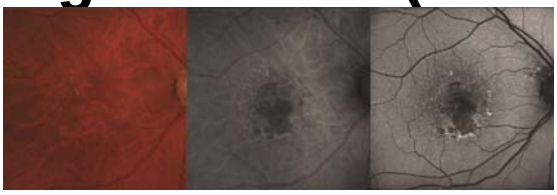
‘Dry’ Age-related Macular Degeneration (AMD)



Adnan Tufail
Moorfields Eye Hospital

Moorfields Eye Hospital NHS NHS Foundation Trust | UCL | uclpartners ACADEMIC HEALTH SCIENCE PARTNERSHIP | NHS National Institute for Health Research

Declaration of Interest

Consultant for the following companies

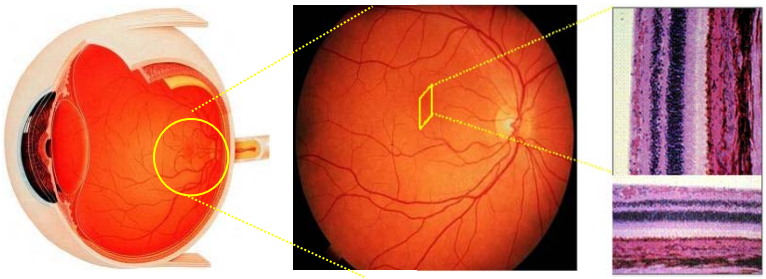
Allergan, Novartis, Bayer, GSK, Neuronsystems, Thrombogenics

Aim

- **Overview of the disease**
  - Disease Definitions
  - Epidemiology
  - Natural History
- **Diagnosis and Management**
  - Clinical & Investigations
  - Current standard of care
- **Potential parameters that predict visual outcome**
- **Methods of quantifying lesion growth**

Background- Normal Vision

- Normal vision occurs when light is focused on the retina
- The macula is the central part of the retina
- The macula has the highest density of photoreceptors which facilitate central vision and permit high resolution vision



AMD (Dry) Pathogenesis

Neural retina (photoreceptor) produces waste throughout life

↓

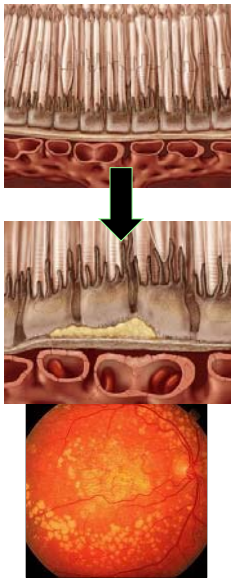
With aging, the ability of RPE cells to digest these molecules decreases

↓

Excessive accumulation of intra and extracellular waste (drusen) results in inflammation

↓

Bruch membrane and the RPE cells degenerate and atrophy sets in leading slowly to severe visual loss



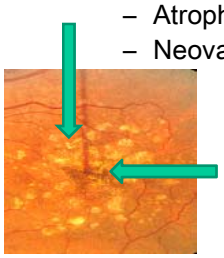
Tufail

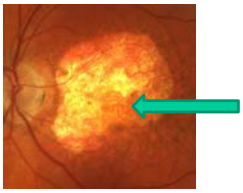
Overview-Disease Definitions

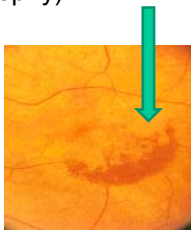
Age-related maculopathy

- Progressive disorder of the macula

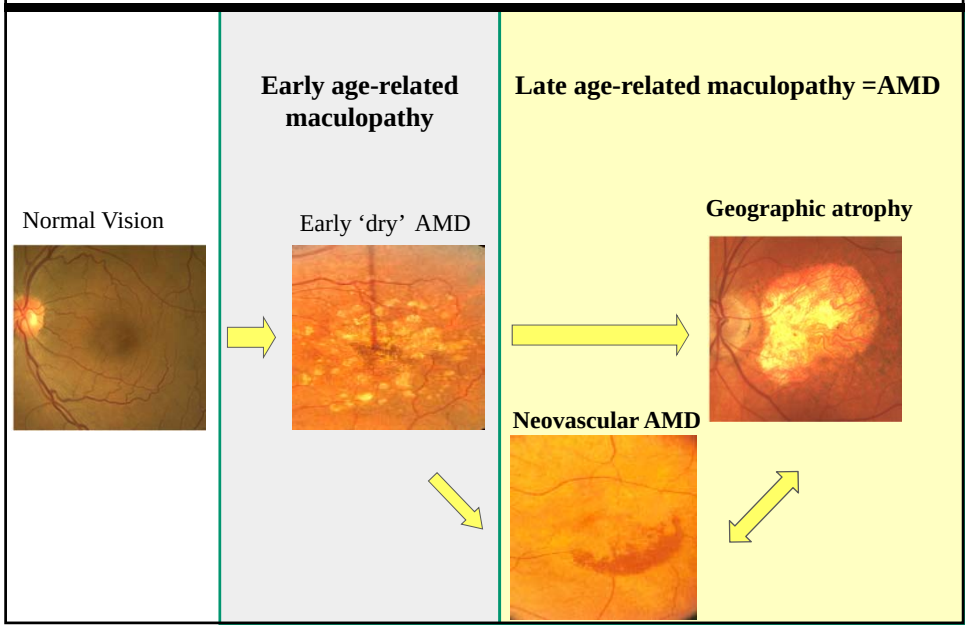
- Characteristic features
  - Drusen deposits >63 microns
  - Pigmentary changes (hypo- or hyper-) of the RPE
  - Atrophic macular degeneration (=geographic atrophy)
  - Neovascular macular degeneration







The 'natural' endpoint for the macula is Geographic Atrophy



Why are we interested in atrophic AMD? A Major Public Health Issue

Medical Need

- AMD is the most common cause of legal blindness in the developed world
- Atrophic AMD is more prevalent with age, and proportion is probably increasing
  - Under diagnosed
  - Treatment of wet AMD with anti-VEGF may result in increased number of patients with atrophy
  - Iceland 50% late AMD population have GA – high fish oil intake

- NO EFFECTIVE TREATMENT AVAILABLE

Classification of Age-related maculopathy in epidemiological studies

Age-related maculopathy (ARM)

- Different shapes/sizes of drusen used in definitions of various studies – as well as functional changes

Most Epidemiological studies use International Classification or similar (WARMGS) [Bird et al Surv Ophthal 1995]

Detection	Grading of colour fundus transparencies using grid 6000 micron diameter
Overall term	Age-related maculopathy
Exclusion	Other diseases mimicking features of ARM e.g. myopia
Early ARM	Drusen>63microns, pigmentary changes
Late ARM=age-related macular degeneration (AMD)	Atrophic or neovascular
-atrophic AMD=geographic atrophy	Sharply delineated lesion >175 microns diam with apparent absence of RPE in which enhance choroidal vessel visibility
- exudative AMD	RPE detachment, neovascular membrane, subretinal heam, scar

Atrophic AMD will become more common

- The increase in population aged over 80 is expected to be more than five fold by 2050
- One major implication of this demographic change is the emergence of conditions that are directly related to aging

Risk Factors for development of Late 'dry' AMD (GA)

Only consistent risk factors for incident GA

Systemic

1- Smoking

2- total serum cholesterol

(Risk factors for Incident AMD: Pooled findings from 3 continents, Tomany et al. Ophthalmol 2004)

3-Age (RR, 2.81 [95% CI, 1.33–5.94] for 79 years vs. 50–59 years)

Ocular

1. greater retinal area covered by drusen and pigment change

(RR, 5.10 [95% CI, 2.57–10.1] for >25% vs. <10%), RPE depigmentation (RR, 2.64 [95% CI, 1.26–5.53), RPE hyperpigmentation (RR, 10.4 [95% CI, 4.51–24.0] for >250microns vs. none)

(CAPT Res Group Ophthalmol 2008)

(

How many people are affected with the Atrophic form of AMD?

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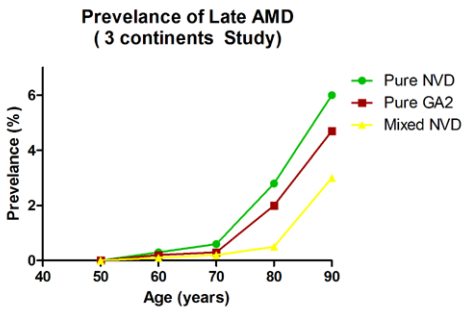
GA exponential increase with age

Prevalence over 90 years 22%

20% of legal blindness from AMD

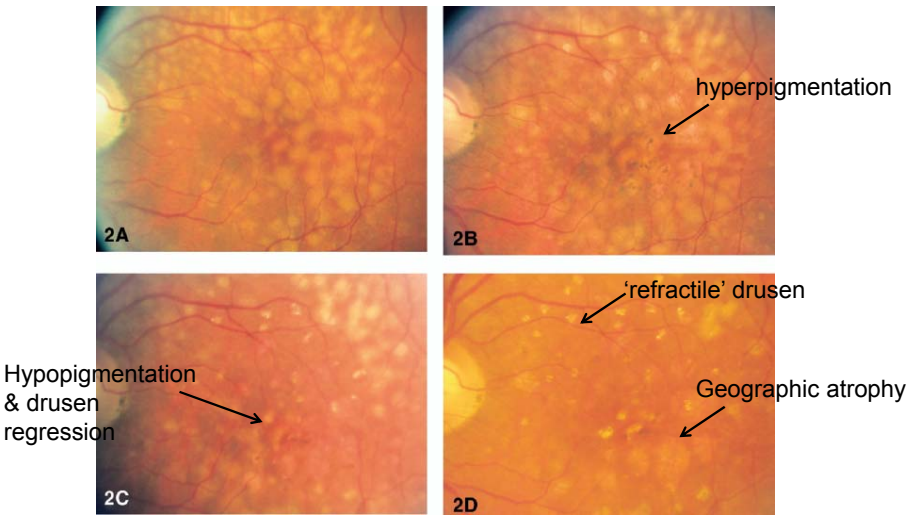


Risk factors for Incident AMD: pooled findings from 3 continents Ophthalmology 2004

What is Happening in Atrophic AMD?

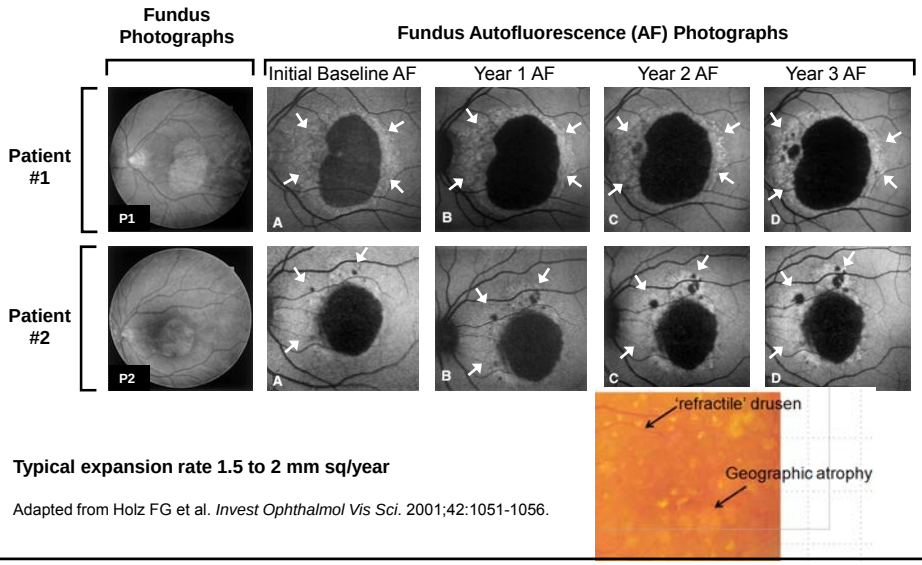
- What do we see when we examine the eye?
- What is happening to the structures of the eye?
- What do we think is happening at a microscopic and cellular level?
- How should we measure disease progression in clinical studies?
- What are the potential therapeutic approaches?

What do we see when we examine the eye?



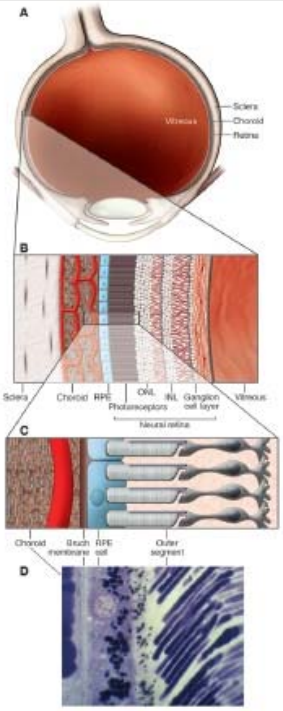
45% unifocal, 18% multifocal, 37% merged lesion Klein et al AJO 2008

Lipofuscin Autofluorescence Precedes Death of Photoreceptor and RPE Cells in Patients With Age-related Macular Degeneration



Typical expansion rate 1.5 to 2 mm sq/year

Adapted from Holz FG et al. *Invest Ophthalmol Vis Sci.* 2001;42:1051-1056.



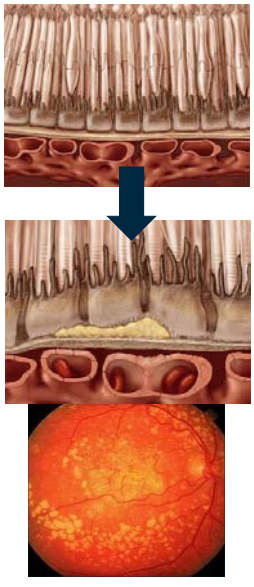
What is happening to the structures of the eye?

Neural retina (photoreceptor) produces waste throughout life

With aging, the ability of RPE cells to digest these molecules decreases

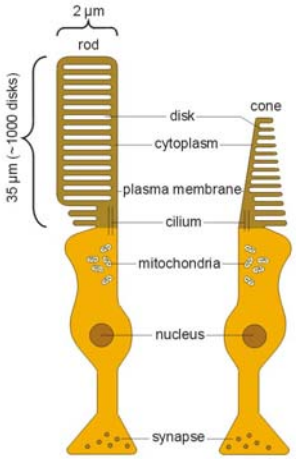
Excessive accumulation of intra(residual bodies) and extracellular waste (drusen) results in inflammation

Bruch membrane and the RPE cells degenerate and atrophy sets in, associated with choroicapillaris atrophy and photoreceptor loss leading slowly to severe visual loss



What is happening to the structures of the eye?

- Rods cells lost with age (30% by age 90)
- Cone cells relatively well preserved with age
- In patients with GA, rod cells lost before cones, but cones seem structurally abnormal

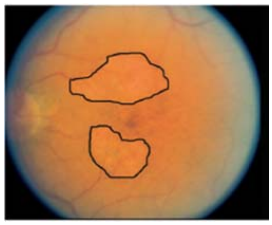


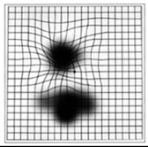
Cone Degeneration in Aging and Age-Related Macular Degeneration

Elizabeth J. Shelley, BSc(Hons); Michele C. Madigan, PhD; Riccardo Natoli, BSc(Hons); Philip L. Penfold, PhD; Jan M. Provis, PhD

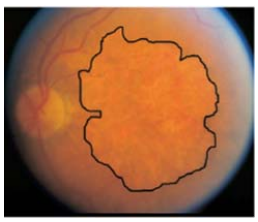
What does the patient experience?

Extrafoveal GA
Poor vision in dim light
Difficulty reading
Impaired Contrast
Reasonable central VA
50% loose 3+ lines
vision within 2 years





Subfoveal GA
Severe central vision loss
Eccentric fixation



Ophthalmology. 1997 October ; 104(10): 1677–1691.

Visual Function Abnormalities and Prognosis in Eyes with Age-related Geographic Atrophy of the Macula and Good Visual Acuity

Janet S. Sunness, MD[1,2], Gary S. Rubin, PhD[1], Carol A. Applegate, COT[1], Neil M. Bressler, MD[2], Marta J. Marsh, MD[3], Barbara S. Hawkins, PhD[3], and David Haselwood, BA[1]

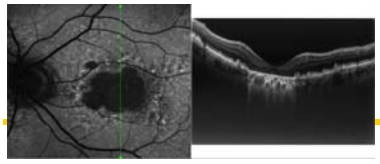
Diagnosis and Management

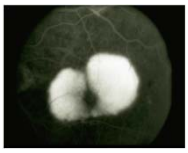
Clinical & Investigations

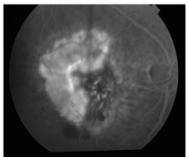
- Diagnosis usually made clinically
- Atrophy in the presence of drusen/rpe change with the exclusion of other mimicking disorders

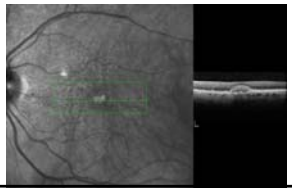
Current standard of care

- No proven intervention halts progression of GA
- Smoking cessation?
- AREDS vitamins may prevent nAMD but theoretically may worsen atophy
- Removing drusen (laser etc) increased risk of nAMD

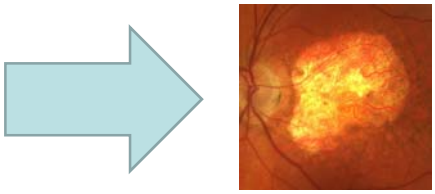




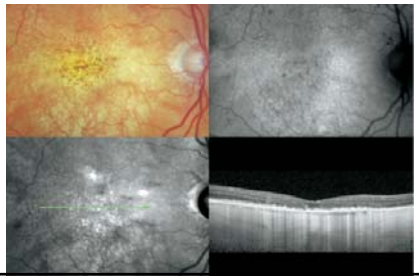




More than on cause of Atrophic AMD different therapeutic approaches

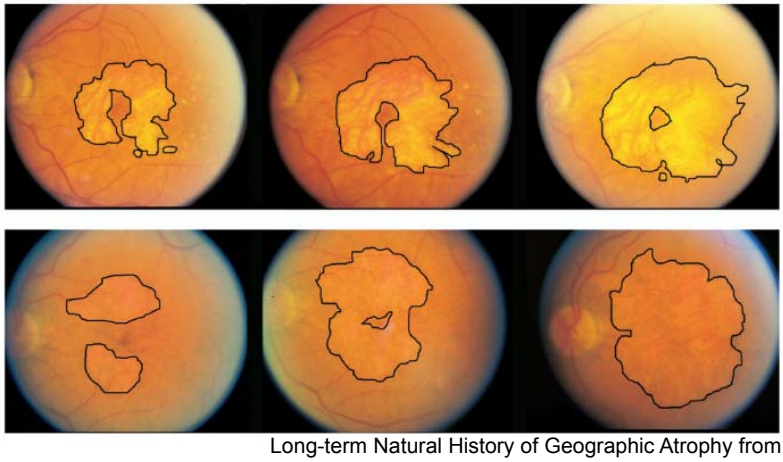


cf age-related choroidal atrophy Spaide AJO 2008



Natural History of Geographic Atrophy

(Sunness et al. Ophthalmol 2007)
Atrophy expands at median 2.1mmsq/yr)



Long-term Natural History of Geographic Atrophy from Age-Related Macular Degeneration:Sunness et al Ophthalmol 2007

EPIDEMIOLOGY

SECTION EDITOR: LESLIE HYMAN, PhD

Change in Area of Geographic Atrophy in the Age-Related Eye Disease Study

AREDS Report Number 26

*The AREDS Research Group**

- Digitised colour photos
- Median time to develop central GA (after GA diagnosis) 2.5yrs {95% CI 2-3}
- Av VA decrease after 'central' GA development 3.7 letters initially then 22 letters at 5 years

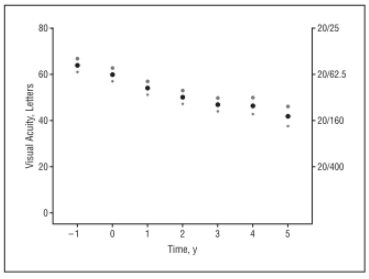
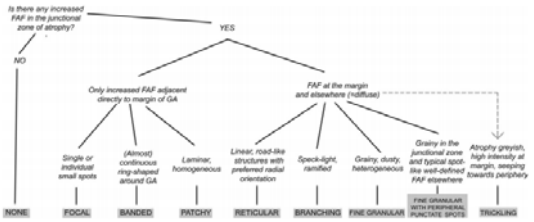


Figure 5. Mean visual acuity over time following development of central geographic atrophy. The small dots indicate 95% confidence intervals.

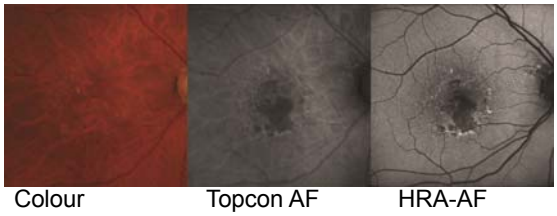
Potential biomarkers affecting progression of GA

- **Genetics**- none proven for CFH, C2, C3, APOE, or TLR3 genes. There was a nominally significant association with the LOC387715/ARMS2/HTRA1
  (Progression of geographic atrophy and genotype in AMD Klein et al Ophthalmol 2010)
- **Systemic disease** – none to date eg. BMI, CHD, diabetes > cholesterol
  (Dreyhaupt et al Methods Inf Med 4/2007)
- **Rate of progression-** 1.52 mm(2)/year (IQR, 0.81 to 2.33)
  (*Holz et al AJO 2007)*
- **Autofluoresence Pattern** – yes -banded (median 1.81 mm(2)/year) diffuse FAF pattern (1.77 mm(2)/year) were significantly higher compared to eyes without FAF abnormalities (0.38 mm(2)/year) and focal FAF patterns (0.81 mm(2)/year, P < .0001).



How should we measure disease progression in clinical studies?

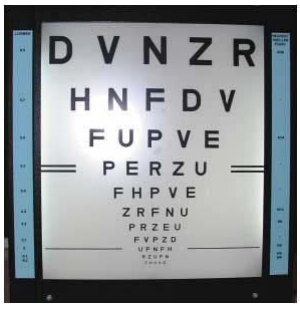
- **Structural**
  - Colour
  - AF
  - OCT
  - IR reflectance

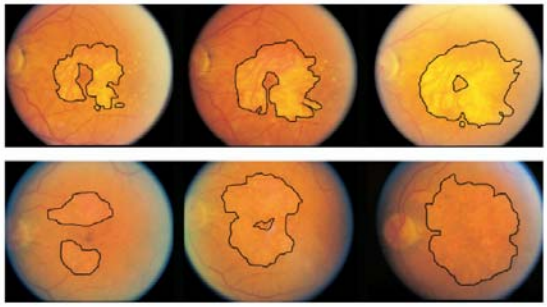


Colour Topcon AF HRA-AF
Schmitz-Valckenberg et al IOVS 2009

- **Functional**
  - microperimetery
  - VA – standard or low luminance
  - Reading
  - Dark adaptation
  - Contrast sensitivity

Why is the standard endpoint of high contrast visual acuity problematic?





Sunness et al. Ophthalmol 2007

Alternatives

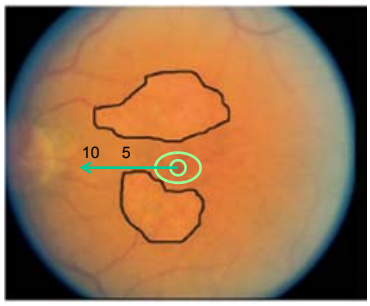
•Low-luminance visual acuity

Sunness JS et al.. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. Ophthalmology. 2008 Sep;115(9):1480-8

•Reading Speed

Patel PJ, Chen FK, Da Cruz L, Rubin GS, Tufail A. Test-retest variability of reading performance metrics using MNREAD in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011 Jun 1;52(6):3854-9

Reading Speed



Reading is a complex task – required 2 degrees horizontal 1 above below and about 5 degrees for 'perceptual span'

What is the best parameter to take?

•Maximal reading speed

•Critical print size

Lesion position may affect reading speed – language dependent

Repeatability in AMD for MNread The 95% coefficient of repeatability (CR) was 0.30 logMAR for reading acuity. The CR for critical print size and maximum reading speed varied depending on the analysis method applied

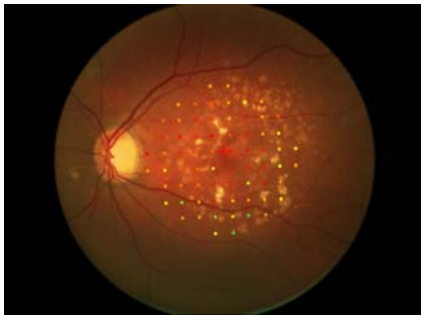
Patel PJ, Chen FK, Da Cruz L, Rubin GS, Tufail A. Test-retest variability of reading performance metrics using MNREAD in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011 Jun 1;52(6):3854-9

Test–Retest Variability of Microperimetry Using the Nidek MP1 in Patients with Macular Disease

Fred K. Chen,[1,2] Praveen J. Patel,[1] Wen Xing,[1] Catey Bunce,[1] Catherine Egan,[1] Adnan T. Tufail,[1] Peter J. Coffey,[2] Gary S. Rubin,[2,3] and Lyndon Da Cruz[1,2]

IOVS July 2009

- Coeff of repeatability of Pointwise sensitivity 5.56db Av sensitivity of central Macula 2.13db for MP-1



•Still has potential to detect Decline in function with Stable VA.

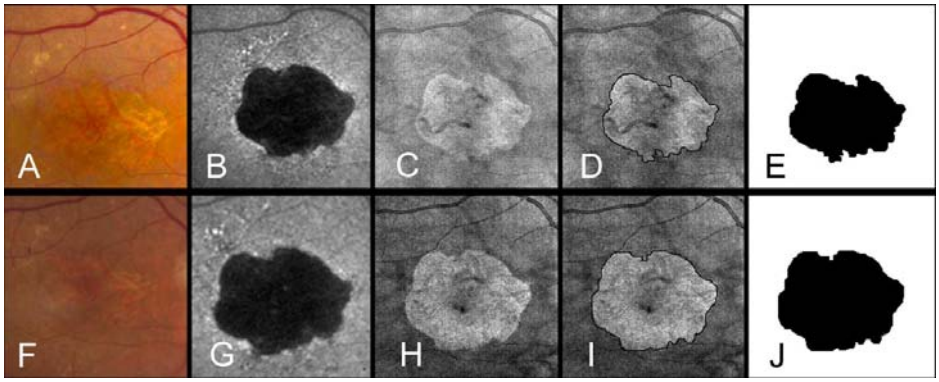
Chen FK, Patel PJ, Webster AR, Coffey PJ, Tufail A, Da Cruz L. Nidek MP1 is able to detect subtle decline in function in inherited and age-related atrophic macular disease with stable visual acuity. Retina. 2011 Feb;31(2):371-9

•How do the different micro perimeters compare and which is best suited to measuring change?

Other Functional tests

- Dark Adaptation
  Delayed cone & rod adaptation *(Owsley Ophthalmol 2001, Brown 1986, Dimitrov IOVS 2008)- What is the best method of measurement what is the repeatability?*
- Contrast Sensitivity
  Impaired in AMD. Intersession 95% coef of repeatability 7 letters *(Patel PJ, Chen FK, Rubin GS, Tufail A. Intersession repeatability of contrast sensitivity scores in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009 Jun;50(6):2621-5)*
- Quality of Life Questionnaires
  Standard questionnaires inadequate to assess tasks in low luminance. (NEI-VFQ, VF-14 only have 1-3 items). 32 Item LLQ developed*) Owsley C, McGwin G Jr, Scilley K, Kallies K. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. Invest Ophthalmol Vis Sci. 2006 Feb;47(2):528-35*

Colour-AF-OCT fundus

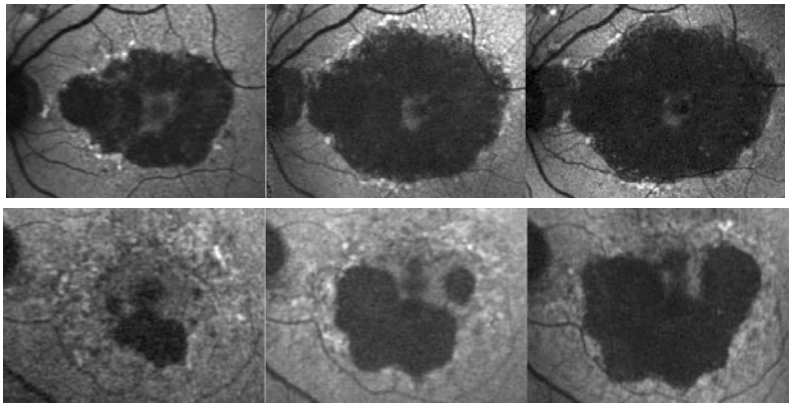


Yehoshua et al Ophthalmology April 2011

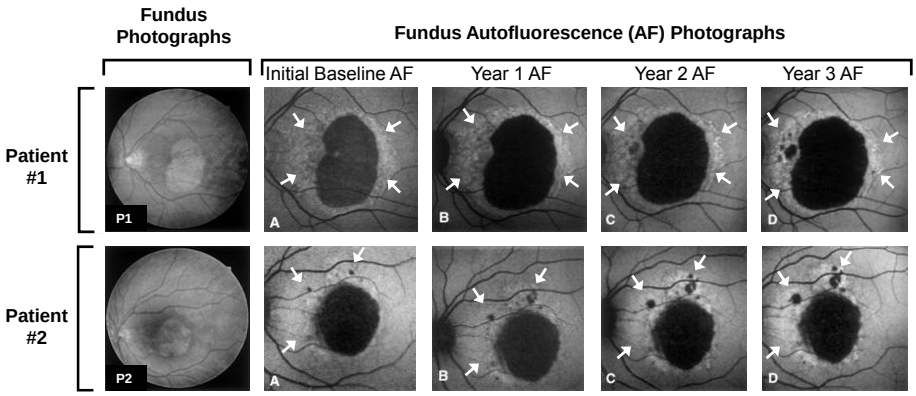
95% limits of agreement for 2 readers of colour images -1.54 to 1.25 mmsq
AREDS report 26

GA progression over time

- Median progression: ca. 1.52 mm^2/year (IQR, 0.81 to 2.33) (range 0 to 13.8)
  Holz et al. 2007 FAM Study Group
- Fovea not involved until the late course of the disease
  Maguire et Vine 1986; Schatz and McDonald 1989; Sunness et al. 1999



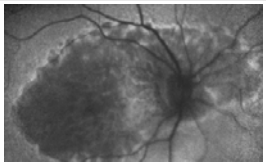
Lipofuscin Autofluorescence Precedes Death of Photoreceptor and RPE Cells in Patients With Age-related Macular Degeneration



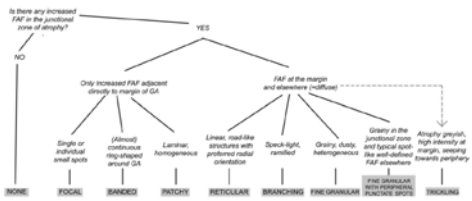
Typical expansion rate 1.5 to 2 mm sq/year

Adapted from Holz FG et al. *Invest Ophthalmol Vis Sci.* 2001;42:1051-1056.

Findings from the FAM study group- implications in clinical trials



- *Holz F et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol. 2007 Mar;143(3):463-72*



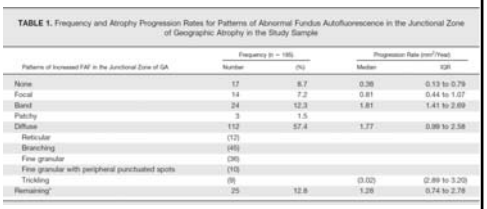


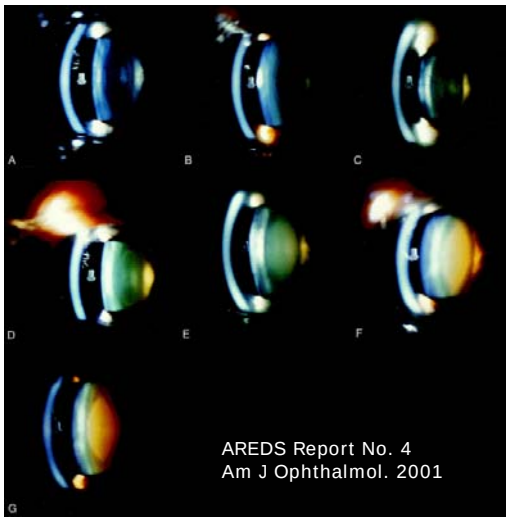
TABLE 1. Frequency and Atrophy Progression Rates for Patterns of Abnormal Fundus Autofluorescence in the Junctional Zone of Geographic Atrophy in the Study Sample

Patterns of Increased FAF in the Junctional Zone of GA	Frequency (n = 195)		Progression Rate (mm²/Year)	
	Number	(%)	Median	IQR
None	17	8.7	0.38	0.13 to 0.79
Focal	14	7.2	0.81	0.44 to 1.07
Band	24	12.3	1.81	1.41 to 2.69
Patchy	3	1.5		
Diffuse	112	57.4	1.77	0.99 to 2.58
Reticular	(12)			
Branching	(45)			
Fine granular	(36)			
Fine granular with peripheral punctuated spots	(10)			
Trickling	(9)		(3.02)	(2.89 to 3.20)
Remaining*	25	12.8	1.26	0.74 to 2.78

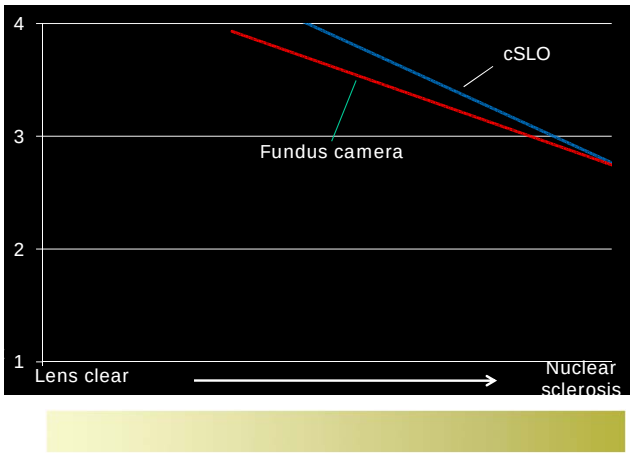
- *Fleckenstein et al.; FAM Study Group. Concordance of disease progression in bilateral geographic atrophy due to AMD. Invest Ophthalmol Vis Sci. 2010*

concordance correlation coefficient between the eyes was 0.310 (95% CI, 0.097–0.495) for visual acuity, 0.706 (95% CI, 0.575–0.801) for GA size, and 0.756 (95% CI, 0.644–0.837) for GA progression rate

Influence of nuclear lens opacities

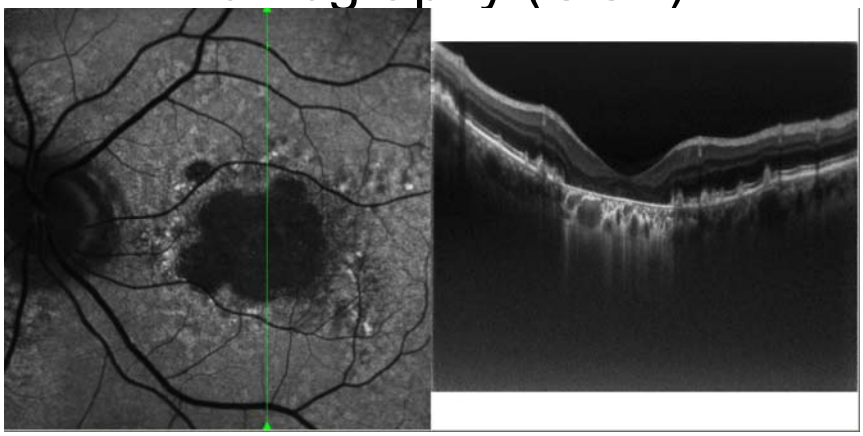


Influence of nuclear lens opacities



Schmitz-Valckenberg S, Fleckenstein M, Göbel AP, Sehmi K, Fitzke FW, Holz FG, Tufail A. Evaluation of autofluorescence imaging with the scanning laser ophthalmoscope and the fundus camera in age-related geographic atrophy. Am J Ophthalmol. 2008 Aug;146(2):183-92

Optical Coherence Tomography (OCT)



Fleckenstein et al. Tracking progression with spectral-domain optical coherence tomography in geographic atrophy caused by age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010 Aug;51(8):3846-52

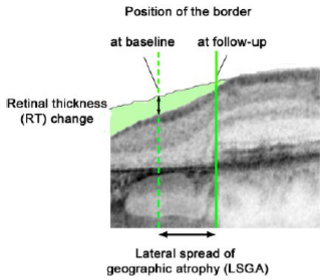


FIGURE 2. Quantification of morphologic changes at the border of GA in SD-OCT imaging. *Solid green vertical line*: position of the border at follow-up. *Dotted green line*: position of the border at baseline. Change in RT (*vertical arrows*) and (*horizontal arrows*) LSGA.

Progression of Geographic Atrophy in Age-Related Macular Degeneration Imaged with Spectral Domain Optical Coherence Tomography

Zohar Yehoshua, MD, MHA, Philip J. Rosenfeld, MD, PhD, Giovanni Gregori, PhD, William J. Feuer, MS, Manuel Falcão, MD, Brandon J. Lujan, MD, Carmen Puliafito, MD, MBA

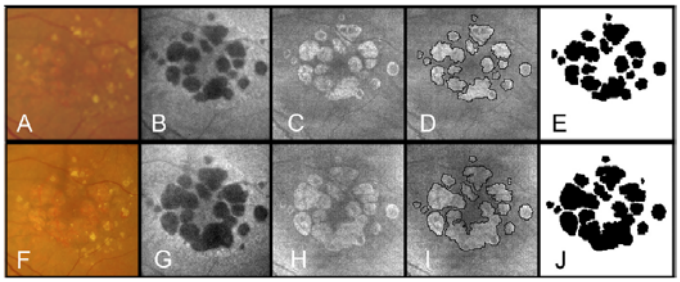


Figure 6. Large, multifocal area of geographic atrophy (GA) as seen by fundus photography (**A**, **F**), fundus camera-based autofluorescence* (**B**, **G**), and optical coherence tomography (OCT) fundus imaging (**C**, **H**) at baseline (**A–E**) and at the end of a 12-month follow-up period (**F–J**). The boundaries of GA were manually outlined on the OCT fundus image at baseline (**D**) and at the end of the follow-up period (**I**). Areas of GA were calculated as 6.88 mm^2 (**E**) and 9.20 mm^2 (**J**). Frames **E** and **J** show a clear growth in the area of GA over time. This difference was used to calculate the yearly enlargement rate (2.32 mm^2/yr). On a square root scale the ER was 0.41 mm/yr. *Topcon TRC-501X color fundus camera (Topcon Medical Systems, Oakland, NJ) with filters by Spectrotech, Inc. (Saugus, MA) having an excitation bandpass filter centered at a wavelength of 580 nm and a barrier bandpass filter centered at a wavelength of 695 nm.

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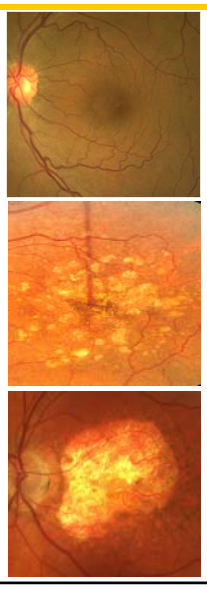
Potential therapeutic Approaches

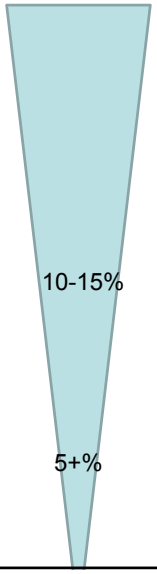
1-Reduce stop stimuli of continuing damage

2-Protect remaining cells from damaging stimuli/ environment

3- Repair/Regenerate damaged cells

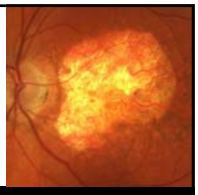
Can we avoid the development of Atrophic AMD?





'Prevention is better than cure'

Summary



- The geographic atrophy form of AMD will become an increasingly common cause of severe vision loss
- No proven treatments yet halt progression
- Current outcomes measures in AMD trials (high contrast VA) may not be optimal for GA trial
- Functional testing in low luminance or test that measure parafoveal function may be most suitable, but noisey
- Structural changes can reproducibly measured and may represent a good endpoint for clinical trials