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Fully Automated Prediction of Geographic Atrophy Growth Using Quantitative Spectral-Domain Optical Coherence Tomography Biomarkers

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Purpose: To develop a predictive model based on quantitative characteristics of geographic atrophy (GA) to estimate future potential regions of GA growth.

Design: Progression study and predictive model.

Participants: One hundred eighteen spectral-domain (SD) optical coherence tomography (OCT) scans of 38 eyes in 29 patients.

Methods: Imaging features of GA quantifying its extent and location, as well as characteristics at each topographic location related to individual retinal layer thickness and reflectivity, the presence of pathologic features (like reticular pseudodrusen or loss of photoreceptors), and other known risk factors of GA growth, were extracted automatically from 118 SD OCT scans of 38 eyes from 29 patients collected over a median follow-up of 2.25 years. We developed and evaluated a model to predict the magnitude and location of GA growth at given future times using the quantitative features as predictors in 3 possible scenarios.

Main Outcome Measures: Potential regions of GA growth.

Results: In descending order of out-of-bag feature importance, the most predictive SD OCT biomarkers for predicting the future regions of GA growth were thickness loss of bands 11 through 14 (5.66), reflectivity of bands 11 and 12 (5.37), thickness of reticular pseudodrusen (5.01), thickness of bands 5 through 11 (4.82), reflectivity of bands 7 through 11 (4.78), GA projection image (4.73), increased minimum retinal intensity map (4.59), and GA eccentricity (4.49). The predicted GA regions in the 3 tested scenarios resulted in a Dice index mean $\pm$ standard deviation of 0.81 ± 0.12, 0.84 ± 0.10, and 0.87 ± 0.06, respectively, when compared with the observed ground truth. Considering only the regions without evidence of GA at baseline, predicted regions of future GA growth showed relatively high Dice indices of 0.72 ± 0.18, 0.74 ± 0.17, and 0.72 ± 0.22, respectively. Predictions and actual values of GA growth rate and future GA involvement in the central fovea showed high correlations.

Conclusions: Experimental results demonstrated the potential of our predictive model to predict future regions where GA is likely to grow and to identify the most discriminant early indicator (thickness loss of bands 11 through 14) of regions susceptible to GA growth. *Ophthalmology 2016;■:1−14 © 2016 by the American Academy of Ophthalmology.*

Geographic atrophy (GA) is the principle cause of severe central visual loss in individuals older than 75 years with nonexudative age-related macular degeneration (AMD) in developed countries.[1−7] Geographic atrophy manifests in the advanced stages of AMD.[8] The appearance of GA is characterized by the loss of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris. In natural history studies of GA, it first appears in the parafoveal location, progresses around the fovea, and then moves through the fovea with concomitant loss of central visual acuity,[3,9] and these GA characteristics have been used for the design of interventional trials.[10−13] Although being able to predict the locations of future GA involvement could be important for emerging therapies and patient counseling, it remains a challenging problem that is unsolved to date. The development of an algorithm to predict future areas of GA involvement would allow for better understanding of the pathogenesis and could affect the follow-up regimen of AMD patients with GA. This technology also may help to assess whether potential therapies can prevent or slow GA progression by providing better biomarkers of GA and using them to determine the risk of central vision loss.

Phenotypic factors used to describe GA size and enlargement and that may be related to the appearance and progression of GA have been studied previously from the observation of fundus images acquired using diverse imaging technology. Studies of infrared reflectance imaging have identified the presence of drusen, hyperpigmentation, and reticular pseudodrusen as risk factors for GA progression.[3,14,15] Autofluorescence imaging has identified different

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hyperautofluorescence patterns of the RPE and photoreceptors at the margins of GA that may be associated with different growth characteristics of GA.[16–19] Using spectral-domain (SD) optical coherence tomography (OCT) images, studies have identified that subretinal drusenoid deposits and abnormalities of the RPE and photoreceptors at the margins of GA may be associated with the expansion of GA.[16,20–25] However, none of these imaging strategies have predicted reliably the specific areas in the macula where GA is likely to appear or have been able to predict the specific pattern of GA growth over a given interval.

Compared with fundus autofluorescence and infrared reflectance, SD OCT allows the axial differentiation of retinal structures, generating 3-dimensional representations composed of a set of 2-dimensional images (called B-scans) and allowing an additional characterization of GA[26] (Fig 1). Spectral-domain OCT has become a key diagnostic technology in retinal diseases in recent years[27–32] and is valuable in providing detailed imaging characteristics of disease phenotypes. Spectral-domain OCT enables accurate identification of GA in a projection image (seen on the white outline in Fig 1C), whereas anatomic alterations within areas surrounding GA may allow for quantification of features associated with future GA growth. The ability of OCT images to provide useful biomarkers predicting the progression to the exudative form of AMD has been reported previously,[33] and previous studies indicate that OCT minimum intensity within the retina[25] and many other characteristics quantified via SD OCT may be useful as biomarkers[16,20–24] of progression in the advanced nonexudative form. Because of the above advantages of OCT imaging, SD OCT seems to be an appropriate imaging method for automatically characterizing size, location, and progression of GA lesions. Given the laborious and challenging task of manually inspecting the large collection of planar B-scans (typically hundreds of images) acquired for each 3-dimensional SD OCT cube, automated[34] and semiautomated[35,36] methods also have been developed for the segmentation and quantification of GA in SD OCT images. However, to our knowledge, there is no published method that accurately identifies potential regions where GA is likely to grow using SD OCT features in a quantitative, fully automated, and reproducible manner.

In this study, we segmented the GA-affected regions in longitudinal SD OCT scans (collection of scans acquired at successive time points) from a set of patients diagnosed with advanced nonexudative AMD using an automated method.[34,37] A set of quantitative imaging features characterizing the size and shape of GA, as well as characteristics at each axial scan location related to retinal layer thicknesses and reflectivity, the presence of pathologic features (like reticular pseudodrusen or loss of photoreceptors), and other known risk factors of GA growth were extracted automatically from SD OCT images. We identified which of these quantifications seemed promising to predict GA progression and developed and evaluated a computational model to predict the regions of future GA growth in unseen data, which may yield a more accurate

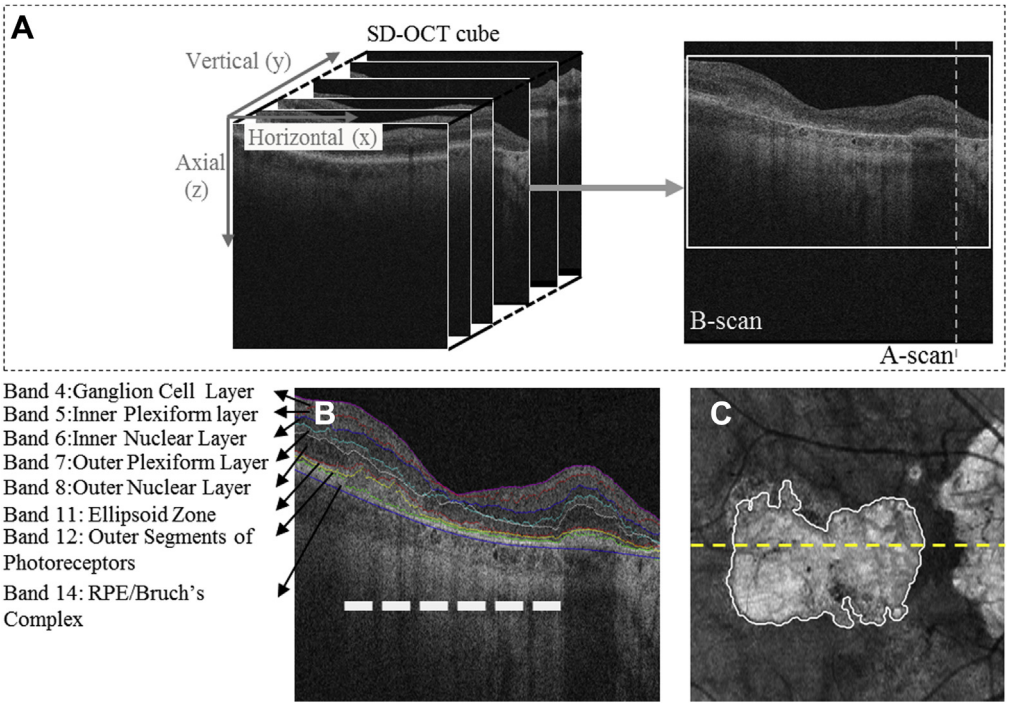

Figure 1. **A**, Example of a spectral-domain (SD) optical coherence tomography (OCT) cube, with indications of the axial, horizontal, and vertical directions and B-scan and A-scan nomenclature (dashed line). **B**, Automated geographic atrophy (GA) segmentation results with the IN•OCT consensus nomenclature[39] from a representative OCT B-scan. The white dashed line indicates the segmented GA areas. **C**, En face projection image[35] with GA outlined, where the GA region has been segmented using our automated method.[34,37] The dashed horizontal yellow line indicates the location of the B-scan shown in (**A**) and (**B**). RPE = retinal pigment epithelium.