



# **MCAC Summary of Evidence AMD Methods and Medicines**

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# Intro - Objectives

- MCAC Purpose
- Age-Related Macular Degeneration (AMD)
- Hx Coverage (Mr. C)
- Epidemiology
- Literature Search
- Data
- Conclusions
- Recommendations



# MCAC Purpose

## The Ability to Rx AMD then and now

IF we could Weigh it .....



Laser  
photocoag

The excess  
weight would  
be **PDT,**  
**Anti-VEGF,**  
**Vitamins**

Leading Cause,  $\approx 30$  years,  
New revolution in AMD treatment  
Outcome Measurement – R&N



# Medicare Payment

Medicare will be asked to cover these new treatments



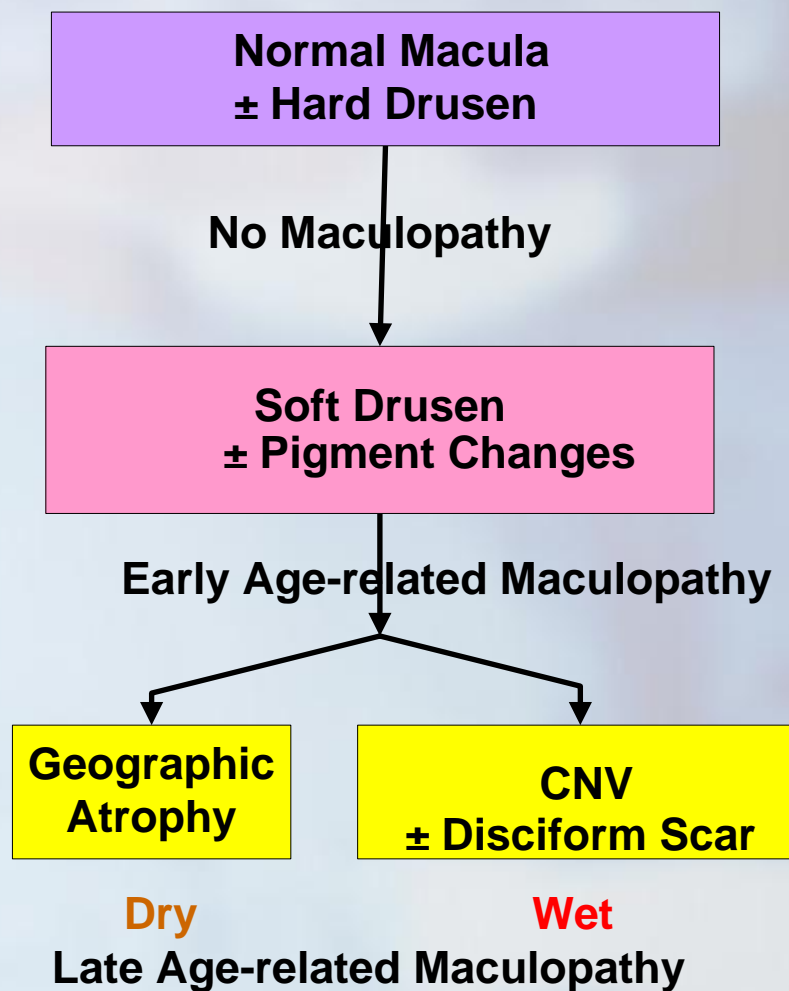


# AMD

- Central Vision
- Dry
  - Drusen (soft)
  - Pigmentary
  - Geographic Atrophy (GA)
- Wet – Choroidal neovascularization (CNV)



# AMD Types/Progression



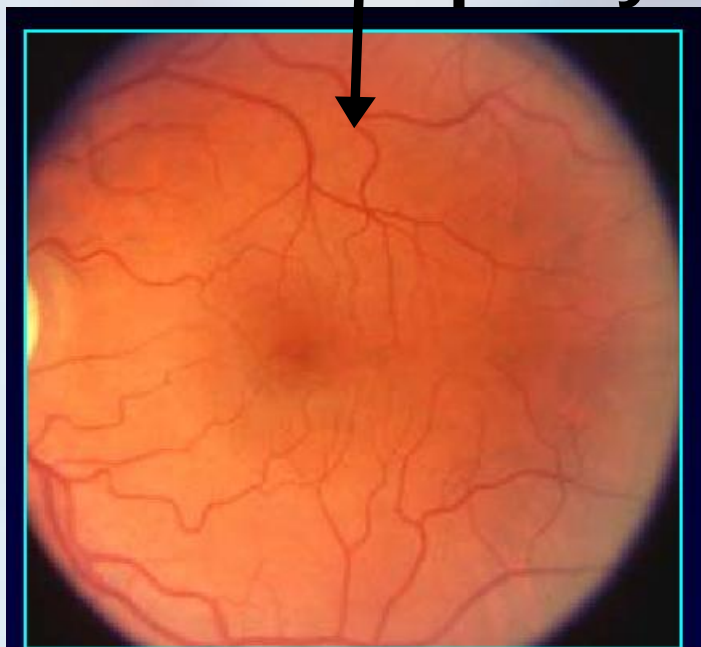




# Dry AMD

**Normal Macula  
± Hard Drusen**

**No Maculopathy**



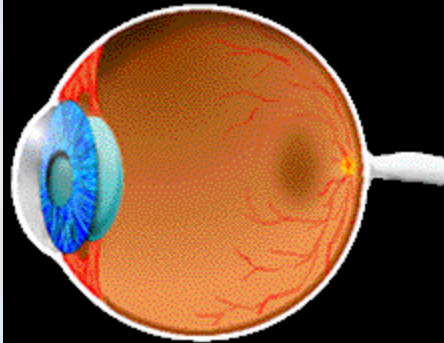
**No AMD**

Courtesy Rick Ferris MD, NEI, NIH



# Dry AMD (cont.)

Dry (Atrophic) Macular Degeneration



Soft Drusen  
± Pigment Changes

Early Age-related Maculopathy

## Age-Related Macular Degeneration



Courtesy Rick Ferris MD, NEI, NIH



# Advanced Dry AMD



**Geographic  
Atrophy**

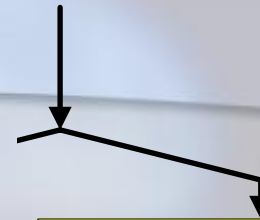
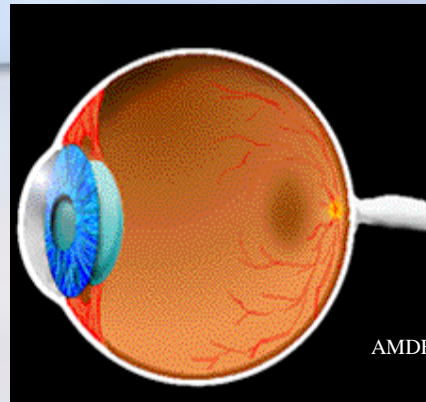
**Dry**

**Late AMD**

Courtesy Steve Charles MD

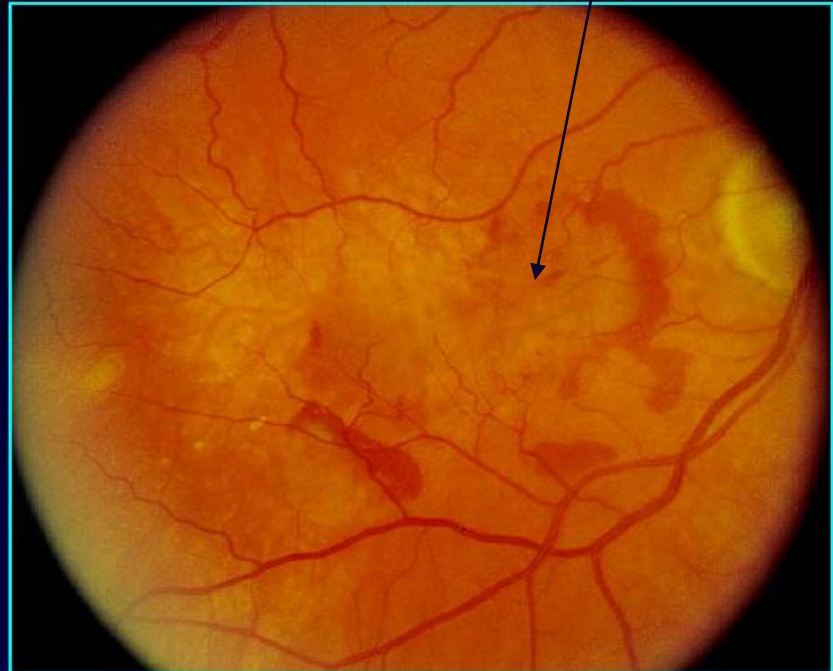


# Progression to Exudative/CNV



**CNV  
± Disciform Scar**

**Wet Late AMD**



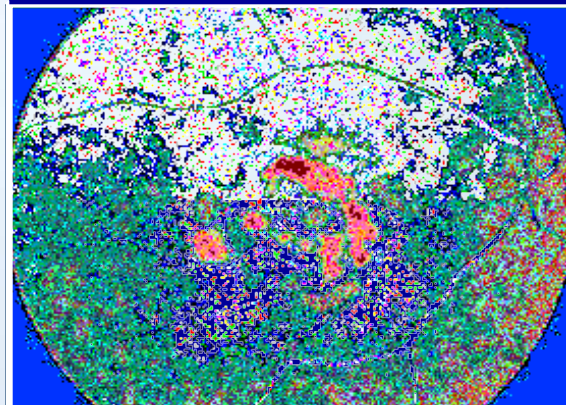
**CMS**



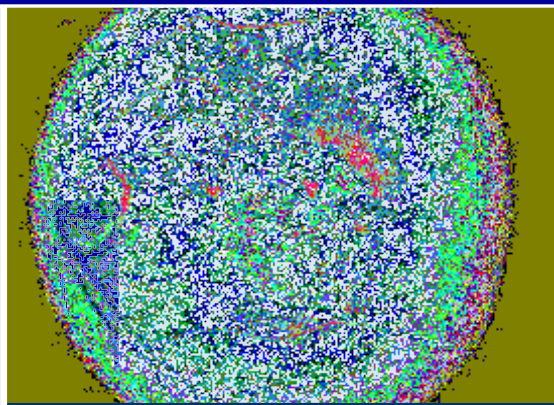


# Wet AMD

## *Angiographic Subtypes of Neovascular AMD*

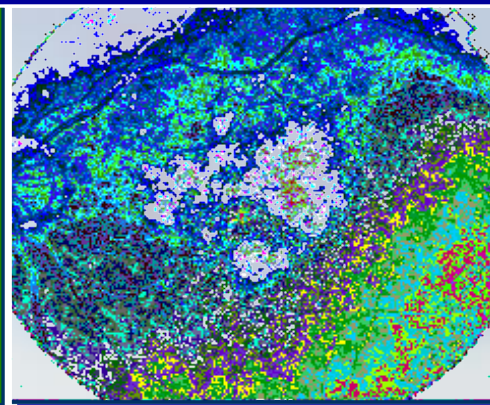


**Predominantly Classic**  
 $\geq 50\%$  classic



**Minimally Classic**  
 $< 50\%$  classic

Courtesy EyeTech corp.



**Pure Occult**  
(0% classic)



# AMD - Sight

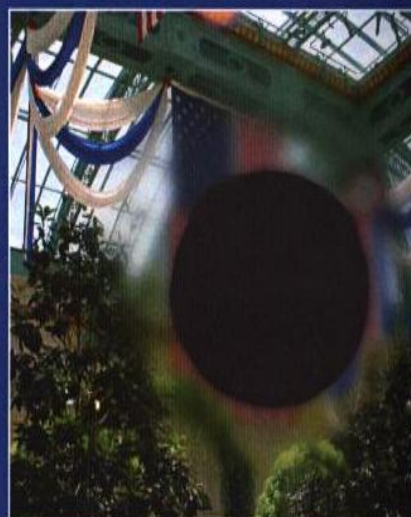
## Vision Loss from AMD



**Normal vision**



**Early AMD**



**Late AMD**

Dr. Betty J. Larson, LRD, FADA



# Epidemiology

## Prevalence (Friedman, 2004; Klein, 1992)

- 8M USA
- 85-90% Dry
- 1.75 M Advanced (GA)
- 0% - age 50-55
- 7.1% 75 yrs
- Exudative in 1.2% (1.6% advanced)







# Epidemiology (cont.)

- **Incidence** (Klein, Beaver Dam)
  - **Early**
    - Overall - 12.1% cumulative over 10 yrs
  - **Late**
    - Overall - 2.1% over 10 yrs
    - Exudative - 4.1%  $\geq$  75 years over 10 years (0% for 43-54 year olds)
    - GA - 3.0%  $\geq$  75 years over 10 years (0% for 43-54 year olds)



# Epidemiology (cont.)

- Risk Factors (Klein 1992; Seddon 2001)
  - Modifiable
    - Smoking
    - Sunlight
    - Anti-oxidant
    - Obesity
  - Non-Modifiable
    - Age
    - Gender
    - Family History
    - Ethnicity



# Data

- Laser, IVI, vitamins, watchful waiting
- Outcomes - final, intermediate



# Evidence Review

## Literature Search

A **PubMed-Medline Search** – 2 parts was performed using

- 1) ("Process Assessment (Health Care)"[MeSH] OR "Outcome Assessment (Health Care)"[MeSH]) AND ("Macular Degeneration"[MeSH]). This search yielded 520 possible references
- 2) (macular degeneration) AND (([clinical Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random\*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]). This search yielded 2610 possible references
- Included 110 papers relevant to our MCAC objectives re: AMD, its treatment and outcome measures. The papers ranged in date from 1976-2005



# Literature Search

	Data re: treatment			Data re: Outcome Measurement		
	# A	# NA	% A	# A	# NA	% A
<b>RCT's</b>	<b>23</b>	<b>0</b>	<b>100</b>	<b>1</b>	<b>0</b>	<b>100</b>
<b>NRCT's</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Cohort</b>	<b>15</b>	<b>5</b>	<b>75</b>	<b>21</b>	<b>11</b>	<b>64</b>
<b>Reviews</b>	<b>3</b>	<b>3</b>	<b>100</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Other</b>	<b>8</b>	<b>3</b>	<b>73</b>	<b>12</b>	<b>3</b>	<b>80</b>
<b>Total</b>	<b>49</b>	<b>13</b>	<b>79</b>	<b>34</b>	<b>14</b>	<b>71</b>
<b>Grand Total</b>	<b>83 acceptable</b>			<b>27 not acceptable = 75 %</b>		

A= Acceptable, NA = Not Acceptable





# Visual Acuity

- [illegible]



# Data (outcome measures)

QOL (Addressed by Duke TA)



# Data (outcome measures)

## Visual Function (Overall)

Paucity of strict validation data,  
definition, standardization



# Data – Outcome Measures

- **Contrast Sensitivity**

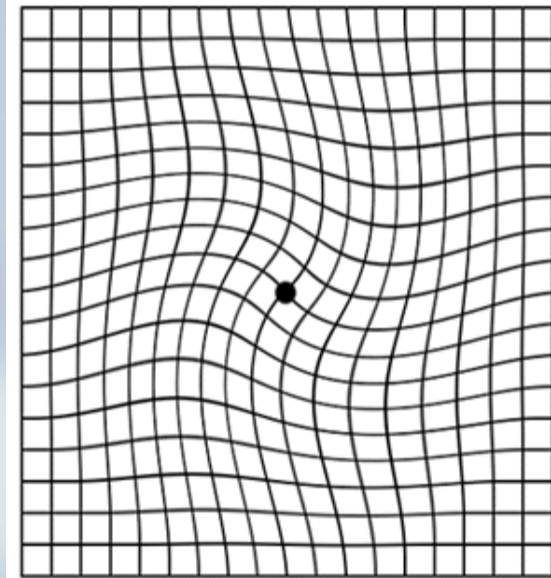
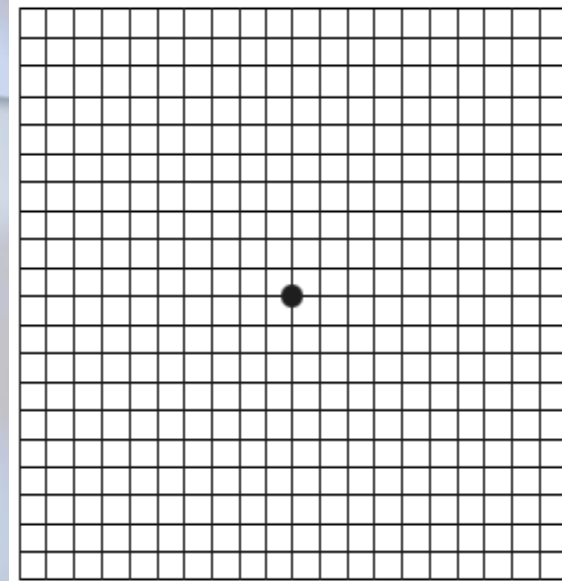
- **Pelli, 1988, developed a new letter chart decreasing contrast by  $1/\sqrt{2}$  from group to group of letters - used at 3m**
  - **Used often in studies**
- **Greeves et al., 1988, showed that a 20dB chart was a good screening device for macular disease, with a supplementary test**
- **Lennerstrand, 1989 – Optotype charts better than electronic tests**
- **Mones, 2004 – Review – claimed good evidence for use of CS in CNV due to AMD as part of overall vision function**
- **Evidence from good trials re: validation in AMD sparse**



# Data – Outcome Measures

## Amsler Grid

- **Studies indicate that Amsler grid tests have poor validity, sensitivity and specificity re: AMD**
- **Good data are sparse and non-supportive**







# Data – Outcome Measures

## Size, type, and number of CNV/lesions

- We found that many studies used this as a measure of need for treatment and tracking of progression of AMD
- But we did not find studies that validated this as an outcome measure though it is intuitively sensible to use it as such



# Data – Outcome Measures

## Fundus Photos

- **Klein et al., 1991** – a detailed precise method for grading AMD – varying but good reliability/validity - not doable by all – described in an upcoming talk this AM
- **Bird et al., 1995** – methods for taking and grading transparencies. No validation methods
- **Scholl et al., 1993** – Reproducibility with a revised version of the grading system established by the International AMD Epidemiological Study Group
- **Van Leeuwen et al., 2003** – Digital images as good as transparencies
- **Generally good data on grading and staging**



# Data – Outcome Measures

## Visual Fields

- **Central visual field automated testing widely used**
- **Nazemi, 2005 -The authors concluded 3-D computer-automated threshold Amsler grid tests**
  - May demonstrate characteristic scotoma patterns in patients with AMD that conform to the respective fluorescein angiograms
  - Show promise as an effective tool in accurately evaluating, characterizing, *and monitoring* scotomas in patients with AMD with potential as a screening tool for the early diagnosis of AMD
- **Paucity of validity data on use in AMD**



# Data – Outcome Measures

## • Optical Coherence Tomography (OCT)

### • Hee et al., 1996 - 90 patients with unRx'd exudative AMD, OCT to FA identification/classification of CNV

- Authors conclude useful in measuring subretinal and intraretinal fluid, subfoveal CNV, *and monitoring CNV before and after laser photocoagulation*

### • Salinas et al., 2005. Prospective observational case series OCT in CNV before and after PDT in AMD in 53 patients (62 eyes)

- Results – Sensitivity for detecting CNV activity was over 95% whether or not Diagnosis of AMD was before or after treatment
- Authors conclude OCT useful for indicating CNV activity. May serve as a complementary technique for deciding the need for PDT and re-treatment in patients with AMD

### • Similar results in consecutive case series by Sandhu 2005

### • Data strength weak – no RCTs found



# **Data – Outcome Measures**

## **C-Reactive Protein (and fundus photos)**

- **Patients from 2 centers of the Age-Related Eye Disease (AREDS) trials**
- **Elevated CRP level is an independent risk factor for AMD (Seddon et al., 2004)**





# **Data – Outcome Measures**

## **Reading Speed**

- **Elliott, 2001 tested 15 persons with AMD on reading speed on the Bailey – Lovie chart – slower and may be way of monitoring AMD progress**
- **Paucity of data**



## Data – Outcome Measures

### Scanning Laser Ophthalmoscope (SLO)

- **Fujii et al. (2003) Increasing disease duration as assessed by scanning laser ophthalmoscope microperimetry is associated with worse fixation pattern and retinal sensitivity deterioration**
- **This *may* indicate a use for this instrument in following progression of AMD**
- **Evidence is weak**



# Data – Outcome Measures

**The following proposed or tested outcome measures had currently little or no good data to support/validate them for use in AMD and are mentioned for completeness**

- **Face Recognition/Facial Expression discrimination Tejeria, 2002**
- **Macular Mapping Test score – Bartlett et al., 2005**
- **Macular Computerized Psychophysical Test (MCPT) – Loewenstein, 2003 – high sensitivity**
- **Glare Recovery (Photostress) – Sensitive – not specific**



# Data (Studies)

## **Macular Photocoagulation Study MPS (RCT multicenter – 1980s - NIH)**

- Argon and Krypton halted early – reduced VA loss
  - Normotensives vs. hypertensives
- Well-demarcated areas of classic CNV had better visual prognosis with laser photocoagulation, than observation
- Dramatically reduced severe visual acuity loss in Argon trial



# Data (cont.)

## Submacular Surgery Trial-SST (RCT)

***Goal*** - For CNV in patients with AMD, does SS improve or decrease vision less, than observation alone

- 228 observed, 226 surgery
- 44% observed vs. 41% surgical successful
- Submacular surgery is not helpful for these commonly-found lesions in AMD patients' eyes
- Some positive results, however, on NEI-VFQ, Surgery as compared to Observation





# Data (cont.)

## **TAP -Treatment of Age-Related Macular Degeneration with Photodynamic Therapy**

- **RCT Multicenter US and Europe Subfoveal CNV**  
**- 402 PDT vs. 207 observation – 2 years**
- **53% PDT vs. 38% less than 15 letters lost at 24 mos., more exaggerated in predom. classic (59% v 31%)**
- **Minimally classic group no effect demonstrated**
- **PDT prevents VA loss in certain cases subfoveal CNV**



# Data (cont.)

## Radiation Therapy for AMD Study (RADS) RCT

- **Randomized 205 CNV patients with AMD to a treatment group (n=101) and control group each given 8 fractions of 2 Grays and sham respectively**
- **No effect on treatment vs. observed as measured by mean reduction in VA**



# Data (cont.)

## Macugen (RCT-2 studies combined) (Gragoudas et al. 2004)

- 4 groups of  $\approx 300$  pts randomized to observation, 0.3, 1.0, or 3.0mg IVI q 6wks for 1 yr.
- Endpoint loss of less than 15 letters VA
- All groups -25% of pts with some PDT treatment
- Overall efficacy was demonstrated, for all three doses of Macugen individually and as a group (70% vs. 55%)



# Data (cont.)

## Anecortave Acetate RCT - D'Amico et al, 2003

- Juxtapapillary deposition of 3, 15, and 30 mg vs. control (sham) in subfoveal CNV - 32 patients each group
- At month 12, anecortave acetate (15 mg) administered at 6-month intervals was statistically superior to the placebo for 3 measures of clinical efficacy:
  - *mean change* from baseline vision
  - *stabilization of vision* (<3 logMAR line change), and
  - *prevention of severe vision loss* (decrease of  $\geq 6$  logMAR lines from baseline)



# Data (cont.)

## Other agents

- Ranibizumab
- Triamcinolone
- Squalamine
- Others (see trials list in Summary)





# FDA Approvals for New AMD Treatments

- Verteporfin
- Pegaptanib
- Anecortave Acetate (approvable)
- Next???



*"The F.D.A. is nuts about it."*



# Data (cont.)

## **AREDS Age-Related Eye Disease Study – RCT**

- 4,757 participants, 55-80, 11 clinical centers nationwide
- Four treatments: 1) zinc alone; 2) antioxidants alone; 3) a combination of antioxidants and zinc; or 4) a placebo
- Outcome measures (6 yrs +)
  - Photographic assessment progression/treatment for advanced AMD and
  - Visual acuity loss from baseline ( $\geq 15$  letters)
- High levels of antioxidants and zinc significantly reduced the odds for the development of advanced AMD and associated vision loss in comparison with placebo
- Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD



# Observations

- **Cutoff points and outcome measures were different in many well-designed trials e.g., VA**
- **Conditions of measurement were very often not mentioned, detailed**
- **We found that the inclusion and exclusion criteria varied widely in trials re: treatment and measurement of AMD. There did not appear to be any standardization or consistency across trials, even when they were measuring the same outcomes with a similar treatment effect**



# Conclusions

- **There is a general paucity of data that clearly validate the standard measurement testing modalities in and of themselves, with the exception of some VA measures, Fundus Photos, and QOL (to be presented)**
- **The literature does make reference to a large number of ways to measure outcomes of AMD**
- **Different RCTs and other AMD studies used different and widely diverse inclusion and exclusion criteria.**
- **Different RCTs and other studies used different or undefined conditions for measuring various outcome measures**
- **Follow-up in different clinical trial studies ranged from months to over 6 years or more, with most varying from 1 to 2 or 3 years at present**



# Conclusions

- **Data re: laser, intravitreal injection, and vitamins may be sufficient at present to assess the health benefit of these modalities in AMD when compared to watchful waiting only**
- **Other modalities may be on the verge of, or close to showing a health benefit when compared to watchful waiting**
- **There is sufficient evidence in the literature to determine whether or not treatments such as PDT and Photocoagulation, can positively affect some of the outcome measures submitted before this MCAC**





# Recommendations

- **Further evaluation of AMD treatments as new data are presented and published**
- **Standardization of inclusion and exclusion criteria for RCTs on AMD, where possible**
- **Standardization of cutoff points and methods of measuring outcomes for AMD**
- **Clinical trials should be designed with attention to CMS evidentiary needs**
- **Studies to fill in the gaps in our knowledge need to be conducted e.g.,**
  - Well designed validation studies for outcome measures \*;
  - Combination studies of the new drugs coming out, and those already proven of benefit in AMD. Combinations may be more effective than any single drug/treatment alone

