# The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration

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Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that leads to progressive and irreversible loss of visual function. Geographic atrophy is defined by the presence of sharply demarcated atrophic lesions of the outer retina, resulting from loss of photoreceptors, retinal pigment epithelium (RPE), and underlying choriocapillaris. These lesions typically appear first in the perifoveal macula, initially sparing the foveal center, and over time often expand and coalesce to include the fovea. Although the kinetics of GA progression are highly variable among individual patients, a growing body of evidence suggests that specific characteristics may be important in predicting disease progression and outcomes. This review synthesizes current understanding of GA progression in AMD and the factors known or postulated to be relevant to GA lesion enlargement, including both affected and fellow eye characteristics. In addition, the roles of genetic, environmental, and demographic factors in GA lesion enlargement are discussed. Overall, GA progression rates reported in the literature for total study populations range from 0.53 to 2.6 mm$^2$/year (median, ~1.78 mm$^2$/year), assessed primarily by color fundus photography or fundus autofluorescence (FAF) imaging. Several factors that could inform an individual's disease prognosis have been replicated in multiple cohorts: baseline lesion size, lesion location, multifocality, FAF patterns, and fellow eye status. Because best-corrected visual acuity does not correspond directly to GA lesion enlargement due to possible foveal sparing, alternative assessments are being explored to capture the relationship between anatomic progression and visual function decline, including microperimetry, low-luminance visual acuity, reading speed assessments, and patient-reported outcomes. Understanding GA progression and its individual variability is critical in the design of clinical studies, in the interpretation and application of clinical trial results, and for counseling patients on how disease progression may affect their individual prognosis. *Ophthalmology 2018;125:369-390 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD), characterized by progressive and irreversible loss of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris.[1,2] Although atrophic lesions typically appear first in the perifoveal macula, sparing the foveal center, over time these lesions often expand and coalesce to include the fovea. Both the rate and the nature of GA progression are highly variable among individual patients, and evidence suggests specific characteristics may be important in predicting GA lesion enlargement.

Geographic atrophy is estimated to affect approximately 5 million globally, and its prevalence increases exponentially with age.[3,4] Geographic atrophy is typically bilateral,[5] and lesion occurrence and enlargement result in irreversible visual function loss. Perifoveal atrophy affects visual performance, including reading, driving, and low-light vision,[6−8] whereas foveal involvement may profoundly affect central visual acuity (VA).[5]

To date, there are no approved treatments to reverse, prevent, or reduce the rate of GA progression, although several potential therapies are in clinical trials. Understanding GA progression and the interindividual and intraindividual disease variability is critical for clinical trial design, interpretation and application of trial results, and counseling patients and caregivers regarding the prognosis and potential impact of GA progression on quality of life.

In this review, we synthesize the current understanding of GA progression and factors that are potentially prognostic for disease progression. We begin by reviewing methodology for identifying and monitoring GA, and summarize GA progression findings from observational and interventional studies. Subsequently, anatomic, genetic, and other potential factors associated with disease progression are discussed. Finally, we discuss the impact of GA progression on visual function.

## Defining Geographic Atrophy

Geographic atrophy secondary to AMD is currently defined by the presence of sharply demarcated atrophic lesions of the outer retina, resulting from loss of photoreceptors, RPE, and underlying choriocapillaris, leading to irreversible loss of visual function. Geographic atrophy lesions are directly visualized by multiple imaging modalities[9–16] (Fig 1), identified by specific features in each, including increased visibility of underlying choroidal vessels with a sharp-edged border (color fundus photography [CFP]), lack of lipofuscin autofluorescence (fundus autofluorescence [FAF]), and light hypertransmission through retinal layers OCT. Recently, the Classification of Atrophy Meetings group recommended that non-neovascular AMD trials include CFP, FAF, near-infrared reflectance (NIR), and spectral-domain or swept-source OCT.[15] These and other modalities for visualizing GA are discussed next.

Tables 1 and 2 summarize definitions of GA in the International Classification of Diseases (ICD) current (ICD 10th Revision; ICD 10th Revision Clinical Modification)[17–20] and proposed (ICD 11th Revision)[21] versions and as implemented in clinical and epidemiologic studies, respectively. Geographic atrophy is referred to in the literature as a form of advanced[15,22] or late[23] AMD. Minimum sizes to define atrophic patches vary; the commonly used Wisconsin Grading System includes lesions ≥175 μm in diameter.[24,25] An eye may have 1 (unifocal) or multiple (multifocal) atrophic lesions, which when summed determine the total lesion area.

The change in total GA lesion area over time (e.g., millimeters squared per year) is currently the most frequently used and accepted endpoint for assessing GA progression and efficacy of therapeutic interventions in clinical trials,[16] most of which aim to reduce the lesion enlargement rate.

### Color Fundus Photography

By CFP, GA lesions are defined as sharply demarcated areas of RPE hypopigmentation, with clear visibility of underlying choroidal vessels. The historical standard for imaging GA, CFP was the primary modality of large epidemiologic studies and disease classification systems. However, CFP cannot visualize many lesion characteristics associated with GA progression.

### Fundus Autofluorescence

By FAF (short-wavelength), GA lesions appear as areas of decreased autofluorescence (hypoautofluorescence) due to loss of RPE cells containing intrinsic fluorophores such as lipofuscin. Fundus autofluorescence imaging using a blue excitation wavelength (488 nm) and confocal scanning laser ophthalmoscopy is the predominant modality for assessing GA lesion size and progression, and is the modality currently accepted by regulators, for example, the European
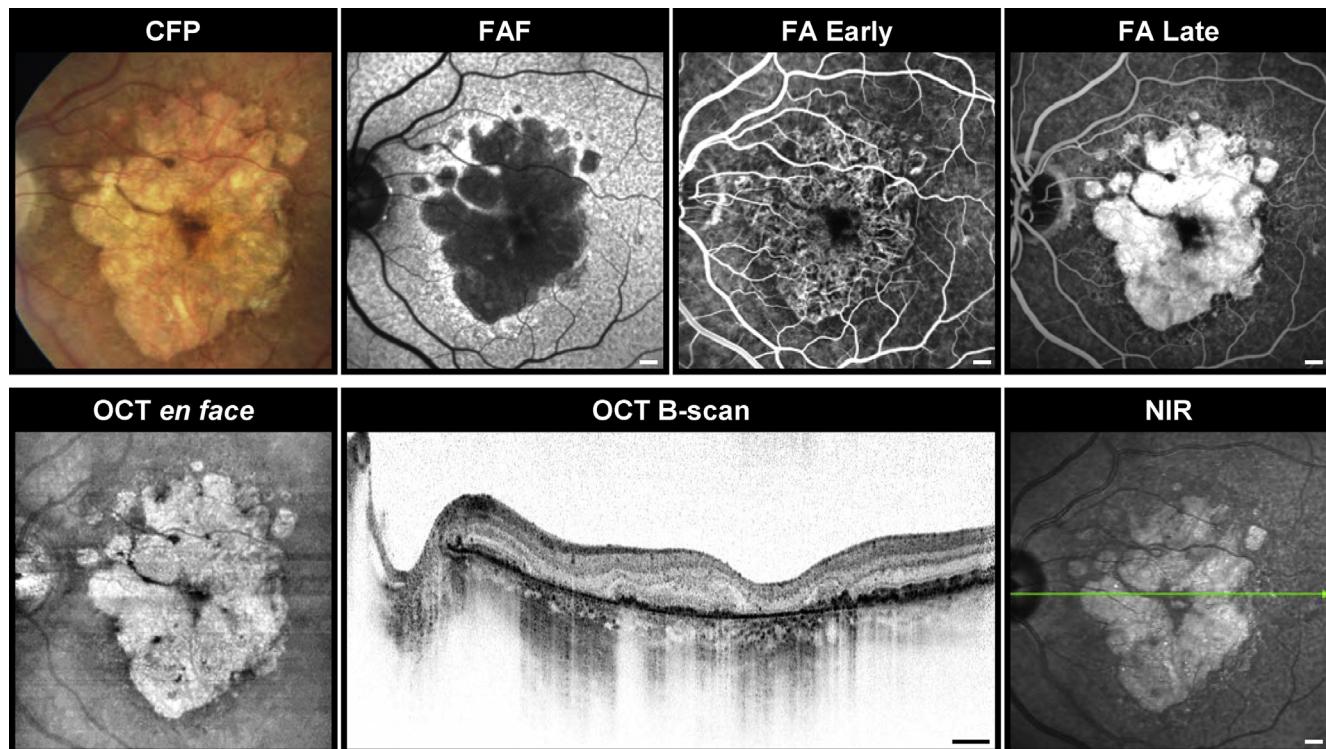


**Figure 1.** Multimodal imaging of geographic atrophy (GA). Example images of GA from 1 eye using color fundus photography (CFP), fundus autofluorescence (FAF), fluorescein angiography (FA), near-infrared reflectance (NIR), and spectral-domain OCT. Scale bars = 500 μm.

Table 1. Definitions of Nonexudative Age-Related Macular Degeneration in the International Statistical Classification of Diseases Versions 10, 11 Beta Draft, 10 Clinical Modification, and Proposed 11

| ICD-10[17] and ICD-10-CM (2016)[18] | ICD-11 Beta Draft[21] | ICD-10-CM (2017)[19,20] and Proposed ICD-11 |
|---|---|---|
| • Current international version of ICD by the WHO<br>• Former (FY2016) US version of the ICD-10-CM by the CDC | • Draft international version of ICD-11 by the WHO; revisions still in progress | • Current (FY2017) US version of the ICD-10-CM<br>• Proposed update to international version of ICD-11 by the WHO |
| **H35.31**<br>**Nonexudative AMD**<br>Any AMD with no choroidal neovascularization, including early/intermediate AMD and GA | **Early AMD**<br>Consists of a combination of multiple small drusen, few intermediate drusen (63–124 μm in diameter), or RPE abnormalities<br>**Intermediate AMD**<br>Consists of extensive intermediate drusen, at least 1 large druse (≥125 μm in diameter), or GA not involving the center of the fovea<br>**Advanced Dry AMD**<br>Characterized by ≥1 of the following (in the absence of other causes): GA of the RPE and choriocapillaris involving the center of the fovea | **H35.31X0 Stage Unspecified**<br>**H35.31X1 Early AMD**<br>Combination of multiple small drusen (≤63 μm), few intermediate drusen (>63 and ≤124 μm), or RPE abnormalities<br>**H35.31X2 Intermediate AMD**<br>Extensive intermediate drusen (>63 and ≤124 μm) or at least 1 large druse (>125 μm)<br>**H35.31X3 Advanced Atrophic AMD without Subfoveal Involvement**<br>GA not involving the center of the fovea<br>**H35.31X4 Advanced Atrophic AMD with Subfoveal Involvement**<br>GA involving the center of the fovea |

AMD = age-related macular degeneration; CDC = Centers for Disease Control and Prevention (United States); CM = Clinical Modification (used in the United States); FY = fiscal year; GA = geographic atrophy; ICD = International Classification of Diseases; RPE = retinal pigment epithelium; WHO = World Health Organization; X = 1, 2, or 3 for right eye, left eye, or bilateral, respectively.

Medicines Agency and U.S. Food and Drug Administration, for clinical trials. Flood-illuminated and green-wavelength widefield FAF systems also are available. Geographic atrophy lesions on FAF are also characterized by abnormal patterns of hyperautofluorescence surrounding the atrophic regions.[26]

Typically, FAF signals are "definitely decreased" in areas of GA, although some lesions may also present with "probable or questionable decreased FAF" as is particularly seen with the diffuse-trickling FAF phenotype (an example of this appears in Fig 5A, patient no. 3).[27] Also, as the fovea appears darker than surrounding areas in a healthy retina from normal luteal pigment, evaluating foveal integrity in the presence of GA by short-wavelength FAF alone may be challenging.[28] In these cases, adjunctive use of other imaging modalities such as NIR and OCT can be instrumental in confirming lesion boundaries.

### Near-Infrared Reflectance

Near-infrared reflectance imaging uses near-infrared wavelengths (787–820 nm), longer than FAF, which are minimally absorbed by media opacities, neurosensory layers, and macular luteal pigments. Geographic atrophy lesions on NIR usually appear brighter than nonatrophic regions, and NIR can aid in detecting foveal lesion boundaries, where image contrast appears lower on FAF.[28–30] However, subfoveal choroidal thickness can also influence NIR intensity and may introduce variability over images.[31]

### Near-Infrared Autofluorescence

By near-infrared autofluorescence, atrophic areas appear hypoautofluorescent from the lack of melanin, which is autofluorescent in the infrared spectrum and enriched in RPE cells.[32] Similar to NIR, advantages of near-infrared autofluorescence include that it is unaffected by luteal pigment, although commercial near-infrared autofluorescence devices were recently discontinued. Eyes with dark irides also have strong autofluorescence from underlying choroidal melanocytes, and therefore this signal may "wash out" areas of RPE cell loss that would otherwise appear hypoautofluorescent,[32] making atrophy borders difficult to identify.

### Fluorescein Angiography

By fluorescein angiography, GA lesions are identified as well-defined areas of early hyperfluorescence termed "window defects," created when RPE loss enhances visualization of underlying choroidal vasculature perfused with intravascular fluorescein dye. Late staining of surrounding choroidal stromal tissue may blur GA margins in later phases of fluorescein angiography, rendering its detection less precise.

### OCT

By OCT, GA lesions are generally identified by the loss of outer retinal layers corresponding to the RPE and photoreceptors. However, consensus in demarcating lesion boundaries on OCT has not yet been reached, in part because

numerous distinct lesion features are visible on both cross-sectional and en face OCT compared with purely en face modalities, including CFP and FAF. For example, "nascent GA," a drusen-associated atrophy preceding development of complete outer retinal atrophy, was identified on OCT by subsidence of the outer plexiform layer and inner nuclear layer, and a wedge-shaped band within the outer plexiform layer.[33] The GA lesion boundaries on OCT have been defined by an abrupt increase in choroidal reflectivity below Bruch's membrane from loss of absorbing outer retinal structures and RPE (choroidal hypertransmission); RPE, photoreceptor, and choriocapillaris layer loss; and external limiting membrane absence/descent.[12,14,34,35]

In addition to resolving fine retinal details, spectral-domain OCT is widely available and comfortable for patients, whereas newer swept-source OCT devices have faster acquisition and use longer wavelengths with better tissue penetration.[15] Consequently, OCT, for both cross-sectional and en face imaging, is emerging as a preferred modality to assess GA lesion features. Compared with FAF or CFP, to date fewer studies have used OCT to define GA borders or measure progression.

### OCT Angiography

OCT angiography detects blood flow by analyzing changes in tissue reflectivity occurring between rapidly acquired images, enabling 3-dimensional reconstruction of retinal and choroidal vasculature. Absence of choriocapillaris flow within a GA lesion has been reported with OCT angiography.[36–38] Alterations in choriocapillaris flow outside the GA lesion are also apparent in some eyes with GA.[36,37] However, short interscan intervals could make choriocapillaris flow reductions appear as choriocapillaris loss.[36,39]

### Multicolor Confocal Scanning Laser Ophthalmoscopy

Multicolor images are composite images acquired by simultaneous confocal scanning lasers of blue, green, and red/near-infrared wavelengths, which penetrate retinal layers at different depths: inner retina–vitreoretinal interface, retinal blood vessels/intraretinal features, and outer retina/choroid, respectively.[40] The GA lesion boundaries may be more readily identified with multicolor images than CFP[9] and with less interference from media opacities.[40]

### Methods

Studies reporting on GA progression (Table 2) and factors associated with GA progression (Tables 3 and 4) were identified via a PubMed literature search using the terms "geographic atrophy," "atrophy," "macular degeneration," "progression," "enlargement," and "growth," and sorted for relevance (detailed Supplemental Methods are available at www.aaojournal.org). Table 2 inclusion also required reporting of lesion enlargement rate; studies were excluded if they had ≤15 patients, identified patients retrospectively, did not report on an all-comers population, or were subanalyses of

an included study. Studies are plotted in Figure 2A if baseline lesion size and progression rate were reported.

## Geographic Atrophy Progression and Prognostic Factors

Overall, GA progression rates reported in the literature for total study populations range from 0.53[41] to 2.6[42] mm$^2$/year (median, ~1.78 mm$^2$/year; Table 2, Fig 2A). Within a study, GA progression rates demonstrate both interindividual and intraindividual variability (Fig 2B). Factors potentially prognostic for an individual's progression rate include lesion features in affected (Fig 3) and fellow eyes (Fig 4); genetic, environmental, and demographic factors may also contribute (Table 3).

An individual's prior progression rate is prognostic for his/her future progression rate.[42] Modeling progression in the Age-Related Eye Disease Study (AREDS) for baseline lesion sizes of ≥0.5 disc area (DA) (defined as ≥1.33 mm$^2$)[5] resulted in a linear model of lesion growth.[5]

## Lesion Features and Specific Characteristics of the Affected Eye

### Lesion Size

Baseline GA lesion size (Fig 3A) is consistently associated with progression; smaller baseline lesion size is associated with lower progression rates.[5,13,26,41,43–48] For example, in the observational study by Sunness et al,[42] lesions measuring <1.3 mm$^2$, 1.3 to 8.3 mm$^2$, and ≥8.3 mm$^2$ had progression rates of 0.8 mm$^2$/year, 2.1 mm$^2$/year, and 3.0 mm$^2$/year, respectively. In the Fundus Autofluorescence in Age-related Macular Degeneration (FAM) study, the median progression rate of the lowest baseline size quartile (0.74 mm$^2$/year for lesions <1 DA = 2.54 mm$^2$) was significantly lower than that of larger lesion quartiles (mm$^2$/year, 1–3 DAs: 1.56 mm$^2$/year; 3–5 DAs: 1.80 mm$^2$/year; 5–10 DAs: 1.88 mm$^2$/year).[26] However, it is unclear whether the association between baseline lesion size and progression rate is prognostic for an individual's disease progression or reflects heterogeneity of disease severity within a study, in which individual baseline lesion sizes range from <1 to >40 mm$^2$.[5,43,46]

Studies may report progression rates normalized for baseline lesion size, using the square-root transformation or other mathematical strategies.[47] When applied to the AREDS data set, the association between baseline lesion size and progression rate was no longer significant.[47]

### Lesion Focality and Configuration

Eyes with multifocal lesions (Fig 3A) have GA enlargement rates significantly higher than eyes with unifocal lesions (e.g., 11.97 vs. 2.24 mm$^2$/5 years[49]; 1.97 vs. 1.05 mm$^2$/year,[13] respectively).[13,48–54] In the observational study by Sunness et al,[43] eyes starting with unifocal lesions and progressing to multifocal, horseshoe, ring, or solid configurations had greater GA progression rates than eyes with a stable

Table 2. Definitions and Progression Rates of Geographic Atrophy in Observational and Interventional Studies

| Reference, Study | Study Type | Study Size | Length of Follow-up | Modality for Measuring GA | Definition of GA for Grading GA Lesions | Baseline Lesion Area, mm$^2$ | GA Enlargement Rate | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mm$^2$/y | SQRT: mm/y |
| **Interventional Studies** | | | | | | | | |
| Domalpally et al, 2016[10] AREDS2 | Interventional: vitamins, supplements | 2048e/2202p* | 5 yrs (range, 2–6 yrs) | CFP, FAF | CFP: Minimum size of drusen circle I-2 (lesion diameter ≥430 µm, area 0.15 mm$^2$) with at least 2 of circular shape, well-demarcated edges, loss of RPE. FAF: Well-defined homogenously black areas with minimum size of drusen circle I-2 (lesion diameter ≥430 µm, area 0.15 mm$^2$). | CFP: 5.5±6.4 FAF: 6.0±6.8 [N=860]* | CFP: 1.45 (SE, 0.06) FAF: 1.43 (SE, 0.06) | CFP: 0.30 FAF: 0.29 |
| Jaffe et al, 2015[54] GATE Tandospirone phase III clinical trial NCT00890097 | Interventional: tandospirone (AL8309B) | 768e/768p | 24 mos | FAF | For inclusion: well-demarcated area of atrophy with at least 1 lesion ≥1.25 mm$^2$ to total ≤20 mm$^2$ and with hyperautofluorescence adjacent to atrophy. For grading: using RegionFinder image analysis software, with the minimum lesion size of 0.05 mm$^2$. Grading by Duke and GRADE Reading Centers. | Vehicle: 7.6±4.5 AL8309B 1.0%: 7.4±4.6 AL8309B 1.75%: 7.5±4.4 | Vehicle: 1.71 (95% CI, 1.585 –1.830) AL8309B 1.0%: 1.73 (95% CI, 1.595–1.855) AL8309B 1.75%: 1.76 (95% CI, 1.626–1.890) | NR |
| Lindblad et al, 2009[5] AREDS | Interventional: early AMD/ vitamins | Total: 3640p; with GA: 251e/181p | 6 yrs [md] | CFP | General AREDS definition: definite GA definitely or questionably involving the center of the macula; minimum atrophic lesion size with a diameter of circle I-1, or 175 µm.[24] For GA progression subanalysis inclusion: Cumulative GA area ≥0.5 DAs (1.33 mm$^2$) within 1500 µm of the fovea. Central GA: definite GA involving the center point of the fovea. Grading by the University of Wisconsin Fundus Reading Center. | 5.8 (SEM, 0.42 mm$^2$) 4.3 [md] (range, 1–45) | 1.78 (SEM, 0.086) | NR |

(Continued)

Table 2. (Continued.)

| Reference, Study | Study Type | Study Size | Length of Follow-up | Modality for Measuring GA | Definition of GA for Grading GA Lesions | Baseline Lesion Area, mm$^2$ | GA Enlargement Rate | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mm$^2$/y | SQRT: mm/y |
| Mata et al, 2013[55] Fenretinide phase II clinical trial NCT00429936 | Interventional: fenretinide | 246e/246p | 24 mos | CFP | For inclusion: total atrophic area 1–8 DAs (2.54–20.32 mm$^2$), GA within 500 μm of fovea, not characterized as patchy or focal by FAF. Grading by Digital Angiographic Reading Center. | Placebo: 8.17±4.50 [md] Fenretinide 100 mg: 8.10±4.78 [md] Fenretinide 300 mg: 9.06±5.03 [md] | Placebo: 2.03±1.24 [md] Fenretinide 100 mg: 2.14±1.66 [md] Fenretinide 300 mg: 1.95±1.22 [md] | NR |
| Yaspan et al, 2017[56] Mahalo Lampalizumab phase II clinical trial NCT01229215 | Interventional: lampalizumab | 123e/123p | 18 mos | FAF, CFP | For inclusion: presence of GA in both study and fellow eyes; for the study eye, GA lesion 2.5–17.5 mm$^2$ residing completely within FAF imaging field with banded or diffuse FAF patterns adjacent to the GA lesion. For grading: GA lesion progression from baseline to 18 mos was evaluated by FAF for the primary endpoint; grading by CFP was a secondary endpoint. Grading by GRADE Reading Center (screening/inclusion) and Doheny Image Reading Center (GA lesion measurements). | FAF: Sham: 8.85±4.18 Lampalizumab 10 mg every other month: 8.56±4.90 Lampalizumab 10 mg monthly: 8.56±3.86 | Baseline to 18 mos: FAF: Sham: 2.9 mm$^{2\dagger}$ Lampalizumab 10 mg every other month: 3.1 mm$^{2\dagger}$ Lampalizumab 10 mg monthly: 2.3 mm$^{2\dagger}$ CFP: Sham: 2.8 mm$^{2\dagger}$ Lampalizumab 10 mg every other month: 2.7 mm$^{2\dagger}$ Lampalizumab 10 mg monthly: 2.2 mm$^{2\dagger}$ | Baseline to 18 mos by FAF: Sham: 0.5 mm$^2$ Lampalizumab 10 mg every other month: 0.5 mm$^2$ Lampalizumab 10 mg monthly: 0.4 mm$^2$ |
| Zhang et al, 2011[57] CNTF/NT-501 phase II clinical trial | Interventional: CNTF/NT-501 | 51e/51p | 12 mos | CFP | ≥1 Well-defined, approximately circular patch ≥175 μm in greatest linear dimension of partial or complete RPE depigmentation. Grading by Hoover Rehabilitation Services for Low Vision and Blindness, Greater Baltimore Medical Center. | Sham: 9.84±8.41 NT-501 low dose: 11.41±7.56‡ NT-501 high dose: 7.23±5.29‡ | Sham: 2.42±1.95 NT-501 low dose: 2.19±1.87‡ NT-501 high dose: 2.03±1.04‡ | NR |
| Yehoshua et al, 2014[58] COMPLETE Eculizumab phase II clinical trial NCT00935883 | Interventional: eculizumab | 30e/30p | 26 wks (primary) and 52 wks | en face SD OCT | For inclusion: total GA area 1.25–18 mm$^2$. For grading: manual tracing and imaging analysis software. Grading by Bascom Palmer Eye Institute. | Placebo: 4.6±3.6 (SQRT: 2.02±0.74 mm) Eculizumab: 7.3±4.8 (SQRT: 2.55±0.94 mm) | NR | 26 wks: Placebo: 0.18±0.15§ Eculizumab: 0.19±0.12§ 52 weeks: Placebo: 0.37±0.22§ Eculizumab: 0.37±0.21§ |

Table 2. (Continued.)

| Reference, Study | Study Type | Study Size | Length of Follow-up | Modality for Measuring GA | Definition of GA for Grading GA Lesions | Baseline Lesion Area, mm² | GA Enlargement Rate | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mm²/y | SQRT: mm/y |
| Observational Studies | | | | | | | | |
| Schmitz-Valckenberg et al, 2016[13] GAP NCT00599846 | Observational | 413e/413p | Up to 18 mos | CFP, FAF | Inclusion: unifocal or multifocal lesions with at least 1 lesion ≥1.25 mm² (0.5 DA) and total lesion size ≤17.5 mm². Areas with reduced autofluorescence signal detectable and quantifiable by semiautomated imaging analysis with the minimum lesion size of 0.05 mm². Grading by Duke and GRADE Reading Center. | FAF: 7.0±0.3 CFP: 8.4±0.3 | FAF: 1.85 (SE, 0.1)[#] CFP: 1.57 (SE, 0.1)[#] | NR |
| Holz et al, 2007[26] FAM NCT00393692 | Observational | 195e/129p | 1.8 yrs [md] | FAF | Areas with reduced autofluorescence signal detectable and quantifiable by semiautomated imaging analysis software; total area of all lesions (unifocal and multifocal). Grading by GRADE Reading Center. | 7.04 [md] (IQR, 3.12−10.0) | 1.74 1.52 [md] (IQR, 0.81−2.33) | NR |
| Klein et al, 2008[48] BDES | Large epidemiology (general population) | Total: 4926p With GA: 184e/95p Analyzed for progression: 53e/32p | 5 yrs | CFP | Wisconsin Age-Related Maculopathy Grading System protocol:[25] GA defined as sharply defined area of dropout of the RPE, exposing choroidal blood vessels, with atrophic lesions ≥ standard circle I-1 (175-μm diameter) to be considered definitely present. | 4.62±6.00[¶] | 6.35 (SE, 1.01) mm² over 5 yrs | NR |
| Sunness et al, 1999,[43] 2007[42] Wilmer Eye Institute Natural History Study | Observational | 123e/123p | 3 yrs [md] | CFP | ≥1 discrete areas of RPE loss >500 μm in greatest linear diameter. Color change relative to surrounding RPE and more prominent visualization of choroidal vessels. | 7.37 [md]** (range, 0.3−59.7)** 2.9 DAs [md] (range, 0.1−23.5 DAs) | 2.2 DAs (5.59 mm²)** over 2 yrs (range, 0−10.9 DAs for 2 yrs) 1.8 DAs [md] (4.57 mm²)** over 2 yrs | NR |
| | | 212e/131p | 4.3 yrs [md] | | | 10.4 | 2.6 2.1 [md] | NR |
| Biarnes et al, 2015[44] GAIN NCT01694095 | Observational | 109e/82p | 18 mos [md] | FAF | Inclusion: unifocal or multifocal areas of RPE atrophy on CFP with at least 1 area ≥0.5 DA (1.27 mm²). Grading: Using the Region Finder software. | 6.85 [md] (IQR, 3.14−11.88) | 1.76 (IQR, 1.01−2.44; range, 0.11−5.55) 1.62 [md] | NR |

Table 2. (Continued.)

| Reference, Study | Study Type | Study Size | Length of Follow-up | Modality for Measuring GA | Definition of GA for Grading GA Lesions | Baseline Lesion Area, mm$^2$ | GA Enlargement Rate | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mm$^2$/y | SQRT: mm/y |
| Abdillahi et al, 2014[59] | Observational | 97e/97p | NR | FAF | Inclusion: all cases with clearly detectable GA on FAF images, multifocal or unifocal. Grading performed via Region Finder software as described.[60] | 6.09±5.10 (range, 0.22–23.70) | 2.07±1.01 (range, 0.51–4.13) | NR |
| Yehoshua et al, 2011[49] | Observational | 86e/64p | 1.24 yrs | En face SD OCT | As outlined by graders on image analysis software (Adobe Photoshop; Adobe, San Jose, CA). | 4.59 3.15 [md] (range, 0.12–16.635) | 1.20±0.88 (range, 0.01–3.62) 1.03 [md] | 0.28±0.17 0.26 [md] (range 0.01–0.82) |
| Jeong et al, 2014[45] | Observational | 86e/86p | 12 mos | FAF | Well-demarcated black areas corresponding to dead/absent RPE. Excluded areas <0.02 mm$^2$. | 11.12 (range, 0.42–44.65) | 1.14 | NR |
| Joachim et al, 2013[50] BMES | Large epidemiology (general population) | Total: 3654p With GA: 82e/57p Analyzed for progression: 28e/19p | 5, 10, and 15 yrs | CFP | Grading closely followed Wisconsin Age-Related Maculopathy Grading System protocol.[25] | Baseline GA: 5.0±7.0 Incident GA: 4.6±4.5 | 1.95 | NR |
| Caire et al, 2014[61] Spanish Multicenter AMD Study | Observational | 73e/73p | 2 yrs | FAF | For inclusion: On CFP, ≥1 sharply demarcated area >175 μm within the macula with an apparent absence of RPE cells. For grading: dark atrophic regions as outlined using image analysis software (Adobe Photoshop, San Jose, CA). | NR | 1.31–1.67 | NR |
| Batioglu et al, 2014[41] | Observational | 54e/35p | 18 mos [md] | FAF | Grading performed via Region Finder software as described.[60] | 2.46 [md] (range, 0.16–19.3) | 0.53 [md] (range, 0–2.50) | NR |
| Simader et al, 2014[14] | Observational | 48e/24p | 12 mos | FAF | Inclusion: bilateral GA with at least 1 GA lesion ≥1.25 mm$^2$. Grading: as recognized by imaging analysis software region overlay device of the (Heidelberg Eye Explorer, Heidelberg, Germany). Grading by Vienna Reading Center. | 8.88±8.91 | 2.34 (total at 12 mos: 11.22±10.53) | NR |

Table 2. (Continued.)

| Reference, Study | Study Type | Study Size | Length of Follow-up | Modality for Measuring GA | Definition of GA for Grading GA Lesions | Baseline Lesion Area, mm² | GA Enlargement Rate | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mm²/y | SQRT: mm/y |
| Nunes et al, 2013[62] | Observational | 30e/30p | 1 year | En face SD OCT | Inclusion: at least 1 eye with GA lesion 1.25−18 mm². Grading: as recognized by imaging analysis software (Adobe Photoshop) and manual tracing.[49] | SQRT: 2.37±0.90 mm | NR | 0.37±0.21 |
| Stetson et al, 2014[63] | Observational | 24e/24p | 52 weeks | En face OCT | Inclusion: at least 1 eye with GA lesion 1.25−18 mm². Grading: presence of areas of increased Illumination below the RPE; manually traced from sub-RPE slabs. | SQRT: 2.0±0.78 | NR | 0.4±0.24 |

Values are mean ± standard deviation unless otherwise specified. The GA enlargement rates provided as millimeters squared per year or SQRT as millimeters per year unless these values were not reported as such in the cited study.

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; BDES = Beaver Dam Eye Study; BMES = Blue Mountains Eye Study; CI = confidence interval; CFP = color fundus photography; CNTF = ciliary neurotrophic factor; COMPLETE = Complement Inhibition with Eculizumab for the Treatment of Nonexudative Age-Related Macular Degeneration; DA = disc area; e = eyes; FAF = fundus autofluorescence; FAM = Fundus Autofluorescence in Age-related Macular Degeneration; GA = geographic atrophy; GAIN = Characterization of Geographic Atrophy Progression in Patients with Age-Related Macular Degeneration; GAP = Geographic Atrophy Progression; GATE = Geographic Atrophy Treatment Evaluation; IQR = interquartile range; md = median; NR = not reported; p = patients; RPE = retinal pigment epithelium; SD = spectral domain; SE = standard error; SEM = standard error of the mean; SQRT = square-root transformation.

*GA was detected in 2048 eyes by FAF and in 1693 eyes by CFP from a total of 2202 participants with varying follow-up. Baseline GA area reported only for eyes with GA detectable on both CFP and FAF (N = 860).[10]

†GA lesion progression reported as adjusted mean change from baseline to 18 months, that is, least-squares mean change adjusted for baseline GA area.[56]

‡NT-501 implants released CNTF at either 5 ng/day (low dose) or 20 ng/day (high dose) before implant.

§The 2 eculizumab treatment groups were pooled for analysis (n = 10 each), receiving either eculizumab (group 1) 600 mg or (group 2) 900 mg weekly for 4 weeks, followed by (group 1) 900 mg or (group 2) 1200 mg every 2 weeks until week 24.

¶Lesion size change from baseline at 12 months; annualized GA progression rate through 18 months (or early exit) not reported.[13]

#Size of GA lesion at visit of first detection.[48]

**Calculated from 1 DA = 2.54 mm², using the definition provided in Sunness et al, 1999.[43]
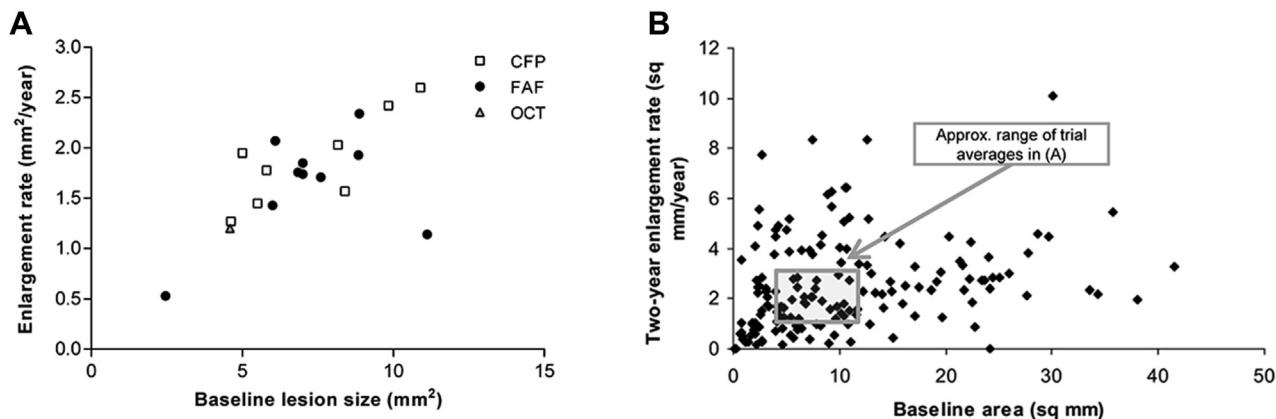
**Figure 2.** Progression rates of geographic atrophy (GA) in the literature. **A,** Values of GA enlargement rates for studies included in Table 2, plotted against baseline lesion size. When available, mean values were selected over median values. If not provided in the reference, annualized GA enlargement rates were calculated from the available values (e.g., derived the 1-year from a 2-year rate). For interventional trials, the sham/placebo/vehicle arms are plotted. **B,** Rates of GA progression from individuals from the natural history study by Sunness et al.[42] Inset box shows the range of average values from (**A**); note the variability in individual enlargement rates and how enlargement rates for most individuals fall outside of the average range. Reprinted from *Ophthalmology*, Sunness et al,[42] "The Long-Term Natural History of Geographic Atrophy from Age-Related Macular Degeneration: Enlargement of Atrophy and Implications for Interventional Clinical Trials." Pages 271-277, copyright (2007) with permission from Elsevier. CFP = color fundus photography; FAF = fundus autofluorescence.

configuration. To quantify this, a GA circularity index (GACI) was proposed based on GA lesion perimeter and deviation from circularity.[51] Eyes with the lowest GACI (i.e., lesions deviating most from a circle) were generally multifocal and had higher progression rates versus eyes with higher GACI (square-root transformation, GACI $<0.25$ vs. $>0.75$: 0.40 vs. 0.21 mm/year; $P < 0.001$).[51]

### Lesion Location

Extrafoveal GA lesions progress faster than foveal lesions (Figs 3A, 5B). In the Geographic Atrophy Progression study, extrafoveal versus foveal (300-µm diameter foveal-centered circle) lesions progressed at significantly greater rates (2.05 vs. 1.28 mm$^2$/year, respectively; $P = 0.001$).[13] An analysis of directional progression kinetics among FAM study patients with baseline foveal sparing also revealed that lesion progression toward the periphery was 2.8-fold faster than progression toward the fovea (square-root transformation: 0.319 vs. 0.116 mm/year, respectively).[28]

Geographic atrophy lesions may grow into foveal-surrounding horseshoe or ring shapes.[43] The progression of GA from first appearance to foveal center involvement has been reported to occur over 2.5 years (median),[5] although patients may have foveal GA at initial diagnosis.[5,48] Among other hypotheses, it was speculated that preferential foveal sparing reflects the relatively lower susceptibility of cone versus rod photoreceptors to cell death.[64,65]

### Fundus Autofluorescence Patterns

In most eyes, the dark, hypoautofluorescent patches signifying GA lesions are surrounded by varying degrees of hyperautofluorescence, particularly at junctional regions of atrophy. Because hyperautofluorescence can indicate lipofuscin density, it has been hypothesized that excessive lipofuscin accumulation contributes to GA pathogenesis.[66] Alternatively,

histologic studies suggest hyperautofluorescence reflects a clumping or vertical stacking of fluorophore-containing cells, and FAF patterns may reflect disorganization of cellular layers.[67,68]

The FAM study investigated the correlation between FAF hyperautofluorescence patterns and GA progression rates as its primary objective.[26] The FAF patterns (Fig 3A) were classified as none, focal, banded, patchy, or diffuse; diffuse patterns were further categorized as reticular, branching, fine-granular, fine-granular with peripheral punctate spots, or trickling.[26] At baseline, more than half of eyes displayed diffuse FAF patterns. The GA progression rate was associated with FAF patterns, with the lowest observed in eyes with no or focal patterns and the highest with banded or diffuse patterns (median, 0.38, 0.81, 1.81, 1.77 mm$^2$/year, respectively; none + focal vs. banded + diffuse, $P < 0.0001$). Eyes with the diffuse-trickling pattern represented a subgroup with particularly rapid progression (median, 3.02 mm$^2$/year).[26] This relationship between FAF patterns and GA progression rate has been replicated to some extent in other cohorts.[13,41,45,52]

The Characterization of Geographic Atrophy Progression in Patients with Age-related Macular Degeneration (GAIN) study reported that FAF patterns are associated with the GA progression rate, but also with baseline lesion size and follow-up duration.[44] Eyes with a focal pattern or no FAF changes had smaller baseline GA areas than eyes with banded or diffuse patterns. The authors speculated that FAF patterns reflect disease severity or duration and may evolve from no FAF changes or focal pattern to diffuse or banded patterns.[44] Whether there is a spatial correlation between FAF patterns and future location of GA lesion development or extension is currently unclear.[26,66,69] Further longitudinal studies following an individual's FAF pattern over time are needed to elucidate the relationship between FAF patterns and GA progression.
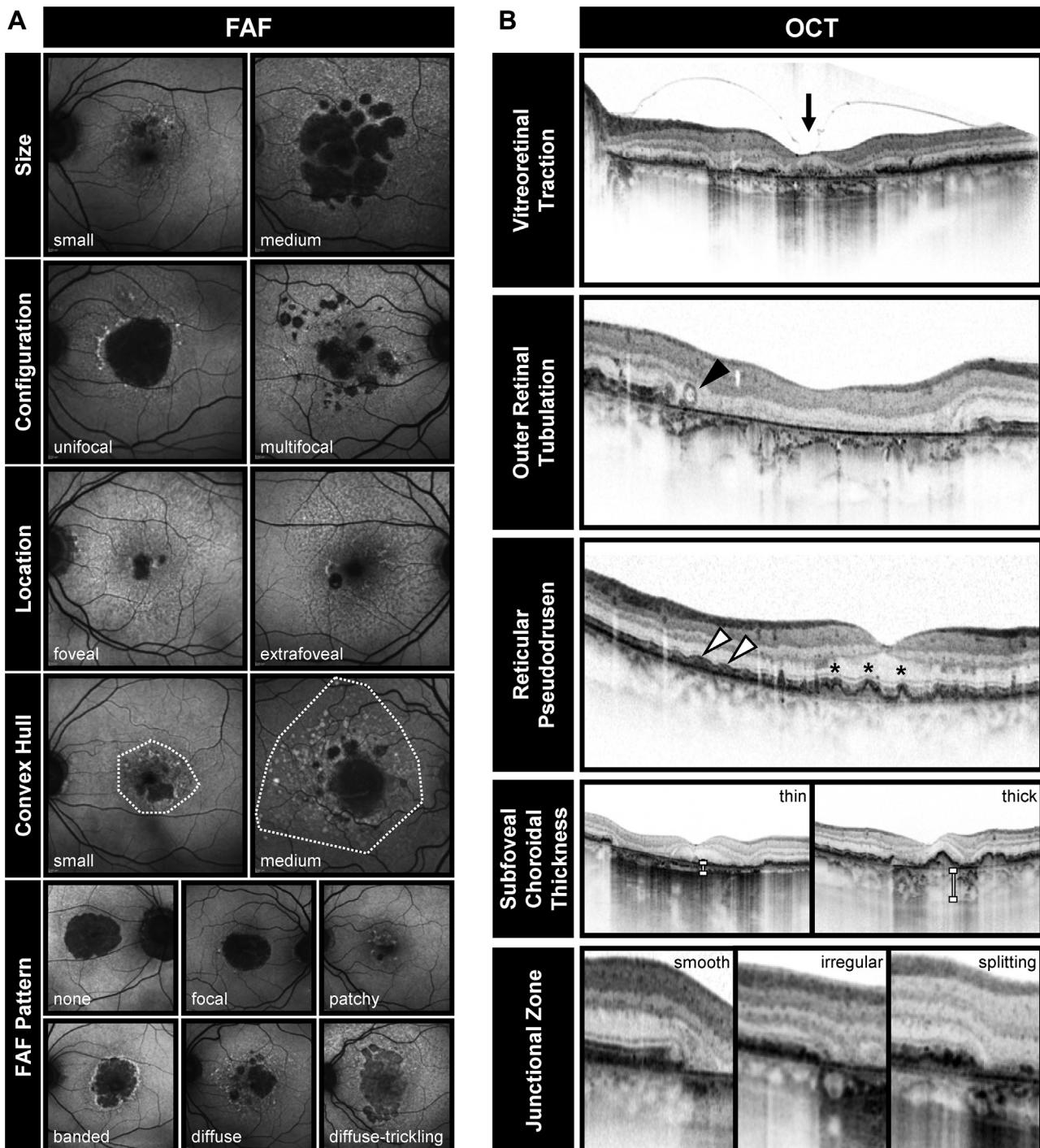
**Figure 3.** Lesion features associated with progression of geographic atrophy (GA). Lesion features on (**A**) fundus autofluorescence (FAF) and (**B**) OCT. *Dotted line:* extent of convex hull; *black arrow:* vitreoretinal traction; *black arrowhead:* outer retinal tubulation; *white arrowheads:* reticular pseudodrusen; *asterisks:* soft drusen; *vertical bar:* choroidal thickness.

## Extent of Abnormal Fundus Autofluorescence

Geographic atrophy progression rates have been positively correlated with the extent of hyperautofluorescence surrounding the lesion, defined as rim-area focal hyperfluorescence[70,71] or as the convex hull (convex polygon outlining the increased FAF area surrounding the lesion) ([Fig 3](#)A).[72]

## Junctional Zone Features

Structural abnormalities at the junctional zone of atrophy on OCT, including irregular RPE elevations,[52] splitting of the band corresponding to the RPE–Bruch's membrane complex,[52] and increased inner nuclear layer thickness,[73] are associated with faster progression rates compared with
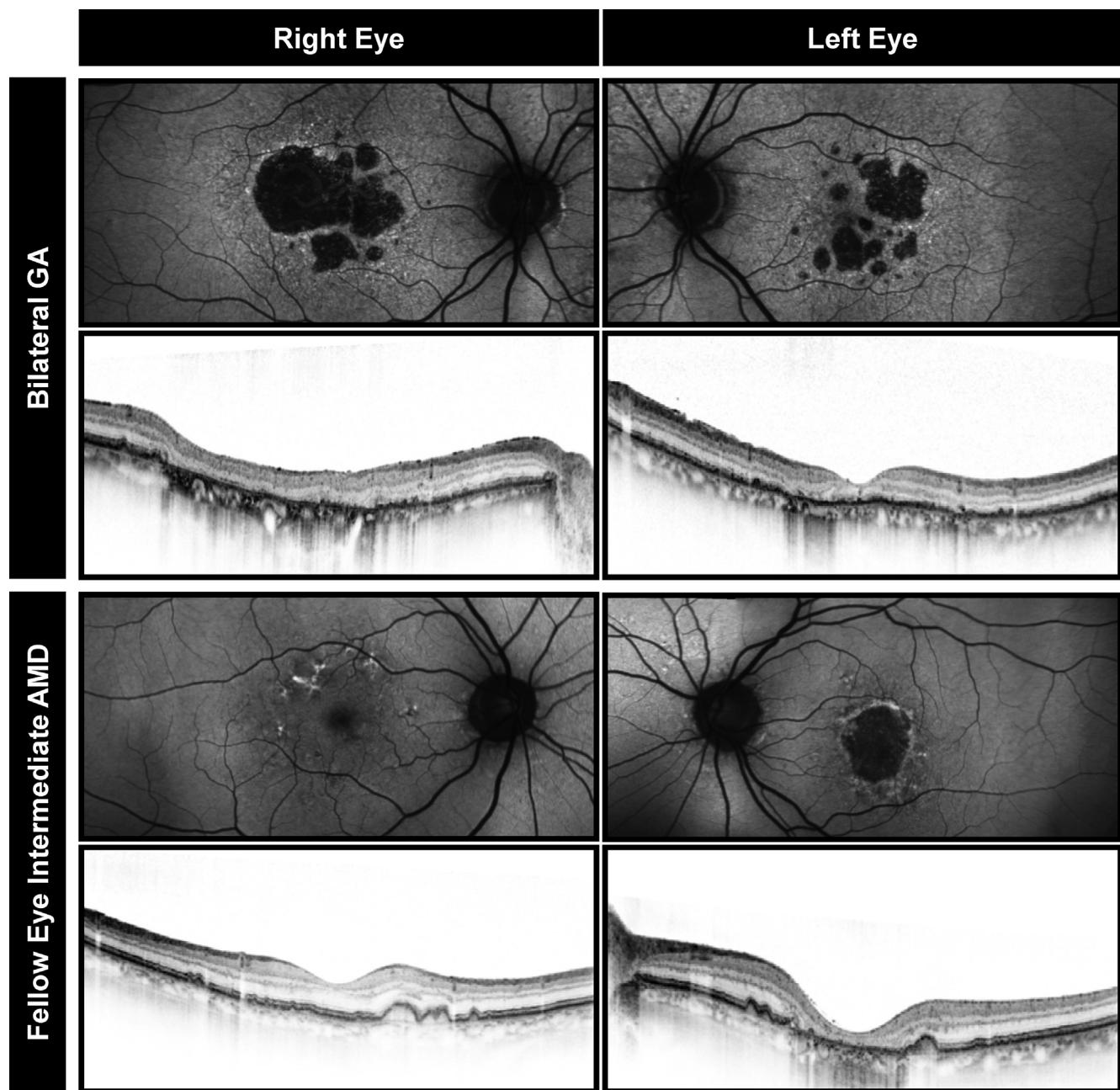
**Figure 4.** Fellow eye features associated with geographic atrophy (GA) progression rate in the affected eye. Fundus autofluorescence and OCT images from left and right eyes of the same patient. **Top,** Bilateral GA; both eyes are at risk for a relatively higher rate of GA lesion progression. **Bottom,** Geographic atrophy in the affected eye (*left*) and intermediate age-related macular degeneration (AMD) in the fellow eye (*right*); the affected eye is at risk for a relatively lower rate of GA lesion progression.

lesions with smooth margins (Fig 3B). Splitting of the RPE–Bruch's membrane complex band is also seen in eyes with the rapid-progressing diffuse-trickling phenotype seen on FAF.[27] These features correlate with hyperautofluorescent areas on FAF[74] and may reflect the presence of excessive basal laminar deposits detectable once a critical vertical extension of extracellular material is reached.[27]

## OCT Minimum Intensity

Minimum intensity is the lowest image intensity from each A-scan from the sub-RPE slab region. Excluding the fovea, minimum intensity values were significantly higher in areas of lesion growth and correlated with overall progression rate. Areas of increased minimum intensity corresponded to
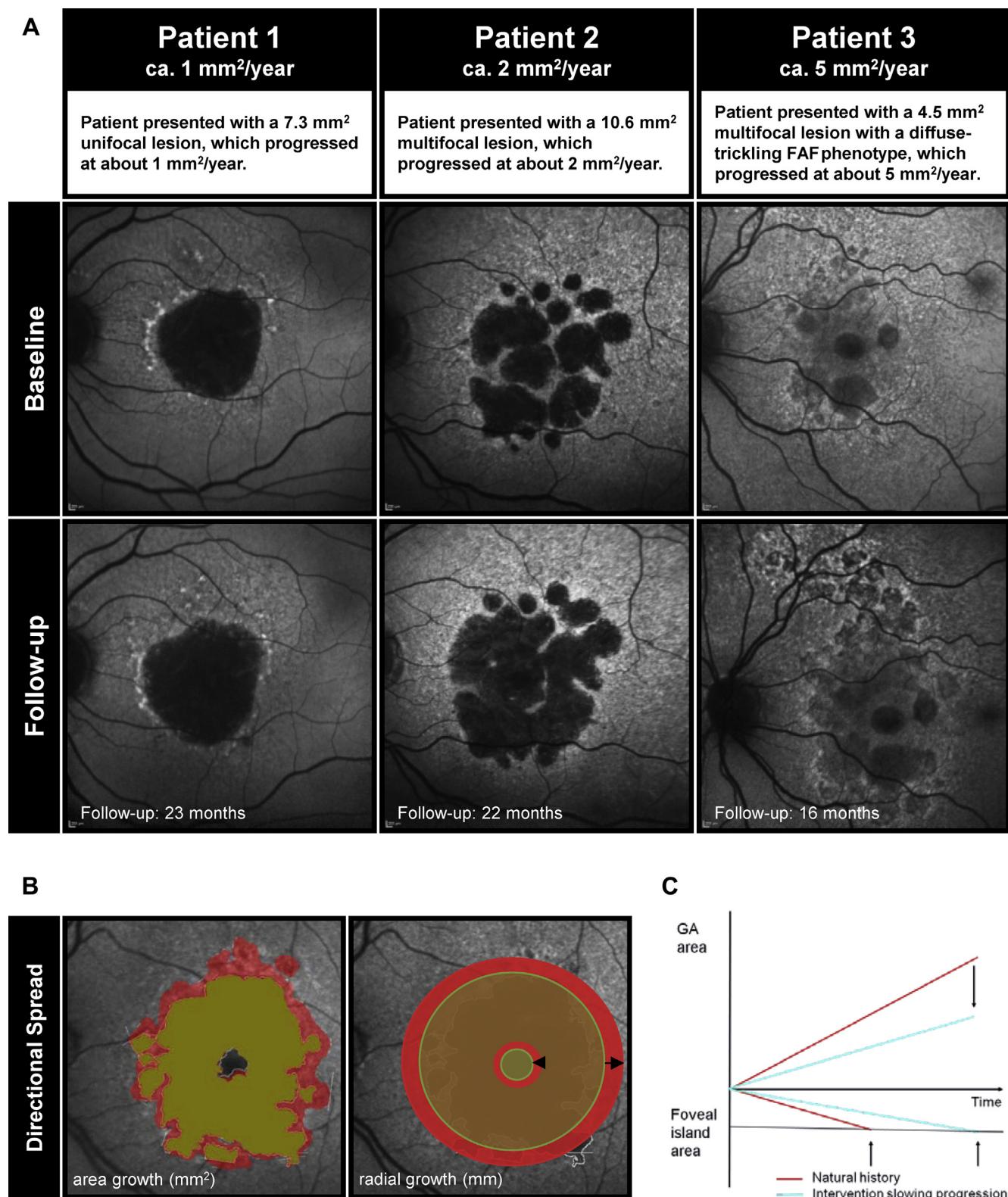
**Figure 5.** Progression of geographic atrophy (GA). **A,** Fundus autofluorescence (FAF) images from 3 patients presenting with different lesion types and their GA lesion progression rates from baseline to follow-up. **B,** Projected directional spread of atrophy; note greater spread of atrophy in the periphery than toward the center.[28] **C,** The diagram drafts the potential impact of interventions that reduce overall GA progression on total GA area and on the relatively longer preservation of the spared fovea (foveal island area).

Table 3. Demographic, Environmental, and Genetic Factors Evaluated for Association with Geographic Atrophy Progression

| Publication | Lindblad et al, 2009[5] | Yehoshua et al, 2015[76] | Yaspan et al, 2017[56] | Holz et al, 2007[26] | Klein et al, 2008[48] | Klein et al, 2010[77] | Biarnes et al, 2015[44] | Jeong et al, 2014[45] | Joachim et al, 2013[50] | Caire et al, 2014[61] | Grassmann et al, 2015[78] | Scholl et al, 2009[79] | Fleckenstein et al, 2016[80] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient cohort (study) | AREDS | COMPLETE | Mahalo | FAM | BDES | AREDS | GAIN | Patients at Kangdong Sacred Heart Hospital, Seoul, Korea | BMES | Spanish multicenter | AREDS and FAM | FAM | FAM |
| No. of patients included in risk factor analysis | 181 | 30 | 29* | 129 | 32 | 114 | 82 | 86 | 26 | 73 | 388 | 99 | 355 |
| **Demographics and environmental factors** | | | | | | | | | | | | | |
| Age | N | | | N | N | | N | N | | ↑ [RP] | N | | |
| Gender | N | | | | N | | N | N | | ↑ [RP] | N | | |
| Race | | | | | | | | | | | | | |
| Smoking | N | | | N | N | | N | | ↑† | ↑ [RP] | | | |
| Body mass index | N | | | N | N | | N | | | ↑ [RP] | | | |
| Hypertension/blood pressure | | | | N | N | | N | N | | | | | |
| Diabetes | | | | N | | | | N | | | | | |
| Heavy drinking status | | | | | N | | | | | | | | |
| Hyperlipidemia | | | | N | | | | | | | | | |
| Hypercholesterolemia | | | | | | | | | | | | | |
| Sedentary lifestyle | | | | | N | | | | | | | | |
| **Genetic factors/single nucleotide polymorphisms** | | | | | | | | | | | | | |
| Family history of AMD | | | | N | | | N | | | | | | |
| CFH (rs1061170) c.402His | | | | | | N | | | ↑† | ↑ [RP] | N | N | ↑ [DT] |
| CFH (rs800292) | | | | | | | | | | | N | N | ↑ [DT] |
| CFH (rs88292) c.62Ile | | | | | | | | | | ↓ [RP] | | | |
| CFH (rs1410996) c.2237-543G | | | | | | | | | | | | | |
| CFH (rs6677604) | | | | | | | | | | | N | | N [DT] |
| ARMS2/LOC387715 (rs10490924) c.69Ala | | | | | | ↑ | | | N† | | ↑ | N | N [DT] |
| C3 (rs2230199) | | | N* | | | N | | | | | ↓ | N | N [DT] |
| C3 (rs4151667) c.102Gly | | | | | | | | | | N | | | N [DT] |
| C2 (rs9332739) | | | | | | N | | | | | | | |
| APOE (rs7412) | | | | | | N | | | | | N | | N [DT] |
| APOE (rs429358) | | | | | | N | | | | | N | | N [DT] |
| TLR3 (rs3775291) | | | | | | N | | | | | | | |
| CFB (rs4151667) c.9His | | | | | | | | | | | N | | N [DT] |
| CFB (rs12614, rs641153) c.32Gln | | | | | | | | | | ↓[RG] | | | |

Table 3. (Continued.)

| Publication | Lindblad et al, 2009[5] | Yehoshua et al, 2015[76] | Yaspan et al, 2017[56] | Holz et al, 2007[26] | Klein et al, 2008[48] | Klein et al, 2010[77] | Biarnes et al, 2015[44] | Jeong et al, 2014[45] | Joachim et al, 2013[50] | Caire et al, 2014[61] | Grassmann et al, 2015[78] | Scholl et al, 2009[79] | Fleckenstein et al, 2016[80] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Genetic factors/single nucleotide polymorphisms (Continued) | | | | | | | | | | | | | |
| CFB (rs438999) | | | | | | | | | | | | | N [DT] |
| CFI (rs2285714) | | N | | | | | | | | | N | | |
| CFI (rs17440077) | | | ↑* | | | | | | | | N | | N [DT] |
| PLA2G12A_ rs2285714 | | | | | | | | | | | | | |

Some patient cohorts were analyzed in multiple publications, as noted in the table.
AMD = Age-related macular degeneration; AREDS = Age-Related Eye Disease Study; BDES = Beaver Dam Eye Study; BMES = Blue Mountains Eye Study; COMPLETE = Complement Inhibition with Eculizumab for the Treatment of Nonexudative Age-Related Macular Degeneration; DT = associated with diffuse-trickling phenotype versus non-diffuse-trickling phenotype (specific to Fleckenstein et al, 2016[80]); FAM = Fundus Autofluorescence in Age-related Macular Degeneration; GA = geographic atrophy; GAIN = Characterization of Geographic Atrophy Progression in Patients with Age-Related Macular Degeneration; N = not significant: variable was analyzed and reported as not associated with geographic atrophy progression; RG = relative growth: reported as significantly associated with the relative growth of a geographic atrophy lesion over baseline (specific to Caire et al, 2014[61]); RP = rate of progression: reported as significantly associated with the rate of geographic atrophy lesion progression (specific to Caire et al, 2014[61]); SNP = single nucleotide polymorphism; ↑ = significantly associated with increased risk of geographic atrophy progression; ↓ = significantly associated with decreased risk of geographic atrophy progression.
*Patients (n = 29) evaluated in the sham treatment group for association of GA progression with the C3 (rs2230199) and CFI (rs17440077) SNPs. Similar results were reported within the lampalizumab monthly treatment group (n=25). Statistical significance was not calculated for the effect of the SNP on GA progression within the sham treatment arm.[76]
†Significance not calculated; no statistics provided in publication.

hyperreflectivity, or atrophy, of the outer nuclear/Henle fiber layers on cross-sectional scans.[63]

## Ellipsoid Zone Disruption

The area of ellipsoid zone disruption on OCT may predict the location of future GA progression, but not progression rate.[81] In a study assessing the ellipsoid zone using en face OCT, 43% of eyes demonstrated a pattern of disruption outside the baseline GA lesion that predicted the 1-year location of GA progression.[62]

## Outer Retinal Tubulations

Outer retinal tubulations (Fig 3B) are branching tubular structures in the outer nuclear layer oriented parallel to en face OCT scans, appearing as circles on cross-sectional scans.[82–84] Composed of surviving cone photoreceptors enclosed by Müller glial processes, outer retinal tubulations are a degenerative response to outer retinal injury in areas of RPE loss.[82–84] The presence[52] and absence[85] of outer retinal tubulations were both reported with greater GA enlargement rates; the reason for this conflict is unclear and requires further study.

## Choroidal Thickness

In a small cohort, reduced subfoveal choroidal thickness correlated with higher progression rates.[86] In addition, the fast-progressing diffuse-trickling FAF pattern demonstrates a significantly thinner choroid than non-diffuse-trickling phenotypes.[87] Overall, eyes with GA have reduced subfoveal choroidal thickness compared with age-matched healthy eyes,[87–89] although one study reported this reduction was limited to the group of eyes with reticular pseudodrusen.[89]

## Vitreoretinal Traction

Vitreoretinal traction (Fig 3B) on OCT is associated with GA progression (presence vs. absence, 2.99 vs. 1.45 mm$^2$/year; $P < 0.001$).[59] Mechanical stress of vitreoretinal traction may affect the natural history of GA; structural distortion of the RPE layer has been hypothesized.[59]

## Reticular Pseudodrusen

Eyes with GA have a high prevalence of reticular pseudodrusen (Fig 3B),[47,90–92] which correlate with subretinal drusenoid deposits anterior to the RPE layer on OCT and histopathology.[93,94] Their presence strongly associates with the progression of intermediate AMD to GA,[50,92,95–97] but might not correlate with GA lesion progression rates.[98] Reticular pseudodrusen regression is associated with outer retinal atrophy development in some eyes[99] and may predict future locations of GA development.[47,53] Reticular pseudodrusen are also associated with the development of multifocal lesion configurations,[47,53] which progress faster than unifocal configurations.[13–15,20,21,24–26]

Table 4. Lesion Characteristics Identified as Prognostic for Geographic Atrophy Progression Rate or Location

| | Lesion Characteristics Prognostic for Higher Progression Rate | Locations with High Risk of Future Lesion Development |
|---|---|---|
| Affected eye | High evidence:<br>• Larger baseline lesion size[5,13,26,41–47]<br>• Multifocal lesion[13,47–53]<br>• Perilesional FAF pattern = banded, diffuse (diffuse-trickling)[13,26,41,44,45,52]<br>• Nonfoveal location; progression toward the periphery[1,13,28,42,43]<br><br>Moderate evidence:<br>• Prior higher progression rate[42]<br>• Greater extent of abnormal hyperautofluorescence[70–72]<br>• Structural abnormalities at the junctional zone by OCT[27,52,73]<br><br>Low evidence:<br>• Presence of vitreoretinal traction[59]<br>• Presence of outer retinal tubulations[52,85] | Moderate evidence:<br>• Reticular pseudodrusen presence[47,53]<br><br>Low evidence:<br>• Ellipsoid zone disruption[62,81] |
| Fellow eye | High evidence:<br>• Bilateral GA[42,78,101]<br>• Higher progression rate in fellow eye[5,42,43,100]<br><br>Moderate evidence:<br>• CNV in the fellow eye[42,101] | |

Characteristics were rated as "high," "moderate," or "low" based on the available evidence to date supporting their association with GA progression. High: factor was identified as significantly associated with GA progression in multiple studies, including large prospective trials identified in Table 2. Low: factor was identified as significantly associated with GA progression in 1 or 2 small studies, or with conflicting evidence. Moderate: evidence for significant association of intermediate quality.
CNV = choroidal neovascularization; FAF = fundus autofluorescence; GA = geographic atrophy.

## Fellow Eye Characteristics

The presence of GA in 1 eye is a strong predictor of future GA in the second eye. In AREDS, the median time from unilateral to bilateral GA was estimated at 7 years.[5] Overall, intereye progression rates are highly correlated among patients with bilateral GA, although there is some individual variability.[5,42,43,100] Fellow-eye disease status also associates with progression; GA progresses at greater rates when the fellow eye has GA (bilateral GA), lower rates when the fellow eye has early/intermediate AMD, and intermediate rates when the fellow eye has choroidal neovascularization.[42,78,101]

## Genetic, Environmental, and Demographic Factors

Although many studies have identified genetic, environmental, and demographic characteristics associated with GA development, evidence for their effect on GA progression is sparse. No consistent demographic or environmental factors have been linked to GA progression rate, including age, gender, hypertension, or diabetes (Table 3). Smoking status predicted faster GA progression in the Blue Mountains Eye Study[49] and Multicenter Group on AMD[61] cohorts, but not in FAM[26] or AREDS.[5] Different findings among studies may reflect the patient populations, cohort size, or variable collection and analysis methods.

There is strong evidence for a role for genetics in the development of advanced AMD.[102,103] The largest genome-wide association study to date identified 52 variants in 34 loci involved in the complement cascade, lipid metabolism, extracellular matrix remodeling, and other pathways, nearly all of which confer a similar risk of neovascular AMD and GA.[75]

In contrast, no single nucleotide polymorphism examined has been consistently linked to GA progression rate (Table 3). Of note, ARMS2_rs10490924 was significantly associated with increased GA progression in the AREDS[77] and AREDS + FAM[78] combined cohorts, but not in the FAM cohort alone.[78,79] Single nucleotide polymorphisms in C3,[78] CFH,[50,61] CFI,[56] and CFB[61] have also been linked to GA progression, but the results have not been replicated. Additional large studies with appropriate controls for potential confounders are needed to confirm these findings. To this end, several ongoing interventional and observational studies are prospectively evaluating potential effects of genetic factors on GA progression.[104]

## Geographic Atrophy Progression and Visual Function

Although GA lesion enlargement is the most widely used and reproducible assessment of GA progression, it also correlates with visual function decline and thus disease severity. Best-corrected VA (BCVA), the standard vision assessment, often underrepresents functional deficits.[43]

Paracentral scotomas may substantially reduce the visual field, yet, depending on the extent of foveal sparing, patients may retain the ability to read individual letters and thus have relatively preserved BCVA.[7] Accordingly, there is not a robust correlation between BCVA changes and lesion enlargement.[13]

Several alternative measures are being explored to capture the full visual deficit in GA, including microperimetry, low-luminance VA (LLVA), reading speed, and patient-reported outcomes.

### Microperimetry

Microperimetry, which measures threshold light sensitivity at multiple points over the macula, can assess visual function loss associated with GA progression. Decreases in retinal sensitivity occur as GA progresses[105–107] and correlate with lesion enlargement over time.[108] The decrease in retinal sensitivity over the junctional zone can be abrupt, although nonatrophic regions in eyes with GA show reduced retinal sensitivity compared with eyes without evident atrophy.[109] Retinal sensitivity reductions are observed with increased autofluorescence in the junctional zone on FAF[110] and observations by OCT, including external limiting membrane loss,[111] RPE elevation,[112] inner-segment ellipsoid band integrity loss,[112] and the presence of hyperreflective foci.[112] Clinical trials are beginning to incorporate microperimetry as a secondary endpoint to validate its utility to monitor GA progression.[16,113,114]

### Low-Luminance Visual Acuity

Low-luminance VA measures visual function under reduced illumination. Deficits in LLVA are associated with higher GA lesion progression rates.[58] The difference between BCVA and LLVA, the "low luminance deficit," may predict subsequent VA loss.[7]

### Reading Speed

Reading speed reflects the extent of the visual field, that is, whether the central visual field is preserved enough to read entire words or sentences versus individual letters.[7] Maximum reading rate correlates with GA area[115,116] and worsens as GA progresses.[115] Low maximum reading rate (≤96 vs. 97–141 words per minute) at baseline was a significant risk factor for ≥3-line VA loss at 2 years.[7] Reading speed may serve as an important functional marker of GA progression and a potential predictor of future visual function loss.

### Patient-Reported Outcomes

Questionnaire-based methods for measuring visual function have been applied to AMD, including the 25-item National Eye Institute Visual Function Questionnaire[117] and Activities of Daily Vision Scale.[118] These assess the patient's perception of how his/her visual deficit affects daily activities, including recognizing faces, driving, or reading newspapers.[119,120] The Functional Reading Independence Index was developed for patients with GA; the Functional Reading Independence Index score decreased more in patients with greater lesion enlargement over 18 months.[121] The Functional Reading Independence Index and reading speed have received support from the European Medicines Agency to promote data sharing for eventual qualification as a novel methodology.[122] Future studies will need to assess how changes in patient-reported outcomes correlate with GA progression.

## Discussion

Geographic atrophy is an irreversible, progressive, bilateral, vision-threatening disorder, but how, when, and to what degree GA compromises visual function depends not only on the lesion size but also on the rate, location, and directionality of lesion enlargement (Fig 5). In this review, we discussed factors associated with the rate and future location of GA lesion progression (Table 4).

There is considerable interpatient variability in GA progression rates (Fig 2B), whereas average rates from various studies fall into a fairly narrow range (Table 2).[5,10,13,14,26,41–45,48–50,54–59,61–63] In addition, GA affects visual function in different ways and time scales. This review discussed factors that could inform an individual's prognosis, several of which were replicated in multiple cohorts: baseline lesion size, lesion location, multifocality, FAF patterns, and fellow-eye status (Table 4). These identified prognostic factors are not necessarily independent and may describe different features of GA phenotypes. Identification of prognostic factors for disease severity and progression can inform models of disease progression[123] and may reflect differences in the pathophysiologic mechanisms of GA.

For the first time, several therapeutic agents for GA are in phase II and III clinical trials, including complement pathway inhibitors, agents targeting oxidative stress or inflammation, and stem cell therapies. Excepting early-stage stem cell trials, these investigational therapeutics aim to reduce the rate of, rather than halt or reverse, GA progression. Therefore, it is critical that eye care professionals and patients understand how different degrees of reduction in GA lesion enlargement will affect long-term visual function outcomes in order to manage expectations with respect to a patient's individual prognosis. In addition, it raises the clinical question regarding how early treatment, once available, should be initiated.

Currently, there is no systematic method for rating an individual's GA severity that incorporates various lesion characteristics, particularly those affecting visual function. For example, although lesion size is important, the degree of foveal involvement and impact of parafoveal lesions are key to relating GA lesions to visual function. Therefore, a standardized GA severity scale is necessary to assess a patient's disease severity at a given time and subsequently track disease progression. A validated scale could help standardize GA classification, predict progression, monitor progression over time, facilitate discussion with patients about disease progression and potential future treatments, and provide a holistic view of GA disease status.

In conclusion, many factors potentially prognostic for GA progression have been identified, yet a broader understanding of how these factors interact and relate to visual function, particularly for individual patients, is lacking. Standardized definitions and language surrounding GA are needed, including a multimodal definition of lesion borders and a GA severity measure encompassing more than lesion size; some of this is being addressed by the Classification of Atrophy Meetings initiatives.[15,124] Further large-scale studies are needed to synthesize and unify the understanding of GA progression.

## Acknowledgments

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## Footnotes and Financial Disclosures

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## Pictures & Perspectives
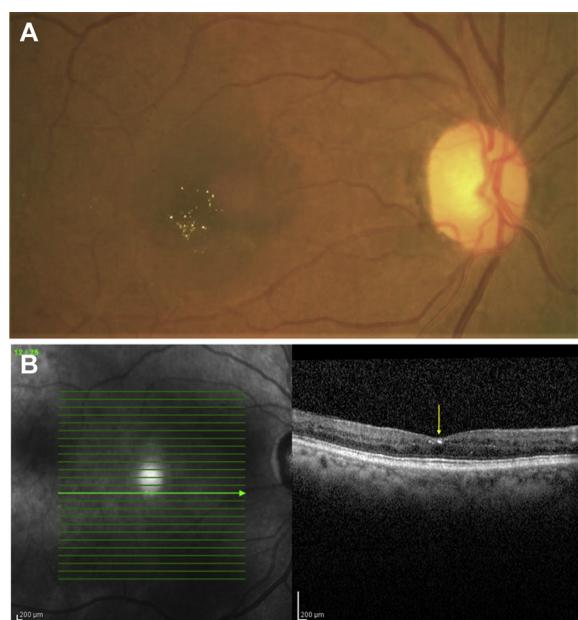


**West African Crystalline Maculopathy in a Nigerian Woman**

A 56-year-old asymptomatic Nigerian woman with diabetes and no known family history of ocular disease presented for routine ocular examination and was found to have yellow highly-refractile crystals clustered in bilateral foveas (Fig 1**A**; left eye not shown, but similar in appearance). She had no exogenous risk factors for crystalline retinopathy, such as use of cathaxanthine or tamoxifen. OCT through crystals revealed hyperreflective foci (*arrow*) in the inner retinal layers (Fig 1**B**). These findings are consistent with a diagnosis of West African crystalline maculopathy, a condition first reported by Sarraf et al (Sarraf D, Ceron O, Rasheed K, et al. West African crystalline maculopathy. *Arch Ophthalmol*. 2003;121:338-342.) in 6 patients from the Igbo tribe of Southeast Nigeria. Kola nuts, genetics, and retinal vascular disease have been proposed as potential causes of this maculopathy, but its definitive etiology remains unclear. (Magnified version of Fig 1**A**-**B** is available online at www.aaojournal.org.)

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