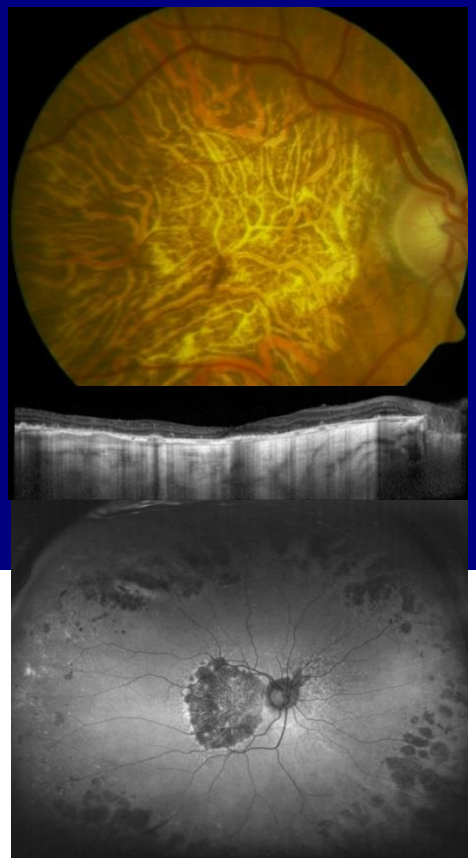
Developing Treatments for Dry Age-related Macular Degeneration – Workshop



Anatomical Endpoints

Cynthia A. Toth, M.D.

Department of Ophthalmology, Duke University Medical Center, Durham, NC
Department of Biomedical Engineering, Duke University, Durham, NC

Disclosures

I have the following financial relationships to disclose:

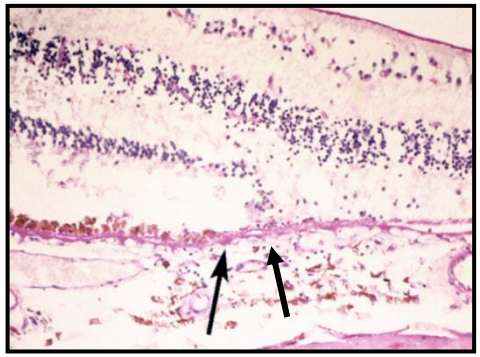
- Research Support through my University from
  National Eye Institute
  Genentech, Bioptigen,
  The Hartwell Foundation, Research to Prevent Blindness,
  The Arnold and Mabel Beckman Foundation
- Royalties through my University from Alcon for surgical technologies
- Patents pending in image processing and OCT

Duke University has a financial interest in Bioptigen

Recording Anatomical endpoints

- GA: a sharply demarcated area of apparent absence of RPE, with visible choroidal vessels

  Sarks SH. Br J Ophthalmol1976
  Sarks JP et al Eye 1988
  AREDS Report #26 Arch Ophthalmol 2009



- Histopathology/biopsy:
  - Not feasible
- *In vivo* imaging:
  - Retinal photographs
    - Multi-spectral imaging, visible and infrared
    - Wide field imaging
  - Fluorescein angiography
  - Fundus autofluorescence
  - Optical Coherence Tomography

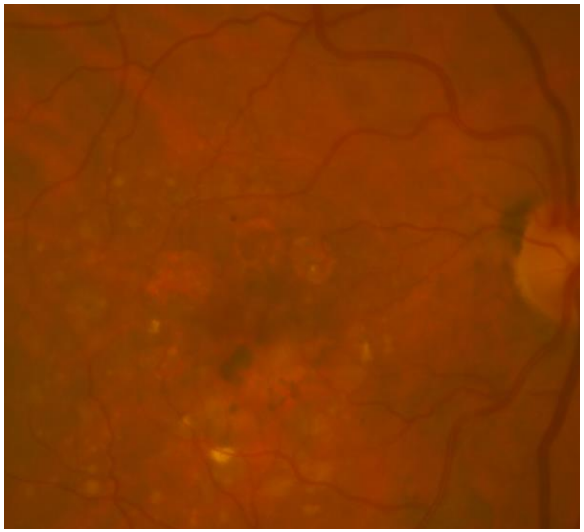
Imaging Anatomical endpoints

- Different methods
  - Often complementary
  - Strengths and weaknesses
- Extract qualitative and quantitative data extraction
- Involvement of foveal center as endpoint
- Influence of history or genotype

Color Photography

- Classical endpoint
- Used in multiple trials
- Impact of cataract on image

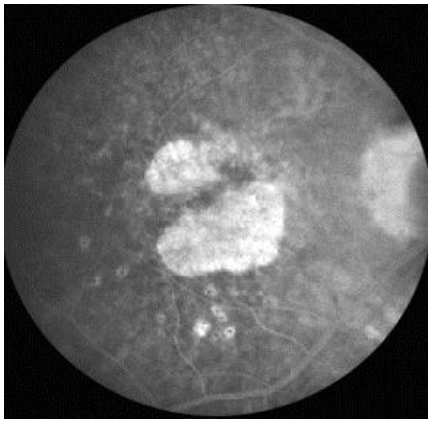


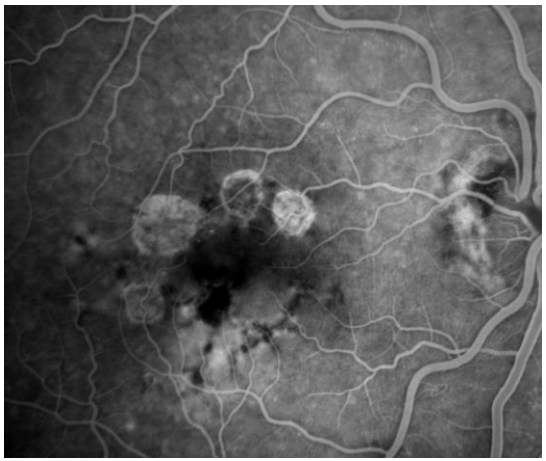


Sunness et al IOVS 1999
Sunness et al Ophthalmol 1999
Sunness et al Ophthalmol 2007

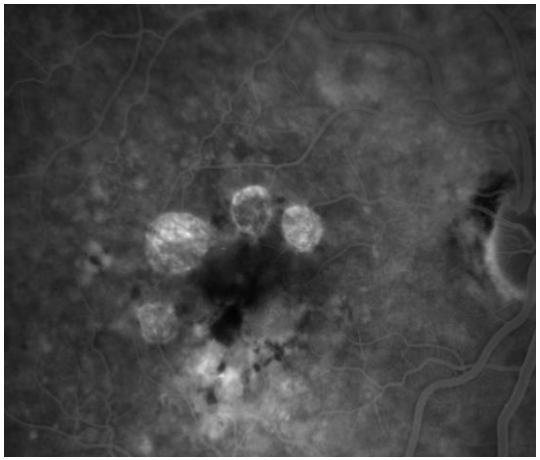
Fluorescein Angiography

- Requires Intravenous injection
- Useful in examination for leakage



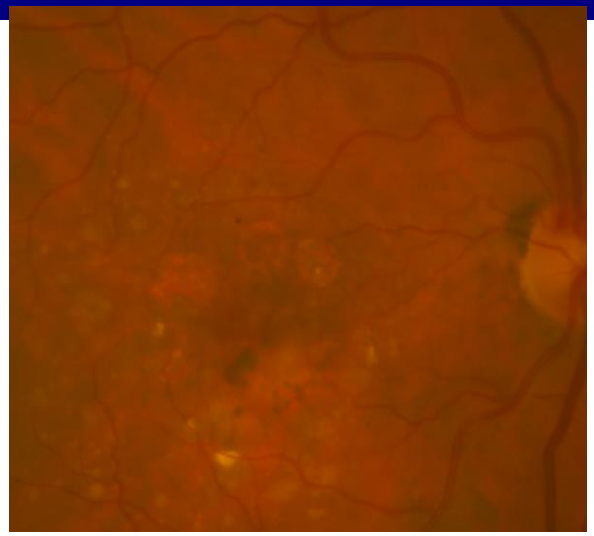


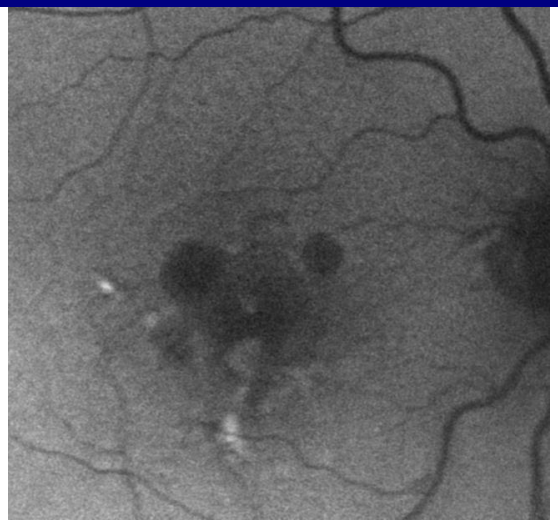
Mid AV phase



Late

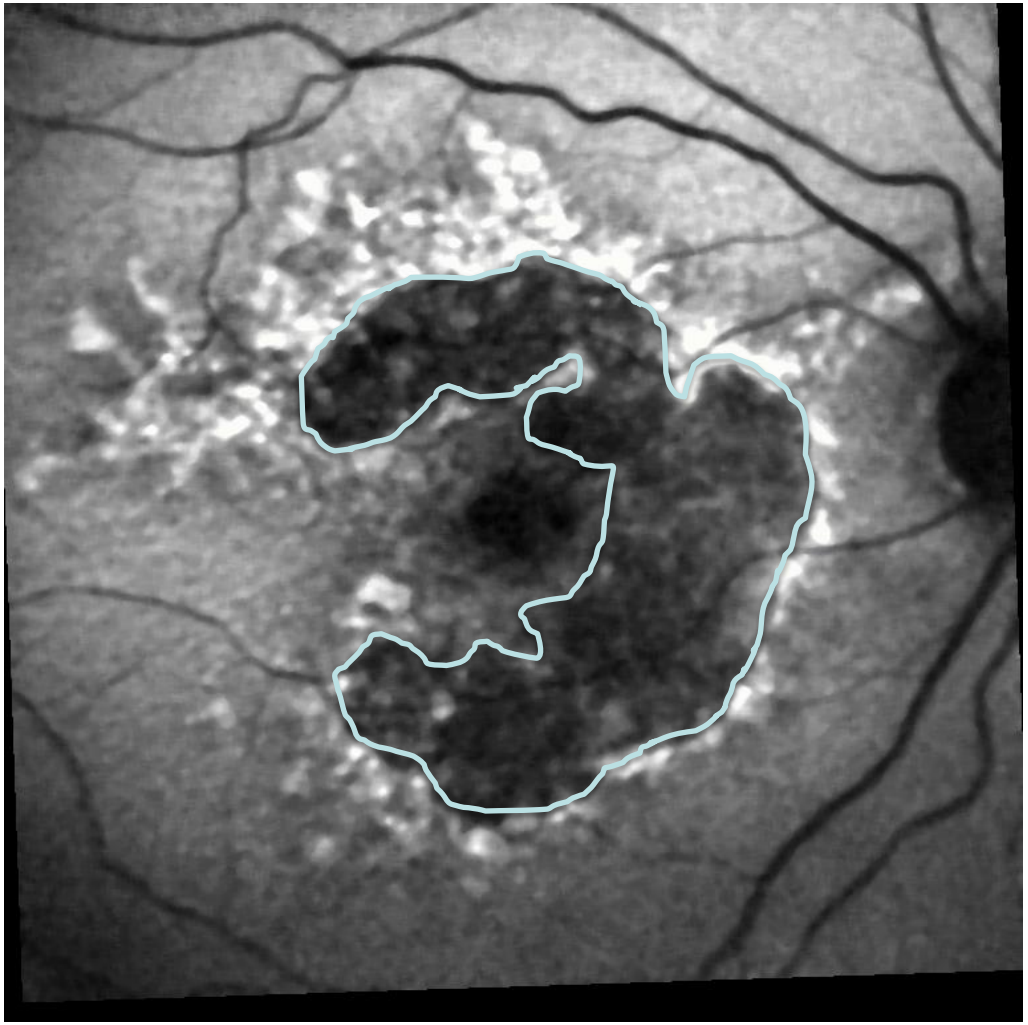
Fundus Autofluorescence



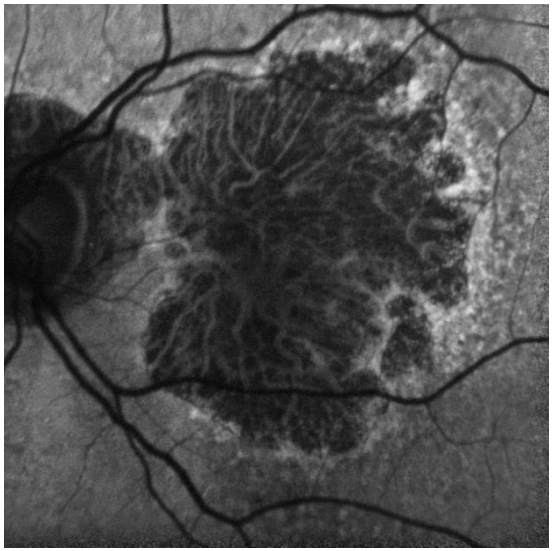
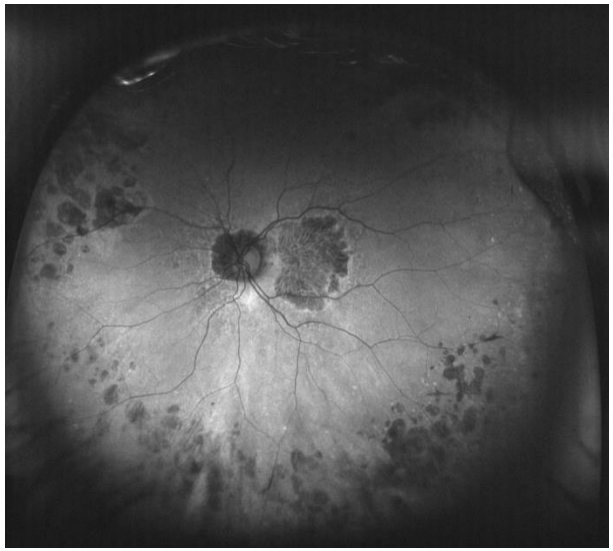
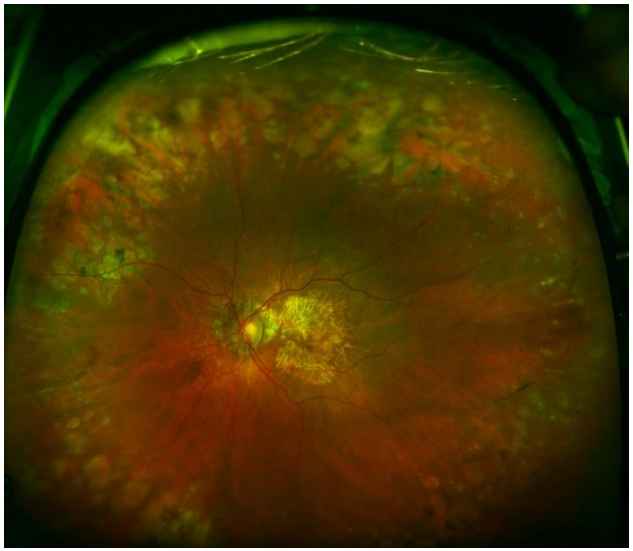


- Blue
  - Excitation at 488 nm: optically pumped solid-state laser
  - Emission 500 – 700 nm with a barrier filter
- Green
  - Excitation at 514 nm
  - Wolf-Schnurrbusch IOVS 2011
- Infrared
  - Excitation at 787 nm
  - Keilhauer and Delori IOVS 2006

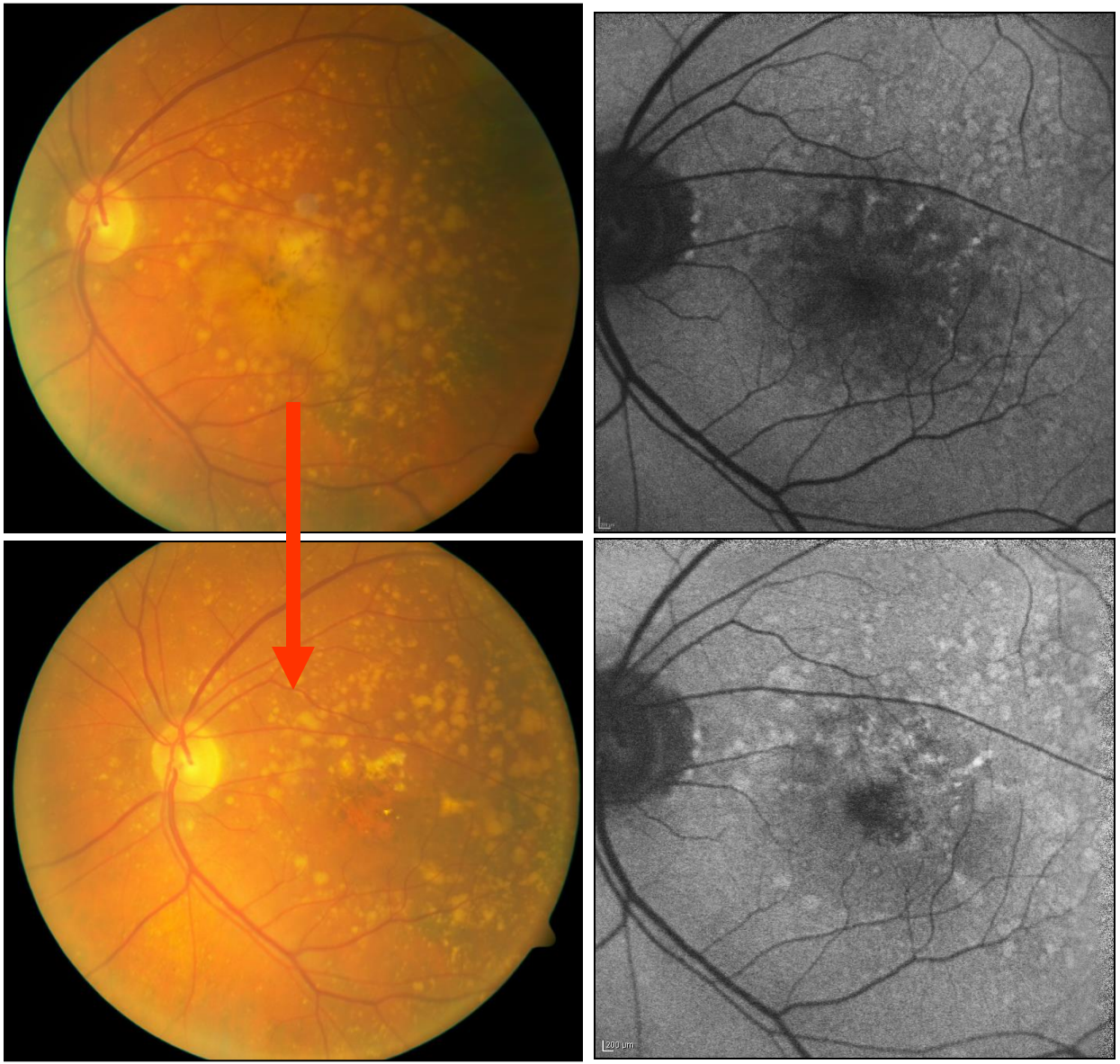
Quantitative assessment of GA



Wide-field autofluorescence

GA with drusen regression

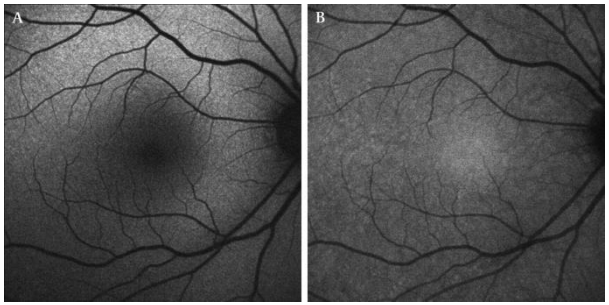


Foveal Center

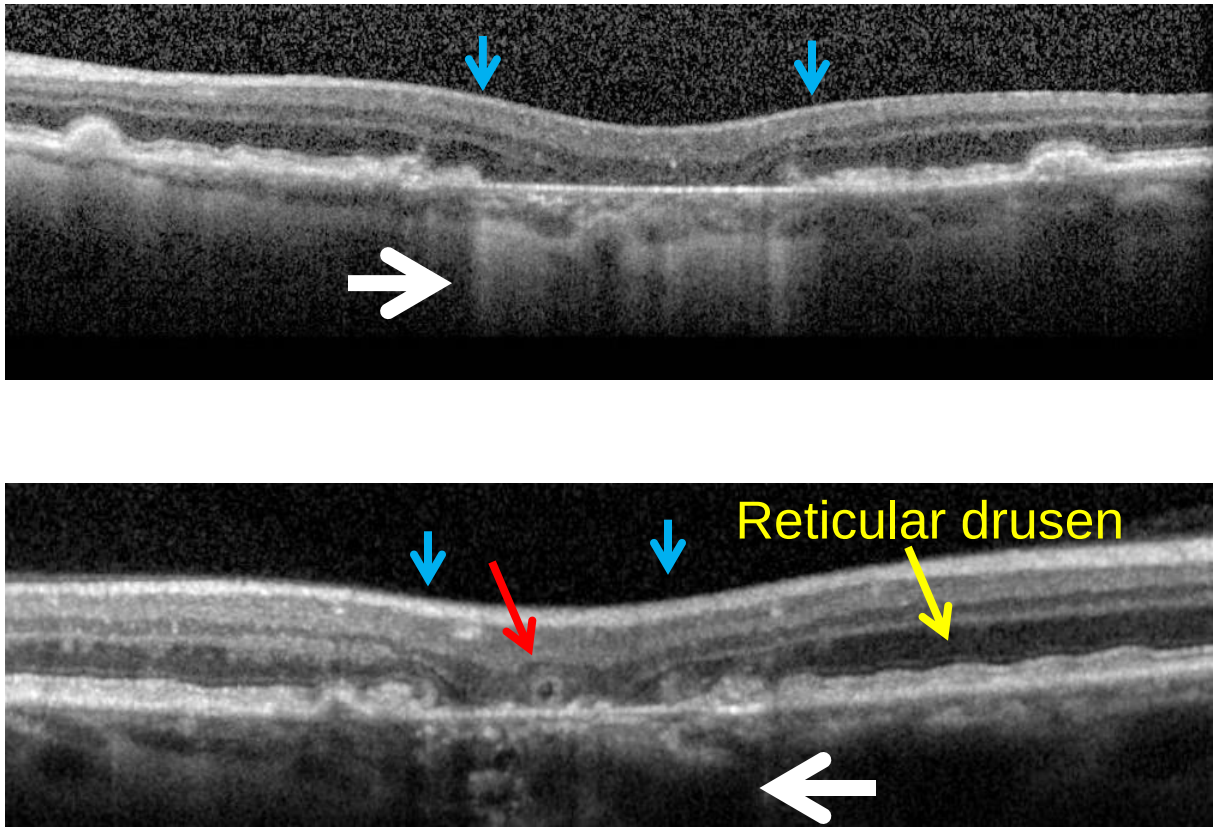
- Difficult to assess on CFP
  - Sunness et al IOVS 1999
  - Sunness et al Ophthalmol 1999
  - Sunness et al Ophthalmol 2007
- Blue light FAF
- Green light FAF does not have a dark central spot
  - Wolf-Schnurrbusch et al IOVS 2011
- Near IR FAF, bright macula

Blue FAF

Blue FAF Near IR- FAF



Optical coherence tomography-based Retinal and choroidal morphology in GA



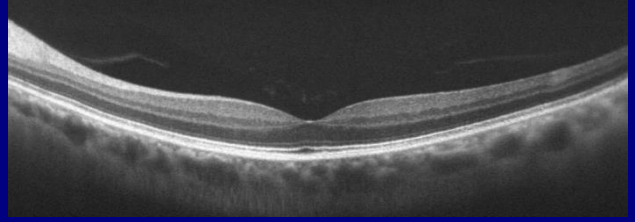
Outer Retinal Tubulation (ORT)

Loss of:

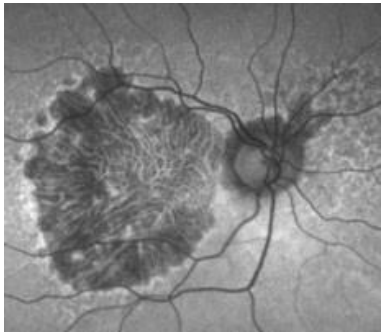
- Outer plexiform layer
- Henle's fiber layer
- Photoreceptor nuclei
- External limiting membrane
- Ellipsoid zone (inner segment)
- Interdigitation zone
- Retinal pigment epithelium

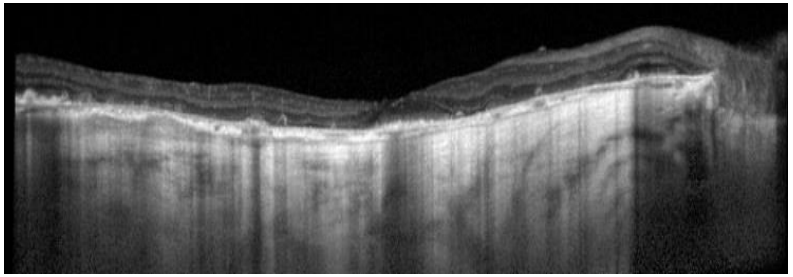
Gain of:

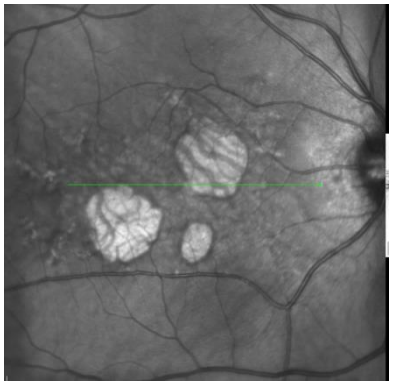
- Reflectance signal into choroid and sclera

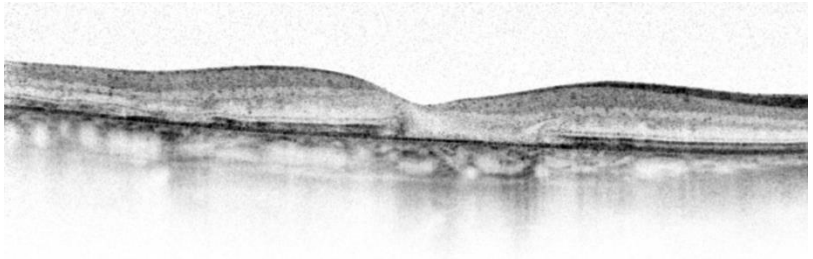


Optical coherence tomography

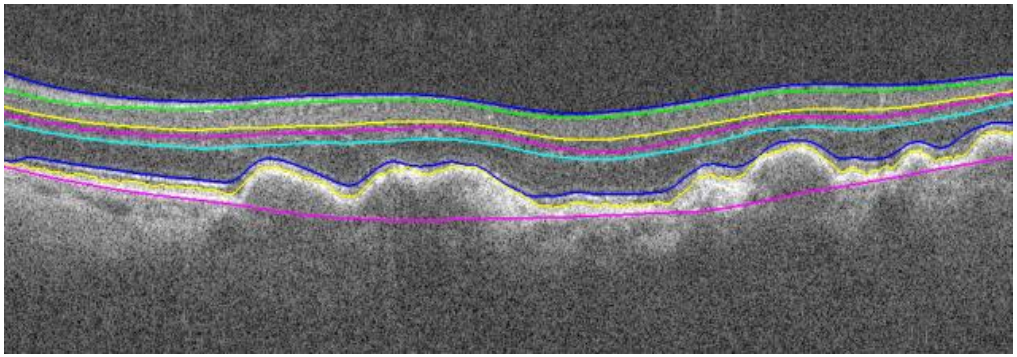


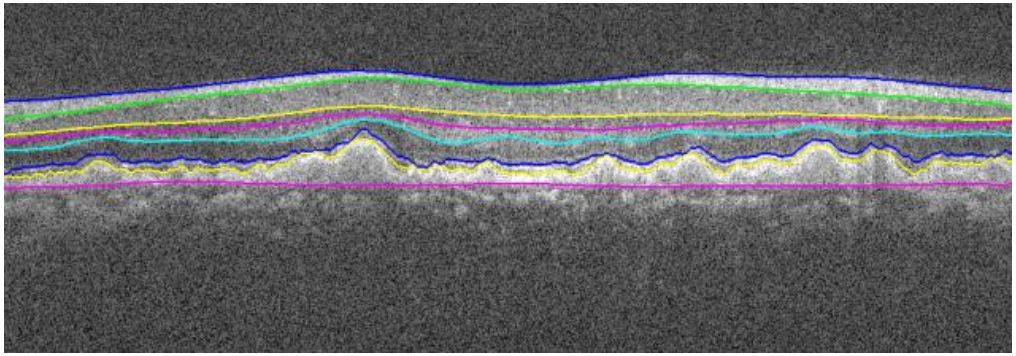


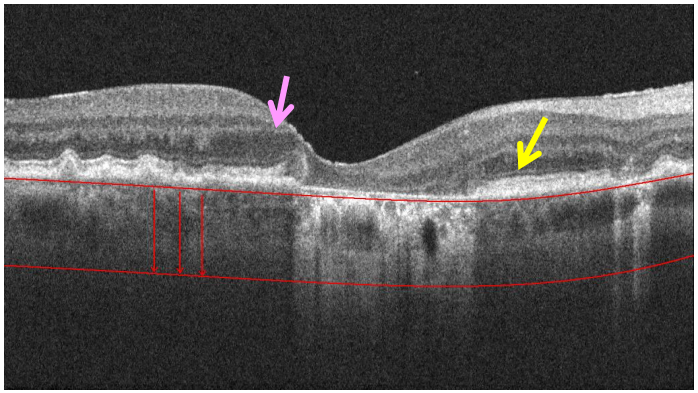


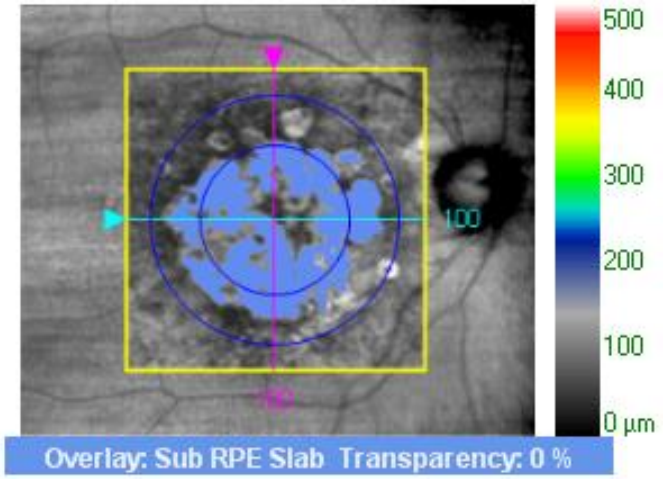


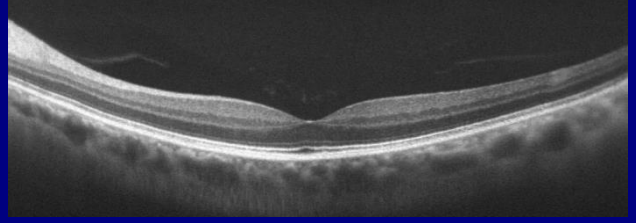
Segmentation of critical layers





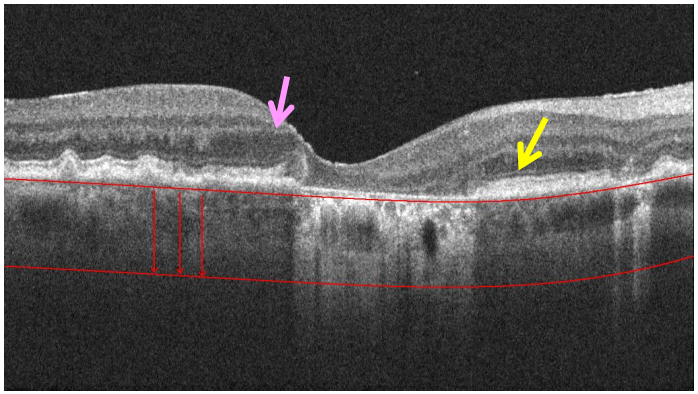


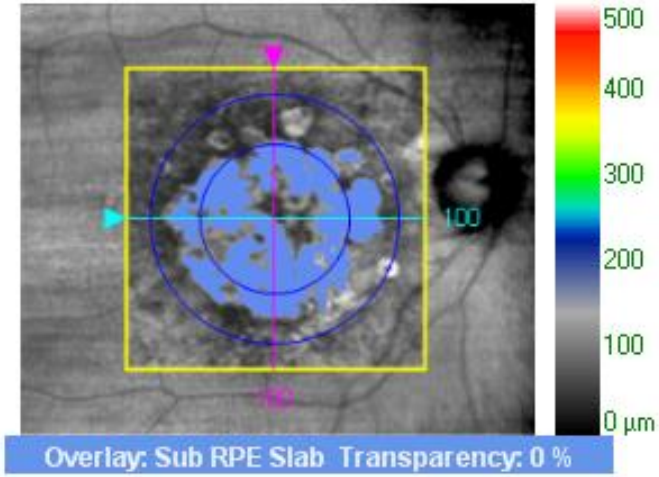




Optical coherence tomography

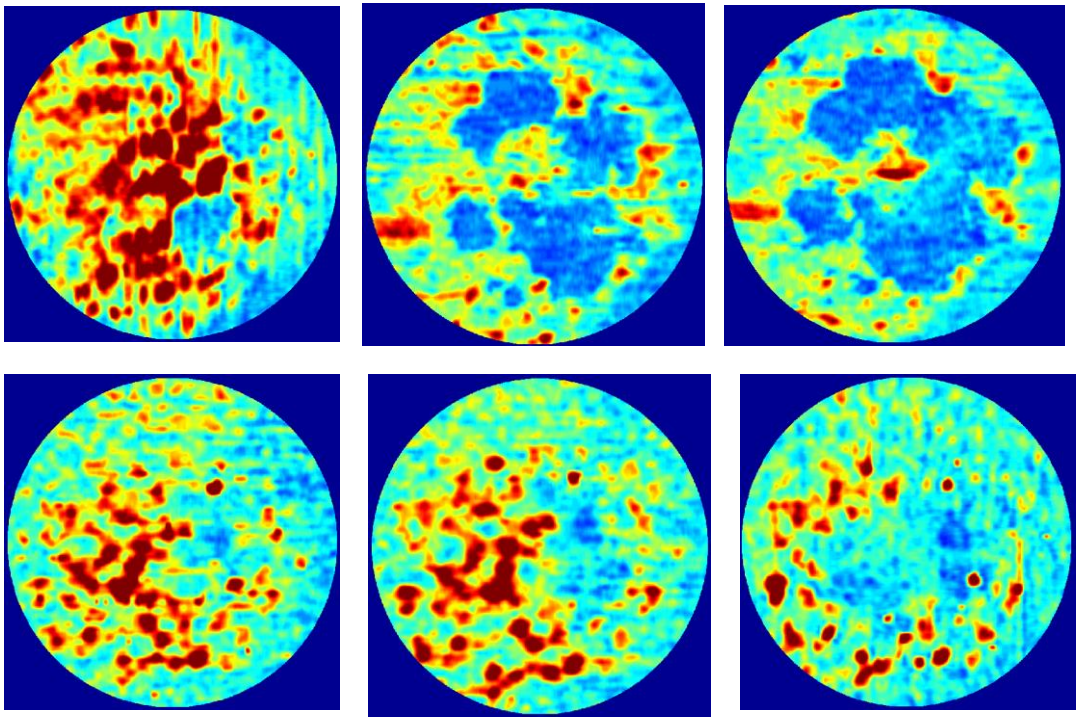
- SDOCT to measure GA
  - Yehoshua et al IOVS 2013
  - Simader C et al AJO 2014
  - Schutze et al Acta Ophthalmol 2011





OCT quantitative analyses

- Quantitative assessment of drusen volumes and atrophy over time



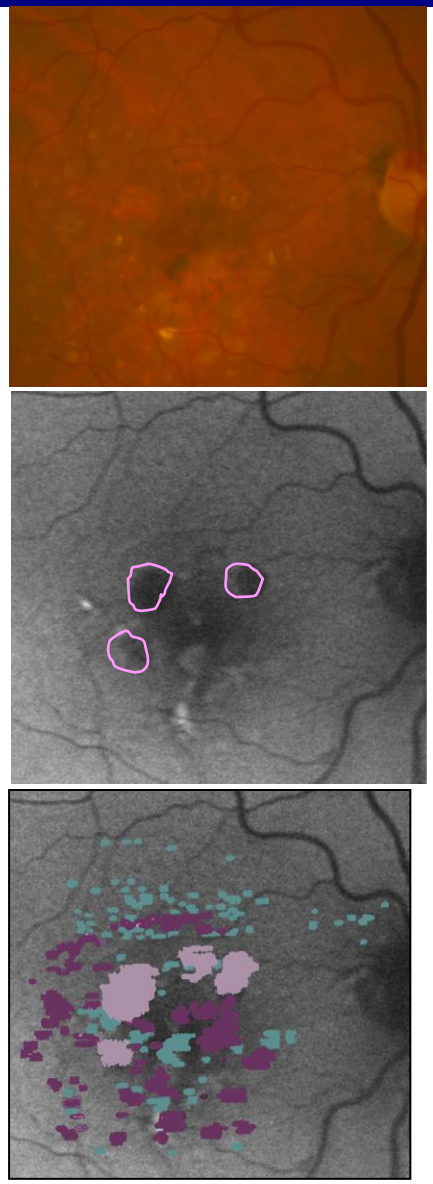
Baseline Year 1 Year 2

OCT findings precede atrophy

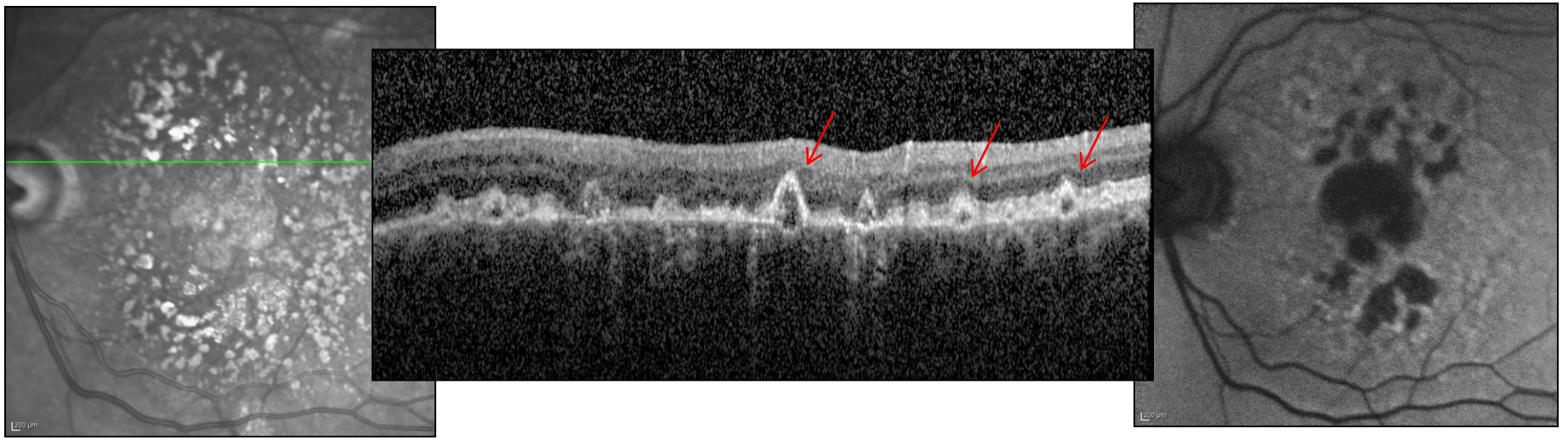
Nathoo et al AJO 2014
Folgar et al ARVO 2013
Wu Z et al Ophthalmol 2014

GA on OCT versus Autofluorescence

- SDOCT vs FAF
  - Sayegh et al Ophthalmol 2011
  - Hu et al IOVS 2013
  - Simader C et al AJO 2014

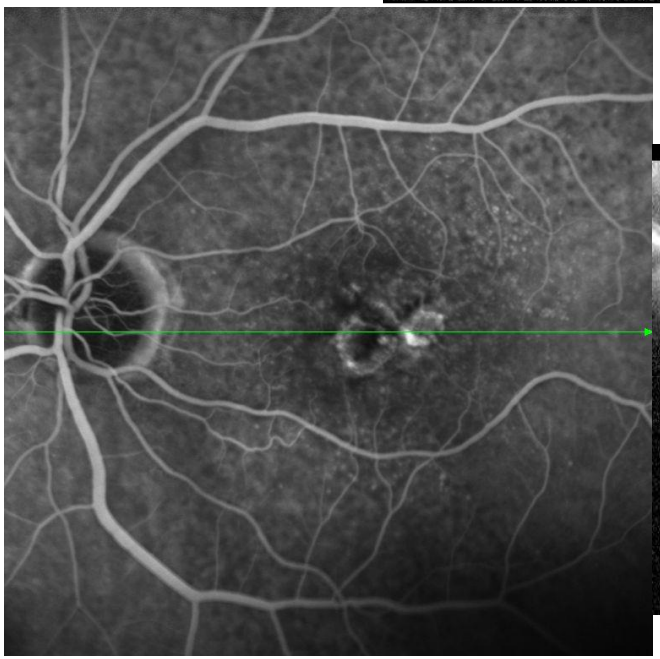


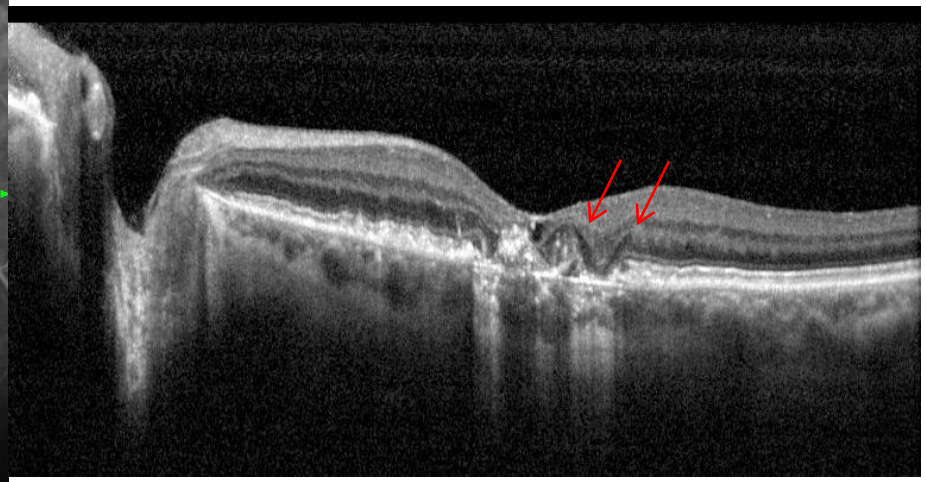
On OCT imaging: hyporeflective drusen in eyes with GA



Leuschen et al *Ophthalmology* 2013

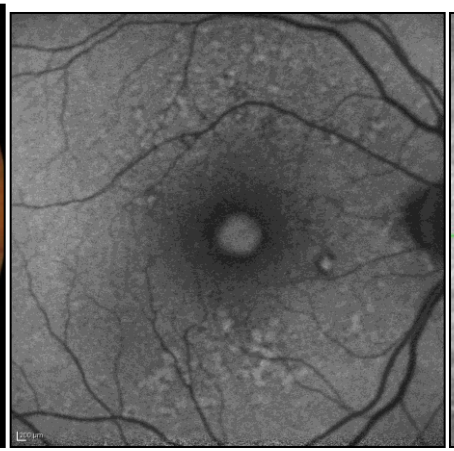
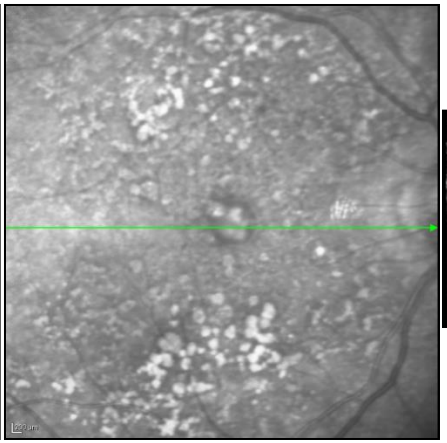
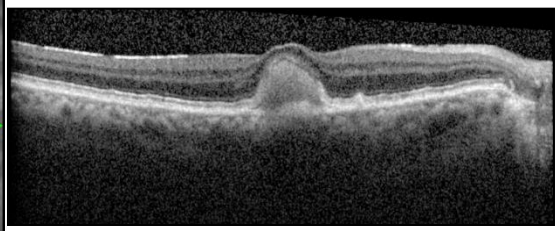
On OCT imaging: Hyporeflective wedge-shaped retinal bands precede GA

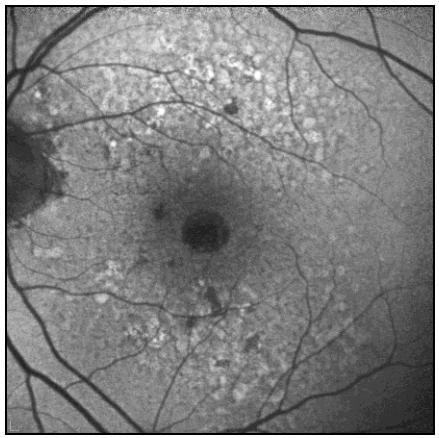
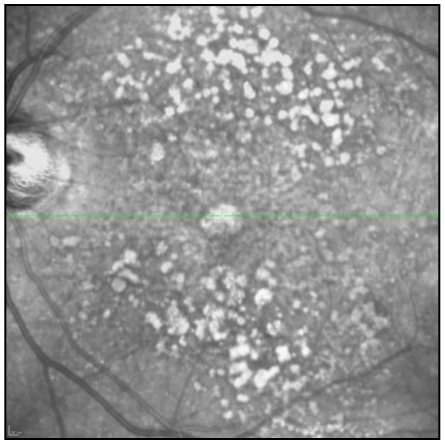
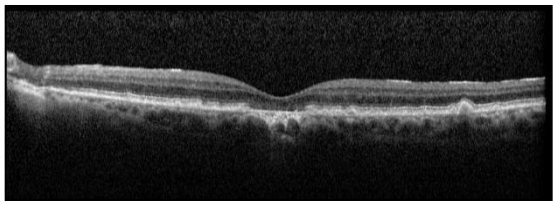
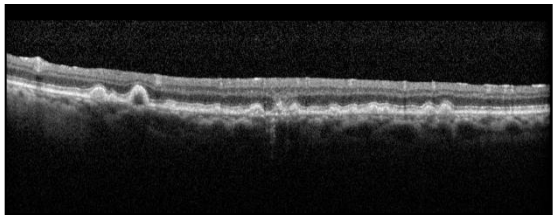




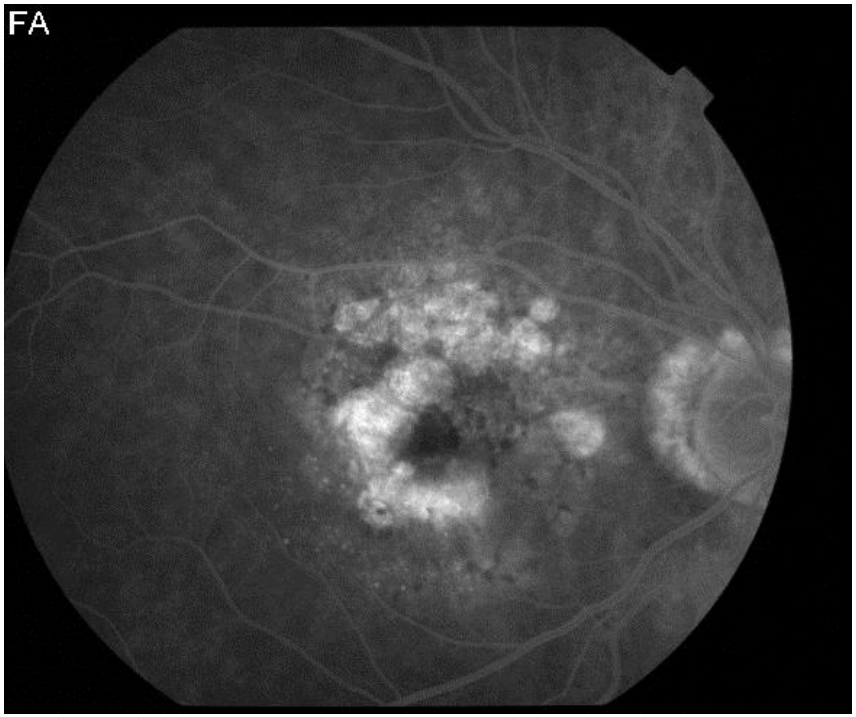
Wu Z et al *Ophthalmology* 2014

Vitelliform lesion resulting in GA

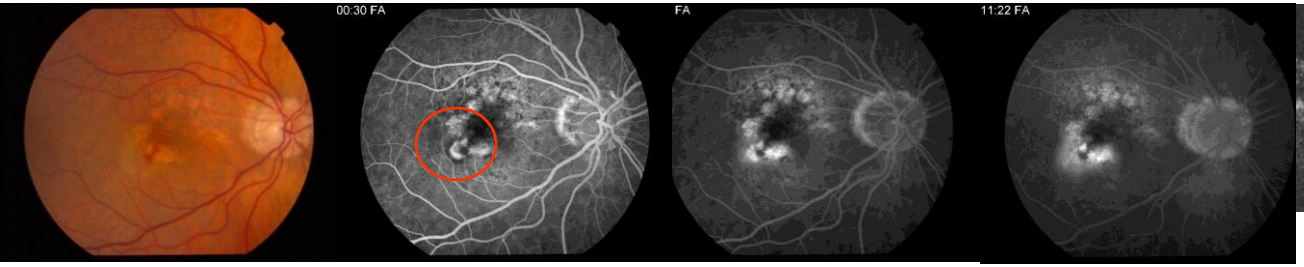
Geographic Atrophy in the antiVEGF era

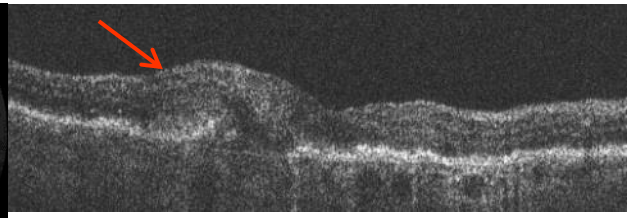


Comparisons of AMD Treatments Trials

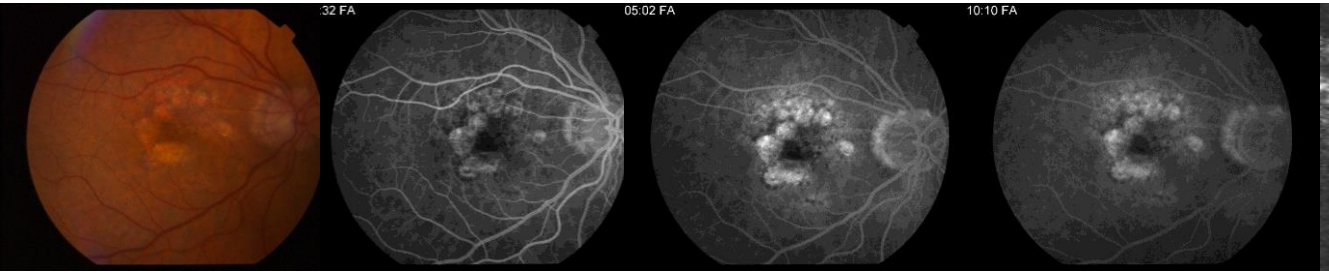
Comparisons of AMD Treatments Trials
Geographic Atrophy in the antiVEGF era

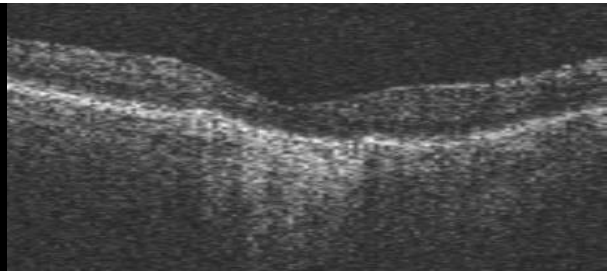
Baseline



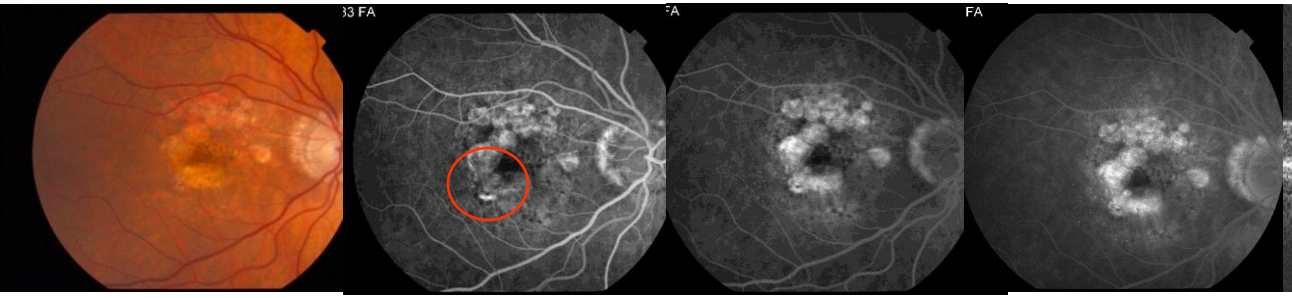


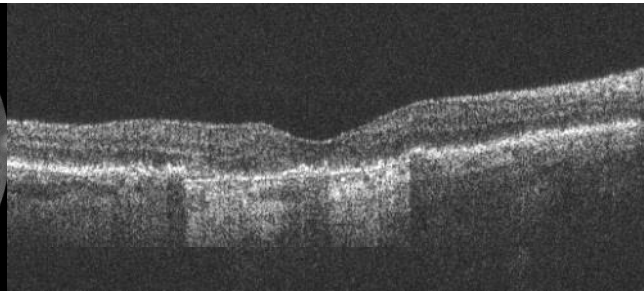
Year 1



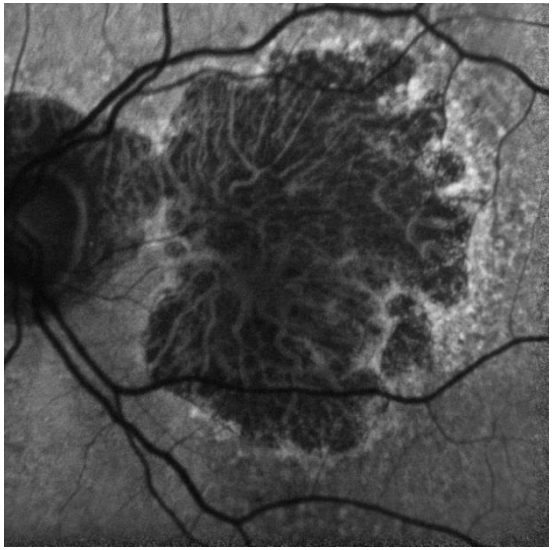


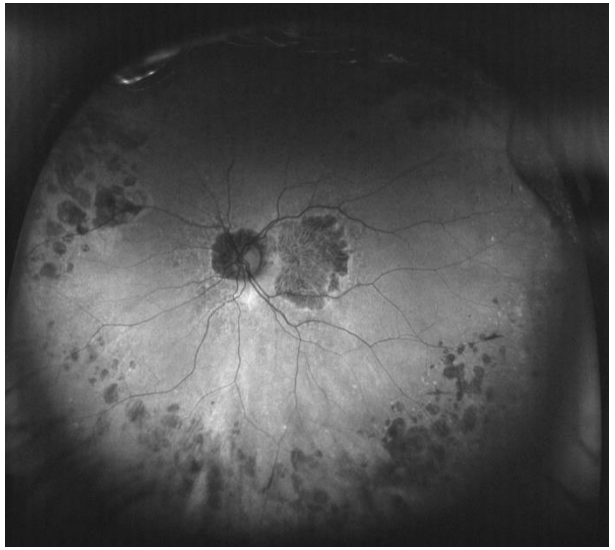
Year 2

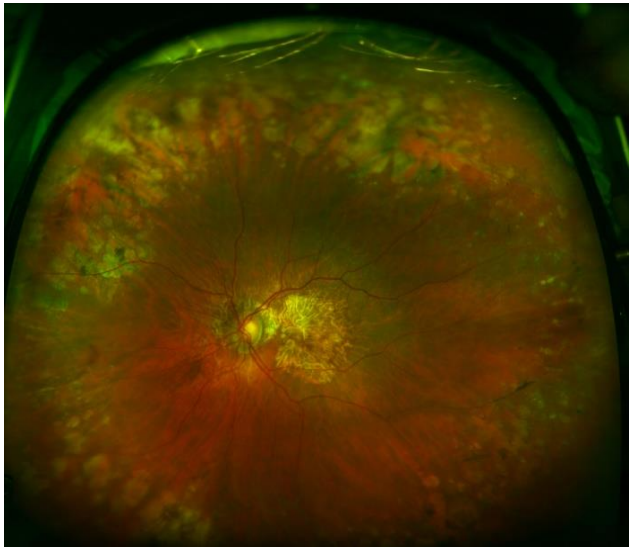


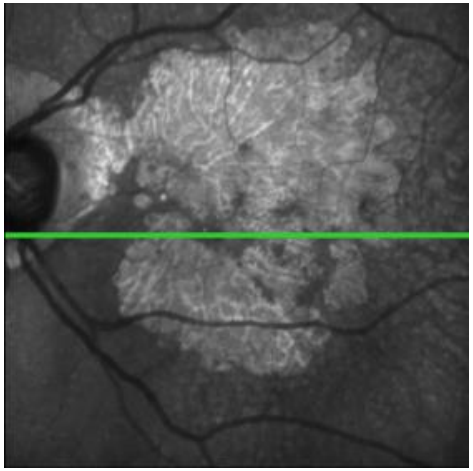


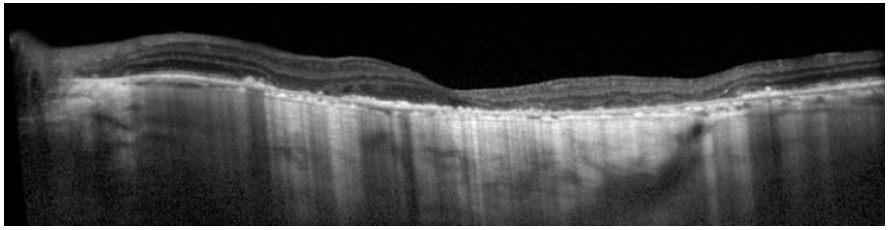
Anatomic endpoints from imaging

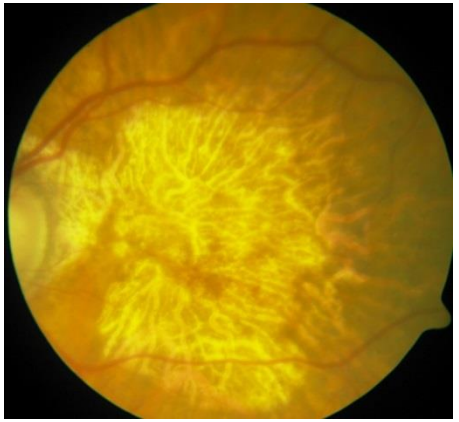












Imaging Anatomical endpoints

- Different methods
  - Often complementary
  - Strengths and weaknesses
- Extract qualitative and quantitative data extraction
- Involvement of foveal center as endpoint
- Influence of history or genotype
- Different if the endpoint is onset of atrophy or progression of atrophy