AMD:
The past, present and future

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disclosures

- Apellis
- Icare/Centervue
- Genentech
- LKC Technologies
- Notal Vision
- Regeneron
- Science Based Health
- Visible Genomics

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Introduction

- **Exciting time to be interested in AMD**
- **Great strides in treatment, diagnostics and understanding of amd over last 15-20 years**
- **Past treatments**
- **Current treatments and Diagnostic Equipment**
- **Potential future Treatments**

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THE PAST…..

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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 ≅ 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 ETDRS 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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THE PRESENT….

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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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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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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)
- ~~Omega-3 fatty acids (DHA/EPA)~~

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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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How do I use this information?

- 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

Gerzon J, et al. *Rev Optom.* 2017;suppl1-11 [www.reviewofoptometry.com/CMSDocuments/2017/10/maculogici.pdf]. Accessed 7/14/2021.

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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

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-trials). URLs accessed 1/30/2020.

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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. Halo FG, et al. *Br J Ophthalmol.* 2016;100:1623-1628. American Society of Retina Specialists (ASRS). Intravitreal injections. (www.asrs.org/content/documents/fact-sheet-30-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 1/30/2020.

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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

CST = central subfield thickness.

1. Brown DM, et al. *Ophthalmology.* 2009;116:57-65.e5. 2.Nguyen QD, et al. *Invest Ophthalmol Vis Sci.* 2011;52: abstract 3873. 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 (Vabysmo™)

- FDA approved January 3, 2022 for AMD and DME
- Roche /Genetech
- First bi-phasic antibody for intraocular use
- One arm: Vegf-A inhibitor
- Other arm: Angiopoietin-2 (Ang-2)inhibitor
  - 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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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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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
  - 2% developed at least 1 episode of endophthalmitis (3x that of injections)
- Studies underway for DME, DR s DME and AMD at 9mo interval

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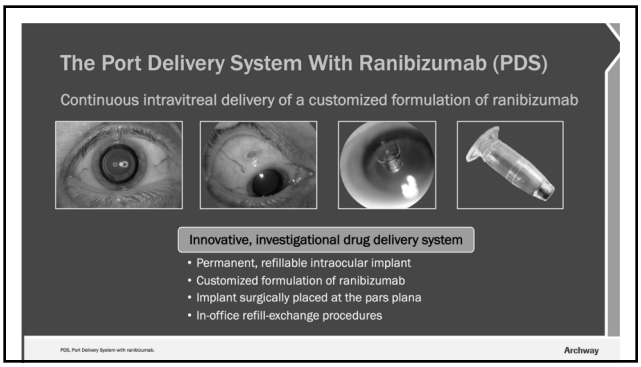

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Newest Anti-VEGF

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

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Biosimilar

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

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MacuLogix's AdaptDx

- **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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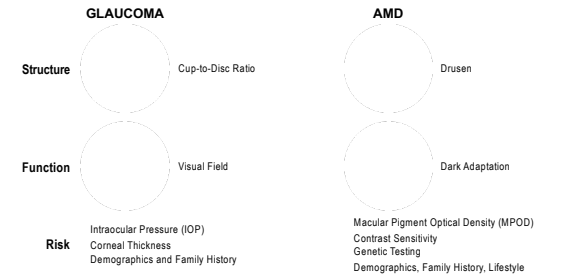
Standard of Care Comparison: Two Multifactorial Diseases



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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 visit

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AdaptDx Validated in Multi-Site Study

sources: Jackson GR, et al. Invest Ophthalmol Vis Sci. 2014;55(3):1437-1441

JOHNS HOPKINS MEDICINE

VERITAS HARVARD

PENNSTATE 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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AdaptDx Advantages

- No preadaptation required
- Protocols as rapid as 5 minutes
- Low patient burden
- Easy to operate
- CPT 92284 ($64 avg.)
- FDA 510K cleared (K100954)

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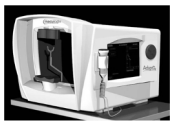
Successful Precedent

Glaucoma

Humphrey Perimeter
- Psychophysical test
- 5 minute duration
- $65 reimbursement (CPT 92083)
- ***Current*** eye care profit center

AMD



MacuLogix AdaptDx
- Psychophysical test
- 5 minute duration
- $65 reimbursement (CPT 92284)
- ***New, potentially larger*** eye care profit center

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Adapt Dx Pro

- Now available as head-borne unit
- Eliminates need for dedicated room
- On Board assistant (THEIA) minimizes tech time

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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
  - In glaucoma, use both structure and function to help monitor
  - Why not the same in AMD…

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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 Questionaire scores

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

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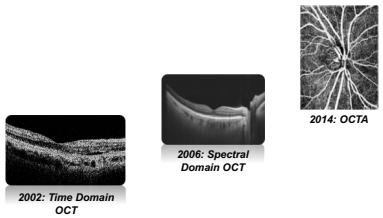
OCT Angiography: The Next Chapter in Posterior Imaging

Images retinal microvasculature without injection

Displays structure and function from a single imaging system



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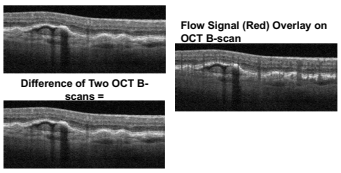
Principles of AngioVue OCTA

OCTA uses motion contrast to detect flow from OCT data

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



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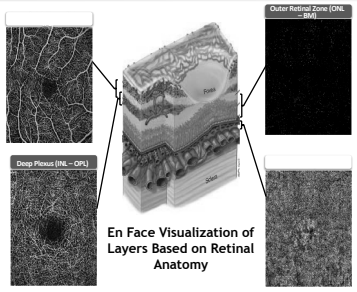
Enface OCTA Slabs: Based on Retinal Anatomy



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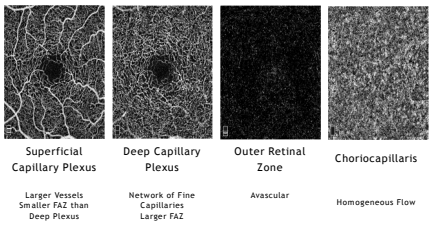
Normal



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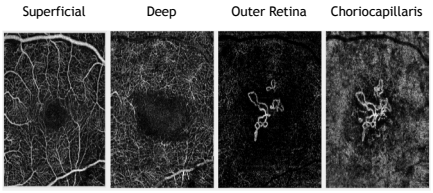
Pathology Example (CNVM)



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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
- May be of use with GA, to determine active vs dormant lesions

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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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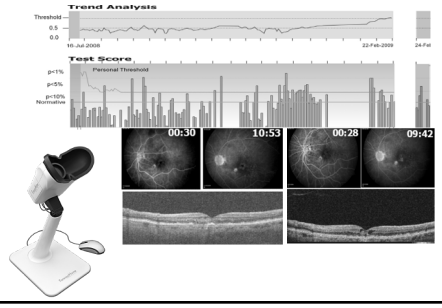
Foresee Home



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

Visit **1**

Visit **2**

Converts after office visit

More likely to lose vision

Converts between office visits

Converts before office visit

Less likely to lose vision

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

Accurately taking the test[1,2]
- Fixation
- Testing distance
- Test questions
- Compliance

Cortical completion[1]

Low sensitivity; subjectivity exam to exam, patient to patient[1]

References: 1. Midena E, Vujosevic S. *Ophthalmic Res*. 2015;55(1):24-30. 2. Isaac DL, et al. *Arq Bras Oftalmol*. 2007;70(5):771-774. 3. Liu TY, et al. *JAMA Ophthalmol*. 2013;131(12):1552-1560. 4. Wong TY, et al. *Ophthalmology*. 2008;115(1):116-126.

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ForeseeHome® product overview

Reference: Data on File.

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AREDS2-HOME Study

ForeseeHome plus standard care arm	Intent to Treat (ITT) population results	Standard care arm
763 participants	1520 participants	757 participants
51 CNV events	Mean follow up 1.4 yr ± 0.6 years Mean VA at entry 20/25	31 CNV events
• Routine monitoring • Patient symptoms • ForeseeHome		• Routine monitoring • Patient symptoms

***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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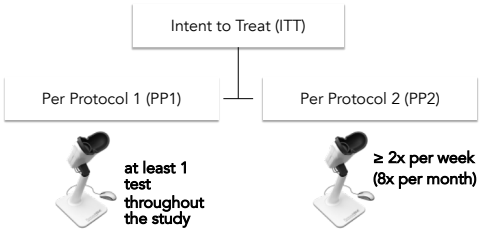
ForeseeHome Arm



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

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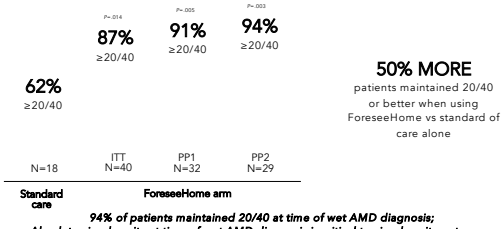
More patients who used ForeseeHome maintained ≥20/40 VA



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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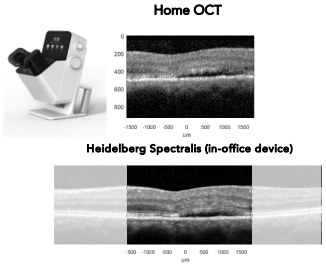
Patient Self-operated Home OCT provides high quality images

- 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



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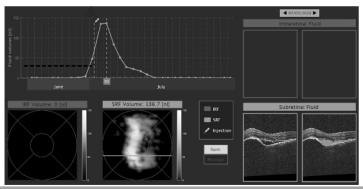
Fluid volume is tracked over time to enable individualized remote patient monitoring and alerts

- Physician reviews monthly an interactive **Surveillance Report** to manage patient
- Physician can set eye-specific **Fluid Alert Criteria** for intra- and subretinal fluid
- **Notifications** are sent to physician for decision to bring patient to office and to treat



REMOTE MONITORING CLINIC for patient device provisioning, benefits verification, engagement, compliance, and alert management

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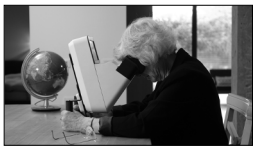
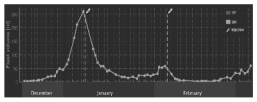
Clinical trial results show excellent system performance

- **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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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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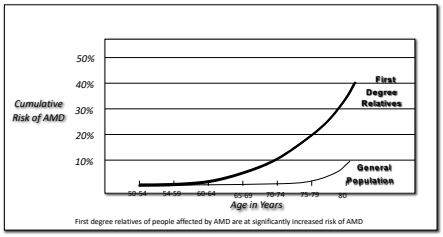
Is AMD in our DNA?



First degree relatives of people affected by AMD are at significantly increased risk of AMD

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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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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: 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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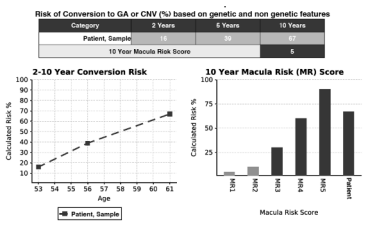
Patient Report



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AMD Risk Testing for a Full Spectrum of Patients

AMDiGuard DNA Progression Assessment

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)

AMDiGuard DNA Risk Assessment

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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Visible Genomics 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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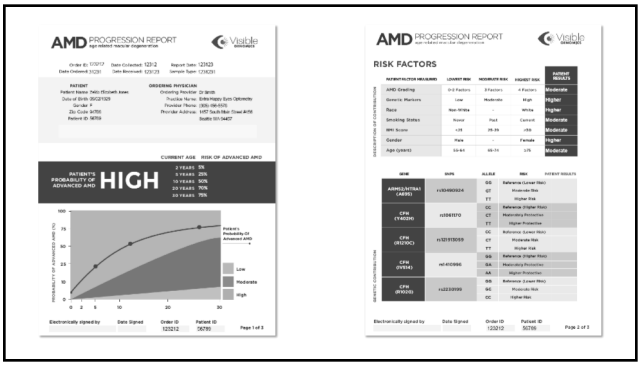

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How can we use this information?

- 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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THE FUTURE….

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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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Geographic atrophy treatment

- Estimated that 1.2 million Americans suffer from GA
  - > 5 million globally
  - 42% of pts with GA are legally blind
  - Incidence increases with age
  - Responsible for over 20% of all vision loss in pts with AMD
- Treatment geared at decrease in lesion growth
- Various targets being investigated

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Pegcetacoplan

- 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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pegcetacoplan

- Phase 3 DERBY and OAKS
  - Sept 9, 2021
- OAKS: met primary endpoint
  - 16%-22% reduction in lesion growth at 1 year
- DERBY: did NOT meet primary endpoint
  - 11%-12% reduction in lesion growth at 1 year
- FDA ruling expected Feb 2023

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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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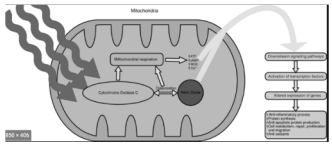
Photobiomodulation (pbm) for AMD

- **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 (3× 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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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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ARTICLE IN PRESS

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

A Multicenter Cohort Study (SEVEN-UP)

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

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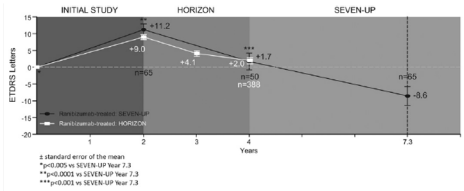
Not such a rosy bottom line..



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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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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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