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

Monika Fleckenstein, MD,[1] Paul Mitchell, MD, PhD,[2] K. Bailey Freund, MD,[3,4] SriniVas Sadda, MD,[5,6] Frank G. Holz, MD,[1] Christopher Brittain, MBBS,[7] Erin C. Henry, PhD,[8] Daniela Ferrara, MD, PhD[8]

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 2017;■:1–22* © *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.

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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

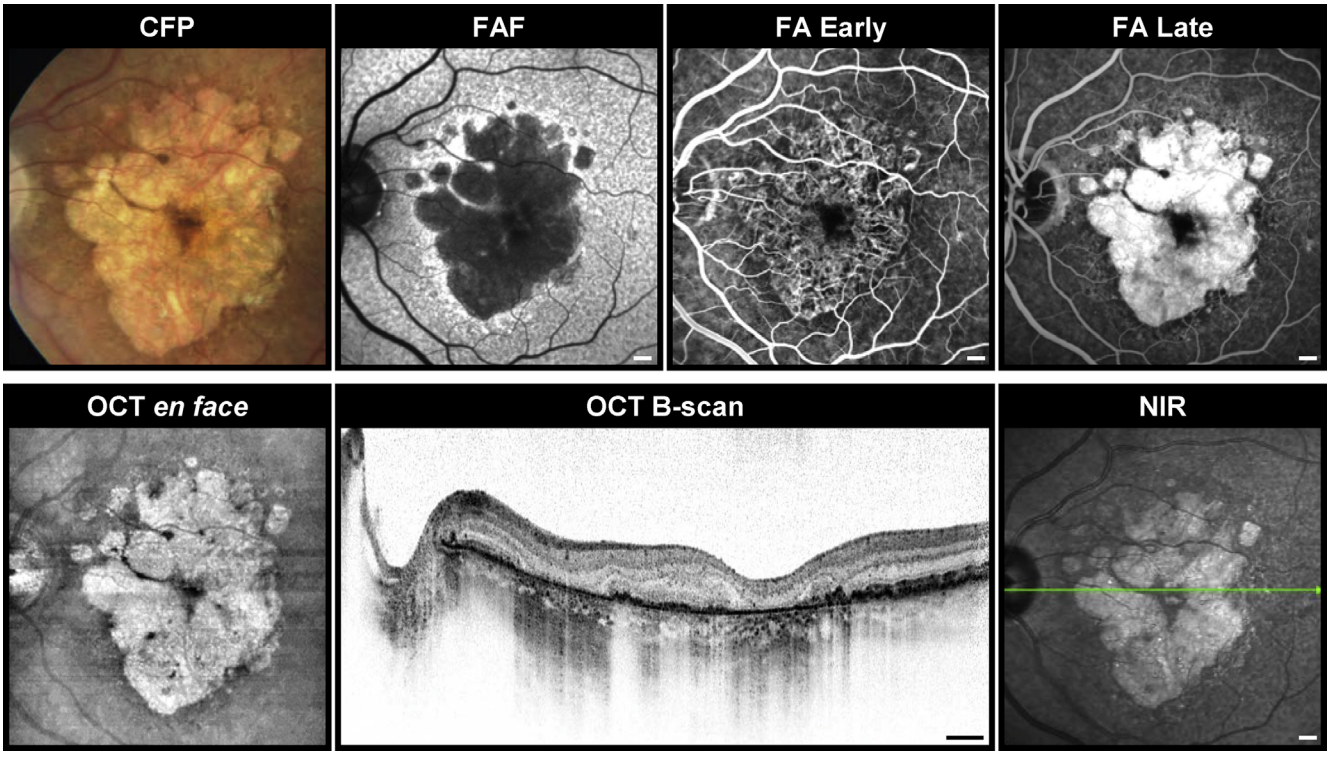

Figure 1. Multimodal imaging of geographic atrophy (GA). Example images of GA from 1 eye using color fundus photography (CFP), fundus autofluorescence (FAF), fluorescein angiography (FA), near-infrared reflectance (NIR), and spectral-domain OCT. Scale bars = 500 μm.