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GEOGRAPHIC ATROPHY: Contemporary Approaches to Diagnosis and Referral and a Review of the Pipeline


ROGER A. GOLDBERG, MD, MBA
PROGRAM CHAIR


MICHAEL CHEN, OD


GEETA LALWANI, MD


ERIC NUDLEMAN, MD, PHD


NATALIE A. TOWNSEND, OD

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GEOGRAPHIC ATROPHY: Contemporary Approaches to Diagnosis and Referral and a Review of the Pipeline

Faculty

Roger A. Goldberg, MD, MBA
Program Chair
Retina Specialist
Bay Area Retina Associates
Walnut Creek, CA

Michael Chen, OD
Optometrist
Silicon Valley Eyecare
Santa Clara, CA

Geeta Lalwani, MD
Retina Specialist
Rocky Mountain Retina Associates
Boulder, CO

Eric Nudleman, MD, PhD
Associate Professor of Clinical Ophthalmology
UC San Diego Shiley Eye Institute
San Diego, CA

Natalie A. Townsend, OD
Optometrist
Bascom Palmer Eye Institute
Miami, FL

Content Source

This continuing medical education (CE/CME) activity captures content from a virtual roundtable discussion.

Activity Description

This roundtable discussion brings together optometric and ophthalmic experts in retinal disease to discuss the state of geographic atrophy (GA), how best to manage patients, and the pipeline therapies that have the potential to significantly alter the course of disease for many patients.

Target Audience

This certified CE/CME activity is designed for optometrists and ophthalmologists.

Learning Objectives

Upon completion of this activity, the participant should be able to:

- **Discuss** the prevalence of age-related macular degeneration
- **Articulate** the burden of illness linked to GA
- **Understand** the pathogenesis of GA
- **Describe** disease detection and factors influencing progression
- **Review** the therapeutic interventions that have been explored as well as those in the pipeline

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Digital Edition

This supplement is part of a full curriculum, including webinars, available at: https://evolvemeded.com/course-group/recognition-referral-best-practices-for-managing-patients-with-ga.

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

1. Please rate your confidence in your ability to understand the pathogenesis of geographic atrophy (GA) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Which of the following is the No. 1 risk factor for advanced GA and age-related macular degeneration (AMD)?

a. Age
b. Family history
c. Smoking history
d. Gender

3. You are seeing an 80-year-old patient with non-neovascular AMD in both eyes. You obtain fundus autofluorescence (FAF) to better characterize her GA. After obtaining this imaging, you unfortunately find that her pattern of GA puts her at increased risk of GA progression. What pattern of abnormal FAF did she likely demonstrate?

a. Normal
b. Patchy
c. Focal
d. Trickling

4. What is the prevalence of wet and dry AMD in the United States?

a. 5 million
b. 11 million
c. 22 million
d. 33 million

5. All of the following factors play a role in the development of GA EXCEPT:

a. Diet
b. Lifestyle
c. Smoking
d. Cataract status

6. What race has the highest prevalence of AMD?

a. White
b. African American
c. Asian
d. American Indian

7. All of the following risk alleles have been linked with the development of early AMD or GA, EXCEPT?

a. CFH
b. ARMS2
c. Y402H
d. BEST2

8. Which of the following statements about depression rates and AMD is TRUE?

a. Depression rates are higher among patients with AMD and GA compared with those who do not have AMD
b. Depression rates are lower among patients with AMD and GA compared with those who do not have AMD
c. Depression rates are similar among patients with AMD and GA compared with those who do not have AMD
d. Depression rates and the presence of AMD are not correlated

9. What is a good test a clinician can use to identify reading difficulty in patients with GA?

a. Best corrected visual acuity
b. Contrast sensitivity
c. Reading speed tests
d. Humphrey visual fields

10. According to the literature, what percentage of patients with GA do not feel confident with night driving?

a. ~28%
b. ~48%
c. ~68%
d. ~88%

11. Which of the following statements about GA lesion size and progression is TRUE?

a. Larger lesions and multifocal lesions progress the fastest
b. Larger lesions progress the fastest but multifocal lesions progress the slowest
c. Larger lesions progress the slowest but multifocal lesions progress the fastest
d. Larger lesions and multifocal lesions progress the slowest

GEOGRAPHIC ATROPHY: CONTEMPORARY APPROACHES TO DIAGNOSIS AND REFERRAL AND A REVIEW OF THE PIPELINE

Given the promise that one or more late-stage pipeline candidates can safely and effectively treat geographic atrophy (GA)—and therefore receive approval from regulatory bodies such as the FDA—it is prudent for eye care providers to consider how forthcoming changes may alter clinical dynamics. If a drug is eventually approved for the treatment of GA, the relationship between optometry and ophthalmology will become more intertwined: optometrists will be tasked with diagnosing, documenting, and promptly referring patients who can most benefit from therapy, and retina specialists will be charged with fielding a surge of patient who were previously unable to receive treatment.

With these impending developments in mind, I sat down with two optometrists and two retina specialists to review how GA is managed, discuss which elements of current treatment paradigms will shift in the coming years, and examine which forthcoming innovations may be key to unlocking widespread treatment for GA.

—Roger A. Goldberg, MD, MBA

Q | **Roger A. Goldberg, MD, MBA:** Before we get into a discussion of GA, in particular, we should review the prevalence and presentation of age-related macular degeneration (AMD) in general. What top-level details does the modern clinician need to know about AMD in order to have the context needed to understand GA?

Eric Nudleman, MD, PhD: AMD is a macular disorder that affects patients' central vision.[1] It is chronic in nature, and has been found to be linked to a number of risk factors both controllable (e.g., smoking status) and uncontrollable (e.g., age, genotype).[2] AMD can be subtyped as exudative AMD (also called neovascular AMD, or wet AMD) or nonexudative AMD (also called dry AMD).[3] We call the advanced nonexudative disease geographic atrophy based on certain clinical and imaging characteristics.

Approximately 11 million Americans have AMD of any kind; globally, approximately 170 million patients have AMD.[4] Among the 11 million Americans with AMD, it is estimated that 1 million of them have GA.[5] At this advanced stage of dry AMD, patients present with central scotomas and loss of visual acuity.[6]

Q | **Dr. Goldberg:** A disease that is progressive and irreversible such as GA is frustrated by the fact that there is no approved therapy. Currently, clinicians mostly document and characterize GA as best they can. What does an optometrist look for and emphasize during an exam?

Natalie A. Townsend, OD: When a patient with suspected GA visits my clinic, I tend to comb their chart for some of the risk factors Dr. Nudleman described. Age, which is the leading risk factor for developing AMD, is of obvious concern.[7-9] White patients have a much higher prevalence of AMD than patients of other races,[10] so that is something to also look out for on a chart. Given the link between obesity and AMD development, I may examine a chart for height and weight information.[11]

Other risk factors are sometimes acquired upon examination and history gathering. A patient's smoking status or smoking history may not be documented, but will likely come to the forefront during a conversation with the patient. Given that current smoking status is associated with the development of late-stage AMD, knowledge of smoking status is an important detail to gather during exam.[12]

It should be noted that some risk factors are difficult to obtain in a clinical setting. Acquisition of genetic information is challenging and sometimes impractical. Still, it should be noted that the risk alleles CFH and ARMS2 have been linked with the development of early AMD,[12] and that the CFH variant Y402H has been linked with the development of GA.[13]

"Before there were therapies on the horizon for GA, many clinicians used dry AMD and GA interchangeably. The closer we get to accessing a therapy, the more important accurate language will be."

–Geeta Lalwani, MD

Dr. Nudleman: Other diseases can cause atrophy to the retinal pigment epithelium (RPE), so considering GA risk factors could be important during the course of a diagnosis. It is very unlikely that a patient in their 50s has GA, for example. If a younger patient who is a nonsmoker and seems otherwise healthy presents to my clinic with RPE damage, I would be inclined to further explore whether he or she has an inherited retinal dystrophy or a drug-induced toxicity.

Geeta Lalwani, MD: It is encouraging to see that the field has settled on use of more accurate nomenclature. Before there were therapies on the horizon for GA, many clinicians used dry AMD and GA interchangeably. The closer we get to accessing a therapy, the more important accurate language will be.

I'm excited that we may soon be able to assist patients with GA. Vision loss due to GA is linked with significant quality of life worsening. Anecdotally, we hear from our patients that activities of daily living such as exercise, household chores, personal hygiene, and reading are severely affected by GA. We also know that depression rates are higher among patients with AMD (including GA) compared with those who do not have AMD.[14] If we can address our patients' vision and also affect these other areas of their lives, then the consequences of our intervention may be stronger than we anticipate.

Michael Chen, OD: Conversations with patients who have GA are difficult. Often, when I tell them that they have advanced AMD, they are optimistic that they can receive an intravitreal injection like friends or family have had. Learning that they have a form of AMD for which there is no treatment leaves them feeling lost.

Such experiences are articulated in the literature. Patients who have been diagnosed with wet AMD and have undergone therapy resulting in preserved or improved visual function report feeling "cautiously optimistic," whereas patients who have GA have reported feeling "profound loss" about their future.[15] To Dr. Lalwani's point, collaboration between optometry and ophthalmology may lead to improvements in our patients' mental health if accurate diagnoses and referrals from referring eye care providers result in therapy administered by retina specialists.

Q | Dr. Goldberg: Dr. Chen, what are some of the common complaints you hear from your patients with GA?

Dr. Chen: Many of the patients with GA we see are referred to us because we provide low-vision services in our practice. The main complaint we have from our patients with GA is linked to reading difficulty, which can be frustrating for them because their overall visual acuity remains relatively strong. This makes sense, given that fovea-sparing GA lesions allow patients to read individual letters on an eye chart but not full words.[16] In patients such as these, reading speed tests, which help assess the quality of the visual field outside of the macula, may be useful tools in tracking progression of visual loss (Figure 1; see sidebar *Measuring Visual Function in Patients With GA* for more discussion).[16]

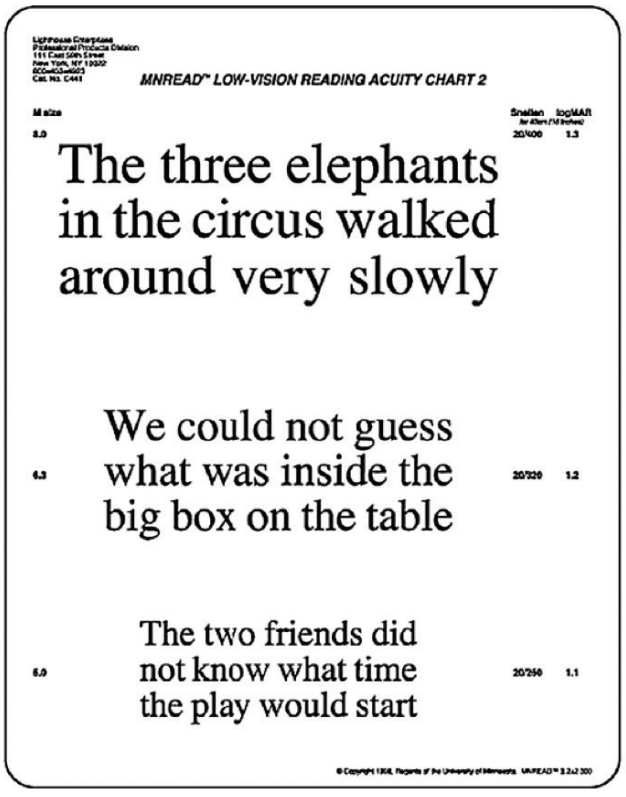

Figure 1. Patients with foveal-sparing GA are sometimes able to read individual letters on an eye chart, leading to BCVA measurements which may belie their practical visual function. Using a reading speed test, which requires a patient to use a larger segment of their overall visual field, may be a more effective tool for tracking visual function decline in patients with GA.

Dr. Lalwani: I practice in Boulder, CO, and the geographic region from which my clinic draws patients is wider than that of a more densely populated area. In some cases, patients drive 2 or 3 hours for an appointment. For patients with GA, driving ability and confidence may be severely compromised. Just over half (52%) of patients with GA do not feel confident with day driving, and a vast majority (88%) do not feel confident with night driving.[17]

When patients with GA who should not be driving arrive at my clinic, they are often accompanied by family members or other ancillary support systems. A good way to maintain trust with patients and their support systems is to have honest conversations about what steps can be taken to make sure that patients both keep themselves safe and maintain control of their day-to-day lives.

Q | Dr. Goldberg: Dr. Lalwani, do you have any sense of whether the GA patients you see are referred from an optometrist or general ophthalmologist?

Dr. Lalwani: It's a mixed bag. Some of the patients I see demonstrate something on a primary eye care examination that prompts a referral to a retina specialist, and I'm always happy to examine those patients to hopefully shed some light on their condition and advise as necessary. Other patients are already in my clinic for

MEASURING VISUAL FUNCTION IN PATIENTS WITH GA

Dr. Goldberg: Snellen visual acuity evaluations are useful for assessing vision in a number of disease states, but tend to underrepresent functional deficits in patients with GA.[1] In the body of this discussion, Dr. Chen outlined the benefits of reading speed tests. What other evaluations might be used to assess visual utility in patients with GA?

Dr. Townsend: Low-luminance visual acuity has been shown to be effective at predicting the rate of visual loss in patients with GA who present with good baseline VA,[2] and was described by Sadda et al as a "more sensitive measurement for assessing the risk of visual decline" compared with standard visual acuity evaluations.[3]

Dr. Chen: Some eye care providers may find patient questionnaires to be useful for a subjective evaluation of how GA affects activities of daily living. One such GA-specific survey, the Functional Reading Independence Index, found that scores decreased as lesion sizes increased.[4] This survey has been cleared for use as a methodology in Europe for the past 6 years.[5]

1. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390.
2. Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115(9):1480-1488, 1488.e1-2.
3. Sadda SR, Chakravarthy U, Birch DG, Staurenghi G, Henry EC, Brittain C. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina*. 2016;36(10):1806-1822.
4. Kimel M, Leidy NK, Tschosik E, et al. Functional Reading Independence (FRI) index: a new patient-reported outcome measure for patients with geographic atrophy. *Invest Ophthalmol Vis Sci*. 2016;57(14):6298-6304.
5. Rasi G. Letter of support for reading speed and functional reading independence (FRI) index in geographic atrophy [press release]. January 25, 2015; European Medicines Agency.

other reasons when we detect GA, and others present with vision issues that we then determine are linked with AMD.

The patients who worry me most are the ones who are lost between referral and presentation—that is, those who learn from their primary eye care provider that no treatment is approved by the FDA for the treatment of GA and therefore decide that follow-up with a retina specialist is futile.

Dr. Nudleman: I share the frustration of my patients with GA who are routinely presenting for examination and evaluation, only to hear that exam findings confirm what they already know: that their vision is deteriorating. As clinicians who cannot offer therapy at this time, we are left with showing patients images of their disease progression and discussing lifestyle modifications.

IMAGING AND CLASSIFICATION

Q | **Dr. Goldberg:** Imaging GA via any number of modalities allows clinicians to track GA progression. What are some of the platforms that the panelists use most often?

Dr. Townsend: As someone who practices in an academic clinic with access to advanced imaging equipment, I often track mid-stage AMD and early GA on fundus autofluorescence (FAF) and OCT. Whenever I think disease has progressed to the point that a retina specialist should examine the patient, or if I think that some aberration observed on examination is worthy of further exploration, I refer promptly to an in-house retina specialist. Still, I recognize that my access to both imaging technology and retina specialists is unique in optometry: Not all of my optometric colleagues will have a retina specialist in the same building to refer to, and many of them will not have FAF platforms in their offices.

Dr. Chen: Dr. Townsend is right that FAF is not as ubiquitous in optometry as it might be in the retina specialist's clinic. Some optometrists have access to OCT, which is another reliable imaging platform for tracking GA. My clinic uses both FAF and OCT, and relies on FAF reports as a patient education tool. Interpreting FAF images is more straightforward than interpreting OCT images, and patients often quickly grasp what they're seeing in these images.

Dr. Goldberg: The use of FAF allows clinicians to easily determine if a patient's GA lesions have reached the fovea, and to track its growth over time. Patients seem to respond visually to the en face view offered by the FAF image versus an OCT b-scan, though sometimes the OCT transmission defects are also a good patient education tool. Of course, data about lesion location, size, focality, and autofluorescence characteristics on FAF can inform our conversations with patients about prognosis.

Q | The panel's optometrists are leveraging FAF and OCT. What imaging modalities do the retina specialists on the panel use?

Dr. Lalwani: I use OCT imaging as a go-to modality for most cases. Dr. Chen is correct to point out that FAF provides images that are very useful for patient education, but until we have a therapy that can treat GA, use of more than one modality is more of an academic exercise than a clinical one. That said, if and when we get a treatment for GA, FAF may prove to be the most effective imaging modality for determining which patients are best suited for intervention.

I should note that, given the dearth of treatment options for GA, I usually collaborate with the patient's primary eye care provider for monitoring purposes. It's possible that the patient is receiving care that involves FAF if they are going to a practice similar to Dr. Chen's clinic.

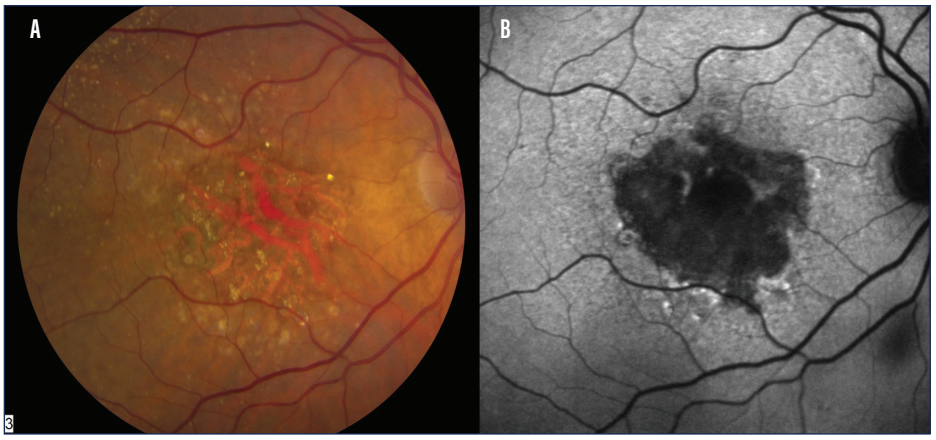

Figure 2. Color fundus photography (A) and FAF (B) may both be used for imaging lesion areas. One benefit of using FAF is that lesion border areas are clearly demarcated, leading to classification of lesion types.

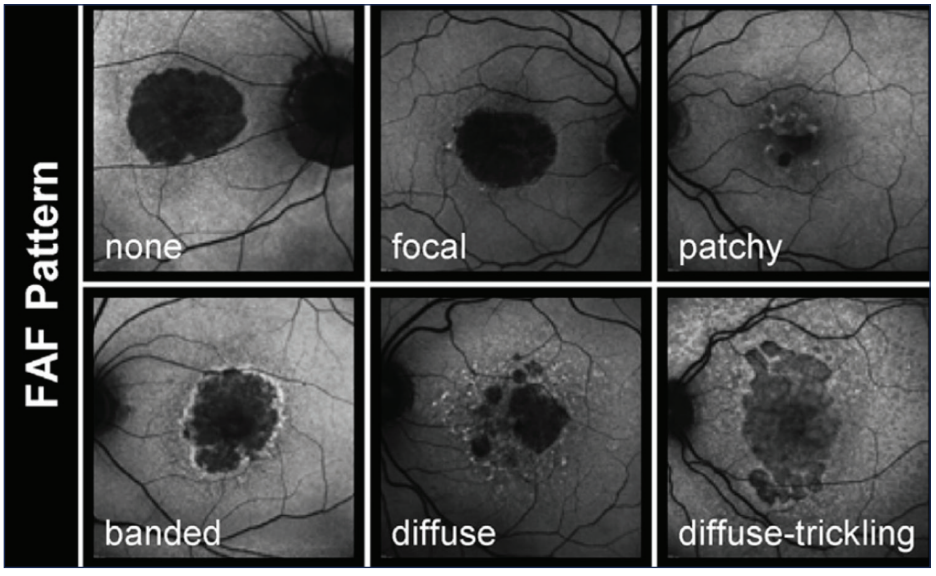

Figure 3. There are six main classifications for lesions as depicted on FAF. Banded lesions and diffuse-trickling lesions are likely to progress quickly, and lesions that cannot be categorized (ie, have no discernable pattern) progress the slowest.

Dr. Nudleman: Knowing the fellow eye status of patients is important when tracking GA. Finger et al found that among unilateral choroidal neovascularization (CNV) patients with reticular pseudodrusen (RPD) but no signs of AMD in the fellow eye, GA was significantly more likely to develop in the fellow eye when compared with patients who had no RPD.[18] Use of OCT imaging in both eyes is prudent in patients with unilateral disease and RPD given the risk of conversion to GA.

In much the same way that Dr. Chen finds FAF imaging useful as a teaching instrument, I find color fundus photography (CFP) to be an educational tool (Figure 2). That is not to say that I find CFP to have clinical utility superior to FAF. The limitations associated with CFP for GA monitoring, such as the platform's inability to image RPD and morphologic changes to the RPE,[19] usually lead me away from using it for GA lesion tracking. Observations of CFP's shortcomings have been noted elsewhere in the literature, such as a study by Khanifar et al which found that, although CFP was effective at measuring GA lesion size, FAF led to more reproducible results.[20]

Q | **Dr. Goldberg:** Using CFP or FAF images as teaching tools is smart, as it allows the patient to learn more about their disease. What degree of detail to you go into with these images? Do you, for example, educate patients about foveal versus extrafoveal lesions? Do you tell them how their prognosis may be affected by these details?

Dr. Lalwani: I do not provide patients with a specific prognosis based on imaging findings, but rather focus on how support systems and lifestyle adjustments may mitigate future vision loss. I take this angle due to the wide range of variable outcomes in patients with GA.

Dr. Townsend: I use a similar strategy. We cannot predict the future, but we can control the present. Finding ways to sustain activities of daily living that have not yet been lost—whether through interventions such as magnifiers or through referral to a low-vision specialist—should be our goal for now.

Dr. Nudleman: I often show my patients their imaging outcomes, as I mentioned earlier. If I have FAF images, I might point out lesions that are noncentral or multifocal and compare them to images I have from years prior to demonstrate that their disease is indeed progressing.

Q | **Dr. Goldberg:** Can you speak more about lesion classification on FAF imaging?

Dr. Nudleman: Generally speaking, there are six types of lesions as depicted on FAF: focal, patchy, banded, diffuse, diffuse-trickling, and unclassifiable (Figure 3). If constant hyperautofluorescence on the lesion border is observed, then the lesion is considered banded. Focal lesions do not have that hyperautofluorescent band. Patchy lesions may have portions of noncontiguous hyperautofluorescence at the margin. Unifocal lesions of unusual pattern may be considered uncategorized. Diffuse patterns are "characterized by levels of abnormal increased FAF intensities extending beyond the border zone of GA,"[21] and diffuse-trickling patterns show coalescent lobular atrophic lesions.[21]

Categorizing lesions on FAF can help determine prognosis. In general, unifocal lesions progress slower than multifocal lesions,

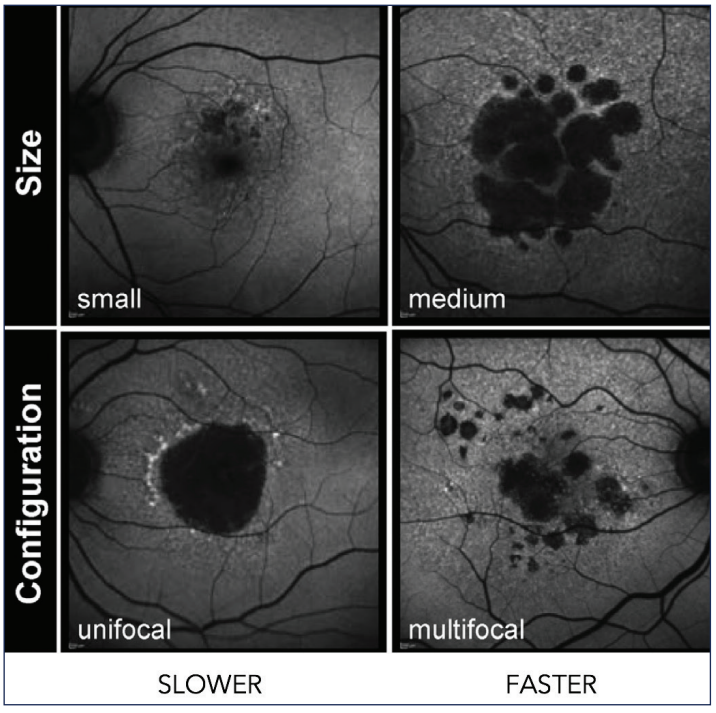

Figure 4. Lesion size and configuration can be used to estimate the rate at which GA will progress. In general, larger lesions and multifocal lesions progress the fastest.

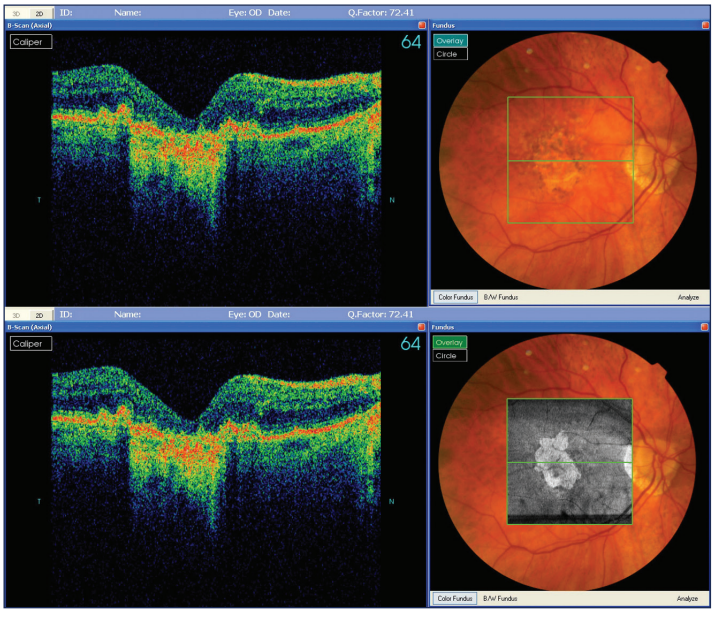

Figure 5. Use of OCT alongside FAF may provide the most detailed imaging reports. Cross-sectional OCT imaging (left panels) provide evidence of retinal tissue disruption but fail to provide the level of detail regarding lesion borders that FAF affords when it is layered atop the OCT image (bottom). Use of FAF and OCT in tandem could be effective for characterizing GA progression.

and small lesions progress slower than medium and large lesions (Figure 4).[22] Diffuse-trickling lesions have demonstrated the fastest rate of progression, followed by diffuse lesions, banded lesions, focal lesions, and uncategorizable lesions.[23]

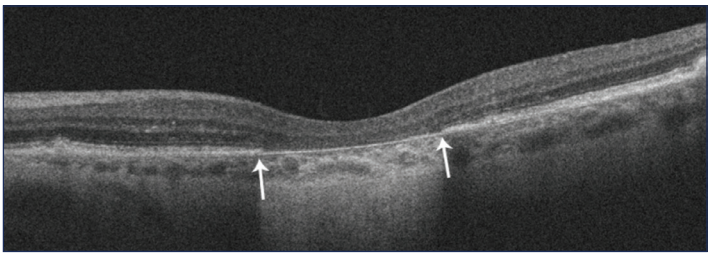

Figure 6. The area between the arrows of this OCT scan shows an area of hypertransmission that is greater than 250 µm, thereby fulfilling one of the necessary requirements for cRORA.

Dr. Chen: I mentioned earlier that I use both OCT and FAF to image GA patients, and generally use FAF imaging to show patients how their disease has progressed. In some instances, patients find OCT images to be more detailed. The literature has plenty of examples illustrating the ability of OCT to depict microstructural alterations related to GA[24] or OCT's use in predictive modeling.[25] Clinicians seeking the most nuanced understanding of a patient's disease may wish to use FAF and OCT in tandem (Figure 5).

Dr. Goldberg: Clinicians who rely on the classification system established by the Classification of Atrophy Meeting (CAM) group will find greater utility in OCT imaging. The CAM group's nomenclature relies on findings from OCT scans and subtypes GA into two conditions: complete RPE and outer retinal atrophy (cRORA) and incomplete RPE and outer retinal atrophy (iRORA).[26] Patients with cRORA must have all of the following:

- Hypertransmission of ≥ 250 µm (Figure 6)
- Zone of attenuation/disruption of RPE+/-Bruch's layer complex of ≥ 250 µm
- Evidence of overlying photoreceptor degeneration with features that include all of the following: outer nuclear layer thinning, external limiting membrane loss, ellipsoid zone loss
- Absence of scrolled RPE or RPE tear

If we eventually have access to a drug that can treat GA, we may find that some patients have a higher likelihood of treatment success based on lesion or disease type. Use of FAF (to subtype lesions) or OCT (to subtype stage of disease per the CAM group's scheme) may guide our treatment paradigms in that sense.

Dr. Townsend: We'll have a more in-depth discussion in the next section about pipeline candidates, but it's worth noting that a subanalysis of the phase 2 FILLY study, which examined the safety and efficacy of pegcetacoplan for the treatment of GA, found that patients who were dosed with pegcetacoplan were significantly less likely to progress from iRORA to cRORA.[27] SriniVas Sadda, MD, who helped lead the CAM group, said that "the data supports further exploration of the potential of pegcetacoplan for earlier intervention in the course of GA."[28] Further, pooled data from the phase 3 DERBY and OAKS studies evaluating pegcetacoplan found that GA lesion growth was significantly reduced among patients with extrafoveal lesions.[29]

These data point to the potential for imaging to have a role in the treatment of GA. If further data find that lesion location (ie, extrafoveal vs foveal) or maturity of disease (ie, iRORA vs cRORA) are factors in the degree to which intervention can be effective, optometrists and general ophthalmologists may develop guiding principles for referral.

Dr. Lalwani: To build off Dr. Townsend's points, we may find that halting GA progression early in the disease course—say, when a patient has iRORA or when only extrafoveal lesions are present—could be key to maximizing the potential of further therapies. Given that the CAM group's classification scheme relies on OCT imaging, it may be worth it for clinicians to refine their use and interpretation of OCT for GA diagnosis and monitoring.

Dr. Nudleman: The question of who will receive treatment is a hot topic at the moment—and I don't expect it to cool off any time soon. It will be challenging to draw a line in the sand to determine which patients receive therapy. Patients know that GA is a progressive disease, both because they have experience with slowly deteriorating quality of vision and because eye care providers have done a good job at educating them.

Retina clinics will be tasked with administering our current volume of wet AMD patients in addition to a wave of potential GA patients. Given that any therapy for GA will likely require frequent treatment, I'm unsure how the field will move forward once a therapy is approved by regulatory bodies.

Dr. Lalwani: One part of patient education will be setting expectations. Patients who grasp that they have a type of AMD that will be treated with an intravitreal injection might expect their vision to improve, the way it often does with wet AMD therapy. In the case of GA, we are halting progression, not restoring vision. Patients need to understand this, lest they end up disappointed and discouraged from continuing therapy.

Dr. Chen: In a way, GA therapy may end up being similar to glaucoma intervention, insofar that the goal is to arrest development of disease rather than reverse the course of a disease.

PIPELINE CANDIDATES FOR GEOGRAPHIC ATROPHY

Q | **Dr. Goldberg:** The treatment candidates for GA that are furthest along in the pipeline target components of the complement system, which is part of the body's immune system. What is the complement system and why is it important?

Dr. Lalwani: The complement system is comprised of three pathways: classical, lectin, and alternative (Figure 7). All three pathways converge on complement component 3, also called C3.[30] Further downstream of C3 is C5, which is cleaved via enzymatic reaction in two parts, C5a and C5b, the latter of which joins C6, C7, C8, and C9 to form membrane attack complex (MAC).[31] MAC formation results in cell death by creating a pore in a cell membrane that results in lysis.[31]

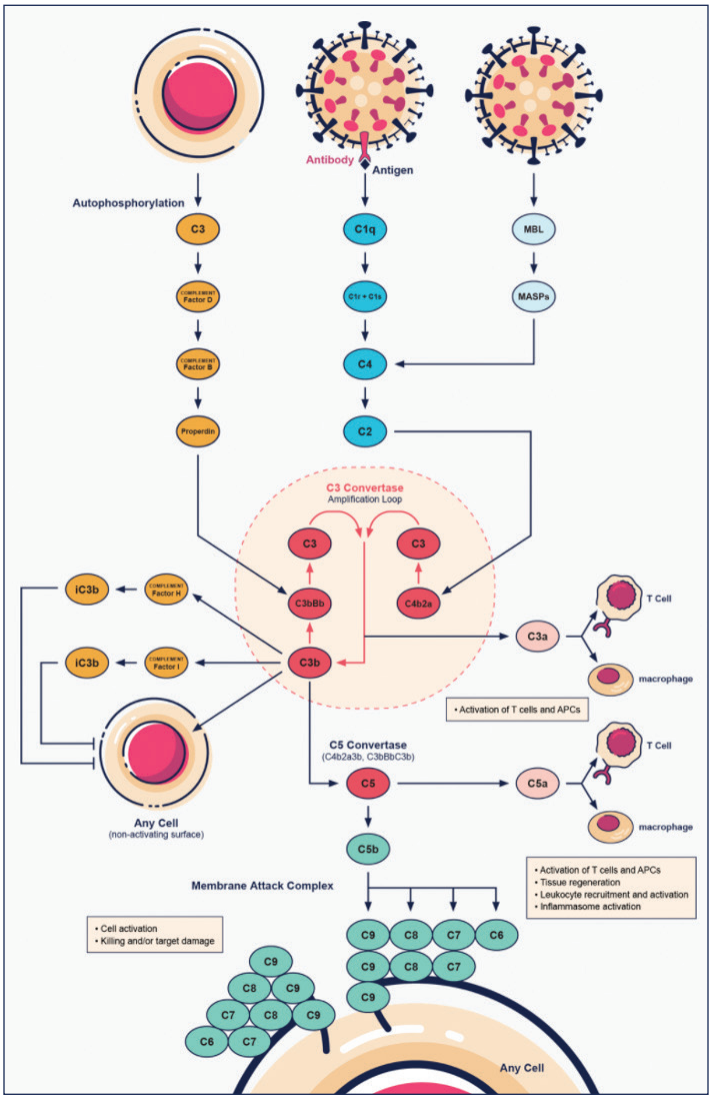

Figure 7. Pipeline candidates for GA have targeted elements of the complement cascade. All three complement pathways converge on C3, and again at C5, the cleavage of which results in the formation of MAC, leading to cell lysis and death.

Dr. Chen: I'm glad to see we're having this discussion. Eye care providers may need a refresher on the complement system, and we will require a more nuanced understanding of this biologic pathway the closer we get to a treatment for GA.

Q | **Dr. Goldberg:** Earlier in the discussion we mentioned pegcetacoplan, which has been evaluated for the treatment of GA in the phase 3 DERBY and OAKS studies. What were the findings of those studies, and what can we expect regarding submission of pegcetacoplan to regulatory bodies?

Dr. Lalwani: In the phase 3 DERBY and OAKS studies, patients were randomly assigned to receive pegcetacoplan or sham injection every month or every other month (EOM).[29]

In OAKS, a significant reduction in GA lesion growth was observed in the monthly and EOM arms compared with pooled

sham patients.[29] Among monthly patients, the reduction was 22%, and among EOM patients, the reduction was 16%.[29]

Reductions in GA lesion growth in the monthly and EOM arms were not statistically significant in DERBY.[29] However, in a prespecified analysis of the combined DERBY and OAKS datasets, researchers determined that monthly and EOM treatment significantly reduced GA lesion growth by 17% and 14%, respectively.[29]

Regarding safety, the pooled groups experienced rates of new onset exudation of 6.0% (monthly), 4.1% (EOM), and 2.4% (sham). Rates of endophthalmitis (0.05%) and intraocular inflammation (0.21%) were unremarkable.[29]

A New Drug Application is scheduled for FDA submission in the first half of 2022.[29]

Q | Dr. Goldberg: The other drug candidate that is far along in the pipeline is avacincaptad pegol. What are the latest data on that front?

Dr. Nudleman: Avacincaptad pegol targets the inhibition of C5 convertase.[32,33] Researchers in the pivotal phase 2b/3 GATHER1 study found that patients who were dosed monthly with avacincaptad pegol experienced a significant reduction in mean rate of GA growth at month 12 in low-dose (2 mg) and high-dose (4 mg) groups.[33] The drug will be evaluated a second pivotal trial, the GATHER2 study, with a final study readout at 24 months.[34]

Dr. Lalwani: I would advise anyone who wants to compare the results of the pivotal studies for pegcetacoplan and avacincaptad pegol to proceed with the caveat that the enrollment criteria for these two trials were not identical, therefore complicating any attempts at an apples-to-apples comparison. The exclusion of patients with foveal lesions in one trial but not the other, for example, creates two datasets so distinct that direct comparisons could be problematic.

Q | Dr. Goldberg: Several other drug candidates for the treatment of GA are in phase 1 and/or phase 2. Do any of the data from those drugs stand out as particularly promising?

Dr. Nudleman: Among the drugs you're referring to are the C3 inhibitor NGM621,[35] the complement factor I–targeting GT005,[36-38] the complement factor H inhibitor GEM103,[39,40] and the MAC inhibitor HMR59.[41] All of these drugs have potential to treat GA, and some have shown encouraging results in phase 1 or phase 2 studies.

Still, I would remind clinicians that past phase 1 and phase 2 studies in GA have sparked excitement, only to show that the drugs they examined were ineffective in phase 3 pivotal studies. Researchers in the phase 3 studies Chroma and Spectri, which evaluated complement factor D inhibitor lampalizumab for the treatment of GA, found that the drug did not demonstrate a statistically significant mean change from baseline in GA lesion area compared with patients in the sham arms.[42] It was a major disappointment in the eye care community, as the drug had shown promise in earlier studies. With that history lesson in mind, we are wise to wait until phase 3 studies are complete before we begin postulating how some pipeline therapies could help patients.

"We still have a long way to go—and GA trials take a long time to conduct, given the slow rate of disease progression—but we should be encouraged that the candidates in the pipeline target a variety of biologic mechanisms that may be responsible for GA."

—Michael Chen, OD

Dr. Chen: Knowing that there are so many companies working toward GA treatments is promising. We still have a long way to go—and GA trials take a long time to conduct, given the slow rate of disease progression—but we should be encouraged that the candidates in the pipeline target a variety of biologic mechanisms that may be responsible for GA.

Dr. Lalwani: I can envision future conversations in which we determine that GA is actually a variety of similar diseases that all result in an anatomically indistinguishable mechanism for tissue death. Our colleagues in oncology have experienced a reframing of cancer similar to what I just described. If that occurs in our field, we may find ourselves treating certain types of GA with gene therapy and other types with complement inhibitors.

Dr. Townsend: If that is indeed the future of GA, optometrists may be tasked with acquiring more precise data about patients at presentation. Ordering genetic testing at the point of optometric presentation could, for example, expedite the treatment process for future patients who could then present to the retina clinic for treatment with sophisticated data already in hand. ■

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GEOGRAPHIC ATROPHY: CONTEMPORARY APPROACHES TO DIAGNOSIS AND REFERRAL AND A REVIEW OF THE PIPELINE

Release Date: January 1, 2022
CME/COPE Expiration Date: January 31, 2023

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DEMOGRAPHIC INFORMATION

___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week
(with the disease targeted
in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the prevalence of AMD	_____	_____	_____
Articulate the burden of illness linked to GA	_____	_____	_____
Understand the pathogenesis of GA	_____	_____	_____
Describe disease detection and factors influencing progression	_____	_____	_____
Review the therapeutic interventions that have been explored as well as those in the pipeline	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to understand the pathogenesis of geographic atrophy (GA) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Which of the following is the No. 1 risk factor for advanced GA and age-related macular degeneration (AMD)?

a. Age
b. Family history
c. Smoking history
d. Gender

3. You are seeing an 80-year-old patient with non-neovascular AMD in both eyes. You obtain fundus autofluorescence (FAF) to better characterize her GA. After obtaining this imaging, you unfortunately find that her pattern of GA puts her at increased risk of GA progression. What pattern of abnormal FAF did she likely demonstrate?

a. Normal
b. Patchy
c. Focal
d. Trickling

4. What is the prevalence of wet and dry AMD in the United States?

a. 5 million
b. 11 million
c. 22 million
d. 33 million

5. All of the following factors play a role in the development of GA EXCEPT:

a. Diet
b. Lifestyle
c. Smoking
d. Cataract status

6. What race has the highest prevalence of AMD?

a. White
b. African American
c. Asian
d. American Indian

7. All of the following risk alleles have been linked with the development of early AMD or GA, EXCEPT?

a. CFH
b. ARMS2
c. Y402H
d. BEST2

8. Which of the following statements about depression rates and AMD is TRUE?

a. Depression rates are higher among patients with AMD and GA compared with those who do not have AMD
b. Depression rates are lower among patients with AMD and GA compared with those who do not have AMD
c. Depression rates are similar among patients with AMD and GA compared with those who do not have AMD
d. Depression rates and the presence of AMD are not correlated

9. What is a good test a clinician can use to identify reading difficulty in patients with GA?

a. Best corrected visual acuity
b. Contrast sensitivity
c. Reading speed tests
d. Humphrey visual fields

10. According to the literature, what percentage of patients with GA do not feel confident with night driving?

a. ~28%
b. ~48%
c. ~68%
d. ~88%

11. Which of the following statements about GA lesion size and progression is TRUE?

a. Larger lesions and multifocal lesions progress the fastest
b. Larger lesions progress the fastest but multifocal lesions progress the slowest
c. Larger lesions progress the slowest but multifocal lesions progress the fastest
d. Larger lesions and multifocal lesions progress the slowest

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CE/CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low_____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low_____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____
Change in nonpharmaceutical therapy _____
Change in diagnostic testing _____
Choice of treatment/management approach _____
Change in current practice for referral _____
Change in differential diagnosis _____
My practice has been reinforced _____
I do not plan to implement any new changes in practice _____

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
Would you recommend this program to your colleagues	___ Yes	___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this activity; may we contact you by email in 3 months to see if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____

_____

MODERNOPTOMETRY