AOS Thesis

Validated Prediction Models for Macular Degeneration Progression and Predictors of Visual Acuity Loss Identify High-Risk Individuals

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• PURPOSE: To determine predictive factors and risk scores for conversion to overall advanced age-related macular degeneration (AMD), geographic atrophy (GA), neovascular disease (NV), and loss of vision, and to validate the model for AMD in an external cohort.

• METHODS: Progression to advanced AMD was evaluated using stepwise survival analysis. Risk scores including genetic, demographic, behavioral, and ocular factors were derived for 3 AMD endpoints and were validated and calibrated in a large independent cohort. Vision loss of 15 or more letters was evaluated as a new endpoint in genetic analyses.

• RESULTS: Eight common and rare variants in genes *CFH, C3, ARMS2, COL8A1,* and *HSPH1/B3GALTL* conferred a significantly higher risk of transition to advanced AMD. Three loci (*C2, CFB, RAD51B*) were associated with lower rate of progression. A protective effect was suggested for *CTRB1* and *PELI3*. The age-adjusted area under the curve (AUC) for the composite model including 13 loci model was 0.900 over 12 years (0.896 in the validation cohort). Generally, progressors had a higher risk category and nonprogressors had a lower risk category when genetic factors were considered. Furthermore, there was heterogeneity between models for GA and NV. The model was calibrated in the validation cohort. Determinants of visual loss included age, education, body mass index, smoking, and several common and rare genetic variants.

• CONCLUSION: Eyes with the same baseline macular grade had a wide range of estimated probability of subsequent progression and visual loss based on the validated risk score. Identifying high-risk individuals at an earlier stage using predictive modeling could lead to improved preventive and therapeutic strategies in the era of precision medicine. NOTE: Publication of this article is sponsored by the American Ophthalmological Society. (Am J Ophthalmol 2019;198:223–261. © 2018 Elsevier Inc. All rights reserved.)

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AGE-RELATED MACULAR DEGENERATION (AMD) IS A progressive and degenerative disease affecting the central part of the retina, and is the leading cause of irreversible vision loss in the United States.[1–3] The prevalence of this disease is rising with the growth of our aging population. Over 1.75 million individuals in the United States have the advanced forms of AMD, a number that is projected to rise dramatically.[4] The worldwide prevalence for all AMD was estimated at 196 million people, and the global burden of disease will likely increase to 288 million by 2040.[5] While the visual impact associated with early and intermediate stages of AMD can be minimal, some affected individuals progress to advanced disease. These advanced subtypes of geographic atrophy (GA) and neovascular disease (NV) are commonly associated with visual impairment and blindness, affecting quality of life and leading to loss of independence.[6–8] Although anti–vascular endothelial growth factor (VEGF) injections are an effective treatment for many patients with NV,[9] some patients do not respond, there is a large treatment burden, and visual loss continues over time. There is no treatment for GA. Thus, prevention of advanced disease and finding new and effective treatments remains a significant challenge. Identifying individuals with early and intermediate disease at high risk of progression to advanced stages would lead to earlier intervention and reduced burden of visual loss due to AMD.

The etiology of AMD is multifactorial, with both genetic and modifiable factors contributing to personal risk. The network of modifiable factors associated with reducing AMD risk is well established and highlights the importance of a healthy lifestyle.[3] Despite the potential modification of disease risk through diet and healthy behaviors, genetic factors confer substantial risk in AMD onset and progression[10] and cannot, at present, be modified. The identification of the impact of genetic risk factors on progression is therefore critical in the context of clinical care and disease management.

AMD is a common, polygenic disease wherein multiple common variants, defined as variants with a minor allele frequency ≥ 5%, contribute varying amounts to personal risk. Genome-wide association studies (GWAS) have been instrumental in the identification of these common variants,

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including complement factor H (*CFH*) Y402H, *CFH* (rs1410996), complement factor B (*CFB*), complement component 2 (*C2*), complement component 3 (*C3*), and complement factor I (*CFI*).[11–16] These complement-related loci are now well established in their roles to confer AMD risk, and lend further support to the theory that inflammation and immune processes play a critical role in the pathogenesis of AMD.[17,18] Common loci in the angiogenesis, extracellular matrix, and immune pathways have also been identified as AMD risk factors.[3,19–25]

Rare and low-frequency variation, defined as a minor allele frequency < 5%, is carried by a smaller proportion of the population, although these variants have larger effect sizes and functional impact. For instance, the first confirmed rare variant for AMD, *CFH* R1210C, confers the strongest genetic risk for AMD to date, with an odds ratio (OR) greater than 20.[26] This mutation is also associated with an earlier age at advanced AMD diagnosis,[26] extensive drusen accumulation throughout the macula, and extramacular drusen.[27] Through the use of methodology we proposed in 2010 to study densely affected families not explained by known loci,[28] other rare variants in *CFH* were discovered.[29–31] Rare variants in *C3* (K155Q), *CFI*, and complement component 9 (*C9*, P167S) also confer AMD risk,[32,33] whereas the low-frequency variant *CFH*1050Y and rare pellino E3 ubiquitin protein ligase family member 3 (*PELI3*) variant have shown a protective effect.[19]

These loci have been reported to confer varying levels of risk of AMD prevalence in case-control studies. However, many are also strong genetic predictors of progression of this disease over time, as determined by the analysis of large, prospective cohorts.[34–40] Progression is typically defined as the transition from early and intermediate stages to advanced clinical phenotypes. *CFH* Y402H and *ARMS2* were the first loci determined to be independently and significantly associated with progression,[34] followed by *CFH* rs1410996, *C2* E318D, *CFB* R32Q, *C3* R102G, *RAD51B*, and *COL8A1*,[35,36,39] as well as the highly penetrant, rare variants *CFH* R1210C and *C3* K155Q.[39,40] In a separate study evaluating specific transitions between AMD disease states, 2 additional variants in the lipid pathway were determined to affect progression from 1 stage to another.[37] *LIPC* conferred a protective effect against transitioning from intermediate disease to NV, and *ABCA1* was associated with a lower risk of progression from early to intermediate AMD.[37]

Many loci have been shown to be related to both GA and NV, namely those found in the complement pathway, and studies have assessed whether some variants may be more strongly associated with 1 advanced subtype compared to the other.[34,37,41,42] *ARMS2* was the first locus identified to confer a greater risk of developing NV compared to GA.[41,42] A recent genome-wide association study confirmed this relationship for *ARMS2*, and suggested that variants in *MMP9*, *CETP*, and *SYN3-TIMP3* loci may also differ between the 2 advanced subtypes.[43] No other variants associated with advanced disease have been determined to have a differential effect on the advanced AMD subtypes.

Gene therapy is not yet available for AMD prevention or management. However, because new genetic risk factors for AMD are being identified, particularly the rare variants with larger effect sizes, and gene therapies for AMD are currently being developed to target specific genotypes in the era of precision medicine, it is increasingly important to consider the utility of evaluating individual genetic susceptibility, especially for progression to advanced stages. Interest in predictive modeling is therefore growing and proper methodology is essential.[44]

Since 2006, we have developed a series of algorithms that predict risk for progression to advanced stages of AMD over time, and these models have achieved high predictability of up to 0.94, with perfect discrimination between groups indicated by a value of 1.0.[14,34–40] Although numerous loci are associated with AMD risk, only a subset has been evaluated prospectively to determine associations with risk of progression to advanced disease. We hypothesize that a large subset of genetic factors will be predictive of progression to overall advanced AMD, together with other predictors, and will aid in accurately identifying high-risk individuals who will develop vision-threatening AMD in the future. We also hypothesize that there will be differences in risk profiles for progression to the 2 distinct clinical manifestations of GA and NV.

It is not sufficient to identify the set of genetic factors that best determine which patients will progress to advanced stages of AMD and which patients will not. These risk factors must be validated in order to influence the management of this disease.[38,40] Our study reported herein enhances the existing AMD literature by adding validation of the model using a larger external cohort with similar baseline stages of AMD and the same covariates in the model.

This study also expands the scope of predictive modeling to a functional endpoint, since despite the progressive visual impairment associated with advanced stages of AMD, the genetics underlying visual acuity (VA) loss have not been evaluated, and no composite model has been established for this endpoint. We therefore also test the hypothesis that several genetic factors are related to visual loss and calculate a prediction model for progression to this functional endpoint.

METHODS

• **OVERVIEW:** Predictors of progression to advanced disease, GA and NV outcomes, and derivation of the risk prediction model were initially assessed in the Age-Related Eye Disease Study (AREDS) cohort, the "derivation" cohort. The model was then validated using the independent Seddon Longitudinal Cohort, the "validation cohort."

Calibration of the derived model in the validation cohort was determined. The impact of genetic factors in addition to demographic, behavioral, and ocular predictors on risk of progression to advanced AMD was evaluated. A separate prediction model was derived for visual loss of 15 or more letters using the AREDS cohort. Sample cases with varying risk scores and subsequent outcomes are presented, which can be reviewed in the on-line risk calculator, www.seddonamdriskscore.org.[45]

We implemented rigorous methods in these prospective analyses, both for derivation of the prediction models and to ascertain the validity of our results. In previous studies we used eye-specific analyses, including studies of risk factors for progression over time,[27,46–50] which consider that individual eyes can progress to different stages of disease and at different time points. In contrast, person-specific analyses result in classification of the individual as a progressor or nonprogressor when the first eye progresses.

Validation of the derived composite model included the following: (1) application of a genetic risk model derived from AREDS to an external, independent cohort with the similar demographic, lifestyle, ocular, and genetic data; (2) determination of the sensitivity and specificity of this risk model in the validation cohort to evaluate the accurate classification of the disease outcome; and (3) calibration of the model in the external cohort. We also report new analyses: calculation of the net reclassification improvement (NRI), a measure of model assessment and quantification of the contribution of genetic factors that has not been previously applied to AMD progression, and statistical assessment of the differences or heterogeneity of the models for GA and NV. Validation of risk factors enhances the likelihood that the prediction model will be generalizable and useful in detecting high-risk individuals for inclusion in clinical trials and for potential discovery of new treatments.

• **DERIVATION COHORT: AGE-RELATED EYE DISEASE STUDY POPULATION:** Data from the AREDS, a multicenter randomized clinical trial, were used in analyses to develop the model (referred to herein as the derivation cohort). All research adhered to the tenets of the Declaration of Helsinki and was performed under approved institutional review board protocol prior to the initiation of the study. The protocol was approved by a data and safety monitoring committee for 11 participating ophthalmic centers. Written informed consent was obtained from all participants prior to enrollment. This trial was registered at clinicaltrials.gov as NCT00594672.

Details of the AREDS have been previously reported.[51] The AREDS evaluated the effect of antioxidant and mineral supplements on AMD and cataract risk, and assessed progression to advanced stages of AMD. Participants were aged 55-80 years at baseline and were required to have at least 1 eye with a VA no worse than 20/32. At least 1 eye was also required to be free from eye disease that might complicate the assessment of AMD, and the eye could not have had previous ocular surgery except for cataract extraction and unilateral photocoagulation for AMD. Participants were excluded from enrollment based on illness or other disorders that would complicate long-term longitudinal follow-up or compliance with the study protocol. This study enrolled a total of 4757 participants in the United States from 1992 to 1998. This analysis included 2894 individuals or 5600 eyes, of which 5355 had complete genetic data. In this cohort, 1193 eyes progressed to advanced AMD: 599 to GA and 704 to NV (could also transition from GA). Among the 1149 progressing eyes with complete genetic data, 578 progressed to GA and 677 to NV. The mean follow-up time was 9.3 years and the interquartile range was 8-11 years.

• **VALIDATION COHORT: SEDDON LONGITUDINAL AMD REGISTRY AND BIOREPOSITORY COHORT:** Risk prediction models derived from the AREDS cohort were validated using data from the Seddon Longitudinal Cohort, a large independent AMD cohort. All participants were enrolled in ongoing genetic and epidemiologic studies of AMD including a registry and biorepository of genetic and other biologic samples, as well as prospective assessment of progression and risk factors for disease, beginning in 1985 (J.M.S., Principal Investigator). Participants were derived from clinic populations and nationwide referrals and were prospectively followed. This research adhered to the tenets of the Declaration of Helsinki and was performed under approved institutional review board protocol. Written informed consent was obtained for all participants.

A total of 2865 participants were recruited for the Seddon Longitudinal AMD Cohort. The selection criteria are outlined in Figure 1. Subjects were eligible for this study of disease progression if they had at least 1 eye with nonadvanced AMD at baseline and at least 1 year of follow-up. Participants with advanced disease in both eyes at baseline could not progress to advanced AMD, and therefore were not eligible for inclusion in the analyses reported herein. In order to maintain consistency with AREDS (the derivation cohort), for these analyses only the subset of eligible participants in the validation cohort aged between 55 and 80 years at the baseline visit were included. A total of 2497 participants met the above inclusion criteria.

In addition, exclusions were made for the following: (1) incomplete genetic data required for validation of the risk prediction algorithm derived from the AREDS cohort; and (2) incomplete lifestyle data, including assessments for level of education, body mass index (BMI), and smoking. A total of 341 participants were excluded based on these criteria. The final validation cohort for analysis comprised 2156 participants and 3955 individual eyes. In the validation cohort with complete genetic data, 686 eyes progressed to advanced AMD: 357 to GA and 364 to NV. The mean follow-up time was 9.8 years with an interquartile range of 7.9-12.0 years.

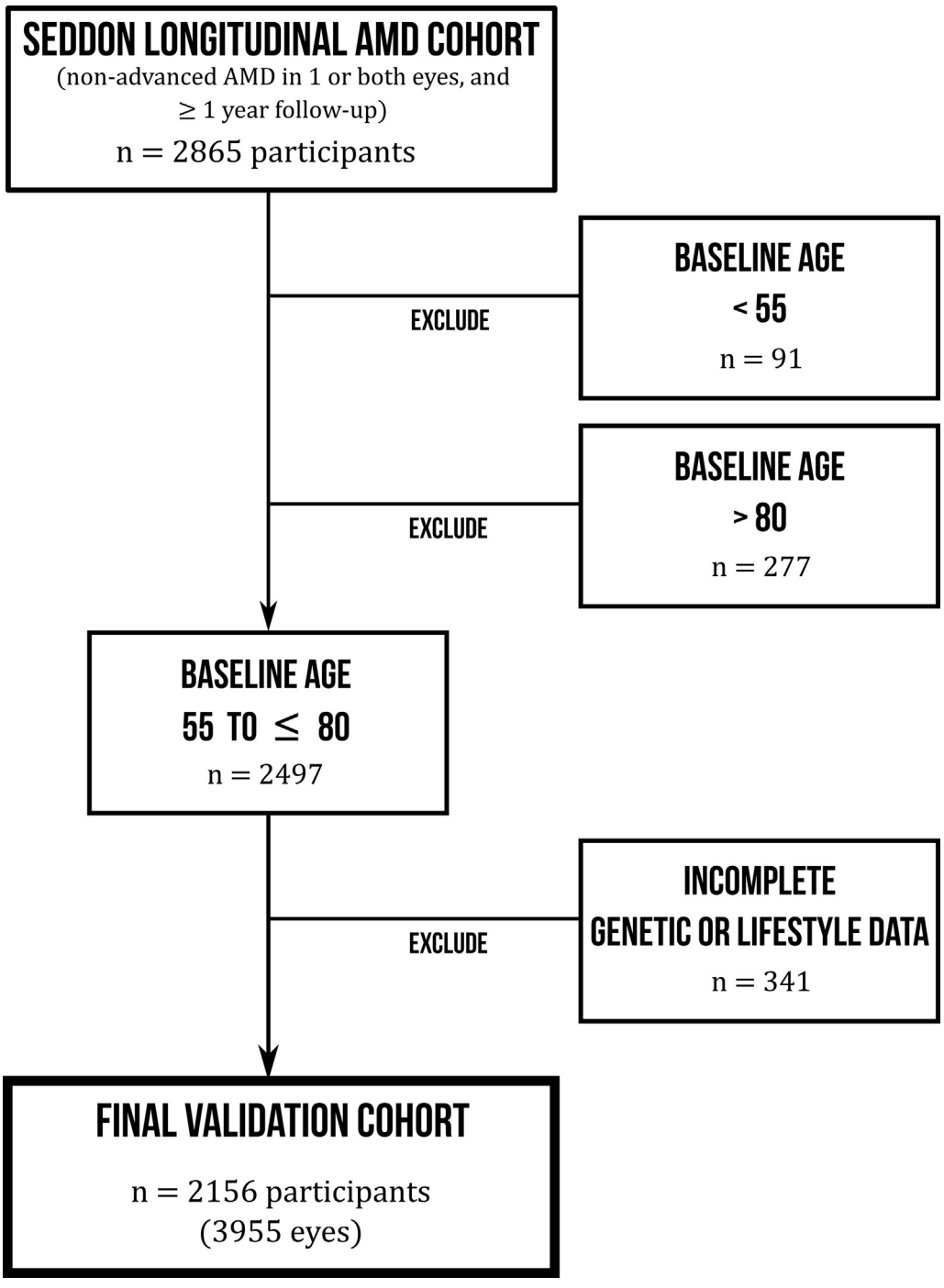

FIGURE 1. Flow chart illustrating the selection of participants for inclusion in the validation cohort from the Seddon Longitudinal Age-Related Macular Degeneration Cohort.

Ocular Examinations and Clinical Records. For the validation cohort, a baseline ocular examination was conducted upon enrollment into the study. The participant's current ophthalmologist or another ophthalmologist who agreed to participate was recruited to perform the examination. Detailed protocols and standardized clinical data forms were designed by J.M.S. Refraction, best-corrected visual acuity, and cataract status were assessed; intraocular pressure was measured; and iris color was classified. A dilated examination including a detailed evaluation of the macula was performed, and previous ocular records were obtained. Color fundus photographs were obtained in up to 7 standard fields based on the modified Airlie House classification, adopted by the Early Treatment Diabetic

Retinopathy Study (ETDRS) and previously described elsewhere.[52] Briefly, images were obtained using 30-degree fundus cameras with the following standard field definitions: 1, centered on the optic disc; 2, centered on the macula; 3, temporal to the macula; and fields 4-7, tangential to horizontal lines passing through the upper and lower poles of the disc and to a vertical line passing through its center.

Study examination data and all available ocular images were evaluated by J.M.S., and subjects were assigned a baseline AMD grade in both eyes. Subsequent clinical records and imaging were obtained annually by the research team and these were assigned follow-up grades by J.M.S. to allow for prospective analyses of this cohort.

Risk Factor Data and Measurements. Demographic, behavioral, and medical data were collected at baseline for both cohorts using standardized risk factor questionnaires. Questionnaires included information related to demographic characteristics, cigarette smoking, and medical history. Height, weight, and blood pressure were measured at baseline. BMI (kg/m^2) was calculated [weight (kg)/height $(m)^2$].

• **PROGRESSION TO ADVANCED AGE-RELATED MACULAR DEGENERATION:** The Clinical Age-Related Maculopathy Staging (CARMS)[53] system was applied to both the model-fitting and validation cohorts to determine AMD phenotypes in each eye at baseline and for all follow-up visits. In the AREDS cohort, phenotype data for all follow-up visits were based on the AREDS AMD Severity Scale.[54] This classification system was used to categorize individual eyes using the CARMS system. CARMS grades were assigned as follows: grade 1, no AMD, no drusen or only a few small drusen $<$ 63 μm; grade 2, early AMD, intermediate-size drusen 63-124 μm; grade 3, intermediate AMD, large drusen $\geq$ 125 μm. Grades 2 and 3 were further subdivided. For grade 2 eyes, 3 subtypes were delineated: grade 2A, several small drusen or $<$ 15 intermediate-size drusen 63-124 μm; grade 2B, no drusen, abnormalities in the retinal pigment epithelium (RPE); and grade 2C, drusen and RPE abnormalities. For grade 3 eyes, 2 subtypes were defined: grade 3A, several intermediate-size drusen or any large drusen; and grade 3B, drusenoid RPE detachment. Advanced eyes were categorized into 1 of 2 advanced stages of disease: grade 4, the advanced dry subtype, GA (including both central and noncentral forms) that was primary GA and not secondary or subsequent to treatment for NV; and grade 5, NV, or advanced exudative AMD, with choroidal neovascularization (CNV). In the validation cohort, nonadvanced eyes were classified using the CARMS system based on all available phenotype data including the ocular examination, clinical records, and ocular imaging.

• **MACULAR PHENOTYPIC OUTCOMES:** Three anatomic endpoints related to progression to advanced AMD and the advanced AMD subtypes (GA and NV) were prospectively evaluated during this study. Eyes that progressed were defined by a transition from no AMD, early AMD, or intermediate AMD to either GA or NV. The following criteria were used to classify progression: (1) no advanced disease was present at baseline, and an eye became advanced (GA or NV) during follow-up; (2) GA was present in a specific eye at baseline and developed NV during follow-up; and (3) no advanced disease was present at baseline, and an eye developed GA during follow-up and subsequently developed NV. Eyes that developed NV were censored and were considered to be in an absorbing state, meaning that follow-up was terminated. Eyes could not retroactively develop GA in these analyses. Participants with advanced disease in both eyes at baseline were excluded from all analyses of progression to advanced disease.

• **VISUAL ACUITY:** Visual acuity (VA) was evaluated as another outcome of interest in the derivation cohort. All AREDS participants had a best-corrected VA of 20/32 or better in at least 1 eye at baseline. VA was evaluated using the ETDRS logMAR chart. VA was assessed every 6 months. Progression to visual loss over time was defined as decline in VA of 15 letters or more in an individual eye. Normal vision was defined as 95-100 letters. Visual loss was classified as mild (75-90 letters), moderate (55-70 letters), or severe (35-50 letters). Eyes with profound visual loss (15-30 letters) or near blindness (0-10 letters) at baseline were excluded from all analyses of visual acuity. Eyes were included in VA analyses regardless of baseline AMD grade.

• **DEMOGRAPHIC AND BEHAVIORAL COVARIATES:** Baseline demographic, behavioral, and ocular characteristics were determined for each participant. The following covariates were evaluated as risk factors for progression and visual loss: age (55-64, 65-74, $\geq$75), sex, race (white, nonwhite [Black, Hispanic, Asian/Pacific Islander, other]) education ($\leq$high school, $>$high school), BMI ($<$25, 25-29, $\geq$30), and smoking status (never, past, current).

• **GENOTYPING AND GENETIC DATA:** The DNA samples for the AREDS study population were purchased from the AREDS repository. The DNA samples for the validation cohort were obtained from enrolled study participants according to the standard study protocol. Genotypes were determined using array-based genotyping and gene sequencing platforms as previously described.[14,19,25,26,32] All single nucleotide polymorphisms (SNPs) had a high genotype call rate ($>$ 98%), none deviated from Hardy-Weinberg equilibrium ($P < 10^{-3}$), and none failed a differential missing test between groups being compared. PLINK was used to perform all quality control steps.[55]

Numerous SNPs were previously shown to be associated with AMD and provide the basis for evaluating the effects of different genes on each individual anatomic endpoint in

a new predictive model. We classified genetic data into the following physiology-based categories: (1) complement pathway; (2) angiogenesis pathway; (3) lipid pathway; (4) immune/inflammatory pathway; (5) components of the extracellular matrix; and (6) DNA repair and protein binding. Although some of the SNPs are involved in more than 1 potential pathway, they were grouped as described below for these analyses.

Ten unique genetic loci were classified as complement pathway SNPs: complement factor H (*CFH*) Y402H (rs1061170); *CFH* rs1410996; *CFH* R1210C (rs121913059); *CFH* N1050Y (rs35274867); complement factor B (*CFB*) R32Q (rs641153); complement factor I (*CFI*) rs10033900; complement component 2 (*C2*) E318D (rs9332739); complement component 3 (*C3*) R102G (rs2230199); *C3* K155Q (rs147859257); and complement component 9 (*C9*) P167S (rs34882957).

Two loci associated with the angiogenesis pathway were vascular endothelial growth factor A (*VEGFA*) rs943080[25] and transforming growth factor beta receptor 1 (*TGFBR1*) rs334353.

Five SNPs were assessed as genetic risk factors in the lipid pathway: lipase C, hepatic type (*LIPC*) rs10468017; adenosine triphosphate binding cassette transporter 1 (*ABCA1*) rs1883025; cholesteryl ester transfer protein (*CETP*) rs3764261; apolipoprotein C1/apolipoprotein E (*APOC1/APOE*) rs4420638; and apolipoprotein H (*APOH*) rs1801689.

Six SNPs in our analyses have been reported to have some involvement in the immune/inflammatory pathway: age-related maculopathy susceptibility 2/high-temperature requirement A serine peptidase 1 (*ARMS2*) rs10490924; pellino E3 ubiquitin protein ligase family member 3 (*PELI3*) rs145732233; tumor necrosis factor receptor superfamily member 10A (*TNFRSF10A*) rs13278062; solute carrier family 16 member 8 (*SLC16A8*) rs8135665; paired immunoglobin-like type 2 receptor beta/paired immunoglobin-like type 2 receptor alpha (*PILRB/PILRA*) rs11769700; and transmembrane protein 97/vitronectin (*TMEM97/VTN*) rs704.

Five loci have been associated with the extracellular matrix pathway: collagen type VIII alpha 1 chain (*COL8A1*) rs13095226[25,37,39]; collagen type IV alpha 3 chain (*COL4A3*) rs11884770; ADAM metallopeptidase with thrombospondin type 1 motif 9 (*ADAMTS9*) rs6795735; tissue inhibitor of metalloproteinase 3 (*TIMP3*) rs9621532; and chymotrypsinogen B1(*CTRB1*) rs8056814.

Three genetic loci related to DNA repair and protein binding were RAD51 paralog B (*RAD51B*) rs8017304; nuclear protein localization 4 homolog/tetraspanin 10 (*NPLOC4/TSPAN10*) rs9895741; and heat shock protein family H member 1/beta 3-glucosyltransferase (*HSPH1/B3GALTL*) rs9542236.

• **STATISTICAL ANALYSIS:** All statistical analyses evaluated individual eyes, with both eyes contributing to the results, accounting for correlation of progression times in the 2 eyes.[27,46–50] Rather than person-based analyses of the worst eye only, we account for eye-specific outcomes (progression to 3 distinct advanced AMD outcomes and visual acuity loss) and eye-specific covariates (such as baseline AMD grade). The application of eye-specific methodology also allows for the differentiation between participants who develop an outcome in a single eye compared to developing outcomes in both eyes. These methods result in a larger sample size with a resulting increase in statistical power.

The distributions of demographic, behavioral, ocular, and genetic risk factors were evaluated for progressors and nonprogressors to advanced AMD (GA or NV), and separately for progression to GA and NV. Univariate associations between each risk factor and progression were evaluated using Generalized Estimating Equations (Table 1), allowing for the use of correlated data in these eye-specific analyses.

Incidences of the various AMD outcomes were analyzed over the duration of available follow-up. Progression to each endpoint was evaluated using survival analysis methodology with the individual eye as the unit of analysis (using PROC PHREG with the aggregate option in SAS 9.4, allowing for the use of correlated data in eye-specific analyses).[56] These associations were assessed using Cox proportional hazards models. Hazard ratios (HRs) were estimated and 95% confidence intervals (CI) were calculated. Multivariate associations between progression to various endpoints and demographic, environmental, and ocular variables were evaluated (Table 2), and then associations between each individual SNP and overall AMD (Table 3) and GA and NV (Table 4) were assessed, adjusting for age, sex, education, BMI, baseline grade, and smoking.

Separate risk prediction models were determined for progression to advanced AMD, GA, and NV based on stepwise regression methods (Table 5). These stepwise regression models allow for the variables most predictive of a specific outcome to be determined based on an automatic procedure. The procedure involves each explanatory variable being separately considered for inclusion or exclusion from a predictive model based on a set of criteria that are specified a priori. The STEPWISE selection option of PROC PHREG was used, with $P < .05$ for a SNP to enter the model and $P < .10$ to remain in the model. Each model included age, sex, education, BMI, smoking history, and baseline grade. The nongenetic factors were included in all models given that they have been shown a priori to be predictive of progression to advanced AMD. All SNPs for which genotype data were obtained (n = 31) were evaluated together and were subsequently included or not included in the final models. The stepwise procedure was used to select genetic loci that were most predictive of progression to each outcome after controlling for the nongenetic variables mentioned previously. Visual loss greater than 15 letters was assessed using the same methods as those described above for progression to advanced AMD.

TABLE 1. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Progression to Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Derivation Cohort

	Overall Advanced AMD			GA			NV		
	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]
Sample size[b]	n = 1193	n = 4407		n = 599	n = 4407		n = 704	n = 4407	
Demographic									
Age (y)									
≥75	224 (18.9)	386 (8.8)	<.0001	112 (18.8)	386 (8.9)	<.0001	139 (20.0)	386 (8.9)	<.0001
65 to 74	773 (65.3)	2808 (63.9)		387 (64.9)	2808 (63.9)		457 (65.7)	2808 (63.9)	
55 to 64	187 (15.8)	1203 (27.4)		97 (16.3)	1203 (27.4)		100 (14.4)	1203 (27.4)	
Sex									
Male	508 (42.6)	1915 (43.5)	.84	273 (45.6)	1915 (43.5)	.45	280 (39.8)	1915 (43.5)	.16
Female	685 (57.4)	2492 (56.6)		326 (54.4)	2492 (56.6)		424 (60.2)	2492 (56.6)	
Race									
White	1184 (99.3)	4197 (95.2)	<.0001	597 (99.7)	4197 (95.2)	.0003	697 (99.0)	4197 (95.2)	<.0001
Nonwhite	9 (0.8)	210 (4.8)		2 (0.3)	210 (4.8)		7 (1.0)	210 (4.8)	
Behavioral									
Education									
≤ High school	458 (38.4)	1355 (30.8)	<.0001	231 (38.6)	1355 (30.8)	.001	280 (39.8)	1355 (30.8)	<.0001
> High school	735 (61.6)	3052 (69.3)		368 (61.4)	3052 (69.3)		424 (60.2)	3052 (69.3)	
Body mass index									
<25	362 (30.3)	1519 (34.5)	.009	182 (30.4)	1519 (34.5)	.05	213 (30.3)	1519 (34.5)	.03
25 to 29.9	488 (40.9)	1864 (42.3)		240 (40.1)	1864 (42.3)		293 (41.6)	1864 (42.3)	
≥30	343 (28.8)	1023 (23.4)		177 (29.6)	1024 (23.2)		198 (28.1)	1024 (23.2)	
Smoking									
Never	468 (39.2)	2223 (50.4)	<.0001	249 (41.6)	2223 (50.4)	.0008	265 (37.6)	2223 (50.4)	<.0001
Past	620 (52.0)	1978 (44.9)		304 (50.8)	1978 (44.9)		370 (52.6)	1978 (44.9)	
Current	105 (8.8)	206 (4.7)		46 (7.7)	206 (4.7)		69 (9.8)	206 (4.7)	
Ocular									
Baseline AMD grade									
1	29 (2.4)	2156 (48.9)	<.0001	4 (0.7)	2156 (48.9)	<.0001	25 (3.6)	2156 (48.9)	<.0001
2	127 (10.7)	1260 (28.6)		49 (8.2)	1260 (28.6)		84 (11.9)	1260 (28.6)	
3	1037 (86.9)	991 (22.5)		546 (91.2)	991 (22.5)		595 (84.5)	991 (22.5)	
Genetic loci									
Complement pathway									
CFH Y402H: rs1061170									
TT	187 (15.7)	1584 (35.9)	<.0001	98 (16.4)	1584 (35.9)	<.0001	103 (14.6)	1584 (35.9)	<.0001
CT	540 (45.3)	2027 (46.0)		261 (43.6)	2027 (46.0)		325 (46.2)	2027 (46.0)	
CC	466 (39.1)	796 (18.1)		240 (40.1)	796 (18.1)		276 (39.2)	796 (18.1)	
CFH: rs1410996									
TT	40 (3.4)	719 (16.3)	<.0001	22 (3.7)	719 (16.3)	<.0001	21 (3.0)	719 (16.3)	<.0001
CT	361 (30.3)	1988 (45.2)		176 (29.5)	1988 (45.2)		211 (30.0)	1988 (45.2)	
CC	790 (66.3)	1694 (38.5)		399 (66.8)	1694 (38.5)		471 (67.0)	1694 (38.5)	
CFH R1210C: rs121913059									
CC	1156 (98.8)	4327 (99.7)	.009	582 (98.8)	4327 (99.7)	.005	680 (98.7)	4327 (99.7)	.009
CT	14 (1.2)	12 (0.3)		7 (1.2)	12 (0.3)		9 (1.3)	12 (0.3)	
C2 E318D: rs9332739									
GG	1151 (96.5)	4056 (92.1)	<.0001	583 (97.3)	4056 (92.1)	.0001	676 (96.0)	4056 (92.1)	.001
CG/CC	42 (3.5)	349 (7.9)		16 (2.7)	349 (7.9)		28 (4.0)	349 (7.9)	
CFB R32Q: rs641153									
CC	1094 (92.5)	3662 (83.8)	<.0001	552 (92.6)	3662 (83.8)	<.0001	645 (92.7)	3662 (83.8)	<.0001
TC/TT	89 (7.5)	707 (16.2)		44 (7.4)	707 (16.2)		51 (7.3)	707 (16.2)	

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TABLE 1. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Progression to Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Derivation Cohort (*Continued*)

	Overall Advanced AMD			GA			NV		
	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]
CFI: rs10033900									
CC	282 (23.6)	1184 (26.9)	.004	141 (23.5)	1184 (26.9)	.01	166 (23.6)	1184 (26.9)	.02
CT	563 (47.2)	2165 (49.2)		272 (45.4)	2165 (49.2)		343 (48.7)	2165 (49.2)	
TT	348 (29.2)	1052 (23.9)		186 (31.1)	1052 (23.9)		195 (27.7)	1052 (23.9)	
C3 R102G: rs2230199									
CC	569 (47.8)	2714 (61.6)	<.0001	288 (48.2)	2714 (61.6)	<.0001	335 (47.7)	2714 (61.6)	<.0001
CG	510 (42.8)	1497 (34.0)		257 (43.1)	1497 (34.0)		299 (42.5)	1497 (34.0)	
GG	112 (9.4)	192 (4.4)		52 (8.7)	192 (4.4)		69 (9.8)	192 (4.4)	
C3 K155Q: rs147859257									
TT	1117 (95.5)	4287 (98.8)	<.0001	557 (94.6)	4287 (98.8)	<.0001	664 (96.4)	4287 (98.8)	<.0001
GT	53 (4.5)	52 (1.2)		32 (5.4)	52 (1.2)		25 (3.6)	52 (1.2)	
C9 P167S: rs34882957									
GG	1129 (96.5)	4261 (98.2)	.004	566 (96.1)	4261 (98.2)	.008	666 (96.7)	4261 (98.2)	.02
AG	41 (3.5)	78 (1.8)		23 (3.9)	78 (1.8)		23 (3.3)	78 (1.8)	
CFH N1050Y: rs35274867									
AA	1148 (98.7)	4146 (97.2)	.01	578 (98.8)	4146 (97.2)	.03	677 (98.7)	4146 (97.2)	.05
TA	14 (1.2)	116 (2.7)		6 (1.0)	116 (2.7)		9 (1.3)	116 (2.7)	
TT	1 (0.1)	5 (0.1)		1 (0.2)	5 (0.1)		0 (0.0)	5 (0.1)	
Angiogenesis pathway									
VEGFA: rs943080									
CC	231 (19.7)	968 (22.3)	.12	117 (19.9)	968 (22.3)	.48	137 (19.9)	968 (22.3)	.11
CT	611 (52.2)	2190 (50.5)		312 (53.0)	2190 (50.5)		351 (50.9)	2190 (50.5)	
TT	328 (28.0)	1181 (27.2)		160 (27.2)	1181 (27.2)		201 (29.2)	1181 (27.2)	
TGFBR1: rs334353									
TT	702 (60.0)	2481 (57.2)	.17	335 (56.9)	2481 (57.2)	.93	433 (62.8)	2481 (57.2)	.02
GT	399 (34.1)	1579 (36.4)		216 (36.7)	1579 (36.4)		221 (32.1)	1579 (36.4)	
GG	69 (5.9)	279 (6.4)		38 (6.5)	279 (6.4)		35 (5.1)	279 (6.4)	
Lipid pathway									
LIPC: rs10468017									
CC	654 (54.9)	2267 (51.5)	.06	343 (57.3)	2267 (51.5)	.01	363 (51.6)	2267 (51.5)	.39
TC	467 (39.2)	1784 (40.5)		223 (37.2)	1784 (40.5)		296 (42.1)	1784 (40.5)	
TT	71 (6.0)	348 (7.9)		33 (5.5)	348 (7.9)		44 (6.3)	348 (7.9)	
ABCA1: rs1883025									
CC	679 (56.9)	2411 (54.8)	.19	345 (57.6)	2411 (54.8)	.32	402 (57.1)	2411 (54.8)	.16
TC	447 (37.5)	1706 (38.8)		219 (36.6)	1706 (38.8)		268 (38.1)	1706 (38.8)	
TT	67 (5.6)	284 (6.5)		35 (5.8)	284 (6.5)		34 (4.8)	284 (6.5)	
CETP: rs3764261									
CC	471 (39.9)	1934 (44.0)	.002	236 (39.6)	1934 (44.0)	.03	273 (38.8)	1934 (44.0)	.003
AC	549 (46.1)	1986 (45.2)		280 (47.0)	1986 (45.2)		323 (46.0)	1986 (45.2)	
AA	170 (14.3)	476 (10.8)		80 (13.4)	476 (10.8)		107 (15.2)	476 (10.8)	
APOC1/APOE: rs4420638									
AA	855 (73.1)	3085 (71.1)	.22	427 (72.5)	3085 (71.1)	.46	506 (73.4)	3085 (71.1)	.30
GA	315 (26.9)	1254 (28.9)		162 (27.5)	1254 (28.9)		183 (26.6)	1254 (28.9)	
APOH: rs1801689									
AA	1101 (94.7)	3972 (93.1)	.07	557 (95.2)	3972 (93.1)	.06	651 (94.9)	3972 (93.1)	.10
AC	62 (5.3)	292 (6.8)		28 (4.8)	292 (6.8)		35 (5.1)	292 (6.8)	
CC	0 (0.0)	3 (0.1)		0 (0.0)	3 (0.1)		0 (0.0)	3 (0.1)	
Immune/inflammatory pathway									
ARMS2/HTRA1: rs10490924									
GG	368 (31.0)	2564 (58.2)	<.0001	184 (30.8)	2564 (58.2)	<.0001	201 (28.7)	2564 (58.2)	<.0001
TG	581 (48.9)	1559 (35.4)		297 (49.8)	1559 (35.4)		341 (48.6)	1559 (35.4)	

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TABLE 1. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Progression to Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Derivation Cohort (*Continued*)

	Overall Advanced AMD			GA			NV		
	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]
TT	240 (20.2)	284 (6.4)		116 (19.4)	284 (6.4)		159 (22.7)	284 (6.4)	
PELI3: rs145732233									
CC	1159 (99.7)	4221 (99.1)	.06	583 (99.8)	4221 (99.1)	.06	684 (99.7)	4221 (99.1)	.18
TC	3 (0.3)	40 (0.9)		1 (0.2)	40 (0.9)		2 (0.3)	40 (0.9)	
TNFRSF10A: rs13278062									
TT	335 (28.6)	1179 (27.2)	.99	166 (28.2)	1179 (27.2)	.32	207 (30.0)	1179 (27.2)	.27
GT	556 (47.5)	220 (50.7)		266 (45.2)	220 (50.7)		338 (49.1)	220 (50.7)	
GG	279 (23.9)	960 (22.1)		157 (26.7)	960 (22.1)		144 (20.9)	960 (22.1)	
SLC16A8: rs8135665									
CC	724 (61.9)	2771 (63.9)	.15	360 (61.1)	2771 (63.9)	.07	426 (61.8)	2771 (63.9)	.11
TC	379 (32.4)	1394 (32.1)		192 (32.6)	1394 (32.1)		225 (32.7)	1394 (32.1)	
TT	67 (5.7)	174 (4.0)		37 (6.3)	174 (4.0)		38 (5.5)	174 (4.0)	
PILRB/PILRA: rs11769700									
TT	739 (63.5)	2701 (63.3)	.70	381 (65.1)	2701 (63.3)	.57	424 (61.8)	2701 (63.3)	.37
CT	376 (32.3)	1397 (32.7)		180 (30.8)	1397 (32.7)		234 (34.1)	1397 (32.7)	
CC	48 (4.1)	169 (4.0)		24 (4.1)	169 (4.0)		28 (4.1)	169 (4.0)	
TMEM97/VTN: rs704									
AA	278 (23.9)	1014 (23.7)	.65	139 (23.8)	1014 (23.7)	.86	168 (24.5)	1014 (23.7)	.64
AG	582 (50.0)	2089 (49.0)		294 (50.3)	2089 (49.0)		336 (49.0)	2089 (49.0)	
GG	303 (26.1)	1164 (27.3)		152 (26.0)	1164 (27.3)		182 (26.5)	1164 (27.3)	
Extracellular matrix									
COL8A1: rs13095226									
TT	916 (76.8)	3613 (82.0)	.0004	454 (75.8)	3613 (82.0)	.002	538 (76.4)	3613 (82.0)	.001
CT	255 (21.4)	748 (17.0)		131 (21.9)	748 (17.0)		155 (22.0)	748 (17.0)	
CC	22 (1.8)	44 (1.0)		14 (2.3)	44 (1.0)		11 (1.6)	44 (1.0)	
COL4A3: rs11884770									
CC	638 (54.9)	2243 (52.6)	.06	304 (52.0)	2243 (52.6)	.69	395 (57.6)	2243 (52.6)	.008
TC	452 (38.9)	1675 (39.3)		239 (40.9)	1675 (39.3)		253 (36.9)	1675 (39.3)	
TT	73 (6.3)	349 (8.2)		42 (7.2)	349 (8.2)		38 (5.5)	349 (8.2)	
CTRB1: rs8056814									
GG	1017 (87.0)	3504 (80.7)	<.0001	512 (86.9)	3504 (80.7)	.0009	602 (87.5)	3504 (80.7)	<.0001
AG	149 (12.8)	786 (18.1)		76 (12.9)	786 (18.1)		84 (12.2)	786 (18.1)	
AA	3 (0.3)	50 (1.2)		1 (0.2)	50 (1.2)		2 (0.3)	50 (1.2)	
ADAMTS9: rs6795735									
CC	366 (31.3)	1271 (29.3)	.17	190 (32.3)	1271 (29.3)	.08	210 (30.5)	1271 (29.3)	.49
TC	569 (48.6)	2098 (48.4)		289 (49.1)	2098 (48.4)		333 (48.3)	2098 (48.4)	
TT	235 (20.1)	970 (22.4)		110 (18.7)	970 (22.4)		146 (21.2)	970 (22.4)	
TIMP3: rs9621532									
AA	1101 (92.3)	3939 (89.5)	.01	553 (92.3)	3939 (89.5)	.04	654 (92.9)	3939 (89.5)	.01
CA/CC	92 (7.7)	464 (10.5)		46 (7.7)	464 (10.5)		50 (7.1)	464 (10.5)	
DNA repair/protein binding									
RAD51B: rs8017304									
AA	510 (43.6)	1716 (39.6)	.0003	244 (41.4)	1716 (39.6)	.05	310 (45.0)	1716 (39.6)	.0002
GA	555 (47.4)	2004 (46.2)		290 (49.2)	2004 (46.2)		321 (46.6)	2004 (46.2)	
GG	105 (9.0)	619 (14.3)		55 (9.3)	619 (14.3)		58 (8.4)	619 (14.3)	
NPLOC4/TSPAN10: rs9895741									
GG	456 (39.2)	1822 (42.7)	.04	240 (41.0)	1822 (42.7)	.37	263 (38.3)	1822 (42.7)	.02
AG	526 (45.2)	1880 (44.1)		259 (44.3)	1880 (44.1)		310 (45.2)	1880 (44.1)	
AA	181 (15.6)	565 (13.2)		86 (14.7)	565 (13.2)		113 (16.5)	565 (13.2)	

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TABLE 1. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Progression to Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Derivation Cohort (*Continued*)

	Overall Advanced AMD			GA			NV		
	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]	Progressors	Nonprogressors	*P* Value[a]
HSPH1/B3GALTL: rs9542236									
TT	347 (29.7)	1453 (33.5)	.004	180 (30.6)	1453 (33.5)	.02	199 (28.9)	1453 (33.5)	.005
CT	555 (47.4)	2108 (48.6)		273 (46.4)	2108 (48.6)		336 (48.8)	2108 (48.6)	
CC	268 (22.9)	778 (17.9)		136 (23.1)	778 (17.9)		154 (22.4)	778 (17.9)	

AMD = age-related macular degeneration; GA = geographic atrophy; NV = neovascular disease.

[a]*P* values calculated using Generalized Estimating Equations in order to account for inter-correlation in eye-specific analyses for 12-year progression.

[b]Sample sizes for each genetic variable presented in the table may not be equal to the overall sample size. Some participants do not have genetic information available for all genetic loci evaluated. Also note that the sum of the sample sizes for GA and NV do not equal the sample size for advanced AMD, as the sample for NV includes eyes that had GA at baseline.

TABLE 2. Multivariate Associations Between Demographic, Behavioral, and Ocular Factors and Progression to Overall Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Derivation Cohort

	Overall Advanced AMD		Progression to GA		Progression to NV	
	HR (95% CI)[a]	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Demographic						
Age (y)						
≥75	*Referent*		*Referent*		*Referent*	
65 to 74.9	0.69 (0.59-0.81)	<.0001	0.72 (0.58-0.89)	.003	0.68 (0.57-0.83)	.0001
55 to 64.9	0.49 (0.40-0.62)	<.0001	0.55 (0.41-0.74)	.0001	0.46 (0.35-0.60)	<.0001
Sex						
Female	*Referent*		*Referent*		*Referent*	
Male	0.97 (0.34-1.12)	.64	1.20 (0.99-1.46)	.06	0.83 (0.69-0.99)	.04
Race						
Nonwhite	*Referent*		*Referent*		*Referent*	
White	4.11 (2.20-7.67)	<.0001	8.38 (2.11-33.33)	.003	2.72 (1.34-5.53)	.006
Behavioral						
Education						
≤High school	*Referent*		*Referent*		*Referent*	
>High school	0.79 (0.69-0.91)	.0007	0.81 (0.67-0.97)	.03	0.79 (0.67-0.94)	.006
Body mass index						
<25	*Referent*		*Referent*		*Referent*	
25 to 29.9	1.16 (0.99-1.36)	.08	1.05 (0.84-1.32)	.66	1.18 (0.97-1.44)	.10
≥30	1.41 (1.19-1.68)	.0001	1.35 (1.06-1.71)	.01	1.35 (1.08-1.67)	.007
Smoking						
Never	*Referent*		*Referent*		*Referent*	
Past	1.26 (1.09-1.45)	.002	1.04 (0.85-1.27)	.70	1.40 (1.17-1.68)	.0002
Current	2.22 (1.71-2.88)	<.0001	1.46 (1.01-2.10)	.05	2.49 (1.83-3.40)	<.0001
Ocular						
Baseline AMD grade						
1	*Referent*		*Referent*		*Referent*	
2	6.90 (4.46-10.67)	<.0001	18.92 (6.80-52.65)	<.0001	5.17 (3.18-8.39)	<.0001
3	46.8 (31.22-70.19)	<.0001	152.59 (57.05-408.17)	<.0001	25.97 (16.61-40.61)	<.0001

AMD = age-related macular degeneration; CI = confidence interval; GA = geographic atrophy; HR = hazard ratio; NV = neovascular disease. HRs are adjusted for all variables listed in the table.

[a]HRs and 95% CIs were estimated using Cox proportional hazards models for 12-year progression using the individual eye as the unit of analysis.

TABLE 3. Multivariate Associations Between Individual Genetic Loci and Progression to Advanced Age-Related Macular Degeneration in the Derivation Cohort

	Multivariate Model I[a]		Multivariate Model II[b]	
Genetic Loci	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Complement pathway				
CFH Y402H: rs1061170	1.41 (1.29-1.55)	<.0001	1.15 (1.02-1.30)	.02
CFH: rs1410996	1.68 (1.50-1.89)	<.0001	1.47 (1.26-1.71)	<.0001
CFH R1210C: rs121913059	2.34 (1.43-3.80)	.0007	4.37 (2.76-6.91)	<.0001
C2 E318D: rs9332739	0.61 (0.43-0.87)	.007	0.61 (0.43-0.87)	.006
CFB R32Q: rs641153	0.58 (0.44-0.75)	<.0001	0.72 (0.55-0.94)	<.0001
CFI: rs10033900	1.08 (0.99-1.18)	.10	1.06 (0.97-1.16)	.22
C3 R102G: rs2230199	1.28 (1.16-1.42)	<.0001	1.27 (1.14-1.41)	<.0001
C3 K155Q: rs147859257	1.84 (1.35-2.50)	.0001	1.99 (1.48-2.70)	<.0001
C9 P167S: rs34882957	1.12 (0.81-1.55)	.50	0.92 (0.68-1.25)	.59
CFH N1050Y: rs35274867	0.61 (0.36-1.05)	.07	1.17 (0.71-1.93)	.54
Angiogenesis pathway				
VEGFA: rs943080	0.98 (0.89-1.08)	.73	1.01 (0.92-1.11)	.87
TGFBR1: rs334353	0.95 (0.85-1.06)	.35	0.92 (0.82-1.02)	.10
Lipid pathway				
LIPC: rs10468017	.94 (0.84-1.04)	.21	0.96 (0.86-1.07)	.43
ABCA1: rs1883025	.98 (0.88-1.09)	.72	0.98 (0.88-1.10)	.77
CETP: rs3764261	1.10 (1.00-1.21)	.04	1.08 (0.98-1.19)	.14
APOC1/APOE: rs4420638	1.00 (0.87-1.16)	.99	0.94 (0.81-1.09)	.41
APOH: rs1801689	0.74 (0.55-1.00)	.05	0.87 (0.66-1.15)	.32
Immune/inflammatory pathway				
ARMS2/HTRA1: rs10490924	1.55 (1.41-1.71)	<.0001	1.49 (1.35-1.64)	<.0001
PELI3: rs145732233	0.32 (0.09-1.09)	.07	0.28 (0.07-1.12)	.07
TNFRSF10A: rs13278062	1.08 (0.99-1.19)	.09	1.03 (0.93-1.13)	.61
SLC16A8: rs8135665	1.05 (0.94-1.18)	.40	1.06 (0.95-1.19)	.28
PILRB/PILRA: rs11769700	1.05 (0.94-1.17)	.42	1.04 (0.93-1.16)	.49
TMEM97/VTN: rs704	0.98 (0.89-1.08)	.69	0.92 (0.84-1.02)	.10
Extracellular matrix				
COL8A1: rs13095226	1.22 (1.06-1.41)	.005	1.18 (1.02-1.37)	.03
COL4A3: rs11884770	0.95 (0.86-1.06)	.34	0.95 (0.86-1.06)	.36
CTRB1: rs8056814	0.79 (0.65-0.96)	.02	0.85 (0.70-1.03)	.10
ADAMTS9: rs6795735	0.98 (0.89-1.08)	.64	1.01 (0.92-1.11)	.86
TIMP3: rs9621532	0.74 (0.58-0.94)	.02	0.81 (0.63-1.04)	.09
DNA repair/protein binding				
RAD51B: rs8017304	0.86 (0.77-0.95)	.003	0.85 (0.77-0.95)	.003
NPLOC4/TSPAN10: rs9895741	1.08 (0.98-1.19)	.10	1.06 (0.96-1.16)	.26
HSPH1/B3GALTL: rs9542236	1.17 (1.07-1.29)	.0005	1.14 (1.04-1.25)	.005

AMD = age-related macular degeneration; CI = confidence interval; HR = hazard ratio.

[a]Multivariate Model I: HRs for 12-year progression, risk per allele, adjusted for age, sex, race, education, and baseline AMD grade.

[b]Multivariate Model II: HRs reflect risk per allele, adjusted for age, sex, race, education, baseline AMD grade, body mass index, smoking status, and all other genetic loci in the table.

To assess heterogeneity, or whether there were differences in results between the 2 advanced outcomes, progression to GA or NV, we conducted analyses of the 2 subtypes and determined if any differences observed were statistically significant. Competing-risks regression approaches were used based on the data duplication method of Lunn and McNeil,[57] where a separate record was created to identify and compare risk factors consisting of genetic and nongenetic variables between progression to GA and NV. The set of genes considered in these analyses were all genes that were related to advanced AMD in the stepwise regression models.

Age-adjusted areas under the receiver operating curve (AUCs) were calculated for progression to overall advanced AMD, the 2 advanced subtypes, and VA loss using methodology previously described.[39,58,59] The AUC is an index that evaluates how well a specific model can discriminate between progressors and nonprogressors to

TABLE 4. Multivariate Associations Between Individual Genetic Loci and Progression to Geographic Atrophy and Neovascular Disease Subtypes in the Derivation Cohort

	GA				NV			
	Multivariate Model I[a]		Multivariate Model II[b]		Multivariate Model I[a]		Multivariate Model II[b]	
Genetic Loci	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Complement pathway								
CFH Y402H: rs1061170	1.47 (1.29-1.67)	<.0001	1.05 (0.86-1.28)	.63	1.53 (1.36-1.72)	<.0001	1.17 (1.00-1.35)	.04
CFH: rs1410996	1.76 (1.50-2.06)	<.0001	1.45 (1.14-1.85)	.003	1.87 (1.62-2.17)	<.0001	1.45 (1.19-1.76)	.0002
CFH R1210C: rs121913059	2.84 (1.34-6.03)	<.0001	3.94 (1.90-8.15)	.001	2.66 (1.45-4.88)	.002	4.25 (2.05-8.79)	<.0001
C2 E318D: rs9332739	0.45 (0.26-0.80)	.006	0.64 (0.34-1.21)	.17	0.66 (0.43-1.02)	.06	0.72 (0.48-1.10)	.13
CFB R32Q: rs641153	0.53 (0.37-0.77)	.0007	0.74 (0.48-1.12)	.16	0.53 (0.37-0.75)	.0003	0.73 (0.52-1.03)	.07
CFI: rs10033900	1.13 (0.99-1.29)	.08	1.14 (0.97-1.32)	.10	1.08 (0.96-1.21)	.20	1.00 (0.90-1.12)	.97
C3 R102G: rs2230199	1.30 (1.12-1.50)	.0005	1.16 (0.98-1.39)	.09	1.34 (1.18-1.53)	<.0001	1.25 (1.09-1.42)	.001
C3 K155Q: rs147859257	2.21 (1.49-3.28)	<.0001	2.59 (1.64-4.08)	<.0001	1.72 (1.08-2.73)	.02	1.24 (0.75-2.04)	.40
C9 P167S: rs34882957	1.27 (0.80-2.01)	.32	0.87 (0.53-1.43)	.40	1.08 (0.71-1.63)	.73	0.83 (0.54-1.30)	.42
CFH N1050Y: rs35274867	0.57 (0.26-1.25)	.16	0.94 (0.32-2.78)	.91	0.59 (0.28-1.23)	.16	1.26 (0.62-2.58)	.53
Angiogenesis pathway								
VEGFA: rs943080	0.97 (0.85-1.11)	.64	0.98 (0.84-1.14)	.76	1.01 (0.90-1.14)	.85	1.07 (0.94-1.21)	.30
TGFBR1: rs334353	1.03 (0.89-1.20)	.68	0.98 (0.82-1.17)	.79	0.89 (0.77-1.03)	.11	0.83 (0.72-0.96)	.01
Lipid pathway								
LIPC: rs10468017	0.88 (0.76-1.02)	.09	0.90 (0.75-1.08)	.26	0.97 (0.85-1.10)	.63	1.02 (0.89-1.16)	.83
ABCA1: rs1883025	0.97 (0.83-1.13)	.70	1.05 (0.88-1.26)	.58	0.95 (0.83-1.09)	.45	0.95 (0.83-1.10)	.51
CETP: rs3764261	1.09 (0.96-1.24)	.20	1.02 (0.87-1.20)	.78	1.14 (1.01-1.29)	.03	1.08 (0.96-1.23)	.21
APOC1/APOE: rs4420638	1.03 (0.84-1.27)	.77	0.98 (0.77-1.25)	.88	1.00 (0.83-1.20)	1.0	0.93 (0.78-1.12)	.46
APOH: rs1801689	0.62 (0.41-0.95)	.03	0.93 (0.60-1.44)	.74	0.72 (0.49-1.06)	.10	0.88 (0.58-1.34)	.56
Immune/inflammatory pathway								
ARMS2/HTRA1: rs10490924	1.59 (1.39-1.81)	<.0001	1.42 (1.21-1.65)	<.0001	1.75 (1.55-1.97)	<.0001	1.57 (1.39-1.78)	<.0001
PELI3: rs145732233	0.21 (0.04-1.22)	.08	0.26 (0.03-2.01)	.20	0.34 (0.06-1.96)	.23	0.39 (0.06-2.51)	.32
TNFRSF10A: rs13278062	1.17 (1.02-1.33)	.03	1.12 (0.95-1.31)	.18	1.04 (0.92-1.17)	.55	0.92 (0.82-1.04)	.20
SLC16A8: rs8135665	1.08 (0.92-1.26)	.35	1.11 (0.92-1.34)	.29	1.03 (0.89-1.19)	.69	1.01 (0.88-1.17)	.89
PILRB/PILRA: rs11769700	1.03 (0.87-1.21)	.75	0.97 (0.79-1.19)	.78	1.10 (0.96-1.27)	.18	1.13 (0.98-1.31)	.09
TMEM97/VTN: rs704	0.99 (0.86-1.13)	.82	1.06 (0.85-1.34)	.60	0.97 (0.86-1.09)	.59	0.94 (0.83-1.07)	.35
Extracellular matrix								
COL8A1: rs13095226	1.34 (1.09-1.64)	.006	1.26 (0.98-1.61)	.07	1.24 (1.04-1.48)	.02	1.18 (0.99-1.41)	.07
COL4A3: rs11884770	1.04 (0.89-1.20)	.65	1.13 (0.95-1.34)	.16	.089 (0.78-1.01)	.07	0.86 (0.75-0.98)	.03
CTRB1: rs8056814	0.79 (0.60-1.04)	.09	0.88 (0.65-1.19)	.40	0.74 (0.58-0.95)	.02	0.83 (0.65-1.06)	.14
ADAMTS9: rs6795735	0.34 (0.82-1.07)	.34	0.90 (0.77-1.05)	.19	1.02 (0.90-1.15)	.80	1.08 (0.96-1.21)	.22
TIMP3: rs9621532	0.71 (0.51-0.99)	.04	0.82 (0.56-1.19)	.30	0.66 (0.47-0.93)	.02	0.75 (0.53-1.06)	.10
DNA repair/protein binding								
RAD51B: rs8017304	0.87 (0.76-1.01)	.06	0.97 (0.82-1.15)	.71	0.81 (0.72-0.92)	.002	0.81 (0.71-0.92)	.002
NPLOC4/TSPAN10: rs9895741	1.06 (0.92-1.22)	.39	1.01 (0.86-1.19)	.89	1.13 (1.00-1.28)	.05	1.11 (0.99-1.25)	.08
HSPH1/B3GALTL: rs9542236	1.19 (1.05-1.35)	.008	1.08 (0.93-1.26)	.29	1.23 (1.09-1.38)	.0007	1.12 (0.99-1.26)	.08

AMD = age-related macular degeneration; CI = confidence interval; GA = geographic atrophy; HR = hazard ratio; NV = neovascular disease.
[a]Multivariate Model I: HRs for 12-year progression, risk per allele, adjusted for age, sex, race, education, and baseline AMD grade.
[b]Multivariate Model II: HRs reflect risk per allele, and are adjusted for age, sex, race, education, baseline AMD grade, body mass index, smoking status, and all other genetic loci in the table.

each endpoint. The AUC for each endpoint was based on the risk prediction model determined by the STEPWISE methodology. The risk score for each endpoint was used to calculate the AUC that corresponds to the probability that a random progressing eye over a specific time period had a higher risk score than a random nonprogressing eye that was followed for at least as long as that time period.

Risk scores for progression to each anatomic endpoint were calculated using regression coefficients of all demographic, behavioral, ocular, and genetic factors in the STEPWISE models. The hazard ratio for the ith subject is given from the Cox proportional hazards model by $\lambda_i = \exp(\sum_{j=1}^{J} \beta_j x_{ij})$, where β_j is the regression coefficient for the jth variable and x_{ij} is the value of the jth variable for the ith subject. The corresponding estimate of the

TABLE 5. Stepwise Selection of Genetic Factors Predictive of Progression to Overall Advanced Age-Related Macular Degeneration, Geographic Atrophy, Neovascular Disease, and Visual Acuity Loss in the Derivation Cohort

	Overall Advanced AMD		Progression to GA		Progression to NV		VA Loss ≥ 15 Letters	
	N =1149/5355[a]		N = 578/5355		N = 677/5355		N = 1423/4943	
Genetic Loci	HR (95% CI)[b]	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Complement pathway								
CFH Y402H: rs1061170	1.14 (1.02-1.29)	.03			1.17 (1.01-1.36)	.04		
CFH: rs1410996	1.46 (1.26-1.69)	<.0001	1.54 (1.28-1.86)	<.0001	1.40 (1.16-1.69)	.0004	1.30 (1.19-1.43)	<.0001
CFH R1210C: rs121913059	4.18 (2.79-6.27)	<.0001	4.30 (2.10-8.83)	<.0001	4.02 (1.92-8.40)	.0002	3.01 (1.67-5.41)	.0002
C2 E318D: rs9332739	0.60 (0.43-0.85)	.004						
CFB R32Q: rs641153	0.71 (0.54-0.93)	.01			0.69 (0.49-0.96)	.03		
CFI: rs10033900			1.16 (1.00-1.34)	.06				
C3 R102G: rs2230199	1.27 (1.15-1.41)	<.0001	1.19 (1.00-1.41)	.05	1.24 (1.09-1.41)	.001	1.23 (1.12-1.35)	<.0001
C3 K155Q: rs147859257	2.00 (1.50-2.66)	<.0001	2.66 (1.74-4.06)	<.0001			1.43 (1.05-1.94)	.02
Angiogenesis pathway								
TGFBR1: rs334353					0.83 (0.72-0.96)	.01		
Immune/inflammatory pathway								
ARMS2/HTRA1: rs10490924	1.47 (1.34-1.62)	<.0001	1.44 (1.23-1.67)	<.0001	1.57 (1.39-1.77)	<.0001	1.33 (1.22-1.45)	<.0001
PELI3: rs145732233	0.29 (0.07-1.18)	.08						
Extracellular matrix								
COL8A1: rs13095226	1.18 (1.03-1.37)	.02	1.29 (1.02-1.64)	.04	1.19 (1.00-1.42)	.05		
COL4A3: rs11884770					0.85 (0.74-0.98)	.02		
CTRB1: rs8056814	0.84 (0.69-1.02)	.07						
DNA repair/protein binding								
RAD51B: rs8017304	0.85 (0.77-0.94)	.001			0.81 (0.71-0.93)	.002	0.86 (0.79-0.94)	.001
HSPH1/B3GALTL: rs9542236	1.14 (1.04-1.25)	.004						
AUC ± standard error[c]	0.90 ± 0.005	–	0.87 ± 0.008	–	0.86 ± 0.008	–	0.72 ± 0.008	–

AMD = age-related macular degeneration; AUC = area under the curve; CI = confidence interval; GA = geographic atrophy; HR = hazard ratio; NV = neovascular disease; VA = visual acuity.

[a]Sample sizes reported as (numerator/denominator), where the numerator is equal to the number of eyes that progressed during follow-up and the denominator is equal to the number of eligible eyes at baseline, among participants with complete genetic data. Note that the number of eligible eyes does not equal 2 times the number of persons, as some people only contributed 1 eye to the analysis if the fellow eye had advanced AMD at baseline. Also note that the sum of the sample sizes for GA and NV disease do not equal the sample size for advanced AMD, as the sample for NV includes eyes that had GA and developed NV.

[b]HRs for 12-year progression represent risk per allele, and are adjusted for age, sex, race, education, baseline AMD grade, body mass index, smoking status, and all other single nucleotide polymorphisms in the table.

[c]All AUC statistics are age-adjusted in order to minimize confounding by age.

survival function for the ith subject is given by $S_0(t)^{\lambda_i}$, where is $S_0(t)$ is equal to the baseline survival function. It was estimated using the baseline option of PROC PHREG in SAS 9.4, where survival is defined as not having the outcome. The baseline survival function was estimated from a subject who was in the reference category for all covariates.

Probability of progression based on the risk score over specific time periods was defined as per our previous models: (1) very low (<1%); (2) low (1% to <10%); (3) medium (10% to <30%); (4) high (30% to <50%); (5) very high (≥50%). Probability of progression to advanced AMD, GA, and NV at 5 and 10 years from baseline was calculated, adjusted for competing mortality risks.

Risk score distributions including demographic, behavioral, ocular, and genetic variables were obtained for eyes that either progressed to advanced AMD within a 5-year period or did not progress and were followed for at least 5 years among eyes with intermediate AMD at baseline, and a box plot was obtained comparing the risk score distributions for the 2 groups.

The composite risk scores derived from the AREDS (derivation) cohort were applied to the Seddon Longitudinal Cohort (validation cohort). The 3 models predicting progression to overall advanced AMD, GA, and NV were independently validated, and age-adjusted AUCs were calculated as described previously. The sensitivity and specificity for the prediction model for progression to overall advanced AMD were calculated for a variety of risk

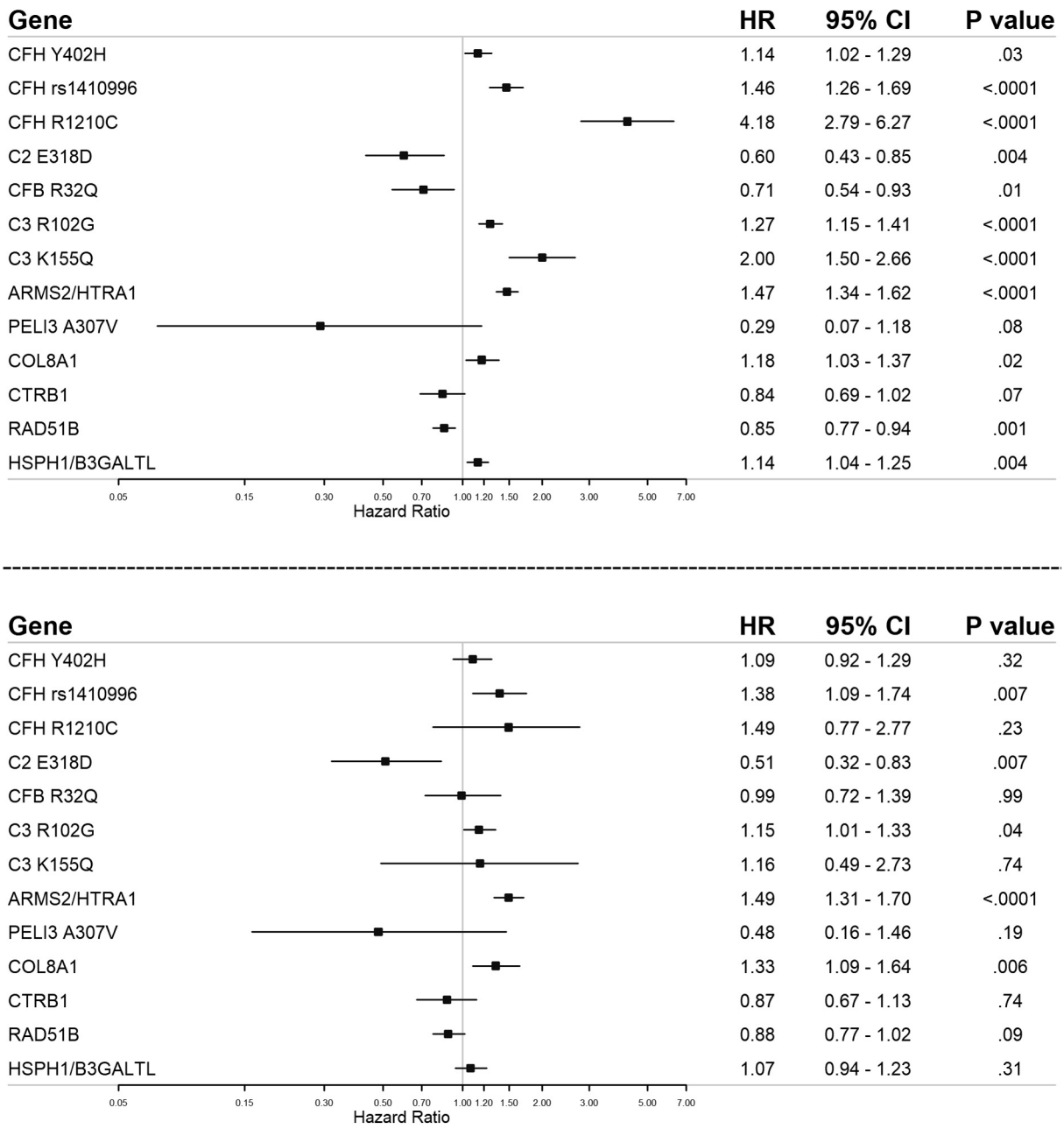

FIGURE 2. Genetic loci in the composite risk model associated with progression to advanced age-related macular degeneration over 12 years. The forest plot displays risk of progression per effective allele based on multivariate stepwise models. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for each locus on a log scale. Results are shown for the derivation cohort (Top) and validation cohort (Bottom).

score cutoffs. Sensitivity was defined as the proportion of progressing eyes that had a risk score greater than or equal to a given threshold. Specificity was defined as the proportion of nonprogressing eyes that had a risk score lower than a predetermined threshold and were followed for as long as the follow-up interval (ie, these eyes did not progress to advanced disease during the follow-up interval). Our goal was to select a risk threshold where both sensitivity and specificity were at least 80%.

Calibration. We stratified the set of eyes with baseline intermediate AMD by risk decile according to the derivation sample risk score for progression to overall advanced AMD. For each decile, we fit a Kaplan-Meier curve and calculated the 5-year survival probability for overall AMD and the corresponding 5-year incidence (1-survival estimate). We then multiplied these incidence rates by the number of people in each decile to obtain the observed count of progressors in each risk decile. Similarly, we calculated

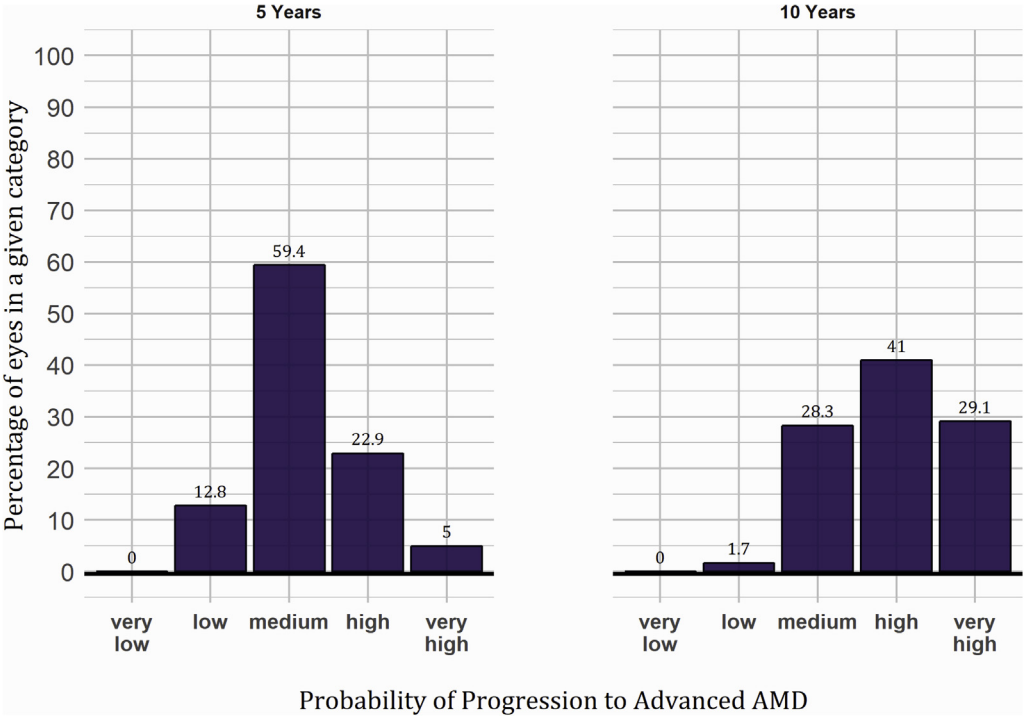

FIGURE 3. Probability of progression to advanced age-related macular degeneration endpoint (AMD) over 5 years and 10 years among eyes with intermediate disease at baseline based on demographic, behavioral, ocular, and genetic variables (the risk score) in the derivation cohort group. Probability of progression was defined as (1) very low (< 1%); (2) low (1% to < 10%); (3) medium (10% to < 30%); (4) high (30% to < 50%); (5) very high (≥50%).

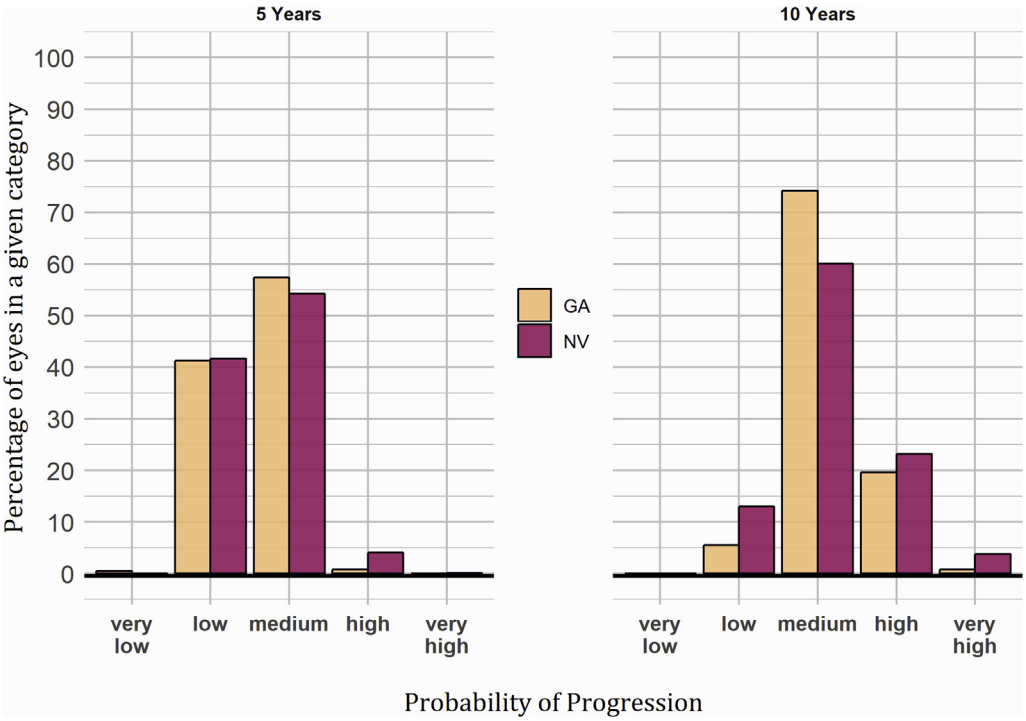

FIGURE 4. Probability of progression to geographic atrophy (GA) and neovascular disease (NV) endpoints over 5 years and 10 years among eyes with intermediate disease at baseline based on demographic, behavioral, ocular, and genetic variables (risk score) in the derivation cohort group. Probability of progression was defined as (1) very low (< 1%); (2) low (1% to < 10%); (3) medium (10% to < 30%); (4) high (30% to < 50%); (5) very high (≥50%).

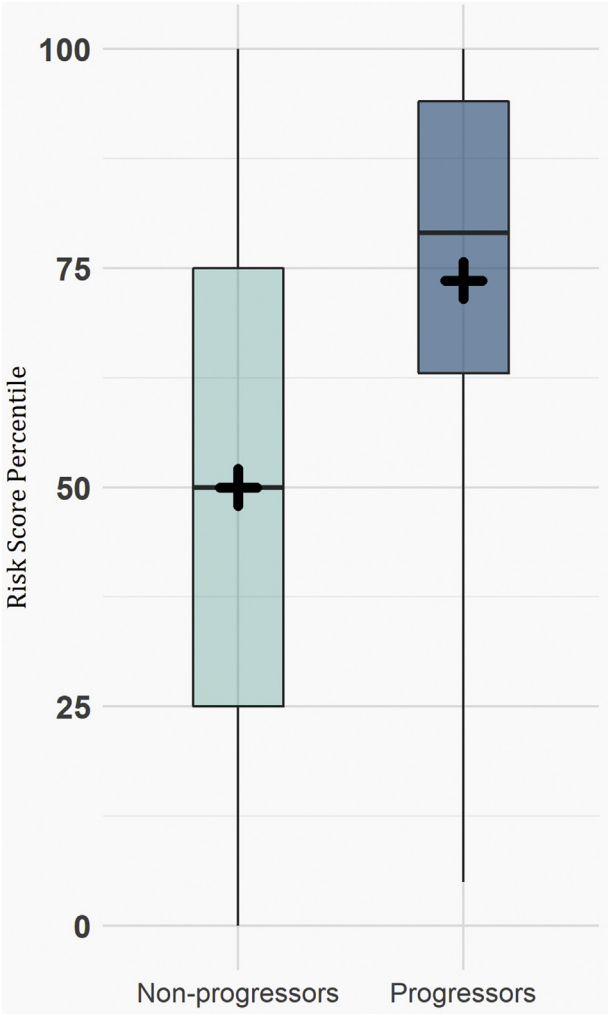

FIGURE 5. Box plot depicting risk score percentile for progressors to advanced age-related macular degeneration over 10 years and nonprogressors among eyes with intermediate disease at baseline. The percentiles were calculated from the sample of nonprogressing eyes. The horizontal line represents the median and the + sign represents the arithmetic mean. The top and bottom of the box depict the upper and lower 25th percentile.

the baseline survival function from the derivation cohort = S_0 (5) = survival probability at 5 years for eyes with zero values for all covariates. Then, for each eye in a risk decile in the validation sample, we calculated S (5) = S_0 $(5)^{\exp(\beta * X)}$, where X is a vector of risk factors and β is a vector of regression coefficients corresponding to these risk factors, to obtain the estimated 5-year survival probability in an individual eye in a particular risk decile, and the corresponding 5-year incidence, which equals 1 minus survival probability. We then added up the eye-specific incidences of all eyes in a particular decile to obtain the expected count within a decile. We then used Poisson regression methods[60] to compare the observed (O) to expected (E) decile specific counts, by regressing the observed count using an intercept-only model with a log link, and the log [E] as an offset. The estimated E/O ratio is given by exp (-α), where α is the estimated intercept from the model, and the corresponding 95% CI is given by exp [-α ± 1.96 × SE(α)]. The *P* value is obtained from $2 \times [1 - \Phi(|z|)]$, where $z = \alpha/SE(\alpha)$ from the Poisson regression model, and Φ is the cumulative standard normal cumulative distribution function (c.d.f.)

Net Reclassification Improvement. Net reclassification improvement (NRI) methods[61,62] were used to compare the improvement in the performance of our composite risk prediction model based on the inclusion of genetic data. The NRI is calculated separately for progressors and nonprogressors and quantifies the "correct" movement in risk of progression, specifically to a higher risk category for progressors and a lower risk category for nonprogressors when genes are considered. For progressors, the NRI is calculated as the difference in the proportion of eyes with a higher risk category for the model with genes compared to the model without genes minus the proportion of eyes with a lower risk category for the model with genes compared to the model without genes. For nonprogressors, the NRI is similarly defined as the difference in the proportion of eyes with a lower risk category for the model with genes compared to the model without genes minus the proportion of eyes with a higher risk category for the model with genes compared to the model without genes. An overall NRI was calculated by adding the individual NRIs for progressors and nonprogressors. The NRI was calculated separately for 5- and 10-year incidence of progression, where eyes that progressed did so within the predetermined follow-up interval and eyes that did not progress were followed for as long as the follow-up interval. These analyses were done separately for the derivation and validation cohorts, based on the risk function of the derivation cohort as determined by the stepwise model risk functions shown in Table 5. In addition, we assessed the probability of progression for 24 representative eyes with intermediate AMD at baseline using models with or without genetic variables.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). *P* values less than .05 were considered statistically significant.

RESULTS

• **DERIVATION COHORT:** The distributions of demographic, behavioral, ocular, and genetic characteristics within the derivation sample are presented in Table 1 for progression to overall advanced AMD, GA, and NV. The mean age of participants in the derivation cohort

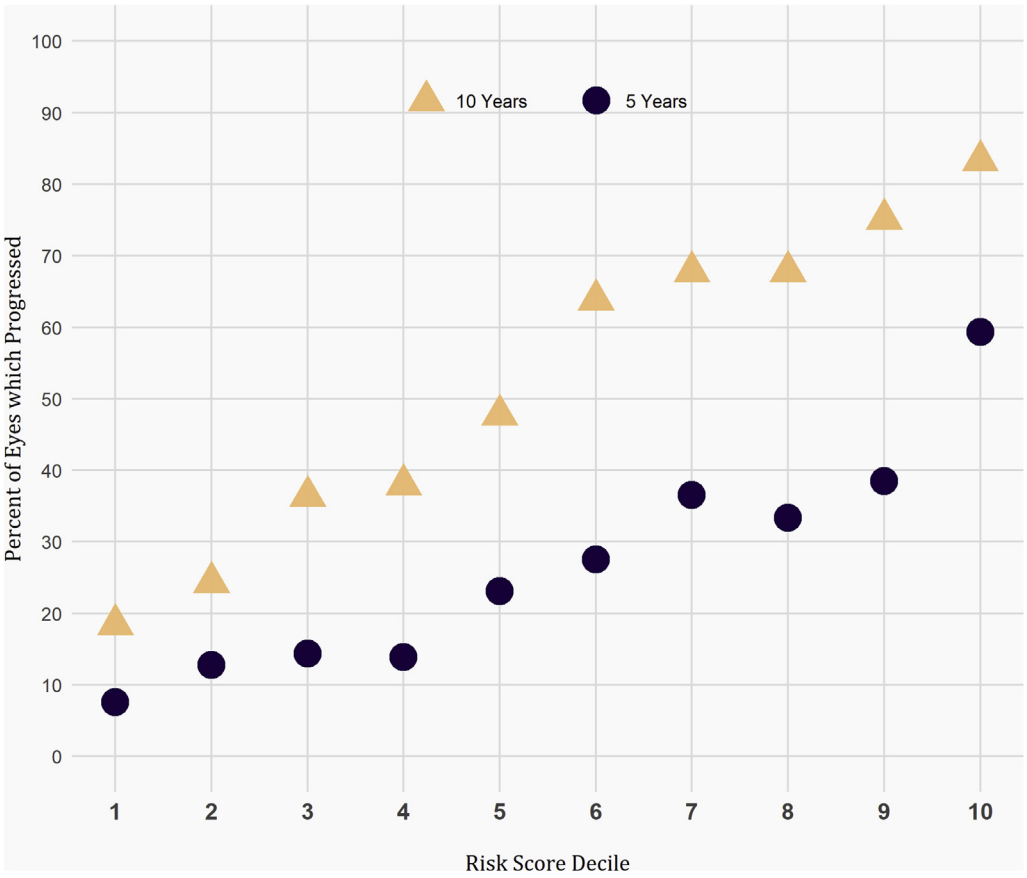

FIGURE 6. Plot of percentage of eyes that progressed over 5 or 10 years according to risk score deciles.

was 68.7 years. The sample was 43.6% male. For each outcome, progressors and nonprogressors significantly differed in terms of their age, race, level of education, BMI, smoking status, and baseline AMD grade. Progressors to overall advanced AMD tended to be older ($P < .0001$) and white ($P < .0001$), and had a lower level of education ($P < .0001$), a higher BMI ($P = .009$), a history of past or current cigarette smoking ($P < .0001$), and more advanced stages of AMD at baseline ($P < .0001$). There was no difference observed between men and women ($P = .84$). Similar results were observed for progression to the GA and NV subtypes.

Genotypes for loci in the complement pathway differed between progressors and nonprogressors. A higher number of risk alleles was associated with progression to overall advanced AMD, GA, and NV for common variants in *CFH* Y402H, *CFH* rs1410996, and *C3* R102G ($P < .0001$ for all common complement SNPs) and the rare variants *CFH* R1210C ($P = .009$) and *C3* K155Q ($P < .0001$). A significantly lower rate of progression was observed with protective alleles in *C2* E318D and *CFB* R32Q. A protective relationship was observed between low-frequency

TABLE 6. Probability of Progression to Advanced Age-Related Macular Degeneration Over 5 or 10 Years Based on the Composite Risk Score in the Derivation Cohort

Risk Score	HR	95% CI	*P* Value
5 Years			
Quintile 1	Ref		
Quintile 2	1.30	0.86-1.95	.213
Quintile 3	2.71	1.89-3.90	<.0001
Quintile 4	3.67	2.59-5.20	<.0001
Quintile 5	5.82	4.16-8.16	<.0001
10 Years			
Quintile 1	Ref		
Quintile 2	1.72	1.30-2.27	.0001
Quintile 3	3.04	2.35-3.93	<.0001
Quintile 4	4.11	3.19-5.29	<.0001
Quintile 5	5.91	4.61-7.58	<.0001

CI = confidence interval; HR = hazard ratio.

Model for the risk score includes age, sex, race, education, body mass index, smoking, baseline macular status, and 13 common and rare genetic variants.

TABLE 7. Multivariate Associations Between Demographic, Behavioral, and Ocular Factors and Progression to Overall Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Validation Cohort

	Progressors (N = 743)	Nonprogressors(N = 3660)	HR (95% CI)[a]	*P* Value
Demographic				
Age (y)				
≥75	237 (31.9)	622 (17.0)	*Referent*	
65 to 74.9	384 (51.7)	1964 (53.7)	0.55 (0.45-0.67)	<.0001
55 to 64.9	122 (16.4)	1074 (29.3)	0.37 (0.28-0.50)	<.0001
Sex				
Female	413 (55.6)	1856 (50.7)	*Referent*	
Male	330 (44.4)	1804 (49.3)	1.32 (1.10-1.59)	.003
Race				
Nonwhite	4 (0.4)	54 (1.5)	*Referent*	
White	739 (99.5)	3606 (98.5)	3.70 (1.07-12.5)	.04
Behavioral				
Education				
≤ High school	312 (42)	1183 (32.3)	*Referent*	
> High school	431 (58)	2477 (67.7)	0.76 (0.63-0.91)	.003
Body mass index				
<25	254 (34.2)	1311 (35.8)	*Referent*	
25 to 29.9	334 (45)	1524 (41.6)	0.97 (0.79-1.19)	.79
≥30	155 (20.9)	825 (22.5)	1.09 (0.86-1.39)	.48
Smoking				
Never	262 (35.3)	1529 (41.8)	*Referent*	
Past	420 (56.5)	1908 (52.1)	1.17 (0.97-1.41)	.10
Current	61 (8.2)	223 (6.1)	1.72 (1.19-2.48)	.004
Ocular				
Baseline AMD grade				
1	32 (4.3)	2125 (58.1)	*Referent*	
2	151 (20.3)	842 (23)	10.2 (6.65-15.5)	<.0001
3	560 (75.4)	693 (18.9)	36.4 (24.4-54.4)	<.0001

AMD = age-related macular degeneration; CI = confidence interval; GA = geographic atrophy; HR = hazard ratio; NV = neovascular disease.

[a]HRs and 95% CIs were estimated using Cox proportional hazards models for 12-year progression using the individual eye as the unit of analysis. HRs are adjusted for all variables listed in the table.

variant *CFH* N1050Y and overall advanced AMD and GA, and a suggestive effect was observed between this SNP and NV. Risk alleles in *CFI* and *C9* P167S were also significantly associated with higher rates of progression to overall advanced AMD, GA, and NV. *TGFBR1* was associated with a reduced rate of progression to NV, although no significant associations were observed for progression to overall advanced AMD and GA.

In the lipid pathway, protective alleles in *LIPC* were significantly associated with a lower rate of progression to GA ($P = .01$), with a suggestive result observed for overall advanced AMD ($P = .06$). *APOH* revealed a similar suggestive, protective effect for both endpoints ($P = .07$). Risk alleles in *CETP* were associated with a higher risk of progression to overall advanced AMD ($P = .002$), GA ($P = .03$), and NV ($P = .003$). No differences in progression were observed for *ABCA1* or *APOC1/APOE*.

Evaluation of the genes present in the immune/inflammatory pathway revealed significant associations between risk alleles in *ARMS2* and progression to overall advanced AMD, GA, and NV (all $P < .0001$). A beneficial effect of the protective allele in *PELI3* was suggested for overall advanced AMD and GA (both $P = .06$), with a nonsignificant trend in the same direction observed for NV. Genotypes in *TNFRSF10A*, *SLC16A8*, *PILRB/PILRA*, and *TMEM97/VTN* did not differ between progressors and nonprogressors for any of the 3 advanced AMD outcomes.

In the extracellular matrix pathway, a higher number of risk alleles in *COL8A1* was associated with a higher rate of progression to overall advanced AMD ($P = .0004$), GA ($P = .002$), and NV ($P = .001$) endpoints. The *CTRB1* variant had a protective effect for these outcomes ($P < .0001$ to $P = .0009$). A similar protective relationship was observed for alleles in *COL4A3* with regard to progression to NV ($P = .008$), with a suggestive effect for overall advanced AMD ($P = .06$). *TIMP3* was also associated with a reduced rate of progression to all 3 outcomes ($P = .01$, $P = .04$, and $P = .01$ for overall advanced AMD, GA, and NV, respectively). No

TABLE 8. Associations Between Specific Genetic Variants and Risk of Progression to Advanced Stages of Age-Related Macular Degeneration: Derivation and Validation Cohorts

	Derivation Cohort		Validation Cohort	
	N = 1149/5355[a]		N = 686/3955	
Genetic Loci	HR (95% CI)[b]	*P* Value	HR (95% CI)	*P* Value
Complement pathway				
CFH Y402H: rs1061170	1.14 (1.02-1.29)	.03	1.09 (0.92-1.29)	.32
CFH: rs1410996	1.46 (1.26-1.69)	<.0001	1.38 (1.09-1.74)	.007
CFH R1210C: rs121913059	4.18 (2.79-6.27)	<.0001	1.49 (0.77-2.77)	.23
C2 E318D: rs9332739	0.60 (0.43-0.85)	.004	0.51 (0.32-0.83)	.007
CFB R32Q: rs641153	0.71 (0.54-0.93)	.01	0.99 (0.72-1.39)	.99
C3 R102G: rs2230199	1.27 (1.15-1.41)	<.0001	1.15 (1.01-1.33)	.04
C3 K155Q: rs147859257	2.00 (1.50-2.66)	<.0001	1.16 (0.49-2.73)	.74
Immune/inflammatory pathway				
ARMS2/HTRA1: rs10490924	1.47 (1.34-1.62)	<.0001	1.49 (1.31-1.70)	<.0001
PELI3: rs145732233	0.29 (0.07-1.18)	.08	0.48 (0.16-1.46)	.19
Extracellular matrix				
COL8A1: rs13095226	1.18 (1.03-1.37)	.02	1.33 (1.09-1.64)	.006
CTRB1: rs8056814	0.84 (0.69-1.02)	.07	0.87 (0.67-1.13)	.74
DNA repair/protein binding				
RAD51B: rs8017304	0.85 (0.77-0.94)	.001	0.88 (0.77-1.02)	.09
HSPH1/B3GALTL: rs9542236	1.14 (1.04-1.25)	.004	1.07 (0.94-1.23)	.31

HR = hazard ratio.

[a]Sample sizes reported as (numerator/denominator), where the numerator is equal to the number of eyes that progressed during follow-up and the denominator is equal to the number of eligible eyes at baseline, among participants with complete genetic data.

[b]HRs for 12-year progression reflect risk per allele, and are adjusted for age, sex, race, education, baseline grade, body mass index, smoking status, and all other single nucleotide polymorphisms in the table.

significant associations with progression to overall advanced AMD, GA, or NV were observed for *ADAMTS9*.

Three loci associated with DNA repair and protein binding were also evaluated. *RAD51B* was significantly associated with a protective effect against progression to overall advanced AMD ($P = .0003$) and NV ($P = .0002$). *HSPH1/B3GALTL* was associated with an increased rate of progression to each of these outcomes ($P = .004$ to $P = .02$). *NPLOC4/TSPAN10* was associated with a higher rate of progression to overall advanced AMD ($P = .04$) and NV ($P = .02$) with an increasing number of risk alleles.

The multivariate associations between the demographic, behavioral, and ocular factors and progression are presented in Table 2 for each advanced AMD outcome. Participants who were older, were white, were obese (defined as a BMI ≥ 30), had a high school education or less, and had a history of past or current cigarette smoking had a higher risk of progression to advanced AMD over time. A more advanced AMD grade at baseline was also significantly associated with progression to overall advanced AMD, GA, and NV.

Each genetic locus was evaluated for its independent association with progression over time. Associations between each genetic factor and progression to overall advanced AMD are displayed in Table 3, and are adjusted for age, sex, race, level of education, and baseline grade in the multivariate model I. A second multivariate model of progression adjusting for all 31 genetic features and all other covariates, including smoking status and BMI, is also displayed (multivariate model II). This model, which also adjusted for age, sex, race, education, baseline AMD status, education, BMI, and smoking status, served as the basis for each of our stepwise models of progression (later presented in Table 5). The adjusted associations with the various genetic factors for progression to the GA and NV subtypes separately are displayed in Table 4. Some differences were seen for loci in the complement pathway between the 2 adjusted models. The effects of *CFH* Y402H and *CFH* 1410996 were somewhat weaker in multivariate model II when all other loci were considered. On the other hand, the effect of the rare variant *CFH* R1210C was stronger in multivariate model II (HR: 2.34 and 4.37; $P = .0007$ and $P < .0001$, respectively). The variant *CFH* N1050Y exhibited a suggestive protective effect in multivariate model I (HR: 0.61; $P = .07$), but not in multivariate model II. Differences in effect were also noted for *TIMP3*, with a weaker association observed for this variant when all the other genes were considered.

Similar trends in the complement pathway to those reported above for the predictive variants *CFH* Y402H,

TABLE 9. Area Under the Curve Statistics for Progression to Overall Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease in the Derivation and Validation Cohorts at 5, 10, and 12 Years After Baseline

	Derivation Cohort			Validation Cohort		
	Progressors	Nonprogressors	AUC ± SE	Progressors	Nonprogressors	AUC ± SE[a]
5 years						
Overall advanced AMD	590	4758	0.873 ± 0.008	316	2995	0.852 ± 0.011
GA	280	5063	0.859 ± 0.011	162	2992	0.870 ± 0.014
NV	331	5012	0.853 ± 0.011	159	3119	0.825 ± 0.017
10 years						
Overall advanced AMD	1056	3559	0.900 ± 0.005	595	1752	0.876 ± 0.008
GA	579	3946	0.866 ± 0.008	315	1752	0.887 ± 0.010
NV	620	3908	0.861 ± 0.008	302	1910	0.828 ± 0.013
12 years						
Overall advanced AMD	1149	4206	0.900 ± 0.005	686	1268	0.896 ± 0.007
GA	578	4777	0.870 ± 0.008	357	1268	0.899 ± 0.009
NV	677	4678	0.860 ± 0.008	364	1408	0.836 ± 0.012

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; AUC = area under the curve; GA = geographic atrophy; NV = neovascular disease; SE = standard error.

[a]Calculated by applying the composite risk score derived from the derivation cohort to the independent validation cohort.

CFH 1410996, *CFH* R1210C, and *CFH* N1050Y were observed for progression to GA and NV. In addition, the common *C3* variant, R102G, exhibited a weaker effect in multivariate model II for both endpoints. Different relationships were observed for the rare *C3* variant with regard to GA and NV. When adjusting for all other genes, the rare K155Q variant was a stronger predictor of progression to GA (HR: 2.59; $P < .0001$) and a weaker predictor for NV (HR: 1.24; $P = .40$). The loci identified as significantly associated with each endpoint were ultimately selected as the most predictive of progression in the multivariate stepwise risk prediction models.

• **STEPWISE RISK PREDICTION MODELS:** *Progression to Overall Advanced Age-Related Macular Degeneration*. A multivariate stepwise model identified 13 common and rare variants that were predictive of progression to overall advanced AMD. This model, in addition to the stepwise models for progression to GA, NV, and VA loss ≥ 15 letters, are presented in Table 5. Eight SNPs conferred a greater risk and 5 conferred a lower risk of progression. The following variants conferred a higher risk of progression: *CFH* Y402H (HR: 1.1; 95% CI: 1.0-1.3; $P = .03$), *CFH* rs1410996 (HR: 1.5; 95% CI: 1.3-1.7; $P < .0001$), *CFH* R1210C (HR: 4.2; 95% CI: 2.8-6.3; $P < .0001$), *C3* R102G (HR: 1.3; 95% CI: 1.2-1.4; $P < .0001$), *C3* K155Q (HR: 2.0; 95% CI: 1.5-2.7; $P < .0001$), *ARMS2* (HR: 1.5; 95% CI: 1.3-1.6; $P < .0001$), *COL8A1* (HR: 1.2; 95% CI: 1.0-1.4; $P = .02$), and *HSPH1/B3GALTL* (HR: 1.1; 95% CI: 1.0-1.3; $P = .004$). Variants in *C2* E318D (HR: 0.6; 95% CI: 0.4-0.9; $P = .004$), *CFB* R32Q (HR: 0.7; 95% CI: 0.5-0.9; $P = .01$), and *RAD51B* (HR: 0.9; 95% CI: 0.8-0.9; $P = .001$) were significantly associated with a protective effect, with lower rates of progression to this endpoint. A protective effect was also suggested per effective allele for *CTRB1* (HR: 0.8; 95% CI: 0.7-1.0; $P = .07$) and *PELI3* A307V (HR: 0.3; 95% CI: 0.1-1.2; $P = .08$). The age-adjusted AUC for this composite risk model, including 13 genetic loci as well as demographic, behavioral, and ocular covariates, was 0.90 over 12 years. This high AUC indicates excellent discrimination between progressors to advanced AMD

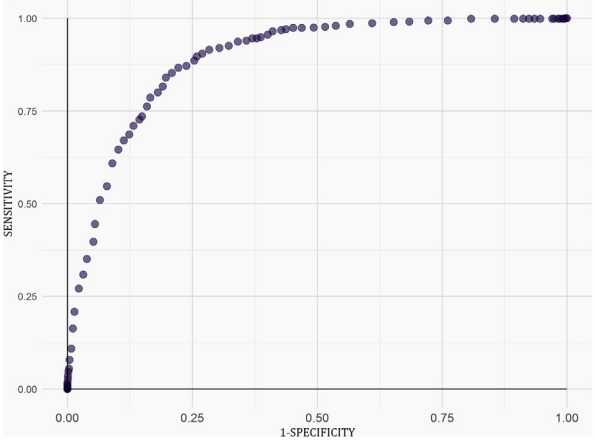

FIGURE 7. Receiver operating characteristic curve for 12-year progression to overall advanced age-related macular degeneration in the validation cohort according to the validated risk model that includes demographic, lifestyle, ocular, and genetic factors. Area under the curve = 0.896.

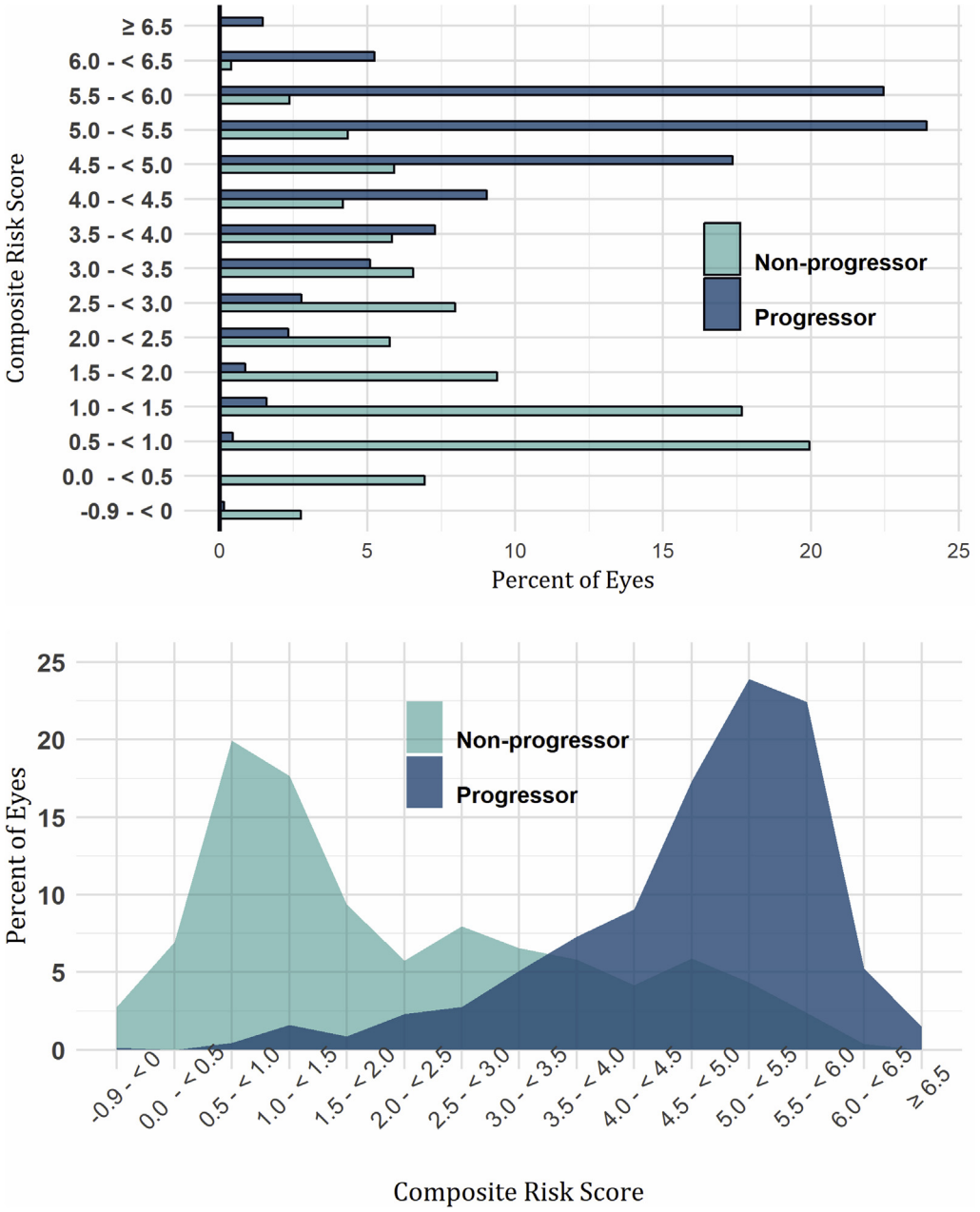

FIGURE 8. Distribution of risk scores for progressors to incident advanced age-related macular degeneration over 12 years and for nonprogressors separately in the validation cohort, according to the composite risk score based on demographic, behavioral, ocular, and genetic variables.

and nonprogressors. Results of this multivariate stepwise model are also illustrated in Figure 2 (Top).

Progression to Geographic Atrophy. Seven SNPs were predictive of progression to the GA endpoint in the multivariate stepwise model, with an AUC of 0.87. A higher risk of progression to GA was observed per effective allele for *CFH* rs1410996 (HR: 1.5; 95% CI: 1.3-1.9; $P < .0001$), *CFH* R1210C (HR: 4.3; 95% CI: 2.1-8.8; $P < .0001$), *C3* K155Q (HR: 2.7; 95% CI: 1.7-4.1; $P < .0001$), *ARMS2* (HR: 1.4; 95% CI: 1.2-1.7; $P < .0001$), and *COL8A1* (HR: 1.3; 95% CI: 1.0-1.6; $P = .04$). Higher risk was also suggested for *CFI* rs10033900 (HR: 1.2; 95% CI: 1.0-1.3; $P = .06$) and *C3* R102G (HR: 1.2; 95% CI: 1.0-1.4; $P = .05$). The AUC for this model was .87.

Progression to Neovascular Disease. Ten variants were included in the multivariate model for progression to NV. Increased risk of progression was associated with a higher number of risk alleles for *CFH* Y402H (HR: 1.2; 95% CI:

TABLE 10. Net Reclassification Improvement Analysis Comparing Progression Probability Categories Among Progressors and Nonprogressors to Advanced Stages of Age-Related Macular Degeneration Over 5 Years Based on a Composite Risk Model With No Genes Versus a Composite Risk Model With Genes in the Derivation Cohort

		Probability of Progression Based on the Composite Risk Model With Genes[c]					
	Probability of Progression[a]	Very Low	Low	Medium	High	Very High	Total
Progressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.2)
	Low	1 (1.6)	52 (85.3)	8 (13.1)	0 (0.0)	0 (0.0)	61 (10.3)
	Medium	0 (0.0)	15 (4.0)	216 (56.8)	128 (33.7)	21 (5.5)	380 (64.4)
	High	0 (0.0)	0 (0.0)	34 (24.6)	59 (42.8)	45 (32.6)	138 (23.4)
	Very high	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	4 (0.7)
	Total	7 (1.2)	68 (11.5)	258 (43.7)	191 (32.4)	66 (11.2)	590 (100.0)
Nonprogressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	1909 (94.1)	120 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	2029 (42.6)
	Low	89 (6.7)	1208 (90.6)	36 (2.7)	0 (0.0)	0 (0.0)	1333 (28.0)
	Medium	0 (0.0)	202 (16.9)	767 (64.2)	208 (17.4)	18 (1.5)	1195 (25.1)
	High	0 (0.0)	4 (2.0)	98 (49.8)	77 (39.1)	18 (9.1)	197 (4.1)
	Very high	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	2 (50.0)	4 (0.1)
	Total	1998 (42.0)	1534 (32.2)	903 (19.0)	285 (6.0)	38 (1.0)	4758 (100.0)

AMD = age-related macular degeneration; NRI = net reclassification improvement.

NRI for progressors: 0.25; P < .0001.

NRI for nonprogressors: -0.001; P = .86.

Overall NRI: 0.25; *P* < .0001.

[a]Probability of progression was defined as (1) very low (<1% risk); (2) low (1% to <10% risk); (3) medium (10% to <30% risk); (4) high (30% to <50% risk); (5) very high (≥50% risk).

[b]Composite risk model including age, sex, race, education, body mass index, smoking status, and baseline AMD grade.

[c]Composite risk model including age, sex, race, education, body mass index, smoking status, baseline AMD grade, and 13 loci determined to be associated with progression to advanced stages of AMD.

1.0-1.4; *P* = .04), *CFH* rs1410996 (HR: 1.4; 95% CI: 1.2-1.7; *P* = .0004), *CFH* R1210C (HR: 4.0; 95% CI: 1.9-8.4; *P* < .0002); *C3* R102G (HR: 1.2; 95% CI: 1.1-1.4; *P* = .001), *ARMS2* (HR: 1.6; 95% CI: 1.4-1.8; *P* < .0001), and *COL8A1* (HR: 1.2; 95% CI: 1.0-1.4; *P* = .05). Protective effects were observed for *CFB* R32Q (HR: 0.7; 95% CI: 0.5-1.0; *P* = .03) and *RAD51B* (HR: 0.8; 95% CI: 0.7-0.9; *P* = .002), as well as 2 newly identified variants that have not been previously associated with progression to advanced stages of AMD: *TGFBR1* (HR: 0.8; 95% CI: 0.7-1.0; *P* = .01) and *COL4A3* (HR: 0.8; 95% CI: 0.7-1.0; *P* = .02). The AUC for this multivariate model was 0.86. The stepwise model for VA loss of at least 15 letters is discussed below, along with all results related to this outcome.

As described in the methods, 5 categories were used to define rate of progression over specified time intervals: (1) very low (<1%); (2) low (1% to <10%); (3) medium (10% to <30%); (4) high (30% to <50%); and (5) very high (≥50%). Figure 3 illustrates the cumulative incidence of progression to overall advanced AMD among eyes with intermediate AMD (CARMS grade 3) at baseline over a 5- and 10-year interval, while Figure 4 illustrates the comparison between GA and NV. Rate of progression was calculated based on the composite risk score derived from the risk models for progression to each endpoint. Among eyes with the same grade of intermediate AMD at baseline, the 5-year cumulative incidence of progression to an advanced AMD outcome varied according to risk score profile. This profile reflects not only the underlying genetic disposition toward specific disease states but also individual risk based on age, sex, race, education, BMI, and smoking. Approximately 59% of eyes were predicted to have a medium risk of progression to overall advanced AMD over 5 years based on the composite risk score. No eyes were predicted to have very low risk of progression, 13% had low risk, about 23% had high risk, and 5% had very high risk of progression. Similar results were observed for progression from intermediate AMD to the advanced subtypes GA and NV, with most eyes (57% and 54%, respectively) classified as having medium risk for progression to both advanced subtypes at 5 years.

A box plot figure comparing the risk score distributions including demographic, behavioral, ocular, and genetic variables for progressors from intermediate AMD at baseline to advanced AMD within 10 years and nonprogressors followed for at least 10 years among eyes is shown in Figure 5. Although there is some overlap between these distributions, the median value and risk score distributions of the

TABLE 11. Net Reclassification Improvement Analysis Comparing Progression Probability Categories Among Progressors and Nonprogressors to Advanced Stages of Age-Related Macular Degeneration Over 10 Years for a Composite Risk Model With No Genes Versus a Composite Risk Model With Genes in the Derivation Cohort

	Probability of Progression[a]	Probability of Progression Based on the Composite Risk Model With Genes[c]					
		Very Low	Low	Medium	High	Very High	Total
Progressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	3 (37.5)	5 (62.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.8)
	Low	1 (0.9)	60 (56.1)	45 (42.1)	1 (0.9)	0 (0.0)	107 (10.1)
	Medium	0 (0.0)	2 (1.2)	59 (36.0)	81 (49.4)	22 (13.4)	164 (15.5)
	High	0 (0.0)	2 (0.3)	82 (11.9)	310 (45.1)	293 (42.7)	687 (65.1)
	Very high	0 (0.0)	0 (0.0)	2 (2.2)	14 (15.6)	74 (82.2)	90 (8.5)
	Total	4 (0.4)	69 (6.5)	188 (17.8)	406 (38.5)	389 (36.8)	1056 (100.0)
Nonprogressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	816 (69.2)	364 (30.9)	0 (0.0)	0 (0.0)	0 (0.0)	1180 (33.2)
	Low	198 (13.3)	1139 (76.4)	152 (10.2)	1 (0.1)	0 (0.0)	1490 (41.9)
	Medium	0 (0.0)	36 (12.8)	156 (55.3)	74 (26.2)	16 (5.7)	282 (7.9)
	High	0 (0.0)	9 (1.6)	209 (36.8)	241 (42.4)	109 (19.2)	568 (16.0)
	Very high	0 (0.0)	0 (0.0)	5 (12.8)	17 (43.6)	17 (43.6)	39 (1.1)
	Total	1014 (28.5)	1548 (43.5)	522 (14.7)	333 (9.4)	142 (4.0)	3559 (100.0)

AMD = age-related macular degeneration; NRI = net reclassification improvement.

NRI for progressors: 0.33; $P < .0001$.

NRI for nonprogressors: -0.068; $P < .0001$.

Overall NRI: 0.26; $P < .0001$.

[a]Probability of progression was defined as (1) very low (<1% risk); (2) low (1% to <10% risk); (3) medium (10% to <30% risk); (4) high (30% to <50% risk); (5) very high (≥50% risk).

[b]Composite risk model including age, sex, race, education, body mass index, smoking status, and baseline AMD grade.

[c]Composite risk model including age, sex, race, education, body mass index, smoking status, baseline AMD grade, and 13 loci determined to be associated with progression to advanced stages of AMD.

progressing eyes are substantially higher than the median value and risk score distributions of nonprogressing eyes. At 5 years, the separation between groups was slightly less (Supplemental Figure; Supplemental Material available at AJO.com).

The percentages of eyes that progressed from intermediate AMD to advanced AMD over 5 or 10 years according to risk score deciles are displayed in Figure 6. For example, in the 10-year period, there is approximately 20% progression in the lowest risk decile, which increases to approximately 50% at the fifth risk decile and over 80% at the 10th risk decile. For the 5 years, there is approximately 10% progression in the lowest risk decile, which increases to approximately 25% at the fifth risk decile and approximately 60% at the 10th risk decile.

To identify eyes with higher risk of progression from intermediate to advanced AMD, we divided the composite risk scores into quintiles and estimated the hazard ratio of progression within 5 or 10 years. As shown in Table 6, the HR of progression compared with quintile 1 is 1.30 for quintile 2 (95% CI = 0.86-1.95, $P = .21$), 2.71 for quintile 3 (95% CI = 1.89-3.90, $P < .001$), 3.67 for quintile 4 (95% CI 2.59-5.20, $P < .001$), and 5.82 for quintile 5 (95% CI = 4.16-8.16, $P < .001$). At 10 years, the HRs are somewhat higher and quintile 2 also becomes significantly associated with progression compared to quintile 1. Therefore, the composite risk score is strongly related to risk of progression and identifies a very high-risk group with almost a 6-fold higher risk of progression in the top quintile compared to the lowest quintile. Thus, a combination of several common and a few rare variants plus the other variables in the model can identify a high-risk population with a magnitude of risk comparable to the risk conferred by some single rare genetic variants.

The average percentage of eyes that were projected to progress over 5- and 10-year follow-up intervals was also calculated. In this derivation cohort, the mean risk of progression to advanced AMD over 5 years was 23.7%, indicating medium risk. Over 10 years, the average rate of progression was high, and increased to 40.5%. Average risks for progression to GA and NV were 12% and 13%, respectively, at 5 years and 25.4% and 23.6%, respectively, at 10 years.

• **VALIDATION COHORT:** Among 2156 participants included in the validation cohort, the mean age was 68.8 years and sample was 54.3% female. These demographics are consistent with the population included in the derivation cohort analyses reported above. The distribution of

TABLE 12. Net Reclassification Improvement Analysis Comparing Progression Probability Categories Among Progressors and Nonprogressors to Advanced Stages of Age-Related Macular Degeneration Over 5 Years for a Composite Risk Model With No Genes Versus a Composite Risk Model With Genes in the Validation Cohort

		Probability of Progression Based on the Composite Risk Model With Genes[c]					
	Probability of Progression[a]	Very Low	Low	Medium	High	Very High	Total
Progressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.9)
	Low	0 (0.0)	54 (91.5)	5 (8.5)	0 (0.0)	0 (0.0)	59 (18.7)
	Medium	0 (0.0)	19 (8.1)	149 (63.4)	56 (23.8)	11 (4.7)	235 (74.4)
	High	0 (0.0)	0 (0.0)	2 (12.5)	8 (50.0)	6 (37.5)	16 (5.1)
	Very high	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	6 (1.9)	73 (23.1)	156 (49.4)	64 (20.3)	17 (5.4)	316 (100.0)
Nonprogressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	1495 (96.0)	62 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1557 (52.0)
	Low	55 (8.0)	628 (91.3)	5 (0.7)	0 (0.0)	0 (0.0)	688 (23.0)
	Medium	0 (0.0)	111 (15.9)	491 (70.3)	91 (13.0)	5 (0.7)	698 (23.3)
	High	0 (0.0)	4 (9.3)	12 (27.9)	25 (58.1)	2 (4.7)	43 (1.4)
	Very high	0 (0.0)	2 (22.2)	6 (66.7)	1 (11.1)	0 (0.0)	9 (0.3)
	Total	1550 (51.8)	807 (26.9)	514 (17.2)	117 (3.9)	7 (0.2)	2995 (100.0)

AMD = age-related macular degeneration; NRI= net reclassification improvement.

NRI for progressors: 0.18; P < .0001.

NRI for nonprogressors: 0.009; P = .17.

Overall NRI: 0.19; $P < .0001$.

[a]Probability of progression was defined as (1) very low (<1% risk); 2) low (1% to < 10% risk); 3) medium (10% to < 30% risk); 4) high (30% to < 50% risk); 5) very high (≥50% risk).

[b]Composite risk model including age, sex, race, education, body mass index, smoking status, and baseline AMD grade.

[c]Composite risk model including age, sex, race, education, body mass index, smoking status, baseline AMD grade, and 13 loci determined to be associated with progression to advanced stages of AMD.

demographic, behavioral, ocular, and genetic factors among progressors and nonprogressors is shown in Table 7. Comparable to the derivation cohort, older age ($P < .0001$), white race ($P = .04$), a low level of education ($P = .003$), and current cigarette smoking ($P = .004$), were significantly associated with a higher risk of progression to advanced AMD in the validation cohort. A more advanced stage of AMD at baseline was also a risk factor for progression ($P < .0001$). Interestingly, women had a lower risk of progression compared to men ($P = .003$). Higher BMI was not significantly associated with progression to advanced AMD.

Effect estimates for the 13 loci identified as most predictive of progression to overall advanced AMD in the derivation cohort are displayed in Table 8 for both the derivation and validation cohorts. *CFH* rs1410996, *C2* E318D, *C3* R102G, *ARMS2*, and *COL8A1* variants were significantly associated with progression to overall advanced AMD in the validation cohort. All other variants trended in the expected direction based on the results from the derivation cohort. It is not surprising that rare and low-frequency variants, which have a large impact on a smaller number of individuals, were not significantly associated with AMD risk in the validation analysis. Rare genotypes are often not validated in a relatively smaller sample size, as they are carried by a small proportion of the population. Results of this multivariate stepwise model are illustrated in Figure 2 (Bottom) and are in conjunction with the effect estimates observed in the derivation cohort. The direction of the effect is similar for most genes, and replicates the major genes with higher allele frequency.

Risk models from the derivation cohort were applied to the independent validation cohort. The AUCs for progression to the overall advanced AMD, GA, and NV endpoints at 5, 10, and 12 years after baseline are shown in Table 9 for the validation and derivation samples. For the validation cohort, the AUCs (±standard error) were 0.852 ± 0.011, 0.876 ± 0.008, and 0.896 ± 0.007 for progression to overall advanced AMD at 5, 10, and 12 years, respectively. These results are very comparable to and only slightly lower than the results observed in the derivation cohort for the same outcomes: 0.873 ± 0.008, 0.900 ± 0.005, and 0.900 ± 0.005, respectively, at 5, 10, and 12 years. For progression to GA and NV subtypes separately, the AUCs were 0.859 ± 0.011 and 0.853 ± 0.011, respectively, at 5 years for the derivation sample, and were 0.870 ± 0.014 and 0.825 ± 0.017 at 5 years for the validation sample. The AUCs in the validation cohort were slightly higher for GA and slightly lower for NV.

TABLE 13. Net Reclassification Improvement Analysis Comparing Progression Probability Categories Among Progressors and Nonprogressors to Advanced Stages of Age-Related Macular Degeneration Over 10 Years for a Composite Risk Model With No Genes Versus a Composite Risk Model With Genes in the Validation Cohort

		Probability of Progression Based on the Composite Risk Model With Genes[c]					
	Probability of Progression[a]	Very Low	Low	Medium	High	Very High	Total
Progressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	4 (30.8)	9 (69.2)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.2)
	Low	2 (1.7)	78 (66.1)	38 (32.2)	0 (0.0)	0 (0.0)	118 (19.8)
	Medium	0 (0.0)	1 (0.8)	54 (40.3)	58 (43.3)	21 (15.7)	134 (22.5)
	High	0 (0.0)	2 (0.7)	62 (20.5)	139 (45.9)	100 (33.0)	303 (50.9)
	Very high	0 (0.0)	0 (0.0)	0 (0.0)	5 (18.5)	22 (81.5)	27 (4.5)
	Total	6 (1.0)	90 (15.1)	154 (25.9)	202 (34.0)	143 (24.0)	595 (100.0)
Nonprogressors							
Probability of progression based on the composite risk model with no genes[b]	Very low	545 (73.0)	202 (27.0)	0 (0.0)	0 (0.0)	0 (0.0)	747 (42.6)
	Low	98 (15.6)	468 (74.3)	64 (10.2)	0 (0.0)	0 (0.0)	630 (36.0)
	Medium	0 (0.0)	19 (12.3)	75 (48.7)	56 (36.4)	4 (2.6)	154 (8.8)
	High	0 (0.0)	0 (0.0)	79 (39.3)	88 (43.8)	34 (16.9)	201 (11.5)
	Very high	0 (0.0)	0 (0.0)	12 (60.0)	4 (20.0)	4 (20.0)	20 (1.1)
	Total	643 (36.7)	689 (39.3)	230 (13.1)	148 (8.5)	42 (2.4)	1752 (100.0)

AMD = age-related macular degeneration; NRI = net reclassification improvement.

NRI for progressors: 0.26; $P < .0001$.

NRI for nonprogressors: -0.08; $P < .0001$.

Overall NRI: 0.17; $P < .0001$.

[a]Probability of progression was defined as (1) very low (<1% risk); (2) low (1% to <10% risk); (3) medium (10% to <30% risk); (4) high (30% to <50% risk); (5) very high (≥50% risk).

[b]Composite risk model including age, sex, race, education, body mass index, smoking status, and baseline AMD grade.

[c]Composite risk model including age, sex, race, education, body mass index, smoking status, baseline AMD grade, and 13 loci determined to be associated with progression to advanced stages of AMD.

We calculated positive and negative predictive values for this composite risk model of progression, using a cutoff of approximately 80% for sensitivity and specificity. These values correspond to a risk score of 4. For the validation cohort, the sensitivity was 80.0%: out of a total of 686 eyes that progressed to advanced AMD, there were 549 eyes with a risk score ≥ 4. The specificity of the model was 81.9%; of 1268 eyes that did not progress, 1039 eyes had a risk score < 4. These sensitivity and specificity values were calculated over a follow-up interval of 12 years for the validation cohort (Figure 7). Receiver operating characteristic curves for progression to overall advanced AMD at 5 and 10 years were similar. These models include age, sex, race education, baseline AMD grade, BMI, smoking status, and the 13 genetic factors determined to be most predictive of progression in the derivation sample: 5 common and rare loci in *CFH* and *C3*, 7 common loci in *C2*, *CFB*, *ARMS2*, *COL8A1*, *CTRB1*, *RAD51B*, and *HSPH1/B3GALTL*, and a rare variant in *PELI3*. There was a moderate increase in the AUC between 5 and 10 years. AUCs for this model in the derivation and validation cohorts were similar.

A histogram and an area graph of the risk scores for progressors and nonprogressors to overall advanced AMD over 12 years in the validation cohort are presented in Figure 8. The observed distribution indicates a good separation between the 2 groups based on the composite model including demographic, lifestyle, ocular, and genetic factors. Risk scores were substantially different between the 2 groups, with higher scores among eyes that progressed to advanced disease compared to eyes that did not, although there was some overlap between the 2 groups.

• **COMPARING RISK PREDICTION WITH AND WITHOUT GENES:** Assessment of models with and without genetic factors are displayed in Tables 10-13 for both cohorts. Results of the NRI for the derivation cohort at 5 years are presented in Table 10. Among progressors, changes in risk score groups dependent on genetic predictors were primarily observed in the medium- or high-risk groups. Approximately 40% of progressing eyes changed from medium-risk to a high-risk or very high-risk group in a model with genes compared to a model without genes, and 32% transitioned from high to very high risk (NRI: 0.25; $P < .0001$). There were no differences between models in the analyses of nonprogressing eyes: some eyes moved to a higher- or lower-risk group in a model with genes, but these transitions occurred in approximately equal numbers (NRI: -0.001; $P = .86$). The overall NRI (calculated as the sum of the NRIs for progressors and nonprogressors) was statistically significant (NRI: 0.25;

TABLE 14. Heterogeneity of Risk Profile Between Geographic Atrophy and Neovascular Disease in the Derivation Cohort

	GA		NV		
	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value	*P* Het[b]
Genetic loci					
CFH Y402H: rs1061170	1.08 (0.91-1.27)	.397	1.17 (1.00-1.36)	.052	.440
CFH: rs1410996	1.49 (1.20-1.86)	.0003	1.47 (1.20-1.79)	.0002	.894
CFH R1210C: rs121913059	4.12 (2.09-8.10)	<.0001	4.78 (2.59-8.83)	<.0001	.751
C2 E318D: rs9332739	0.40 (0.21-0.75)	.004	0.68 (0.44-1.04)	.072	.161
CFB R32Q: rs641153	0.73 (0.50-1.07)	.106	0.62 (0.44-0.89)	.008	.493
CFI: rs10033900	1.08 (0.95-1.24)	.236	1.02 (0.91-1.15)	.694	.483
C3 R102G: rs2230199	1.24 (1.06-1.44)	.006	1.20 (1.05-1.38)	.008	.772
C3 K155Q: rs147859257	2.15 (1.43-3.23)	.0002	1.67 (1.07-2.62)	.024	.402
TGFBR1: rs334353	1.00 (0.86-1.17)	.999	0.83 (0.72-0.95)	.009	.057
ARMS2/HTRA1: rs10490924	1.38 (1.20-1.57)	<.0001	1.58 (1.39-1.79)	<.0001	.105
PELI3: rs145732233	0.23 (0.03-1.74)	.152	0.37 (0.05-2.61)	.318	.727
COL8A1: rs13095226	1.24 (0.99-1.55)	.063	1.17 (0.98-1.41)	.088	.698
COL4A3: rs11884770	1.09 (0.94-1.27)	.270	0.87 (0.75-1.00)	.055	.021
CTRB1: rs8056814	0.81 (0.61-1.08)	.153	0.76 (0.58-0.99)	.040	.704
RAD51B: rs8017304	0.92 (0.79-1.07)	.264	0.76 (0.66-0.87)	<.0001	.034
HSPH1/B3GALTL: rs9542236	1.14 (0.99-1.30)	.061	1.16 (1.02-1.31)	.023	.853
Nongenetic variables					
Age					
75+	1.00 (referent)		1.00 (referent)		
55-64	0.48 (0.34-0.67)	<.0001	0.40 (0.30-0.54)	<.0001	.385
65-74	0.65 (0.52-0.82)	.0002	0.70 (0.57-0.86)	.001	.626
Sex					
Female	1.00 (referent)		1.00 (referent)		
Male	1.17 (0.95-1.44)	.135	0.89 (0.74-1.08)	.240	.035
BMI					
<25	1.00 (referent)		1.00 (referent)		
25-29	1.20 (0.94-1.52)	.146	1.21 (0.97-1.50)	.086	.949
30+	1.50 (1.15-1.95)	.003	1.38 (1.08-1.76)	.009	.614
Smoking					
Never	1.00 (referent)		1.00 (referent)		
Current	1.72 (1.14-2.61)	.010	2.47 (1.75-3.48)	<.0001	.142
Past	1.09 (0.89-1.35)	.403	1.41 (1.16-1.71)	.001	.058
Race					
Nonwhite	1.00 (referent)		1.00 (referent)		
White	4.89 (1.22-19.67)	.025	1.51 (0.73-3.12)	.263	.138
Education					
≤ High school	1.00 (referent)		1.00 (referent)		
> High school	0.81 (0.66-0.99)	.040	0.73 (0.61-0.87)	.001	.397
Baseline AMD grade					
1	1.00 (referent)		1.00 (referent)		
2	16.78 (6.02-46.81)	<.0001	5.15 (3.05-8.69)	<.0001	.043
3	113.73 (42.28-305.94)	<.0001	22.46 (13.75-36.69)	<.0001	.004

AMD = age-related macular degeneration; BMI = body mass index; CI = confidence interval; GA = geographic atrophy; HR = hazard ratio; NV = neovascular disease.

[a]Based on a multivariate model for 12-year progression with all risk factors included. Hazard ratios for genetic loci calculated per minor allele.

[b]*P* het = *P* value for heterogeneity based on a competing risk proportional hazards model, using the data duplication method of Lunn and McNeil, Biometrics, 1995.

$P < .0001$), indicating that when genetic factors were considered, progressors were in a higher-risk group.

Even more striking results were observed at 10 years of follow-up (Table 11). Most differentiation occurred in the medium- or high-risk groups, and there was movement to an even higher-risk group based on the model with genes. Over 60% of progressing eyes within the medium-risk category, according to the model with no genes, transitioned to

TABLE 15. Calibration of Risk Model for Progression to Advanced Age-Related Macular Degeneration[a]

Risk (Decile)	N	Observed # Events	Expected # Events
1	113	14.83	7.72
2	115	11.61	12.58
3	114	17.09	16.23
4	115	27.12	18.95
5	115	14.50	22.04
6	114	30.49	25.24
7	114	20.12	29.52
8	116	40.55	35.03
9	114	44.67	40.54
10	114	45.98	55.36
Total	1144	266.98	263.21

Ratio (expected/observed) = 0.986 (95% CI 0.87-1.11); $\chi^2 = 0.054$; P value = .816 (indicating adequate calibration of the model).

[a]Data were based on progression over 5 years comparing observed and expected number of eyes progressing in the validation dataset according to deciles of the risk score from the derivation sample among eyes with baseline intermediate age-related macular degeneration.

a high-risk or very high-risk group in the model with genes, and over 40% in the high-risk group transitioned from high to very high risk (NRI: 0.33; $P < .0001$). The net number of subjects moving higher vs moving lower was 344 of 1056 eyes (33%). Among nonprogressing eyes, when comparing models with and without genes, the net number of subjects moving higher vs lower was 247 out of 3559 subjects (7%), with NRI = 0.26; $P < .0001$. If addition of genetic loci was unrelated to progression, then these 2 values (33% and 7%) would be the same. However, the overall NRI = 33% minus 7% = 26% was significantly higher than 0, indicating that a risk model including genetic loci was a better discriminator between progressing and nonprogressing eyes than a model without genetic loci.

In the validation cohort analyses, similar results were observed for progressors and nonprogressors over 5 and 10 years of follow-up. At 5 years (Table 12), the NRIs for progressors and nonprogressors were 0.18 and 0.009 ($P < .0001$ and $P = .17$, respectively), with an overall NRI of 0.19 ($P < .0001$). Table 13 displays the NRIs for progressors (0.26; $P < .0001$), nonprogressors (-0.08; $P < .0001$), and overall NRI (0.17; $P < .0001$) in the validation cohort at 10 years, which were similar to those observed in the derivation cohort.

• **HETEROGENEITY OF RISK PROFILES BETWEEN GEOGRAPHIC ATROPHY AND NV:** We evaluated whether risk models differed between the 2 types of advanced disease: GA and NV (Table 14). Genetic analyses were based on number of risk alleles in variants related to GA or NV in Table 4. There was higher HR for the *ARMS2* variant for NV compared with GA, and both were significant, but the heterogeneity between HRs for NV and GA was not significant in these analyses. Three genes showed a significantly different HR for GA and NV. These included the *RAD51B* gene, which showed a significant inverse association with NV, HR = 0.76 (95% CI 0.66-0.87) but not GA (HR = 0.92, 95% CI 0.79-1.07). The 2 HRs were significantly different, with the P value for heterogeneity, P (het), = .034. In addition, there was significant heterogeneity for *COL4A3*, which showed a borderline association with NV, HR = 0.87 (95% CI 0.75-1.00) and no association with GA (HR = 1.09, 95% CI 0.94-1.27), with P (het) = .021. There was borderline significant heterogeneity for the gene *TGFBR1*, which showed a significant inverse association with NV, HR = 0.83 (95% CI 0.72-0.95) and no association with GA (HR = 1.00, 95% CI 0.86-1.17), and the P (het) was .057.

In addition, there were 2 nongenetic variables that showed significant heterogeneity between GA and NV: sex and initial AMD grade. Compared to grade 1, there were significant associations between baseline grade 2 and 3 and progression for both GA and NV, with higher risk for progression with baseline grade 3 compared with baseline grade 2. However, the association between baseline grade 3 and progression was significantly stronger for progression to grade 4 compared with progression to grade 5, with P (het) = .004. Regarding sex, men had a slightly lower risk than women for NV and a slightly higher risk for GA. When assessing heterogeneity, the difference in sex associations between NV and GA was significant, with P (het) = .035.

• **CALIBRATION RESULTS:** The prediction model was calibrated in the validation cohort using the coefficients from the derivation cohort model. As shown in Table 15 and Figure 9, we found an expected/observed (E/O) ratio of 0.99 (95% CI 0.87-1.11) and $P = .82$, for testing the null hypothesis of an intercept = 0. Results indicate that the calibration of the model for intermediate AMD eyes for progression to advanced AMD is adequate in the validation sample.

• **APPLICATION OF THE ONLINE RISK CALCULATOR:** To facilitate clinical use of the algorithm in Table 5, we developed an online calculator that enhances our previous calculator.[38] A physician can enter genotypes, together with baseline AMD grade and demographic factors, to obtain a 2-, 5-, and 10-year risk of progression in individual eyes. The calculator allows for the evaluation of individual risk and can be used to assess varying risk profiles based on a specific subset of demographic, behavioral, ocular, and genetic factors. Our composite risk model for prediction progression to advanced AMD is available online at www.seddonamdriskscore.org.[45]

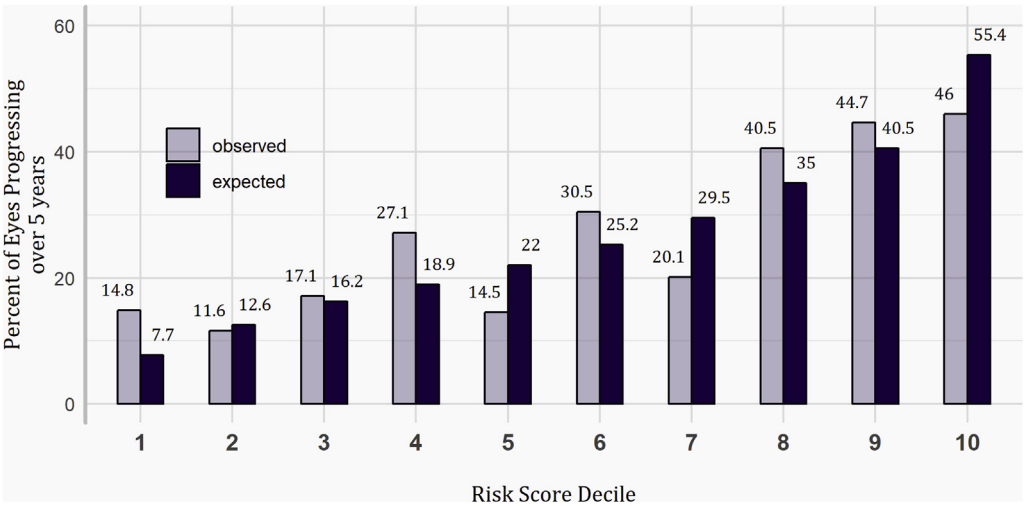

FIGURE 9. Calibration of the risk model for progression to advanced age-related macular degeneration over 5 years comparing observed and expected number of eyes progressing in the validation cohort.

Representative results applying the online calculator for white and nonwhite subjects are shown in Table 16. The median risk of progression was 25.6% over 5 years. However, there was a wide variation in progression rates among individuals with the same AMD grade at baseline, ranging from 1.6% to 56.5% over a 5-year period, which underscores the potential value of the risk score models in helping to counsel patients and assist with disease management and prognosis. The variation observed among individual eyes with the same baseline status is reinforced by the results of the NRI. In addition, for the 24 eyes in Table 16 with intermediate AMD, risk for 5-year progression was compared between models with and without genes. Results indicate that for 8 of the 24 eyes, the 5-year cumulative incidence of progression increased by 1 level (for example, low to medium or medium to high, as defined above) and for 4 eyes, the 5-year cumulative incidence of progression decreased by 1 level (for example, medium to low or high to medium, as defined above) in the model with genes compared to the model without genes. In addition, for 8 of the 24 eyes, the relative probability of progression in the model with genes compared to the model without genes differed by at least 2-fold. This indicates that the clinical discussion with individual patients may vary depending on whether genetic variants are considered or not. A table similar to Table 16 for a risk model including drusen size as an additional risk factor is provided in Supplemental Table 1 (Supplemental Material available at AJO.com; also provided in online calculator). The stepwise model with drusen size is presented in Supplemental Table 2 (Supplemental Material available at AJO.com).

The calculations described above assume complete data, including demographic, behavioral, and ocular characteristics, and genetic data for each individual participant. In a clinical setting, it is possible that some patients may have some missing data for a variable number of risk factors. To address the issue of possible missing data for users of the online calculator, we created 2 distinct modules (A and B) that accounted for the availability of the data. These modules were defined as follows: A: all macular phenotypes and genetic variants known; B: all macular phenotypes known, genetic variables unknown. The NHANES 2009 data were used to impute values for missing demographic and behavioral factors for each module; in particular, the proportion of participants with specific levels of education, smoking, and BMI as a function of age-sex groups was estimated. Finally, in module A, for subjects who may be missing a few of the 13 genetic variants, the population prevalence of specific alleles was used to estimate the probabilities of genotypes for an individual gene that was substituted for presence or absence of a particular genotype.

• **PROGRESSION TO LOSS OF VISUAL ACUITY:** In addition to our analyses of advanced AMD endpoints, we evaluated the occurrence of VA loss of at least 15 letters over 12 years. The distributions of demographic, behavioral, ocular, and genetic characteristics among those who developed this level of visual loss and those who did not are presented in Table 17. Those experiencing VA loss ≥ 15 letters were older ($P < .0001$), were white ($P < .0001$), had a lower level of education ($P < .0001$), had a higher BMI ($P = .0001$), and had a history of cigarette smoking ($P < .0001$). These participants also had more advanced stages of AMD at baseline ($P < .0001$). Visual loss was similar among men and women ($P = .54$).

The genotypes for several loci in the complement pathway differed with regard to VA loss. A higher number of risk alleles was associated with VA loss ≥ 15 letters for common variants in *CFH* Y402H ($P < .0001$), *CFH* rs1410996 ($P < .0001$), and *C3* R102G ($P < .0001$), and the rare variants *CFH*

TABLE 16. Cumulative Incidence of Progression to Advanced Age-Related Macular Degeneration at 2, 5, 10, and 12 Years Based on the Composite Risk Score, Adjusting for Mortality Risks for a Representative Sample of 24 Right and Left Eyes With Intermediate-Stage Disease at Baseline

	Subject No.											
	1	2	3	4	5	6	7	8	9	10	11	12
Eye	OD	OD	OD	OD	OD	OD	OD	OD	OD	OD	OD	OD
Age	72.4	76.8	77.8	79.9	57.6	78.4	77.9	80.3	67.2	72.8	71.6	64.9
Sex	F	M	M	M	F	F	F	F	M	F	F	M
Education	> HS	≤ HS	≤ HS	> HS	≤ HS	≤ HS	≤ HS	≤ HS	≤ HS	≤ HS	≤ HS	> HS
Body mass index	25.4	32.5	28.8	24.3	31.9	27.4	23.0	26.8	30.9	44.0	28.2	25.8
Smoking	Never	Never	Past	Past	Never	Never	Never	Never	Past	Past	Past	Never
Race (white)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Complement pathway												
CFH Y402H: rs1061170	TT	CT	CC	CC	TT	CT	CT	CT	TT	CC	CC	TT
CFH: rs1410996	TT	CT	CC	CC	CT	CT	CT	CC	CT	CC	CC	TT
CFH R1210C: rs121913059	CC	CC	CC	CC	CT	CC	CC	CC	CC	CC	CC	CC
C2 E318D: rs9332739	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG
CFB R32Q: rs641153	CC	CC	CC	CC	CC	CC	CC	CC	CT	CC	CC	CC
C3 R102G: rs2230199	CG	CG	CC	CC	CC	CG	GG	CC	CC	CC	CC	CC
C3 K155Q: rs147859257	TT	GT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT
Immune/inflammatory pathway												
ARMS2/HTRA1: rs10490924	GT	GT	GG	TT	GT	GG	GT	GT	GT	GT	GG	GG
PELI3: rs145732233	CC	CC	CC	CC	CC	CC	CT	CC	CC	CC	CC	CC
Extracellular matrix												
COL8A1: rs13095226	TT	CT	TT	CT	TT	TT	TT	TT	CT	TT	TT	TT
CTRB1: rs8056814	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	AG	AG
DNA repair/protein binding												
RAD51B: rs8017304	GA	GA	AA	AA	AA	AA	AA	GG	GA	AA	AA	GG
HSPH1/B3GALTL: rs9542236	CT	CT	CT	CT	TT	TT	CT	CT	CT	CT	CT	CC
2-year cumulative incidence, %	4.2	29.3	14.5	23.1	20.1	8.4	4.5	11.4	6.4	18.7	4.0	0.6
5-year cumulative incidence, %	10.5	55.1	31.0	44.6	45.1	19.8	10.8	25.4	15.9	41.1	10.2	1.6
10-year cumulative incidence, %	20.7	69.7	45.9	57.7	73.8	33.5	19.5	39.9	30.6	64.1	20.1	3.4
12-year cumulative incidence, %	25.5	71.4	49.2	59.4	82.6	38.0	22.8	43.8	37.2	70.1	24.8	4.4
5-year cumulative incidence no genes, %	18.6	33.2	33.1	23.0	22.0	30.0	26.9	28.9	32.9	32.9	8.2	5.2

	Subject No.											
	13	14	15	16	17	18	19	20	21	22	23	24
Eye	OS	OS	OS	OS	OS	OS	OS	OS	OS	OS	OS	OS
Age	69.8	58.2	67.3	73.9	65.6	76.0	71.6	69.8	79.9	67.7	65.5	57.6
Sex	F	F	F	F	F	M	F	M	F	M	M	M
Education	> HS	> HS	≤ HS	> HS	≤ HS	> HS	≤ HS	≤ HS	> HS	≤ HS	≤ HS	> HS
Body mass index	35.8	34.5	24.5	28.9	28.5	13.4	28.3	29.4	26.2	25.7	26.0	29.9
Smoking	Past	Past	Never	Past	Past	Past	Never	Never	Never	Past	Current	Never
Race (white)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Complement pathway												
CFH Y402H: rs1061170	CC	CT	TT	CC	CT	CC	CC	CC	CC	CT	TT	TT
CFH: rs1410996	CC	CT	CT	CC	CT	CC	CC	CC	CC	CC	CT	CT
CFH R1210C: rs121913059	CC	CC	CC	CC	CT	CC	CC	CC	CC	CC	CC	CC
C2 E318D: rs9332739	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG
CFB R32Q: rs641153	CC	CC	CC	CC	CC	CT	CC	CC	CC	CC	CC	CC
C3 R102G: rs2230199	CG	CG	CG	CG	CG	CC	GG	CC	CG	CC	CC	CC
C3 K155Q: rs147859257	TT	GT	TT	TT	TT	TT	TT	TT	TT	TT	CC	TT
Immune/inflammatory pathway												
ARMS2/HTRA1: rs10490924	GG	TT	GG	TT	GG	GG	GG	GT	GG	GT	GG	GG
PELI3: rs145732233	CC	CC	CC	CC	CC	CC	CT	CC	CC	CC	CC	CC

Continued on next page

TABLE 16. Cumulative Incidence of Progression to Advanced Age-Related Macular Degeneration at 2, 5, 10, and 12 Years Based on the Composite Risk Score, Adjusting for Mortality Risks for a Representative Sample of 24 Right and Left Eyes With Intermediate-Stage Disease at Baseline (*Continued*)

	Subject No.											
	13	14	15	16	17	18	19	20	21	22	23	24
Extracellular matrix												
COL8A1: rs13095226	TT	TT	TT	TT	TT	CT	TT	TT	CT	TT	CC	TT
CTRB1: rs8056814	GG	GG	GG	GG	GG	AG	GG	GG	AG	GG	GG	GG
DNA repair/protein binding												
RAD51B: rs8017304	GA	AA	GG	GG	GA	GA	GG	AA	AA	GA	AA	AA
HSPH1/B3GALTL: rs9542236	CC	TT	TT	CC	CT	TT	CC	CT	CT	CC	CT	CT
2-year cumulative incidence, %	13.0	20.0	3.3	18.6	27.3	4.7	3.5	12.8	12.1	10.8	4.5	1.1
5-year cumulative incidence, %	30.4	44.9	8.6	40.7	56.5	11.2	8.8	29.5	26.9	25.7	11.4	3.0
10-year cumulative incidence, %	52.9	73.5	18.0	62.9	81.8	19.8	17.6	49.9	41.8	45.6	22.8	6.6
12-year cumulative incidence, %	61.0	82.4	22.9	68.6	87.1	22.9	21.9	56.6	45.6	53.0	28.4	8.7
5-year cumulative incidence no genes, %	27.1	21.1	21.6	22.2	29.2	24.9	23.5	22.7	23.2	22.2	14.1	3.8

HS = high school; N = no; Y = yes.
Results shown for derivation cohort.

R1210C ($P = .02$) and *C3* K155Q ($P = .0001$). A significantly lower rate of visual loss was observed with protective alleles in *C2* E318D ($P = .007$) and *CFB* R32Q ($P = .001$). A similar protective effect was observed with *CFH* N1050Y ($P = .007$). In the angiogenesis pathway, *VEGFA* was significantly associated with VA loss ($P = .02$), and a suggestive effect was observed for *TGFBR1* ($P = .08$).

In the lipid pathway, a suggestive effect was observed for *CETP* ($P = .07$). In the immune pathway, significant associations were observed with risk alleles in *ARMS2* ($P < .0001$). *CTRB1* was associated with a protective effect against visual acuity loss ($P = .0004$), as were alleles in *COL4A3* ($P = .05$) and *TIMP3* ($P = .04$); these loci are associated with the extracellular matrix pathway. The DNA repair and protein binding genes *RAD51B* ($P = .001$) and *HSPH1/B3GALTL* ($P = .005$) were also associated with this outcome.

The multivariate analyses for the endpoint of VA loss, adjusting for all of the variables (demographic, behavioral, and ocular factors), are presented in Table 18. Similar to the results of the univariate analyses, participants who had a higher risk of VA loss over time were older, were white, and had a higher BMI, a lower level of education, and a history of cigarette smoking. Multivariate associations between genetic factors and VA loss are reported in Table 19, including a multivariate model with all 31 genetic variants. These models were adjusted for age, sex, race, level of education, and baseline grade (model I), and the fully adjusted model also included BMI, smoking, and all of the genetic loci (model II). The multivariate stepwise analysis for VA loss ≥ 15 letters led to the identification of 6 genetic variants associated with VA loss (shown in Table 5), which are the same genetic variants that were significantly related to VA loss in multivariate model II in Table 19. Four of the 6 were in the complement pathway and were associated with a higher risk of visual loss: *CFH* rs1410996 (HR: 1.30; 95% CI:1.19-1.43; $P < .0001$), *CFH* R1210C (HR: 3.01; 95% CI: 1.67-5.41; $P = .0002$), *C3* R102G (HR: 1.23; 95% CI: 1.12-1.35; $P < .0001$), and *C3* K155Q (HR: 1.43; 95% CI: 1.05-1.94; $P = .02$). The *ARMS2* variant increased risk of visual loss (HR: 1.33; 95% CI 1.22-1.45; $P < .0001$), and *RAD51B* was significantly associated with a protective effect against VA loss (HR: 0.86; 95% CI: 0.80-0.94; $P = .001$). All of the genes associated with VA loss were also significantly associated with progression to overall advanced AMD, although not all genes associated with AMD progression retained significance in the stepwise model for VA. The AUC for this composite predictive model for VA loss was 0.72.

DISCUSSION

WE HAVE DEVELOPED SEVERAL MODELS, INCLUDING THE earliest model in 2006 with the 3 known genetic variants at the time (*CFH*, *ARMS2*, and *C2*), followed by inclusion of additional newly reported genes as well as demographic, behavioral, and ocular factors.[14,34–40] This current work differs from and expands upon previous work in several ways: by adding recently discovered genetic variants, many of which had not been previously evaluated for their association with AMD progression; a larger independent validation cohort with similar baseline grades, which has the same variables in the model as the derivation cohort, allowing for valid comparisons of the risk models; new methods for assessing the impact of the

TABLE 17. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Visual Acuity Loss in the Derivation Cohort

	VA Loss ≥ 15 Letters,[a] N (%) (N = 1650)	VA Loss < 15 Letters, N (%) (N = 3620)	*P* Value[b]
Demographic			
Age (y)			
≥75	893 (54.1)	1275 (35.2)	<.0001
65 to 74	724 (43.9)	2261 (62.5)	
55 to 64	33 (2.0)	84 (2.3)	
Sex			
Male	715 (43.3)	1612 (44.5)	.54
Female	935 (56.7)	2008 (55.5)	
Race			
White	1621 (98.2)	3467 (95.8)	<.0001
Nonwhite	29 (1.8)	153 (4.2)	
Behavioral			
Education			
≤ High school	628 (38.1)	1132 (31.3)	<.0001
> High school	1022 (61.9)	2488 (68.7)	
Body mass index			
<25	481 (29.2)	1244 (34.4)	.0001
25 to 29.9	716 (43.4)	1537 (42.5)	
≥30	453 (27.5)	839 (23.2)	
Smoking			
Never	688 (41.7)	1782 (49.2)	<.0001
Past	825 (50.0)	1655 (45.7)	
Current	137 (8.3)	183 (5.1)	
Ocular			
Baseline AMD grade			
1	258 (15.6)	1624 (44.9)	<.0001
2	256 (15.5)	958 (26.5)	
3	903 (54.7)	928 (25.6)	
4	79 (4.8)	16 (0.4)	
5	134 (8.1)	69 (1.9)	
Genetic loci			
Complement pathway			
CFH Y402H: rs1061170			
TT	375 (22.7)	1237 (34.2)	<.0001
CT	755 (45.8)	1630 (45.0)	
CC	520 (31.5)	753 (20.8)	
CFH: rs1410996			
TT	120 (7.3)	570 (15.7)	<.0001
CT	577 (35.0)	1574 (43.5)	
CC	953 (57.8)	1476 (40.8)	
CFH R1210C: rs121913059			
CC	1634 (99.0)	3609 (99.7)	.02
CT	16 (1.0)	11 (0.3)	
C2 E318D: rs9332739			
GG	1563 (94.7)	3342 (92.3)	.007
CG/CC	87 (5.3)	278 (7.7)	
CFB R32Q: rs641153			
CC	1460 (88.5)	3065 (84.7)	.001
TC/TT	190 (11.5)	55 (15.3)	
CFI: rs10033900			
CC	398 (24.1)	926 (25.6)	.25
CT	810 (49.1)	1179 (49.1)	

Continued on next page

TABLE 17. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Visual Acuity Loss in the Derivation Cohort (*Continued*)

	VA Loss ≥ 15 Letters,[a] N (%) (N = 1650)	VA Loss < 15 Letters, N (%) (N = 3620)	*P* Value[b]
TT	442 (26.8)	915 (25.3)	
C3 R102G: rs2230199			
CC	846 (51.3)	2228 (61.5)	<.0001
CG	670 (40.6)	1224 (33.8)	
GG	134 (8.1)	168 (4.6)	
C3 K155Q: rs147859257			
TT	1596 (96.7)	3566 (98.5)	.0001
GT	54 (3.3)	54 (1.5)	
C9 P167S: rs34882957			
GG	1605 (97.3)	3545 (97.9)	.16
AG	45 (2.7)	75 (2.1)	
CFH N1050Y: rs35274867			
AA	1627 (98.6)	3518 (97.2)	.007
TA	23 (1.4)	98 (2.7)	
TT	0 (0.0)	4 (0.1)	
Angiogenesis pathway			
VEGFA: rs943080			
CC	330 (20.0)	851 (23.5)	.02
CT	846 (51.3)	1813 (50.1)	
TT	474 (28.7)	956 (26.4)	
TGFBR1: rs334353			
TT	993 (60.2)	2062 (57.0)	.08
GT	559 (33.9)	1332 (36.8)	
GG	98 (5.9)	226 (6.2)	
Lipid pathway			
LIPC: rs10468017			
CC	878 (53.2)	1889 (52.2)	.37
TC	666 (40.4)	1464 (40.4)	
TT	106 (6.4)	267 (7.4)	
ABCA1: rs1883025			
CC	919 (55.7)	2015 (55.7)	.76
TC	636 (38.5)	1377 (38.0)	
TT	95 (5.8)	228 (6.3)	
CETP: rs3764261			
CC	685 (41.5)	1615 (44.6)	.07
AC	770 (46.7)	1606 (44.4)	
AA	195 (11.8)	399 (11.0)	
APOC1/APOE: rs4420638			
AA	1196 (72.5)	2853 (78.8)	.43
GA	454 (27.5)	1037 (28.6)	
APOH: rs1801689			
AA	1546 (93.7)	3385 (93.5)	.72
AC	104 (6.3)	233 (6.4)	
CC	0 (0.0)	2 (0.1)	
Immune/inflammatory pathway			
ARMS2/HTRA1: rs10490924			
GG	612 (37.1)	2068 (57.1)	<.0001
TG	753 (45.6)	1283 (35.4)	
TT	285 (17.3)	269 (7.4)	
PELI3: rs145732233			
CC	1640 (99.4)	3591 (99.2)	.43

Continued on next page

TABLE 17. Univariate Associations Between Demographic, Behavioral, Ocular, and Genetic Factors and Visual Acuity Loss in the Derivation Cohort (*Continued*)

	VA Loss ≥ 15 Letters,[a] N (%) (N = 1650)	VA Loss < 15 Letters, N (%) (N = 3620)	*P* Value[b]
TC	10 (0.6)	29 (0.8)	
TNFRSF10A: rs13278062			
TT	477 (28.9)	979 (27.0)	.50
GT	808 (49.0)	1847 (51.0)	
GG	365 (22.1)	794 (21.9)	
SLC16A8: rs8135665			
CC	1022 (61.9)	2310 (63.8)	.11
TC	544 (33.0)	1167 (32.2)	
TT	84 (5.1)	143 (4.0)	
PILRB/PILRA: rs11769700			
TT	1038 (62.9)	2279 (63.0)	.89
CT	554 (33.6)	1201 (33.2)	
CC	58 (3.5)	140 (3.9)	
TMEM97/VTN: rs704			
AA	381 (23.1)	873 (24.1)	.74
AG	823 (49.9)	1760 (48.6)	
GG	446 (27.0)	987 (27.3)	
Extracellular matrix			
COL8A1: rs13095226			
TT	1305 (79.1)	2940 (81.2)	.10
CT	324 (19.6)	639 (17.7)	
CC	21 (1.3)	41 (1.1)	
COL4A3: rs11884770			
CC	917 (55.6)	1914 (52.9)	.05
TC	630 (382)	1414 (39.1)	
TT	103 (6.2)	292 (8.1)	
CTRB1: rs8056814			
GG	1420 (86.1)	2952 (81.5)	.0004
AG	221 (13.4)	625 (17.3)	
AA	9 (0.5)	43 (1.2)	
ADAMTS9: rs6795735			
CC	510 (30.9)	1062 (29.3)	.85
TC	770 (46.7)	1783 (49.3)	
TT	370 (22.4)	775 (21.4)	
TIMP3: rs9621532			
AA	1512 (91.6)	3250 (89.8)	.04
CA/CC	138 (8.4)	370 (10.2)	
DNA binding/protein repair			
RAD51B: rs8017304			
AA	727 (44.1)	1453 (40.1)	.001
GA	756 (45.8)	1642 (45.4)	
GG	167 (10.1)	525 (14.5)	
NPLOC4/TSPAN10: rs9895741			
GG	683 (41.4)	1506 (41.6)	.95
AG	741 (44.9)	1611 (44.5)	
AA	226 (13.7)	503 (13.9)	
HSPH1/B3GALTL: rs9542236			
TT	480 (29.1)	1226 (33.9)	.005
CT	834 (50.5)	1732 (47.8)	

AMD = age-related macular degeneration; VA = visual acuity.

[a]Sample sizes for each genetic variable may not be equal to the overall sample size. Some participants do not have genetic information available for all genetic loci evaluated.

[b]*P* values calculated using Generalized Estimating Equations in order to account for inter-correlation in eye-specific analyses.

TABLE 18. Multivariate Associations Between Demographic, Behavioral, and Ocular Factors and Visual Acuity Loss in the Derivation Cohort

	HR (95% CI)[a]	*P* Value
Demographic		
Age (y)		
≥75	*Referent*	
65 to 74.9	0.72 (0.63-0.82)	<.0001
55 to 64.9	0.41 (0.34-0.50)	<.0001
Sex		
Female	*Referent*	
Male	0.90 (0.81-1.01)	.08
Race		
Nonwhite	*Referent*	
White	1.57 (1.11-2.21)	.01
Behavioral		
Education		
≤ High school	*Referent*	
> High school	0.86 (0.77-0.96)	.009
Body mass index		
<25	*Referent*	
25 to 29.9	1.15 (1.01-1.31)	.04
≥30	1.35 (1.17-1.56)	<.0001
Smoking		
Never	*Referent*	
Past	1.20 (1.06-1.34)	.003
Current	1.82 (1.48-1.56)	<.0001
Ocular		
Baseline AMD grade		
1	*Referent*	
2	1.52 (1.28-1.81)	<.0001
3	4.11 (3.56-4.74)	<.0001
4	10.25 (8.04-13.07)	<.0001
5	7.26 (5.70-9.25)	<.0001

AMD = age-related macular degeneration; CI = confidence interval; HR = hazard ratio; VA = visual acuity.

[a]HRs and 95% CIs for 12-year progression were estimated using Cox proportional hazards models using the individual eye as the unit of analysis, adjusted for all variables listed in the table.

polygenic model; and evaluation of VA loss as a functional outcome in risk prediction analyses.

The methodologic approach of eye-specific analyses using both eyes, as we applied in analyses of separate topics previously, enhances the person-based analyses of the worse eye. The analysis of individual eyes accounts for eye-specific covariates (namely, level of macular disease severity) and additionally differentiates between participants who progress in a single eye compared with those who progress in both eyes.

We derived composite risk prediction models for progression to advanced AMD, as well as GA and NV separately, in the derivation cohort and achieved a high level of discrimination in a large external validation cohort. We also demonstrated the added value of genes when comparing models with and without genes and this result was observed in both cohorts. Results add to the growing literature and evidence that individuals vary considerably in their risk of progression and visual loss over time, depending on a combination of demographic, behavioral, ocular, and genetic variables. These models can be used for future clinical care and management, for selection of higher-risk individuals for screening, for identification of subjects at high risk of advanced disease and visual loss at an earlier stage for inclusion in randomized clinical trials testing new treatments, and for understanding the pathophysiology of the disease.

These prospective analyses also add new information regarding risk and protective genetic variants associated with progression of AMD. We identified 13 common or low-frequency genetic variants independently associated with risk of progression to overall advanced AMD: 7 in the complement pathway, 2 in the immune/inflammatory pathway, 2 in the extracellular matrix pathway, and 2 in the DNA repair/protein binding pathway. A set of 4 loci in 3 genes were consistently predictive of each AMD outcome: the common, noncoding *CFH* variant (rs1410996), the rare variant *CFH* R1210C, and common variants in *C3* R102G and *ARMS2*. When assessing progression to GA and NV separately, there were some differences in the models with significant heterogeneity for genetic and nongenetic factors. Variants in *TGFBR1*, *RAD51B*, and *COL4A3* were associated with progression to the NV subtype, whereas the *CFI* and *C3* K155Q variants tended to be associated with higher risk of progression to GA, although the heterogeneity was not significant. We previously reported that the genetic variant in *ARMS2* on chromosome 10 conferred a larger risk for development of NV relative to GA, although it increases risk for both subtypes.

In addition to the obvious phenotypic differences between GA and NV, and a few possible genetic differences, there have been other differences noted between GA and NV. Response to supplementation with antioxidants differs: participants with NV have a more beneficial response to antioxidant supplementation than do those with GA. There are differences regarding various dietary modifications and gene–diet associations.[46–49,63–65] Distinct clinical features preceding each subtype have also been identified with OCT imaging[50] and histopathologic observations in postmortem ocular tissue.[66]

Novel analyses were conducted to evaluate the impact of the risk model on predicting functional loss of vision. Many, but not all, of the genes related to progression to advanced disease were also related to this outcome. Common and rare variants in *CFH* and *C3* were associated with a higher risk of VA loss, as was *ARMS2*, while the *RAD51B* variant conferred a protective effect. These 6 loci were consistently observed to be associated with AMD risk as well as visual loss, including progression to overall advanced AMD, GA, and NV. Differences existed for only 2 loci: the rare *C3* K155Q was not associated with NV, and the protective *RAD51B* was not associated with GA. Demographic

TABLE 19. Associations Between Individual Genetic Loci and Visual Acuity Loss in the Derivation Cohort

	Multivariate Model I[a]		Multivariate Model II[b]	
Genetic Loci	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Complement pathway				
CFH Y402H: rs1061170	1.16 (1.01-1.25)	<.0001	0.97 (0.87-1.08)	.56
CFH: rs1410996	1.29 (1.18-1.40)	<.0001	1.32 (1.17-1.49)	<.0001
CFH R1210C: rs121913059	1.90 (1.12-3.21)	.02	2.93 (1.63-5.28)	.0003
C2 E318D: rs9332739	0.84 (0.65-1.08)	.16	0.86 (0.66-1.11)	.25
CFB R32Q: rs641153	0.87 (0.73-1.03)	.09	0.88 (0.73-1.06)	.18
CFI: rs10033900	1.00 (0.93-1.08)	.99	1.00 (0.93-1.08)	.98
C3 R102G: rs2230199	1.22 (1.12-1.33)	<.0001	1.22 (1.11-1.34)	<.0001
C3 K155Q: rs147859257	1.28 (0.93-1.74)	.13	1.43 (1.04-1.98)	.03
C9 P167S: rs34882957	0.92 (0.67-1.25)	.59	0.78 (0.55-1.11)	.17
CFH N1050Y: rs35274867	0.64 (0.41-1.00)	.05	0.93 (0.60-1.44)	.74
Angiogenesis pathway				
VEGFA: rs943080	1.07 (0.99-1.15)	.10	1.07 (0.98-1.16)	.13
TGFBR1: rs334353	0.97 (0.88-1.06)	.47	0.94 (0.85-1.03)	.17
Lipid pathway				
LIPC: rs10468017	0.98 (0.89-1.07)	.60	0.99 (0.91-1.09)	.90
ABCA1: rs1883025	1.03 (0.94-1.23)	.52	1.01 (0.92-1.11)	.85
CETP: rs3764261	1.05 (0.97-1.13)	.24	1.02 (0.94-1.11)	.66
APOC1/APOE: rs4420638	1.01 (0.90-1.14)	.88	1.02 (0.90-1.15)	.81
APOH: rs1801689	1.03 (0.83-1.28)	.77	1.15 (0.91-1.45)	.24
Immune/inflammatory pathway				
ARMS2/HTRA1: rs10490924	1.37 (1.27-1.48)	<.0001	1.33 (1.23-1.45)	<.0001
PELI3: rs145732233	0.97 (0.51-1.86)	.94	0.80 (0.38-1.70)	.56
TNFRSF10A: rs13278062	1.03 (0.96-1.12)	.41	0.98 (0.90-1.06)	.57
SLC16A8: rs8135665	1.01 (0.92-1.11)	.84	1.03 (0.93-1.13)	.60
PILRB/PILRA: rs11769700	0.99 (0.90-1.09)	.79	1.00 (0.91-1.11)	.95
TMEM97/VTN: rs704	1.02 (0.95-1.11)	.54	1.01 (0.93-1.10)	.78
Extracellular matrix				
COL8A1: rs13095226	1.03 (0.91-1.16)	.66	1.04 (0.91-1.18)	.61
COL4A3: rs11884770	0.96 (0.88-1.05)	.33	0.95 (0.87-1.05)	.30
CTRB1: rs8056814	0.93 (0.81-1.08)	.36	0.92 (0.79-1.07)	.28
ADAMTS9: rs6795735	1.01 (0.94-1.09)	.78	1.02 (0.94-1.11)	.63
TIMP3: rs9621532	0.83 (0.68-1.00)	.05	0.89 (0.72-1.10)	.26
DNA repair/protein binding				
RAD51B: rs8017304	0.89 (0.82-0.97)	.006	0.86 (0.79-0.94)	.0009
NPLOC4/TSPAN10: rs9895741	0.99 (0.92-1.07)	.82	0.99 (0.91-1.07)	.74
HSPH1/B3GALTL: rs9542236	1.07 (1.00-1.16)	.06	1.06 (0.98-1.15)	.13

AMD = age-related macular degeneration; CI = confidence interval; HR = hazard ratio.

[a]Multivariate Model I: HRs for 12-year progression reflect risk per allele, and are adjusted for age, sex, race, education, and baseline AMD grade.

[b]Multivariate Model II: HRs reflect risk per allele, and are adjusted for age, sex, race, education, baseline AMD grade, body mass index, smoking status, and all other genetic loci in the table.

features, lifestyle factors including smoking and BMI, and baseline ocular status were also significantly associated with visual loss. The composite model achieved relatively high discrimination between those who lost vision over time and those who did not.

We demonstrated that a combination of several common and a few rare variants plus the other variables in the model can identify a very high-risk population with a magnitude of risk comparable to the risk conferred by some single rare genetic variants. Seven of the 13 loci were in the complement pathway: 5 common variants and 2 rare variants. The highest quintile of the risk score conferred almost a 6-fold higher risk of progression from intermediate to advanced disease. Although such a composite or polygenic model can identify high-risk populations, it may not identify functional, actionable, and "druggable" targets like the individual

rare genetic variants. On the other hand, such a score can be useful to reduce the size and duration, and therefore cost, of clinical trials,[36] and for incorporation into management or decision making regarding timing of follow-up visits and preventive measures. These same methods outlined here and in our earlier models[39] could also be modified to include only genetic loci in a particular pathway (ie, complement, lipid pathway, etc).

AUCs achieved in these analyses indicate a high discriminatory ability of the composite risk model to differentiate progressors from nonprogressors or between those who lose vision and those who do not. The AUCs for our prediction models began at 0.70, and have since achieved excellent separation of groups as a result of incorporating additional common and rare variants, indicated by an AUC approaching 0.90.[39,40] Our highest observed AUC was 0.94[67] and was calculated based on a model that incorporated plasma complement biomarkers as a predictive measure of AMD progression, in addition to demographic, behavioral, ocular, and genetic variables. To further enhance discrimination between groups, additional biomarkers could be added, such as optical coherence tomography parameters,[50] or other functional data like low-luminance vision.[68] It is clear that AUCs for AMD are quite high relative to risk models for other common disorders. For example, AUCs for the Framingham Heart Study, a large longitudinal cohort evaluating risk factors for cardiovascular disease, reach only 0.65.[69] In breast cancer, AUCs reach approximately 0.60, and are often lower.[60,70]

The relative contribution of genes and genetic susceptibility to AMD risk has been a subject of discussion. Macular phenotypes have been considered the primary predictors of future disease. However, drusen in the early and intermediate stages of AMD, as well as the presence of advanced disease in the fellow eye are in the causal pathway for progression, and these features are also associated with the AMD genes. The inclusion of ocular covariates in our past and present prediction models attenuates the association between genetic factors and AMD risk and underestimates the true effect of the genetic component. A model that included the grade of the fellow eye was evaluated and most of the genes in the model were similar (Supplemental Table 3; Supplemental Material available at AJO.com). Results suggest that genes contribute to the risk burden associated with progression to advanced AMD subtypes, an observation that is further confirmed in validation analyses.

We previously reported a validation analysis for a risk prediction model containing 6 loci in a smaller independent cohort using the person as the unit of analyses,[38] and conducted a split-sample validation in our 10-gene model.[40] In both models, the AUCs for the total and validation samples were similar. The study reported herein differs in that eyes were the unit of analyses, and the validation cohort is a larger, independent, and well-characterized prospective cohort with data on the same demographic, lifestyle, ocular, and genetic risk factors as the derivation cohort. AUCs for the derivation and validation cohorts were similar. This report also includes evaluation of one of the largest subsets of genetic loci at the time of this submission, for their independent associations with progression to both advanced AMD and VA loss.

Determination of the sensitivity and specificity of our risk model in the validation cohort revealed that the model could highly discriminate between progressors and nonprogressors. In addition to the new analyses, strengths of our study include the extensive follow-up time in both cohorts and a large number of eyes that progressed to each outcome during the follow-up interval in both the derivation and the validation cohorts.

In summary, new genetic variants associated with AMD risk in case-control studies were evaluated prospectively for their independent effects on progression from nonadvanced to advanced AMD as well as subsequent visual loss. A subset of genes along with demographic, behavioral, and ocular factors were determined to be most predictive of conversion to advanced AMD. A model was assessed for the functional outcome of visual loss of 15 or more letters, and predictors were some of the same covariates, including modifiable and genetic factors. When GA and NV were assessed separately, there were some differences in the models with significant heterogeneity for genetic and nongenetic factors. The most important pathways associated with AMD progression and transition to advanced stages of GA and NV with visual loss involve the complement, inflammatory, and immune systems; lipid and collagen matrix pathways; and DNA repair mechanisms.

Our composite risk models were highly predictive of changes over time to visually disabling forms of the disease, as evidenced by high AUC statistics and significant NRI statistics. The model also calibrated well in the external cohort. These assessments of NRI and calibration were conducted in a completely independent cohort with similar baseline grades and data on the same covariates that were used in deriving the model. Inclusion of genetic data enhanced the risk classification of individual eyes. This comprehensive external validation of the AMD risk model strengthens and underscores the generalizability and use of such a model in primarily white populations to identify patients at high risk of progression. Such individuals can have more intensive monitoring, which will lead to earlier detection of the transition to late stages of AMD. New imaging modalities may contribute to this composite model to detect high-risk subgroups.[50] Anticipating that interventions will become available for high-risk individuals with intermediate AMD who have not yet progressed, it is prudent to identify who they are so clinical trials can focus on this population. The precision medicine approach could facilitate the discovery and delivery of new treatments prior to visual loss.

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