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Imaging, Genetic, and Demographic Factors Associated With Conversion to Neovascular Age-Related Macular Degeneration

Secondary Analysis of a Randomized Clinical Trial

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Supplemental content

IMPORTANCE Risk factors associated with the development of neovascular age-related macular degeneration (AMD) have been identified. However, population size and methods to integrate imaging, genetic, and demographic factors associated with conversion to neovascular AMD are limited, specifically when treatment is administered in 1 eye.

OBJECTIVE To determine the imaging, genetic, and demographic factors associated with conversion from nonneovascular to neovascular AMD in fellow eyes.

DESIGN, SETTING, AND PARTICIPANTS This post hoc secondary analysis of the 24-month phase 3 multicenter, double-masked, active treatment-controlled HARBOR trial included 686 fellow eyes with nonneovascular AMD at baseline. Imaging features describing the presence, number, extent, density, and relative reflectivity of drusen were automatically extracted from spectral-domain optical coherence tomography scans. Genetic analysis included 34 single-nucleotide polymorphisms. Least absolute shrinkage and selection operator regression was performed to narrow imaging features. Survival analysis and Cox proportional hazards regression were performed to determine the association of the selected imaging features and genetic and demographic factors with conversion to neovascular AMD. Data were collected from November 2016 through October 2017 and analyzed from October 2017 through October 2018.

EXPOSURE Nonneovascular AMD in the fellow eye.

MAIN OUTCOMES AND MEASURES Features associated with conversion to neovascular AMD. Hazard ratios (HRs) and their 95% CIs were calculated.

RESULTS Among the 686 fellow eyes included in the analysis (406 [59.2%] women; mean [SD] age, 78.12 [8.28] years), 154 (22.4%) converted to neovascular AMD. Female sex was significantly associated with conversion to neovascular AMD (HR, 1.57; 95% CI, 1.11-2.20; $P = .009$). After controlling for demographic and treatment effects, drusen area within 3 mm of the fovea (HR, 1.45; 95% CI, 1.24-1.69; HR for 1-SD increase, 1.36 [95% CI, 1.20-1.54]) and mean drusen reflectivity (HR, 3.97; 95% CI, 1.11-14.18; HR for 1-SD increase, 1.32 [95% CI, 1.02-1.71]) were significantly associated with conversion to neovascular AMD. In addition, 1 genetic variant (rs61941274) was found to be associated with conversion to neovascular AMD.

CONCLUSIONS AND RELEVANCE Two imaging features (total en face area of drusen restricted to a circular area 3 mm from the fovea and mean drusen reflectivity) and 1 genetic variant (*ACAD10* locus) were associated with conversion to neovascular AMD. Drusen characteristics may be associated with conversion to neovascular AMD despite treatment in 1 eye.

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Age-related macular degeneration (AMD) is a leading cause of visual loss. The 2 main forms of AMD are nonneovascular and neovascular. Nonneovascular AMD is characterized by a progressive dysfunction of the retinal pigment epithelium (RPE), photoreceptor loss, and retinal degeneration.[1,2] Neovascular AMD is characterized by choroidal neovascularization (CNV) involving the growth of abnormal vessels underneath and into the retina.[1,2] Intraretinal or subretinal leakage, hemorrhage, and RPE detachments may occur with neovascular AMD, resulting in a rapid decline in vision.[1] Early detection and intervention of advanced neovascular AMD have been shown to improve visual outcomes.[3] Analysis of imaging features and other factors at the early nonneovascular AMD stages may help in understanding individual risk factors for disease progression and conversion to neovascular AMD.

Drusen-related features are the hallmarks of AMD that change with its progression. Several imaging techniques are used to evaluate drusen. Optical coherence tomography (OCT) has had a profound effect on the assessment, early detection, and monitoring of the progression of AMD. In addition, machine learning applications have been recently developed to leverage quantitative imaging features on OCT images to create models of AMD progression.[4-8] A set of quantitative spectral-domain OCT (SD-OCT) features have been shown to be associated with conversion to an advanced exudative AMD stage.[5] These features include drusen number, morphologic features, and reflectivity properties. Imaging features observed in fundus photographs, such as drusen extent and pigmentation, and their association with AMD progression have been extensively studied.[9] In addition, correlations of drusen features observed in SD-OCT and color fundus photography have also been performed, in which SD-OCT hyperreflectivity has been shown to represent the same anatomical lesion as macular hyperpigmentation on color fundus photographs.[10]

Nonimaging risk factors that have been shown to be associated with advanced AMD include age, sex, educational attainment, history of a fellow eye with AMD, and smoking.[11-14] Given that models have been successful in identifying AMD progression, it is important to study imaging and nonimaging features in patients with nonneovascular AMD in 1 eye that later converts to neovascular AMD when the first eye is receiving treatment. Results will allow us to determine imaging features associated with conversion despite the effect of systemic absorption of anti-vascular endothelial growth factor therapies.

We performed a retrospective analysis of quantitative features derived from OCT images in the HARBOR study,[15] which evaluated the efficacy and safety of ranibizumab administered intravitreally to patients with CNV secondary to AMD in 1 eye, and we analyzed the association of these imaging features with conversion to neovascular AMD in the fellow eye. Given that patients with neovascular AMD in 1 eye are at a high risk of developing neovascular AMD in the fellow eye, the fellow eye data from the HARBOR study was ideal to evaluate factors associated with conversion. The main objective of our study was to quantify the association between extracted features from SD-OCT images and conversion to neovascular AMD and assess whether other genetic and demographic factors also play a role in such associations. This analysis may allow us to determine factors potentially associated with conversion despite treatment effect.

Key Points

Question What are the imaging, genetic and demographic factors associated with conversion to neovascular age-related macular degeneration in patients undergoing treatment for late disease in 1 eye?

Findings In this post hoc secondary analysis of a randomized clinical trial of 686 fellow eyes with nonneovascular age-related macular degeneration, total en face area of drusen restricted to a circular area 3 mm from the fovea, mean drusen reflectivity, and 1 genetic variant (rs61941274, *ACAD10* locus) were associated with conversion to neovascular age-related macular degeneration after controlling for demographic and treatment effects.

Meaning Drusen characteristics restricted to a circular area 3 mm from the fovea and mean drusen reflectivity may help identify progression in age-related macular degeneration.

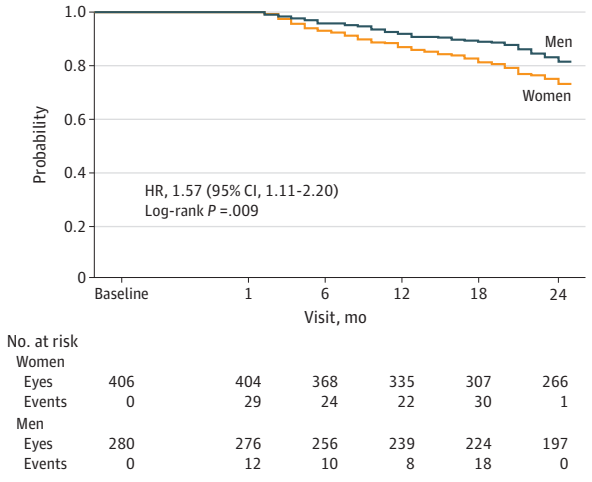
Methods

Population and Definition of Progression to Neovascular AMD

This study was a retrospective, post hoc secondary analysis of the HARBOR randomized clinical trial[16] (NCT00891735). We collected data for the fellow eye of HARBOR participants from November 2016 through October 2017. The study design, methods, and primary 12- and 24-month outcomes have been published previously.[15] In brief, HARBOR was conducted at 100 investigator sites that evaluated the efficacy and safety of 2 doses and 2 regimens of ranibizumab in 1097 patients 50 years or older. Patients with subfoveal neovascular AMD were randomized 1:1:1:1 to receive ranibizumab, 0.5 mg monthly, 0.5 mg as needed, 2.0 mg monthly, or 2.0 mg as needed after 3 monthly loading doses, for 24 months. The study was conducted in accordance with Good Clinical Practice, applicable US Food and Drug Administration regulations, the Health Insurance Portability and Accountability Act, and the tenets of the Declaration of Helsinki.[17] The randomized clinical trial was performed by Genentech with a detailed research agreement. The institutional review board of Stanford University waived the need for consent because this was a secondary data analysis project and posed negligible patient risk to the patients. All data used were completely deidentified.

Key ocular inclusion criteria for the study eye were (1) best-corrected visual acuity, using Early Treatment Diabetic Retinopathy Study charts, of 20/40 to 20/320 (Snellen equivalent); (2) CNV lesions with a classic CNV component, occult CNV, or some classic CNV component where permissible; and (3) total area of lesion of less than 12 disc areas or 30.48 mm^2. Conversion to neovascular AMD was determined if a fellow eye with nonneovascular AMD at baseline received any treatment for neovascular AMD at any point during the 2-year follow-up. Nonneovascular AMD at baseline was determined

Figure 1. Kaplan-Meier Survival Curves for Eyes With Conversion From Nonneovascular to Neovascular Age-Related Macular Degeneration by Sex



No. at risk						
Women						
Eyes	406	404	368	335	307	266
Events	0	29	24	22	30	1
Men						
Eyes	280	276	256	239	224	197
Events	0	12	10	8	18	0

Log-rank test indicates a statistically significant difference between men and women.

if no neovascular AMD was reported from the eye history case report forms and if no CNV was present on fundus angiography images.[18] Baseline demographic, visual acuity, and genetic variants were assessed, along with image analysis from OCTs.

OCT Image Analysis and Image Feature Extraction

Drusen characteristics were computed automatically using software algorithms described previously.[5] Each OCT volume was processed using proprietary Cirrus Review Software (Carl Zeiss Meditec, Inc) to automatically segment the location of the RPE in the form of a surface and generate a topographic map describing the regions of substantial RPE elevation. The location and extent of individual drusen were also automatically segmented for each OCT volume[6] using a process that takes the segmented location of the RPE layer and an estimation of the inner segment/outer segment junction as inputs to automatically outline drusen within the volume. The result of this processing is a topographic map indicating RPE elevation with respect to a Bruch membrane estimation and the 3-dimensional segmentation of drusen locations for each considered OCT volume (eFigure in the Supplement).[5] The collection of B-scans within the SD-OCT volume and the corresponding 3-dimensional segmentation of drusen locations within the volume were processed to generate 15 imaging features (eTable 1 in the Supplement). In this study, imaging features at month 2 were used as a baseline to allow for further comparisons with feature changes over time (feature evolution), calculated as the delta difference between points.

Single-Nucleotide Polymorphisms

Patients in the HARBOR study underwent sequencing for 34 hypothesized single-nucleotide polymorphisms. The selection of these single-nucleotide polymorphisms was based on previous meta-analyses and genome-wide association studies[19,20] that highlighted the contributions of rare and common variants associated with AMD incidence. The 34 loci were identified from more than 12 million variants, including 163 714 directly genotyped, most of which were rare, protein-altering variants.[19]

Statistical Analyses

Data were collected from November 2016 through October 2017 and analyzed from October 2017 through October 2018. Univariate, bivariate, and multivariate analyses were performed to determine potential associations in baseline demographic, visual acuity, genetic, and imaging factors with conversion to neovascular AMD. The bivariate associations were evaluated using the χ^2 test, unpaired 2-tailed *t* test, and the Wilcoxon Mann-Whitney test where appropriate. Least absolute shrinkage and selection operator (LASSO) regression was used as a shrinkage method to narrow imaging features. For analysis of incident neovascular AMD in the fellow eye, we assessed conversion during the 2-year study period using survival analysis. The log-rank test was used to determine significance between Kaplan-Meier curves. Cox proportional hazards regression analysis was performed for final modeling. Our bivariate analysis for genetic variants and LASSO regression for imaging features guided the variables to be included in the final model. Along with the imaging and genetic factors, we included age, sex, and treatment arm to control for confounding. Hazard ratios (HRs) and their 95% CIs were determined for each covariate. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc). Python software (Python Software Foundation) was used to graph the Kaplan-Meier curves. The α level for statistical significance was set a priori at 2-sided $P < .05$. Bonferroni adjustment was applied to *P* values for the genetic analysis.

Results

Among 686 fellow eyes with nonneovascular AMD at baseline (406 women [59.2%] and 280 men [40.8%]; mean [SD] age, 78.12 [8.28] years), 154 (22.4%) had conversion to neovascular AMD. Our bivariate analysis showed that older patients (mean [SD] age, 79.5 [7.6] vs 77.9 [8.4] years; $P = .02$) and women (106 of 154 [68.8%] vs 300 of 532 [56.4%]; $P = .006$) were more likely to experience conversion to neovascular AMD (eTable 2 in the Supplement). **Figure 1** shows the Kaplan-Meier plot for sex (HR, 1.57; 95% CI, 1.11-2.20; $P = .009$). Treatment in 1 eye was not associated with conversion to neovascular AMD in the fellow eye.

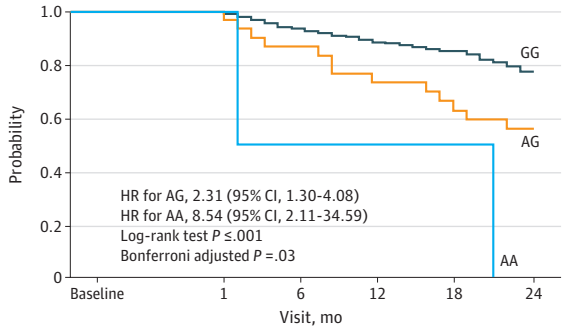
The distributions of all genetic variants in eyes with conversion to neovascular AMD vs those without are shown in eTable 2 in the Supplement. Among the genetic variants, rs61941274 (*ACAD10* locus [OMIM 611181]) was significantly associated with conversion to neovascular AMD (140 of 154 [95.5%] vs 474 of 532 [89.1%]; $P = .03$ after Bonferroni correction), but with a low genotype distribution of the minor allele AA. **Figure 2** displays the Kaplan-Meier survival curves for eyes with conversion to neovascular AMD by rs61941274 status. The

log-rank test indicates a statistically significant difference between genotypes taking GG as reference, with HRs of 2.31 (95% CI, 1.30-4.08) for AG and 8.54 (95% CI, 2.11-34.59) for AA.

Results of the automated LASSO regression used to select the imaging features are shown in **Figure 3**. Drusen area of 3 mm from the fovea and drusen reflectivity were the main features included in the selected model.[21] Drusen area within 3 mm of the fovea was highly correlated with drusen volume of 3 mm^3 (r = 0.83; P < .001). However, a drusen area of 3 mm^2 was selected as a better fit. Given that the standard and mean drusen reflectivity were highly correlated (r = 0.88; P < .001), mean drusen reflectivity was included in our Cox proportional hazards regression models. Drusen area within 3 mm of the fovea (HR, 1.42 [95% CI, 1.23-1.64]; HR for 1-SD increase, 1.34 [95% CI, 1.19-1.51]) and reflectivity (HR, 4.56 [95% CI, 1.44-14.42]; HR for 1-SD increase, 1.36 [95% CI, 1.08-1.72]) were significantly associated with conversion to neovascular AMD. The HRs for their evolution at month 2 for all models are shown in eTable 3 in the Supplement.

The **Table** displays the multivariate associations between variables selected for the final model and conversion to neovascular AMD. Significant associations remained for a drusen area within 3 mm of the fovea and mean drusen reflectivity after controlling for demographic and treatment effect. The HR for drusen area was 1.45 (95% CI 1.24-1.69) for every 1-U increase and 1.36 (95% CI, 1.20-1.54) for every 1-SD increase. That is, for every 1-U increase in the total en face area of drusen restricted to a 3-mm circle around the fovea, patients were at an approximately 1.45 times higher risk of conversion to neovascular AMD. The HR for mean drusen reflectivity was 3.97 (95% CI, 1.11-14.18) for every 1-U increase and 1.32 (95% CI, 1.02-1.71) for every 1-SD increase. Similarly, for every 1-U increase in mean drusen reflectivity, patients were at an approximately 3.97 times higher risk of converting to neovascular AMD.

Figure 2. Kaplan-Meier Survival Curves for Eyes With Conversion From Nonneovascular to Neovascular Age-Related Macular Degeneration by rs61941274 (*ACAD10* locus) Status



No. at risk						
GG						
Eyes	581	531	555	490	456	399
Events	0	33	28	22	41	1
AG						
Eyes	31	31	26	22	19	15
Events	0	4	3	3	3	0
AA						
Eyes	2	2	1	1	1	0
Events	0	1	0	0	1	0

Log-rank test indicates a statistically significant difference between genotypes, with GG as reference. HR indicates hazard ratio.

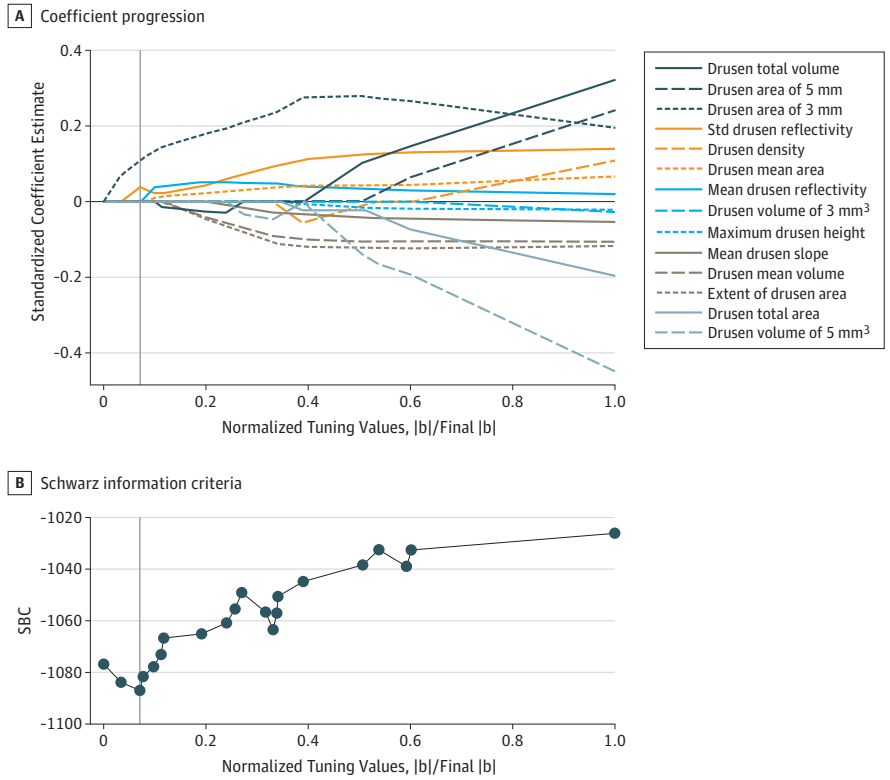
Discussion

This study combined OCT imaging features and genetic, demographic, and treatment effects to assess associations with conversion to neovascular AMD in patients with late AMD in 1 eye. We revealed the following main imaging features to be potentially associated with conversion to neovascular AMD: (1) the area occupied by all the individual drusen regions in the OCT topographic map within 3 mm of the fovea center and (2) mean drusen reflectivity, defined as the mean value of normalized pixel intensity inside drusen regions. Drusen reflectivity is a reflection of pigmentary abnormalities, which have been shown consistently to be associated with increased risk with use of fundus photography; in this analysis, drusen reflectivity was extracted from OCT images.[9] Our model also included 1 genetic variant (rs61941274 [*ACAD10* locus]) that was associated with conversion to neovascular AMD.

Use of artificial intelligence applications in ophthalmic imaging has been increasing rapidly. Analysis of features from OCT images and the development of algorithms to estimate progression of AMD have been applied to improve early diagnosis and prevention.[4-8,22,23] de Sisternes et al[5] were among the first to automatically extract drusen features from SD-OCT images to estimate future AMD progression from an early or intermediate nonexudative stage to an advanced exudative stage. They characterized several quantitative features related to drusen morphologic features and their change over time and reported that the maximum height of the detected drusen appeared to be a significant discriminator for progression within 18 months. Total area of drusen was significantly higher for cases progressing within 30 months.[5] The same features were extracted from SD-OCT images for this study and analyzed to assess the association with conversion to neovascular AMD. Our results are in line with previous models, in which drusen area and reflectivity were associated with AMD progression. Schmidt-Erfurth et al[8] used drusen features similar to those defined by de Sisternes et al,[5] in addition to layer thickness, to estimate the occurrence of CNV conversion in the HARBOR data set. Although the reported model did not reach the accuracy observed previously,[5] it further reinforced the possibility of using OCT imaging features, such as drusen area and reflectivity, to estimate CNV occurrence.

Drusen volume within a central 3-mm circle is another OCT imaging feature that has been associated with progression to late AMD.[24] Similar to our study, Abdelfattah et al[24] analyzed whether fellow eyes underwent progression to late AMD. They reported that patients with a drusen volume of greater than 0.03 mm^3 had a greater than 4-fold increased risk for developing AMD compared with those with a lower drusen volume. Drusen volume within a central 3-mm circle has also been used as one of the criteria to develop an OCT-based scoring system for progression to late AMD.[7] Lei et al[7] developed a simple OCT-based scoring system composed of drusen volume within a central 3-mm circle of at least 0.03 mm^3, intraretinal hyper-

Figure 3. Automated Least Absolute Shrinkage and Selection Operator Regression to Select Imaging Features Associated With Conversion From Nonneovascular to Neovascular Age-Related Macular Degeneration



Drusen area within 3 mm of the fovea and drusen reflectivity are the main features that were included in the selected model based on the Schwarz information criteria (SBC).[21] Standardized coefficients are shown as a function of the step number. The normalized tuning values are the L1 norm of the regression coefficients divided by the L1 norm of the ordinary least squares solution. The vertical line indicates the selected step.

Table. Multivariate Cox Proportional Hazards Regression Analysis Between Imaging Features, Demographics, and Genetic Variants and Conversion to Neovascular AMD

Variable	HR (95% CI)	*P* Value
Age	1.01 (0.98-1.03)	.64
Female	1.40 (0.94-2.09)	.10
Drusen area within 3 mm of foveal	1.45 (1.24-1.69)	<.001
	1.36 (1.20-1.54)[a]	
Mean drusen reflectivity	3.97 (1.11-14.18)	.03
	1.32 (1.02-1.71)[a]	
rs61941274 (*ACAD10* locus)		
GG	1 [Reference]	NA
AG	2.39 (1.31-4.35)	.004
AA	10.20 (2.38-43.74)	.002
Ranibizumab treatment arm		
0.5 mg monthly	1 [Reference]	NA
0.5 mg as needed	1.12 (0.68-1.84)	.65
2.0 mg as needed	0.78 (0.45-1.31)	.33
2.0 mg monthly	0.94 (0.55-1.58)	.80

Abbreviations: AMD, age-related macular degeneration; HR, hazard ratio; NA, not applicable.

[a] Indicates HR for 1-SD increased risk.

reflective foci, hyporeflective foci within a drusenoid lesion, and subretinal drusenoid deposits. The investigators reported that the risk of progression was 3 times higher for an eye assigned to category IV than for an eye in category III and 16.4 times higher than for an eye in category II based on the number of risk factors and whether the fellow eye had evident CNV or atrophy (category values indicate severity of disease; the higher the number, the worse the disease). In our analysis, we found that drusen area and volume were associated with conversion to neovascular AMD. However, a drusen area within 3 mm of the fovea was highly correlated with a drusen volume of 3 mm^3 (r = 0.83, P < .001). Given this high correlation, when combined with the other features to explain the appearance of neovascular AMD, only one feature was needed to obtain a good linear model, and only one was selected by LASSO. In this case, the combination of drusen area with other selected features seemed to produce a better linear model than drusen volume.

In addition to drusen area, we found that mean drusen reflectivity was associated with conversion to neovascular AMD. Our findings that area and hyperreflectivity were associated with conversion to neovascular AMD are in line with those of studies showing that area of drusen and extent of pigmentation affected risk[8,9,25] and are in line with the Age-Related Eye Disease Study severity scale for AMD progression.[9] Drusen area and hyperreflective foci from OCT images were also among the features reported by Schmidt-Erfurth et al[8] in their automated machine learning predictive model. Drusen reflectivity in OCT has been shown to anatomically correlate to drusen hyperpigmentation on fundus photographs.[10] In our study, hyperreflectivity also represented hyperpigmentation, with

mean drusen reflectivity determined by the mean value of the normalized pixel intensity (values 0-1) inside drusen regions observed in a collection of OCT B-scans. Given that OCT measurements were extracted from multiple points in this study, we were also interested in studying the early evolution of imaging features. Our preliminary results (eTable 3 in the Supplement) suggest that drusen area is a more important and significant feature across time than reflectivity. In addition to imaging features, our analysis considers other potential factors associated with conversion to neovascular AMD, providing a unique data-integration model.

Risk prediction for progression of AMD has been a major research area, given that AMD has several confirmed demographic, environmental, and genetic factors associated with its development and progression.[26-28] In our bivariate analysis, we found that age and female sex were associated with conversion to neovascular AMD. These 2 demographic factors have been shown to be associated with AMD in several studies.[27,29] We found that fellow eyes with conversion to neovascular AMD had a higher mean age than fellow eyes without conversion. In addition, more women than men had conversion to neovascular AMD.

With regard to our analysis of genetic variants, we found that rs61941274 was associated with conversion to neovascular AMD. However, the distribution of the minor allele AA was low. The automated predictive machine learning analysis performed by Schmidt-Erfurth et al[8] did not highlight this variant as a critical quantitative feature. Their conclusion could be attributed to the different outcome definitions and analytic approaches to model building. The outcome in our study was based on clinical criteria and did not incorporate imaging features. Estimation of CNV in the study by Schmidt-Erfurth et al[8] was predominantly done by manual grading of OCT features such as thickening of subretinal layers and increase in drusen size. In addition, the model-building approach in our study did not include all the features in a single automated prediction model but treats features separately, combining machine learning and explanatory model-building approaches. The rs61941274 variant on the *ACAD10* gene has been recently reported as a novel loci for AMD.[19,30] The gene is hypothesized to be associated with AMD via fatty acid oxidation.[30] In a genome-wide association study, Fritsche et al[19] reported an odds ratio of 1.51 for the association between rs61941274 and advanced AMD.

Limitations

This study has several limitations. First, the data for eyes analyzed for the progression of AMD come from a controlled clinical trial setting in which imaging data might differ between centers, and our results may not be applicable or generalizable to a real-world clinical population. A second limitation is the moderate sample size, which may have also contributed to the lack of significant results for apparent demographic and genetic risk factors previously shown to be associated with progression to neovascular AMD. Given the rarity of AMD progression, obtaining larger data sets with OCT imaging in patients with AMD is difficult. Last, our feature-extraction algorithm targets areas where drusen is present. Some hyperreflectivity may not have been identified if it was not overlying a drusen. The analysis performed in this study also did not include correlation of hyperreflectivity in OCT images to hyperpigmentation on fundus photographs.

Conclusions

Despite these limitations, this post hoc secondary analysis of the HARBOR trial provides additional insight into 2 main SD-OCT imaging features (total en face area of drusen restricted to a circular area 3 mm from the fovea and mean drusen reflectivity) and 1 genetic variant (*ACAD10* locus) that were associated with conversion to neovascular AMD after controlling for treatment effects. Drusen characteristics may be associated with conversion to neovascular AMD despite treatment in 1 eye. This study also highlights the use of a clinical outcome measure and a combined machine learning and explanatory model-building approach for AMD progression. Our results may further aid in earlier diagnosis of conversion to neovascular AMD to prevent severe visual loss. Additional long-term prospective studies from various populations are required to further uncover the roles of imaging and their evolution; demographic, environmental, and genetic factors; and computation of gene-imaging and gene-environment risk scores for AMD progression.

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Concept and design: Hallak, de Sisternes, Osborne, Rubin, Leng.
Acquisition, analysis, or interpretation of data: Hallak, de Sisternes, Osborne, Yaspan, Leng.
Drafting of the manuscript: Hallak, Rubin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hallak, Yaspan.
Obtained funding: Osborne.
Administrative, technical, or material support: de Sisternes, Osborne, Rubin, Leng.
Supervision: de Sisternes, Osborne, Rubin, Leng.

Conflict of Interest Disclosures: Dr de Sisternes reported being employed by Carl Zeiss Meditec, Inc, outside the submitted work and issue of patent US9737205B2 for evaluating the progression of age-related macular degeneration. Dr Osborne reported receiving grants from Genentech during the conduct of the study and personal fees from Genentech/Roche outside the submitted work. Dr Yaspan reported employment by Genentech/Roche outside the submitted work and stock and stock options from Genentech/Roche. Dr Rubin reported receiving grants from Stanford University during the conduct of the study and issue of patent US9737205B2 for evaluating the progression of age-related macular degeneration. Dr Leng reported receiving grants from Genentech/Roche during the conduct of the study and receiving grants from Topcon and personal fees from Zeiss, Regeneron, Allergan, Iridex, 23&Me, and Valeant outside the submitted work. No other disclosures were reported.

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Roche providing variables, including images, from a previous clinical study (HARBOR); management and analysis of these variables were performed at Stanford University.

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