Geographic Atrophy

& Emerging Therapeutic Targets

The Angiogenesis Foundation

Educational Toolkit for Clinicians:

Geographic Atrophy

& Emerging Therapeutic Targets

Developed by:

The Angiogenesis Foundation

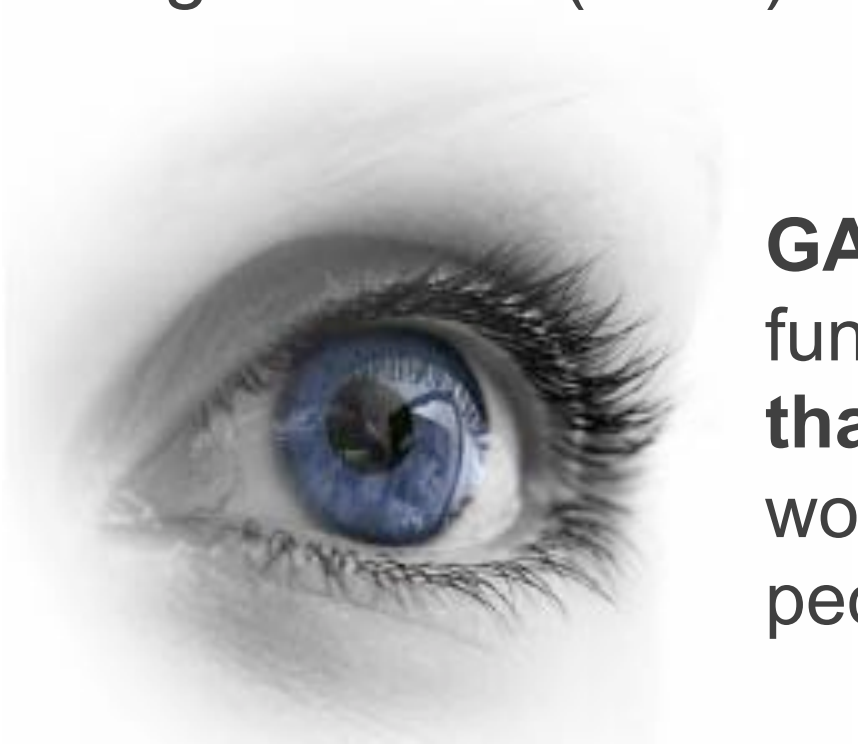
Center of Excellence for Retinal Disorders

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.

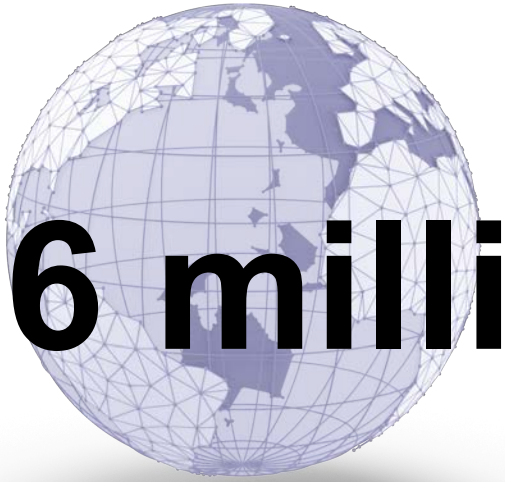
Rudnicka, Alicja R. et al. "Age and Gender Variations in Age-Related Macular Degeneration Prevalence in Populations of European Ancestry: A Meta-Analysis." *Ophthalmology* 119.3(2012): 571–580.

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.

Wong WL et al. "Global Prevalence of Age-related Macular Degeneration and Disease Burden Projection for 2020 and 2040: A Systematic Review and Meta-analysis." *Lancet Glob Health.* 2.2 (2014):e106–e116.

Burden of Dry AMD



196 million

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.

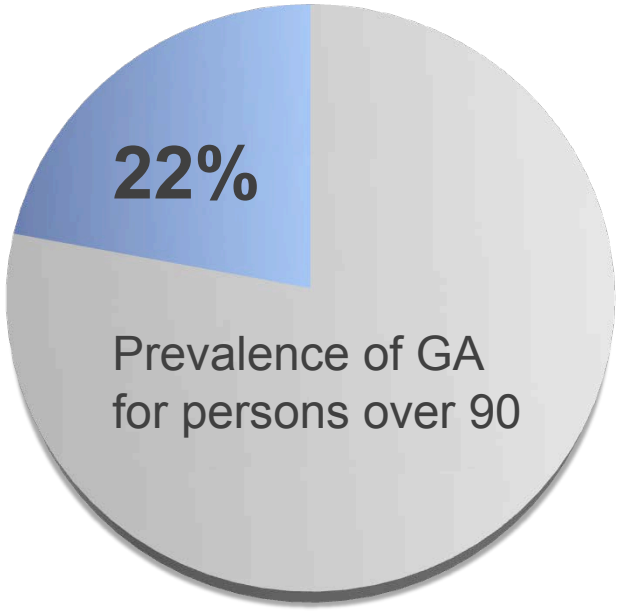
Ferris FL. "Age-Related Macular Degeneration and Blindness due to Neovascular Maculopathy." *Arch Ophthalmol.*102.11(1984):1640-1642
Wong WL et al. "Global Prevalence of Age-related Macular Degeneration and Disease Burden Projection for 2020 and 2040: A Systematic Review and Meta-analysis." *Lancet Glob Health*. 2.2 (2014):e106–e116.

Burden of GA

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.



Buch H, Vinding T, Nielsen NV et al. "14-year Incidence Progression and Visual Morbidity of Age-related Maculopaty: The Copenhagen City Eye Study." *Ophthalmology.*112 (2005):787-798.
Vaz F and Picoto M, "Georgraphic Atrophy" -- *http://www.amdbook.org/content/geographic-atrophy-0*

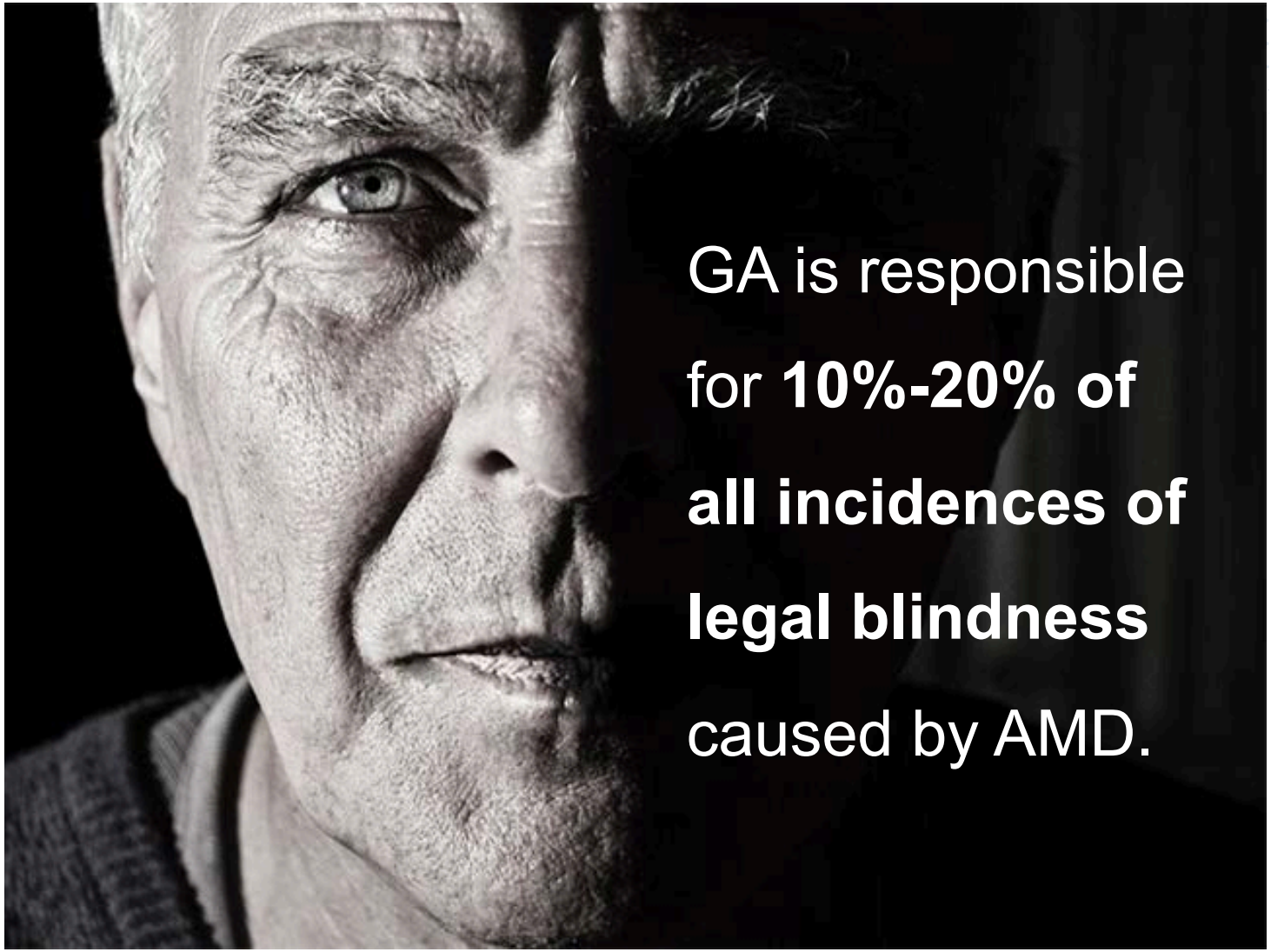
Burden of GA

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.

Buch H, Vinding T, Nielsen NV et al. "14-year Incidence Progression and Visual Morbidity of Age-related Maculopaty: The Copenhagen City Eye Study." *Ophthalmology.*112 (2005):787-798.
Ferris FL, Fine SL, Hyman L. "Age-Related Macular Degeneration and Blindness due to Neovascular Maculopathy." *Arch Ophthalmol.*102.11(1984):1640-1642
Klein R, Klein BE, Linton KL. "Prevalence of Age-related Maculopathy. The Beaver Dam Eye Study." *Ophthalmology.* 99 (1992):933-943.
Sikorav A, Semoun O, Zweifel S, et al "Prevalence and Quantification of Geographic Atrophy Associated with Newly Diagnosed and Treatment-naïve Exudative Age-related Macular Degeneration" *British Journal of Ophthalmology* 101.4 (2016): 438-444
The Eye Diseases Prevalence Research Group*. "Prevalence of Age-Related Macular Degeneration in the United States." *Arch Ophthalmol.* 2004;122(4):564-572.
Wong WL, Su X, Li X, et al. "Global Prevalence of Age-related Macular Degeneration and Disease Burden Projection for 2020 and 2040: A Systematic Review and Meta-analysis." *Lancet Glob Health.* 2.2 (2014):e106–e116.

Burden of GA



Ferris FL, Fine SL, Hyman L. "Age-Related Macular Degeneration and Blindness due to Neovascular Maculopathy." *Arch Ophthalmol.*102.11(1984):1640-1642

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

Chen Y, Zeng J, Zhao C, Wang K, Trood E, Buehler J, Weed M, Kasuga D, Bernstein PS, Hughes G, et al. "Assessing Susceptibility to Age-related Macular Degeneration with Genetic Markers and Environmental Factors". *Arch Ophthalmol*. 129 (2011):344–351.
Fleckenstein M, Schmitz-Valckenberg S, Adrion C, Visvalingam S, Göbel AP, Mössner A, et al. "Progression of Age-related Geographic Atrophy: Role of the Fellow Eye." *Invest Ophthalmol Vis Sci* 52 (2011): 6552–6557.
Postel EA, Agarwal A, Caldwell J, et al. "Complement Factor H Increases Risk for Atrophic Age-Related Macular Degeneration." *Ophthalmology*.113 (2006):1504–1507.
Age-Related Eye Disease Study Research Group. "Risk Factors for the Incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) *AREDS Report No. 19*." *Ophthalmology* 112.4 (2005): 533–539.

GA Genetic Risk Factors

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.

Postel EA, Agarwal A, Caldwell J, et al. "Complement Factor H Increases Risk for Atrophic Age-Related Macular Degeneration." *Ophthalmology*.113 (2006):1504-1507.
Dominiek DG, Cornelia MD, Oostra BA, et al. "Complement Component C3 and Risk of Age-Related Macular Degeneration. *Ophthalmology.*" 115 (2009):474-480
Seddon JM, Yu Y, Miller EC, et al. "Rare variants in CFI, C3 and C9 are Associated with High Risk of Advanced Age-related Macular Degeneration." *Nat Genet* 45 (2013):1366–70.
Fritsche, Lars G. et al. "Age-Related Macular Degeneration: Genetics and Biology Coming Together." *Annual review of genomics and human genetics 15* (2014): 151–171.
Caire J, Recalde S, Velazquez-Villoria A, Garcia-Garcia L. "Growth of Geographic Atrophy on Fundus Autofluorescence and Polymorphisms of *CFH*, *CFB*, *C3*, *FHR1-3*, and *ARMS2* in Age-Related Macular Degeneration." *JAMA Ophthalmol.*132.5 (2014):528-534.
Fritsche LG, Chen W, Schu M, et al. "Seven New Loci Associated with Age-related Macular Degeneration." *Nat Genet* 45.4 (2013):433-439
Abecasis GR, Yashar BM, Zhao Y, et al. "Age-related macular degeneration : a High Resolution Genome Scan for Susceptibility Loci in a Population Enriched for Late Stage Disease. *Am J Hum Genet*. 74 (2004):482-494.
McKay, Gareth J. et al. "Evidence of Association of *APOE* with Age-Related Macular Degeneration - a Pooled Analysis of 15 Studies." *Human mutation* 32.12 (2011): 1407–1416.

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.

Normal Vision

GA effects over time

Scotomas (dark or blind spots) | Impaired facial recognition | Decreased reading speed | Low luminance deficit (LLD)

Suness JS, Rubin GS, Broman A, et al. "Low luminance Visual Dysfunction as a Predictor of Subsequent Visual Loss From Geographic Atrophy in Age-Related Macular Degeneration." *Ophthalmology.* 115 (2008):1480-1488

Suness JS, Applegate CA, Bressler NM, et al. "Visual Function Abnormalities and Prognosis in Eyes with Age-Related Geographic Atrophy of the Macula and Good Visual Acuity." *Ophthalmology*. 104.10 (1997):1677-1691.

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.

Danis, Ronald P, Jeremy A Lavine, and Amitha Domalpally. “Geographic Atrophy in Patients with Advanced Dry Age-Related Macular Degeneration: Current Challenges and Future Prospects.” *Clinical Ophthalmology* (Auckland, N.Z.) 9 (2015): 2159–2174.
Suness JS, Applegate CA, Bressler NM, et al. “Visual Function Abnormalities and Prognosis in Eyes with Age-Related Geographic Atrophy of the Macula and Good Visual Acuity.” *Ophthalmology.* 104.10 (1997):1677-1691.

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.

Sunness JS, Applegate CA, Bressler NM, et al. "Visual Function Abnormalities and Prognosis in Eyes with Age-Related Geographic Atrophy of the Macula and Good Visual Acuity." *Ophthalmology*. 104.10 (1997):1677-1691.

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.

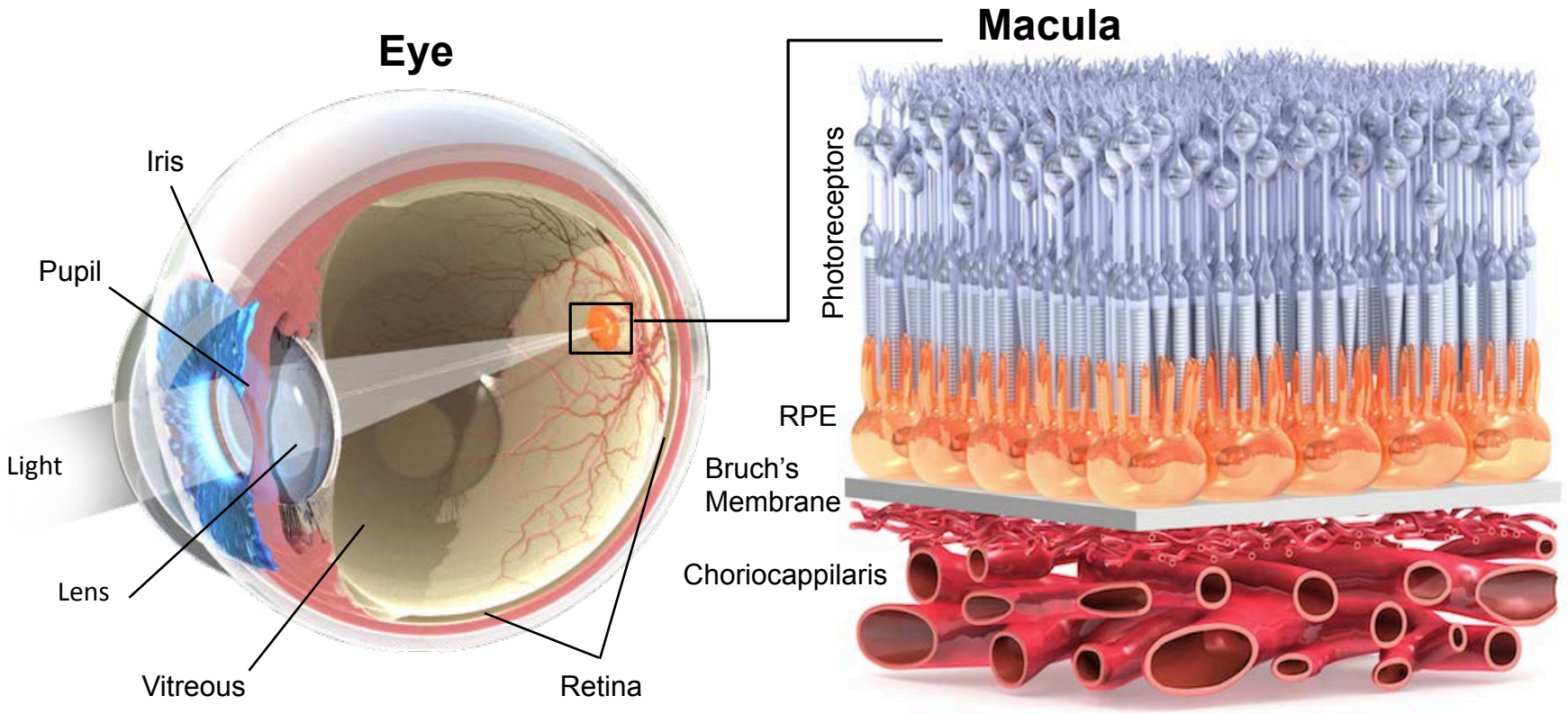
Suness JS, Rubin GS, Broman A, et al. "Low luminance Visual Dysfunction as a Predictor of Subsequent Visual Loss From Geographic Atrophy in Age-Related Macular Degeneration." *Ophthalmology.* 115 (2008):1480-1488

Suness JS, Applegate CA, Bressler NM, et al. "Visual Function Abnormalities and Prognosis in Eyes with Age-Related Geographic Atrophy of the Macula and Good Visual Acuity." *Ophthalmology*. 104.10 (1997):1677-1691.

Clinical Progression to Geographic Atrophy

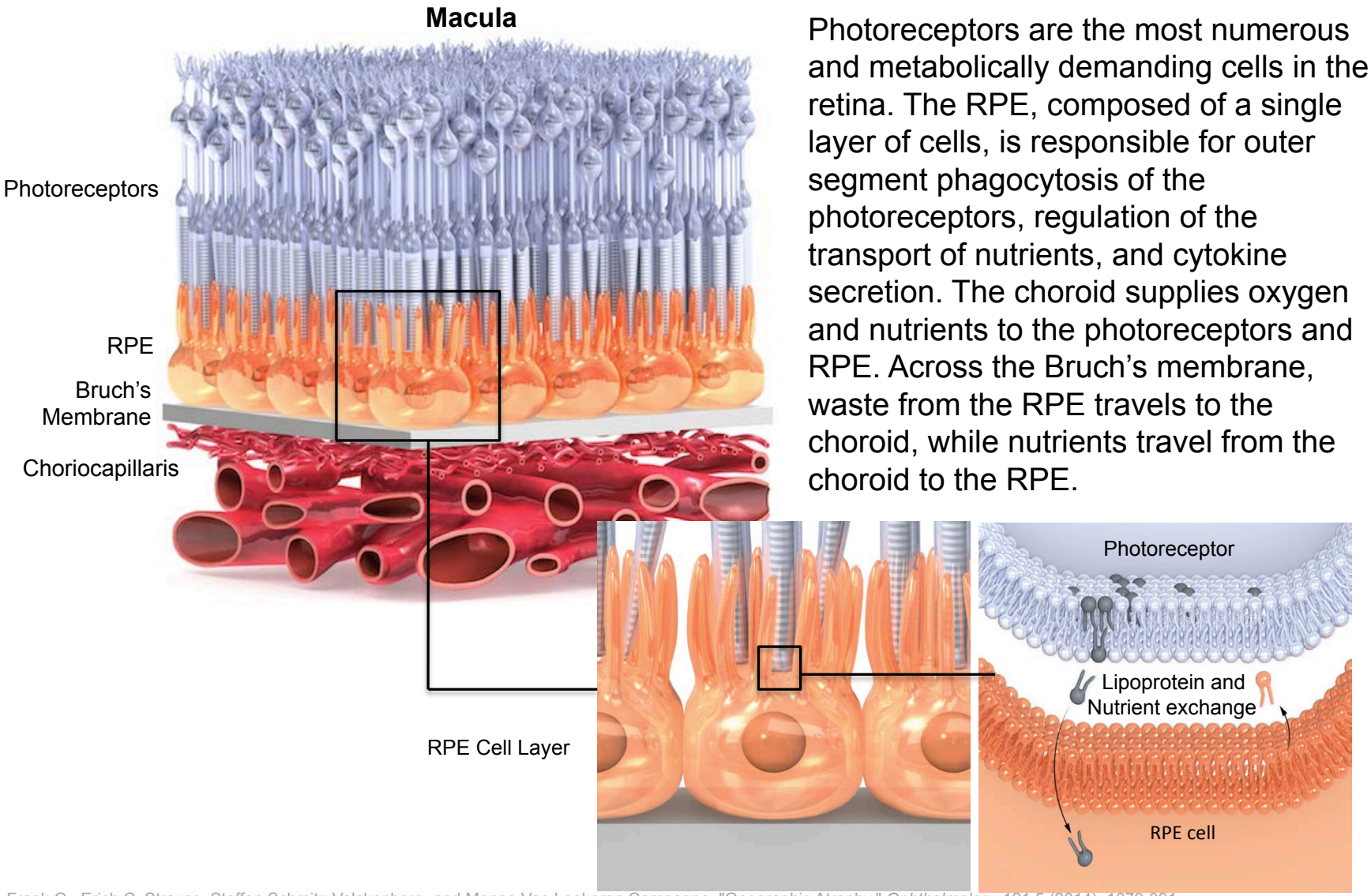
1. Healthy Retina

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.



Bhutto et al"Understanding Age-Related Macular Degeneration (AMD): Relationships between the Photoreceptor/retinal Pigment epithelium/Bruch's Membrane/choriocapillaris Complex." *Molecular Aspects of Medicine* 2012(33.4) 295–317
Lindblad AS et al Age-Related Eye Disease Study Research Group. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26

1. Healthy Retina (cont'd)

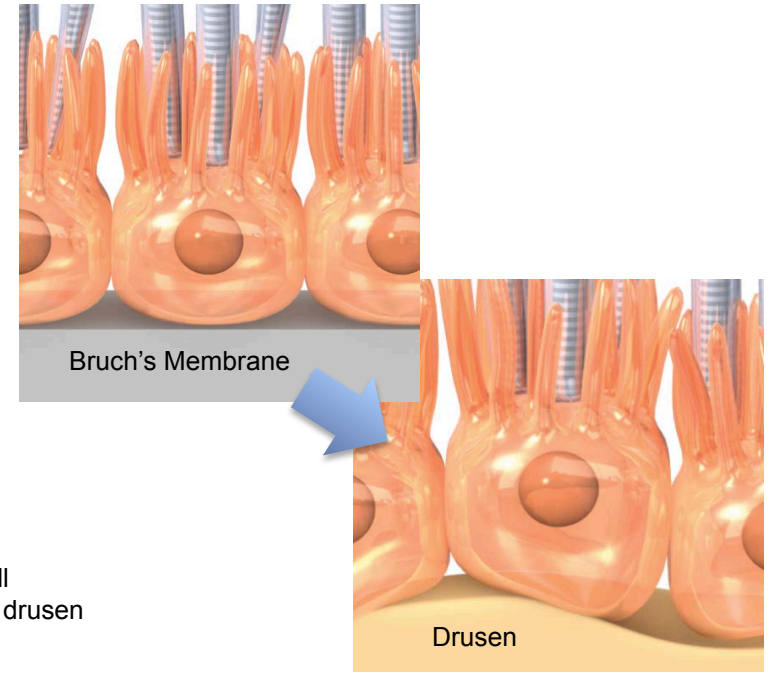


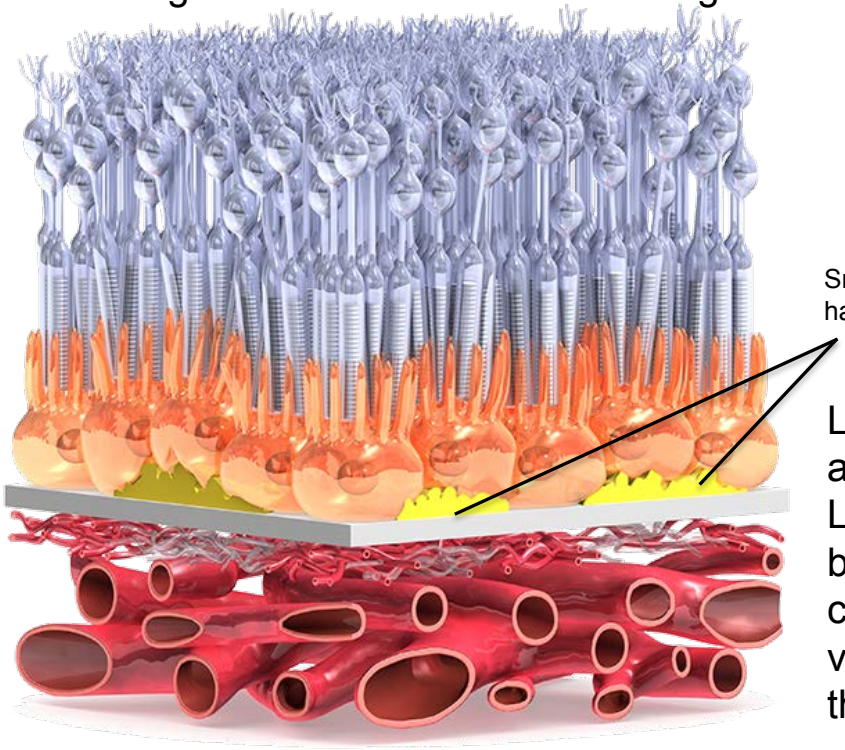
Photoreceptors are the most numerous and metabolically demanding cells in the retina. The RPE, composed of a single layer of cells, is responsible for outer segment phagocytosis of the photoreceptors, regulation of the transport of nutrients, and cytokine secretion. The choroid supplies oxygen and nutrients 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.

Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.
Bhutto I, Lutty G. "Understanding Age-related Macular Degeneration (AMD): Relationships Between the Photoreceptor/retinal Pigment Epithelium/Bruch's Membrane/Choriocapillaris Complex." *Mol Aspects Med* 33 (2012):295–317.

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.



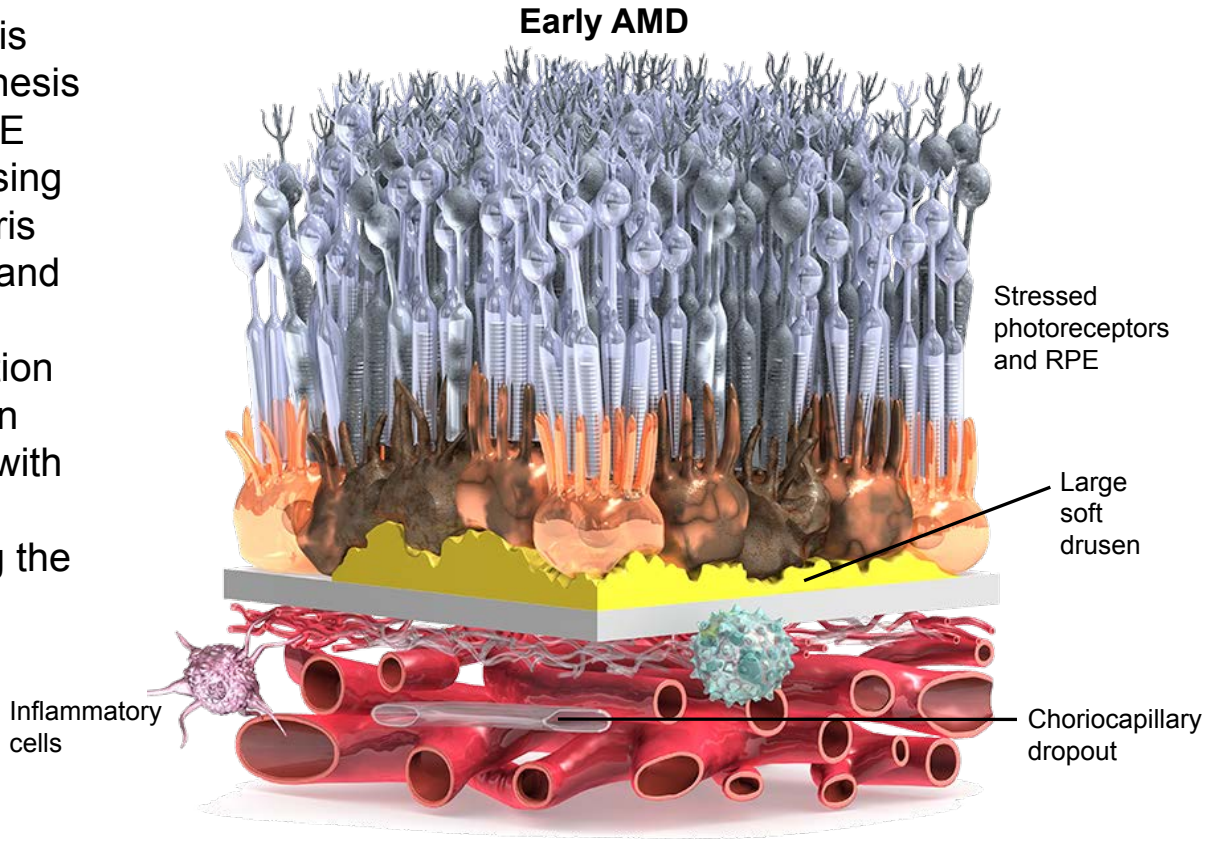


Lipid-proteins are produced by the RPE cells as they remove waste from the photoreceptors. Lipoproteinous deposits that accumulate between the RPE and Bruch's membrane are called drusen. These deposits can be detected, via fundus photography, as light-yellow spots on the retina.

Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.
Jarrett, Stuart G., and Michael E. Boulton. "Consequences of Oxidative Stress in Age-Related Macular Degeneration." *Mol Asp Med* 33.4 (2012): 399–417
Del Priore LV, Kuo YH, Tezel TH. "Age-related changes in human RPE cell density and apoptosis proportion in situ." *Invest Ophthalmol Vis Sci*. 43 (2002): 3312–3318.
Ebrahimi KB, Handa JT. "Lipids, Lipoproteins, and Age-related Macular Degeneration." *J Lipids* [serial online] 2011;2011:802059. Available at: http://www.hindawi.com/journals/jl/2011/802059/.
Gass, J D. "Drusen and Disciform Macular Detachment and Degeneration." *Transactions of the American Ophthalmological Society* 70 (1972): 409–436.

3. Pathogenesis of AMD

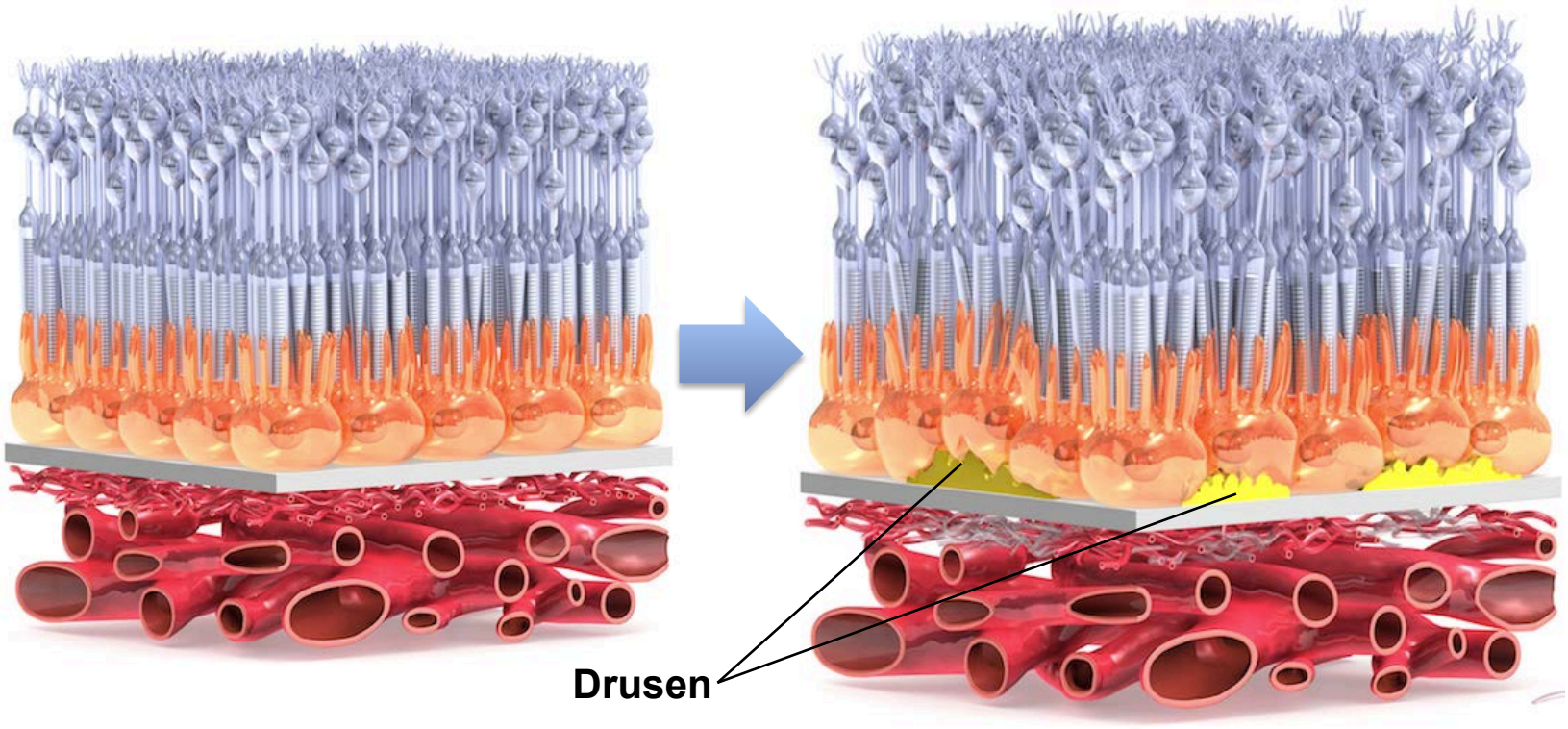
The following is one hypothesis used to describe the pathogenesis of AMD: In early AMD, the RPE has reached its waste processing capacity limit and cellular debris can be seen. Photoreceptors and RPE cells start to become disorganized. Local inflammation is induced by the accumulation and oxidation of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

Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.
Friedman E. "A Hemodynamic Model of the Pathogenesis of Age-related Macular Degeneration." *Am J Ophthalmol*.124.5 (1997):677–682.
Johnson LV, Leitner WP, Staples MK, Anderson DH. "Complement Activation and Inflammatory Processes in Drusen Formation and Age Related Macular Degeneration." *Exp Eye Res*. 73 (2001):887–96.

3. Pathogenesis of AMD (cont'd)



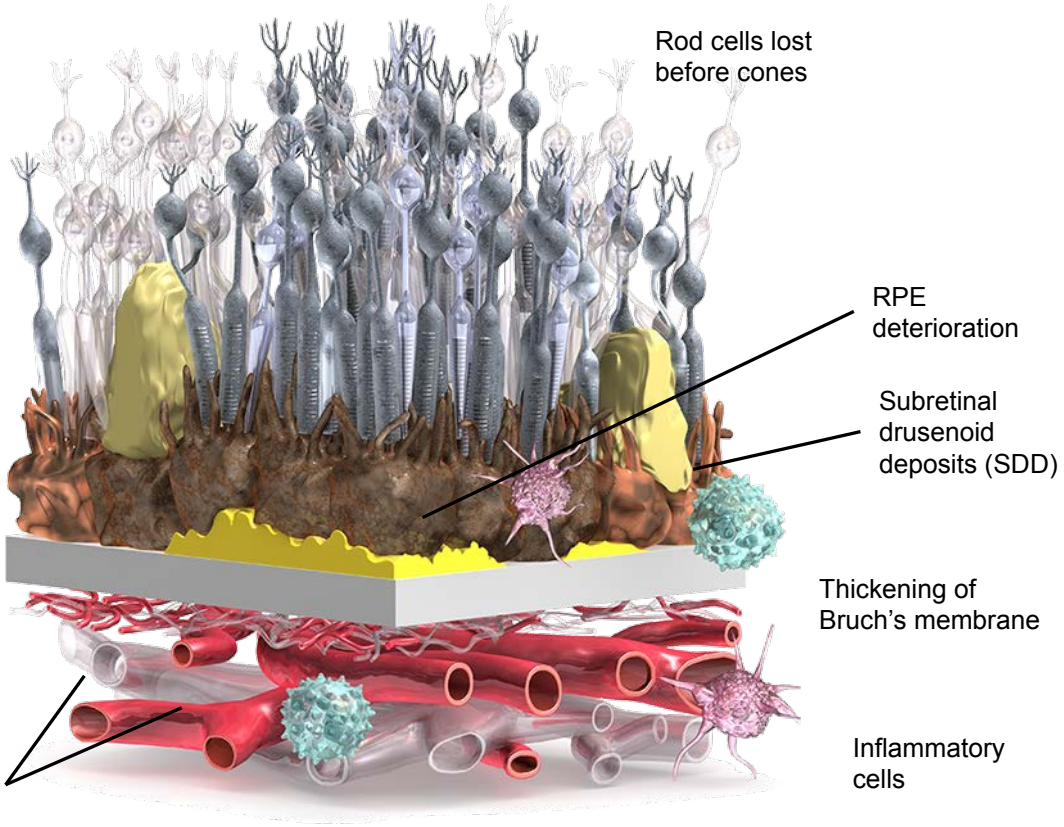
Early AMD is characterized by the appearance of **drusen** (yellow deposits of lipids and proteins) underneath the retina. Drusen appear beneath the retinal pigment epithelium, above or within Bruch's membrane.

Danis, Ronald P, Jeremy A Lavine, and Amitha Domalpally. "Geographic Atrophy in Patients with Advanced Dry Age-Related Macular Degeneration: Current Challenges and Future Prospects." *Clinical Ophthalmology* (Auckland, N.Z.) 9 (2015): 2159–2174.

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.

Intermediate AMD

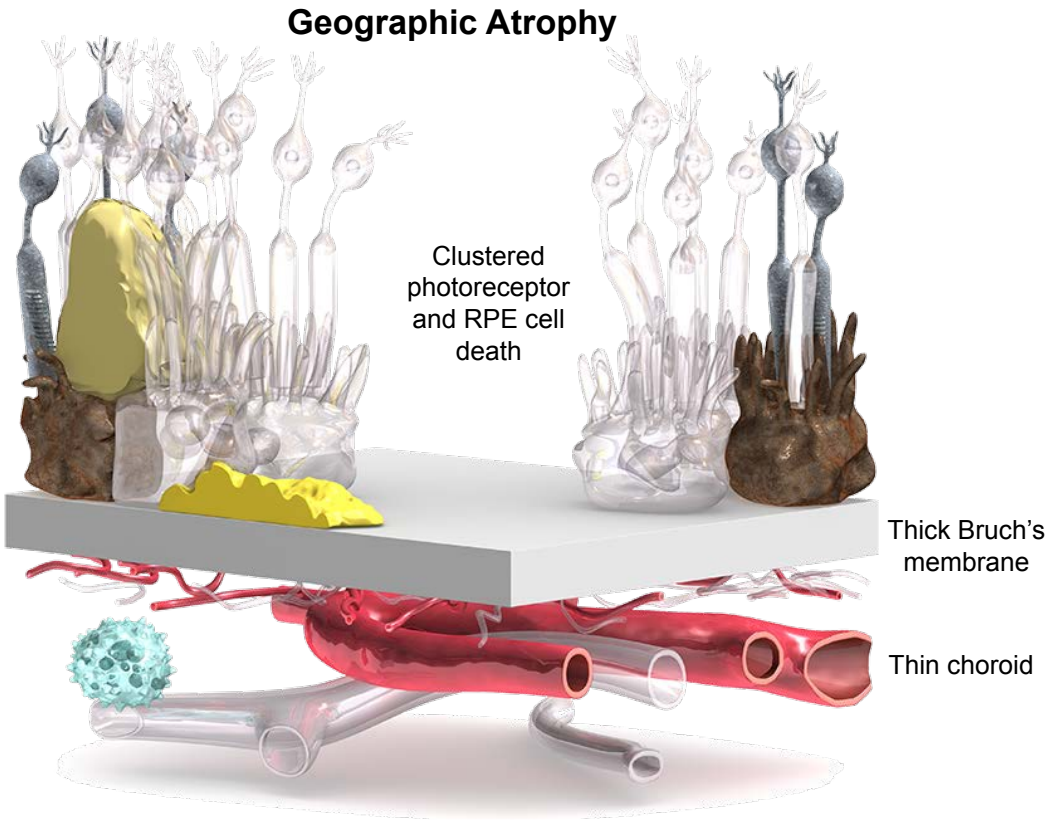


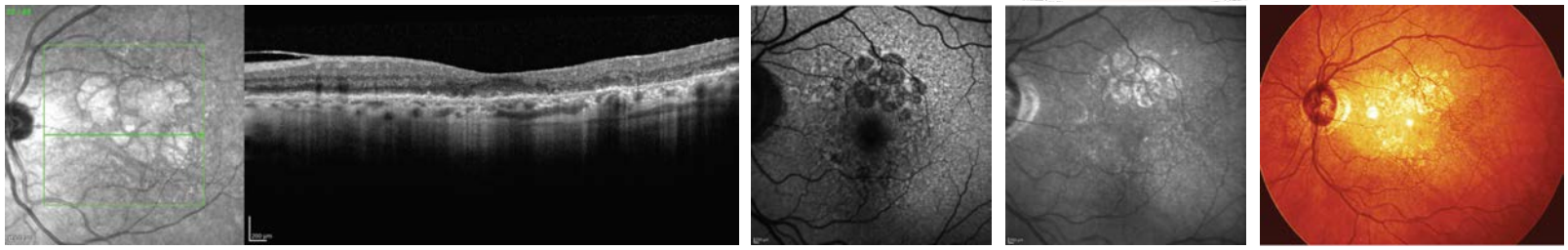
The formation of the MAC leads to cell lysis, cell death, and increased inflammation. SDDs appear, Bruch's membrane becomes thicker, and photoreceptors, RPE cells, and choriocapillaris begin to die off, leaving further disorganized cell layers in the outer retina. Evidence of ghost vessels in the region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

Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.
Dunkelberger, Jason R., and Wen-Chao Song. "Complement and its Role in Innate and Adaptive Immune Responses." *Cell Research* 20.1 (2009): 34-50.
Moore DJ, Hussain AA, Marshall J. "Age-related Variation in the Hydraulic Conductivity of Bruch's Membrane" *Ivest Opthamol Vis Sci*. 36.7 (1995) 1290-1297
Ambati, Jayakrishna, John P. Atkinson, and Bradley D. Gelfand. "Immunology of Age-Related Macular Degeneration." *Nature reviews. Immunology* 13.6 (2013): 438–451.

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

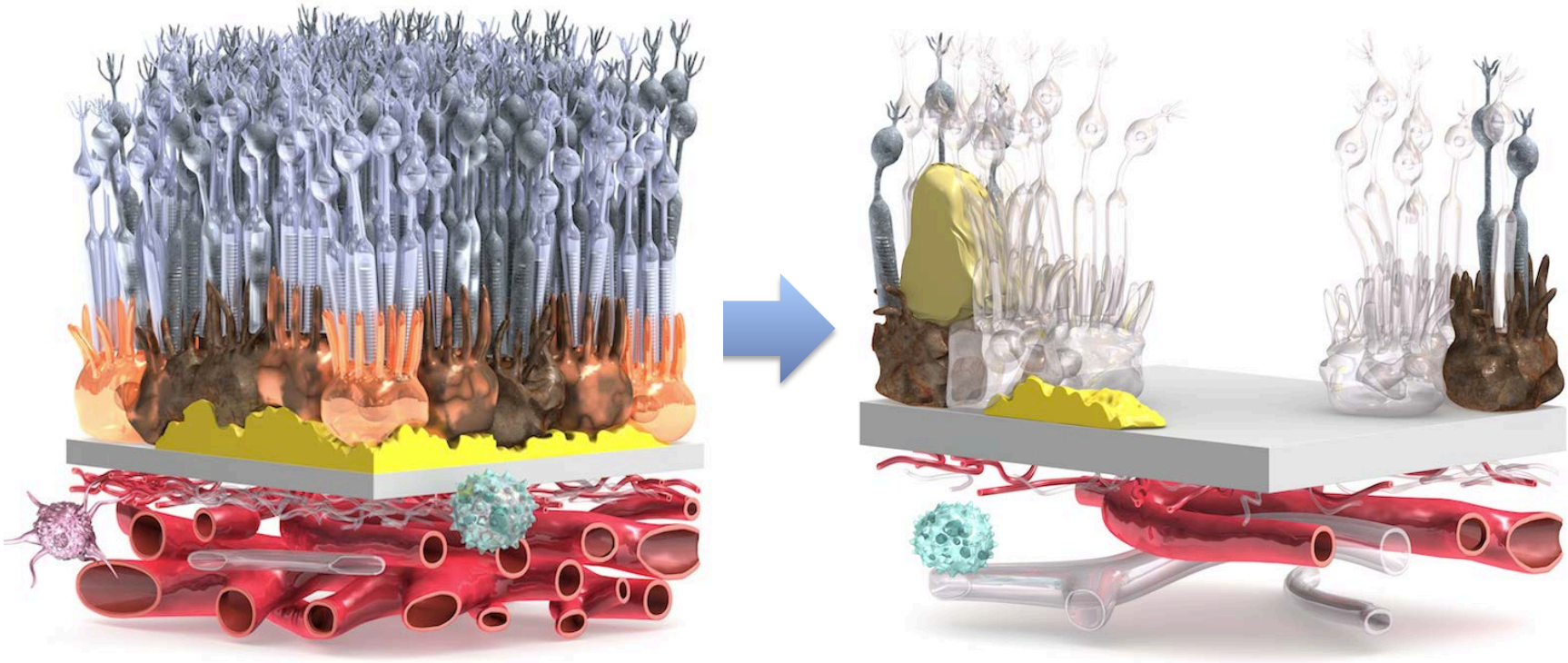
Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.
Srinivas S, Chakravarthy U, et al. "Clinical Endpoints for the Study of Geographic Atrophy Secondary to Age-related Macular Degeneration." *Retina*. 36 (2016):1806–1822

Geographic Atrophy

Diagnosis and Clinical Imaging

GA Diagnosis: Overview

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

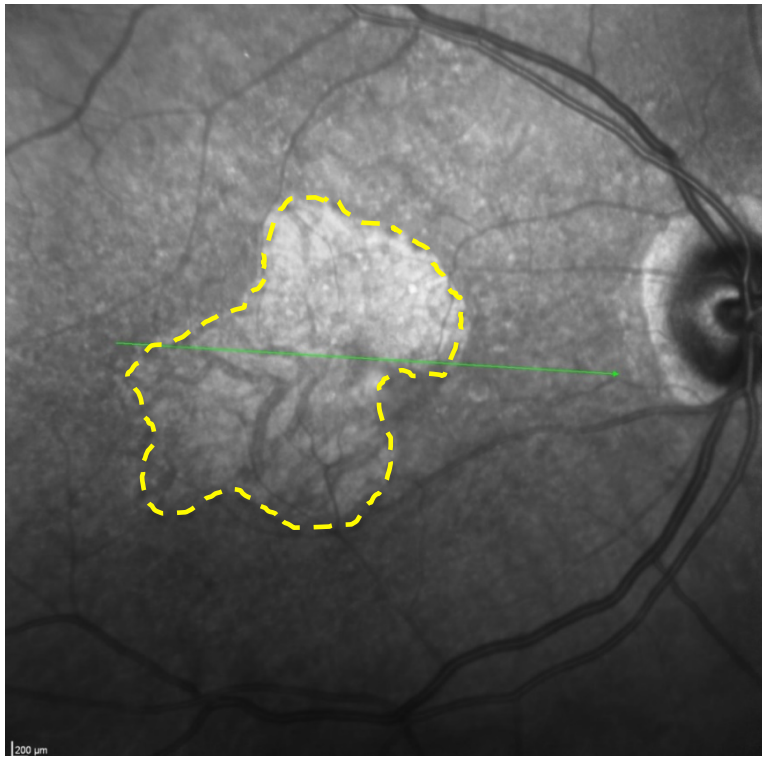


Early AMD **Geographic Atrophy**

Danis et al "Geographic Atrophy in Patients with Advanced Dry Age-Related Macular Degeneration: Current Challenges and Future Prospects." *Clinical Ophthalmology* 2015 (9) 2159–2174.

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.



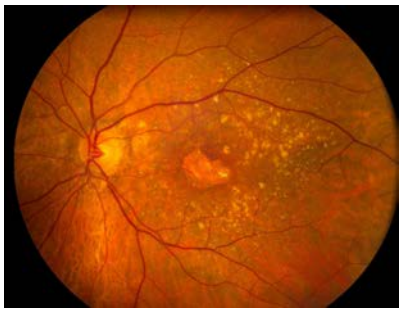
GA most commonly starts around the center of the macula. As the lesion expands into the fovea, visual function severely decreases.

Srinivas S, Chakravarthy U, et al. "Clinical Endpoints for the Study of Geographic Atrophy Secondary to Age-related Macular Degeneration." *Retina,* 36 (2016): 1806–1822
Danis, Ronald P, Jeremy A Lavine, and Amitha Domalpally. "Geographic Atrophy in Patients with Advanced Dry Age-Related Macular Degeneration: Current Challenges and Future Prospects." *Clinical Ophthalmology* (Auckland, N.Z.) 9 (2015): 2159–2174.

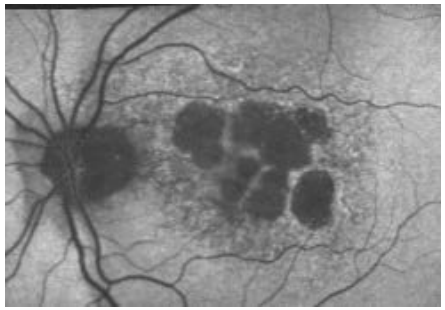
Clinical Imaging Methods for GA

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

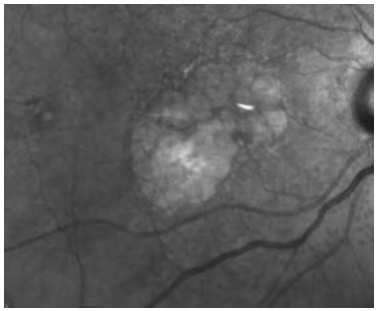
- **Color Fundus Photography** (CFP)
- **Fundus Autofluorescence** (FAF)
- **Near Infrared Reflectance Imaging** (NIR)
- **Optical Coherence Tomography** (OCT)



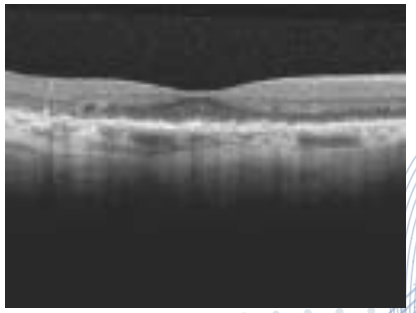
CFP



FAF



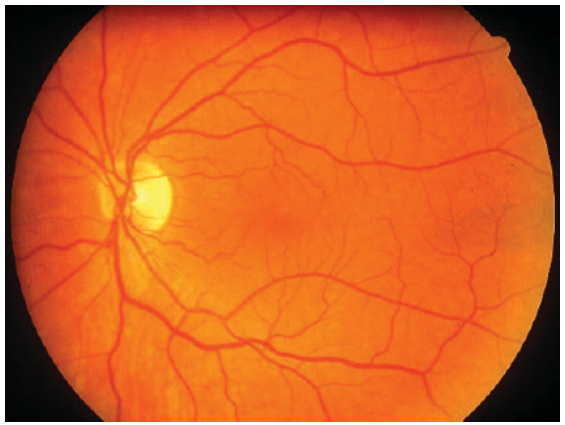
NIR



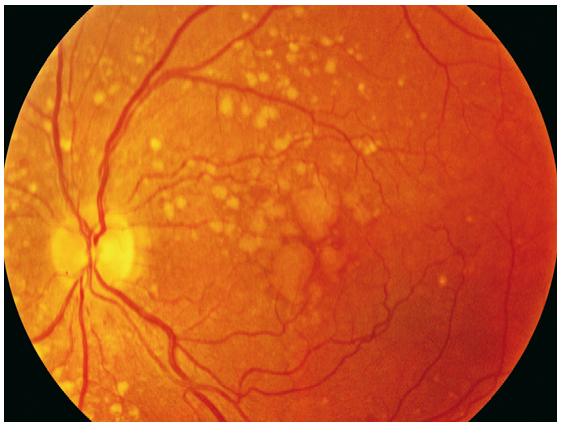
OCT

Color Fundus Photography (CFP)

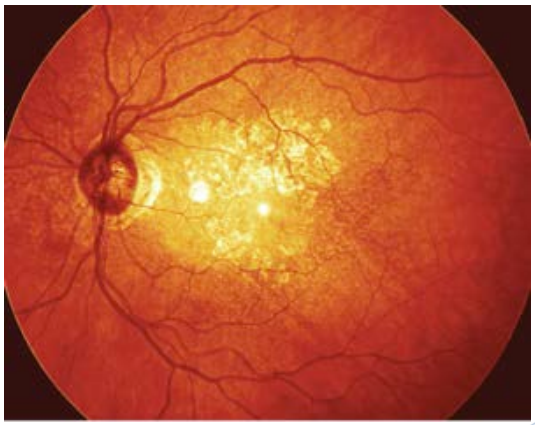
CFP is used to identify drusen and GA lesions by color. In CFP analysis for GA, depigmented areas are compared to areas of normal pigmentation. Depigmented regions with sharply demarcated borders and areas of increased visibility of choroidal vessels define GA lesions.



Normal



Intermediate AMD



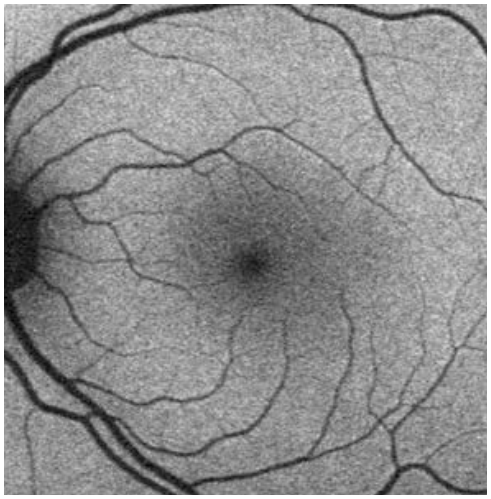
GA

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.

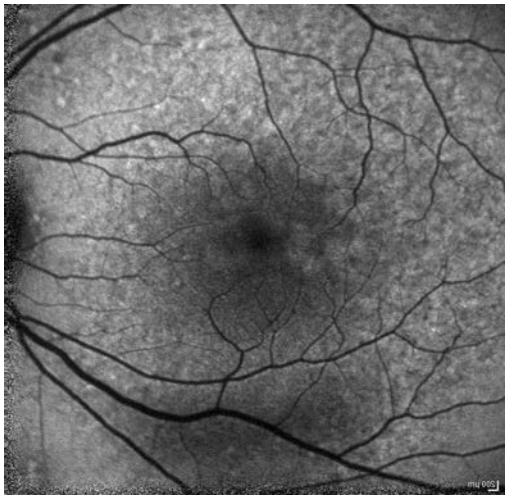
Khanifar, Aziz A. et al. "Comparison of Color Fundus Photographs and Fundus Autofluorescence Images in Measuring Geographic Atrophy Area." *Retina (Philadelphia, Pa.)* 32.9 (2012): 1884–1891.

Fundus Autofluorescence (FAF)

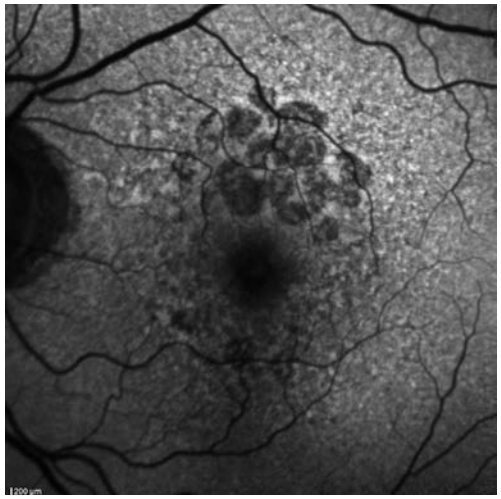
FAF has become the standard imaging technology for the morphological assessment of GA, and is often used together with CFP. FAF utilizes the naturally-occurring fluorophore called lipofuscin, found in the RPE, to detect pigment abnormalities.



Normal



Intermediate AMD



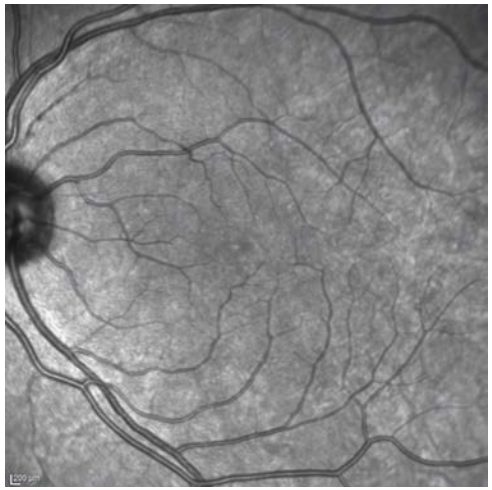
GA

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.

Yung, Madeline, Michael A. Klufas, and David Sarraf. "Clinical Applications of Fundus Autofluorescence in Retinal Disease." *Int J Retin Vitr* 2.12 (2016).

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.



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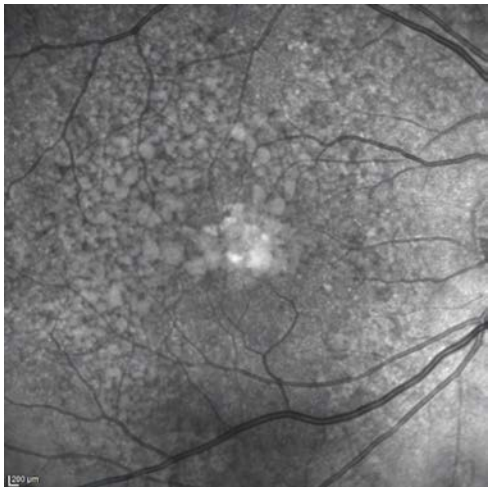
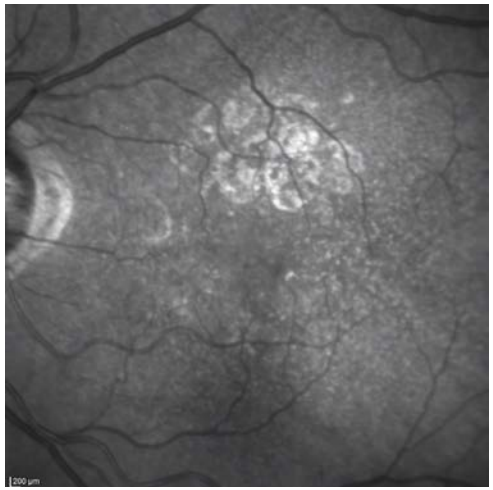


Intermediate AMD

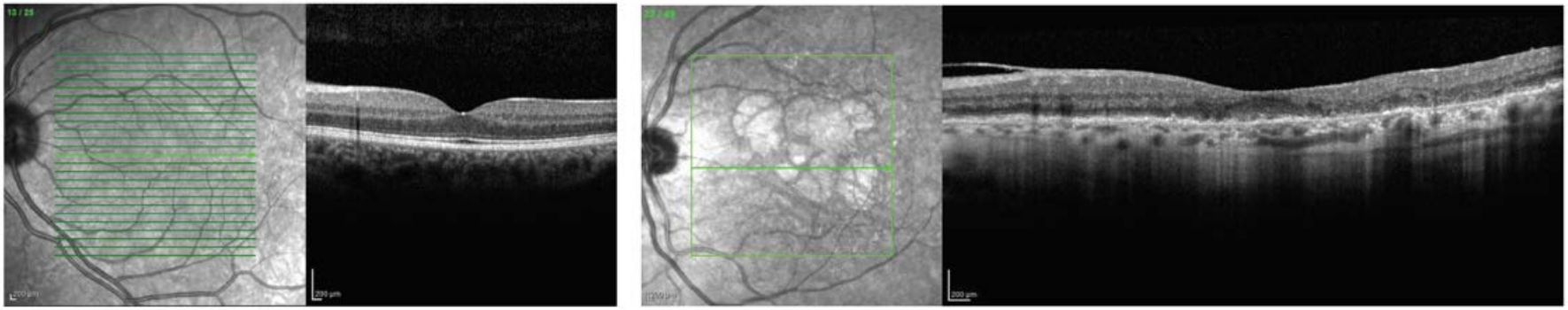


GA

Marsiglia, Marcela et al. "Association Between Geographic Atrophy Progression and Reticular Pseudodrusen in Eyes With Dry Age-Related Macular Degeneration." *Investigative Ophthalmology & Visual Science* 54.12 (2013): 7362–7369.
Morgan, Jessica I. W. et al. "High-Resolution Adaptive Optics Retinal Imaging of Cellular Structure in Choroideremia." *Investigative Ophthalmology & Visual Science* 55.10 (2014): 6381–6397.

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.

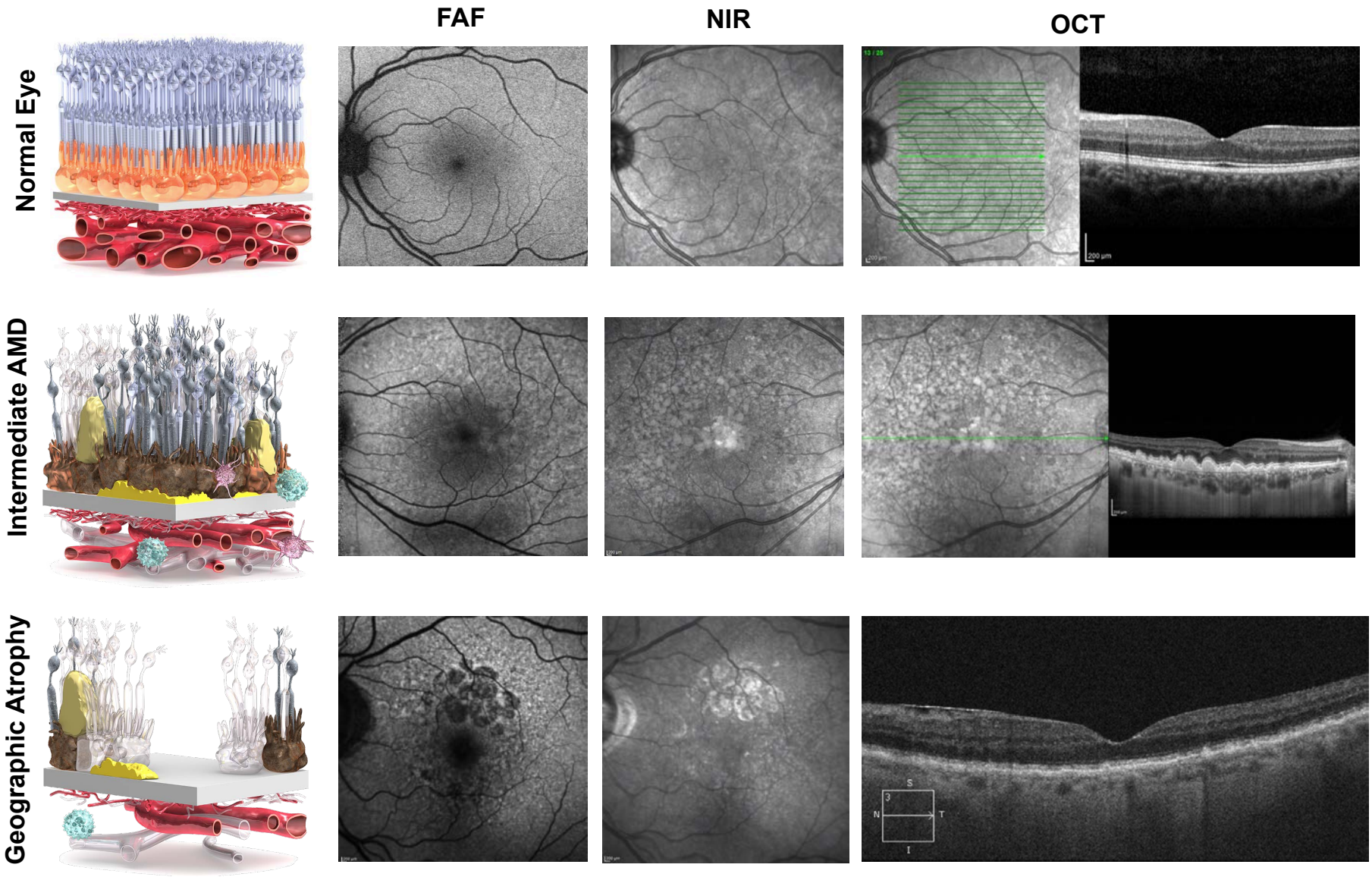


Normal GA

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

Lau, Tiffany et al. “En-Face Optical Coherence Tomography in the Diagnosis and Management of Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy.” *Indian Journal of Ophthalmology* 63.5 (2015): 378–383.

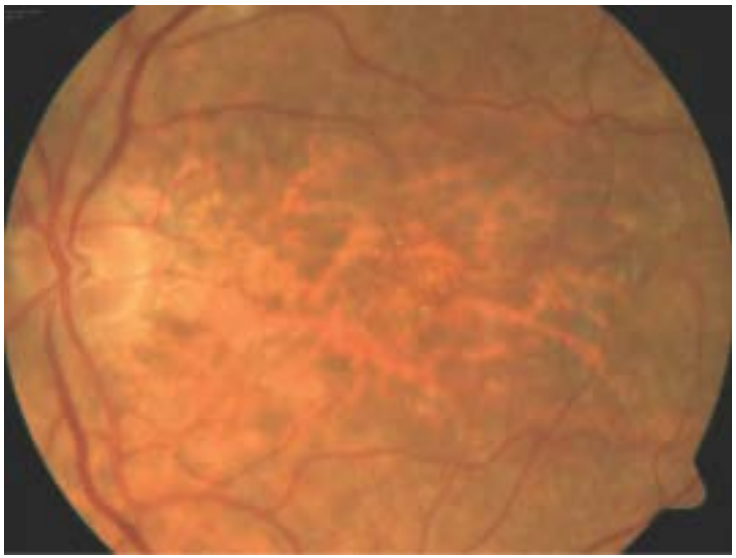
Progression to GA

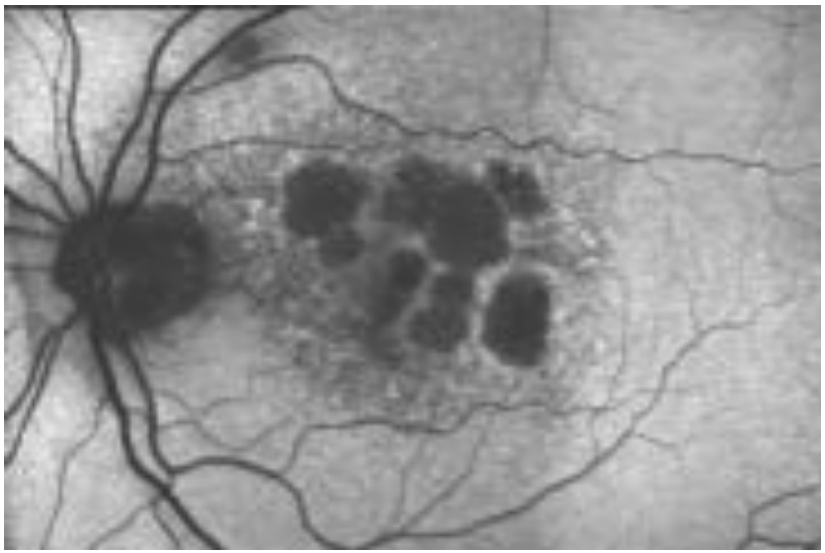


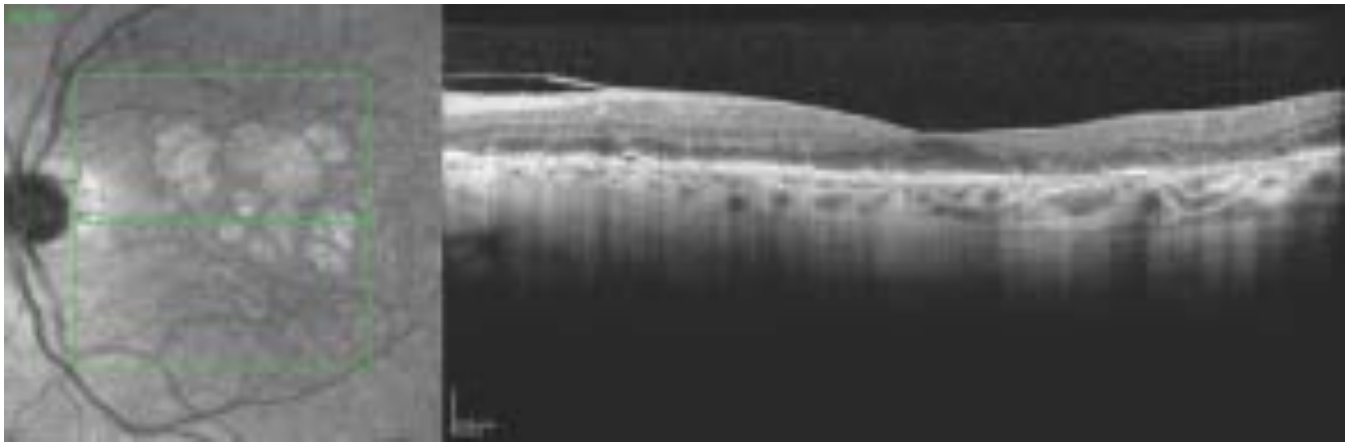
Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.

GA Lesion Expansion

CFP, FAF, and OCT imaging of a patient's retina with GA:

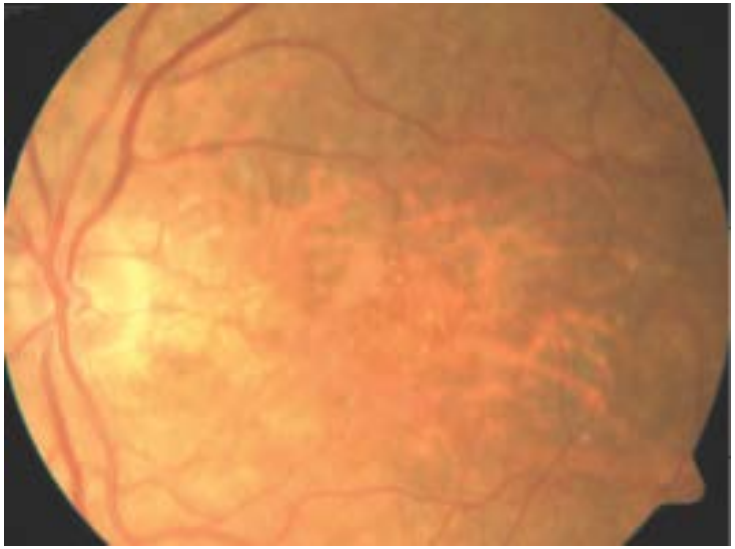


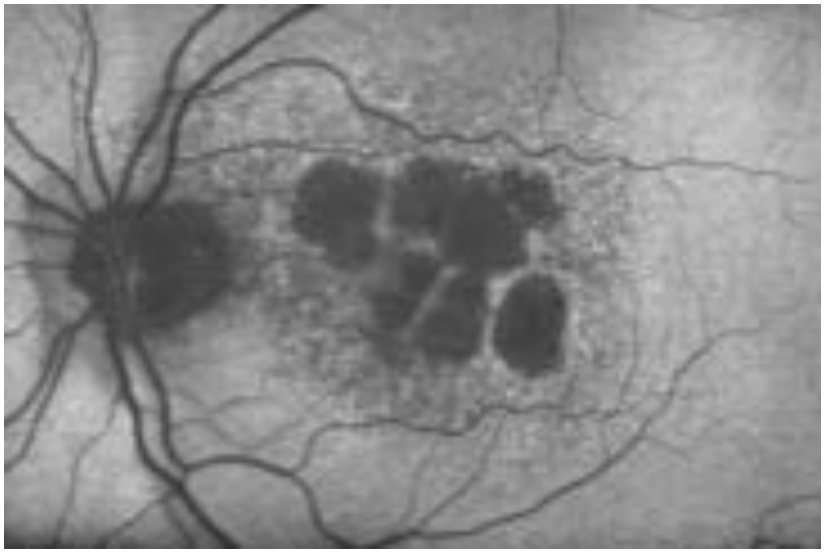


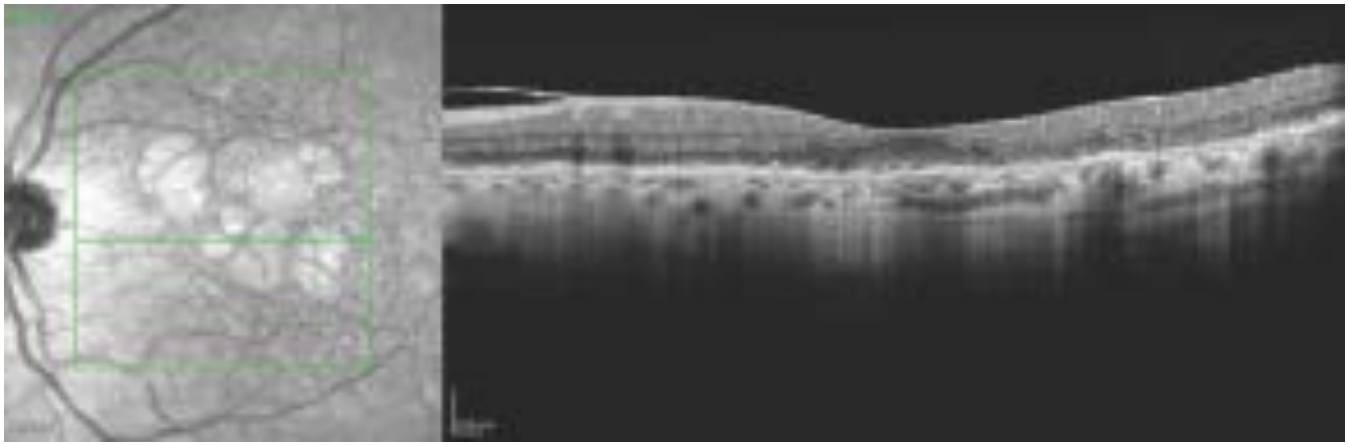


GA Lesion Expansion

CFP, FAF, and OCT imaging of the same patient's retina with GA one year later:







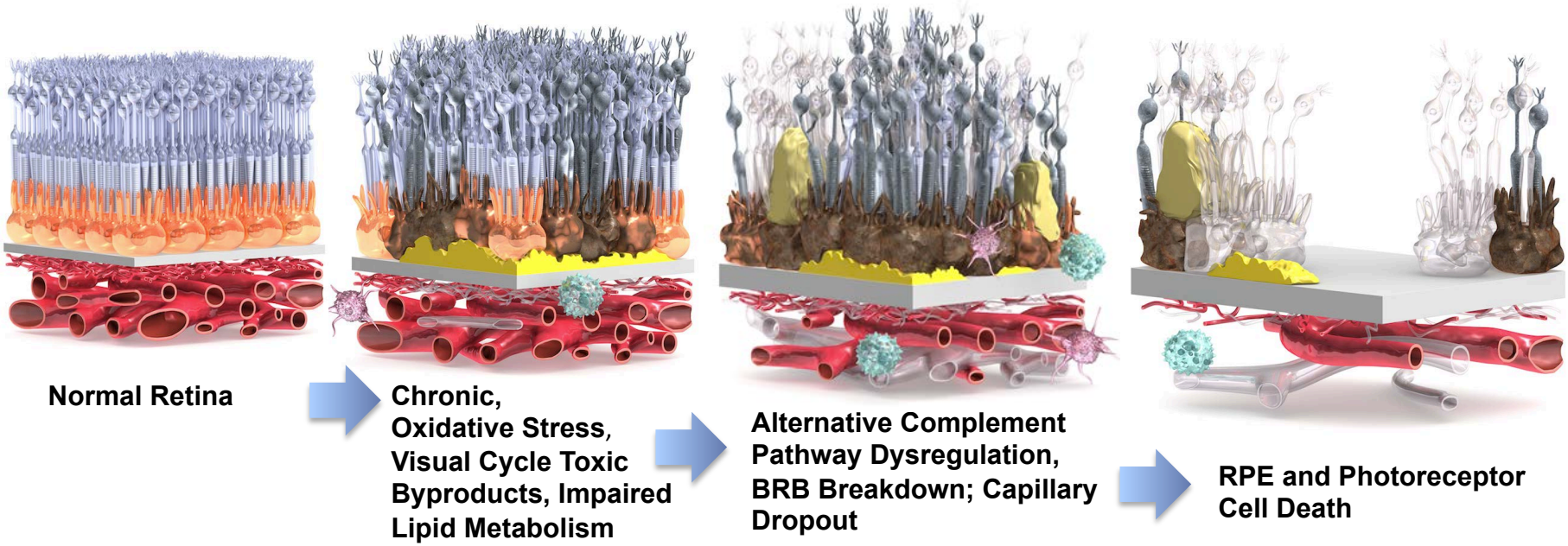
Geographic Atrophy

Pathways and Mechanisms

Potential Targets for Future Therapies

Review: GA Etiology

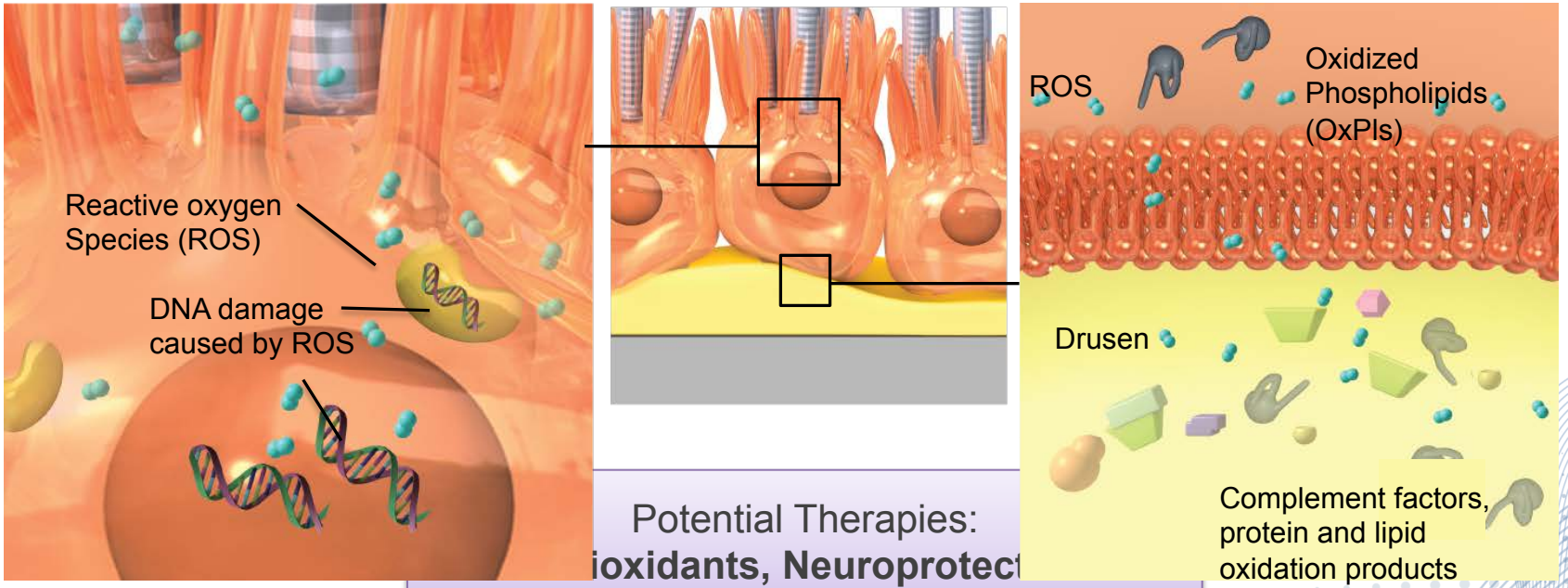
The progression from a healthy retina, to early and intermediate AMD, to GA seems to begin with chronic oxidative stress, inflammation and immune attack, followed by choriocapillaris dropout and cell death of the RPE and photoreceptors. Underlying causes and mechanisms for this process include visual 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.



Fritsche, Lars G. et al. “Age-Related Macular Degeneration: Genetics and Biology Coming Together.” *Annual Review of Genomics and Human Genetics* 15 (2014): 151–171. PMC.
Holz, Frank G., Erich C. Strauss, Steffen Schmitz-Valckenberg, and Menno Van Lookeren Campagne. "Geographic Atrophy." *Ophthalmology* 121.5 (2014): 1079-091.

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.



Jarrett, Stuart G., and Michael E. Boulton. "Consequences of Oxidative Stress in Age-Related Macular Degeneration." *Mol Asp Med* 33.4 (2012): 399–417

Shaw, Peter X. et al. "Oxidative Stress, Innate Immunity, and Age-Related Macular Degeneration." *AIMS molecular science* 3.2 (2016): 196–221.

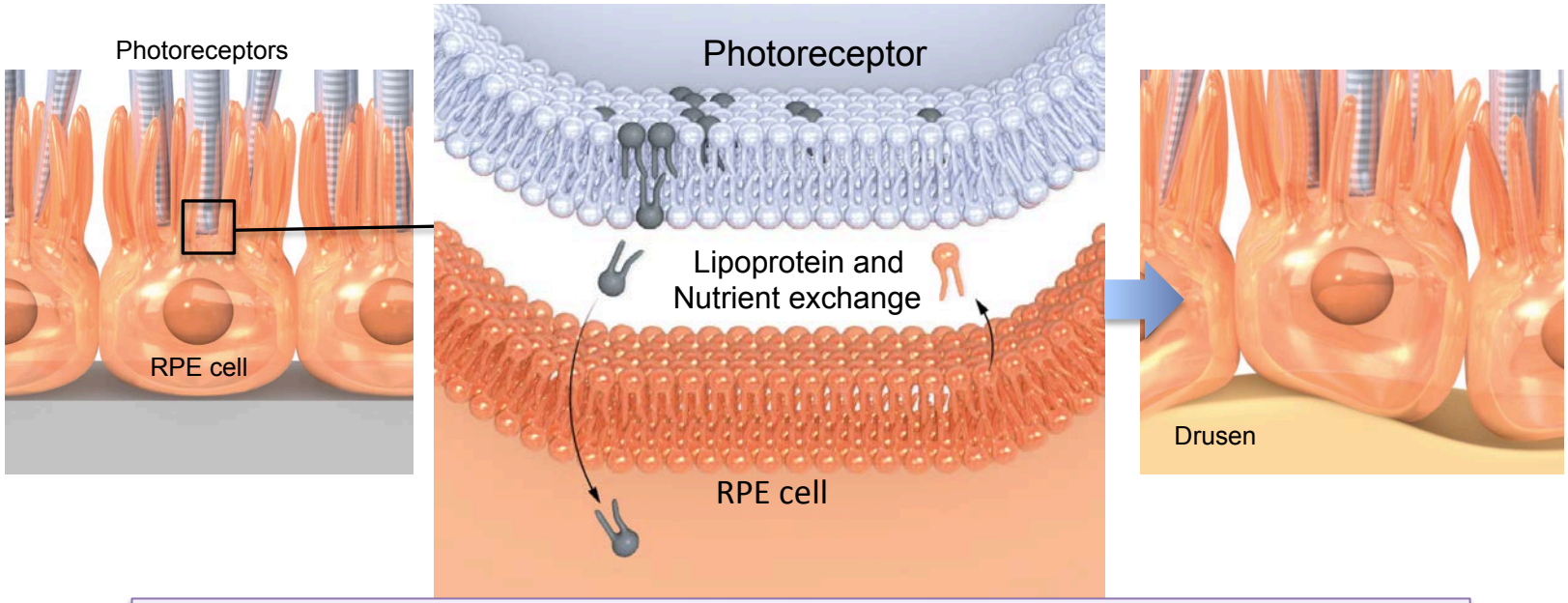
Miller YI, Choi SH, Wiesner P, et al. "Oxidation-specific Epitopes are Danger-associated Molecular Patterns Recognized by Pattern Recognition Receptors of Innate Immunity. *Circ Res* 108 (2011): 235–48.

Stahl W, Sies H. Bioactivity and Protective Effects of Natural Carotenoids. *Biochimica et biophysica acta*.1740.2 (2005):101–107.

Li Y, Song D, Song Y, et al. "Iron-induced Local Complement Component 3 (C3) Up-regulation via Non-canonical Transforming Growth Factor (TGF)-β Signaling in the Retinal Pigment Epithelium." *J Biol Chem*. 2015 May 8;290(19):11918-34.

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.

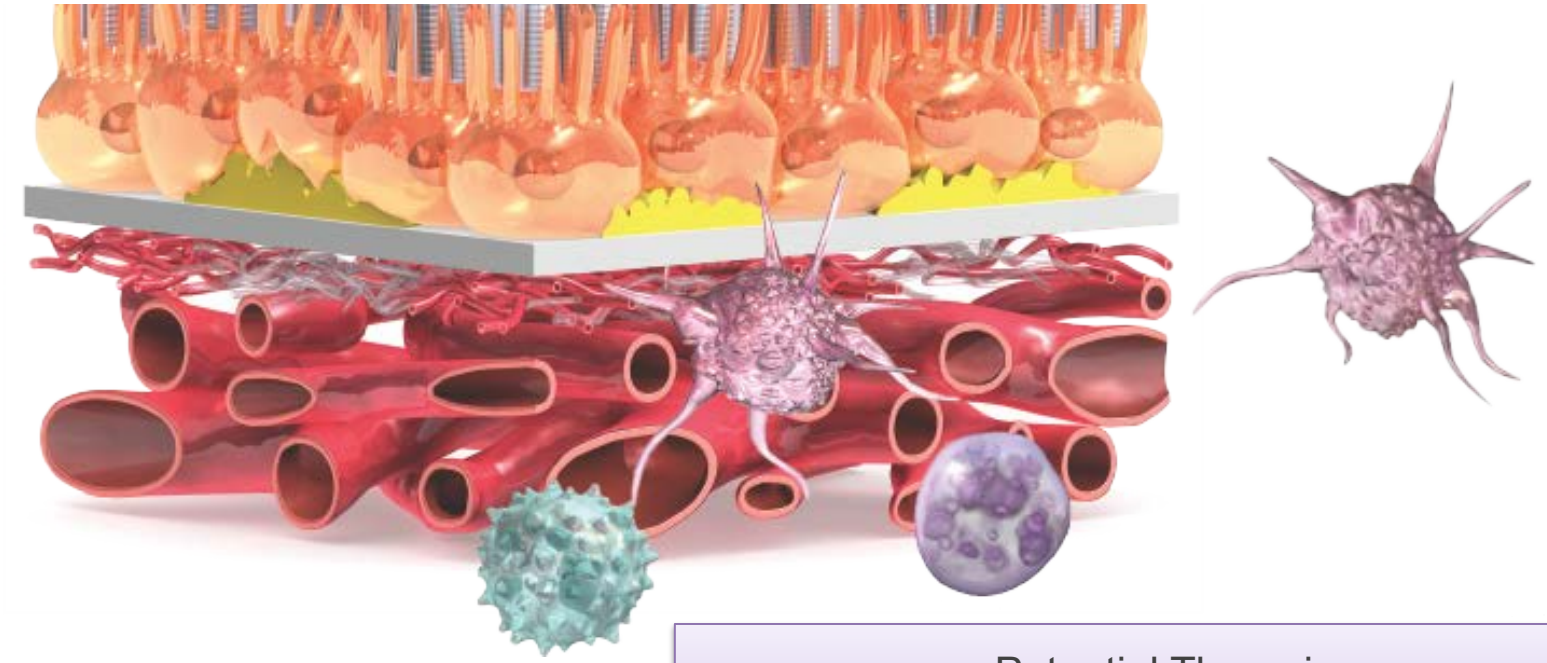


Potential Therapies:
Visual Cycle Modulators, LDL-lowering drugs, autophagy-regulating kinases AMPK and mTOR

Jarrett, Stuart G., and Michael E. Boulton. "Consequences of Oxidative Stress in Age-Related Macular Degeneration." *Molecular Aspects of Medicine* 33.4 (2012): 399–417.
Mata, Nathan L., Ryo Kubota, and Pravin U. Dugel. "Visual Cycle Modulation: A Novel Therapeutic Approach For Treatment of GA In Dry AMD." *Retinal Physician* 10.May (2013): 20-23.
Maeda A, Maeda T, Golczak M, et al. "Effects of Potent Inhibitors of the Retinoid Cycle on Visual Function and Photoreceptor Protection From Light Damage in Mice." *Mol Pharmacol.* 70 (2006): 1220-1209.
Guymer, Robyn H et al. "Can HMG Co-A Reductase Inhibitors ('statins') Slow the Progression of Age-Related Macular Degeneration? The Age-Related Maculopathy Statin Study (ARMSS)." *Clinical Interventions in Aging* 3.3 (2008): 581–593.
Mitter SK, Rao HV, Qi X *et al.* "Autophagy in the retina: a potential role in age-related macular degeneration." *Adv. Exp. Med. Biol.*723,83–90 (2012).

Inflammation and Immune Attack

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.

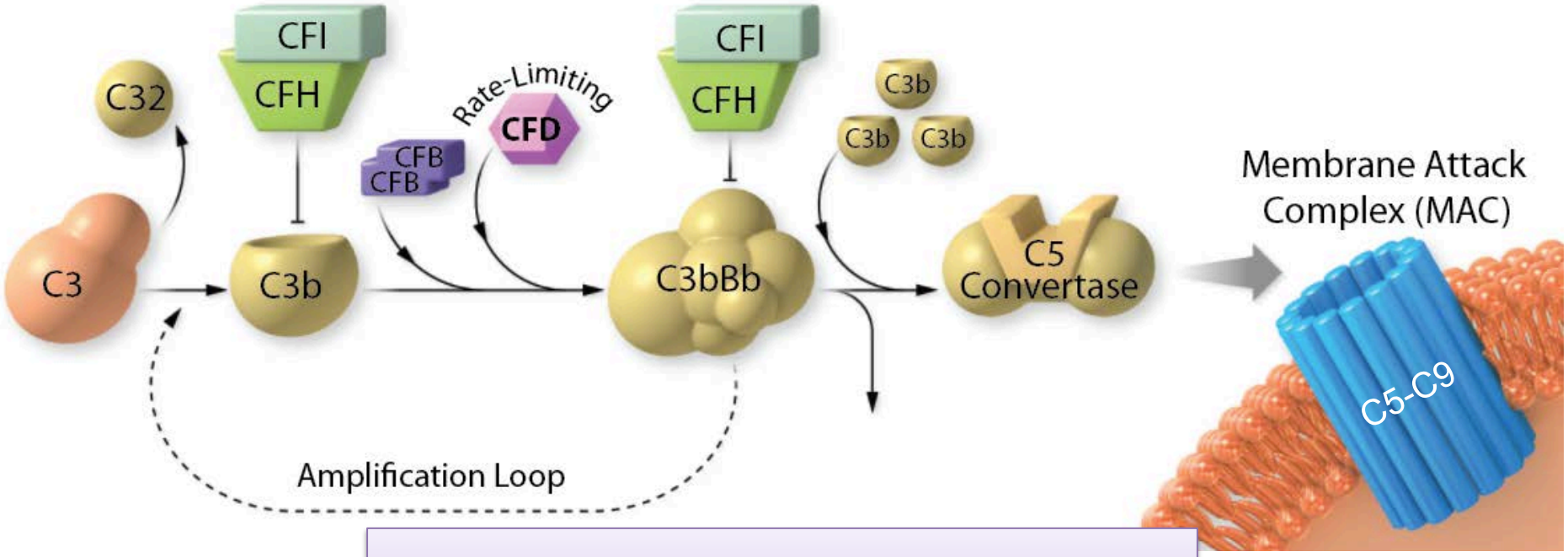


Potential Therapies:
Anti-inflammatory agents

Ambati, Jayakrishna, John P. Atkinson, and Bradley D. Gelfand. "Immunology of Age-Related Macular Degeneration." *Nature reviews. Immunology* 13.6 (2013): 438–451.
Jiangyuan Gao, Ruozhou Tom Liu, Sijia Cao, et al. "NLRP3 Inflammasome: Activation and Regulation in Age-Related Macular Degeneration," *Mediators of Inflammation*, vol. 2015.
Levy O, Calippe B, Lavalette S, Hu SJ, Raoul W, Dominguez E, Housset M, Paques M, Sahel JA, Bemelmans AP, et al. "Apolipoprotein E Promotes Subretinal Mononuclear Phagocyte Survival and Chronic Inflammation in Age-related Macular Degeneration. *EMBO Mol Med.* 7 (2015):211–226.
McKay, Gareth J. et al. "Evidence of Association of *APOE* with Age-Related Macular Degeneration - a Pooled Analysis of 15 Studies." *Human mutation* 32.12 (2011): 1407–1416.

Alternative Complement Pathway

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

Chen Y, Zeng J, Zhao C, Wang K, Trood E, Buehler J, Weed M, Kasuga D, Bernstein PS, Hughes G, et al. "Assessing susceptibility to age-related macular Degeneration with Genetic Markers and Environmental Factors." *Arch Ophthalmol*. 129 (2011):344–351.

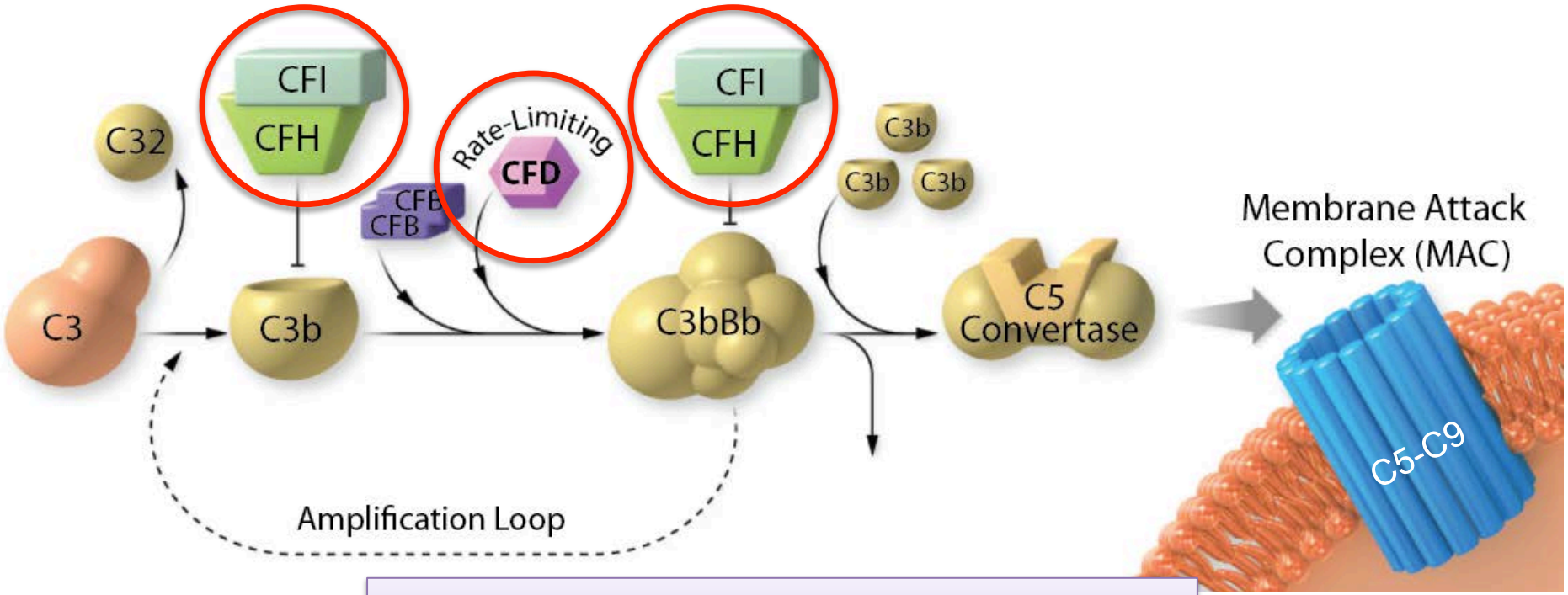
Ambati, Jayakrishna, John P. Atkinson, and Bradley D. Gelfand. "Immunology of Age-Related Macular Degeneration." *Nature reviews. Immunology* 13.6 (2013): 438–451.

Tan, Perciliz L., Catherine Bowes Rickman, and Nicholas Katsanis. "AMD and the Alternative Complement Pathway: Genetics and Functional Implications." *Human Genomics* 10 (2016): 23.

Fritsche, Lars G. et al. "Age-Related Macular Degeneration: Genetics and Biology Coming Together." *Annual review of genomics and human genetics 15* (2014): 151–171.

Alternative Complement Pathway

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.

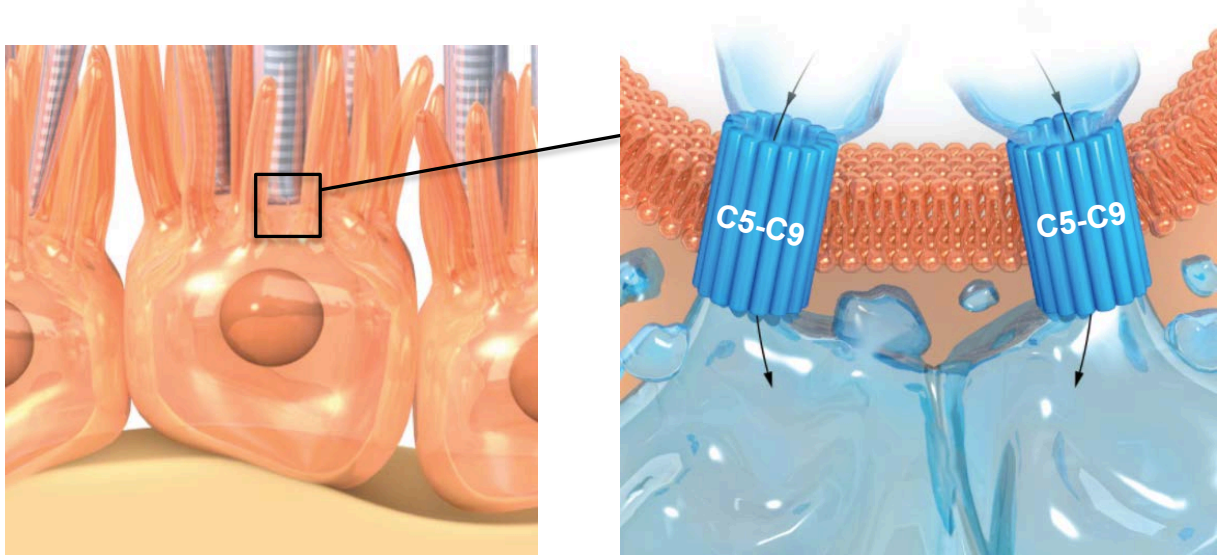


Potential Therapies:
Alternative complement inhibitors

Warwick, Alasdair et al. "Age-Related Macular Degeneration: A Disease of Systemic or Local Complement Dysregulation?" Ed. Lindsay Farrer. *Journal of Clinical Medicine* 3.4 (2014): 1234–1257.
Stanton, Chloe M. et al. "Complement Factor D in Age-Related Macular Degeneration." *Investigative Ophthalmology & Visual Science* 52.12 (2011): 8828–8834.
Katschke, Kenneth J. et al. "Inhibiting Alternative Pathway Complement Activation by Targeting the Factor D Exosite." *The Journal of Biological Chemistry* 287.16 (2012): 12886–12892.
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.



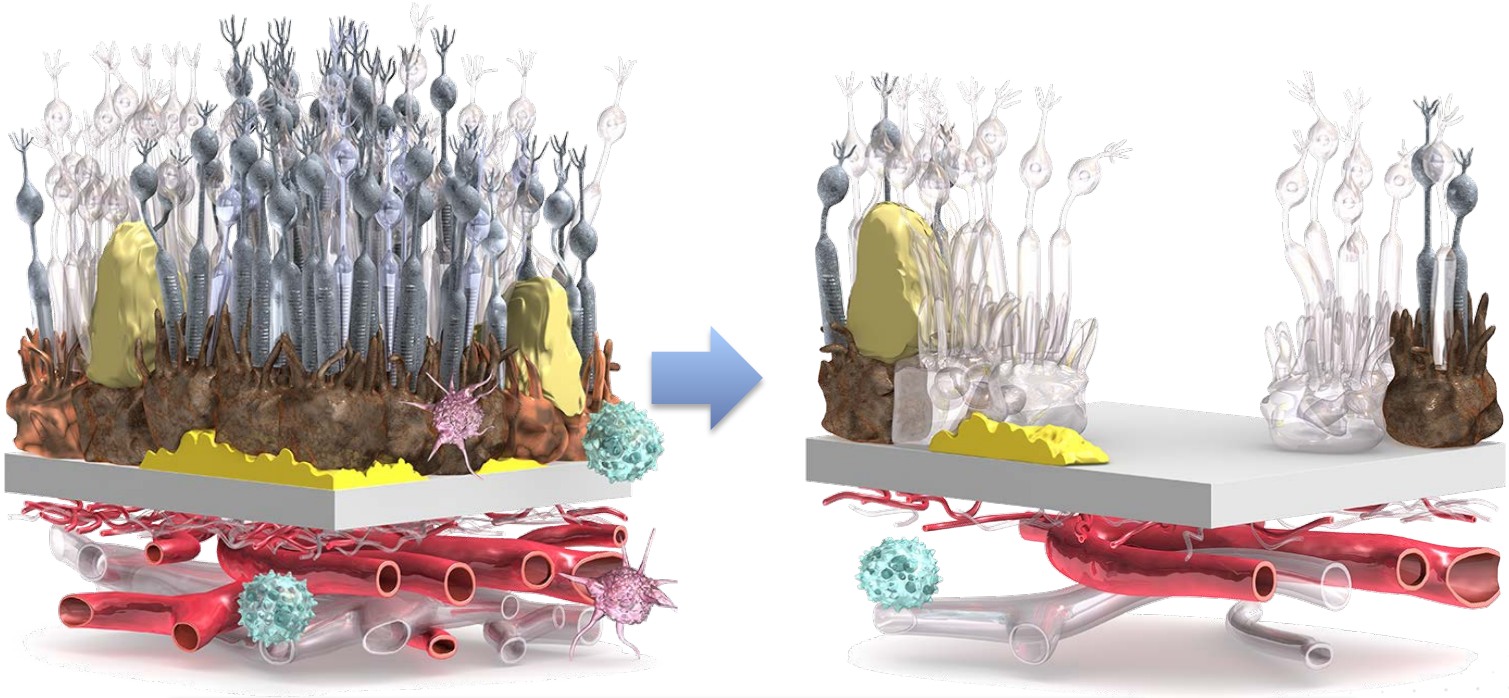
Membrane Attack Complex (MAC):
composed of complement factors C5-C9

Potential Therapies:
Alternative complement inhibitors

Mullins, Robert F. et al. "The Membrane Attack Complex in Aging Human Choriocapillaris: Relationship to Macular Degeneration and Choroidal Thinning." *The American Journal of Pathology* 184.11 (2014): 3142–3153. 6

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

Ambati et al. "Immunology of Age-Related Macular Degeneration." Nature reviews. *Immunology* 13.6 (2013): 438–451. PMC.
Hanus et al. "Current Therapeutic Development for Atrophic Age-Related Macular Degeneration." *The British Journal of Ophthalmology* 100.1 (2016): 122–127.
Carr AJ et al. Protective Effects of Human IPS-derived Retinal Pigment Epithelium Cell Transplantation in the Retinal Dystrophic Rat. *PloS one*. 2009;4 (12):e8152.

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.cinicaltrials.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®

A Safety Study of CNTO 2476 in Patients With Age-Related Macular Degeneration - ClinicalTrials.gov/ct2/show/NCT01226628
A Safety and Efficacy Study of Brimonidine Intravitreal Implant in Geographic Atrophy Secondary to Age-related Macular Degeneration - Full Text View - ClinicalTrials.gov
Zhang et al "Ciliary Neurotrophic Factor Delivered by Encapsulated Cell Intraocular Implants for Treatment of Geographic Atrophy in Age-related Macular Degeneration." *PNAS* 108.15 (2011): 6241-245.
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.
A Phase 2/3 Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura® (Anti-C5 Aptamer) in Subjects With Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration - Full Text View - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/NCT02686658.
Clinical Study to Evaluate Treatment With ORACEA® for Geographic Atrophy (TOGA) - Tabular View - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/record/NCT01782989.

CHROMA and SPECTRI

ROCHE/ GENENTECH

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, lampilizumab every 4 weeks, and lampilizumab 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

Roche Initiates Phase III Trials for Lampalizumab, First Potential Treatment for Geographic Atrophy (GA), F. Hoffmann-La Roche Ltd, 15 Sept. 2014, www.roche.com/investors/updates/inv-update-2014-09-15.htm.

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.

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

ZIMURA

OPTHOTECH

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.

A Phase 2/3 Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura® (Anti-C5 Aptamer) in Subjects With Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration - Full Text View - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/NCT02686658.
Ophthotech, www.ophthotech.com/product-candidates/arc1905/.

TOGA

UNIVERSITY OF VIRGINIA

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

Clinical Study to Evaluate Treatment With ORACEA® for Geographic Atrophy (TOGA), www.retinavitreous.com/trials/toga.php.
Clinical Study to Evaluate Treatment With ORACEA® for Geographic Atrophy (TOGA) - Tabular View - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/record/NCT01782989.

Ongoing Clinical Trials

(As of August 2017)

MOA	Product	Sponsor	Indication	Phase	Mode of Delivery
Inhibition of complement C3	APL-2	Apellis Pharmaceuticals	GA/AMD	II	Intravitreal injection
Antioxidant, slows DNA damage, reduced ROS levels	metformin	University of California, San Francisco	Nondiabetic GA/dry AMD	II	Daily oral tablets
Neuroprotection	brimonidine	Allergan	GA/AMD	II	Intravitreal inplant
Inhibition of glial cell activation	Minocycline	National Eye Institute (NEI)	GA/dry AMD	II	Daily oral capsules
Iron-chelation, antioxidant	Alpha Lipoic Acid (ALA)	University of Pennsylvania	GA/dry AMD	II	Daily oral capsules

Ongoing Clinical Trials

(As of August 2017)

MOA	Product	Sponsor	Indication	Phase	Mode of Delivery
Human umbilical tissue–derived cells	CNTO 2476	Janssen Research & Development	GA/ AMD	II	Subretinal administration
hESC-derived RPE cells	OpRegen	Cell Cure Neurosciences	Nondiabetic GA/dry AMD	I/II	Subretinal transplantation
hESC-derived RPE cells seeded on polymeric substrate	CPCB-RPE1	Regenerative Patch Technologies	Advanced dry AMD	I/II	Subretinal transplantation
Transpalpebral microcurrent electrical stimulation	Nova Oculus	The Eye Machine Canada	vision loss associated with dry AMD	I/II	Externally applied microcurrent electrical stimulation

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.

Schaal, Karen B. et al. “Anatomic Clinical Trial Endpoints for Nonexudative Age-Related Macular Degeneration.” *Ophthalmology*, vol. 123, no. 5, 2016, pp. 1060–1079. doi:10.1016/j.ophtha.2016.01.034.
Sunness JS, Rubin GS, Applegate CA, et al. “Visual Function Abnormalities and Prognosis in Eyes with Age-related Geographic Atrophy of the Macula and Good Visual Acuity.” *Ophthalmology*.104 (1997): 1677– 1691.

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)**

Sadda, Srinivas R., Usha Chakravarthy, David G. Birch, Giovanni Staurenghi, Erin C. Henry, and Christopher Brittain. "Clinical Endpoints For The Study Of Geographic Atrophy Secondary To Age-Related Macular Degeneration." *Retina*. 36.10 (2016): 1806-822.
Pelli DG, Robson JG. "The design of a new letter chart for measuring contrast sensitivity." *Clin Vis Sci* 2 (1988):187–199.

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.

Sadda, Srinivas R., Usha Chakravarthy, David G. Birch, Giovanni Staurenghi, Erin C. Henry, and Christopher Brittain. "Clinical Endpoints For The Study Of Geographic Atrophy Secondary To Age-Related Macular Degeneration." *Retina*. 36.10 (2016): 1806-822.
Kapre A, Kimel M, Bressler NM, et al. "Sensitivity of Functional Reading Independence (FRI) Index to Change in Size of Geographic Atrophy." *Philadelphia, PA: International Society for Pharmacoeconomics and Outcomes Research*; 2015.
Mangione CM, Lee PP, Gutierrez PR, et al. "Development of the 25-item National Eye Institute Visual Function." Questionnaire.*Arch Ophthalmol*. 119 (2001): 1050–1058.

The Angiogenesis Foundation

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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Brandon Busbee, MD
Tennessee Retina, Nashville, TN, USA

Usha Chakravarthy, MD, FRCS, PhD
The Queen's University of Belfast, Belfast, UK

Chi Chao Chan, MD
National Eye Institute (NEI), NIH

Monika Fleckenstein, MD, PhD
University of Bonn, Bonn, Germany

Mark Gillies, MBBS, PhD
University of Sydney, Sydney, Australia

Robyn Guymer, MBBS, PhD
University of Melbourne, Melbourne, Australia

Frank G. Holz, MD
University of Bonn, Bonn, Germany

Jean Francois Korobelnik, MD
Bordeaux University Hospital, Bordeaux, France

Andrew Lotery, MD
Southampton General Hospital, Southampton, UK

David G. Miller, MD
Retina Associates of Cleveland, USA

Jordi Monés, MD, PhD
Institut de la Màcula, Barcelona, Spain

Francisco J. Rodriguez, MD
Universidad del Rosario, Bogotá, Colombia

Srinivas R. Sadda, MD
UCLA, Los Angeles, CA, USA

Harinderjit Singh, MD
Southeast Retina Center, Augusta, GA, USA

Eric Souied, MD, PhD
Hopital Intercommunal de Creteil, France

Giovanni Staurenghi, MD
University of Milan, Milan, Italy

Robert A. Stoltz, MD, PhD
Georgia Retina, Marietta, GA, USA

Nadia Waheed, MD
Tufts Medical School, Medford, MA, USA

Shusheng Wang, PhD
Tulane University, New Orleans, LA, USA

David Wong, MD
St. Michael's Hospital, Toronto, Canada

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Educational Resource

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