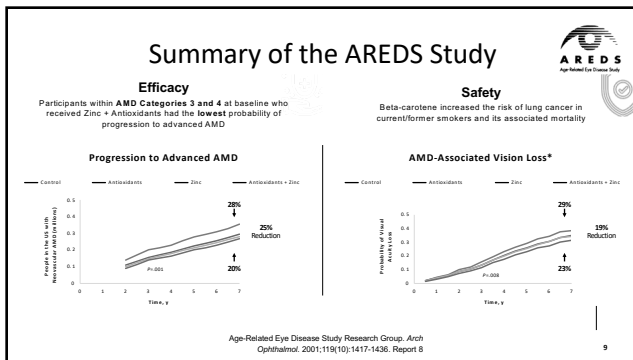
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- ### AREDS2
- Well discussed results
 - Addition of L/Z
 - Dosage of Zinc
 - Deletion of B-carotene
 - Non-inclusion of Fish oil
 - Key messages
 - OPERA
 - HOME
 - 10 year f/u study

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- ### What's Old is New
- AREDS2 10 year results announced earlier this year
 - The results can be seen as either very exciting or very boring...

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AREDS2 Follow-on Study

Final follow-up for subset of AREDS2 participants: 10-years

N=3,887 (6,360 eyes)

Patients randomized to receive lutein/zeaxanthin and/or omega-3 fatty acids or placebo
Secondary randomization for 0 or 15 mg beta-carotene and 25 vs 80 mg zinc

Follow-up with AREDS2 participants by phone every 6 months for 5 years to collect safety data

Objectives

Assess the long-term effects of adding lutein-zeaxanthin and omega-3 fatty acids to AREDS supplements on:

- AMD progression
- Incidence of adverse side effects

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AREDS2 Primary Endpoint: Progression to Late AMD

Progression to late AMD – Hazard Ratio

	5 years	10 years
Lutein/Zeaxanthin	0.90 (P = 0.12)	0.88 (P = 0.04)
DHA/EPA	0.97 (P = 0.70)	0.97 (P = 0.65)
Lutein/Zeaxanthin/DHA/EPA	0.89 (P = 0.10)	0.92 (P = 0.13)
Placebo (original AREDS formulation)	1.00	1.00

- Key Takeaways:
 - Adding Lutein/Zeaxanthin to the original AREDS formula provided a 10% reduction in progression to late AMD compared to the original AREDS formulation alone
 - Addition of Omega-3 FA DHA/EPA had no benefit
 - These results were sustained through 10 years

As presented at ARVO 2021 by E. Chew 13

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AREDS2 Secondary Endpoint: Combined Arms

Main Effect Progression to Late AMD

Combined Arms Main Effect Progression to Late AMD – Hazard Ratio

	5 years	10 years
Lutein/Zeaxanthin	0.91 (P = 0.05)	0.91 (P = 0.03)
DHA/EPA	0.98 (P = 0.74)	1.01 (P = 0.91)
Low Zinc	1.06 (P = 0.32)	1.04 (P = 0.48)
Beta Carotene	1.07 (P = 0.31)	1.04 (P = 0.50)

- Key Takeaways:
 - Using a factorial study design, combining the arms that had Lutein/Zeaxanthin to increase sample size, the addition of Lutein/Zeaxanthin provided a similar ~10% reduction in progression to late AMD
 - Addition of Omega-3 FA DHA/EPA had no effect on progression
 - Reduction of Zinc level had no effect on progression
 - These results were sustained through 10 years

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Participants Taking AREDS 2 Supplements with L/Z (vs Beta-carotene)

Had ~20% Reduced Progression to NV AMD (10 Years)

Hazard Ratio (96% CI)

Category	Effect Size (96% CI)
Neovascular AMD	
L/Z Main Effect	0.91 (0.81-1.01)
AREDS-5+L/Z w/o B-C vs AREDS-5+B-C	0.81 (0.68-0.98)
Geographic Atrophy	
L/Z Main Effect	0.96 (0.86-1.07)
AREDS-5+L/Z w/o B-C vs AREDS-5+B-C	1.06 (0.87-1.30)

Significant effect of L/Z (vs beta-carotene) also appears at 5 years

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The LXXVI Edward Jackson Memorial Lecture 2020

by Dr. Emily Chew

- Re-iterated results of AREDS1 and AREDS2
- Regarding Mediterranean diet: benefits in incident AMD and to late AMD (especially high fish consumption in AREDS 1&2)
- “This would suggest that it is never too early or too late to adopt a healthy diet, such as the Mediterranean diet.”
- Genetics seems to affect efficacy of Med diet to late AMD

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Lifestyle

- First realize that most Americans do not have a healthy lifestyle
- Less than 7% (4.4-6.3%) engage in 5/5: Not smoking, ideal body weight, exercise, not alcohol in excess, healthy diet¹
 - Average less than 2/5 and almost 50% did 2 or less
- AHA Life's simple 7
 - Smoking, physical activity (150 or 75), body mass index, diet, blood pressure, total cholesterol, and blood glucose. Score of 14 is ideal
 - Even 1-point improvement is statistically significant in decreasing AMD²
- Blue light may not be the answer
 - Approx 11k eyes, no stat sig difference in incident wet AMD or wet AMD outcomes in blue blocking vs traditional IOLs³

1. Hecht et al. Healthy Behaviours NHANES. A J Prev Med. 8/2020 2. De La Cruz et al. Cardio Health and Oc Dz. Am J Med. 7/2020. 3. Achiron et al. Blue light IOLs and AMD. Opthth 7/2020. image from heart.org

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Nutrition in General: Mediterranean diet

- Med Diet to prevent progression to Advanced AMD¹
 - Over 13200 eyes from AREDS and AREDS2
 - HR .78/.71/.84 for most adherent to Med diet for advance to Advanced AMD, GA, Wet AMD
 - HR .69 when added in Fish
 - CFH alleles influenced (decreased) benefit of Med Diet + Fish
 - HR .79 to progress to large drusen (NOTE: LATE AMD IS NOT THE ENDPOINT HERE!)
- Med Diet conferred 41% decreased risk of Adv AMD in approx. 5000²
 - When comparing top vs lowest tertile of intake of vegetables, fruits, legumes, cereals, fish, meat, dairy, alcohol, and the monounsaturated-to-saturated FA ratio

1. Keenan et al. Med Diet and Advanced AMD (AREDS1 and 2). Opthth 2020. 2. Merle et al. Med Diet and Adv AMD: EyeRisk. Opthth 3/19

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Diet and lifestyle matter

- Coimbra Eye Study (report 3) compared age matched AMD vs "normal"
- OR .69 for frequent physical activity
- .OR .62 for high vs low Med diet
 - Fruit was only individual (of 9) component to be beneficial on its own
- Group without AMD had higher caffeine, fiber, beta-carotene, vit C & E
- Physical activity more pertinent than education, biometrics, smoking and demographics

Raimundo et al. Med Diet, Lifestyle and AMD Coimbra #3. Acta Ophal 12/2019

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Anti-VEGF Agents

- VEGF is a primary driver of blood vessel growth and leakage in AMD
- Anti-VEGF agents block and neutralize VEGF
 - Results in decreased intra- and sub-retinal fluid
 - May also decrease risk of scar tissue formation
- Serious adverse effects (endophthalmitis) rare
- Less serious events (subconjunctival hemorrhage, vitreous hemorrhage, floaters) are also uncommon

Fong SP, et al. Clin Ophthalmol. 2018;12:1877-1886. You KY, et al. Invest Ophthalmol. 2019;16:1888. Nay PL, et al. Br J Ophthalmol. 2016;100:1629-1636. American Society of Retina Specialists (ASRS). Retinal Vein Occlusions. www.asrs.org/RetinalVeinOcclusions.aspx. Janghorbani M, et al. Br J Ophthalmol. 2013;97:210-219. Living well with low vision. <https://wwwvision.gov.au/2013/09/23/living-well-with-low-vision/>. WHO accessed 12/08/2020.

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“Wet” AMD

- Neovascular “wet” AMD
 - Mainstay of treatment consists of serial intravitreal injection of anti-VEGF agents

Anti-VEGF Agents	Pegaptanib (Macugen®)	Ranibizumab (Lucentis®)	Aflibercept (Eylea®)	Brolucizumab (Beovu®)	Bevacizumab (Avastin®)
FDA approval	2004	2006	2011	2019	Not approved
Pivotal studies	VISION	ANCHOR MARINA IVAN	VIEW 1 and 2	HAWK HARRIER	CATT

– VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies

WVF - vascular endothelial growth factor.
AMD. AMD preferred practice guidelines, 2019 (www.aao.org/preferred-practice-guidelines/age-related-macular-degeneration-amyd). Kulkarni K, Prasad A. Rev Ophthalmol. 17(1):2006. <https://www.researchgate.net/publication/304161464>.

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Anti-VEGF Agents: Delivery and Dosage

- Delivered intravitreally
- Dosing schedule and agent used varies
- In general
 - Loading dose with 1 injection per month for 3 months, then inject based on FA, OCT, or other clinical findings
 - Reduces patient burden while still delivering good results

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Anti-VEGF Agents: Outcomes

Lucentis ¹	Eylea ^{2,3}	Beovu ⁴
<ul style="list-style-type: none"> • 94% stable vision at 2 years • 34–41% gained 15 letters or more • Average gain of 11.3 letters at 1 year and 10.7 letters at 2 years 	<ul style="list-style-type: none"> • 95% of patients treated maintained acuity • 7.9–10.9 letters mean improvement of vision 	<ul style="list-style-type: none"> • ~30% gained at least 15 letters by year 1 • Less fluid and greater reduction in CST vs aflibercept • At 1 year, half of subjects on 3-month dosing

1. Brown DM, et al. Ophthalmology. 2009;116:1744-45. 2. Nguyen QD, et al. Invest Ophthalmol of Vis Sci. 2011;52: abstract 8079. 3. Schmidt-Erfurth V, et al. Invest Ophthalmol of Vis Sci. 2011;52: abstract 1610. 4. Gupta N, et al. Ophthalmology. 2020;127:72-84.

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Vabysmo™

- Farcimab FDA approved January 3, 2022 for AMD and DME
- AMD: 4 initial monthly doses, then every 2,3 or 4 mos, based on outcome
- DME: 4 initial monthly doses, then every 1-4 mos, based on outcomes
- COMINO and BALATON studies underway to evaluate efficacy and safety in people with macular edema following RVO

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How can we have longer duration?

- Genentech Port Delivery System (PDS)
- LADDER Study: PHASE II reported
 - 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
- Archway Phase III (7/2020)
 - 98% no refill before planned at 24 wks
 - BCVA and CST equivalent to monthly Lucentis
 - 2 refills vs 10.7 Lucentis injections over 12mos

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Beovu (brolucizumab)

- Novartis
- FDA approved Oct 9, 2019
- Greater fluid resolution than previous agents with similar vision gains on 3 mos dosing
- Based on Hawk and Harrier Phase 3 trials

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Beovu (brolucizumab)

- Hawk and Harrier Study: compared to Eylea
 - 30% of pts gained at least 15 letters by year 1
 - Greater reduction in central retinal thickness at week 16 and 1 year than Eylea
 - Fewer pts with subretinal fluid than Eylea
 - Real key is extended dosing
 - After 3 monthly loading doses
 - By year 1, > ½ pts on 3 mos dosing
 - Rest were 2 mos dosing
 - Safety profile similar to Eylea

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Beovu update

- In Feb, 2020, American Society of Retinal Specialists (ASRS) issued a warning reporting 14 cases of retinal vasculitis following injection of Beovu
 - 11/14 were occlusive and resulted in vision loss
- In March, Novartis concluded that retinal vasculitis, retinal artery occlusion, or severe vision loss occurred in 8.75-10.08 out of 10,000 injection
- Added to warning label
 - Intraocular inflammation in 4% of pts
 - Artery occlusion in 1%
- Advised to avoid if pts had h/o inflammation to any other anti-Vegf agent
- Has somewhat falling out of favor with retinal specialist due to these issue

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Anti-Vegf Biosimilars

- 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."
- Currently, 2 FDA approved Ranibizumab Biosimilars
 - Byoviz (Samsung) approved Sept 2021
 - Cimerli (Coherus) approved Oct 2022
- Many in development
 - Ranibizumab \cong 5
 - Aflibercept \cong 8
 - Bevacizumab \cong 1 Outlook Pharmaceuticals (Lytenava) August 30 NOT approved

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Geographic atrophy

- Estimated that 1.2 million Americans suffer from GA
 - > 5 million globally
 - 42% of pts with GA are legally blind
 - Incidence increases with age
 - Prevalence roughly quadruples every 10 years
 - Responsible for over 20% of all vision loss in pts with AMD

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Geographic atrophy

- Once thought to be slowly progressive, studies of natural history of GA paint a different picture
 - 16% of pts with bilateral GA progressed to blindness in better seeing eye, with median time to progression of 6.2 years
 - 67% were ineligible to drive with a median time to progression of 1.6 years
 - 40% of pts with bilateral GA lost greater than 10 letters in the better seeing eye, with a median time to progression of 2.4 years.

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Geographic atrophy

- | | |
|---|--|
| <p>Environmental/Demographic risk factors</p> <ul style="list-style-type: none"> • Age • Smoking • Diet • High Metabolic Intake • High BMI • Comorbidities | <p>Others</p> <ul style="list-style-type: none"> • Genetic (CFH/ARMS2) <ul style="list-style-type: none"> – As much as 70% risk may be genetic • Drusen Formation • Oxidation • Immune response/Inflammation <ul style="list-style-type: none"> – Overaction of complement system |
|---|--|

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Geographic atrophy

- Lesions grow with time, at various rates
 - Larger lesions, multi-focal lesions, extrafoveal lesions grow faster
- Treatment geared at decrease in lesion growth
- Various targets being investigated
 - Complement system: C3, c5

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SYFOVRE (Pegcetocoplan)

- Pegcetocoplan (Apellis): synthetic molecule that downregulates C3 complement pathway
- FDA approved for treatment of GA Feb 2023
- Delivered intravitreally
- Phase II Studies: 246 pts
 - At 12 mos, 29% lower rate of GA progression with monthly injections vs sham
 - No difference in visual acuity

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SYFOVRE

- Phase 3 OAKS and DERBY: 12 mos results
 - Primary endpoint to show reduced GA growth vs sham
- OAKS (637): met primary endpoint
 - 16%-22% reduction in lesion growth at 1 year
- DFERBY: did NOT meet primary endpoint
 - 11%-12% reduction in lesion growth at 1 year
- No change in visual acuity

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SYFOVRE

- Phase 3 OAKS and DERBY: 24 mos
 - Treatment was found to be accelerated with longer treatment, with greatest benefit between 18 and 24 mos.
- OAKS:
 - 22% reduction in lesion size in monthly group vs sham
 - 18% reduction in every other month
- DERBY
 - 18% reduction in lesion size in monthly group
 - 17% reduction in every other month
- Again, no improvement in VA noted
- GALE study underway to evaluate long-term safety and efficacy

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SYFOVRE

- Demonstrated to have favorable safety profile
- Most common adverse events
 - Ocular discomfort, vitreous floaters, conjunctival hemorrhage, transient intraocular inflammation, acute IOP
- Endophthalmitis in <1% (about 1 in 3000)
- Increased rates of neovascular AMD
 - 112% in monthly cohort, 7% every other month vs 3% in control

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SYFOVRE

- No notable difference in BCVA at 24 mos in either treated group
 - Perhaps due to relatively short time frame
- Recent ad hoc analysis
 - Demonstrated loss of 5.6 fewer ETDRS letters at 24 mos in pts with GA located farther away from foveal center

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SYFOVRE™

- FDA approved Feb 17, 2023
- First FDA approved med for treatment of GA
- 15 mg (0.1 ml of 150 mg/ml) administered by intravitreal injection to affected eye once every 25 to 60 days

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Izervay (Avacincpatad Pegol)

- Intravitreal Injection developed by Iveric Bio (Astellas)
- FDA approved August 5, 2023
- Blocks complement pathway c5a and c5b
- GATHER 1 /Gather 2 Study: 286 pts
 - At 12 mos, 27% (2 mg) and 28% (4 mg) less GA growth vs Sham with monthly injections
 - At 18 mos, 28% and 30%
 - Reduced rate of vision loss noted

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izervay

- Safety: Most adverse events were injection related
 - Subconjunctival hemorrhage 13%
 - Increased IOP 9%
- No cases of endophthalmitis over 18 mos in studies
- Approx. 7% progression to neovascular AMD

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IZERVAY

- Ad hoc analysis:
 - Lower proportion of pts treated with 2 mg experienced a 15-letter loss from baseline vs sham
 - Further, 56% risk reduction in persistent vision loss vs sham at 12 mos

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GTO05

- GTO05: investigational gene therapy designed to induce expression of CF-I after subretinal delivery
 - Gyroscope therapeutics, bought by Novartis
 - \$800 M up front, potential \$700M more
 - CF-I down regulates CF
 - CF related to inflammation and GA lesion progression
- Stage II studies showed well tolerated and had positive effects on lesion size and acuity
- Phase III studies underway
 - Looking for pts with GA and CF-I rare variants (\approx 3-5%) vs all GA pts

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Impaired Dark Adaptation is Earliest Biomarker of AMD

RESEARCH SHOWS:
Impaired dark adaptation identifies subclinical AMD
at least three years before

it can be seen with imaging, OCT or clinical exam.



Prospective Study of Subclinical AMD

- Sample consisted of 325 adult's w/o clinically detectable AMD
- At baseline, 24% of the subjects exhibited impaired dark adaptation
- AMD status determined at 3-year follow-up visit

** sources: Owsley, C et al. Ophthalmology. 2016;123(2):344-351.

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Same Disease at Every Stage

AMD is all one disease, no matter the stage

Subclinical AMD
Early AMD
Intermediate AMD

=

AMD

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Continuum of AMD similar to Glaucoma

- First you must identify the disease with structure and function
- Then you MONITOR the disease with structure and function
- Then you decide when to potentially refer based on structure and function

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Can Dark Adaptation play a role in established AMD??

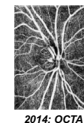
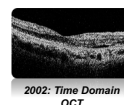
- 65 patients w established AMD followed for 4 yrs
- Decline in DA correlated w pt reported function
- Accelerated in eyes w more severe AMD and especially in eyes developing Subretinal Drusenoid Deposits
- Worsening DA correlated w Low Luminance Questionnaire scores

Chen et al. DA as Functional Measure in AMD. Ophth 6/19.

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OCT Angiography: The Next Chapter in Posterior Imaging

Displays structure and function from a single imaging system



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Principles of AngioVue OCTA

OCTA uses motion contrast to detect flow from OCT data

- o Rapidly acquires multiple cross-sectional images from a single location on the retina
- o Flow is the difference in signal between two sequential B-scans

Difference of Two OCT B-scans =

Flow Signal (Red) Overlay on OCT B-scan

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Enface OCTA Slabs: Based on Retinal Anatomy

En Face Visualization of Layers Based on Retinal Anatomy

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Normal

Superficial Capillary Plexus

Deep Capillary Plexus

Outer Retinal Zone

Choriocapillaris

Larger Vessels
Smaller FAZ than Deep Plexus

Network of Fine Capillaries
Larger FAZ

Avascular

Homogeneous Flow

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Pathology Example (CNVM)

Superficial

Deep

Outer Retina

Choriocapillaris

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OCTA Advantages in AMD

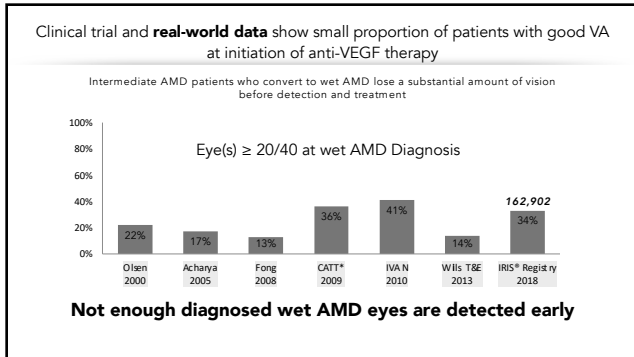
- Locate small CNVMs as soon as possible to get prompt treatment
- Help in deciding referral patterns
- Track changes in lesion size to see if therapy is working
- To Differentiate from other conditions that may appear similar

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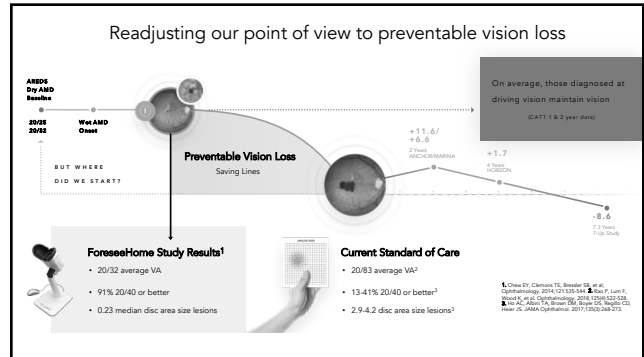
HOME study

- 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
- 60% of Medicare patients will pay \$0.00 for monthly monitoring

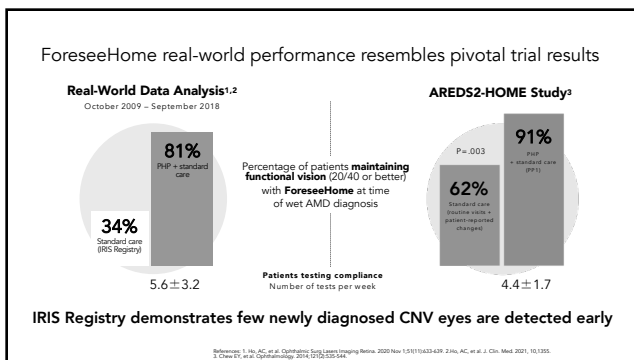
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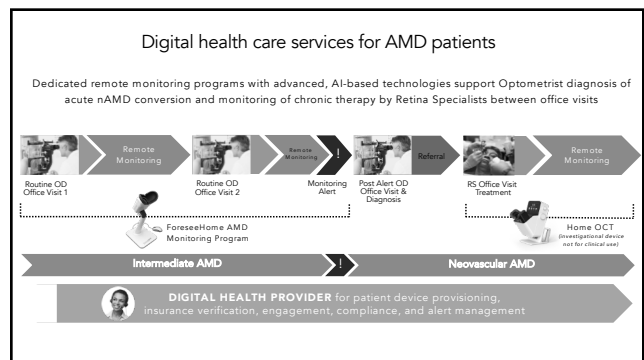
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Home OCT for monitoring chronic therapy of neovascular AMD between office visits

- Monitoring of intra- and subretinal fluid based on daily patient self-imaging
- Easy-to-use, patient-operated device
- Takes less than one minute per eye
- AI algorithm analyzes images on cloud
- Remote diagnostic clinic, provider of monitoring program, reports changes meeting physician-selected fluid volume thresholds to referring physician
- 24/7 physician access to all data

Home Device

Home OCT Image

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Clinical trial results show excellent system performance

- Cohorts**
>450 patients, 800 eyes, 6,400 OCT scans
- Usability**
90% of exudative AMD patients self-imaged successfully
- Image Quality**
Sensitivity and specificity of ophthalmologist identifying fluid was 97% and 95%, respectively
- Fluid Quantification**
Nano-liter amounts of fluid in the retina can be tracked automatically

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Results of first U.S. prospective longitudinal Home OCT feasibility study

- **Cohort:** 15 pts., 29 eyes, 3 mos. follow-up
- **Self-imaging duration:** 40 s (median)
- **Image quality:** 97% good or better
- **Scans eligible for AI fluid quantification:** 93%
- **Patient scan frequency:** 5.7 days per week
- **Patient feedback:** Positive survey results
- **Fluid identification by doctor vs. AI:** 83% agreement; disagreements only in eyes with small amounts of fluid.
- *In some cases, the treat and extend regimen exposed the retina to fluid for several weeks.*

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Is AMD in our DNA?

- **AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk**
- **Other 30% is environmental/lifestyle**
- **Risk factors**
 - **Non-modifiable:** age, race, gender
 - **Modifiable:** Smoking, increased BMI, poor diet/nutrition, UV exposure

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Major genetic factors

- CFH
 - Single most important genetic component
 - CFH Y402H
- ARMS2/HTRA1
 - Second most important gene in AMD
- C3
 - Another component of the complement system
- ND2
 - Mitochondrial oxidative phosphorylation molecule
- Others

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Genetic Factors and Risk: More than additive!

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

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AMD Genetic Testing: Arctic DX

Macula Risk NXG
Looks at 15 SNPs as well as smoking, BMI, age and AMD status to determine AMD patients who may progress to advanced AMD and vision loss in

- 2 years
- 5 years
- 10 years

Cheek Swab

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AMD Risk Testing for a Full Spectrum of Patients

<p>AMDIGuard DNA Progression Assessment</p> <p>For people ≥55yo with or without AMD findings</p> <p>For people <55yo WITH AMD findings</p> <ul style="list-style-type: none"> • Assesses a patient's risk of progression to advanced AMD within 2, 5, 10, 20 and 30 years • Delaying progression to advanced AMD with secondary prevention including AREDS vitamins, increased surveillance (home monitoring) 	<p>AMDIGuard DNA Risk Assessment</p> <p>For people <55yo without AMD findings</p> <ul style="list-style-type: none"> • Assesses a patient's lifetime risk of developing advanced AMD (GA or CNV) allowing preventive lifestyle changes at younger age • Delaying onset of disease with primary prevention including lifestyle modifications, supplementation (i.e. nutrition) and nutritional intervention
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How can we use this information?

- Increased surveillance for those at higher risk
 - Sooner/more frequent appointments
 - More diligent home monitoring
- More diligence with modifiable risk factors
- Consider earlier vitamin supplementation
- Potential treatments in the future

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Photobiomodulation (pbm) for AMD

- **Principle:** Red or NIR light (600-900 nm) upregulates mitochondrial cytochrome C oxidase, leading to ↑ATP production and ↓inflammation/apoptosis
- PBM ↓ROS in oxidatively stressed cells, including retinal vascular endothelium

AIMS Biophys. 2017; 4(3): 337-361.

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A Non-nutritional treatment for AMD: Photobiomodulation

- LIGHTSITE 1 had 36 subjects and tested 46 eyes
- Two series of treatments (3x per week for 3–4 weeks) over 1 year
- PBM patients had +4 letters at Month 1 and 7
 - 50% of PBM improved at least 5 letters vs 13.6%
 - Stat signif improvement in contrast, drusen volume, drusen thickness and QOL scores
- LIGHTSITE III currently enrolling in the US
 - Primary outcome is VA
 - Uses Valeda system by Lumithera

Markowitz et al. Photobiomodulation for AMD. Retina 8/19

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TXE from ASRS

- 165 eyes in 137 patients treated with at least 12 mos w at least 6 treatments first year and at least 3 every year after
- Average of 8 tx year 1 and 6 in years 2-7
- Mean change over 7 years: Year 1: +8.2 /7.0/4.4/4.2/4.4/4.6/4.6 at 7yrs
- At final follow-up, 23.4% of eyes of males and 25.7% of those of females had lost ≥15 ETDRS letters. A total of 28.1% of eyes of males and 27.7% of those of females had gained ≥15 letters.
- NOTE: At least 6 injections per year

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Intra vs sub retinal fluid

- Eyes with mostly SRFL, we more likely to be inactive after a yr of tx
- Eyes that were mostly inactive or mostly A-SRFL gained 2x letters vs mostly A-NSRFL (7.6 vs 7.5 vs 3.6)
- At 1 yr, vision better in SRFL vs NSRFL 67.5 vs 62.5 letters
- So, it's not just presence of fluid, but it's location

Nguyen et al. Assoc of Anatomical and Clinical Outcomes in NvAMD w AVEGF. Retina 7/21. NSRFL: Not sub-retinal fluid

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Nutrition + injection

- Combination therapy plus 20mg Zeaxanthin¹
 - Intravitreal Anti-VEGF + Steroid + PDT + 20mg Zeaxanthin for wet AMD
 - At 5 yrs: 3 lines gained in 18%
 - **Fellow eye involvement only 21.6% at 5 yrs (less than other studies)**
 - Average treatment cycles was only 2.7 to achieve stability
 - Avg cost over 5 years was 8,000 per eye vs over 70,000 potential if Anti-VEGF alone
 - Points to the need to see nutrition as a therapeutic and not just preventative
- Studies show improved visual function in AMD with carotenoid supplementation
- Can we improve both structure and function (beyond Snellen)?

1. Oik et al. Combination + Z for wet AMD at 5yrs. ASRS 2020

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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)

Simon Brucker, MD, MPH, Robert B. Hubbard, MD, PhD, David S. Fingar, MD, Steven F. Sola, MD, Kang Zhang, MD, PhD for the SEVEN-UP Study Group*

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Long term results

- Retrospective analysis of the Vestrum Health Retina Database shows people lose vision over time (compared to RCCT)
- Pts seen in "real life" 2014-2019 with at least 12mos f/u
- 7.6/19.5/32 injections after years 1/3/5
- +3/-2/-2.2 letters after years 1/3/5
- For comparison in DME:
- 6.2, 15.4, and 26.0 injections after yrs 1/3/5
- +4.7, +3.3, and +3.1 letters after years 1/3/5
- * AMD requires more injections and has poorer results/outcomes
- Worse than DME, which is worse than BRVO than CRVO

Ciulla, T. Presented at ASRS 10/21

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Long term results continued

- Patients that started with 20/40 tended to lose vision
 - Better vision = more vulnerable to vision loss
- Pts with worse vision at initiation were more likely to gain vision at 3 yrs
- Mean change in visual acuity correlated to treatment intensity over time
 - Mean letters gained correlated to mean number of treatments at every time period
- WHAT ROLE DOES THE OD PLAY HERE?

Ciulla, T. Presented at ASRS 10/21

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Consequences of LTFU

- Study comparing patients with a lapse (242) vs control (242)
 - Initial BVCA: 58.9 vs 59.2 letters on ETDRS
 - Initial CSF: 252 vs 259microns
 - Thickness after lapse: 279 vs 253microns
 - Thickness after treatment after lapse: 259 vs 247microns
 - VA after lapse: 54 vs 60 letters
 - VA did not recover a year after recontinuation of treatment

Greenlee et al. Consequences in Lapse in AMD Treatment. Retina 3/21.

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Smoking doesn't help either..

- AMD pts receiving injections for 12 mos
- non-smoker vs quit smokers vs smokers
- Letters gained: 7.7 vs 6.5 vs 3.5
- No difference in number of injections
- Smokers were 6.2yrs younger at initiation

Vittorio et al. Smoking and AntiVEGF in AMD. Retina 9/2020/

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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
 - Macularhope.org
 - Sightmatters.com

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Genetic treatments

- Several companies looking at genetic treatment for AMD
- Viral vectors are used to introduce an anti-VEGF encoding transgene to allow the eye to begin to secrete anti-VEGF
 - Transforms the eye into a "biofactory"
 - Produces its own anti-VEGF supply
 - Reduces need for extrinsic injections
- RGX-314 and ADVM-022

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Gyroscope therapeutics

- GT005: investigational gene therapy designed to induce expression of CF-I after subretinal delivery
 - CF-I down regulates CF
 - CF related to inflammation and GA lesion progression
- Stage II studies showed well tolerated and had positive effects on lesion size and acuity
- Phase III studies underway
 - Looking for pts with GA and CF-I rare variants (\approx 3-5%) vs all GA pts

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Others

- Oracea
 - Low dose oral doxycycline
 - Control inflammation
 - Phase II/III studies underway on GA growth
- Metformin
 - 2021 Article, JAMA ophthalmology
 - 5-10% reduced odds of developing AMD in pts on metformin
 - Further studies needed

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Others

- RPE Patch
 - Graft RPE from stem cells to damaged macula area
 - Recent advances in growing cells as well as surgical technique
 - Many years away from practical use
- Stem cells
 - Small trials show promise
 - May be 10+ years away

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Conclusion

- More options than ever for pts with early to intermediate AMD
 - Vitamins and lifestyle changes
 - New technology
 - Dark adaptation
 - Home Testing
 - Genetic testing
 - More options for wet AMD treatment with more in pipeline
 - If suboptimal vision, don't forget about low vision!!
- "With great power comes great responsibility"
- Uncle Ben, Spiderman

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