Developing Treatments for Dry AMD: A Workshop
Focus on Geographic Atrophy (GA)

Phenotype and Genotype of GA

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Phenotype of Geographic Atrophy (GA)

No Financial Disclosures
Clinical Definition of Geographic Atrophy

- Depigmented Area (175 µ to 433 µ in AREDS2)
- Sharply Demarcated
- Choroidal Vessels Visible
Phenotype of GA: Goals

• Burden of Disease (Functional Challenges)
• Defining the phenotypic characteristics of GA
  – Drusen
  – Reticular Pseudodrusen
  – Geographic Atrophy
• Impact of Phenotypic Heterogeneity
AMD: Disease Background

• AMD is ranked 3rd in the World Health Organization’s review of the leading causes of blindness worldwide.

• In developed countries, AMD is the leading cause of blindness due to the growing number of people over 70 years of age.

• As populations grow and demographic shifts move towards an increase in the predominance of older age groups, the incidence of AMD will increase.
The Eye Diseases Prevalence Research Group

Causes of Blindness in Whites

- AMD: 54.4%
- Other causes
- Diabetic Retinopathy
- Glaucoma
- Cataract

Meta-analysis of population-based studies in US, Australia and Europe

Estimated prevalence and distribution of AMD in US by age, race/ethnicity and gender using data from the 2000 US Census

Prevalence of neovascular AMD and/or GA among individuals aged ≥40 years
- 1.47% overall (1.75 million)
- 1.02% neovascular AMD (1.22 million)
- 0.81% GA (970,000)

Incidence of AMD in 2020
- Increase by >50% from 1.75 million to 2.95 million
### Summary of prevalence of AMD worldwide

<table>
<thead>
<tr>
<th>Study</th>
<th>Any</th>
<th>Early</th>
<th>Late</th>
<th>Neovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Eye Study</td>
<td>8.8%</td>
<td></td>
<td></td>
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<tr>
<td>Beaver Dam Eye Study</td>
<td></td>
<td>1.6%</td>
<td>1.2%</td>
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<tr>
<td>EUREYE</td>
<td>3.32%</td>
<td></td>
<td>2.3%</td>
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<tr>
<td>Rotterdam Eye Study</td>
<td>1.7%</td>
<td></td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Blue Mountains Eye Study</td>
<td>1.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reykjavik Eye Study</td>
<td></td>
<td></td>
<td></td>
<td>GA 3.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7%</td>
</tr>
<tr>
<td>Fungata Study</td>
<td>4.3%*</td>
<td>0.6%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hisayama Study</td>
<td></td>
<td></td>
<td></td>
<td>0.67%</td>
</tr>
<tr>
<td>Singapore Malay Eye Study</td>
<td>3.5%</td>
<td>0.34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beijing Eye Study</td>
<td>1.4%</td>
<td>0.2%</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>INDEYE Study</td>
<td>0.3%</td>
<td>1.2%</td>
<td></td>
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</tr>
</tbody>
</table>

*in participants over 50 years old
Prevalence of Early AMD

![Graph showing the prevalence of early AMD across different age groups and study locations. The x-axis represents the age-group (yr) ranging from 50 to 85, while the y-axis represents the prevalence (%) ranging from 0 to 30. Different lines indicate the prevalence data from Beaver Dam, Rotterdam, EUREYE, Beijing, Barbados, Hisayama, and INDEYE. Each line shows an increasing trend in prevalence with age.](image-url)
Prevalence of Advanced AMD
Clinical Classification of Age-Related Macular Degeneration

Frederick L. Ferris III, MD,1 C. P. Wilkinson, MD,2 Alan Bird, MD,3 Usha Chakravarthy, MD,4 Emily Chew, MD,1 Karl Csaky, MD,5 Srinivas R. Sadda, MD,6 on behalf of the Beckman Initiative for Macular Research Classification Committee*

Objective: To develop a clinical classification system for age-related macular degeneration (AMD).

Design: Evidence-based investigation, using a modified Delphi process.

Participants: Twenty-six AMD experts, 1 neuro-ophthalmologist, 2 committee chairmen, and 1 methodologist.

Methods: Each committee member completed an online assessment of statements summarizing current AMD classification criteria, indicating agreement or disagreement with each statement on a 9-step scale. The group met, reviewed the survey results, discussed the important components of a clinical classification system, and defined new data analyses needed to refine a classification system. After the meeting, additional data analyses from large studies were provided to the committee to provide risk estimates related to the presence of various AMD lesions.

Main Outcome Measures: Delphi review of the 9-item set of statements resulting from the meeting.

Results: Consensus was achieved in generating a basic clinical classification system based on fundus lesions assessed within 2 disc diameters of the fovea in persons older than 55 years. The committee agreed that a single term, age-related macular degeneration, should be used for the disease. Persons with no visible drusen or pigmentation abnormalities should be considered to have no signs of AMD. Persons with small drusen (≤63 μm), also termed druplets, should be considered to have normal aging changes with no clinically relevant increased risk of late AMD developing. Persons with medium drusen (≥63–≤125 μm), but without pigmentary abnormalities thought to be related to AMD, should be considered to have early AMD. Persons with large drusen or with pigmentary abnormalities associated with at least medium drusen should be considered to have intermediate AMD. Persons with lesions associated with neovascular AMD or geographic atrophy should be considered to have late AMD. Five-year risks of progressing to late AMD are estimated to increase approximately 100-fold, ranging from a 0.5% 5-year risk for normal aging changes to a 50% risk for the highest intermediate AMD risk group.

Conclusions: The proposed basic clinical classification scale seems to be of value in predicting the risk of late AMD. Incorporating consistent nomenclature into the practice patterns of all eye care providers may improve communication and patient care.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. Ophthalmology 2013;xxx:xxx © 2013 by the American Academy of Ophthalmology.

*Group members listed after the references in Appendix 1.
“No Apparent Aging Changes”

- No Drusen Within 2 DD of the Fovea
- No Pigmentary Abnormalities
“Normal Aging Changes”

Only Small Drusen Within 2 DD of Fovea

and

No Pigmentary Abnormalities (Thought to be Related to AMD)
“Early AMD”

- Any Medium Drusen (62µ – 125µ) Within 2 DD of Fovea

and

- No Pigmentary Abnormalities (Thought to be Related to AMD)
Any Large Drusen (>125µ) Within 2 DD of Fovea (Includes Drusenoid RPE Detachment) and/or Pigmentary Abnormalities Associated with at Least Medium Drusen
“Late AMD”

- Apparent Signs of Macular Neovascularization Within 2DD of Fovea &/or Associated Signs (Fluid, RPE Elevation, Hemorrhage, Lipid, Fibrosis)

  and/or

- Geographic Atrophy Within 2DD of Fovea Punched-out Retinal Lesions with Sharp Edges and Visible Choroidal Vessels
<table>
<thead>
<tr>
<th>Classification of AMD</th>
<th>Definition Lesions within 2DD of Fovea</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Apparent Aging Changes</td>
<td>No Drusen No RPE Abnormalities*</td>
</tr>
<tr>
<td>Normal Aging Changes</td>
<td>Drusen &lt; 63µ (Drupelets) No AMD-RPE Abnormalities*</td>
</tr>
<tr>
<td>Early AMD</td>
<td>Medium Drusen (63-125µ) No AMD-RPE Abnormalities*</td>
</tr>
<tr>
<td>Intermediate AMD</td>
<td>Any Large Drusen (&gt; 125µ) Any AMD-RPE Abnormalities*</td>
</tr>
<tr>
<td>Late AMD</td>
<td>Neovascular AMD, Any Geographic Atrophy or Both</td>
</tr>
</tbody>
</table>

*Thought to be Related to AMD (at Least Medium Drusen)
How Does GA Develop?

Study Design

- Two AREDS Clinical Centers
- Identify Eyes Developing GA after 4th Yr
- 95 Eyes Identified
- Grade all Photos Prior to GA Development

Ophthalmology 2008;115:1026-1031
Clinical Example

Yearly photos

1993- Baseline  
1999 - Onset of GA
Eyes Graded for Potential Risk Factors

- Drusen Characteristics
- Pigmentary Changes
- Other Features (e.g. Calcification, etc)
Lesions Preceding GA

- Large Confluent Drusen > 250 µ (94%)
  - >>6.5 years
- Hyperpigmentation (96%)
  - 4 years (2-9)
- Hypopigmentation (81%)
  - 2-3 years

Geographic Atrophy
Crystalline Deposits

- Often Present Near Drusen Just Prior to GA (23%)
- May be Unphagocytized Material
Example – Unifocal GA
Example – Unifocal GA

1997 (4 Years)
Example – Unifocal GA

1999 (6 Years)
Example – Unifocal GA

2004 (9 Years)
Progression to Geographic Atrophy

Drusen

Large Confluent Drusen

Hyperpigmentation

Hypopigmentation

Mild RPE Atrophy

Geographic Atrophy

6+ Years

4 Years

2 Years
Progression to Geographic Atrophy

Drusen

- Large Confluent Drusen
  - Hyperpigmentation
  - Hypopigmentation

- Mild RPE Atrophy

- Geographic Atrophy

Angiogenesis

Neovascularization
20 year history of GA development
Initial Appearance of GA

- 24% (23/95) had Center Involvement
- 32% (30/95) had Multiple Areas of GA
VA Score after Central GA

Median VA Score

- 20/40
- 20/160
- N=428
- N=103
- N=2

Years

-1 0 1 2 3 4 5 6 7 8 9 10

VA Score

- 20/2 20/5 20/100 20/200 20/400 20/800 20/160

N=428 N=103 N=2
Development of CNV in Eyes with GA

Event Rate

No CNV in Fellow Eye
CNV in Fellow Eye

Years From First Occurrence of GA
Fundus Lesions

Central Geographic Atrophy (CGA)
Peripheral drusen, reticular changes and GA
Fundus Autofluorescence
OCT in Phenotyping of Age-related Macular Degeneration

Photoreceptor Loss
Entirely Within GA Margin

Geographic Atrophy (GA) Margin

Retinal Pigmented Epithelium

Photoreceptor Loss Bridging Across GA Margin

Start of PR Loss
End of PR Loss

Photoreceptor - Outer Plexiform Layer Junction

500 microns

Ophthalmol 2009;116:1762-1769
GA-Functional Changes

- Dark Adaptation Abnormalities
- Difficulties with Reading
- Problems recognizing faces
- Dense, irreversible scotomas
AMD Classification

Additional Issues

 ROLE OF PSEUDORETICULAR DRUSEN?
Reticular Pseudo-Drusen


“In 1990 we described reticular pseudodrusen as a peculiar yellowish pattern in the macula of age-related macular degeneration AMD patients. In the original description we called this peculiar form of drusen “les pseudo-drusen bleus”, because of their enhanced visibility using blue light.”
Reticular Pseudo-Drusen

Reticular Pseudo-Drusen in Color Photographs

- Defined in AREDS Report 6

_the term “reticular drusen” is applied to the yellowish material that looks like soft drusen arranged in ill-defined networks of broad interlacing ribbons_
Reticular Pseudo-Drusen

Reticular Pseudo-Drusen in Color Photographs

- Reticular drusen associated with high risk of late AMD.

Klein et al.
Reticular Pseudo-Drusen

Reticular Autofluorescence

- Lois et al.: Definition of reticular AF “Ill-defined small areas of decreased AF surrounded by areas of increased AF”  *AJO* 2002;133(3):341-9

- Smith et al.: Correlation between reticular autofluorescence and reticular pseudo-drusen on multiple modalities; “Reticular Macular Disease”
2009 60 yo Female, Neovascular AMD

Reticular Drusen

Large Drusen
Reticular Auftofluorescence

• Reticular drusen represent a common phenotypic hallmark in eyes with Geographic Atrophy.

Holz et al., IOVS, August 2011, Vol 52, No. 9
1991 AREDS Participant-no AMD
2008 AREDS Participant-no AMD
Phenotype of Geographic Atrophy (GA)

Burden of disease-enormous and growing
Drusen and RPE pigmentary changes &
Progression of GA
Reticular Drusen-Role? In AMD