# UPDATE ON AMD 2022

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## Introduction

- AMD is the leading cause of vision loss *in Americans* over the age of 60
- Advanced AMD is the leading cause of vision loss and irreversible blindness *worldwide* in those over the age of 50
- As many as 11 million Americans have some level of AMD
  - Expected to increase to nearly 22 million by 2050
- More than glaucoma (2.2 million) and DR (7.7 million) COMBINED

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## Risk Factors

- Age
  - Risk of AMD increases from 2% in ages 50–59 years to nearly 30% in people aged >85 years
- Race
- Smoking
- Family history/genetics
- UV exposure
- Poor diet
- obesity

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## Two Forms of AMD

- Dry form[1]
  - Characterized by geographic atrophy, drusen, and RPE hyperplasia
  - Most common, approximately 90% of all AMD[2,3]
- Wet form (neovascular)[3]
  - Characterized by subretinal blood, hard exudates, and/or subretinal fluid from CNVM
  - Accounts for only 10% of AMD, yet is responsible for 90% of all legal blindness from AMD[2]

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## Classification of AMD

- No AMD (AREDS category 1)
  - No or few small drusen (<63 um in diameter)
- Early AMD (AREDS category 2)
  - Multiple small drusen
  - few intermediate drusen (63–124 um in diameter)
  - Mild RPE abnormalities

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## Classification of AMD
**(continued)**

- Intermediate AMD (AREDS category 3)
  - Numerous intermediate drusen
  - At least one large druse (≥125 µm in diameter)
  - Geographic atrophy, non-central
- Advanced AMD (AREDS category 4)
  - Central GA
  - Neovascular AMD

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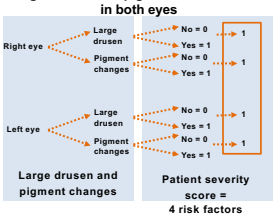
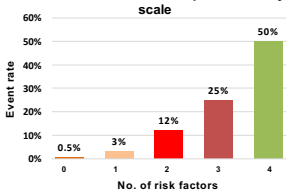
## AREDS Simplified Severity Scale

**Scoring of risk factors for patient with large drusen and pigment abnormalities in both eyes**




**5-year rates* of progression to advanced AMD based on AREDS simplified severity scale**

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## AMD Screening

Patients in the following groups should be screened for AMD

- Patients who are aged >60 years
- Patients with HTN or cardiovascular disease
- Cigarette smokers
- Patients with history of AMD in first-degree family members
- Patients with history of significant cumulative light exposure
- Patients with decreased dark adaptation or other symptoms consistent with AMD

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## AMD Examination

- Examination should include:[1,2]
  - Measurement of visual acuity
  - Dilated retinal examination
  - Amsler grid testing
  - Additional testing as indicated (OCT, FA, photos, etc.)
- Studies show that many patients with AMD go undetected and first present with vision loss
  - In one study, 25% of eyes deemed normal on eye exam had undiagnosed AMD[3]
    - 30% of patients with undiagnosed AMD had large drusen that would have been treatable with nutritional supplements
  - In another study, 78.5% with neovascular AMD had subfoveal lesions, and 37% of patients presented with vision worse than 20/200[4]

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## Introduction

- Exciting time to be interested in AMD
- Many new treatments now available for AMD
  - Years ago, we had nothing at all to offer patients with AMD
- Current Treatments
- Potential Treatments
- New Diagnostic Equipment

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## Dry AMD

- Currently mainstay treatment for Dry AMD revolves around prevention of progression through vitamins, nutrition and lifestyle changes
  - Rheophoresis, Laser, Anecortave Acetate did not prove effective
  - Smoking #1 modifiable risk factor for getting AMD as well as its progression!
    - One study showed 90% of pts with AMD were not advised to quit smoking
- Early detection of conversion from dry to wet may result in better treatment for patients

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## AREDS

- First large scale study looking at nutrition and ocular health
- 3640 pts followed on average for 6.3 years
  - Results released October 2001
- Results showed that 25% risk reduction to developing advanced AMD in pts with intermediate (stage 3) AMD or worse
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 15 mg vitamin A (25,000 IU beta carotene)
  - 80 mg zinc
  - 2 mg copper

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## AREDS 2

- AREDS 2: Enrollment ended June 2008 with ≈4200 patients followed for six years
  - Effect of lutein, zeaxanthin and omega 3 on AMD
  - Effect of eliminating beta carotene on AMD
  - Effect of reducing zinc on AMD
  - Effect of supplements on cataracts
  - Validate the AMD scale from original AREDS
- Results released May 5, 2013

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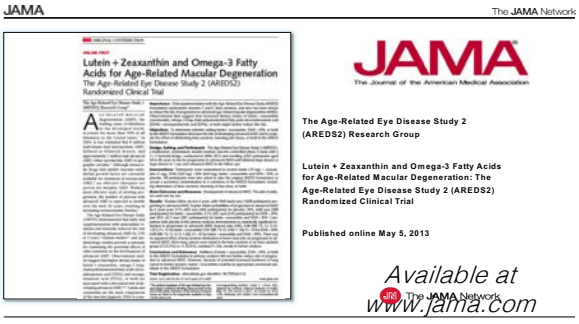


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## AREDS 2

- Major Conclusions:
  - The addition of lutein and zeaxanthin, DHA and EPA or both to the AREDS formulation did not further reduce the risk of progression to advanced AMD
  - Substituting L/Z (10 mg/2 mg) for beta carotene is an appropriate substitution, because of potential increased incidence of lung cancer in former smokers

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## Additional findings

- Lutein and zeaxanthin did provide an additional 10% reduced risk over current supplements
  - In patients with lowest dietary intake of l/z, additional 26% reduced risk
- Decreasing zinc from 80 mg to 25 mg had no significant effect
  - No change recommended (?)
  - Deserves further study
- Competitive absorption of carotenoids

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Age-Related Eye Disease Study 2
The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

### AREDS2 Formulation

Vitamin C (500 mg)

Vitamin E (400 IU)

~~Beta Carotene (15 mg)~~

**Lutein (10 mg)/Zeaxanthin (2 mg)**

Zinc (80 mg zinc oxide)

Copper (2 mg cupric oxide)

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## Smoking and AMD

- Smoking has been shown in multiple studies to be the #1modifiable risk factor for getting AMD as well as its progression
- **One study showed 90% of pts with AMD were not advised to quit smoking**
- **<50 of smokers knew that smoking could may contribute to blindness**

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## Smoking and AMD

- Nurses health study
  - 2.5 fold increase in AMD in current smokers
  - 2.0 fold increase for past smokers
  - Former smokers did not show decreased risk until 15 years after cessation
  - 30% of all AMD related top smoking

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## Smoking and AMD

- Blue Mountain Eye Study: Australia 1992-1994
  - Current smokers had a 4-fold increase in late AMD compared with never-smokers
  - Former smokers had a 3 fold increase in late AMD, esp GA
  - 20% of all cases of blindness related to smoking

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## Smoking and AMD

- New research: *Retina* 2020
  - Current smokers have up to a 7-fold greater risk for nAMD vs non-smokers
    - more aggressive , larger CNVM and worse baseline va in smokers
    - Current smokers were 6.2 years younger than nonsmokers needing treatment
  - Pts who smoked while undergoing anti-vegf treatment experienced inferior 12 and 24 month visual outcomes

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## Diet and AMD

- 2018 Study:
  - 4446 European pts >55
  - Seen every 5 years for 21 years on average
    - Adherence to Mediterranean Diet reduced risk of advanced AMD by 41%
    - Support role of diet rich in fruits, vegetables, legumes and Fish in prevention of AMD

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## Diet and AMD

- 2016
  - Meta-analysis looking at 4202 cases in 128,988 individuals
  - Fish consumption reduced risk of both early and late AMD
  - Both for less than as well as more than 10 year follow up
  - Dark meat fish, esp. tuna fish, intake was associated with reduced risk of AMD
  - Linear association between dose of fish consumption and risk of AMD demonstrated

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## Diet and AMD

- 2019
  - Meta-analysis looking at 26 articles consisting of 211,676 subjects with 7154 cases of AMD from 8 studies
    - 18% reduced risk for total AMD with increased fish intake, both early and late
    - 20% increased risk for total AMD with increased alcohol consumption
    - Increased risk for meat consumption for early AMD, but not late
    - No association with fruits, vegetables, nuts, grain or dairy

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## Diet and AMD

- 2018: Rotterdam Eye Study
  - 4200 pts>55 years followed for 9.1 +/- 5.8 years
  - 754 developed AMD
  - Determined a diet of 200 grams per day of vegetable, fruit two times per day, and fish two times per week is associated with a significantly reduced risk of AMD
    - Only 3.7% of patients adhered to this

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## Diet and AMD

- 2006
- 6734 pts followed for 13 years
  - Red meat more than 10x a week had a additional 47% risk of developing AMD vs those who ate red meat 5 times or less per week, especially early AMD
  - Chicken (white meat) 3.5 times a week had 60% chance less risk of AMD vs. those who ate 1.5 times a week, especially late AMD

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## Exercise and AMD

- 2017 Meta-Analysis, 9 studies, age range 30-97
- Physical activity associated with lower odds of early and late AMD in white population
  - More pronounced with Late AMD
- Suggested that even a small amount of physical activity-as little as 3 hrs per week- may be beneficial

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## Exercise and AMD

- Beaver Dam study
  - 4000 men and women 43-86 years old
  - Those who exercised 3 or more times a week had 70% lower risk for late amd (active lifestyle)
  - 30% lower rates of WET AMD in pts who walked 12 or more blocks 3 times a week

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## Obesity and AMD

- Progression of Age-Related Macular Degeneration Study.
  - 2003, Seddon et al
  - Increased risk for advanced AMD with BMI>25
    - Even more increased if BMI >30
  - Higher waist –hip ration also increased risk for progression
  - 25% reduction for vigorous activity 3x /week vs none
  - Other studies have been less conclusive

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## UV and AMD

- 2016 Study
  - Current sunlight exposure showed no association with early or late AMD
  - Past sunlight exposure (>8 hrs /day) was associated with early AMD
  - Outside working was associated with late AMD
  - No association with iris color and early or late AMD
  - “Sunlight exposure during working life is and important risk factor for AMD, whereas sunlight exposure after retirement has less influence on the disease”

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## UV and AMD

- Beaver Dam Study
  - Pts 43-86. 2764 followed for 10 years
  - People exposed to summer sun for >5 hrs while in teens and 30s were at higher risk of developing AMD at 10 years vs those who had less than 2 hrs
  - Those that were exposed >5hrs but reported wearing hats and wearing sunglasses were at decreased risk vs those that did not
  - People who reported 10 or more severe sunburns during youth vs 1 or no burn were at higher risk

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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<br>MARINA<br>IVAN | VIEW<br>1 and 2 | HAWK HARRIER | CATT |

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

VEGF = vascular endothelial growth factor.

AAO. AMD preferred practice guidelines, 2019 (www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp). Kulkarni K, Prenner JL. *Rev Ophthalmol.* 1/13/2006. (www.reviewofophthalmology.com/article/an-update-on-macugen-triab). URLs accessed 5/30/2020.

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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

Pongsachareonnont P, et al. *Clin Ophthalmol.* 2018;12:1877-1885. Yeo NJY, et al. *Front Pharmacol.* 2019;10:1363. Holz FG, et al. *Br J Ophthalmol.* 2014;100:1623-1628. American Society of Retina Specialists (ASRS). Intravitreal Injections. (www.asrs.org/content/documents/fact-sheet-39-intravitreal-injections.pdf). Sukgen EA, et al. *Int Ophthalmol.* 2017;37:215-219. Living well with low vision. (https://lowvision.preventblindness.org/2013/06/25/betadine-and-eye-pain/). URLs accessed 5/30/2020

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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]**

- **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**

Eylea[2,3]

- 95% of patients treated maintained acuity
- 7.9–10.9 letters mean improvement of vision

Beovu[4]

- ~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;116:57-65.e5. 2.Nguyen QD, et al. *Invest Ophthalmol Vis Sci.* 2011;52: abstract 3073. 3. Schmidt-Erfurth U, et al. *Invest Ophthalmol Vis Sci.* 2011;52:E-Abstract 1650. 4.Dugel PU, et al. *Ophthalmology.* 2020;127:72-84.**

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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

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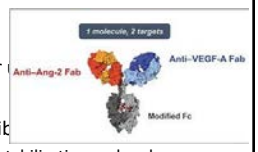
## Faricimab

- Roche/Genetech
- First bi-phasic antibody for intraocular
- One arm: Vegf-A inhibitor
- Other arm: Angiopoietin-2 (Ang-2)inhib
  - growth factor that promotes vascular destabilization and and inflammation
- Dual inhibition of VEGF and Ang-2 have proven more effective than inhibiting either target alone

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## Faricimab

- Avenue/Stairway
  - Looked at 2 doses ( 6.0 and 1.5 mg) of Faricimab vs Lucentis
  - Good anatomic improvement and vision gains similar to Lucentis
    - Mean vision gains of 9.6 to 11.4, depending on dose and schedule
      - Faricimab 6.0 mg q 16 weeks had greatest gain (11.4)
  - TENAYA/LUCERNE
    - Met primary endpoint: people receiving farcimab q 16 weeks achieved VA outcomes that were non-inferior to Eylea q 8 weeks at 1 year
    - Almost half (45%) were injected q 16 weeks

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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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## Susvimo

- Previously known as Port Delivery System with 100mg/ml Ranibizumab
- FDA approved 10/21
- Non-inferior to Lucentis q month
  - Only 1.6% needed rescue injection before 6mo refill (>98% no rescue)(4/246)
  - VA and anatomical outcomes equivalent after 72mos vs monthly injection
    - Regardless of presence or absence of subretinal or intraretinal fluid
  - +.2 letters after 40 weeks vs .5 in monthly injections

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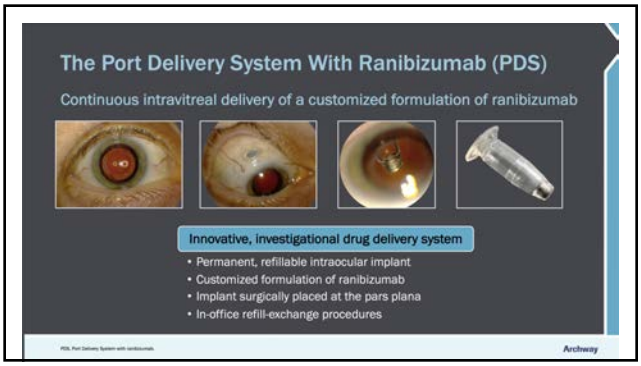


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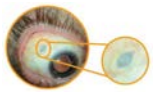
## How can we have longer duration?

- Genentech Port Delivery System (PDS)
- LADDER Study: :PHASE II reported
  - 63-80% didn't need refill for 6 mos depending on dosa
  - 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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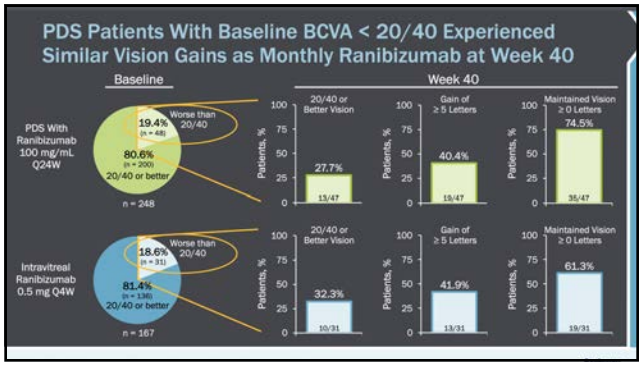


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### Importance of Early Treatment: CNV Lesion Size

- Evidence from many trials is clear: smaller lesions respond better to treatment
- MARINA study[1]: larger CNV lesion size at baseline was associated with greater loss of letters in sham-treatment group and less gain of letters in ranibizumab-treated arms
- ANCHOR study[2]: smaller baseline CNVM lesion size was associated with greater gain of letters in those receiving ranibizumab
- CATT trial[3]: larger area of CNVM at baseline was associated with worse VA at 1 year, less gain in VA at 1 year, and lower proportion of patients gaining ≥3 lines of acuity

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### Importance of Early Treatment: 2020 Analysis of IRIS Registry

- Real-world patients with neovascular AMD who underwent anti-VEGF treatment
- Study included 162,902 eyes
- Results
  - Patients who presented with VA of 20/40 or better at diagnosis maintained mean VA of 20/40 or better for 2 years after initiating treatment
  - Those who presented with VA worse than 20/40 never reached 20/40 at 1 or 2 years
- Conclusion: baseline VA at diagnosis of wet AMD predicts long-term VA outcomes

Early diagnosis before VA is adversely affected is a key factor in preserving vision in patients with wet AMD

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### When Should Patients Be Referred to Retinal Specialist to Consider Treatment?

- Any change in vision or metamorphopsia in patients with AMD should be taken seriously
  - Assume "wet" AMD until proven otherwise
- Unless able to determine no fluid/CNVM, patient should be referred to retinal specialist
- Any patient with "wet" AMD deserves prompt referral to retinal specialist for consideration of treatment
  - Data show patients exhibiting CNVM do better with early detection and prompt treatment![1]

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## Recommendations for All AMD Patients

- Don't smoke
- Exercise regularly
- Keep other medical conditions under control
- Maintain a healthy weight
- Eat a diet high in fruits, vegetables, and fish
- Limit consumption of red meat and foods high in fat
- Protect eyes from sunlight with UV protection and sunglasses
- Take supplements as prescribed by your doctor
- Follow-up as recommended

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## Is AMD Under diagnosed?

- 25% of eyes deemed normal on DFE by eye care provider (both ODs and MDs) had macular characteristics that indicated AMD
  - Of those, 30 % had level that would have been treatable with nutritional supplements
  - Eye care providers knew pts were being specifically screened for AMD
- Another study showed that 79% pts with AMD were first diagnosed with avg acuity of 20/50 from AMD!

– BOTTOM LINE: WE ARE NOT DOING ENOUGH TO DETECT AMD!!!

Prevalence of undiagnosed Age-Related Macular Degeneration in Primary Eye Care Neely DC et al. *JAMA ophthalmol* 2017: 135(6): 57–575

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## Standard of Care Comparison: Two Multifactorial Diseases

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

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## Dark Adaptation

- **Dark adaptation is a sensitive marker for early AMD**
- **The AdaptDx measures dark adaptation**
- **A rapid test of dark adaptation using the AdaptDx has been found to have a 90% sensitivity for detecting dark adaptation impairment associated with AMD**
- **Decreased dark adaptation may precede clinical findings of AMD by as much as 3 years**
- **Dark adaptation is more sensitive than other tests such as Snellen acuity, contrast sensitivity, or visual fields which are about 25% sensitive.**

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## Impaired Dark Adaptation is Earliest Biomarker of AMD

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

RESEARCH SHOWS:
Impaired dark adaptation identifies subclinical AMD
**at least three years before**
it can be seen with imaging, OCT or clinical exam.

UAB ALSTAR Study

**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

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## AdaptDx Validated in Multi-Site Study

sources: Jackson GR, et al. Invest Ophthalmol Vis Sci. 2014;55(2):1427-1431

Johns Hopkins
Harvard
Penn State Hershey College of Medicine

**High Sensitivity**
Correctly identified
90.6%
of confirmed AMD cases

**High Specificity**
Correctly identified
90.5%
of confirmed normal cases

**High Accuracy**
90.6%
overall

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## How can we use this information?

- Detect AMD sooner
  - Start Lifestyle intervention sooner
  - Sooner/more frequent appointments
- Consider earlier vitamin supplementation
- Useful to track progression in pts with mild or worse AMD

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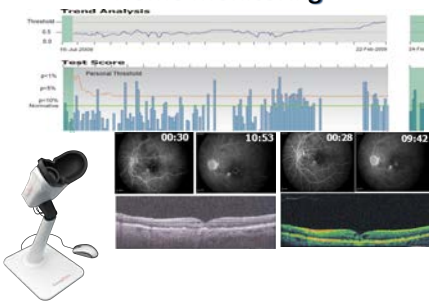
## Home monitoring

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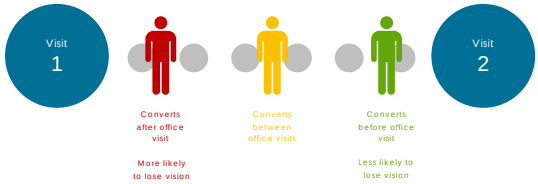
## At-risk Patients May Convert to Wet AMD at Any Point Between Follow-up Visits




Reference: Rauch R, et al. Retina. 2012;32(7):1260-1264.

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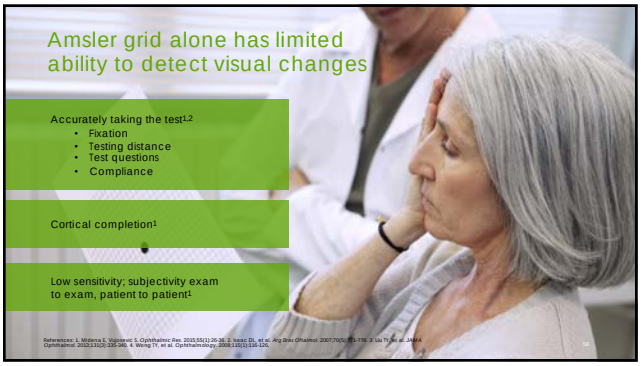
## Amsler grid alone has limited ability to detect visual changes

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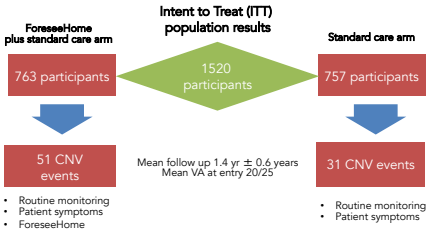
## AREDS2-HOME Study




***Primary outcome:** Change in BCVA from baseline to CNV detection*

Reference: AREDS2-HOME Study Research Group. Ophthalmology. 2014;121(2):535-544.

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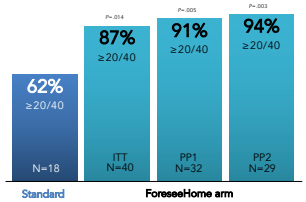
## More patients who used ForeseeHome maintained ≥20/40 VA




**50% MORE**
patients maintained 20/40 or better when using ForeseeHome vs standard of care alone

***94% of patients maintained 20/40 at time of wet AMD diagnosis; Absolute visual acuity at time of wet AMD diagnosis is critical to visual acuity outcomes at year 1***

Reference: AREDS2-HOME Study Research Group. Ophthalmology. 2014;121(2):535-544.

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## Notal Home OCT

- **Notal OCT Analyzer (NOA)**
- **"Uses computer image analysis algorithm to provide automated detection of pathological fluid in exudative retinal disease, including wet AMD, macular edema and retinal vein occlusion"**
- **Performance validated in study comparing sensitivity , specificity and accuracy with 3 retinal specialist**

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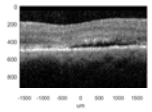
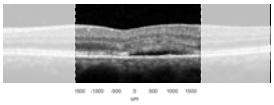
## Patient Self-operated Home OCT provides high quality images

- Patient self-installed and self-operated OCT device
- Monitoring of intra- and subretinal fluid in between office visits
- Provides cross sectional images of the central 10 deg. (3 mm x 3 mm) of the macula in patients with exudative AMD
- 88 B-scans with dense 34 µm spacing ensure high sensitivity of fluid detection
- Test takes approximately 10 sec. per eye
- Device uploads OCT data to cloud

Home OCT



Heidelberg Spectralis (in-office device)



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## Home OCT Performance and Roadmap

- US clinical trial demonstrated 90% of 196 elderly wet AMD patients with VA > 20/400 could self-operate and self-capture readable images following a 2-minute video tutorial (presented at ASRS 2019)
- Human graders identified fluid with SENSITIVITY = 91.5% and SPECIFICITY = 97.0% for Notal Home OCT V2.5 when compared to commercial OCT devices (presented at ASRS 2019)
- Notal Vision's patient-operated, AI-enabled Home OCT system was granted FDA Breakthrough Device Designation Status, and was selected to participate in FDA's OCT Innovation Pilot Program
- Notal Vision plans to bring first devices to patients' homes in 2020 as part of clinical trials with a commercial launch in 2021

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## How can I use this information?

- Key is early detection of conversion for DRY to WET AMD
- Evidence from many trials is clear: smaller lesions respond better to treatment
  - CATT trial[3]: larger area of CNVM at baseline was associated with worse VA at 1 year, less gain in VA at 1 year, and lower proportion of patients gaining ≥3 lines of acuity
- IRIS registry: 160K+ pts treated with anti-VEGF
  - Patients who presented with VA of 20/40 or better at diagnosis maintained mean VA of 20/40 or better for 2 years after initiating treatment
  - Those who presented with VA worse than 20/40 never reached 20/40 at 1 or 2 years

Early diagnosis before VA is adversely affected is a key factor in preserving vision in patients with wet AMD

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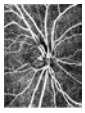
## OCT Angiography: The Next Chapter in Posterior Imaging

Images retinal microvasculature without dye injection

Displays structure and function from a single imaging system

2002: Time Domain OCT

2006: Spectral Domain OCT



2014: OCTA

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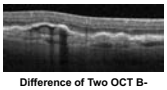
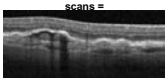
## Principles of AngioVue OCTA

OCTA uses motion contrast to detect flow from OCT data

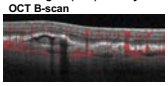
- Rapidly acquires multiple cross-sectional images from a single location on the retina
- Flow is the difference in signal between two sequential B-scans



Difference of Two OCT B-scans =



Flow Signal (Red) Overlay on OCT B-scan



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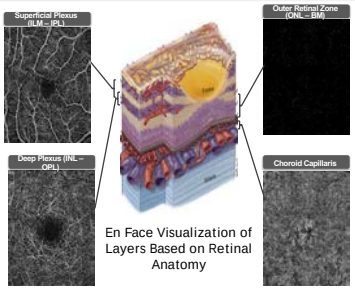
## Enface OCTA Slabs: Based on Retinal Anatomy

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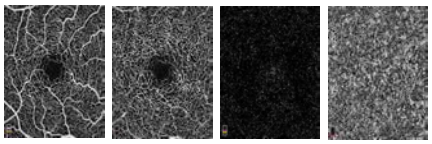
## Normal

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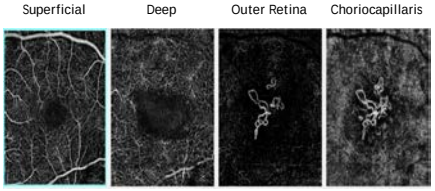
## Pathology Example (CNVM)

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## Fundus Autofluorescence Imaging (FAF)

- Relatively new non-invasive imaging modality developed over past decade
- Has been area of interest in ophthalmic research for over 40 years
- Uses fluorescent properties of lipofuscin

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## Lipofuscin

- Aging or disease to photoreceptors causes accumulation of lipofuscin
- Lipofuscin is composed of mainly of A2E
- Excessive lipofuscin deposition is considered pathological and associated with visual loss
- Considerable evidence that accumulation of lipofuscin can cause cell death and aptosis

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## AMD/GA

- Described as prognostic marker for GA progression
- Increase AF in the 500um margin around areas of GA may help distinguish between slow and fast progressing lesion
- May be useful moving forward with potential treatment of GA
- Also may help distinguish AMD from mimickers

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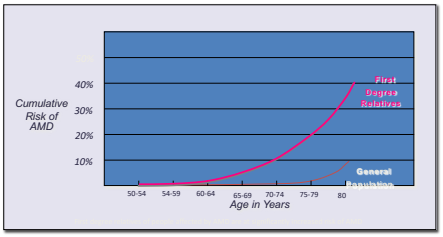
## Is AMD in our DNA?

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## A Prospective Study of 2 Major Age-Related Macular Degeneration Susceptibility Alleles and Interactions With Modifiable Risk Factors

Debra A. Schaumberg, ScD, OD, MPH; Susan E. Hankinson, ScD; Qun Guo, MSc; Eric Rimm, ScD; David J. Hunter, MBBS, ScD

Arch Ophthalmol. 2007;125(1):55-62. doi:10.1001/archopht.125.1.55

- CFH y 402H 2-4 x more likely to get AMD
- ARMS 2: 2.3 -5.6 x more likely
- If highest risk alleles for both, 50 fold increase in AMD
- Smoking and obesity increased risk even further

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## A Prospective Study of 2 Major Age-Related Macular Degeneration Susceptibility Alleles and Interactions With Modifiable Risk Factors

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Arch Ophthalmol. 2007;125(1):55-62. doi:10.1001/archopht.125.1.55

## Assessing Susceptibility to Age-Related Macular Degeneration With Genetic Markers and Environmental Factors

Yahong Chen, MD, PhD; Jane Zeng, MD; Chao Zhao, BS; Kevin Wang, BS; Elizabeth Trood, MD; Jeanette Buehler, BS; Matthew Wood, MD; Daniel Kasuga, MD; Paul S. Bernstein, MD, PhD; Jay Hughes, BS; Victoria Fu, BS; Jessica Chin, MS; Clara Lee, BS; Maureen Crocker, MBA; Matthew Bedell, MD; Francesca Salazar, MD; Zhenglin Yang, MD; Michael Goldbaum, MD; Henry Ferreyra, MD; William R. Freeman, MD; Igor Kozak, MD, PhD; Kang Zhang, MD, PhD

## Prediction Model for Prevalence and Incidence of Advanced Age-Related Macular Degeneration Based on Genetic, Demographic, and Environmental Variables

Johanna M. Seddon,1 Robyn Reynolds,1 Julian Maller,2 Jesen A. Fagerness,3 Mark J. Daly,2 and Bernard Rosner1

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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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## AMD is a Genetic Disease

| Population Attributable Risk | |
|---|---|
| Condition | Genetics (%) |
| Colorectal Cancer | 35 |
| Diabetes II | 26 |
| Coronary Artery Disease | 40 |
| AMD | 70 |

Those with stronger genetic risk develop more advanced disease earlier in life.

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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

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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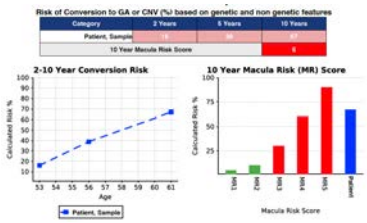
## Patient Report

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## AMD Risk Testing for a Full Spectrum of Patients

**AMD Progression Risk Testing**

For people ≥55yo with or without AMD findings

For people <55yo WITH AMD findings

- 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)

**Lifetime AMD Risk Testing**

For people <55yo without AMD findings

- 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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## AMD Gene Panel

- Based on the latest in AMD Genetics research
- Clinically Proven and Clinically Actionable to be the most impactful variations on AMD progression
- Combines both genetic + non-genetic markers

23andMe SNPs

| Gene | SNP No. | Allele Variants | AMD Risk | Chromosome | Pathway |
|---|---|---|---|---|---|
| ARMS2/HTRA1 (HtrA Serine Peptidase 1) | Rs10490924 (A69S) | GG | Lower Risk (Reference) | 10q26 | Immune/ inflammatory |
| | | GT | Moderate Risk | | |
| | | TT | Higher Risk | | |
| CFH (Complement Factor H) | Rs1061170 (Y402H) | TT | Highly Protective | 1q31 | Complement |
| | | CT | Moderately Protective | | |
| | | CC | Higher Risk (Reference) | | |
| | Rs121913059 (R1210C) | CC | Lower Risk (Reference) | | Complement |
| | | CT | Moderate Risk | | |
| | | TT | Higher Risk | | |
| | Rs1410996 (IVS14) | AA | Highly Protective | | Complement |
| | | GA | Moderately Protective | | |
| | | GG | Higher Risk (Reference) | | |
| C3 (Complement Component 3) | Rs2230199 (R102G) | GG | Lower Risk (Reference) | 19p13 | Complement |
| | | GC | Moderate Risk | | |
| | | CC | Higher Risk | | |



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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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## Potential Therapies

- Currently, there are ≈ 1854 studies evaluating AMD, both Wet and Dry
  - www.clinicaltrials.gov (Sept 2020)
    - More than:
      - glaucoma
      - dry eye
      - diabetic eye disease
- Exciting time to be involved, with many possible therapies that may prove useful for our AMD patients

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## Potential Therapies

- Better Efficacy
  - Better drug
  - Different Mechanism
- Reduced administration
- Different delivery System
  - Eye drops
  - Oral
  - Others

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## Conbercept

- Approved in China for treatment of Wet AMD since 2013
- Similar to other agents, but blocks VEGF-A, B and C as well as PlGF
- AURORA and PHOENIX trials were smaller trials to get approved in China
- Has proven safe ad effective in clinical use
- PANDA study is larger, worldwide study starting to look at conbercert 0.5 mg and 1.0 mg q 12 weeks vs Eylea q 8 weeks in treatment naive wet AMD patients

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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 they 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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## APL-2

- Pegcetacoplan (Apellis): synthetic molecule that downregulates C3 and all complement pathways
- 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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## APL-2

- Phase 3 DERBY and OAKS
  - Sept 9, 2021
- OAKS: 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
- Company moving forward

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## Zimura

- Avacincaptad pegol, Iveric Bio
- Blocks complement pathway c5a and c5b
- GATHER 1 (Phase II) Study: 286 pts
  - At 12 mos, 27% (2 mg) (4 mg) and 28% (4 mg) less GA growth vs Sham
  - At 18 mos, 28% and 30%
- GATHER 2: Phase III study currently enrolling
  - 2 mg vs sham

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## Brimonidine

- Biodegradable, intravitreal insert (Allergan)
- Phase II study:
  - Implanted injected q 6 to 12 mos
  - 29-31% decrease in GA growth at 12 mos
  - Bigger lesions did even better:
    - Lesions >6mm$^2$ had 38% decreased growth
- Phase III in the works

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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 (≅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 form practical use
- Stem cells
  - Small trials show promise
  - May be 10+ years away

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## Conclusion

- AMD Super prevalent!
- AntiVEGF agents best treatment available for wet AMD
- Vitamins and lifestyle changes for pts with dry AMD
- Use new technology to take better care of your AMD pts!
- Look out for new developments in treatments
- Those involving fewer/no injections will ultimately prevail

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