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Optical Coherence Tomography Predictors of Risk for Progression to Non-Neovascular Atrophic Age-Related Macular Degeneration

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Purpose: Appearance of geographic atrophy (GA) on color photography (CP) is preceded by specific features on spectral-domain optical coherence tomography (SD OCT). We aimed to build SD OCT–based risk assessment models for 5-year new onset of GA and central GA on CP.

Design: Prospective, longitudinal study.

Participants: Age-Related Eye Disease Study 2 Ancillary SD OCT study participants with age-related macular degeneration (AMD) with bilateral large drusen or noncentral GA and at least 1 eye without advanced disease (n = 317).

Methods: For 1 eye per participant, qualitative and quantitative SD OCT variables were derived from standardized grading and semiautomated segmentation, respectively, at baseline. Up to 7 years later, annual outcomes were extracted and analyzed to fit multivariate logistic regression models and build a risk calculator.

Main Outcome Measures: New onset of CP-visible GA and central GA.

Results: Over a follow-up median of 4.0 years and among 292 AMD eyes (without advanced disease at baseline) with complete outcome data, 46 (15.8%) developed central GA. Among 265 eyes without any GA on baseline CP, 70 (26.4%) developed CP-visible GA. Final multivariate models were adjusted for age. In the model for GA, the independent predicting SD OCT factors ($P < 0.001–0.03$) were: hyperreflective foci and retinal pigment epithelium (RPE) layer atrophy or absence, followed by choroid thickness in absence of subretinal drusenoid deposits, photoreceptor outer segment loss, RPE drusen complex volume, and RPE drusen complex abnormal thinning volume. For central GA, the factors ($P < 0.001$) were RPE drusen complex abnormal thinning volume, intraretinal fluid or cystoid spaces, hyperreflective foci, and RPE layer atrophy or absence. The models yielded a calculator that computes the probabilities of CP-visible, new-onset GA and central GA after 1 to 5 years.

Conclusions: For AMD eyes with large drusen and no advanced disease, we built a novel risk assessment model—based on age and SD OCT segmentation, drusen characteristics, and retinal pathology—for progression to CP-visible GA over up to 5 years. This calculator may simplify SD OCT grading and with future validation has a promising role as a clinical prognostic tool. *Ophthalmology 2017;124:1764-1777 © 2017 by the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in developed countries.[1] The vision-threatening advanced stages of AMD may be predicted from the clinical phenotype; however, the currently available tools are not sufficient to monitor disease activity and detect early points of change. In the staging of AMD and the assessment of its progression, the imaging modality most commonly used in major epidemiologic studies and severity scales is color photography (CP).[2–7] Although CP shows a 2-dimensional view of the retina, spectral-domain optical coherence tomography (SD OCT) provides 3-dimensional visualization, with high-resolution cross-sectional views, that allows in-depth examination of retinal tissue including delineation of retinal layers and characterization of substructures of AMD pathology.[8–12]

The Age-Related Eye Disease Study 2 Ancillary Spectral-Domain Optical Coherence Tomography (A2A SD OCT) Study aimed to identify specific SD OCT patterns in AMD that can predict vision loss and disease progression from intermediate to advanced stages.[12] In the intermediate stage of AMD, various drusen-related patterns of reflectivity on SD OCT have been discovered[8–14] and found to be early indicators of advancing disease.[14–21] It has been unknown whether such SD OCT features implied a risk of progression to choroidal neovascularization or played a role in the sequence of degeneration in geographic atrophy (GA).

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Previous reports from the A2A SD OCT Study discovered features of intermediate AMD on SD OCT that can serve as biomarkers of disease progression, such as hyperreflective foci.[14,18–21] Incidence of new-onset GA on CP followed after the qualitative SD OCT findings of atypical drusen (i.e., high or low internal reflectivity),[12] OCT-reflective drusen substructures (i.e., cores within drusen),[14] and hyperreflective foci,[18,19] as well as the quantitative SD OCT measurements of the retinal pigment epithelium (RPE) drusen complex volumes, which were accompanied by the SD OCT observation of RPE layer atrophy or absence.[21] Also, as shown by Wu et al,[22,23] atrophy of the RPE and overlying photoreceptors on SD OCT immediately preceded new onset of drusen-associated GA on CP. Briefly, these findings suggested that SD OCT is useful to visualize early indicators of atrophy, rather than neovascularization.[14–21] In an attempt to further clarify the sequence of degenerative events in the atrophic pathway, we focused this report on the A2A SD OCT Study aims pertinent to atrophy and its possible precursors. Specifically, the aim of this article was to identify the SD OCT features that, without interdependence, can collectively predict the probability of new progression from intermediate AMD to more advanced non-neovascular stages over 5 years. We sought to determine an algorithm, using SD OCT features, to predict GA, which is visible on CP.

Methods

The A2A SD OCT Study (ClinicalTrials.gov identifier NCT00734487) was an ancillary observational prospective study of a subset of eyes from the Age-Related Eye Disease Study 2 (AREDS2), with a group of control eyes of aged adults. The AREDS2 (ClinicalTrials.gov identifier NCT00345176) was a multicenter prospective randomized trial conducted to test the effect of oral nutritional supplements on the progression of AMD on CP.[24] The A2A SD OCT Study recruited 349 participants with AMD from 4 AREDS2 clinical sites in the United States (National Eye Institute, Duke Eye Center, Emory Eye Center, and Devers Eye Institute).[12] All AMD participants consented and were enrolled in the AREDS2 Study. At each of the clinical sites, the A2A SD OCT Study was approved by the Institutional Review Board. Informed research consent was obtained before participation from each study participant. The protocol followed tenets of human research as presented in the Declaration of Helsinki. Data were collected, stored, and managed in compliance with Health Insurance Portability and Accountability Act guidelines.

Study Design

The A2A SD OCT Study has been described and is summarized in this article.[12] We studied eyes enrolled in the AREDS2 Study. Participants were receiving the AREDS supplements as part of the standard of care and were randomly assigned to take 1 of the following AREDS2 Study supplements daily: (1) placebo, (2) lutein and zeaxanthin, (3) omega-3 long-chain polyunsaturated fatty acids, or (4) both.[24,25] The AREDS2 inclusion criteria included age between 50 and 85 years, and CP assessed by the reading center (University of Wisconsin Fundus Photograph Reading Center) to be of adequate quality.[24] Enrollment in AREDS2 was restricted to people determined to be at high risk of progression to advanced AMD with (1) bilateral large drusen $\geq$125 μm or noncentral GA (no advanced AMD) or (2) large drusen or noncentral GA in 1 eye and advanced AMD (neovascularization or central GA) in the fellow eye.[24] These eyes could have an AREDS Simple Scale Score of 2, 3, or 4.[7] The study eye was required to lack *advanced* AMD as defined in the AREDS and AREDS2: neovascularization or central GA.[7,24] It is important to note that noncentral GA was not considered advanced AMD per AREDS2 criteria (Table 1).[24] Accordingly, an AREDS2 Study eye (without advanced AMD) may have definite GA not involving the center of the macula with or without evidence of drusen.

In the intervening years during the progress of the A2A SD OCT Study, we recognized new onset of any GA as a critical outcome and SD OCT precursors to CP-defined GA as perhaps more meaningful indicators that are awaiting the progression to GA and central GA. In 2013, the Beckman classification put forward a clear clinical phenotyping definition of *intermediate* AMD: large drusen $\geq$125 μm or any AMD pigmentary abnormalities, without neovascularization or any GA; the presence of any noncentral GA was considered part of the definition of the more advanced class: *late* AMD.[27] Per the original A2A SD OCT Study design, the outcomes were at 2 and 5 years of follow-up, and the primary outcome of atrophy was the CP-based central GA. In this report, the primary outcomes are progression (A) to non-neovascular *advanced* AMD and (B) to non-neovascular *late* AMD based on the first occurrence of the respective outcome

Table 1. Age-Related Eye Disease Study 2 Ancillary Spectral-Domain Optical Coherence Tomography Study Primary Annual Outcomes of Progression to Non-Neovascular Atrophic Stages on Color Fundus Photography

	Study A	Study B
Outcome*	New-onset central GA	New-onset GA
Measure	GA at the foveal center	Any GA (noncentral or central)
AREDS terminology†	Non-neovascular *advanced* AMD	*Intermediate* AMD with GA or non-neovascular *advanced* AMD
Beckman classification‡	Non-neovascular *late* AMD	Non-neovascular *late* AMD
Modality	Color fundus photography	Color fundus photography
Total eyes at risk§,‖	292	265

AMD = age-related macular degeneration; AREDS2 = Age-Related Eye Disease Study 2; GA = geographic atrophy.
*Each outcome was defined as new onset of the respective measure on the designated imaging modality.
†Per AREDS and AREDS2, *advanced* AMD is defined as neovascularization or central GA on color fundus photography.[7,24,26]
‡The Beckman classification defined *late* AMD as neovascularization or any GA.[27]
§One study eye per participant.
‖By definition, eyes at risk of developing the outcome are outcome-free at baseline.