Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates

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Purpose. To determine the association between genetic variants and transition to advanced age-related macular degeneration (AMD), and to develop a predictive model and online application to assist in clinical decision making.

Methods. Among 2951 subjects in the Age-Related Eye Disease Study, 834 progressed from no AMD, early AMD, or intermediate AMD to advanced disease. Survival analysis was used to assess which genetic, demographic, environmental, and macular covariates were independently associated with progression. Attributable risk, area under the curve statistics (AUCs), and reclassification odds ratios (ORs) were calculated. Split-sample validation was performed. An online risk calculator was developed and is available in the public domain at www.seddonamdriskscore.org.

Results. Ten genetic loci were independently associated with progression, including newly identified rare variant *C3* K155Q (hazard ratio: 1.7, 95% confidence interval: 1.2–2.5, $P = 0.002$), three variants in *CFH*, and six variants in *ARMS2/HTRA1*, *CFB*, *C3*, *C2*, *COL8A1*, and *RAD51B*. Attributable risk calculations revealed that 80% of incident AMD is attributable to genetic factors, adjusting for demographic covariates and baseline macular phenotypes. In a model including 10 genetic loci, age, sex, education, body mass index, smoking, and baseline AMD status, the AUC for progression to advanced AMD over 10 years was 0.911. Split-sample validation showed a similar AUC (0.907). Reclassification analyses indicated that subjects were categorized into a more accurate risk category if genetic information was included (OR 3.2, $P < 0.0001$).

Conclusions. Rare variant *C3* K155Q was independently associated with AMD progression. The comprehensive model may be useful for identifying and monitoring high-risk patients, selecting appropriate therapies, and designing clinical trials.

Keywords: age-related macular degeneration, genetics, prediction, progression, risk modeling

The era of personalized medicine and targeted therapies is emerging in many areas of medicine. In ophthalmology, the disease age-related macular degeneration (AMD) stands alone in having several environmental and genetic risk factors with confirmed, combined high impact on its development and progression. The combination of demographic, behavioral, and genetic factors can achieve a high predictive value for progression to advanced stages of disease approaching 90%, unlike any other disease.[1–5] We developed genetic risk algorithms in 2006,[6] subsequently adding nongenetic markers[7] and more common genetic variants,[2–4,8] then recently validated these risk models in an independent study cohort.[5] More genetic loci in a 9 gene model, including the strongly related rare variant in the gene *CFH* (R1210C),[9] and common loci *RAD51B* and *COL8A1*,[10,11] enhanced predictability for transition from early and intermediate stages to advanced disease.[12]

Knowledge about the genetic underpinnings of AMD continues to expand. New, rare genetic variants have been discovered in case-control association studies in the genes *C3*[13–15] and *C9*,[13] as well as a burden of several rare variants in *CFI*.[13] While these variants are uncommon, they have a stronger impact on the development of the disease individually compared with the low to moderate impact of the 20 or more common variants associated with AMD. Given that previous analyses were based on cross-sectional analyses of prevalent cases, and that progression of disease over time can have different underlying predictors, we conducted longitudinal analyses to determine the impact of these new rare variants on transition to the late stages of AMD resulting in visual loss over time. We also assessed the independent association of these new variants on progression, controlling for other genetic and nongenetic predictors. Building upon our previous algorithms, we developed and assessed a new

risk prediction model for progression of AMD (rPPMD) and evaluated the degree to which AMD progression could be attributed to its various components: environmental, ocular, and genetic. In order to lay the groundwork to disseminate these predictive models for clinical use, we developed a software framework and analytics components in the form of an online browser-based calculator (seddonamdriskscore.org, available in the public domain) to demonstrate its use with various subject risk profiles. The rPPMD software components are also designed to be adapted as a stand-alone application for a personal computer or mobile devices such as smartphones and tablets.

Methods

Population and Definition of Progression

Data from the Age-Related Eye Disease Study (AREDS) for Caucasian participants were used for this analysis.[16] Progression was defined as transition from no AMD, early AMD, or intermediate AMD (Clinical Age-Related Maculopathy Staging System [CARMS] grade of 1, 2, or 3) to advanced AMD (CARMS grade 4 or 5) in either eye during a follow-up visit.[2,3,5,12,17] Progressors were classified using the following two criteria: (1) No advanced AMD was present in either eye at baseline and at least one eye became advanced during follow-up, or (2) advanced AMD was present in one eye at baseline and the fellow eye became advanced during follow-up. Follow-up time ranged from 6 months to 13 years (mean 8.8 years). Baseline demographic, environmental, and ocular characteristics were assessed. Genotypes for 10 single nucleotide polymorphisms (SNPs) associated with AMD in eight different genes were obtained using methods previously described.[6,9,10,13] All research adhered to the tenets of the Declaration of Helsinki.

Statistical Analysis

Demographic, environmental, and ocular variables included in the analyses were age (55–64, 65–74, ≥75), sex, education (≤high school, >high school), body mass index (BMI) (<25, 25–29, ≥30), smoking status (never, past, current), presence or absence of unilateral advanced AMD at baseline (either central or noncentral geographic atrophy [GA] in one eye [CARMS grade 4] or neovascular disease [NV] in one eye [CARMS grade 5]), and drusen size in eyes without advanced AMD. Drusen size was reported in micrometers for each nonadvanced eye as follows: <63, 63 to 124, 125 to 249, and ≥250. Subjects with no drusen or questionable presence of drusen were classified together with the <63 μm drusen category. The four AREDS treatment groups (placebo, zinc, antioxidants, and antioxidants plus zinc) were covariates in analyses of incident advanced AMD.

The prevalence of AMD at baseline was evaluated using multivariate logistic regression models to estimate odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. These prevalence models were used to examine the association between demographic, environmental, and genetic variables and three AMD categories at baseline: overall advanced AMD, central or noncentral GA, and NV.

For analyses of incident advanced AMD outcomes, we assessed progression to advanced AMD over 13 years using survival analysis methodology. Cox proportional hazards models used individual subjects as the unit of analysis, and hazard ratios (HRs) were estimated for each covariate. The association between progression to advanced AMD and the genetic variants was evaluated using the Mantel-Haenszel χ^2 test.

Multivariate associations between AMD progression and the genetic variants in the previous "9 gene model" and the new model with 10 SNPs in eight different genes, hereafter referred to as the "10 gene model," were assessed using Cox proportional hazards models. The 10 gene model consists of our previously reported "9 gene model,"[12] with the addition of the *C3* (K155Q) variant[13] found to be independently related to incident advanced AMD in these analyses.

Attributable risks (ARs) were determined for the following variables: (1) environmental factors, (2) genetic factors, and (3) a combination of genetic and environmental factors, adjusting for age, sex, education, and treatment groups. For each of these three subsets, AR was estimated separately for three different AMD outcomes, both with and without baseline macular phenotype variables. The AR estimates the percentage of incident AMD that can be attributed to genetic, environmental, or composite genetic and environmental factors in models with and without macular phenotypes. "Attributable risk" describes the percentage of incident AMD that would be reduced if each individual had genetic and/or environmental factors that were in the most favorable or protective category.

The age-adjusted areas under the receiver operating curve (AUCs) were calculated using methodology previously described.[12,18,19] Areas under the curve were based on the 10 gene model to discriminate between progressors and nonprogressors to advanced AMD, GA, and NV within 10 years.

Risk scores for progression to AMD were calculated using regression coefficients for all demographic, environmental, genetic, and ocular factors. The HR for the *i*th subject is given from the Cox proportional hazards model by

$$\lambda_i = \exp\left(\sum_{j=1}^{J} \beta_j x_{ij}\right), \quad (1)$$

where β_j is the regression coefficient for the *j*th variable and x_{ij} is the value of the *j*th variable for the *i*th subject. The corresponding estimate of the survival function for the *i*th subject is given by $[S_0(t)]^{\lambda_i}$, where $S_0(t)$ is equal to the baseline survival function estimated using the baseline option of PROC PHREG in SAS 9.3 (SAS Institute, Inc., Cary, NC, USA). Supplementary Table S1 provides the 40 regression coefficients used to calculate the 10 gene model risk score.

Cumulative incidence of AMD at 2, 5, and 10 years from baseline, based on the 10 gene model risk score, was calculated for two representative samples of 12 patients each: (1) intermediate AMD (CARMS grade 3 in both eyes) and (2) advanced AMD (grade 4 or 5) in one eye and grade 3 in the fellow eye. These calculations were based on the 10 gene model risk score and were adjusted for competing mortality risks.[20] The cumulative incidence over time *t* without adjusting for mortality risks over time was given by $CI(t) = 1 - S(t)$. Competing mortality risks were adjusted using the 2006 United States Life Tables.[21] Specifically, let P_j = the probability of 1 year mortality risk at age *j* for a specific subject. We computed $\theta_j = \Pi_{q=1}^{j}(1 - P_q)$ equals the probability of being alive after *j* years. Finally,

$$CI_{adj}(t) = C(1)(1 - P_1) + \sum_{j=2}^{t}[CI(j) - CI(j-1)]\left[\theta_j/\theta_{j-1}\right], \quad (2)$$

where $CI_{adj}(t)$ is equal to cumulative incidence adjusted for competing mortality risks.

Analyses presented in this paper are based on a model with complete data for demographic, environmental, genetic, and

ocular variables. It is possible, however, that when using these algorithms in other settings, a subject will have missing data for demographic, environmental, genetic, or ocular risk factors. For this purpose, five different modules (A–E) were created for the online risk calculator based on the availability of macular phenotype variables. The modules for risk prediction were defined as follows: (A) all macular phenotypes known; (B) drusen size known, presence of advanced disease known, but type of advanced disease unknown; (C) drusen size unknown and both presence and type of advanced disease known; (D) drusen size unknown, presence of advanced disease known, but type of advanced disease unknown; (E) all macular phenotypes unknown. For missing demographic or environmental variables, we used NHANES 2009 data to estimate the proportion of subjects with specific levels of education, smoking, and BMI as a function of age–sex groups.[22] For missing genetic risk factors, the models used population prevalence of specific genotypes instead of indicator variables.[23]

Some studies in a variety of applications have revealed that the AUC is a relatively insensitive statistic for identifying improvement in the fit of a model.[24] Therefore, we used reclassification probability methods[12,24,25] to compare competing models by cross-classifying the probability of progression at 5 years according to risk score quintiles for the 0 vs. 10 gene models to estimate the proportion of subjects whose risk category would change after the addition of genetic variables. The approach requires that risk be cross-classified for each level of risk predicted by two distinct models: (1) our current 10 gene model for progression (described above) and (2) a model including no genotype data, or "0 gene model." Both models hold all additional factors constant and differ only by the presence or absence of genes. The reclassification OR equals the ratio of odds for an increase of one 10 gene model quintile holding the 0 gene model constant.[25]

Split-sample validation was used to validate all AUCs.[26] Regression models were derived for two-thirds of the parent sample and validated in the remaining third. Subjects were assigned for each of the complementary data sets using a random uniform number generator.

All statistical analyses were performed using SAS 9.3. The alpha level for statistical significance was set a priori at $P < 0.05$.

Results

Among the total of 2951 subjects, there were 834 progressors to advanced AMD in at least one eye and 2117 nonprogressors. The mean age of the progressors was 70.2 years, while nonprogressors were, on average, 68.1 years of age. Each group was predominately female (55% vs. 57%).

Prevalence data and multivariate associations between demographic, environmental, and genetic variables and AMD status at baseline are shown in Table 1. Older age, fewer years of education, current smoking status, and higher BMI classification were significantly associated with a higher prevalence of overall AMD as well as NV. Among the genetic variables being examined, *CFH* Y402H and *ARMS2/HTRA1* were significantly associated with higher prevalence of each outcome. *C2* E318D, *CFB* R32Q, and *RAD51B* variants were inversely associated with AMD.

New cases of advanced AMD that occurred during the course of the study (incident AMD) were evaluated. Multivariate associations between demographic, environmental, and macular variables among progressors and nonprogressors are shown in Table 2. Older age, current smoking status, BMI $\geq$ 30, and advanced AMD in one eye were significantly associated with the transition to advanced disease. Larger drusen size among both groups of subjects, either with no advanced AMD or with advanced unilateral AMD at baseline, was also significantly associated with progression over time.

The distribution of genetic variants among progressors and nonprogressors and univariate associations between these genes and advanced incident AMD are reported in Table 3. There is a significant positive association between progression to advanced AMD and the number of risk alleles for *CFH* Y402H, *CFH* rs1410996, *ARMS2/HTRA1*, *C3*, *COL8A1*, and *CFH* R1210C. A significant inverse association was also found for "protective" alleles in genes *C2* E318D, *CFB* R32Q, and *RAD51B*. The recently discovered new rare variants *C9* P167S and *C3* K155Q, found to be associated with prevalent disease in our case-control association study,[13] were also associated with progression in these univariate analyses ($P = 0.0006$ and <0.0001, respectively).

Table 4 displays multivariate associations between the genetic variables and progression to advanced AMD with adjustment for demographic, environmental, and macular covariates. Two models were assessed: the previously reported 9 gene model[12] and the 10 gene model that includes the additional genetic *C3* K155Q variant found to be independently associated with incidence of advanced AMD, as shown in this table. The risk genotype (GT) of this new variant is associated with progression to advanced AMD: OR 1.7, 95% CI 1.2 to 2.5. There were significant positive associations between transition to advanced AMD and the genetic variants *CFH* rs1410996, *ARMS2/HTRA1*, *C3* R102G, *COL8A1*, *CFH* R1210C, and *C3* K155Q. Significant inverse associations were identified between progression and *CFB* R32Q and *RAD51B*, with a nonsignificant trend in the same direction for *C2* E318D. The *C9* rare variant, as shown in Table 3, tended to increase risk but did not maintain statistical significance in the multivariate model (OR 1.4, $P = 0.10$), and therefore was not included in the 10 gene model.

Tables 5 and 6 display the ARs and AUCs for progression to advanced AMD, GA, and NV at 10 years using two separate models: with and without macular phenotypes. The calculations considered environmental, genetic, and composite genetic and environmental factors for each outcome group. For overall advanced AMD, the AR for genetic factors was 95.7% in the model adjusted for age, sex, education, and AREDS treatment but without adjustment for macular phenotypes. The AR for genetic factors was lower (80.5%) when macular phenotypes were included as covariates, but 80% of incident AMD was still attributable to genetic factors. Similar ARs were found for GA and NV endpoints. The ARs related to genetic factors with and without macular phenotypes in the model were 75.7% vs. 94.9% for GA, and 77.1% vs. 93.6% for NV, respectively. The ARs related to environmental factors, however, were substantially smaller than those for genetic factors and ranged from approximately 1% to 33%, with the lowest environmental ARs for GA. Although the effect of genes is reduced by controlling for baseline macular phenotype (i.e., intermediate markers), it is clear that genotype information does confer a substantial risk burden for the transition from early or intermediate disease to the advanced stages of AMD.

Areas under the curve for progression over 10 years ranged from 0.79 to 0.92 for each of the three endpoints considered, based on the full 10 gene model with demographic, environmental, genetic, and macular variables. For all three endpoints, there was a significant increase in AUC comparing the 10 gene risk score model including all genetic and

Table 1. Multivariate Associations Between Baseline Demographic, Environmental, and Genetic Variables and Prevalence of Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease

	Prevalence of Advanced AMD OR (95% CI)* $N = 438/2513$	*P* Value	Prevalence of Geographic Atrophy OR (95% CI)* $N = 63/2513$	*P* Value	Prevalence of Neovascular Disease OR (95% CI)* $N = 375/2513$	*P* Value
Age, y						
≥75	Referent		Referent		Referent	
65–74	0.5 (0.4–0.6)	<0.001	0.3 (0.2–0.6)	<0.001	0.5 (0.4–0.7)	<0.001
55–64	0.4 (0.3–0.6)	<0.001	0.7 (0.3–1.4)	0.29	0.3 (0.2–0.5)	<0.001
Sex						
Female	Referent		Referent		Referent	
Male	1.2 (1.0–1.5)	0.11	1.7 (1.0–3.0)	0.05	1.1 (0.9–1.5)	0.31
Education						
≤High school	Referent		Referent		Referent	
>High school	0.5 (0.4–0.6)	<0.001	0.5 (0.3–0.8)	0.01	0.5 (0.4–0.7)	<0.001
Smoking						
Never	Referent		Referent		Referent	
Past	1.3 (1.1–1.7)	0.02	1.3 (0.8–2.3)	0.33	1.4 (1.0–1.8)	0.02
Current	3.5 (2.3–5.1)	<0.001	1.1 (0.3–3.7)	0.90	4.0 (2.7–6.1)	<0.001
BMI						
<25	Referent		Referent		Referent	
25–29	1.3 (1.0–1.6)	0.11	0.5 (0.3–1.0)	0.04	1.5 (1.1–2.0)	0.01
≥30	1.8 (1.4–2.4)	0.001	0.9 (0.5–1.8)	0.86	2.1 (1.5–2.8)	<0.001
CFH:rs1061170, Y402H						
TT	Referent		Referent		Referent	
CT	1.5 (1.1–2.1)	0.02	1.2 (0.5–2.8)	0.69	1.5 (1.1–2.2)	0.02
CC	2.1 (1.4–3.1)	<0.001	2.2 (0.8–5.9)	0.10	2.1 (1.3–3.2)	0.001
CFH:rs1410996						
TT	Referent		Referent		Referent	
CT	1.2 (0.7–2.0)	0.52	1.3 (0.3–5.4)	0.68	1.2 (0.7–2.0)	0.59
CC	1.6 (0.9–2.8)	0.08	2.3 (0.5–9.7)	0.27	1.5 (0.9–2.8)	0.14
ARMS2/HTRA1:rs10490924, A69S						
GG	Referent		Referent		Referent	
GT	2.0 (1.6–2.6)	<0.001	1.7 (0.9–3.0)	0.09	2.1 (1.6–2.8)	<0.001
TT	4.3 (3.1–5.9)	<0.001	4.5 (2.2–8.9)	<0.001	4.3 (3.0–6.0)	<0.001
C2:rs9332739, E318D						
GG	Referent		Referent		Referent	
CG/CC	0.6 (0.4–1.0)	0.07	0.2 (0.03–1.7)	0.14	0.7 (0.4–1.2)	0.16
CFB:rs641153, R32Q						
CC	Referent		Referent		Referent	
CT/TT	0.6 (0.4–0.9)	0.01	1.1 (0.5–2.2)	0.85	0.5 (0.4–0.8)	0.003
C3:rs2230199, R102G						
CC	Referent		Referent		Referent	
CG	1.2 (1.0–1.5)	0.10	1.1 (0.7–2.0)	0.62	1.2 (1.0–1.6)	0.11
GG	1.4 (0.9–2.1)	0.15	1.5 (0.6–4.2)	0.39	1.3 (0.8–2.1)	0.22

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Table 1. Continued

	Prevalence of Advanced AMD OR (95% CI)* $N = 438/2513$	*P* Value	Prevalence of Geographic Atrophy OR (95% CI)* $N = 63/2513$	*P* Value	Prevalence of Neovascular Disease OR (95% CI)* $N = 375/2513$	*P* Value
COL8A1:rs13095226						
TT	Referent		Referent		Referent	
CT	1.4 (1.1–1.8)	0.01	1.3 (0.7–2.4)	0.45	1.4 (1.1–1.9)	0.01
CC	0.6 (0.2–1.8)	0.33	0.8 (0.09–6.5)	0.80	0.5 (0.1–1.9)	0.31
CFH:rs121913059, R1210C						
CC	Referent		Referent†		Referent	
CT	2.0 (0.4–9.5)	0.40	-	-	2.2 (0.5–10.8)	0.33
RAD51B:rs8017304						
AA	Referent		Referent		Referent	
AG	0.8 (0.6–1.0)	0.03	0.9 (0.6–1.6)	0.82	0.7 (0.6–1.0)	0.02
GG	0.8 (0.6–1.1)	0.22	0.5 (0.2–1.3)	0.15	0.8 (0.6–1.2)	0.39
C3:rs147859257, K155Q						
TT	Referent		Referent		Referent	
GT	1.3 (0.7–2.5)	0.47	1.3 (0.3–5.5)	0.77	1.3 (0.6–2.6)	0.48

* Odds ratios are adjusted for all variables in the table.
† Small numbers preclude determination of OR.

environmental covariates to the model with environmental covariates only (*P* values ranged from 0.03 to <0.001). The difference in AUCs was particularly marked for models when macular phenotypes were not included. Conversely, differences in AUC between our 10 gene model and the genetic-only model were small and not statistically significant, particularly if macular phenotypes were included in the model. This indicates that in terms of both AR and AUC, genetic variables contributed additional predictive power compared with models with only environmental variables.

Results for AUCs from the split-sample validation analyses are presented in Supplementary Table S2. There are large differences between models containing only environmental factors compared with both genetic and environmental factors if macular phenotypes are not included ($P < 0.001$). There was a significant difference in AUC for NV comparing environmental versus genetic and environmental models when macular phenotypes were included or not included ($P = 0.042$ and $P < 0.001$, respectively). Overall, the AUC for the genetic plus environmental model was 0.91 if macular phenotypes were included and 0.81 if not included. These results are similar to the AUC results in the overall sample (Table 6).

Two representative sets of subjects were selected to illustrate 2-, 5-, and 10-year cumulative incidence of advanced AMD when applying the 10 gene model risk score algorithm. One subset ($n = 12$), shown in Table 7, included subjects with intermediate AMD in both eyes (CARMS grade 3) and large size of drusen in each eye (125–250 μm). The other subset, as shown in Table 8, included subjects ($n = 12$) with advanced AMD (CARMS grade 4 or 5) in one eye and CARMS grade 3 and large-size drusen in the fellow eye. Among subjects with essentially identical ocular status at baseline, the 5-year cumulative incidence of progression ranged from approximately 6.5% to 64% according to their 10 gene risk score profile, which reflects underlying genetic predisposition, age, sex, smoking, and BMI. Similarly, among subjects with advanced AMD in one eye, the 5-year cumulative incidence of risk of progression in the fellow eye ranged from 8% to 79% based on information derived from the various risk factors in the 10 gene model. This clearly demonstrates that the risk score provides additional information beyond the macular phenotypes. Supplementary Figures S1A through S1C display the input and output of the online risk calculator for the rPPMD model.

The Figure displays the progression rate to incident advanced AMD over 5 years by quintiles cross-classified for the 0 and 10 gene models. Supplementary Figures S2 and S3 provide similar information for progression to GA and NV, respectively. The Figure shows an OR of 3.2 for overall progression at 5 years comparing subjects that differ by one 10 gene model quintile holding the 0 gene model quintile constant, indicating that there is a substantial increase in the accuracy of prediction for the 10 gene model compared with the 0 gene model. Similar ORs for progression to the advanced dry (OR 4.5, $P < 0.001$) and neovascular advanced (OR 3.4, $P < 0.001$) stages of AMD were obtained.

Discussion

New results based on these prospective analyses include the significant association between the rare variant K155Q in the *C3* gene and the transition from earlier stages of maculopathy to the advanced forms, independent of other known AMD loci and other nongenetic risk factors. This variant results in resistance to inactivation by factor H and

Table 2. Multivariate Associations Between Baseline Demographic, Environmental, and Macular Variables and Progression to Incident Advanced Age-Related Macular Degeneration

	Progressors *N* (%)	Nonprogressors *N* (%)	HR* (95% CI)	*P* Value
Total patients	834	2117		
Age, y				
≥75	208 (25)	252 (12)	Referent	
65–74	512 (62)	1412 (67)	0.8 (0.6–0.9)	<0.001
55–64	114 (14)	453 (21)	0.6 (0.5–0.7)	<0.001
Sex				
Female	461 (55)	1200 (57)	Referent	
Male	373 (45)	917 (43)	1.1 (0.9–1.2)	0.48
Education				
≤High school	330 (40)	661 (31)	Referent	
>High school	504 (60)	1456 (69)	0.9 (0.8–1.0)	0.10
Smoking				
Never	327 (39)	1064 (50)	Referent	
Past	434 (52)	945 (45)	1.1 (1.0–1.3)	0.12
Current	73 (9)	108 (5)	1.8 (1.4–2.3)	<0.001
BMI				
<25	252 (30)	718 (34)	Referent	
25–29	344 (41)	902 (42)	1.1 (0.9–1.3)	0.46
≥30	238 (29)	499 (24)	1.2 (1.0–1.5)	0.04
Advanced AMD				
Neither eye	560 (67)	1953 (92)	Referent	
Grade 4	55 (7)	8 (0.3)	8.3 (3.2–19.9)	<0.001
Grade 5	219 (26)	156 (7)	5.8 (2.3–13.2)	<0.001
Advanced AMD in one eye: largest drusen size in nonadvanced eye, μm				
None to <63	7 (3)	46 (29)	Referent	
63–124	45 (17)	61 (36)	3.9 (1.7–8.6)	<0.001
125–249	91 (33)	38 (24)	8.4 (3.9–18.3)	<0.001
≥250	131 (47)	19 (11)	13.8 (6.4–29.5)	<0.001
No advanced AMD: largest drusen size in each eye, μm†				
None to <63, none to <63	19 (3)	861 (44)	Referent	
63–124, none to <63	28 (5)	421 (21)	3.0 (1.7–5.3)	<0.001
63–124, 63–124	36 (6)	181 (9)	7.9 (4.5–13.8)	<0.001
125–249, none to <63	23 (4)	132 (7)	7.2 (3.9–13.3)	<0.001
125–249, 63–124	69 (12)	161 (8)	15.2 (9.1–25.2)	<0.001
125–249, 125–249	93 (17)	102 (5)	29.0 (17.7–47.5)	<0.001
≥250, ≤124	27 (5)	26 (1)	31.0 (17.2–55.9)	<0.001
≥250, 125–249	103 (18)	43 (2)	50.3 (30.8–82.2)	<0.001
≥250, ≥250	162 (29)	26 (1)	72.0 (44.7–116.2)	<0.001

* Hazard ratios are adjusted for all variables in table and the four AREDS treatment groups.
† Baseline measurements for both eyes (with larger drusen size listed first if size differed between eyes).

factor I, and together with the other rare variants results in amplification of the alternative complement pathway.[13] This new variant was added to the other loci shown to be independently associated with AMD progression,[12] along with the nongenetic factors, and the resultant composite 10 gene model was shown to be highly predictive and could differentiate between low, medium, and high risk of progression to advanced AMD even among individuals with the same macular status at baseline. This model can be used to identify unique profiles. For example, a genetic-only risk score can be derived based on a possible 11,664 categories using the data presented in Supplementary Table S1 ($3^6 \times 2^4$). Assessment of AR and reclassification analyses demonstrated that genetic factors contribute information beyond knowledge of macular phenotypes. Areas under the curve for the total sample and split-sample validation analysis were similar.

The relative contribution of genes compared to macular phenotypes has been the subject of some discussion. Macular phenotypes including drusen size and presence of unilateral advanced disease at baseline are strong predictors of the future course of the disease, and are in the causal pathway for progression. They are also associated with the AMD genes. Incorporating them into the predictive modeling, therefore, attenuates the association between genes and outcomes, as shown by the differences in AR and AUC, which are higher for genes when macular phenotypes are not considered. The 10 gene model incorporates the baseline macular phenotype and underestimates the true effect of the genetic component. Even so, genes contribute high information content for the progression of the disease.

Table 3. Univariate Associations Between Genetic Variants and Progression to Incident Advanced Age-Related Macular Degeneration

	Progressors *N* (%)	Nonprogressors *N* (%)	*P* Value*
Total patients	834	2117	
CFH:rs1061170, Y402H			
TT	135 (16)	769 (36)	<0.001
CT	372 (44)	975 (46)	
CC	327 (39)	373 (17)	
CFH:rs1410996			
TT	30 (4)	356 (17)	<0.001
CT	257 (31)	957 (45)	
CC	547 (66)	804 (38)	
ARMS2/HTRA1:rs10490924, A69S			
GG	263 (31)	1235 (58)	<0.001
GT	397 (48)	749 (35)	
TT	174 (21)	133 (6)	
C2:rs9332739, E318D			
GG	802 (96)	1945 (92)	<0.001
CG/CC	32 (4)	172 (8)	
CFB:rs641153, R32Q			
CC	772 (93)	1768 (83)	<0.001
CT/TT	62 (7)	349 (17)	
C3:rs2230199, R102G			
CC	411 (49)	1308 (62)	<0.001
CG	346 (42)	719 (34)	
GG	77 (9)	90 (4)	
COL8A1:rs13095226			
TT	638 (76)	1737 (82)	<0.001
CT	182 (22)	359 (17)	
CC	14 (2)	21 (1)	
CFH:rs121913059, R1210C			
CC	826 (99)	2112 (99.7)	0.008
CT	8 (1)	5 (0.3)	
RAD51B:rs8017304			
AA	362 (43)	842 (40)	0.003
AG	392 (47)	971 (46)	
GG	80 (10)	304 (14)	
C9:rs34882957, P167S			
GG	803 (96)	2082 (98)	<0.001
AG	31 (4)	35 (2)	
C3:rs147859257, K155Q			
TT	799 (96)	2093 (99)	<0.001
GT	35 (4)	24 (1)	

* *P* values calculated by Mantel-Haenszel χ^2.

For example, if someone has bilateral large drusen in both eyes, the risk of progression to advanced disease can vary from 6.5% to 64% depending on the person's demographic, behavioral, and genetic factors. Genetic factors contribute more to the risk than the other variables, as is shown by the AR calculations.

Advantages of this new 10 gene model compared to some others include the incorporation of genes shown to be independently associated with progression, inclusion of demographic and behavioral risk factors, the use of survival analysis for prospective data, reclassification analyses to compare models, and assessment of AR and AUC with and without macular phenotypes. New genes can be assessed for their independent effects on progression and added to the model to further enhance prediction.[27] Limitations include the restriction of our analyses to a Caucasian population; this population, however, has the highest frequency of advanced AMD. We previously reported validation analysis of a model with seven loci in an external independent cohort,[5] and an expansion of this validation to the 10 gene model is under way.

The clinical utility of rPPMD demonstrated above is clinically effective only if such a tool can be disseminated to clinicians. Ideally such a clinical decision tool should be fully integrated into a patient's electronic medical record (EMR) system, allowing the decision support tool access to the patient's demographics, history, genetic profile, and current vitals (e.g., current BMI score and smoking history) to enable screening (initial assessment) and tracking (risk assessment over time) modalities. Integrating decision tools into an EMR system

Table 4. Multivariate Associations Between Genetic Variants and Progression to Incident Advanced Age-Related Macular Degeneration

	9 Gene Model* HR (95% CI)	*P* Value	*P* Trend	10 Gene Model† HR (95% CI)	*P* Value	*P* Trend
CFH:rs1061170, Y402H						
TT	Referent			Referent		
CT	1.1 (0.9–1.4)	0.49	0.26	1.1 (0.9–1.4)	0.49	0.23
CC	1.2 (0.9–1.5)	0.25		1.2 (0.9–1.5)	0.23	
CFH:rs1410996						
TT	Referent			Referent		
CT	2.0 (1.3–3.0)	0.001	<0.001	2.0 (1.3–3.0)	0.001	<0.001
CC	2.4 (1.6–3.7)	<0.001		2.4 (1.6–3.7)	<0.001	
ARMS2/HTRA1:rs10490924, A69S						
GG	Referent			Referent		
GT	1.3 (1.1–1.5)	0.001	<0.001	1.3 (1.1–1.5)	0.001	<0.001
TT	1.8 (1.5–2.4)	<0.001		1.8 (1.5–2.2)	<0.001	
C2:rs9332739, E318D						
GG	Referent			Referent		
CG/CC	0.7 (0.5–1.0)	0.09	-	0.7 (0.5–1.1)	0.09	-
CFB:rs641153, R32Q						
CC	Referent			Referent		-
CT/TT	0.7 (0.5–0.9)	0.01	-	0.7 (0.6–0.9)	0.01	
C3:rs2230199, R102G						
CC	Referent			Referent		
CG	1.2 (1.0–1.3)	0.04	0.005	1.2 (1.0–1.3)	0.05	0.004
GG	1.3 (1.0–1.7)	0.02		1.4 (1.1–1.8)	0.02	
COL8A1:rs13095226						
TT	Referent			Referent		
CT	1.1 (0.9–1.3)	0.35	0.06	1.1 (0.9–1.3)	0.36	0.06
CC	2.1 (1.2–3.6)	0.01		2.1 (1.2–3.6)	0.006	
CFH:rs121913059, R1210C						
CC	Referent			Referent		
CT	2.5 (1.2–5.2)	0.01	-	2.6 (1.3–5.4)	0.01	-
RAD51B:rs8017304						
AA	Referent			Referent		
AG	0.9 (0.7–1.0)	0.04	0.005	0.9 (0.7–1.0)	0.04	0.01
GG	0.7 (0.6–0.9)	0.01		0.7 (0.6–0.9)	0.02	
C3:rs147859257, K155Q						
TT	-	-		Referent		
GT	-	-		1.7 (1.2–2.5)	0.002	-

* Hazard ratios adjusted for age, sex, education, BMI, smoking status, baseline AMD status and drusen size, four AREDS treatment groups, and genes excluding rare *C3* variant (9 gene model).

† Hazard ratios adjusted for age, sex, education, BMI, smoking status, baseline AMD status and drusen size, four AREDS treatment groups, and all genes in the table (10 gene model). *C9* (P167S) was excluded from the 10 gene model (multivariate OR 1.4, $P = 0.10$).

Table 5. Attributable Risk (%) for Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease Considering Environmental, Genetic, and Combined Environmental and Genetic Variables in Models With and Without Macular Phenotypes

	Macular Phenotypes					
	Advanced AMD		Geographic Atrophy		Neovascular Disease	
Model*	No	Yes	No	Yes	No	Yes
Environmental	26.6%	18.8%	8.5%	0.8%	33.1%	23.2%
Genetic	95.7%	80.5%	94.9%	75.7%	93.6%	77.1%
Genetic and environmental	96.9%	84.3%	94.4%	74.7%	95.0%	81.9%

* Environmental factors: BMI and smoking status. Genetic factors: 10 genetic variants. Genetic and environmental factors: full 10 gene model. All models adjust for age, sex, education, and four AREDS treatment groups.

Table 6. Area Under the Curve Statistics (AUCs) for Advanced Age-Related Macular Degeneration, Geographic Atrophy, and Neovascular Disease Considering Environmental, Genetic, and Combined Environmental and Genetic Variables in Models With and Without Macular Phenotypes

	Macular Phenotypes											
	Advanced AMD				Geographic Atrophy				Neovascular Disease			
Model*	No	*P* Value†	Yes	*P* Value†	No	*P* Value†	Yes	*P* Value†	No	*P* Value†	Yes	*P* Value†
Environmental	0.672	<0.001	0.899	0.001	0.682	<0.001	0.916	0.03	0.667	<0.001	0.878	<0.001
Genetic	0.790	<0.001	0.909	0.32	0.786	0.05	0.922	0.59	0.780	0.004	0.892	0.14
Genetic and environmental	0.800	Referent	0.911	Referent	0.790	Referent	0.923	Referent	0.804	Referent	0.896	Referent

* Environmental factors: BMI and smoking status. Genetic factors: 10 genetic variants. Genetic and environmental factors: full 10 gene model. All models adjust for age, sex, education, and four AREDS treatment groups.

† All *P* values are based on a comparison to the "genetic and environmental" referent model for each AUC.

is often difficult and requires full cooperation and software, hardware, and systems support from the EMR provider. It is, therefore, more realistic to disseminate such clinical decision tools as an online browser-based support tool as we have implemented at our website seddonamdriskscore.org, available in the public domain. The underlying software framework and analytics components of the demonstration website, which delegates the risk assessment among the five rPPMD models (A–E) based on available data, is designed to be used on mobile device platforms such as smart cell phones and tablets. The latter implementation supporting patient risk tracking can therefore be used for initial screening as well as long-term risk tracking modes. On the horizon, predictive analyses could aggregate multiple aspects of the patient condition and risk factors, as well as environmental information, and may help guide potential avenues of intervention for both short-term and long-term patient management. Prediction of risk can facilitate the conversation between care provider and patient as well as among the circle of providers involved in the care of the patient (e.g., primary care practitioner and specialist).

In conclusion, new rare variants found to be associated with macular degeneration in the genes *C3* and *C9* in a case-control study were evaluated in this longitudinal analysis for their independent effects on AMD progression. The K155Q variant in *C3* was significantly related to the transition from early or intermediate disease to the advanced stages, independent of other genetic, demographic, environmental, and ocular predictors. This rare variant, in addition to the rare *CFH* R1210C variant and eight common genetic variants independently related to progression to advanced stages of AMD, along with age, sex, education, BMI, smoking, and macular phenotypes, comprised the 10 gene model. The model was highly predictive of progression with an AUC of 0.91, and the genetic component of the model had a high AR of 80%, adjusting for baseline macular status. Genetic loci improved classification of subjects regarding likelihood of progression, especially among

Table 7. Cumulative Incidence of Progression to Advanced Age-Related Macular Degeneration at 2, 5, and 10 Years Based on the 10 Gene Model Risk Score, Adjusting for Mortality Risks for a Representative Sample of 12 Subjects With Intermediate-Stage Age-Related Macular Degeneration in Both Eyes

	1	2	3	4	5	6	7	8	9	10	11	12
Age	77.7	73.4	68.9	57.6	72.2	60.7	74.4	74.9	62.2	69.0	68.5	75.9
Sex	M	F	F	F	M	M	F	M	F	F	M	F
Education*	High	High	High	High	High	Low	Low	Low	High	High	High	High
Smoking	Never	Past	Never	Never	Past	Current	Never	Never	Current	Never	Past	Never
BMI	25–29.9	<25	25–29.9	25–29.9	≥30	≥30	25–29.9	<25	≥30	25–29.9	≥30	25–29.9
Drusen†	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3
Baseline AMD‡	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3	3 3
CFH:rs1061170, Y402H	T T	T T	T T	T T	T T	C C	C C	C T	C T	C T	T T	C T
CFH:rs1410996	T T	T T	T T	T T	T T	C C	C C	C C	C T	C T	C T	C T
ARMS2/HTRA1:rs10490924, A69S	G G	G G	G G	T G	G G	T T	T G	T T	T G	T T	G G	G G
C2:rs9332739, E318D	G G	G G	G G	G G	G G	G G	G G	G G	G G	G G	G G	G G
CFB:rs641153, R32Q	T C	C C	C C	C C	T C	C C	C C	C C	C C	C C	T C	C C
C3:rs2230199, R102G	C G	C C	C C	C G	C C	C G	C G	C G	C C	C C	C C	C C
CFH:rs121913059, R1201C	C C	C C	C C	C C	C C	C C	C C	C C	T C	T C	C C	C C
COL8A1:rs13095226	T T	T T	T T	T T	C T	T T	C C	C C	T T	T T	T T	C T
RAD51B:rs8017304	G A	G A	G A	G G	A A	A A	G A	G A	G G	G A	G A	G A
C3:rs147859257, K155Q	T T	T T	T T	T T	T T	T T	T T	T T	T T	T T	G T	G T
2-y cumulative incidence, %	2.99	2.70	2.61	2.56	3.15	28.53	30.46	36.13	22.39	23.50	8.50	13.36
5-y cumulative incidence, %	6.94	6.67	6.54	6.54	7.65	57.45	58.60	63.92	48.00	49.20	20.00	29.62
10-y cumulative incidence, %	11.69	12.87	13.13	13.78	14.21	81.49	77.30	77.41	74.48	73.25	35.56	47.28

* Education: low, high school or less; high, more than high school.

† Drusen category (OD, OS): 1 = none to <63 (small); 2 = 63 to 124 (intermediate); 3 = 125 to 249 (large); 4 = ≥250 (extra large). Drusen size measurements given in micrometers.

‡ CARMS grade 3 (intermediate AMD).[17]

Table 8. Cumulative Incidence of Progression to Advanced Age-Related Macular Degeneration at 2, 5, and 10 Years Based on the 10 Gene Model Risk Score, Adjusting for Mortality Risks for a Representative Sample of 12 Subjects With Unilateral Advanced-Stage Age-Related Macular Degeneration

	1	2	3	4	5	6	7	8	9	10	11	12
Age	69.4	59.2	69.2	77.4	62.5	66.8	65.8	72.5	58.4	76.3	65.8	68.2
Sex	M	F	M	F	M	F	M	F	M	F	F	M
Education*	High	High	Low	High	Low	Low	Low	Low	High	Low	Low	High
Smoking	Past	Never	Never	Past	Past	Never	Past	Never	Current	Past	Past	Past
BMI	25–29.9	<25	<25	<25	<25	≥30	≥30	<25	25–29.9	25–29.9	≥30	≥30
Drusen†	- 3	3 -	- 3	- 3	- 3	3 -	3 -	3 -	3 -	- 3	- 3	- 3
Baseline AMD‡	5 3	3 5	5 3	5 3	4 3	3 4	3 4	3 4	3 4	4 3	4 3	5 3
CFH:rs1061170, Y402H	T T	T T	T T	T T	T T	C C	C C	C C	C C	C T	C C	C T
CFH:rs1410996	T T	T T	T T	T T	T T	C C	C C	C C	C C	C C	C C	C T
ARMS2/HTRA1:rs10490924, A69S	G G	T G	T G	G G	G G	T G	T T	T T	T G	T T	T G	G G
C2:rs9332739, E318D	G G	G G	G G	G G	G G	G G	G G	G G	G G	G G	G G	G G
CFB:rs641153, R32Q	T C	C C	T T	C C	C C	C C	C C	C C	C C	C C	C C	C C
C3:rs2230199, R102G	C C	C C	C C	C C	C C	C G	C C	C G	C G	C G	C G	C C
CFH:rs121913059, R1210C	C C	C C	C C	C C	C C	C C	C C	C C	C C	C C	C C	T C
COL8A1:rs13095226	T T	C T	T T	T T	T T	C T	T T	T T	T T	C T	C T	T T
RAD51B:rs8017304	G A	G A	A A	G A	G G	G A	A A	G A	A A	A A	G A	A A
C3:rs147859257, K155Q	T T	T T	T T	T T	T T	G T	T T	G T	T T	T T	T T	T T
2-y cumulative incidence, %	3.29	3.72	4.49	5.30	4.72	46.44	42.32	47.11	34.45	50.59	33.55	28.49
5-y cumulative incidence, %	8.09	9.41	10.94	12.51	11.67	78.76	73.99	77.71	66.00	79.23	64.52	56.37
10-y cumulative incidence, %	15.55	19.40	20.63	21.98	22.95	92.78	89.40	89.28	88.05	87.72	86.29	77.67

* Education: low, high school or less; high, more than high school.

† Drusen category (OD, OS): Subjects have advanced AMD in one eye ('-') and nonadvanced (intermediate) AMD in the fellow eye (drusen category 3, intermediate size, 125–249 μm).

‡ One eye has advanced NV (CARMS grade 5) or GA (grade 4), and fellow eye has intermediate AMD (grade 3).

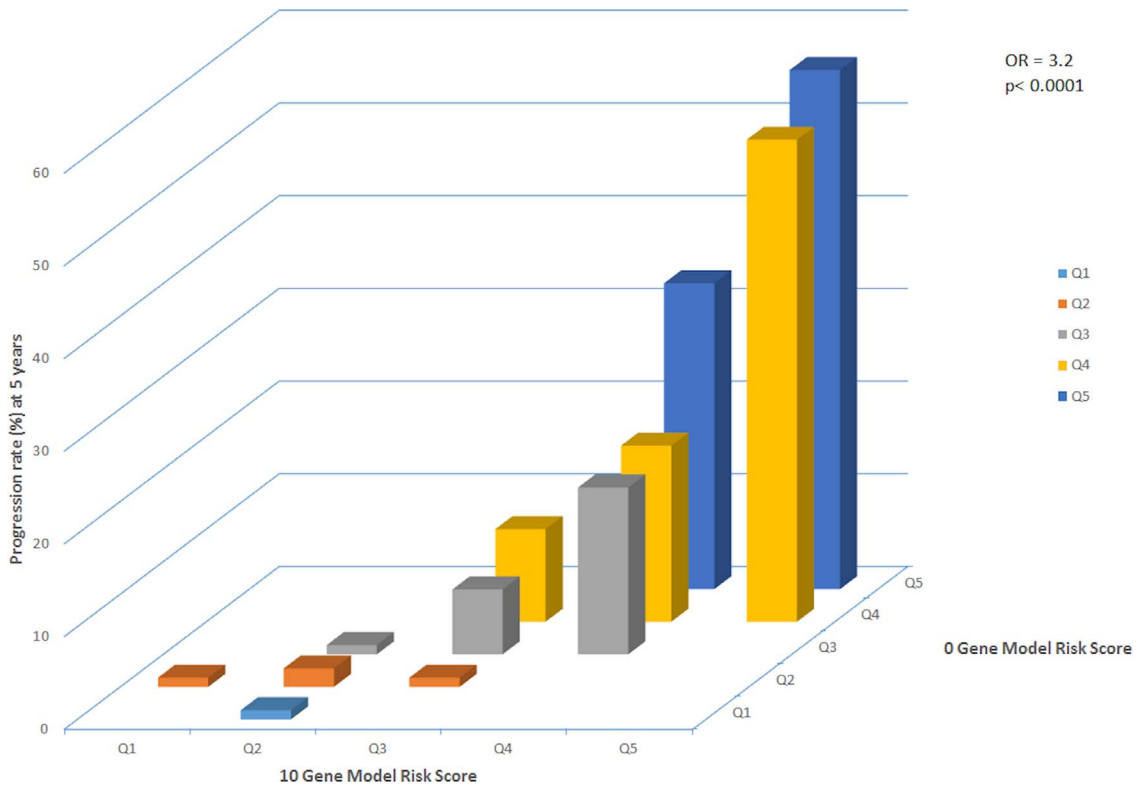

Figure. Cross-classification of progression rates to advanced AMD: 10 gene model versus 0 gene model. Cross-classification of subjects by risk score quintile for the 10 and 0 gene models. Estimated progression rates for each combination of a 10 gene quintile by 0 gene quintile are displayed. OR, odds ratio of progression per one quintile increase in 10 gene model, holding the 0 gene model constant.

individuals with higher risk scores. Results have possible implications for patient management, particularly among those with higher genetic risk.

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References

1. Sobrin L, Seddon JM. Nature and nurture- genes and environment- predict onset and progression of macular degeneration. *Prog Retin Eye Res*. 2014;40:1–15.
2. Seddon JM, Reynolds R, Maller J, Fagerness JA, Daly MJ, Rosner B. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. *Invest Ophthalmol Vis Sci*. 2009;50:2044–2053.
3. Seddon JM, Reynolds R, Yu Y, Daly M, Rosner B. Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. *Ophthalmology*. 2011;118:2203–2211.
4. Yi Y, Reynolds R, Daly MJ, Seddon JM. Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multi-state Markov models. *Invest Ophthalmol Vis Sci*. 2012;53:1548–1556.
5. Seddon JM, Reynolds R, Rosner B. Validation of a prediction algorithm for progression to advanced macular degeneration subtypes. *JAMA Ophthalmol*. 2013;131:448–449.
6. Maller J, George S, Purcell S, et al. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. *Nat Genet*. 2006;38:1055–1059.
7. Seddon J, George S, Rosner B, et al. CFH gene variant Y402H, and smoking, body mass index, environmental associations with advanced age-related macular degeneration. *Hum Hered*. 2006;61:157–165.
8. Seddon JM, Francis PJ, George S, et al. Association of *CFH Y402H* and *LOC387715 A69S* with progression of age-related macular degeneration. *JAMA*. 2007;297:1793–1800.
9. Raychaudhuri S, Iartchouk O, Chin K, et al. A rare penetrant mutation in CFH confers high risk of age-related macular degeneration. *Nat Genet*. 2011;43:1232–1236.
10. Yu Y, Bhangale TR, Fagerness J, et al. Common variants near FRK/COL10A1 and VEGFA are associated with advanced age-related macular degeneration. *Hum Mol Genet*. 2011;20:3699–3709.
11. Fritsche LG, Chen W, Schu M, et al.; for the AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. *Nat Genet*. 2013;45:433–439.
12. Seddon JM, Reynolds R, Yu Y, Rosner B. Three new genetic loci (R1210C, variants in COL8A1 and RAD51B) are independently related to progression to advanced macular degeneration. *PLoS One*. 2014;9:e87047.
13. Seddon JM, Yu Y, Miller EC, et al. Rare variants in *CFI, C3* and *C9* are associated with high risk of advanced age-related macular degeneration. *Nat Genet*. 2013;45:1366–1370.
14. Zhan X, Larson DE, Wang C, et al. Identification of a rare coding variant in complement 3 associated with age-related macular degeneration. *Nat Genet*. 2013;45:1375–1379.
15. Helgason H, Sulem P, Duvvari MR, et al. A rare nonsynonymous sequence variant in *C3* is associated with high risk of age-related macular degeneration. *Nat Genet*. 2013;45:1371–1374.
16. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2011;119:1417–1436.
17. Seddon JM, Sharma S, Adelman R. Evaluation of the clinical age-related maculopathy staging system. *Ophthalmology*. 2006;113:260–266.
18. Hanley J, McNeil B. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
19. Rosner B, Glynn R. Power and sample size estimation for the Wilcoxon rank sum test with application to comparison of C statistics from alternative prediction models. *Biometrics*. 2009;65:188–197.
20. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81:1879–1886.
21. Arias E. United States life tables, 2006. *Natl Vital Stat Rep*. 2010;58:1–40.
22. Centers for Disease Control and Prevention (CDC). *National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data*. Hyattsville, MD: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2009.
23. The 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature*. 2010;467:1061–1073.
24. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med*. 2006;145:21–29.
25. Rosner B, Colditz GA, Iglehart JD, Hankison SE. Risk prediction models with incomplete data with application to prediction of estrogen receptor-positive breast cancer: prospective data from the Nurses' Health Study. *Breast Cancer Res*. 2008;10:R55.
26. Snee RD. Validation of regression models: methods and examples. *Technometrics*. 1977;19:415–428.
27. Yu Y, Triebwasser MP, Wong EKS, et al. Whole-exome sequencing identifies rare, functional CFH variants in families with macular degeneration. *Hum Mol Genet*. 2014;23:5283–5293.

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