Educational Toolkit for Clinicians:

Geographic Atrophy & Emerging Therapeutic Targets

Developed by:

The Angiogenesis Foundation

Center of Excellence for Retinal Disorders

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Geographic Atrophy

Introduction
What is Geographic Atrophy?

Geographic Atrophy (GA) is the advanced atrophic form of Age-related Macular Degeneration (AMD).

GA causes impaired visual function and affects more than 5 million people worldwide, including 22% of people over 90 years old.

What is Geographic Atrophy (GA)?

GA is a leading cause of **impaired visual function** in the elderly. While there are no approved treatments currently available, recent advances in our understanding of AMD mechanisms and risk factors provide a host of potential targets for drug development.

Dry AMD accounts for 90% of diagnosed cases of AMD. The global prevalence of AMD in 2020 is projected to be 196 million, increasing to 288 million in 2040.

Geographic atrophy and wet macular degeneration are always preceded by the dry form of the disease.

Ferris FL. "Age-Related Macular Degeneration and Blindness due to Neovascular Maculopathy." Arch Ophthalmol.102.11(1984):1640-1642
Worldwide, more than 5 million people have geographic atrophy.

- The global prevalence of GA is 0.66% in all ages
- 0.34% between 65-74 years old
- 1.3% between 75-84
- 4.4% over 85 years old.

Global prevalence of GA jumps to 22% at 90 years old.


Vaz F and Picoto M, “Georgraphic Atrophy” -- http://www.amdbook.org/content/geographic-atrophy-0

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Burden of GA

GA is responsible for 10%-20% of all incidences of legal blindness caused by AMD.

Europeans are more likely to be affected by GA than other demographic groups, including Asians, Africans, and Hispanics. Approximately 26% of legal cases of blindness in the United Kingdom are due to GA, and almost 1 million people in the United States are thought to currently be affected by GA, with more than half of the cases occurring bilaterally.

References:

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Burden of GA

GA is responsible for 10%-20% of all incidences of legal blindness caused by AMD.


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GA Risk Factors

GA is associated with a number of genetic markers as well as environmental risk factors.

Risk factors for GA include:
- Genetic polymorphisms
- Advanced age (especially over 85 years old)
- Smoking
- presence of early AMD to GA in the fellow eye
Genes that may play a significant role in GA include:

- Complement Factor H (CFH)
- Complement Factor B (CFB)
- Complement 2 (C2)
- Complement 3 (C3)
- ARMS2

Genes involved in the alternative complement cascade have consistently been implicated in AMD pathogenesis.

Polymorphisms in six complement genes (CFH, CFI, C2/CFB, C3, C9) account for almost 60% of the AMD genetic risk.

*This topic is still a subject of ongoing research and debate.


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Symptoms of GA

GA progression causes a gradual loss of visual function. Symptoms include scotomas (large dark or blind spots in the visual field), difficulty recognizing faces, decreased reading speed (measured in words per minute, wpm), impaired dark adaptation, low luminance deficit (LLD), impaired contrast sensitivity, and difficulty driving at night.


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Visual Function versus BCVA

Because GA can progress in a central fovea-sparing pattern, patients with advanced GA may have significant loss of visual function while still having preserved best-corrected visual acuity (BCVA).

As treatments are developed for GA, quality of life measures, patient-reported outcomes, and measures of visual function will be critically important in determining the value of future therapies.

GA Symptoms: Scotomas

**Patient-Reported Outcome:** Blind spots, Dark spots  
**Visual Function Measure:** Macular perimetry

Because GA can progress without central foveal involvement, researchers have developed standardized ways of testing the central retina within a few degrees of fixation. This way, blind spots in vision can be detected before patients are even aware of them.

GA Symptom: Impaired Facial Recognition

Patient-Reported Symptom: Difficulty recognizing faces

GA lesions may not involve the center of the fovea until the very late stages of the disease. This means that while central vision may be preserved, areas of vision located just outside the point of fixation could be lost to scotomas (blind spots). Both reading speed and facial recognition can be affected by scotomas in these paracentral regions.

Sunness JS. “The natural history of geographic atrophy, the advanced form of age-related macular degeneration.” Mol Vis 1999;5:25.
GA Symptom: Reduced Reading Speed

Patient-Reported Symptom: Difficulty reading

Visual Function Measure: Reading rate (words per minute, wpm)

One of the validated outcomes for GA progression is reading speed. Reading speed is inversely correlated with GA lesion size. Patients with advanced GA have great difficulty in reading due to the paracentral scotomas. Some patients may have 20/20 vision but still experience a loss of reading function.

Sunness JS. "The natural history of geographic atrophy, the advanced form of age-related macular degeneration." Mol Vis 1999;5:25.
GA Symptom: Night Vision Problems

**Patient-Reported Symptom:** Night vision problems, Difficulty driving at night, Difficulty reading in dim lighting

**Visual Function Measures:** Low luminance visual acuity (LLVA), Contrast sensitivity, Dark-adapted foveal sensitivity

Even with good visual acuity (VA), patients with GA may still experience decreased visual function in dim lighting. This symptom can be monitored with both patient-reported outcomes and measures of decreased visual function in low luminance conditions.


Clinical Progression to Geographic Atrophy
In healthy eyes, the photoreceptors, RPE cells, Bruch’s membrane, and the choriocapillaris all function as an interdependent unit. The retinal pigment epithelium (RPE) and choriocapillaris support light-sensing activity of the photoreceptors.
Photoreceptors are the most numerous and metabolically demanding cells in the retina. The RPE, composed of a single layer of cells, is responsible for outer segment phagocytosis of the photoreceptors, regulation of the transport of nutrients, and cytokine secretion. The choroid supplies oxygen and nutrients to the photoreceptors and RPE. Across the Bruch’s membrane, waste from the RPE travels to the choroid, while nutrients travel from the choroid to the RPE.


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2. Age-Related Changes in the Retina

Retinal metabolic demands require a highly oxygen-rich microenvironment. Photo-oxidation waste products, generated during normal retinal function, result in RPE exposure to oxidative stress over time. RPE cells are lost at a rate of 2.3% per decade due to normal ageing, increasing the workload of the remaining cells.

Lipid-proteins are produced by the RPE cells as they remove waste from the photoreceptors. Lipoproteinaceous deposits that accumulate between the RPE and Bruch’s membrane are called drusen. These deposits can be detected, via fundus photography, as light-yellow spots on the retina.

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3. Pathogenesis of AMD

The following is one hypothesis used to describe the pathogenesis of AMD: In early AMD, the RPE has reached its waste processing capacity limit and cellular debris can be seen. Photoreceptors and RPE cells start to become disorganized. Local inflammation is induced by the accumulation and oxidation of lipoproteins, with an excessive accumulation of lipofuscin in the RPE, marking the early pathogenesis of AMD.

Reduced choroidal blood flow may be associated with photoreceptor cell death, preceding the pathological loss of the RPE cells. Patients with early AMD will present with a few drusen as well as hyper or hypopigmentation of the RPE. Increased inflammatory proteins and decreased Complement Factor H (CFH) in the choroid creates a microenvironment favoring activation of the alternative complement pathway.

Early AMD is characterized by the appearance of drusen (yellow deposits of lipids and proteins) underneath the retina. Drusen appear beneath the retinal pigment epithelium, above or within Bruch’s membrane.
4. Progression of AMD

Thickening of the Bruch’s membrane may impede metabolic exchange between the choroid and the RPE. Incomplete breakdown of products from the photoreceptor outer segments result in the formation of subretinal drusenoid deposits (SDD) between the RPE and photoreceptor cells. The local inflammatory microenvironment and altered levels of complement factor regulators further drive the dysregulation of the alternative complement pathway, leading to the formation of the membrane attack complex (MAC) in the choroid and eventually the RPE.

The formation of the MAC leads to cell lysis, cell death, and increased inflammation. SDDs appear, Bruch’s membrane becomes thicker, and photoreceptors, RPE cells, and choriocapillaris begin to die off, leaving further disorganized cell layers in the outer retina. Evidence of ghost vessels in the region of the choriocapillaris becomes detectable.


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5. Widespread, Progressive Tissue Atrophy

It is hypothesized that a combination of inflammation in the retinal microenvironment, immune attack via the alternative complement pathway, DNA damage due to chronic oxidative stress, and reduced oxygen and nutrient supply all contribute to the development and progression of GA. Areas of photoreceptor cell death and RPE loss may first form in the macula peripheral to the fovea, expanding as the disease advances and causing a decrease in visual function.

GA lesions captured using various forms of diagnostic imaging

Geographic Atrophy
Diagnosis and Clinical Imaging
AMD has progressed to GA when well-defined patches of loss of the RPE, photoreceptors, and choriocapillaris are observed using diagnostic imaging.
GA Characterization

Several imaging methods are used, often in combination, to assess and diagnose GA cases. Atrophic lesions are characterized by confluent areas of RPE and photoreceptor cell death, often with a sharp demarcation from healthy retinal tissue. Studies have used varying size definitions to classify GA, with minimum affected area measurements ranging from 10µm to 250µm.

GA most commonly starts around the center of the macula. As the lesion expands into the fovea, visual function severely decreases.


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Clinical Imaging Methods for GA

Several imaging methods are used, often in combination, to assess and diagnose GA cases:

- **Color Fundus Photography** (CFP)
- **Fundus Autofluorescence** (FAF)
- **Near Infrared Reflectance Imaging** (NIR)
- **Optical Coherence Tomography** (OCT)
Color Fundus Photography (CFP)

CFP is used to identify drusen and GA lesions by color. In CFP analysis for GA, depigmented areas are compared to areas of normal pigmentation. Depigmented regions with sharply demarcated borders and areas of increased visibility of choroidal vessels define GA lesions.

Because CFP has limitations in terms of reproducibility over time and predictive measures of lesion enlargement, other imaging modalities for the quantitation of GA area are used to complement the use of CFP.


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Fundus Autofluorescence (FAF)

FAF has become the standard imaging technology for the morphological assessment of GA, and is often used together with CFP. FAF utilizes the naturally-occurring fluorophore called lipofuscin, found in the RPE, to detect pigment abnormalities.

Sharply contrasting boundaries visible on atrophic regions enable a high degree of diagnostic accuracy. Hyperfluorescence patterns indicating stressed RPE cells also provide predictive information on GA lesion growth.


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Near Infrared Reflectance Imaging (NIR)

NIR provides high-resolution visualization of underlying choroidal vessels and areas of GA observed as areas of hyperreflectance. Patterns of hyporeflective clumps may also predict the early stages of GA.


Optical Coherence Tomography (OCT)

OCT yields 2-D and 3-D high-resolution information to provide cross-sectional information for assessment of retinal layers, evaluation of the GA lesion areas, and measurement of GA growth. OCT data can also be compiled to yield en face projection images for comparison with CFP or FAF.

The OCT scan corresponds with the horizontal green line on the accompanying FAF image.
Progression to GA


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GA Lesion Expansion

CFP, FAF, and OCT imaging of a patient’s retina with GA:
GA Lesion Expansion

CFP, FAF, and OCT imaging of the same patient’s retina with GA one year later:
Geographic Atrophy
Pathways and Mechanisms
Potential Targets for Future Therapies
The progression from a healthy retina, to early and intermediate AMD, to GA seems to begin with chronic oxidative stress, inflammation and immune attack, followed by choriocapillaris dropout and cell death of the RPE and photoreceptors. Underlying causes and mechanisms for this process include visual cycle toxic byproducts, impaired lipid metabolism, and dysregulation of the alternative complement pathway. Potential therapies for GA may target contributing factors to each of these mechanistic underpinnings.
Chronic Oxidative Stress

The RPE supports photoreceptors by providing nutrients, managing waste products, and maintaining cell membranes via membrane lipid and lipoprotein exchange. The retina is exposed to high levels of sunlight and oxygen, which causes oxidative stress in the outer retinal environment. Iron overload may contribute to the pathogenesis of AMD as iron can generate reactive oxygen species and upregulate complement component 3 (C3). Oxidative stress can directly lead to DNA damage in affected cells, and can indirectly lead to inflammation and immune attack.

Potential Therapies:
- Antioxidants
- Neuroprotectants

Potential pathological mechanisms include:
- Reactive oxygen species (ROS)
- Oxidized phospholipids (OxPLs)
- Drusen
- Complement factors, protein and lipid oxidation products

References:

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Visual Cycle Toxic Byproducts, Impaired Lipid Metabolism

Accumulated lipoproteins and other cellular waste materials, including byproducts of the visual cycle, collect to form extracellular drusen within the retina. The capacity to clear cytotoxic protein aggregates via autophagy decreases with age. Signaling pathways that influence these mechanisms show potential as therapeutic targets to prevent RPE cell degeneration and AMD development.

Potential Therapies:
Visual Cycle Modulators, LDL-lowering drugs, autophagy-regulating kinases AMPK and mTOR

Drusen consist of a host of compounds which are thought to contribute to inflammation. These include, but are not restricted to: APOE, complement factors, lipid oxidation products (such as OxPLs), immunoglobulins and amyloid β. Inflammation is brought about through activation of the alternative complement pathway and through inflammasome activation.

Inflammation and Immune Attack

Potential Therapies:

- Anti-inflammatory agents

References:

In the eye, a low level of complement activation is necessary for immune surveillance and several membrane bound and soluble regulators prevent excessive activation. Pathway defects lead to either hyperactivation of the alternative complement pathway or its inability to protect endogenous cells from self-complement attack, resulting in increased inflammation that can contribute to AMD progression. Some of the gene variants implicated in GA risk and progression include: CFH, CFB, C2, C3, and CFI.

Potential Therapies:
Alternative complement inhibitors
A genetic polymorphism in CFH can lead to retinal inflammation as a result of uninhibited complement activation. CFD is a rate-limiting enzyme in the activation of the alternative complement pathway, and AMD patients have increased levels of CFD compared to control patients.

Alternative Complement Pathway

Potential Therapies:
- Alternative complement inhibitors


Yaspan et al, "Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration." Sci Transl Med. 21.9 (2017):395
Membrane Attack Complex (MAC)

Choriocapillaris and RPE cells can be targeted for destruction by the alternative complement pathway, via formation of the Membrane Attack Complex (MAC). The MAC is composed of complement factors C5-C9 and causes targeted cell lysis and death.

Potential Therapies:
Alternative complement inhibitors

Photoreceptor and RPE Cell Death

Widespread RPE and photoreceptor cell death is the last stage of atrophic AMD and the hallmark of GA. Atrophic lesions are characterized by regions of complete RPE and photoreceptor cell death, in addition to significant loss of choriocapillaris. As the lesion expands into the fovea, visual acuity severely decreases.

Potential Therapies:

Cell replacement therapy


Geographic Atrophy
Current Clinical Trials
GA Clinical Trials

Phase II and Phase III clinical trials for GA therapies are ongoing, employing strategies such as complement factor D (CFD) inhibition, cell replacement therapy, neuroprotection, and delivery of neurotrophic factors.

For more information, visit www.clinicaltrials.gov.

Phase III clinical trials currently underway:

**Complement factor D inhibition**
CHROMA: Lampalizumab®
SPECTRI: Lampalizumab®

**Complement C5 inhibition**
Zimura® - Anti-C5 Aptamer

**Tetracycline antibiotic**
TOGA: ORACEA®
Drug – Lampalizumab®
• Humanised monoclonal antibody fragment against complement factor D

Trial Design – Phase III
• Compares 10mg intravitreal injections to sham injections administered every 4 or 6 weeks
• 936 total patients
  • Split into sham, lampalizumab every 4 weeks, and lampalizumab every 6 weeks
• Patients differentiated based on presence or absence of complement factor I biomarker
  • Patients with this biomarker showed better improvement in MAHALO phase II clinical trial (44% reduction as opposed to 20% reduction)

Outcome measures
• Primary outcome at 1 year is mean change in lesion area from baseline measured using FAF
• Secondary outcome measured at 2 years focuses on visual function

A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration - Full Text View - ClinicalTrials.gov, ClinicalTrials.gov, clinicaltrials.gov/ct2/show/NCT02247531.
A Study Investigating the Efficacy and Safety of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration - Full Text View - ClinicalTrials.gov., clinicaltrials.gov/ct2/show/NCT02247479.

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Drug – Zimura®

- Anti-C5 aptamer (targets complement factor 5)

Trial Design – Phase II/III

- Compares monthly intravitreal injections of Zimura or sham over a 24 month period
- 300 total patients
  - Randomized 1:1:1
  - Split into sham, Zimura dose 1 and Zimura dose 2

Objectives

- Primary objective at 2 years is mean change in best corrected visual acuity (BCVA)

Continuation of this trial is dependent on results from competitor’s phase III trial.
Drug – ORACEA®
- Tetracycline derivative anti-inflammatory (low dose doxycycline)
- Matrix metalloproteinase inhibitor
- Inhibits activation of microglia

Trial Design – Phase II/III
- Compares 40mg of doxycycline and a placebo pill daily for 24 months
- Patients randomized in a 1:1 ratio after 6 months of observation

Objectives
- Measured at month 6 and month 30
- Primary objective is reduced rate of enlargement in area of GA in the study eye during the treatment period
- Secondary objective looks at change in BCVA
## Ongoing Clinical Trials
(As of August 2017)

<table>
<thead>
<tr>
<th>MOA</th>
<th>Product</th>
<th>Sponsor</th>
<th>Indication</th>
<th>Phase</th>
<th>Mode of Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of complement C3</td>
<td>APL-2</td>
<td>Apellis Pharmaceuticals</td>
<td>GA/AMD</td>
<td>II</td>
<td>Intravitreal injection</td>
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<td>Antioxidant, slows DNA damage, reduced ROS levels</td>
<td>metformin</td>
<td>University of California, San Francisco</td>
<td>Nondiabetic GA/dry AMD</td>
<td>II</td>
<td>Daily oral tablets</td>
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<td>Neuroprotection</td>
<td>brimonidine</td>
<td>Allergan</td>
<td>GA/AMD</td>
<td>II</td>
<td>Intravitreal inplant</td>
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<tr>
<td>Inhibition of glial cell activation</td>
<td>Minocycline</td>
<td>National Eye Institute (NEI)</td>
<td>GA/dry AMD</td>
<td>II</td>
<td>Daily oral capsules</td>
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<td>Iron-chelation, antioxidant</td>
<td>Alpha Lipoic Acid (ALA)</td>
<td>University of Pennsylvania</td>
<td>GA/dry AMD</td>
<td>II</td>
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# Ongoing Clinical Trials
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</thead>
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<tr>
<td>Human umbilical tissue–derived cells</td>
<td>CNTO 2476</td>
<td>Janssen Research &amp; Development</td>
<td>GA/ AMD</td>
<td>II</td>
<td>Subretinal administration</td>
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<td>hESC-derived RPE cells</td>
<td>OpRegen</td>
<td>Cell Cure Neurosciences</td>
<td>Nondiabetic GA/dry AMD</td>
<td>I/II</td>
<td>Subretinal transplantation</td>
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<tr>
<td>hESC-derived RPE cells seeded on polymeric substrate</td>
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<td>Regenerative Patch Technologies</td>
<td>Advanced dry AMD</td>
<td>I/II</td>
<td>Subretinal transplantation</td>
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<td>Transpalpebral microcurrent electrical stimulation</td>
<td>Nova Oculus</td>
<td>The Eye Machine Canada</td>
<td>vision loss associated with dry AMD</td>
<td>I/II</td>
<td>Externally applied microcurrent electrical stimulation</td>
</tr>
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Important Insight: **Endpoints for GA Clinical Trials**

Standard visual tests (e.g., best-corrected visual acuity [BCVA]) do not fully capture the impact of GA on visual function. GA can progress slowly and lesions may enlarge significantly before reaching the fovea. GA lesions often do not affect visual acuity in early stages. Patients can have GA, but still have good visual acuity on an eye chart. Changes in **alternative measures of visual function** may be identified in patients before deterioration in BCVA occurs.


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Assessments of Visual Function

The effects of GA can also be measured through psychophysical and patient-centered tests:

• **LLVA (Low luminance visual acuity)**
  Measures difference in visual acuity between best corrected and low luminance states

• **Contrast sensitivity**
  Measures performance at different degrees of contrast, often using the Pelli-Robson contrast sensitivity chart

• **Microperimetry**
  Patients respond to spots of light shone onto different points on their retina to indicate precise locations of damage

• **Maximum reading speed**
  Calculated as correctly read words per minute (wpm)

• **Patient reported outcomes (PROs)**
Patient Reported Outcomes

Patient reported outcomes are designed to take a wider range of effects into account in the context of how a condition may impact on the patient’s quality of life. There are two main tools used to assess patient reported outcomes in AMD:

• **25-item Visual Function Questionnaire (VFQ-25)**
  
  This questionnaire measures ways in which chronic eye conditions impact everyday aspects of life. It has not been widely studied in relation to GA.

• **Functional Reading Independence (FRI) Index**
  
  This 7-item questionnaire assesses daily-life reading independence and has demonstrated a high degree of sensitivity to GA lesion size and changes in lesion size.


Center of Excellence for Retinal Disorders

The Angiogenesis Foundation’s Center of Excellence for Retinal Disorders has developed this resource to provide accurate, easy to understand, and useful information about GA as an important part of the AMD continuum of care.

The Angiogenesis Foundation is a nonprofit organization dedicated to improving patient outcomes for AMD and other retinal diseases.

For more information on geographic atrophy, visit: www.geographicatrophy.org
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