UPDATE ON AMD 2018

Steven Ferrucci, OD, FAAO
Chief, Optometry Sepulveda VA
Professor, SCCO/MBKU

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

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
• Early detection of conversion from dry to wet may result in better treatment for patients

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

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)

Wet AMD

• Various agents currently being used as intravitreal injection
  – Macugen® (pegatanib sodium) Dec 2004
  – Lucentis (ranibizumab) June 2006
  – Avastin (bevacizumab) Not FDA approved
  – Eylea (afibicert) Nov 2011
Macugen® (pegatanib sodium)

- Anti-vasoactive endothelial growth factor (VEGF) aptamer
  - Developed by OSI Pharmaceuticals, co-marketed with Pfizer
  - Delivered by intravitreal injection
- FDA Approved December 2004
  - Commercially available February 2005
- VISION Study
  - Intravitreous injections of 0.3 mg, 1.0 mg and 3.0 mg every 6 weeks for 48 weeks (8 injections)
    - Loss of less than 15 letters 70% with tx vs 55% w/o tx
    - 33% maintain or lost vision with tx vs 23% w/o tx

Macugen

- Macugen has been widely supplanted by newer agents
  - Most notably Lucentis and Avastin
- Must be injected every 6 weeks for 2 years
  - Eight to nine injections/year may be indicated
  - Cost: VA medication alone is $780. Most places

Lucentis (ranibizumab)

- Antibody fragment which blocks VEGF activity
  - Less specific than Macugen, so perhaps more efficacious
- Delivered by intravitreal injection
- Developed by Genentech and marketed by Novartis
- FDA Approved June 30, 2006

Lucentis

- ANCHOR Study (classic CNVM)
  - 2 Year Phase 3 randomized study
    - 94% of pts treated with 0.3 mg had stable or improved vision vs 64% with Visudyne
    - 36% had gain of 15 letters or more
    - Avg. acuity gain was 11.3 letters vs 9.5 letters lost with Visudyne at one year
    - 31% had VA of 20/40 or better vs only 3% with Visudyne
- MARINA Study (minimally classic/occult)
  - 95% of treated pts vs 62% of controls had less than 15 letter loss
  - 25% treated vs 4.6% of controls had 3 line gain
  - At 2 yrs, 6.6 letter gain with tx vs 14.9 letters lost without

Lucentis

- Results were promising, with better results than Macugen
  - For first time, results showed an actual increase in vision in treated vs untreated group
- Recommended injection: every 4-6 weeks for 2 yrs
- Cost: approx $2500 for medication alone

Lucentis

- Additional studies, PRONTO and PIER, looking at alternative dosing schedules
  - PRONTO: one injection/mos x 3. Then inject based on clinical or OCT findings
  - PIER: one injection/mos x 3. Then inject q 6 months for 2 years
- Results were very similar to original studies, especially with PRONTO
**Avastin (bevacizumab)**

- Drug currently FDA approved for the treatment of metastatic colorectal cancer and certain lung cancers (Genentech)
  - Parent drug of Lucentis. Originally thought to be too large to penetrate retina
  - Currently widely used as treatment for CNVM due to its anti-VEGF properties

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**Avastin**

- First report of intravitreal injection in May 2005
- First case reports published in July 2005
- Within 6 months, global acceptance and widespread clinical use
  - despite lack of large scale studies regarding efficacy, safety and dosing

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**Avastin**

- Major advantage is COST
  - ≈ $50 per 0.3 ml injection
  - 1/40 cost of Lucentis
  - Approx $1k for Macugen/$2.5k for Lucentis
- Issue is there are no large prospective study to judge its efficacy and safety
  - Systemic concern is thrombolytic events
    - Amount used in vitreous is 300-400 fold lower than that administered IV
    - Some controversy remains but continues to be used widely

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**Avastin vs. Lucentis**

**What is the Treatment of Choice?**

- Complications of Age-Related Macular Degeneration Treatment Trial (CATT)
  - NEI/NIH sponsored trial
  - First year results released May 1, 2011 NEJM
- 1208 patients randomized
  - Lucentis with 4 week dosing
  - Avastin with 4 week dosing
  - Lucentis with variable dosing (PRN)
  - Avastin with variable dosing (PRN)

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**CATT: 1 yr results**

- Equivalent effects on visual acuity with same administration
  - Lucentis monthly 8.5 letters gained
  - Avastin monthly 8.0 letters gained
  - Lucentis PRN 6.8 letters gained
  - Avastin PRN 5.9 letters gained
CATT: 1 yr results

- Central retinal thickness:
  - Greater effect in Lucentis monthly group (196um decrease) than in other groups
  - 164 um Avastin monthly
  - 168 Lucentis as needed
  - 152 Avastin as needed
- Fluid on OCT
  - At 4 weeks, no fluid in 27.5% of pts w/Lucentis vs. 17.3% with Avastin
  - At 1 yr, no fluid in 43.7% Lucentis monthly 19.2% Avastin PRN

CATT: 1 yr results

- Adverse effects
  - When dosing regimens combined, slightly more serious adverse events in Avastin group
    - 24.1% for Avastin
    - 19.0% for Lucentis
    - Risk ratio 1.29 for avastin as compared to Lucentis

CATT: 1 yr summary

- Vision with Lucentis vs. Avastin relatively equal over course of first year
  - Some evidence of more effect with Lucentis on anatomical structure, ie more decrease in RT on OCT, but did NOT correlate with improved visual function
  - Some hint that less systemic events with Lucentis
  - HUGE cost differential
- Avastin wins most of the time, with select cases benefiting from Lucentis

CATT: 1 yr results

- Average cost for first year treatment:
  - $23,400 for Lucentis monthly
  - $13,800 for Lucentis PRN
  - $595 for Avastin monthly
  - $385 for Avastin PRN

Cost implications

<table>
<thead>
<tr>
<th>Avastin per year</th>
<th>Lucentis per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per injection: $50</td>
<td>Cost per injection: $2000</td>
</tr>
<tr>
<td>Monthly/yr: $600</td>
<td>Monthly/yr: $2400</td>
</tr>
<tr>
<td>PRN: $350</td>
<td>PRN: $1400</td>
</tr>
<tr>
<td>250,000 Americans:</td>
<td>250,000 Americans:</td>
</tr>
<tr>
<td>Monthly/yr: 150,000,000</td>
<td>Monthly/yr: 6,000,000,000</td>
</tr>
<tr>
<td>PRN/yr: 87,500,000</td>
<td>PRN/yr: 3,500,000,000</td>
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</tbody>
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CATT 2 yr Results

- At end of 2 years, both had similar effects on vision when the dosing regimen was the same
  - Mean gain in acuity, proportion gaining or losing 3 lines, % better than 20/40 all similar
  - Mean gain slightly better for monthly vs. as needed, 2.4 letters
  - Rates of death and thrombotic events similar
  - Pts with serious systemic adverse effects higher with Avastin (39.9% vs. 31.7%)
### CATT 2 yr results
- GA most in Lucentis monthly, but more in both monthly
- Less fluid at 1 and 2 yrs with Lucentis
- Led to 0.6 more injection with Avastin in second yr, 1.5 more over 2 yrs

### Other studies
- Multiple other comparative studies have confirmed no clinically significant differences between Avastin and Lucentis
  - CATT (US)
  - IVAN (Great Britain)
  - MANTA (Austria)
  - GEFAL (France)
  - BRAMD (Netherlands)
  - LUCAS (Norway)

### Eylea
**View 1**
- 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
- 7.9 letter mean improvement of vision (vs. 8.1 with Lucentis monthly)

**View 2**
- 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
- 8.9 letter mean improvement of vision (vs. 9.4 with Lucentis monthly)

### Eylea
- Cost: Eylea ≈ $1850/injection, with injection every 2 months
  - Therefore 1/2 of Lucentis monthly
- Second year study will evaluate use PRN

### Eylea
- Second year results (unpublished) found virtually similar results when Eylea vs. Lucentis used as needed
  - Eylea 4.2 injections for the year
  - Lucentis 4.7

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Other studies
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  - CATT (US)
  - IVAN (Great Britain)
  - MANTA (Austria)
  - GEFAL (France)
  - BRAMD (Netherlands)
  - LUCAS (Norway)
Seven-Up Study

CATT 5 yr Results

- ARVO 2016: 647 patients 328 Lucentis, 319 Avastin
- 5.5 years follow up on average
  - 25 total visits or =4.55/year
- 50% had VA >20/40
- 20% <20/200
- 10% 20/20
  - Loss of 3 letters from baseline
  - Loss of 11 letters from 2 year study endpoint
- Before VEGF: only 10% > 20/40

Role of Genetics in AMD

- Risk
- Progression
- Treatment
- Follow up protocol

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
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

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

AMD Genetic Testing

Macula Risk NXG identifies AMD patients who may progress to vision loss within:
- 2 years
- 5 years
- 10 years

Cheek Swab

Macula Risk - Prognostic Validation - 2012 IOVS

Prospective Assessment of Genetic Effects on Progression to Different Stages of Age-Related Macular Degeneration Using Multistate Markov Models

Yi Yu, Robyn Reynolds, Bernard Rosner, Mark J. Daly, and Johanna M. Seddon


2560 Caucasians
Average Follow up = 10.3 years
5 year predictive power = 0.883 ‘C’ Statistic Score
10 year predictive power = 0.895 ‘C’ Statistic Score

Patient Report

Pharmacogenomics

- Genetics being used in other medical fields to help determine
  - Which drug is most appropriate
  - Which drug might produce less side effects
  - Offer drug that might work best
- Might save time and money
  - No more "trial and error"
CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration

June 26, 2014

Abstract

No Clinically Significant Association between CFH and ARMS2 Genotypes and Response to Nutritional Supplements

Conclusions

The AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes of the CFH and ARMS2 loci did not statistically significantly alter the benefits of AREDS supplements. Genetic testing remains a valuable research tool, but these studies suggest it provides no benefit in managing nutritional supplementation for patients at risk of AMD.

Pharmacogenetics of complement factor H (Y402H) and treatment of exudative age-related macular degeneration with ranibizumab

A Y Lee, A K Raya, S M Kymes, A Shiels, M A Brantley, Jr,

- 37% Higher risk for additional Lucentis Treatments if CFH402H
- CFH TT/Tc treated with Avastin had increase in vision in 53.7% vs. only 10. 5% if CC genotype

Cumulative Effect of Risk Alleles in CFH, ARMS2, and VEGF4 on the Response to Ranibizumab Treatment in Age-Related Macular Degeneration

- If no high risk ARMS2/CFH alleles, mean VA improvement of 10 letters
- If 4 high risk CFH and 2 high risk ARMS2 alleles, no change in VA
- If 6 high risk alleles, loss of 10 letters
- Pts with high risk alleles were 5.2 younger when
Meta-analysis looking at response to anti-VEGF in wet AMD

- 12 articles, 2389
- A69s gene in ARMS 2 shown to predict anti-angiogenic response in east Asian population
- Not predictive in Caucasian populations

### Genetic Treatment

- Defective gene responsible for abnormal VEGF expression can be localized, perhaps a replacement, or fixer gene, can be injected into the eye ONE TIME!
  - Genzyme
    - AAV2-sFLT01
  - Avalanche Biotechnologies
    - AVA-101
  - Oxford BioMedica
    - RetinoStat
  - For Sight Labs
  - NeuroTech

### Avalanche Biotechnologies: AAV2

- Viral vector harboring a gene that encodes a protein (sFLT-1/VEGFR-1) for the treatment of Wet AMD
- 8 eyes with wet AMD
  - Injected with Lucentis, then AAVs, then 2nd Lucentis
  - 5/6 with AAV2 gained +8.7 letters (low dose) or +6.3 (high dose)
  - 3.5 letters in control
  - Only 2/6 needed additional injection in first year
- 2a study in Australia underway (32 pts)
- 2b Enrolling in US late 2015

### Genzyme/ AAV2-sFLT01

- 19 pts with wet AMD were injected with 4 different doses of AAV2-sFLT01, a viral vector that expresses a VEGF neutralizing protein to test safety and tolerability
  - 2 pts in 2nd highest dose group may have had drug related adverse events (intraocular inflammation, resolved with topical steroid)
  - In 11 of the 19 pts that were judged to have reversible subretinal fluid at baseline, 6 improved, 5 did not
- CONCLUSION: intravenous injection of AAV2-sFLT01 seems to be safe and well tolerated. Additional studies are needed

### Spark Therapeutics

- 12/19 FDA approved new gene therapy, voretigene neparvovec (Luxturna)
  - First gene therapy approved in US that is administered directly into the eye
- Targets disease caused by mutations in gene RPE65
  - For Leber’s congenital amaurosis and certain RP variants
  - 1,000-2,000 patients in US

### Spark Therapeutics

- RPE65 provides genetic instruction for making an enzyme that converts light to an electrical signal in the retina
  - Mutations in gene causes reduced or no enzyme activity, and therefore impaired vision
- A viral vector with a healthy RPE65 gene is injected subretinal space
- Oral prednisolone used post op to prevent immune reaction
Spark Therapeutics

- Phase 2 study of 44 people established safety and efficacy
- Phase 3 with 31 participants measured ability to navigate an obstacle course in various light levels over a 1 year period
- Pts that received Luxturna demonstrated significant improvements at low light levels
- Complications included conjunctival hyperemia, cataract, increased IOP and one retinal tear.

Summary

- Knowledge of genetic risk in AMD is important!
  - Increased counseling for patients at high risk
  - Know which patients need to be examined more frequently
  - Sooner/correct vitamin supplementation
  - May have implications regarding response to treatment
  - May guide future treatments
- Beginning of personalized medicine in eyecare!!!!

Potential Therapies

- Currently, there are ≈ 1435 studies evaluating AMD, both Wet and Dry
  - www.clinicaltrials.gov (June 2018)
    - 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

Potential Therapies

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

FoVista (pegpleranib)

- Anti-PDGF agent
- Theory is that when used in conjunction with anti-VEGF agents, will have a better effect due to synergistic effect
- Ophthotech
  - Phase 1/2b studies promising

FoVista

- Initial phase 1 trial to show safety
  - 59% had improvement of three lines or more
- Phase 2b study: 449 patients
  - FoVista/Lucentis combination gained 10.6 letters at 24 weeks, vs. 6.5 with Lucentis alone
    - 62% additional benefit
    - First study to show results BETTER THAN Lucentis
- Phase 3: FoVista 1.5 mg with anti-VEGF vs anti-VEGF monotherapy underway
FoVista: Update

- Dec 2016, Phase 3: 1248 pts with wet AMD
  - FoVista plus Lucentis: mean gain of 10.24 letters at 1 year
  - Lucentis only: mean gain of 10.01
  - Difference of 0.23 letters
  - 24.2% gained >20 letters with combo
  - 22.1% gained >20 letters with Lucentis alone
  - 12.1% lost 5 letters or more with combo
  - 11.2% lost 5 letters with Lucentis alone
  - 13.5% VA of 20/25 or better with combo
  - 13.9% VA of 20/25 or better with Lucentis

STOCK DECREASED 85% OVERNIGHT!!

Rinucumab

- Another PDGF from Regeneron
- CAPELLA study
  - Eylea plus rinucumab vs. Eylea alone for 12 weeks
  - Combo gained 5.8 letters, Eylea 7.5 letters
  - Failed to meet endpoint
  - Will continue study for one additional year

Lampalizumab

- Intravitreal Injection for GA (Roche)
- MAHALO Study
  - 20% reduction in GA lesion progression over 18 mos who monthly injections
  - Subset of pts with CFI injection had 44% reduction
- Phase III: 986 patients currently underway
- CHROMA, SPECTRI STUDIES
  - First results released September
  - Did not show a positive effect vs. no treatment on lesion size
  - No longer listed on company website

Squalamine

- Eye drop derived from shark fin that has shown to have Anti-VEGF, Anti-PDGF, and Anti-bFGF properties
- Phase II trials
  - Primary endpoint of reduced frequency of injections not met
    - 8.2 vs. 6.4 over study
  - Lucentis PRN plus Squalamine bid had increased BCVA vs Lucentis alone
    - 48.3% vs. 21.2% had >15 letters gain
    - 10.4 mean gain vs. 6.3 gain
  - Second study planned to evaluate vi:

Eylea

- On Track to get FDA approval of 12 week dosing by Summer 2018
  - Previously 8 weeks
- Based on VIEW 1 and VIEW 2 studies
  - 51% of pts had treatment interval extended to 12 weeks at start of second year of study
  - Vision was maintained without any safety issues
**Brolucizumab (RTH258)**
- Previously ESBA 1008
- Single chain antibody fragment (scFv)
- Smaller than current agents, yet potentially longer duration
- Phase II study: 194 patients
  - ESBA 1008 0.5, 3, 4.5, or 6 mg vs. 0.5 mg Lucentis
  - At 1 mos, mean VA improvement
    - 6 mg ESBA 1008: 10.4 letters
    - 0.5 mg Lucentis: 6.5 letters

**Brolucizumab (RTH258)**
- HARRIER and HAWK (phase 3 studies)
  - 6 or 3 mg of RTH258 vs. 2 mg Eylea in ≈1800 patients
  - Met primary endpoint at 48 weeks of non-inferiority in mean BCVA vs. Eylea
  - 31% and 41% fewer pts with SRF with tx
  - ≈55% remained on q 12 weeks injection schedule
  - Overall ocular and non-ocular adverse events were comparable to Eylea
  - “These results demonstrate RTH258 has potential to reduce injection burden while providing excellent visual outcomes”

**Replenish®**
- Replenish® drug delivery pump by Alcon/Novartis
- Fully programmable, refillable pump
- Rechargeable to support chronic use
- Applicable to back of eye disorders
- May prove alternative to injections
- Looking at with ESBA 1008/RTH 258 Proof of concept

**LADDER Study**
- Genentech looking at a Rigid Port Delivery System (RPDS)
- Placed through a scleral incision
- Would release a constant influx of meds (Lucentis) rather than serial anti-VEGF injections
- Refillable every 4-6 mos
- Currently in Stage II

**PAN-9080**
- Pan Optica Biotech
- Topical anti-VEGF agent
- Phase 1/2 study
  - Positive response in 45-50% of 20 pts at 8 weeks
    - Decreased Vascular leakage
    - Change in lesion morphology
    - Change in Acuity
    - AE: SPK
- Also looking at role in DR and VO
- Data expected early 2019

**Sunutib (G-102)**
- Graybug Vision
- Encapsulated injectable sustained release formulation of SUTENT (Pfizer)
  - FDA approved 2006 for oral tx of advanced renal cell carcinoma, GI stromal tumors, and pancreatic non-endocrine tumors
- Has Anti-VEGF, Anti-PDGF, stem cell growth factors and other modes of action
- Injected once per 6 mos
- G-103: Yearly injection
- ADAGIO study underway. Phase I End of year, II in 2020
**OPT-302**

- OPHTHEA: Australian Biotech company
- Blocks VEGF-C/D
- Phase 2b studies in US and Europe (351 pts)
  - Lucentis plus two doses of OPT-302 for WET AMD
- Primary Endpoint: change in acuity at 24 weeks
- Secondary Endpoints
  - Decreased retinal thickness
  - ½ pts with > 15 letter gain in acuity
  - Ocular and non-ocular adverse events

**ICON-1**

- Iconic Therapeutics
- Tissue factor TF inhibitor for WET AMD
  - Interferes with TFs ability to drive angiogenesis and inflammation
- EMERGE STUDY: 88 pts
  - Well tolerated
  - In conjunction with anti-VEGF
    - Reduced CNVM lesion size
    - Removed fluid from retina
- Starting Phase 2 studies

**Stem Cells**

- If defective gene responsible for abnormal VEGF expression can be localized, perhaps a replacement, or fixer gene, can be injected into the eye ONE TIME!
  - Genzyme
    - AAV2-sFLT01
  - Avalanche Biotechnologies
    - AWA-101
  - Oxford BioMedica
    - RetinoStat
  - For Sight Labs
  - NeuroTech

**Brimonidine®**

- Glaucoma medication by Allergan
- Long suspected to have neuro-protective properties
  - New studies point at retinal neuroprotection in animals
- BEACON STUDY
  - Evaluating an intravitreal insert for GA
  - 2016 AAO subspecialty day
    - 132ug: 19% reduced rate of regression
    - 265ug: 28%

**APL-2**

- Apellis Pharmaceuticals
- Intravitreal Complement factor C inhibitor for GA
- FILLY Trial: Phase 2 showed decreased rate of lesion progression over 12 mos in monthly and every other month administration
  - Monthly 26%
  - Ever other: 20%
- Phase 3 to start soon
High Dose Atorvastatin
- 26 pts with AMD and large, multiple soft drusen
- High dose 80 mg atorvastatin (generic Lipitor)
  - Typically 10-20 mg/day
  - At 12 mos, 23 completed trial
    - Regression of drusen and acuity gain of 3.3 letters in 10/23
    - None progressed to wet AMD

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

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
- Dark adaptation is more sensitive than other tests such as Snellen acuity, contrast sensitivity, or visual fields which are about 25% sensitive.

AdaptDx Study at VA
- Tested whether the AdaptDx could detect AMD in a typical VA clinical setting
- Rapid test run on 19 AMD patients (AREDS stage: 1 to 3)
- 18 of 19 patients failed to dark adapt before the maximum test time of 6.5 minutes. The diagnostic test sensitivity was 94.7%
- The AdaptDx exhibited similar sensitivity in a working VA clinic compared with a multi-site clinical study
- Next step is to use the AdaptDx to find patients with undiagnosed AMD or subclinical AMD

AREDS 2 home study
- 1520 pt with at least one large drusen and VA 20/60 better
  - 763 with home monitoring, 51 CNVM detected
  - 757 standard monitoring, 31 CNVM detected
    - 4 letters lost with device vs. 9 without
    - 94% had better than 2040 with device vs. 87% without